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(54) HETEROBICYCLIC COMPOUNDS AND THEIR USE FOR THE TREATMENT OF TUBERCULOSIS

HETEROBICYCLISCHE VERBINDUNGEN UND IHRE VERWENDUNG ZUR BEHANDLUNG VON TUBERKULOSE

COMPOSÉS HÉTÉROBICYCLIQUES ET LEUR UTILISATION POUR LE TRAITEMENT DE TUBERCULOSE

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(56) References cited:
WO-A1-2005/042542 **WO-A1-2010/004347**
WO-A1-2010/045987

Description

Technical Field

[0001] The present invention relates to a fused heterocyclic compound.

Background Art

[0002] Human tuberculosis bacteria (Mycobacterium tuberculosis) is widely known among mycobacteria, with which third part of human beings are said to be infected. Mycobacterium africanum, Mycobacterium bovis, Mycobacterium caprae, Mycobacterium pinnipedii, and Mycobacterium microti are known to belong to the tuberculosis bacteria group like human tuberculosis bacteria, and are known as mycobacteria having pathogenicity against human.

[0003] Multidrug chemotherapy for 6 months has been recommended as a treatment for these tuberculosis bacteria. A typical therapy comprises a treatment with 4 agents of rifampicin, isoniazid, pyrazinamide, and ethambutol (or streptomycin) for the first 2 months; and a treatment with 2 agents of rifampicin and isoniazid for the remaining 4 months.

[0004] It has been pointed out however that the medication compliance in the treatment for tuberculosis is poor due to such long-term treatment and adverse effects of the used drugs often cause the treatment to discontinue.

[0005] The adverse effects of these drugs have been reported (Nonpatent Literatures 1 and 2), for example, rifampicin has hepatic disorder, flu syndrome, drug allergy, and contraindication to combination use with other drugs caused by P450-related enzymes; isoniazid has peripheral neuropathy and serious hepatic disorder induced with a combination use with rifampicin; ethambutol has visual loss caused by optic nerve disorder; streptomycin has hearing loss caused by eighth cranial nerve involvement; pyrazinamide has hepatic disorder, gouty attack associated with the uric acid level, and vomiting. Amongst the adverse effects of the above 5 agents used as a first-line drug, in particular, hepatotoxicity commonly-caused by rifampicin, isoniazid, and pyrazinamide is known as the most frequent adverse effect.

[0006] It has been in fact reported that the cases where the standard chemotherapy cannot be carried out due to the adverse effects account for 70% of the cases where the drug administration is discontinued (about 23%, 52 cases) of the total (the total of 228 inpatient cases surveyed) (Nonpatent Literature 3).

[0007] Tuberculosis bacteria resistant to antitubercular agents, multidrug-resistant tuberculosis bacteria, for example have been recently increasing, which has made the treatment of tuberculosis more difficult.

[0008] The World Health Organization (WHO) has reported that among those who have been infected with multidrug-resistant tuberculosis (MDR-TB) resistant to potent rifampicin and isoniazid, 450,000 people have newly developed and 170,000 people have died per year, and multidrug-resistant tuberculosis patients are currently estimated as 1,500,000 in the world. An extensively-drug-resistant tuberculosis (XDR-TB) which has been resistant to many drugs has been identified, which has become a threat to public health in the world (Nonpatent Literature 4).

[0009] Third part of those who have been infected with HIV in the world has been suspected of co-infection with tuberculosis even though not progressing to active tuberculosis (Nonpatent Literature 5). Co-infection of HIV and tuberculosis is fatal, in which one disease can accelerate the progression of the other disease and tuberculosis can easily progress to active tuberculosis. In 2012, about 320,000 people died of tuberculosis associated with HIV, which means that about 25% of the death of HIV infected people were caused by tuberculosis. It has been also reported that patients infected with both HIV and tuberculosis can develop tuberculosis in 20 to 37 times higher risk than usual (Nonpatent Literature 6).

[0010] The American Thoracic Society and Centers for Disease Control and Prevention have recently reported the concept that carriage state itself of tuberculosis bacteria is a potential disease even though not developing to tuberculosis, and the usefulness of active treatment has been established for patients with a higher risk of developing to the disease.

[0011] In view of the current circumstances, a desired profile for antitubercular agents includes (1) those effective for multidrug-resistant tuberculosis bacteria, (2) those which enable a short-term chemotherapy, (3) those with less adverse effects, (4) those effective for latent tuberculosis infection (LTBI).

[0012] Mycobacterium avium and Mycobacterium intracellulare, which are responsible bacteria for recently increasing MAC symptom (Mycobacterium avium-intracellulare complex symptom), as well as other non-tuberculous mycobacteria such as Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium simiae, Mycobacterium scrofulaceum, Mycobacterium szulgai, Mycobacterium xenopi, Mycobacterium malmoense, Mycobacterium haemophilum, Mycobacterium ulcerans, Mycobacterium shimoidei, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium smegmatis, and Mycobacterium aurum have been known as bacteria having pathogenicity in human.

[0013] A typical chemotherapy of lung MAC symptom is polypharmacy based on three drugs of rifampicin, ethambutol, and clarithromycin, and streptomycin or kanamycin is, if needed, used in combination. Another treatment for non-tuberculous mycobacteria symptom currently includes combination use with an antitubercular agent such as rifampicin, isoniazid, ethambutol, streptomycin, kanamycin, a therapeutic agent for common bacterial infection such as a newquinolone agent, a macrolide antibacterial agent, an aminoglycoside antibacterial agent, and a tetracycline antibacterial agent.

[0014] It has been reported however that the treatment for non-tuberculous mycobacteria needs a longer-term medication than that in common bacterial infection, the treatment tends to become refractory, and some have resulted in death. To solve the circumstances, a development of more potent drugs has been desired.

[0015] For example, Patent Literature 1 discloses that 6-nitro-1,2,3,4-tetrahydro[2,1-b]imidazopyrane compounds have a bactericidal activity against tuberculosis bacteria (H37Rv strain) and multidrug-resistant tuberculosis bacteria in vitro and a therapeutic effect in oral administration for a tuberculosis-infected animal model, and thus they are useful as an antitubercular agent.

[0016] Patent Literatures 2 and 3 disclose that 2,3-dihydroimidazo[2,1-b]oxazole compounds have a bactericidal activity against tuberculosis bacteria, multidrug-resistant tuberculosis bacteria, and atypical mycobacteria.

[0017] Patent Literature 4 discloses that nitroimidazooxazine and nitroimidazooxazole compounds can be used as a medicament against human tuberculosis bacteria (Mycobacterium tuberculosis).

[0018] Patent Literature 5 discloses that 6,7-dihydroimidazo[2,1-b][1,3]oxazine compounds have an excellent bactericidal activity against tuberculosis bacteria and multidrug-resistant tuberculosis bacteria.

[0019] The compounds disclosed in the above references, however, structurally differ from and are not similar to the compound of the present invention.

Citation List

Patent Literature

[0020]

[PTL 1] WO 97/01562 (JP-A-11-508270)
[PTL 2] JP-A-2004-149527
[PTL 3] JP-A-2005-320316
[PTL 4] WO 2011/014776
[PTL 5] WO 2012/141338

Non Patent Literature

[0021]

[NPL 1] A Clinician's Guide To Tuberculosis, Michael D. Iseman 2000 by Lippincott Williams & Wilkins, printed in the USA, ISBN 0-7817-1749-3
[NPL 2] Kekkaku 2nd edition, Fumiyuki Kuze, Takahide Izumi, Igaku-shoin 1992
[NPL 3] Kekkaku Vol.74: 77-82, 1999
[NPL 4] Global tuberculosis report 2013
[NPL 5] The Internet Journal of Pulmonary Medicine 2008: Volume 10 Number 1
[NPL 6] The Global Plan To Stop TB 2011-2015

[0022] WO 2010/004347 describes heterocyclic compounds of a certain formula, which are GPCR (GPR119) agonists and are useful as for the treatment of diabetes and obesity.

[0023] WO 2005/042542 concerns a 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound of a certain formula, which has an excellent bactericidal action against Mycobacterium tuberculosis, multi-drug-resistant Mycobacterium tuberculosis, and atypical acid-fast bacteria.

[0024] WO 2010/045987 describes bicyclic nitrogen containing compounds and their use as antibacterials.

Summary of Invention

Technical Problem

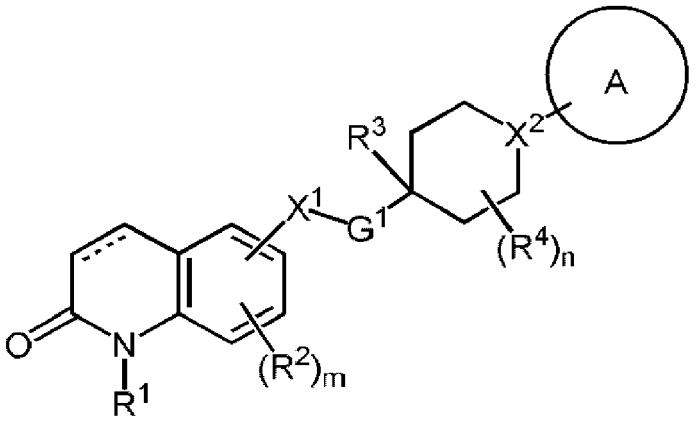
[0025] It is an object of the present invention to provide compounds having an excellent antibacterial activity against tuberculosis bacteria and multidrug-resistant tuberculosis bacteria. It is another object of the present invention to provide compounds having an excellent antibacterial activity against non-tuberculous mycobacteria.

Solution to Problem

[0026] The present inventors have achieved syntheses of novel fused heterocyclic compounds having an excellent

bactericidal activity against tuberculosis bacteria, multidrug-resistant tuberculosis bacteria, and nontuberculous mycobacteria as a result of extensive studies to solve the problem.
The present invention has been accomplished on the basis of this finding.

[0027] In one aspect, the present invention includes a compound of the general formula (1) for use for diagnosing, preventing, and/or treating tuberculosis:



(1)

or a salt thereof, wherein the moiety:

represents single bond or double bond; and

wherein R^1 is

(1) hydrogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl or
(3) C_{1-6} alkyl;

R^2 is

(1) halogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl,
(3) C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) hydroxy;

m is an integer of 0 to 3;
provided that when m is 2 or 3, R^2 may be different from each other;
X^1 is $-CH_2-$, -O-, $-N(R^5)-$, -S-, -SO- or $-SO_2-$;
R^5 is

(1) hydrogen,
(2) C_{1-6} alkyl or
(3) C_{1-7} alkanoyl;

G^1 is C_{1-6} alkylene;
R^3 is

(1) hydrogen,
(2) carboxy,
(3) halogen,

(4) C_{1-6} alkyl, which may have one or more hydroxy,
(5) cyano,
(6) amino which may have one or two substituents independently selected from:

(a) C_{1-6} alkyl and
(b) -C(=O)-R^6 or

(7) -O-R^7;

R^6 is

(1) C_{1-6} alkoxy or
(2) C_{1-6} alkyl, wherein the C_{1-6} alkyl may have amino which may have one or two of the same or different C_{1-6} alkyl;

R^7 is

(1) hydrogen,
(2) amino,
(3) C_{1-7} alkanoyl or
(4) C_{1-6} alkyl;

R^4 is

(1) amino which may have one or two of the same or different C_{1-6} alkyl,
(2) halogen,
(3) cyano,
(4) C_{1-6} alkyl,
(5) oxo,
(6) -O-R^8 or
(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -PH(=O)OH or
(4) benzyl which may have one or more of the same or different C_{1-6} alkoxy;

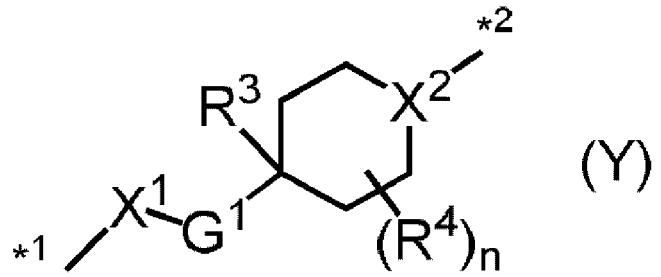
R^9 is

(1) C_{1-6} alkyl,
(2) -G^2-COOH,
(3) amino which may have one or two of the same or different C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) pyrazinyl;

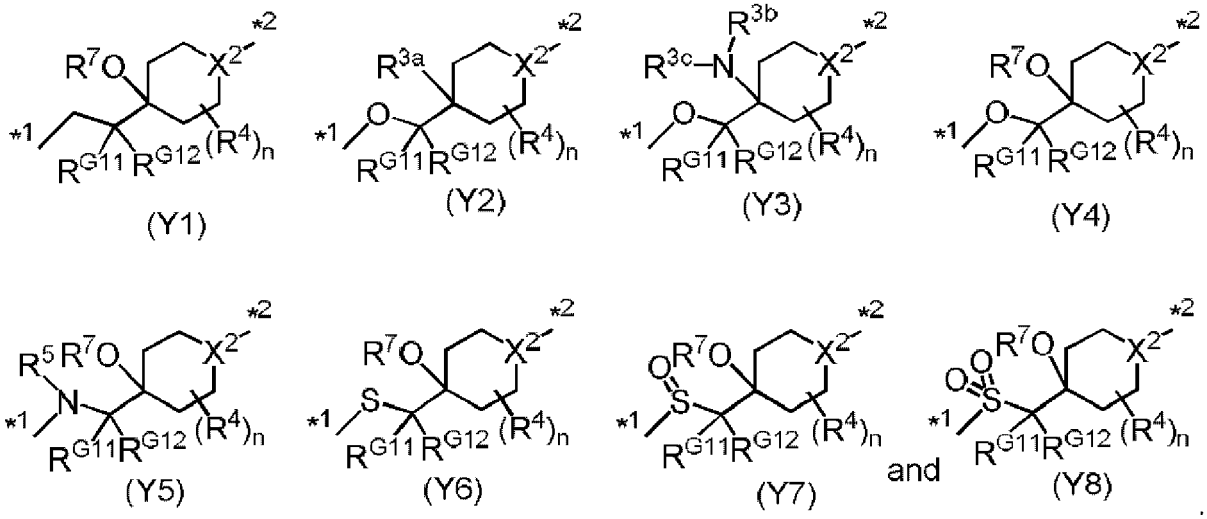
G^2 is C_{1-6} alkylene;
n is an integer of 0 to 8;
provided that when n is 2 or more, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;
X^2 is N or CH;
provided that when X^2 is CH, H of the group may be replaced with R^4 which is defined as above, wherein multiple R^4s in formula (1) may be the same or different from each other; and
Ring A is

(1) aryl which may have one or more substituents, or
(2) heterocyclyl which may have one or more substituents; which is referred hereinafter to as Compound (1).

[0028] Another aspect of the invention relates to compounds as defined above, wherein the partial structure (Y):



wherein *1 is binding point to the partial structure of Formula (X); *2 is binding point to Ring A; and other symbols are as defined for Compound (1), is any one of the structures selected from the group consisting of the following formulae (Y1) to (Y8):



wherein R^{3a} is (1) hydrogen, (2) carboxy, (3) halogen, (4) lower alkyl which may have one or more hydroxy, or (5) cyano;
R^{3b} and R^{3c} are each independently (1) hydrogen, (2) lower alkyl, or (3) -C(=O)-R^6;
R^{G11} and R^{G12} are each independently hydrogen or lower alkyl;
the total number of carbon atoms in R^{G11} and R^{G12} is 0 to 5; and
other symbols are as defined in for Compound 1.

Advantageous Effects of Invention

[0029] Compound (1) in the present invention has specific activities in particular against mycobacteria (such as tuberculosis bacterial genus and non-tuberculous mycobacterial genus), and also has excellent activities against multidrug-resistant tuberculosis bacteria.

[0030] Compound (1) in the present invention shows not only the activities *in vitro* but also the activites *in vivo* in oral administration because the administered compound is favorably distributed in lung tissues which are the primary organ infected with the mycobacterial infectious disease.

[0031] Compound (1) in the present invention does not induce diarrhea as seen in known antibacterial agents with a wide spectrum for common bacteria such as gram-positive bacteria and gram-negative bacteria, and thereby may become a medicinal substance which allows for a long-term administration.

[0032] Compound (1) in the present invention is effective for intracellular parasitic bacteria such as human-origin tuberculosis bacteria which is parasitic in macrophage, and has a stronger bactericidal activity in a low concentration even in a bactericidal test than
conventional antitubercular agents. It is thus expected that the relapse rate in tuberculosis will be reduced, which eventually allows for a short-term chemotherapy.

[0033] Compound (1) in the present invention shows a low inhibitory activity against a drug-metabolizing enzyme, a

low possibility for an enzyme induction of CYP3A, and a low concerns about drug interaction. Thus, the compound is expected for a combination use with conventional drugs or HIV drugs.

[0034] In addition, Compound (1) has a lower toxicity than conventional drugs, and hence the compound is also expected for long-term use in the treatment for latent tuberculosis.

Description of Embodiments

[0035] The phrases and terms used herein are described in detail as below.

[0036] Examples of "lower alkyl" include straight or branched chain alkyl groups having 1 to 6 carbon atoms, and in particular include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and 3-methylpentyl.

[0037] Examples of "lower alkenyl" include straight or branched chain alkenyl groups having 2 to 6 carbon atoms and 1 to 3 double bonds, and include, for example, vinyl (ethenyl), 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, and 5-hexenyl.

[0038] Examples of "lower alkynyl" include straight or branched chain alkynyl groups having 2 to 6 carbon atoms and 1 to 3 triple bonds, and include, for example, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl.

[0039] Examples of "lower alkoxy" include straight or branched chain alkoxy groups having 1 to 6 carbon atoms, and include, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, isohexyloxy, and 3-methylpentyloxy.

[0040] Examples of "lower alkenyloxy" include straight or branched chain alkenyloxy groups having 2 to 6 carbon atoms and 1 to 3 double bonds, and include, for example, vinyloxy (ethenyloxy), 1-propenyloxy, 2-propenyloxy, 2-methyl-1-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 3-methyl-2-butenyloxy, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 4-methyl-3-pentenyloxy, 1-hexenyloxy, 3-hexenyloxy, and 5-hexenyloxy.

[0041] Examples of "lower alkynyloxy" include straight or branched chain alkynyloxy groups having 2 to 6 carbon atoms and 1 to 3 triple bonds, and include, for example, ethynyloxy, 1-propynyloxy, 2-propynyloxy, 1-butynyloxy,2-butynyloxy, 3-butynyloxy, 1-pentynyloxy, 2-pentynyloxy, 3-pentynyloxy, 4-pentynyloxy, 1-hexynyloxy, 2-hexynyloxy, 3-hexynyloxy, 4-hexynyloxy, and 5-hexynyloxy.

[0042] Examples of "lower alkanoyl" include straight or branched chain alkanoyl groups having 1 to 7 carbon atoms, and include, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, and hexanoyl.

[0043] Examples of "lower alkenylcarbonyl" include straight or branched chain alkenylcarbonyl groups having 3 to 7 carbon atoms and 1 to 3 double bonds, and include, for example, vinylcarbonyl (ethenylcarbonyl), 1-propenylcarbonyl, 2-propenylcarbonyl, 2-methyl-1-propenylcarbonyl, 1-butenylcarbonyl, 2-butenylcarbonyl, 3-butenylcarbonyl, 3-methyl-2-butenylcarbonyl, 1-pentenylcarbonyl, 2-pentenylcarbonyl, 3-pentenylcarbonyl, 4-pentenylcarbonyl, 4-methyl-3-pentenylcarbonyl, 1-hexenylcarbonyl, 3-hexenylcarbonyl, and 5-hexenylcarbonyl.

[0044] Examples of "lower alkynylcarbonyl" include straight or branched chain alkynylcarbonyl groups having 3 to 7 carbon atoms and 1 to 3 triple bonds, and include, for example, ethynylcarbonyl, 1-propynylcarbonyl, 2-propynylcarbonyl, 1-butynylcarbonyl, 2-butynylcarbonyl, 3-butynylcarbonyl, 1-pentynylcarbonyl, 2-pentynylcarbonyl, 3-pentynylcarbonyl, 4-pentynylcarbonyl, 1-hexynylcarbonyl, 2-hexynylcarbonyl, 3-hexynylcarbonyl, 4-hexynylcarbonyl, and 5-hexynylcarbonyl.

[0045] Examples of "lower alkanoyloxy" include straight or branched chain alkanoyloxy groups having 1 to 7 carbon atoms, and include, for example, formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pentanoyloxy, tert-butylcarbonyloxy, and hexanoyloxy.

[0046] Examples of "lower alkoxycarbonyl" include straight or branched chain alkoxycarbonyl groups having 2 to 7 carbon atoms, and include, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, and hexyloxycarbonyl.

[0047] Examples of "lower alkylsulfanyl" include straight or branched chain alkylsulfanyl groups having 1 to 6 carbon atoms, and include, for example, methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, butylsulfanyl, tert-butylsulfanyl, pentyl-sulfanyl, and hexylsulfanyl.

[0048] Examples of "lower alkylsulfinyl" include straight or branched chain alkylsulfinyl groups having 1 to 6 carbon atoms, and include, for example, methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, tert-butylsulfinyl, pentyl-sulfinyl, and hexylsulfinyl.

[0049] Examples of "lower alkylsulfonyl" include straight or branched chain alkylsulfonyl groups having 1 to 6 carbon atoms, and include, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, tert-butylsulfonyl, pentyl-sulfonyl, and hexylsulfonyl.

[0050] Examples of "cyclo-lower-alkyl" include cycloalkyl groups having 3 to 6 carbon atoms, and include, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0051] Examples of "cyclo-lower-alkenyl" include cycloalkenyl groups having 3 to 6 carbon atoms, and include, for example, 2-cyclopentenyl, 3-cyclopentenyl, 2-cyclohexenyl, and 3-cyclohexenyl.

[0052] Examples of "cyclo-lower-alkoxy" include cycloalkoxy groups having 3 to 6 carbon atoms, and include, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy.

[0053] Examples of "cyclo-lower-alkenyloxy" include cycloalkenyloxy groups having 3 to 6 carbon atoms, and include, for example, 2-cyclopentenyloxy, 3-cyclopentenyloxy, 2-cyclohexenyloxy, and 3-cyclohexenyloxy.

[0054] Examples of "cyclo-lower-alkylcarbonyl" include cycloalkylcarbonyl groups having 4 to 7 carbon atoms, and include, for example, cyclopropylcarbonyl, cyclobutyl-carbonyl, cyclopentylcarbonyl, and cyclohexylcarbonyl.

[0055] Examples of "cyclo-lower-alkoxycarbonyl" include cycloalkoxycarbonyl group having 4 to 7 carbon atoms, and include, for example, cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, and cyclohexyloxycarbonyl.

[0056] Examples of "aryl" include mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, phenyl, naphthyl, anthryl, and phenanthryl.

[0057] Examples of "aryloxy" include mono-, bi-, or tri-cyclic aromatic hydrocarbon-oxy groups, and include, for example, phenyloxy, naphthyloxy, anthryloxy, and phenanthryloxy.

[0058] Examples of "arylcarbonyl" include mono-, bi-, or tri-cyclic aromatic hydrocarbon-carbonyl groups, and include, for example, phenylcarbonyl, naphthylcarbonyl, anthrylcarbonyl, and phenanthrylcarbonyl.

[0059] Examples of "aryloxycarbonyl" include mono-, bi-, or tri-cyclic aromatic hydrocarbon-oxycarbonyl groups, and include, for example, phenyloxycarbonyl, naphthyloxycarbonyl, anthryloxycarbonyl, and phenanthryloxycarbonyl.

[0060] Examples of "aralkyl" include straight or branched chain alkyl groups having 1 to 3 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 1-naphthylmethyl, and 2-naphthylmethyl.

[0061] Examples of "aralkyloxy" include straight or branched chain alkoxy groups having 1 to 3 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, 1-naphthylmethyloxy, and 2-naphthylmethyloxy.

[0062] Examples of "aralkylcarbonyl" include straight or branched chain alkylcarbonyl groups having 2 to 4 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzylcarbonyl, 1-phenylethylcarbonyl, 2-phenylethylcarbonyl, 1-naphthylmethylcarbonyl, and 2-naphthylmethylcarbonyl.

[0063] Examples of "aralkyloxycarbonyl" include straight or branched chain alkyloxycarbonyl groups having 2 to 4 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzyloxycarbonyl, 1-phenylethyloxycarbonyl, 2-phenylethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, and biphenylylmethyloxycarbonyl.

[0064] Examples of "heterocyclyl" include saturated or unsaturated monocyclic or polycyclic (e.g. bicyclic, tricyclic, spiro-form, or bicyclo-form) heterocyclyl groups comprising at least one (e.g. 1 to 5) heteroatom selected as a ring-constituent atom from oxygen atom, sulfur atom (which may form sulfoxide), and nitrogen atom (which may form amine oxide) besides carbon atoms, and for example include:

(a) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, N-oxide pyridyl, tetrahydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, dihydrotriazinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl, piperazinyl, azepanyl, 1,4-diazepanyl;

(b) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 to 5 nitrogen atoms, for example, decahydroquinolyl, indolyl, dihydroindolyl, isoindolyl, indolizinyl, benzoimidazolyl, dihydrobenzoimidazolyl, quinolyl, dihydroquinolyl, tetrahydroquinolyl, isoquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, carbostyryl, dihydrocarbostyryl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl, dihydrotriazolopyridazinyl, imidazopyridyl, naphthyridinyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolopyridyl, tetrahydropyridoindolyl;

(c) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 or 2 oxygen atoms, for example, furyl, tetrahydropyranyl, tetrahydrofuryl, dioxanyl;

(d) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 to 3 oxygen atoms, for example, benzofuryl, dihydrobenzofuryl, chromanyl, benzodioxanyl, benzodioxolyl;

(e) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl, morpholinyl;

(f) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzooxazolyl, benzooxadiazolyl, benzoisoxazolyl, dihydrobenzooxazinyl, furopyridyl, furopyrrolyl;

(g) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiazolinyl, thiadiazolyl, isothiazolyl, thiazolidinyl;

(h) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 or 2 sulfur atoms and 1 to

3 nitrogen atoms, for example, benzothiazolyl, benzothiadiazolyl, thienopyridyl, imidazothiazolyl, dihydroimidazothiazolyl, thienopyrazinyl;
(i) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 sulfur atom, for example, thienyl;
(j) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 to 3 sulfur atoms, for example, benzothienyl;
(k) saturated or unsaturated 7- to 12-membered heterocyclic spiro groups, for example, azaspiroundecanyl; and
(l) saturated or unsaturated 7- to 12-membered bicyclo heterocyclyl groups, for example, azabicyclo-cyclooctanyl.

[0065] "Heterocyclyloxy" refers to a group of "(heterocyclyl)-O-", and examples of heterocyclyl group include groups as illustrated above in "heterocyclyl".

[0066] "Heterocyclylcarbonyl" refers to a group of "(heterocyclyl)-CO-", and examples of heterocyclyl group include groups as illustrated above in "heterocyclyl".

[0067] "Heterocyclyloxycarbonyl" refers to a group of "(heterocyclyl)-O-CO-", and examples of heterocyclyl include groups as illustrated above in "heterocyclyl".

[0068] Examples of "mono- or di-lower alkylamino" include amino groups which are mono- or di-substituted with straight or branched chain alkyl groups having 1 to 6 carbon atoms, and for example, include mono-lower alkylamino groups such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, and tert-butylamino; di-lower alkylamino groups such as dimethylamino, diethylamino, dipropylamino, dibutylamino, di-isobutylamino, di-sec-butylamino, di-tert-butylamino, and N-ethyl-N-methylamino.

[0069] Examples of "mono- or di-lower alkanoylamino" include amino groups which are mono- or di-substituted with straight or branched chain alkanoyl groups having 1 to 7 carbon atoms, for example, mono-lower alkanoylamino groups such as formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, pentanoylamino, tert-butylcarbonylamino, and hexanoylamino; di-lower alkanoylamino groups such as diformylamino, diacetylamino, dipropionylamino, dibutyrylamino, diisobutyrylamino, dipentanoylamino, di-tert-butylcarbonylamino, and dihexanoylamino.

[0070] Examples of "tri-lower alkylsilyl" include silyl groups which are tri-substituted with straight or branched chain alkyl groups having 1 to 6 carbon atoms, for example, trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl.

[0071] Examples of "lower alkylene" include straight or branched chain alkylene groups having 1 to 6 carbon atoms, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_2CH_3)-$, $-C(CH_3)(CH_2CH_3)-$, $-C(CH_2CH_3)_2-$, $-CH(CH_2CH_2CH_3)-$, $-C(CH_3)(CH_2CH_2CH_3)-$, $-C(CH_2CH_3)(CH_2CH_2CH_3)-$, $-CH(CH(CH_3)_2)-$, $-C(CH_3)(CH(CH_3)_2)-$, $-C(CH_2CH_3)(CH(CH_3)_2)-$, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_2CH_3)-$, $-CH(CH_2CH_3)-CH_2-$, $-(CH(CH_3))_2-$, $-CH(CH_3)-CH_2-CH_2-$, $-CH_2-CH(CH_3)-CH_2-$, $-CH_2-CH_2-CH(CH_3)-$, $-CH_2-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-CH_2-CH_2-$.

[0072] Examples of "halogen" include fluorine, chlorine, bromine, and iodine.

[0073] The phrase "β which may have α" means that β may be substituted with at least one (usually 1 to 10, preferably 1 to 6, more preferably 1 to 3, and 1 or 2 in the case where β is amino or carbamoyl) α, each of β being displaceable at the same or different positions.

[0074] Examples of "substituent" in the phrase "may have one or more substituents" include groups independently selected from:

(A) halogen,
(B) cyano,
(C) nitro,
(D) hydroxy,
(E) carboxy,
(F) sulfo,
(G) sulfanyl,
(H) lower alkyl which may have one or more substituents selected from groups (Ia) and (Ib),
(I) lower alkenyl which may have one or more substituents selected from groups (Ia) and (Ib),
(J) lower alkynyl which may have one or more substituents selected from groups (Ia) and (Ib),
(K) lower alkoxy which may have one or more substituents selected from groups (Ia) and (Ib),
(L) lower alkenyloxy which may have one or more substituents selected from groups (Ia) and (Ib),
(M) lower alkynyloxy which may have one or more substituents selected from groups (Ia) and (Ib),
(N) lower alkanoyl which may have one or more substituents selected from groups (Ia) and (Ib),
(O) lower alkenylcarbonyl which may have one or more substituents selected from groups (Ia) and (Ib),
(P) lower alkynylcarbonyl which may have one or more substituents selected from groups (Ia) and (Ib),
(Q) lower alkanoyloxy which may have one or more substituents selected from groups (Ia) and (Ib),
(R) lower alkoxycarbonyl which may have one or more substituents selected from groups (Ia) and (Ib),

(S) lower alkylsulfanyl which may have one or more substituents selected from groups (Ia) and (Ib),
(T) lower alkylsulfinyl which may have one or more substituents selected from groups (Ia) and (Ib),
(U) lower alkylsulfonyl which may have one or more substituents selected from groups (Ia) and (Ib),
(V) cyclo-lower-alkyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(W) cyclo-lower-alkoxy which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(X) cyclo-lower-alkenyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(Y) cyclo-lower-alkenyloxy which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(Z) cyclo-lower-alkylcarbonylwhich may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(AA) cyclo-lower-alkoxycarbonyl group which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(BB) arylwhich may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(CC) aryloxywhich may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(DD) arylcarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(EE) aryloxycarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(FF) aralkylwhich may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(GG) aralkyloxy which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(HH) aralkylcarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(II) aralkyloxycarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),
(JJ) heterocyclyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(KK) heterocyclyloxy which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(LL) heterocyclylcarbonylwhich may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(MM) heterocyclyloxycarbonyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,
(NN) aminowhich may have one or more substituents selected from groups (Ia) and (Ic), and
(OO) carbamoyl which may have one or more substituents selected from groups (Ia) and (Ic).

The number of any substituents in Compound (1) is not limited as long as chemically applicable, unless otherwise specified.

[0075] The "group (Ia)" includes substituents selected from:

(a) lower alkanoyl which may have one or more substituents selected from groups (IIa) and (IIb),
(b) lower alkenylcarbonyl which may have one or more substituents selected from groups (IIa) and (IIb),
(c) lower alkynylcarbonyl which may have one or more substituents selected from groups (IIa) and (IIb),
(d) lower alkoxycarbonyl which may have one or more substituents selected from groups (IIa) and (IIb),
(e) lower alkylsulfanyl which may have one or more substituents selected from groups (IIa) and (IIb),
(f) lower alkylsulfinyl which may have one or more substituents selected from groups (IIa) and (IIb),
(g) lower alkylsulfonyl which may have one or more substituents selected from groups (IIa) and (IIb),
(h) cyclo-lower-alkyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(i) cyclo-lower-alkoxy which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(j) cyclo-lower-alkenyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(k) cyclo-lower-alkylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(l) cyclo-lower-alkoxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(m) aryl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(n) arylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(o) aryloxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(p) aralkyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(q) aralkylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(r) aralkyloxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(s) heterocyclyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(t) heterocyclylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(v) heterocyclyloxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo, and
(w) carbamoyl which may have one or more substituents selected from groups (IIa) and (IIc).

[0076] The "group (Ib)" includes substituents selected from:

(a) halogen,
(b) cyano,

(c) nitro,
(d) hydroxy,
(e) carboxy,
(f) sulfo,
(g) sulfanyl,
(h) lower alkoxy which may have one or more substituents selected from groups (IIa) and (IIb),
(i) lower alkenyloxy which may have one or more substituents selected from groups (IIa) and (IIb),
(j) lower alkynyloxy which may have one or more substituents selected from groups (IIa) and (IIb),
(k) lower alkanoyloxy which may have one or more substituents selected from groups (IIa) and (IIb),
(l) cyclo-lower-alkenyloxy which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,
(m) aryloxy which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(n) aralkyloxy which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),
(o) heterocyclyloxy which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo, and
(p) amino which may have one or more substituents selected from groups (IIa) and (IIc).

[0077] The "group (Ic)" includes substituents selected from:

(a) lower alkyl which may have one or more substituents selected from groups (IIa) and (IIb),
(b) lower alkenyl which may have one or more substituents selected from groups (IIa) and (IIb), and
(c) lower alkynyl which may have one or more substituents selected from groups (IIa) and (IIb).

[0078] The "group (IIa)" includes substituents selected from lower alkanoyl, lower alkenylcarbonyl, lower alkynylcarbonyl, lower alkoxycarbonyl, lower alkylsulfonyl, cyclo-lower-alkyl, cyclo-lower-alkoxy, cyclo-lower-alkenyl, cyclo-lower-alkylcarbonyl, cyclo-lower-alkoxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, aralkyl, aralkylcarbonyl, aralkyloxycarbonyl, heterocyclyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, mono- or di-lower alkanoylcarbamoyl, and mono- or di-lower alkylcarbamoyl.

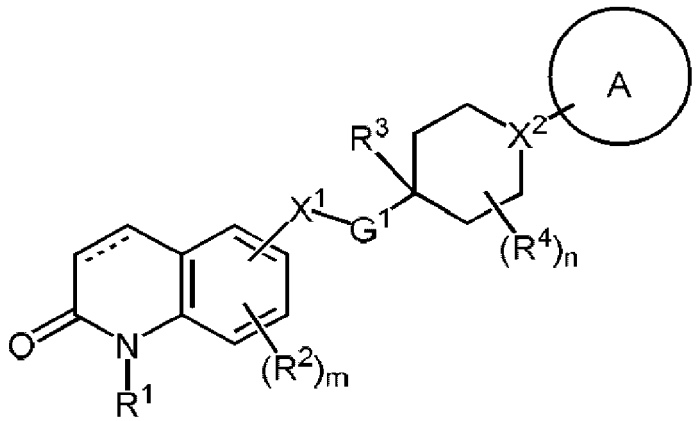
[0079] The "group (IIb)" includes substituents selected from halogen, cyano, nitro, hydroxy, carboxy, sulfo, sulfanyl, amino, lower alkoxy, lower alkenyloxy, lower alkynyloxy, lower alkanoyloxy, lower alkylsulfanyl, lower alkylsulfinyl, cyclo-lower-alkenyloxy, aryloxy, aralkyloxy, heterocyclyloxy, mono- or di-lower alkylamino, and mono- or di-lower alkanoylamino.

[0080] The "group (IIc)" includes substituents selected from lower alkyl, lower alkenyl, and lower alkynyl.

[0081] Each of symbols and structures in the general formula (1) is explained in detail as below.

[0082] In one aspect, the present invention includes the following embodiments:

[1] A compound of the general formula (1) for use for diagnosing, preventing, and/or treating tuberculosis:



(1)

or a salt thereof, wherein the moiety:

represents single bond or double bond; and

wherein R^1 is

(1) hydrogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl or
(3) C_{1-6} alkyl;

R^2 is

(1) halogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl,
(3) C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) hydroxy;

m is an integer of 0 to 3;
provided that when m is 2 or 3, R^2 may be different from each other;
X^1 is $-CH_2-$, -O-, $-N(R^5)-$, -S-, -SO- or $-SO_2-$;
R^5 is

(1) hydrogen,
(2) C_{1-6} alkyl or
(3) C_{1-7} alkanoyl;

G^1 is C_{1-6} alkylene;
R^3 is

(1) hydrogen,
(2) carboxy,
(3) halogen,
(4) C_{1-6} alkyl, which may have one or more hydroxy,
(5) cyano,
(6) amino which may have one or two substituents independently selected from:

(a) C_{1-6} alkyl and
(b) $-C(=O)-R^6$ or

(7) $-O-R^7$;

R^6 is

(1) C_{1-6} alkoxy or
(2) C_{1-6} alkyl, wherein the C_{1-6} alkyl may have amino which may have one or two of the same or different C_{1-6} alkyl;

R^7 is

(1) hydrogen,
(2) amino,
(3) C_{1-7} alkanoyl or
(4) C_{1-6} alkyl;

R^4 is

(1) amino which may have one or two of the same or different C_{1-6} alkyl,
(2) halogen,
(3) cyano,

(4) C_{1-6} alkyl,
(5) oxo,
(6) -O-R^8 or
(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -PH(=O)OH or
(4) benzyl which may have one or more of the same or different C_{1-6} alkoxy;

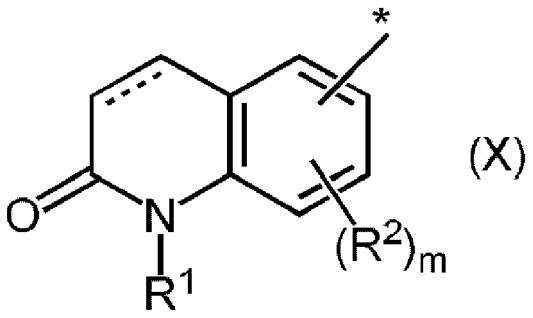
R^9 is

(1) C_{1-6} alkyl,
(2) -G^2-COOH,
(3) amino which may have one or two of the same or different C1-6 alkyl,
(4) C_{1-6} alkoxy or
(5) pyrazinyl;

G^2 is C_{1-6} alkylene;
n is an integer of 0 to 8;
provided that when n is 2 or more, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;
X^2 is N or CH;
provided that when X^2 is CH, H of the group may be replaced with R^4 which is defined as above, wherein multiple R^4s in formula (1) may be the same or different from each other; and
Ring A is

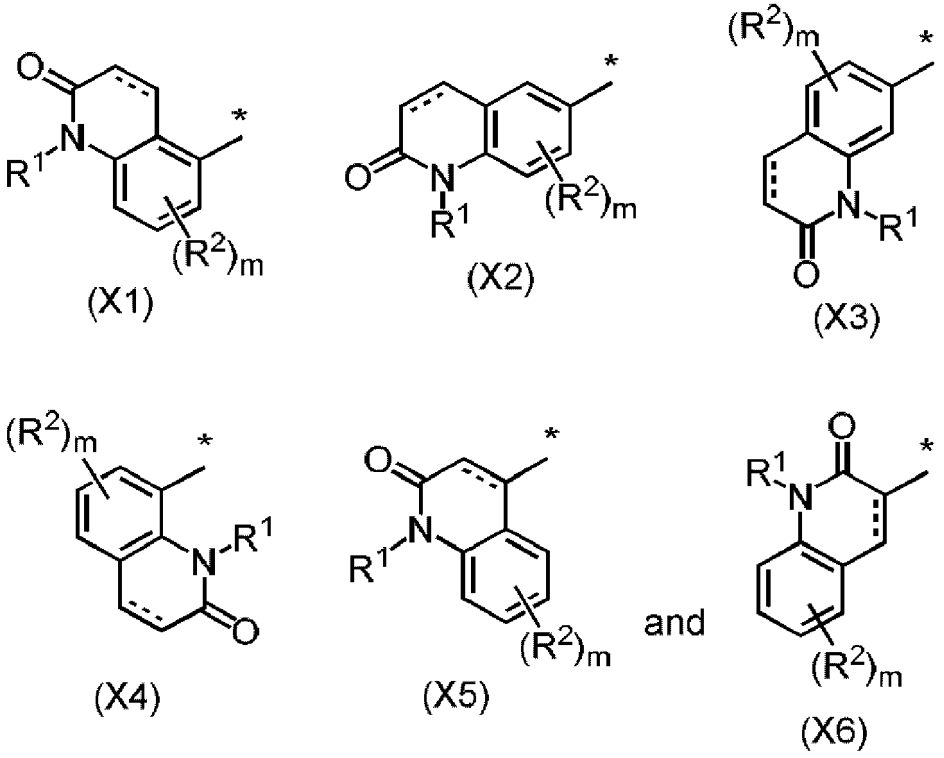
(1) aryl which may have one or more substituents, or
(2) heterocyclyl which may have one or more substituents.

[2] The compound for use according to [1], or a salt thereof, wherein a partial structure (X) of formula (1) is represented by the following partial structure:



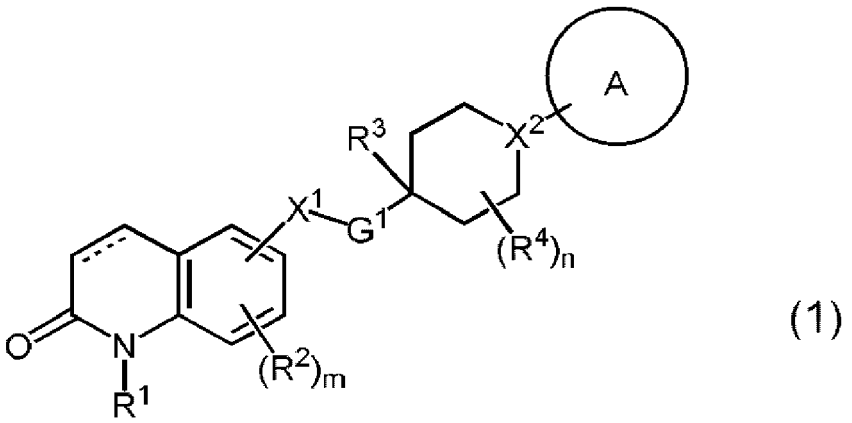
(X)

wherein * is binding point to X^1; and other symbols are as defined in [1], and
the partial structure (X) is any one of the structures selected from the group consisting of the following formulae (X1) to (X6):



wherein the symbols are as defined in the above and in [1].

[3] A compound of the general formula (1):



or a salt thereof,
wherein the moiety:

represents single bond or double bond; and

wherein R^1 is

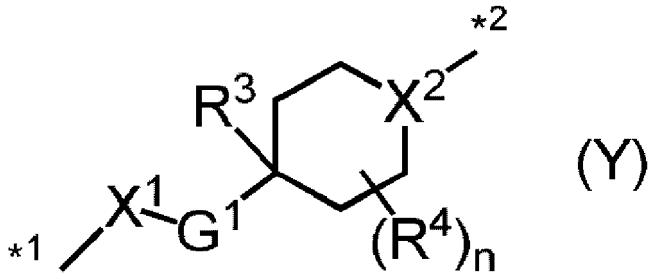
(1) hydrogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl or

(3) C_{1-6} alkyl;

R^2 is

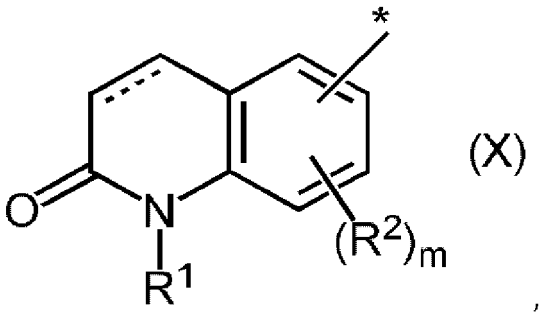
(1) halogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl,
(3) C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) hydroxy;

m is an integer of 0 to 3;
provided that when m is 2 or 3, R^2 may be different from each other;
a partial structure (Y) of formula (1) is represented by the following partial structure:



(Y)

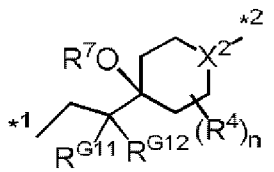
wherein *1 is a binding point to a partial structure (X) of formula (1) and *2 is a binding point to Ring A, and the partial structure (X) of formula (1) is represented by the following partial structure:



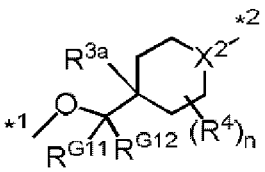
(X)

,

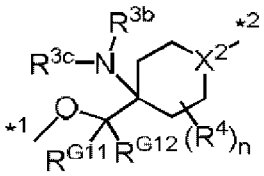
wherein * is a binding paint to X^1,
the partial structure (Y) is any one of the structures selected from the group consisting of the following formulae (Y1) to (Y8):



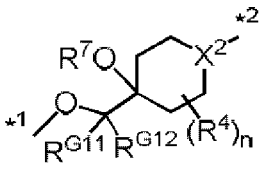
(Y1)



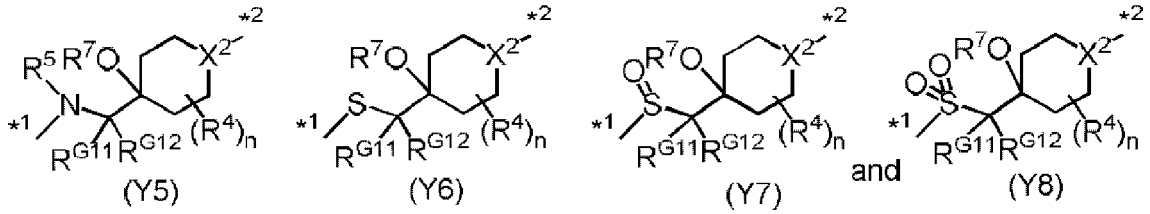
(Y2)



(Y3)



(Y4)



wherein R^{3a} is

(1) hydrogen,
(2) carboxy,
(3) halogen,
(4) C_{1-6} alkyl, which may have one or more hydroxy, or
(5) cyano;

R^{3b} and R^{3c} are each independently

(1) hydrogen,
(2) C_{1-6} alkyl, or
(3) -C(=O)-R^6;

R^{G11} and R^{G12} are each independently hydrogen or C_{1-6} alkyl;
the total number of carbon atoms in R^{G11} and R^{G12} is 0 to 5;
R^5 is

(1) hydrogen,
(2) C_{1-6} alkyl or
(3) C_{1-7} alkanoyl;

R^6 is

(1) C_{1-6} alkoxy or
(2) C_{1-6} alkyl, wherein the C_{1-6} alkyl may have amino which may have one or two of the same or different C_{1-6} alkyl;

R^7 is

(1) hydrogen,
(2) amino,
(3) C_{1-7} alkanoyl or
(4) C_{1-6} alkyl;

R^4 is

(1) amino which may have one or two of the same or different C_{1-6} alkyl,
(2) halogen,
(3) cyano,
(4) C_{1-6} alkyl,
(5) oxo,
(6) -O-R^8 or
(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -PH(=O)OH or

(4) benzyl which may have one or more of the same or different C_{1-6} alkoxy;

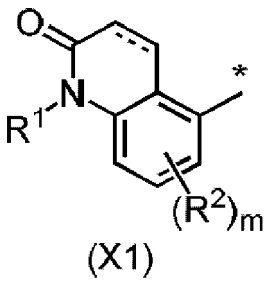
R^9 is

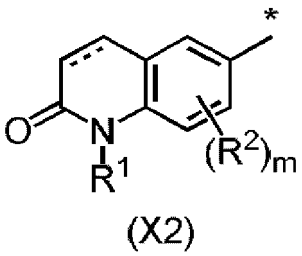
(1) C_{1-6} alkyl,
(2) -G^1-COOH,
(3) amino which may have one or two of the same or different C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) pyrazinyl;

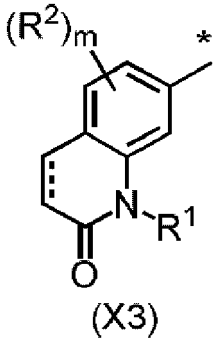
G^2 is C_{1-6} alkylene;
n is an integer of 0 to 8;
provided that when n is 2 or more, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;
X^2 is N or CH;
provided that when X^2 is CH, H of the group may be replaced with R^4 which is defined as above, wherein multiple R^4s in formula (1) may be the same or different from each other; and
Ring A is

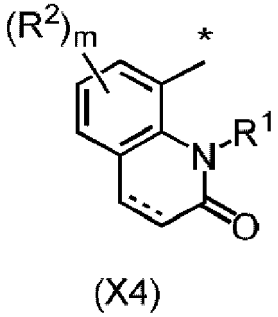
(1) aryl which may have one or more substituents, or
(2) heterocyclyl which may have one or more substituents.

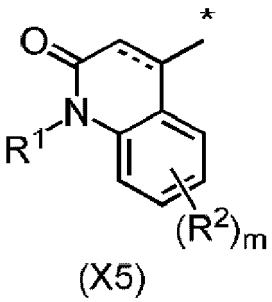
[4] The compound of [3], or a salt thereof, wherein the partial structure (X) is any one of the structures selected from the group consisting of the following formulae (X1) to (X6):


(X1)

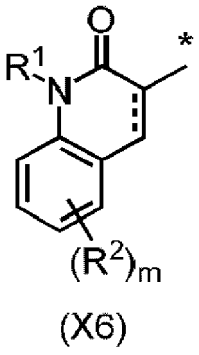

(X2)


(X3)


(X4)


(X5)

and


(X6)

wherein the symbols are as defined in the above and [3].

[5] The compound of either [3] or [4], or a salt thereof, wherein Ring A is aryl or heterocyclyl which may have 1 to 5 substituents independently selected from:

(a) halogen;
(b) cyano;

(c) nitro;
(d) hydroxy;
(e) C_{1-6} alkyl which may have one or more substituents independently selected from:

(i) halogen,
(ii) hydroxy,
(iii) C_{1-6} alkoxy, and
(iv) aryloxy which may have one or more of the same or different halogen ;

(f) C_{1-6} alkoxy which may have one or more substituents independently selected from:

(i) halogen,
(ii) C1-6 alkoxy which may have one or more of the same or different C1-6 alkoxy,
(iii) aryloxy which may have one or more of the same or different halogen ,
(iv) heterocyclyl which may have one or more of the same or different C1-6 alkyl which may have one or more of the same or different halogen, and
(v) amino which may have one or two of the same or different C_{1-6} alkyl;

(g) C_{1-6} alkoxycarbonyl;
(h) C_{1-6} alkylsulfanyl;
(i) aryl which may have one or more of the same or different halogen;
(j) aryloxy; and
(k) aralkyloxy which may have one or more substituents independently selected from:

(i) halogen,
(ii) C_{1-6} alkyl which may have one or more of the same or different halogen, and
(iii) C_{1-6} alkoxy which may have one or more of the same or different halogen.

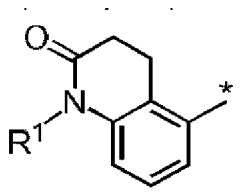
[6] The compound of any one of [3] to [5], or a salt thereof, wherein R^1 is hydrogen.

[7] The compound of any one of [3] to [6], or a salt thereof, wherein R^2 is halogen.

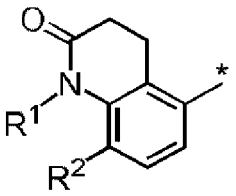
[8] The compound of any one of [3] to [7], or a salt thereof, wherein m is 0, 1 or 2.

[9] The compound of any one of [3] to [8], or a salt thereof, wherein n is 0, 1 or 2.

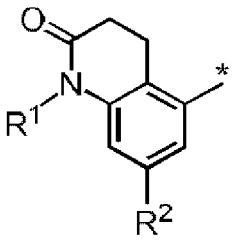
[10] The compound of [3], or a salt thereof, wherein the partial structure (X) is a structure of a formula selected from the group consisting of the formulae (X1-1), (X1-2), (X1-3), (X1-4), (X1-6), and (X1-7):



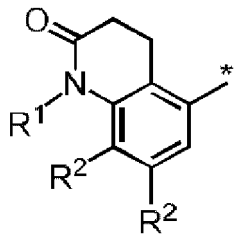
(X1-1)



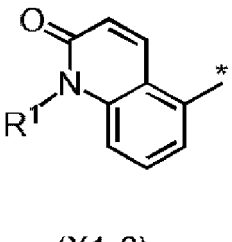
(X1-2)



(X1-3)

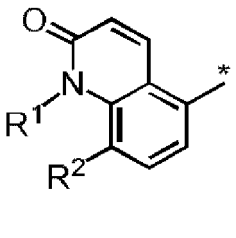


(X1-4)



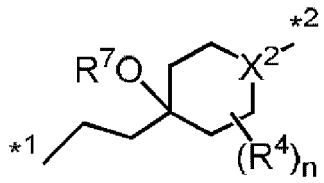
(X1-6)

and

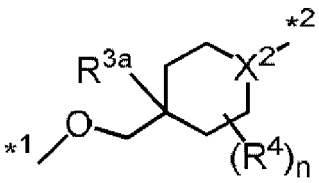


(X1-7)

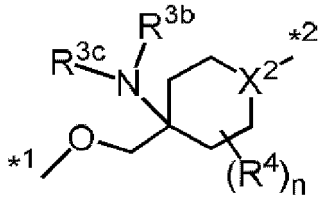
wherein * is binding point to X^1;
R^1 is hydrogen;
R^2 is substituent selected from (1) halogen or (2) C_{1-6} alkyl;
provided that when R^2 may be multiple, each of them may be different from each other;
the partial structure (Y) is a structure of a formula selected from the group consisting of the formulae (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y5-1), and (Y6-1):



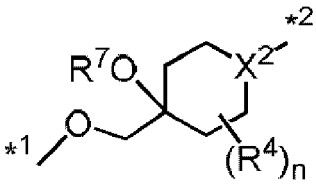
(Y1-1)



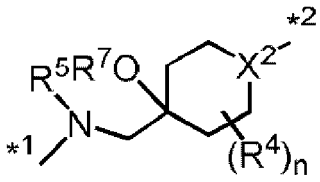
(Y2-1)



(Y3-1)

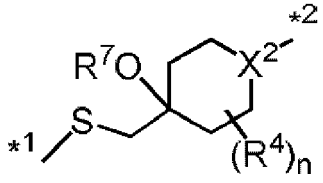


(Y4-1)



(Y5-1)

and



(Y6-1)

wherein *1 is binding point to the partial structure (X);
*2 is binding point to Ring A;
R^5 is hydrogen;
R^{3a} is (1) hydrogen or (2) halogen;
R^{3b} and R^{3c} are each hydrogen;
R^7 is hydrogen;
R^4 is substituent selected from (1) halogen, (2) -O-R^8, (3) -O-C(=O)-R^9, or (4) cyano;
R^8 is (1) hydrogen or (2) C C_{1-6} alkyl;
R^9 is (1) C_{1-6} alkyl or (2) C_{1-6} alkoxy;
n is an integer of 0 to 2;
provided that when n is 2, each of R^4, R^8, and R^9 may be different from each other and may be substituted on the same carbon atom;
X^2 is N or CH;
provided that when X^2 is CH, H of the group may be replaced with R^4 which is defined as above, wherein multiple R^4s in formula (1) may be the same or different from each other; and
Ring A is phenyl or pyridyl which may have 1 to 3 groups independently selected from:

(a) halogen;
(b) C_{1-6} alkoxy which may have (i) halogen and (ii) C_{1-6} alkoxy; or
(c) aralkyloxy which may have one or more of the same or different C_{1-6} alkoxy which may have one or more of the same or different halogen; or

quinolyl which may have 1 to 2 halogen.

[11] The compound of [11], which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one;
5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-{[1-{4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one;
8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy]phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one;
8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3)4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one;
5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S]-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate;
(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate;

5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
trans-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile; and
5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

[12] The compound of [3], which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one;
5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one;
8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one;
5-{[1-[4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one;
8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(35,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-{4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one;
5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-

2(1H)-one;
5-{[(3R,4S)-1-{4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
(3R,4R)-1-(4-chloro-2,5-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate;
(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypipendin-3-yl acetate;
5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxyl-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
trans-1-(4-chloro-2-fluorophenyl)-4-([(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile; and
5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one.

[13] The compound of [3], which is 8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

[14] The compound of [3], which is 8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one.

[15] The compound of [3], which is 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

[16] The compound of [3], which is 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one.

[17] The compound of [3], which is 5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

[18] The compound of [3], which is 5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one.

[19] The compound of [3], which is 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

[20] The compound of [3], which is 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one.

[21] The compound of [3], which is (3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate, or a salt thereof.

[22] The compound of [3], which is (3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate.

[23] A pharmaceutical composition, comprising the compound of any one of [3] to [22], or a salt thereof and a pharmaceutically acceptable carrier.

[24] An agent for diagnosing, preventing, and/or treating tuberculosis, comprising the compound of any one of [3] to [22], or a salt thereof and a pharmaceutically acceptable carrier.

[25] The compound of any one of [3] to [22], or a salt thereof, for use of diagnosing, preventing, and/or treating tuberculosis.

[0083] In one embodiment, m is preferably 0, 1, or 2.

[0084] In another embodiment, G^1 is preferably $-C(R^{G11})(R^{G12})-$; more preferably $-CH_2-$ or $-CH(CH_3)-$.

[0085] In another embodiment, R^{G11} and R^{G12} are each independently hydrogen or lower alkyl; and the total number of carbon atoms in R^{G11} and R^{G12} is 0 to 5. Preferably R^{G11} and R^{G12} are each independently hydrogen or methyl; more preferably R^{G11} is hydrogen or methyl, and R^{G12} is hydrogen.

[0086] Examples of "$-C(R^{G11})(R^{G12})-$" in G^1 include, for example, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_2CH_3)-$, $-C(CH_3)(CH_2CH_3)-$, $-C(CH_2CH_3)_2-$, $-CH(CH_2CH_2CH_3)-$, $-C(CH_3)(CH_2CH_2CH_3)-$, $-C(CH_2CH_3)(CH_2CH_2CH_3)-$, $-CH(CH(CH_3)_2)-$, $-C(CH_3)(CH(CH_3)_2)-$, $-C(CH_2CH_3)(CH(CH_3)_2)-$.

[0087] In another embodiment, n is preferably 0, 1, or 2.

[0088] The "aryl" of "(1) aryl which may have one or more substituents" in Ring A is preferably (a1) phenyl.

[0089] The "heterocyclyl" of "(2) heterocyclyl which may have one or more substituents" in Ring A is preferably selected from:

(a2) pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl),
(a3) N-oxide pyridyl (e.g. N-oxide pyridin-2-yl),
(a4) thienyl (e.g. 3-thienyl),
(a5) quinolyl (e.g. 2-quinolyl, 6-quinolyl),
(a6) isoquinolyl (e.g. 1-isoquinolyl),
(a7) benzothienyl (e.g. benzo[b]thiophen-5-yl),
(a8) quinoxalinyl (e.g. 6-quinoxalinyl),
(a9) benzofuryl (e.g. benzo[b]furan-5-yl),
(a10) benzodioxolyl (e.g. benzo[1,3]dioxol-5-yl),
(a11) benzooxazolyl (e.g. 2-benzooxazolyl), and
(a12) benzoimidazolyl (e.g. 2-benzoimidazolyl).

[0090] Ring A is preferably aryl or heterocyclyl, which is preferably a group selected from the above (a1) to (a12), each of which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);
(b) cyano;
(c) nitro;
(d) hydroxy;
(e) lower alkyl which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);
(f) lower alkoxy which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);
(g) lower alkoxycarbonyl which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. ethoxycarbonyl);
(h) lower alkylsulfanyl which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. methylsulfanyl, ethylsulfanyl);
(i) aryl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);
(j) aryloxy which may have one or more substituents selected from groups (Ia), (Ib), and (Ic) (e.g. phenoxy); and
(k) aralkyloxy which may have one or more substituents selected from groups (Ia), (Ib), and (Ic) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy).

[0091] Ring A is more preferably aryl or heterocyclyl, which is preferably a group selected from the above (a1) to (a12), each of which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);
(b) cyano;
(c) nitro;
(d) hydroxy;
(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);
(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);
(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);
(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);
(i) aryl (e.g. phenyl) which may have halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);
(j) aryloxy (e.g. phenoxy); and
(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy).

[0092] Ring A is further preferably

(1) aryl, which is preferably the group of the above (a1), which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine);
(b) cyano;
(c) nitro;
(d) hydroxy;
(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);
(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);
(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);
(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);
(i) aryl (e.g. phenyl) which may have halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);
(j) aryloxy (e.g. phenoxy); and
(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy); or

(2) heterocyclyl, which is preferably a group selected from the above (a2) to (a12), which may have one or more

substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);
(b) cyano;
(c) lower alkyl (e.g. methyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), and (ii) lower alkoxy (e.g. methoxy) (e.g. methyl, trifluoromethyl, methoxymethyl); and
(d) lower alkoxy (e.g. ethoxy).

[0093] Ring A is particularly preferably

(A1) phenyl which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine);
(b) cyano;
(c) nitro;
(d) hydroxy;
(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);
(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);
(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);
(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);
(i) aryl (e.g. phenyl) which may have halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);
(j) aryloxy (e.g. phenoxy); and
(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy);

(A2) pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl) which may have one or more substituents selected from:

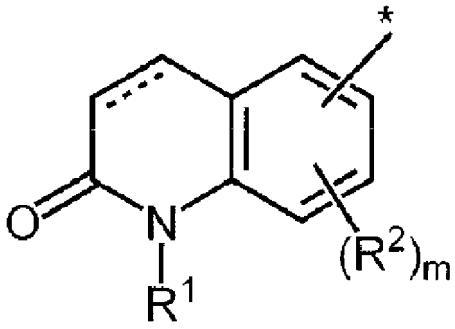
(a) halogen (e.g. fluorine, chlorine, bromine, iodine);
(b) cyano;
(c) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine) (e.g. methyl, trifluoromethyl); and
(d) lower alkoxy (e.g. ethoxy);

(A3) N-oxide pyridyl (e.g. N-oxide pyridin-2-yl) which may have halogen (e.g. chlorine);
(A4) thienyl (e.g. 3-thienyl);
(A5) quinolyl (e.g. 2-quinolyl, 6-quinolyl) which may have halogen (e.g. chlorine, bromine);
(A6) isoquinolyl (e.g. 1-isoquinolyl);
(A7) benzothienyl (e.g. benzo[b]thiophen-5-yl);
(A8) quinoxalinyl (e.g. 6-quinoxalinyl);
(A9) benzofuryl (e.g. benzo[b]furan-5-yl);
(A10) benzodioxolyl (e.g. benzo[1,3]dioxol-5-yl) which may have halogen (e.g. fluorine);
(A11) benzoxazolyl (e.g. 2-benzooxazolyl) which may have halogen (e.g. chlorine); or
(A12) benzimidazolyl (e.g. 2-benzoimidazolyl) which may have one or more substituents selected from:

(a) halogen (e.g. fluorine); and
(b) lower alkyl (e.g. methyl) which may have lower alkoxy (e.g. methoxy) (e.g. methyl, methoxymethyl).

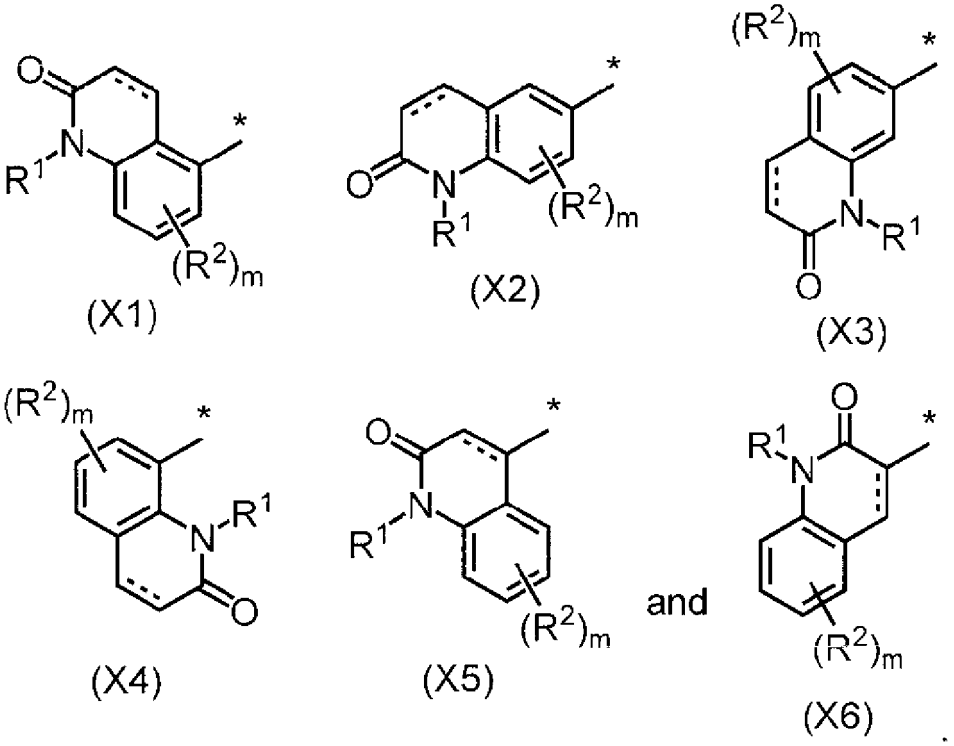
[0094] In the general formula (1), the partial structure (X):

[Chem.15]



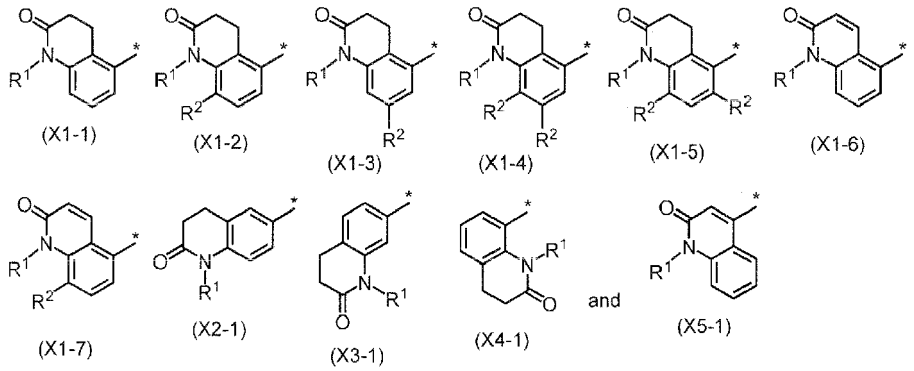
wherein * is the binding point to X^1 and other symbols are the same as defined above, includes a structure selected from the group consisting of the following formulae (X1) to (X6):

[Chem.16]



wherein each symbol is the same as defined above;
preferably a structure of Formula (X1), (X2), (X3), (X4), or (X5); and
more preferably a structure selected from the group consisting of the following formulae (X1-1) to (X5-1):

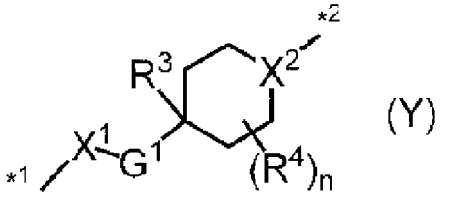
[Chem.17]



wherein each symbol is the same as defined above.

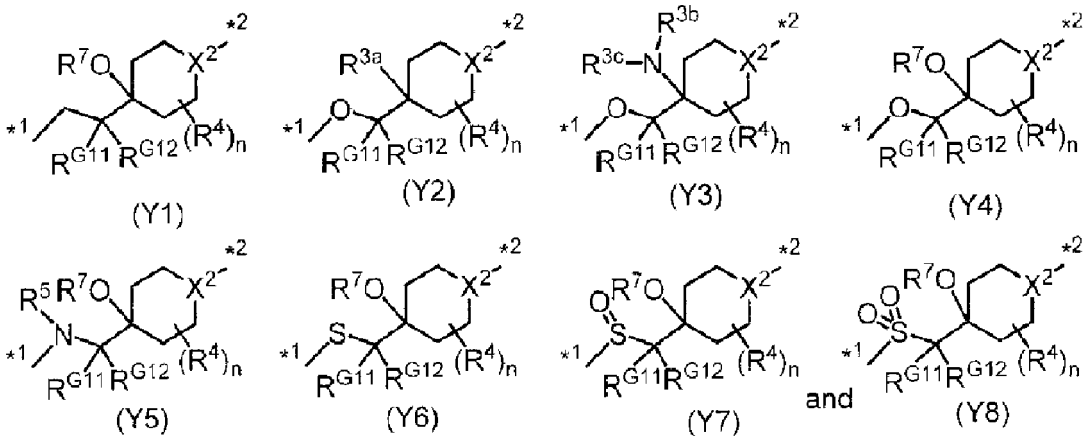
[0095] In the general formula (1), the partial structure (Y):

[Chem.18]



wherein *1 is the binding point to the partial structure of Formula (X); *2 represents the binding point to Ring A; and other symbols are the same as defined above, is preferably a structure selected from the group consisting of the following formulae (Y1) to (Y8):

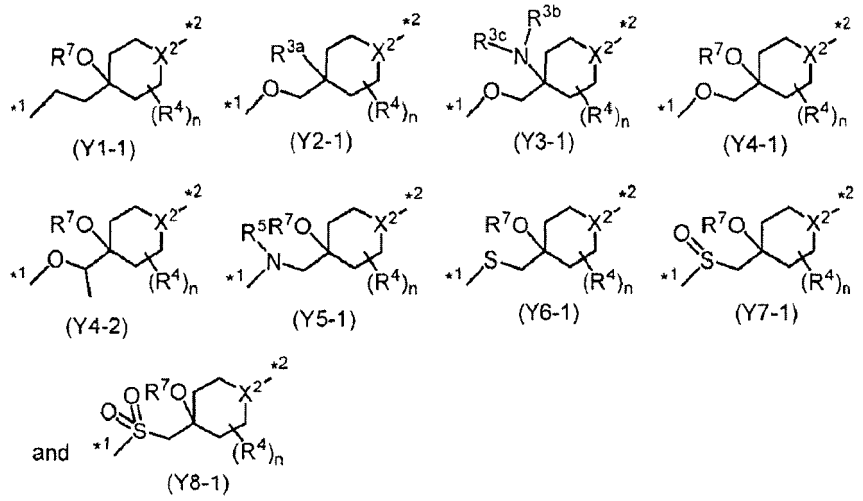
[Chem.19]



wherein R^{3a} is (1) hydrogen, (2) carboxy, (3) halogen (e.g. fluorine), (4) lower alkyl (e.g. methyl) which may have hydroxy (e.g. hydroxymethyl), or (5) cyano; R^{3b} and R^{3c} are each independently (1) hydrogen, (2) lower alkyl (e.g. methyl), or (3) -C(=O)-R^6 (e.g. methoxycarbonyl, acetyl, dimethylaminoacetyl); and other symbols are the same as defined above;

more preferably a structure selected from the group consisting of the following formulae (Y1-1) to (Y8-1):

[Chem.20]



wherein each symbol is the same as defined above.

[0096] In one preferable embodiment, in Formula (I),
the partial structure (X) is a structure selected from the group consisting of the formulae (X1-1), (X1-2), (X1-3), (X1-4), (X1-5), (X1-6), (X1-7), (X2-1), (X3-1), (X4-1), and (X5-1);
the partial structure (Y) is a structure selected from the group consisting of the formulae (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y4-2), (Y5-1), (Y6-1), (Y7-1), and (Y8-1);
R^1 is (1) hydrogen, (2) amino (e.g. amino) which may have one or more of the same or different lower alkyl, or (3) lower alkyl (e.g. methyl);
R^2 is a substituent selected from (1) halogen (e.g. fluorine, chlorine, bromine, iodine), (2) amino (e.g. amino) which may have one or two of the same or different lower alkyl, (3) lower alkyl (e.g. methyl, ethyl), (4) lower alkoxy (e.g. ethoxy), and (5) hydroxy;
each of R^2 may be different when it exists plurally;
R^5 is (1) hydrogen, (2) lower alkyl (e.g. methyl), or (3) lower alkanoyl (e.g. acetyl);
R^{3a} is (1) hydrogen, (2) carboxy, (3) halogen (e.g. fluorine), (4) lower alkyl (e.g. methyl) which may have one or more of hydroxy (e.g. hydroxymethyl), or (5) cyano;
R^{3b} and R^{3c} are each independently (1) hydrogen, (2) lower alkyl (e.g. methyl), or (3) -C(=O)-R^6 (e.g. methoxycarbonyl, acetyl, dimethylaminoacetyl);
R^6 is (1) lower alkoxy (e.g. methoxy), or (2) lower alkyl (e.g. methyl) which may have one or more of the same or different amino which may have one or more of the same or different lower alkyl (e.g. methyl) (e.g. methyl, dimethylaminomethyl);
R^7 is (1) hydrogen, (2) amino, (3) lower alkanoyl (e.g. acetyl), or (4) lower alkyl (e.g. methyl);
R^4 is a substituent selected from (1) amino (e.g. amino, methylamino) which may have one or two of the same or different lower alkyl (e.g. methyl), (2) halogen (e.g. fluorine), (3) cyano, (4) lower alkyl (e.g. methyl), (5) oxo, (6) -O-R^8 (e.g. hydroxy, methoxy, 4-methoxybenzyloxy, -O-PH(=O)OH), and (7) -O-C(=O)-R^9 (e.g. acetoxy, pyrazinylcarbonyloxy, ethoxycarbonyloxy, ethylaminocarbonyloxy, 3-carboxypropionyloxy);
R^8 is (1) hydrogen, (2) lower alkyl (e.g. methyl), (3) -PH(=O)OH, or (4) benzyl which may have one or more of the same or different lower alkoxy (e.g. methoxy) (e.g. 4-methoxybenzyl);
R^9 is (1) lower alkyl (e.g. methyl), (2) -G^2-COOH (e.g. 2-carboxyethyl), (3) amino which may have one or two of the same or different lower alkyl (e.g. ethyl) (e.g. ethylamino), (4) lower alkoxy (e.g. ethoxy), or (5) pyrazinyl;
G^2 is lower alkylene (e.g. -$(CH_2)_2$-);
n is 0, 1, or 2;
provided that when n is 2, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;
X^2 is N or CH;
provided that when X^2 is CH, H of the group may be substituted with R^4 which is defined as above or may be different from the other R^4; and
Ring A is

(1) aryl, which is preferably (a1) phenyl, which may have one or more substituents independently selected from:

(a) halogen (e.g. fluorine, chlorine, bromine);
(b) cyano;
(c) nitro;
(d) hydroxy;
(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have one or more of the same or different halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);
(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have one or more of the same or different lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have one or more of the same or different halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have one or more of the same or different lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have one or two of the same or different lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);
(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);
(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);
(i) aryl (e.g. phenyl) which may have one or more of the same or different halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);
(j) aryloxy (e.g. phenoxy); and
(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have one or more of the same or different halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have one or more of the same or different halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy); or

(2) heterocyclyl, which is preferably a group selected from (a2) pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl), (a3) N-oxide pyridyl (e.g. N-oxidepyridin-2-yl), (a4) thienyl (e.g. 3-thienyl), (a5) quinolyl (e.g. 2-quinolyl, 6-quinolyl), (a6) isoquinolyl (e.g. 1-isoquinolyl), (a7) benzothienyl (e.g. benzo[b]thiophen-5-yl), (a8) quinoxalinyl (e.g. 6-quinoxalinyl), (a9) benzofuryl (e.g. benzo[b]furan-5-yl), (a10) benzodioxolyl (e.g. benzo[1,3]dioxol-5-yl), (a11) benzoxazolyl (e.g. 2-benzoxazolyl), and (a12) benzimidazolyl (e.g. 2-benzimidazolyl), which may have one or more substituents independently selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);
(b) cyano;
(c) lower alkyl (e.g. methyl) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine), and (ii) lower alkoxy (e.g. methoxy) (e.g. methyl, trifluoromethyl, methoxymethyl); and
(d) lower alkoxy (e.g. ethoxy).

[0097] A method of preparing Compound (1) in the present invention is explained as below. Compound (1) in the present invention may be for example prepared according to the preparation methods as below. The preparation methods as below are illustrative and a method of preparing Compound (1) is not limited thereto.

[0098] Examples of "hydrocarbons" as a solvent include, for example, aliphatic hydrocarbons such as hexane and pentane; alicyclic hydrocarbons such as cyclopentane and cyclohexane; aromatic hydrocarbons such as benzene and toluene.
Examples of "halogenated hydrocarbons" as a solvent include, for example, chloroform, dichloromethane.
Examples of "alcohols" as a solvent include, for example, methanol, ethanol, isopropanol, propanol, tert-butanol.
Examples of "ethers" as a solvent include, for example, chain ethers such as diethyl ether, diisopropyl ether, dibutyl ether, and diphenyl ether; circular ethers such as 1,4-dioxane and tetrahydrofurane.
Examples of "esters" as a solvent include, for example, ethyl acetate, ethyl propionate.
Examples of "ketones" as a solvent include, for example, acetone, methyl ethyl ketone, methyl isobutyl ketone.
Examples of "amides" as a solvent include, for example, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone.
Examples of "nitriles" as a solvent include, for example, acetonitrile, propionitrile.
Examples of "sulfoxides" as a solvent include, for example, dimethylsulfoxide.

[0099] Examples of "alkali metal hydroxides" as a base include, for example, sodium hydroxide, potassium hydroxide,

cesium hydroxide.

[0100] Examples of "alkali metal hydrides" as a base include, for example, sodium hydride, potassium hydride, cesium hydride.

[0101] Examples of "alkali metal carboxylates" as a base include, for example, sodium acetate, potassium acetate, sodium butyrate.

[0102] Examples of "alkali metal carbonates" as a base include, for example, sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate.

[0103] Examples of "alkali metal hydrogencarbonates" as a base include, for example, sodium hydrogencarbonate, potassium hydrogencarbonate, cesium hydrogencarbonate.

[0104] Examples of "alkali metal phosphates" as a base include, for example, sodium phosphate, potassium phosphate.

[0105] Examples of "aromatic amines" as a base include, for example, pyridine, lutidine.

[0106] Examples of "tertiary amines" as a base include, for example, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, tetramethylethylenediamine, tetramethylpropylenediamine, 1,8-diazabicyclo[5,4,0]undec-7-ene (diazabicycloundecene).

[0107] Examples of "metal amides" as a base include, for example, lithium diisopropylamide, lithium hexamethyldisilazide.

[0108] Examples of "metal alkoxides" as a base include, for example, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium phenoxide.

[0109] Examples of "protecting group of hydroxy" include, but not limited to, any protecting groups of hydroxy used in the field of synthetic organic chemistry, and include, for example, alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, hydroxymethyl, 2-hydroxyethyl, acetylmethyl); alkenyl (e.g. ethenyl, 1-propenyl, 2-propenyl, 1-methyl-2-propenyl); alkynyl (e.g. ethynyl, 1-propynyl, 2-propynyl, 1-methyl-2-propynyl); formyl; alkyl (alkenyl) carbonyls (e.g. acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, acryloyl, propioloyl, methacryloyl, crotonoyl, isocrotonoyl, (E)-2-methyl-2-butenoyl); arylcarbonyl (e.g. benzoyl, α-naphthoyl, β-naphthoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, 4-toluoyl, 4-anisoyl, 4-nitrobenzoyl, 2-nitrobenzoyl, 2-(methoxycarbonyl)benzoyl, 4-phenylbenzoyl); alkoxycarbonyl (e.g. methoxycarbonyl, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, 9-fluorenylmethyloxycarbonyl); tetrahydro (thio) pyranyl (furanyl) (e.g. tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, tetrahydrothiopyran-2-yl, 4-methoxytetrahydrothiopyran-4-yl, tetrahydrofuran-2-yl, tetrahydrothiofuran-2-yl); silyl (e.g. trimethylsilyl, triethylsilyl, isopropyl dimethylsilyl, tert-butyldimethyl silyl, methyldiisopropyl silyl, methyl di-tert-butylsilyl, triisopropylsilyl, diphenylmethyl silyl, diphenylbutyl silyl, diphenylisopropyl silyl, phenyldiisopropyl silyl); alkoxymethyl (e.g. methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl, tert-butoxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl); alkoxyethyl (e.g. 1-ethoxyethyl, 1-(isopropoxy)ethyl); halogenated ethyl (e.g. 2,2,2-trichloroethyl); aralkyl (e.g. benzyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyldiphenylmethyl, 9-anthrylmethyl, 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl); alkenyloxycarbonyl (e.g. vinyloxycarbonyl, allyloxycarbonyl); aralkyloxycarbonyl (e.g. benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl).

[0110] Examples of "protecting group of carboxy" include, but not limited to, any protecting groups of carboxy used in the field of synthetic organic chemistry, and include, for example, similar groups to the above "alkyl", "alkenyl", "alkynyl", "aralkyl", and "silyl" illustrated in the "protecting group of hydroxy".

[0111] Examples of "protecting group of amino" include, but not limited to, any protecting groups of amino used in the field of synthetic organic chemistry, and include, for example, similar groups to the above "alkyl (alkenyl) carbonyl", "arylcarbonyl", "alkoxycarbonyl", "silyl", "aralkyl", "alkenyloxycarbonyl", and "aralkyloxycarbonyl" illustrated in the "protecting group of hydroxy".

[0112] Examples of "protecting group of terminal acetylene" include, but not limited to, any protecting groups of terminal acetylene used in the field of synthetic organic chemistry, and include, for example, similar groups to the above "silyl" illustrated in the "protecting group of hydroxy".

[0113] Examples of "leaving group" include, for example, halogen (e.g. chlorine, bromine, iodine), alkylsulfonyloxy (e.g. methylsulfonyloxy, ethylsulfonyloxy, trifluoromethyl-sulfonyloxy), arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, 2,4,6-trimethylbenzenesulfonyloxy, 2-nitrobenzenesulfonyloxy, 4-nitrobenzenesulfonyloxy).

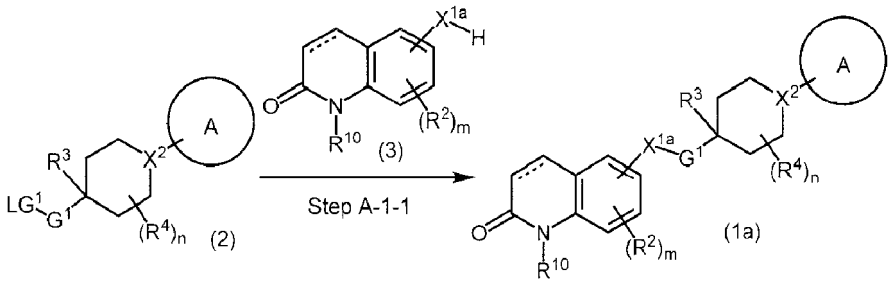
[0114] For the avoidance of doubt it is confirmed that in the general description above, in the usual way the proposal of general preferences and options in respect of different features of the compounds, methods, and compositions constitutes the proposal of general combinations of those general preferences and options for the different features, insofar as they are combinable and compatible and are put forward in the same context.

Preparation method A: General synthetic route 1

[0115]

Scheme A-1

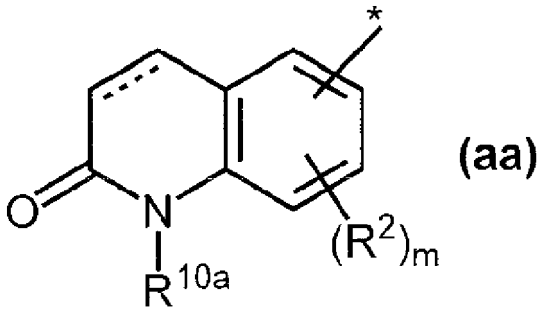
[Chem.21]



wherein X^{1a} represents -O-, -N(R^5)- or -S-; R^{10} represents hydrogen or an amino protective group; LG^1 represents a leaving group; and other symbols are as defined above.

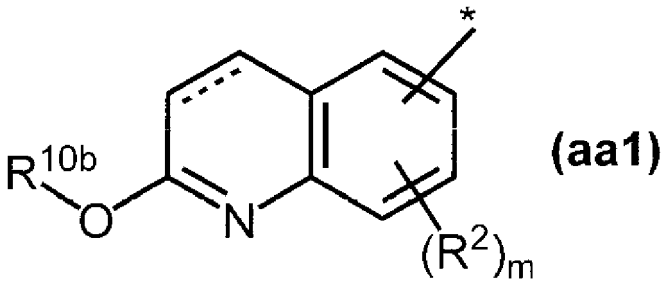
[0116] In the compound having R^{10}, instead of protecting the amino of the amide with R^{10}, it is possible to protect the imidic acid (hydroxyl thereof) which is a tautomer of the amide. Namely, a substructure represented by formula (aa):

[Chem.22]



wherein R^{10a} represents an amino protecting group; * represents a binding point to X^{1a} (X^1); and other symbols are as defined above can be formula (aa1):

[Chem.23]



wherein R^{10b} represents lower alkyl; and other symbols are as defined above.

(Step A-1-1: (2) + (3) -> (1a))

[0117] Among the compounds represented as formula (1), compound (1a) can be obtained, for example, by reacting compound (2) and compound (3) in an inert solvent in the presence of a base.

[0118] The amount of compound (3) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (2).

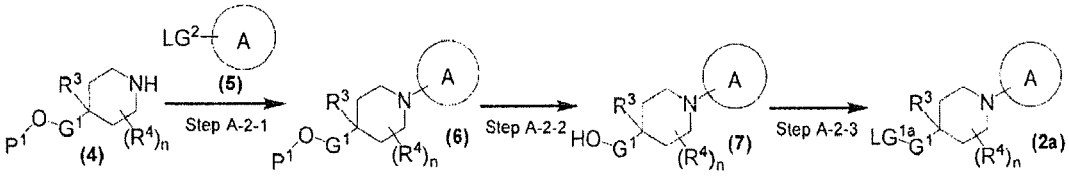
[0119] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (2).

[0120] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0121] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme A-2

[Chem.24]



wherein LG^2 and LG^{1a} each independently represents a leaving group; P^1 represents a hydroxy protecting group; and other symbols are as defined above.

(Step A-2-1: (4) + (5) -> (6))

[0122] Compound (6) can be obtained, for example, by reacting compound (4) and compound (5) in an inert solvent in the presence of a base. The amount of compound (5) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (4).

[0123] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides, alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (4).

[0124] Transition metal catalyst can be used as necessary.

[0125] Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(tert-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (4).

[0126] In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(tert-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (4).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio. The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-2-2: (6) -> (7))

[0127] Compound (7) can be obtained by subjecting compound (6) to a deprotection reaction.

[0128] Any of known reactions may be used as the deprotection reaction, for example, when P^1 is silyl, compound (6) can be deprotected in an inert solvent in the presence of a fluoride source or an acid to give compound (7).

[0129] Examples of the fluoride source include tetrabutylammonium fluoride, hydrofluoric acid and cesium fluoride. The amount of the fluoride source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (6).

[0130] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (6).

[0131] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0132] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-2-3: (7) -> (2a))

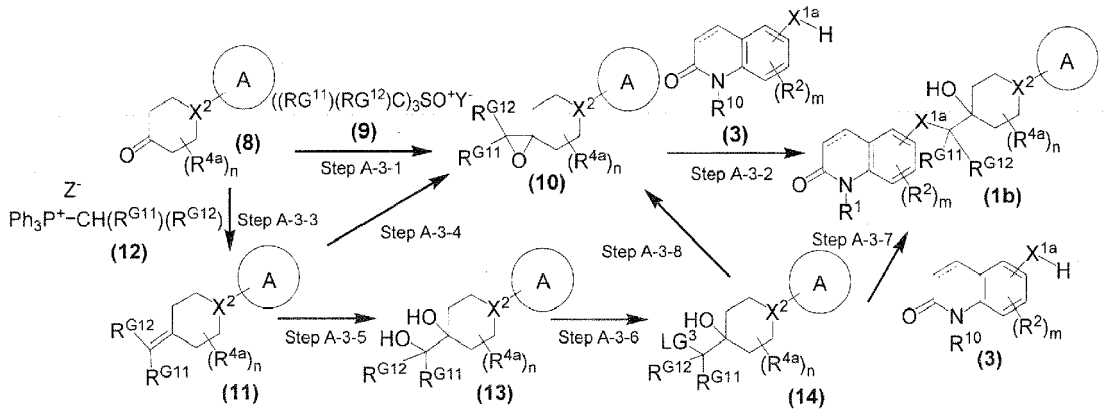
[0133] Among the compounds represented as formula (2), compound (2a) can be obtained by transforming hydroxy in compound (7) to a leaving group by using any known method.

[0134] For example, when the leaving group in compound (2a) is alkylsulfonyloxy or arylsulfonyloxy, compound (7) can be reacted with corresponding sulfonic anhydride (such as trifluoromethanesulfonic anhydride) or sulfonyl halide (such as benzenesulfonyl chloride, p-toluenesulfonyl chloride and methylsulfonyl chloride) etc. in an inert solvent in the presence of a base to provide compound (2a). The amount of sulfonic anhydride or sulfonyl halide used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (7).

[0135] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (7).
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme A-3

[Chem.25]



wherein each R^{4a} independently represents amino optionally having one or more lower alkyl, halogen, cyano, lower alkyl, -O-R^8 or -O-C(=O)-R^9; Y^- and Z^- each independently represents halide ion; LG^3 represents a leaving group; and other symbols are as defined above.

(Step A-3-1: (8) + (9) -> (10))

[0136] Compound (10) can be obtained, for example, by reacting compound (8) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction).

[0137] The amount of compound (9) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (8).

[0138] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8).

[0139] In addition, as necessary, a salt can be added.
Examples of the salt include, for example, halogenated alkali metals such as cesium fluoride, cesium chloride, cesium bromide, cesium iodide, potassium fluoride, potassium chloride, potassium bromide, potassium iodide, sodium fluoride, sodium chloride, sodium bromide, sodium iodide, lithium fluoride, lithium chloride, lithium bromide and lithium iodide. The amount of the salt used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8). Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-3-2: (10) + (3) -> (1b))

[0140] Among the compounds represented as formula (1), compound (1b) can be obtained, for example, by reacting compound (10) with compound (3) in an inert solvent in the presence of a base or in the presence of an acid.

[0141] The amount of compound (3) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (10).

[0142] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 0.01 to 10 molar equivalents, preferably 0.1 to 5 molar equivalents relative to compound (10).

[0143] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (10).

[0144] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0145] The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-3-3: (8) + (12) -> (11))

[0146] Compound (11) can be obtained, for example, by reacting compound (8) with compound (12) in an inert solvent in the presence of a base (Wittig reaction).
The amount of compound (12) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (8).
Examples of the base include, for example, alkali metal hydrides, metal amides, metal alkoxides and organolithium reagent, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8). Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons and ethers, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-3-4: (11) -> (10))

[0147] Compound (10) can be obtained, for example, by reacting compound (11) in an inert solvent in the presence of an oxidizing agent.

[0148] Examples of the oxidizing agent include inorganic peroxides (such as hydrogen peroxide, sodium hypochlorite and sodium periodate), organic peroxides (such as m-chloroperbenzoic acid, perbenzoic acid, peracetic acid and trifluoroperacetic acid) and dioxiranes (such as dimethyldioxirane). The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (11).

[0149] In addition, a base can be used, as necessary.

[0150] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount

of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (11).

[0151] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0152] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-3-5: (11) -> (13))

[0153] Compound (13) can be obtained, for example, by reacting compound (11) with in an inert solvent in the presence of osmium tetraoxide and a reoxidizing agent.

[0154] The amount of osmium tetraoxide used is typically 0.01 to 0.5 molar equivalents relative to compound (11). Also, potassium osmate ($K_2OsO_2(OH)_4$) may be used as an alternative to osmium tetraoxide. In addition, it is possible to use an immobilized catalyst in which osmium tetraoxide is supported on a solvent resistant polymer. Example of immobilized catalyst includes "Osmium Oxide, Immobilized Catalyst I (Os IC-I)" (trade name) (Wako Pure Chemical Industries, Ltd.).

Examples of the reoxidizing agent include, for example, N-methylmorpholine oxide, trimethylamine oxide, tert-butyl hydroperoxide and potassium ferricyanide ($K_3Fe(CN)_6$), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the reoxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (11).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio. The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-3-6: (13) -> (14))

[0155] Compound (14) can be obtained by transforming a specific hydroxy group in compound (13) to a leaving group. Said reaction can be performed under the conditions similar to above step A-2-3.

(Step A-3-7: (14) + (3) -> (1b))

[0156] Among the compounds represented as formula (1), compound (1b) can be obtained, for example, by reacting compound (14) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

(Step A-3-8: (14) -> (10))

[0157] Compound (10) can be obtained, for example, by reacting compound (14) in an inert solvent in the presence of a base.

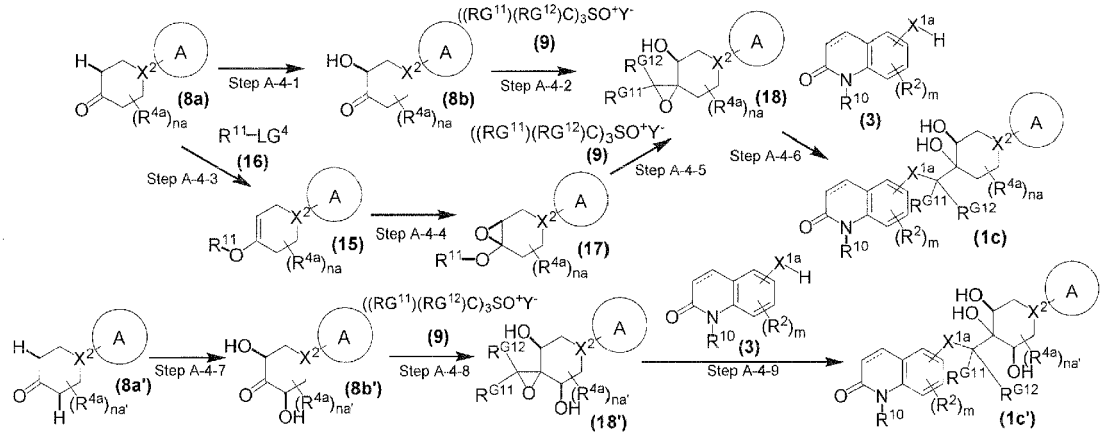
[0158] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (14).

[0159] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0160] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme A-4

[Chem.26]



wherein R^{11} represents tri-lower alkyl-silyl; LG^4 represents a leaving group; na is an integer from 0 to 7; na' is an integer from 0 to 6; and other symbols are as defined above.

(Step A-4-1: (8a) -> (8b))

[0161] Among the compounds represented as formula (8), compound (8b) can be obtained, for example, by subjecting α-aminooxylation by reacting compound (8a) with a nitroso compound in an inert solvent in the presence of a catalyst of proline or a derivative thereof, followed by hydrolysis in the presence of copper (II) sulfate catalyst.

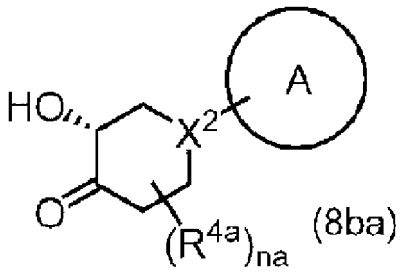
[0162] The amount of copper (II) sulfate used is typically 0.001 to 3 molar equivalents relative to compound (8a).

[0163] Example of the nitroso compound includes nitrosobenzene optionally having one or more substituents. The amount of the nitroso compound used is typically 1 to 10 molar equivalents, preferably 1 to 2 molar equivalents relative to compound (8a).

[0164] Examples of proline or a derivative thereof include LD-proline and 5-(pyrrolidin-2-yl)-1H-tetrazole. The amount of proline or a derivative thereof used is typically 0.001 to 3 molar equivalents relative to compound (8a).

[0165] In addition, by using L-proline and (S)-5-(pyrrolidin-2-yl)-1H-tetrazole etc. as proline or a derivative thereof, typically, it is possible to obtain mostly a compound represented as formula (8ba):

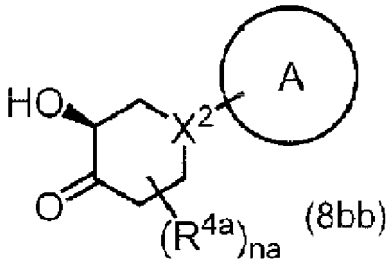
[Chem.27]



as compound (8b).

Alternatively, by using D-proline and (R)-5-(pyrrolidin-2-yl)-1H-tetrazole etc. as proline or a derivative thereof, typically, it is possible to obtain mostly a compound represented as formula (8bb):

[Chem.28]



(8bb)

as compound (8b).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-4-2: (8b) + (9) -> (18))

[0166] Compound (18) can be obtained, for example, by reacting compound (8b) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

(Step A-4-3: (8a) + (16) -> (15))

[0167] Compound (15) can be obtained, for example, by reacting compound (8a) with compound (16) in an inert solvent in the presence of a base.

[0168] The amount of compound (16) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8a).

[0169] In addition, it may possible to add sodium iodide, as necessary. The amount of sodium iodide used is typically 0.01 to 10 molar equivalents, preferably 0.1 to 5 molar equivalents relative to compound (8a).

[0170] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8a).

[0171] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

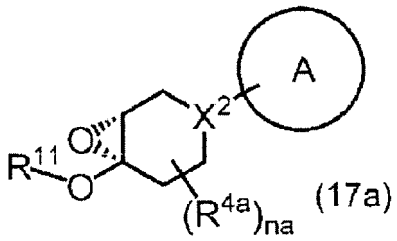
(Step A-4-4: (15) -> (17))

[0172] Compound (17) can be obtained, for example, by reacting compound (15) in an inert solvent in the presence of an oxidizing agent.

[0173] Examples of the oxidizing agent include inorganic peroxides (such as hydrogen peroxide, sodium hypochlorite and sodium periodate), organic peroxides (such as m-chloroperbenzoic acid, perbenzoic acid, peracetic acid and trifluoroperacetic acid) and dioxiranes (such as dimethyldioxirane). The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (15).

[0174] In addition, Shi asymmetric epoxidation is performed by using Shi epoxidizing catalyst (1-O,2-O:4-O,5-O- diisopropylidene -β-D-erythro-2,3-hexodiuro-2,6-pyranose), and it may possible to obtain, mainly, formula (17a):

[Chem.29]



(17a)

wherein each symbol is as defined above
as compound (17). The amount of Shi epoxidizing catalyst used is typically 0.001 to 3 molar equivalents relative to compound (15).

[0175] In addition, when using a ketone compound such as Shi epoxidizing catalyst, an oxidation auxiliary can be used in place of an oxidizing agent. Example of the oxidation auxiliary includes Oxone (registered trade name). The amount of the oxidation auxiliary used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (15).

[0176] In addition, a base can be used, as necessary.

[0177] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (15).

[0178] In addition, an additive agent can be added, as necessary. Example of the additive agent includes ethylenediaminetetraacetic acid disodium salt. The amount of the additive agent used is typically 0.001 to 3 molar equivalents relative to compound (15). Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-4-5: (17) + (9) -> (18))

[0179] Compound (18) can be obtained, for example, by reacting compound (17) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

(Step A-4-6: (18) + (3) -> (1c))

[0180] Among the compounds represented as formula (1), compound (1c) can be obtained, for example, by reacting compound (18) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-3-2.

(Step A-4-7: (8a') -> (8b'))

[0181] Among the compounds represented as formula (8), compound (8b') can be obtained, for example, by subjecting α-aminohydroxylation by reacting compound (8a') with a nitroso compound in an inert solvent in the presence of a catalyst of proline or a derivative thereof, followed by hydrolysis in the presence of copper (II) sulfate catalyst. Said reaction can be performed under the conditions similar to above step A-4-1. The amount of the nitroso compound used is typically 2 to 10 molar equivalents, preferably 2 to 5 molar equivalents relative to compound (8a').

(Step A-4-8: (8b') + (9) -> (18'))

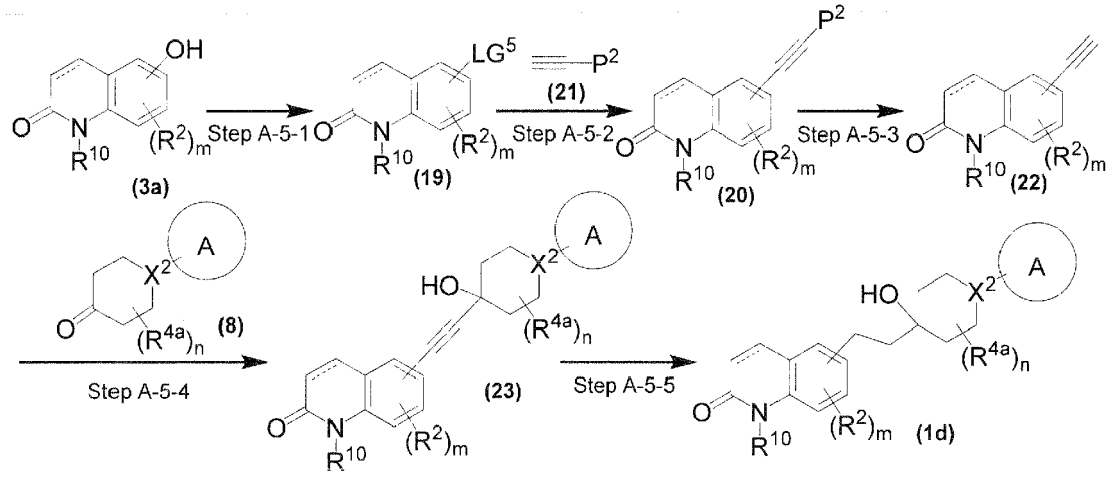
[0182] Compound (18') can be obtained, for example, by reacting compound (8b') with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

(Step A-4-9: (18') + (3) -> (1c'))

[0183] Among the compounds represented as formula (1), compound (1c') can be obtained, for example, by reacting compound (18') with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-3-2.

Scheme A-5

[Chem.30]



wherein LG^5 represents a leaving group; P^2 represents a protecting group on terminal acetylene; and other symbols are as defined above.

(Step A-5-1: (3a) -> (19))

[0184] Compound (19) can be obtained by transforming hydroxy of compound (3a) to a leaving group by using any known method. For example, said reaction can be performed under the conditions similar to above step A-2-3.

(Step A-5-2: (19) + (21) -> (20))

[0185] Compound (20) can be obtained, for example, by reacting compound (19) with compound (21) in an inert solvent, in the presence of base and transition metal catalyst. The amount of compound (21) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (19).

[0186] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (19).

[0187] Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(tert-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro- [1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (19). In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(tert-butyl)phosphine, 2,2' -bis(diphenylphosphino)-1,1' -binaphthyl, 2-(dicyclohexylphosphino)-2' ,4' ,6' -triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (19).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio. The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-5-3: (20) -> (22))

[0188] Compound (22) can be obtained by subjecting compound (20) to a deprotection reaction.

[0189] Any of known reactions may be used as the deprotection reaction, for example, when P^2 is silyl, compound (20) can be deprotected in the presence of a fluoride source or an acid to give compound (22).

[0190] Examples of the fluoride source include tetrabutylammonium fluoride, hydrofluoric acid and cesium fluoride. The amount of the fluoride source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (20).

[0191] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid; organic acids such as methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (20).

[0192] The acid can be used as a solvent, or an additional inert solvent can be used.

[0193] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0194] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-5-4: (22) + (8) -> (23))

[0195] Compound (23) can be obtained, by treating compound (22) with a base in an inert solvent, followed by a reaction with compound (8).

[0196] The amount of compound (8) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (22).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides, organic lithium reagent and a Grignard reagent of secondary or tertiary alkyl, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (22).

Examples of the Grignard reagent of secondary or tertiary alkyl include for example, isopropylmagnesium chloride, isopropylmagnesium bromide and tert-butylmagnesium bromide. Examples of the organic lithium reagent include, for example, isopropyllithium, propyllithium and tert-butylithium.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-5-5: (23) -> (1d))

[0197] Among the compounds represented as formula (1), compound (1d) can be obtained by subjecting compound (23) in the reduction reaction in an inert solvent, in the presence of a hydrogen source and a metal catalyst.

[0198] Examples of the hydrogen source include, for example, hydrogen gas, formic acid, sodium formate, ammonium formate, cyclohexene, phosphinic acid salt and hydrazine. When using hydrogen gas as the hydrogen source, the reaction can be done under the hydrogen pressure of about 1 to 10 atm. The amount of another hydrogen source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (23).

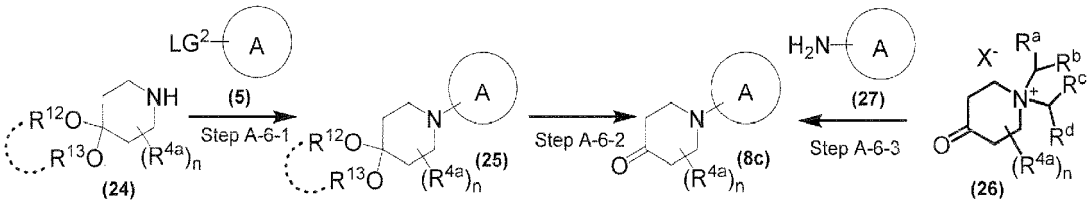
[0199] Examples of the metal catalyst include, for example, palladium on carbon, palladium black, palladium chloride, palladium hydroxide on carbon, platinum oxide, platinum black, platinum-palladium, platinum-carbon, Raney nickel and Raney cobalt. The amount of the metal catalyst used is typically 0.001 to 1000 molar equivalents, preferably 0.01 to 100 molar equivalents relative to compound (23).

[0200] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0201] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme A-6

[Chem.31]



wherein R^{12} and R^{13} each independently represents lower alkyl, or R^{12} and R^{13} may unitedly form an acetal ring; R^a, R^b, R^c and R^d each independently represents hydrogen, lower alkyl optionally having one or more substituents, lower alkenyl optionally having one or more substituents, lower alkoxycarbonyl optionally having one or more substituents, and aryl optionally having one or more substituents or carboxy; X^-represents an inert anion such as halide ion; and other symbols are as defined above.

(Step A-6-1: (24) + (5) -> (25))

[0202] Compound (25) can be obtained, for example, by reacting compound (24) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

(Step A-6-2: (25) -> (8c))

[0203] Among the compounds represented as formula (8), compound (8c) can be obtained, for example, by treating compound (25) with an acid.

[0204] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (25).

[0205] The acid can be used as a solvent, or an additional inert solvent can be used.

[0206] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0207] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-6-3: (26) + (27) -> (8c))

[0208] Among the compounds represented as formula (8), compound (8c) can be obtained, for example, by reacting compound (26) with compound (27) in an inert solvent.

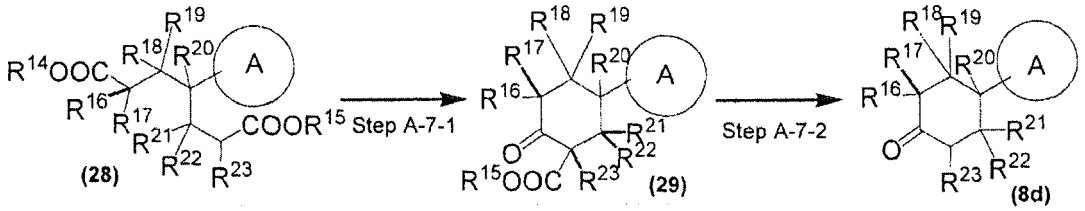
[0209] The amount of compound (27) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (26).

[0210] In addition, an additive agent can be added, as necessary. Examples of the additive agent include, for example, sodium acetate, sodium hydrogen carbonate, potassium carbonate, proline, thioureas,tertiary amines, acetic acid. The amount of the additive agent used is typically 0.01 to 10 molar equivalents, preferably 0.02 to 5 molar equivalents relative to compound (26).

Examples of the inert solvent include, for example, water, alcohols, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio. The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme A-7

[Chem.32]



wherein R^{14} and R^{15} each independently represents lower alkyl; R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} each independently represents hydrogen, amino optionally having one or more lower alkyl, halogen, cyano, lower alkyl, -O-R^8 or -O-C(=O)-R^9; R^{23} represents hydrogen, cyano or lower alkyl; and other symbols are as defined above.

(Step A-7-1: (28) -> (29))

[0211] Compound (29) can be obtained, for example, by subjecting compound (28) to Claisen condensation reaction in an inert solvent in the presence of a base.

[0212] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (28).

[0213] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0214] The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-7-2: (29) -> (8d))

[0215] Compound (8d) can be obtained, for example, by subjecting compound (29) to decarbonation reaction in an inert solvent.

An acid, a base or a salt can be added, as necessary.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio.

Examples of the salt include, for example, halogenated alkali metals such as cesium fluoride, cesium chloride, cesium bromide, cesium iodide, potassium fluoride, potassium chloride, potassium bromide, potassium iodide, sodium fluoride, sodium chloride, sodium bromide, sodium iodide, lithium fluoride, lithium chloride, lithium bromide and lithium iodide.

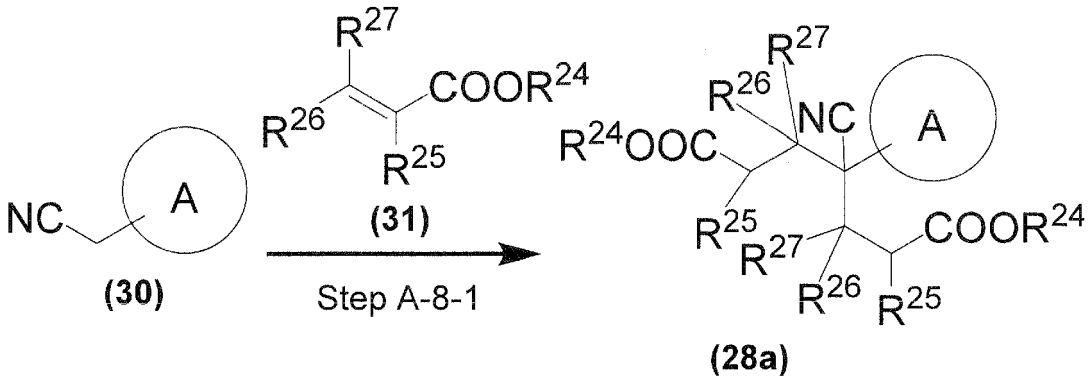
The amount of the acid, base or salt used is typically 1 molar equivalent to excessive amounts relative to compound (29).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme A-8

[Chem.33]



wherein R^{24} represents lower alkyl; R^{25} represents hydrogen, cyano or lower alkyl; R^{26} and R^{27} each independently represents hydrogen, amino optionally having one or more lower alkyl, halogen, cyano, lower alkyl, -O-R^8 or -O-C(=O)-R^9; and other symbols are as defined above.

(Step A-8-1: (30) + (31) -> (28a))

[0216] Among the compounds represented as formula (28), compound (28a) can be obtained, for example, by reacting compound (30) with compound (31) in an inert solvent in the presence of a base (Michael addition reaction).

[0217] The amount of compound (31) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (30).

[0218] Examples of the base include, for example, basic ammonium salts, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (30).

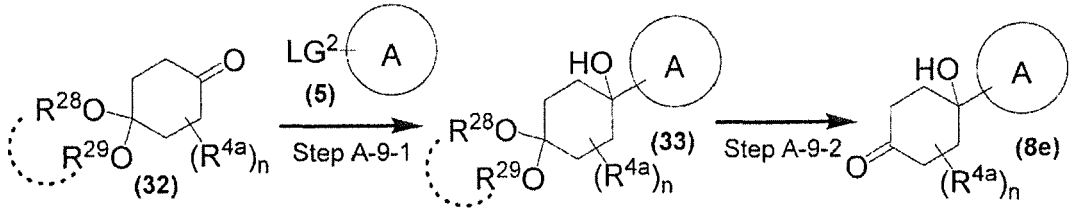
[0219] Examples of the basic ammonium salt include tetramethylammonium hydoxide, tetraethylammonium hydoxide, tetra-n-propylammonium hydoxide, tetraisopropylammonium hydoxide, tetra-n-butylammonium hydroxide and benzyltrimethylammonium hydoxide (Triton-B).

[0220] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, alcohols, ethers, amides, sulfoxides and nitriles, and it is also possible to use any two or more of them in an appropriate ratio.

[0221] The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme A-9

[Chem.34]



wherein R^{28} and R^{29} each independently represents a lower alkyl group, or R^{28} and R^{29} may unitedly form an acetal ring; and other symbols are as defined above.

(Step A-9-1: (32) + (5) -> (33))

[0222] Compound (33) can be obtained, for example, by a magnesiation or lithiation of compound (5) using a method such as halogen-metal exchange method employing a Grignard reagent of secondary or tertiary alkyl or organic lithium

reagent, and then reacting the obtained compound with compound (32).

[0223] The amount of compound (5) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (32).

Examples of the Grignard reagent of secondary or tertiary alkyl include for example, isopropylmagnesium chloride, isopropylmagnesium bromide and tert-butylmagnesium bromide. Examples of the organic lithium reagent include, for example, isopropyllithium, propyllithium and tert-butylithium. The amount of the Grignard reagent of secondary or tertiary alkyl or organic lithium reagent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (32). Examples of the inert solvent include, for example, hydrocarbons, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

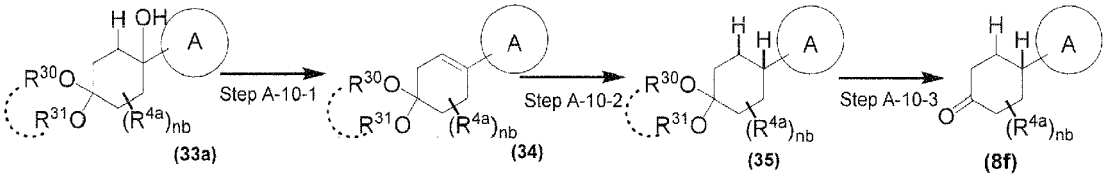
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-9-2: (33) -> (8e))

[0224] Among the compounds represented as formula (8), compound (8e) can be obtained, for example, by treating compound (33) with an acid. Said reaction can be performed under the conditions similar to above step A-6-2.

Scheme A-10

[Chem.35]



wherein R^{30} and R^{31} each independently represents lower alkyl, or R^{30} and R^{31} may unitedly form an acetal ring; nb is an integer of 0 to 7; and other symbols are as defined above.

(Step A-10-1: (33a) -> (34))

[0225] Compound (34) can be obtained, for example, by transforming hydroxy in compound (33a) to a leaving group by using any known method followed by olefination reaction.

[0226] For example, hydroxy of compound (33a) can be transformed to a leaving group by reacting it with sulfonic anhydride (such as trifluoromethanesulfonic anhydride) or sulfonyl halide (such as benzenesulfonyl chloride, p-toluenesulfonyl chloride and methylsulfonyl chloride) in an inert solvent in the presence of a base, followed by an elimination reaction to give compound (34). The amount of sulfonic anhydride or sulfonyl halide used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (33a).

[0227] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (33a).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step A-10-2: (34) -> (35))

[0228] Compound (35) can be obtained by subjecting compound (34) to reduction reaction in an inert solvent, in the presence of a hydrogen source and a metal catalyst. Said reaction can be performed under the conditions similar to above step A-5-5.

(Step A-10-3: (35) -> (8f))

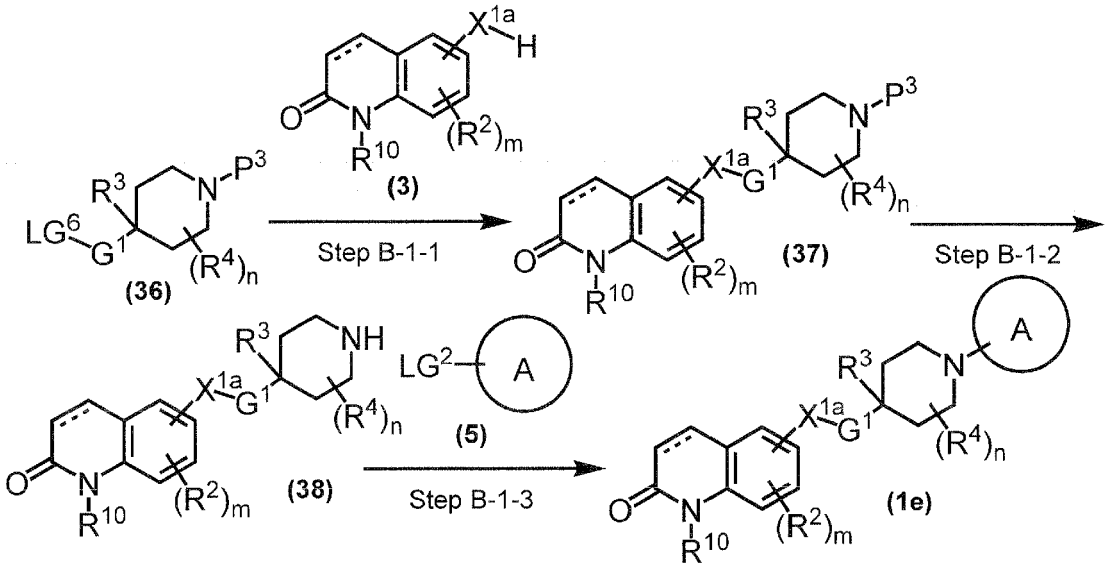
[0229] Among the compounds represented as formula (8), compound (8f) can be obtained, for example, by treating compound (35) with an acid. Said reaction can be performed under the conditions similar to above step A-6-2.

Preparation method B: General synthetic route 2

[0230]

Scheme B-1

[Chem.36]



wherein LG^6 represents a leaving group; P^3 represents an amino protecting group; and other symbols are as defined above.

(Step B-1-1: (36) + (3) -> (37))

[0231] Compound (37) can be obtained, for example, by reacting compound (36) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

(Step B-1-2: (37) -> (38))

[0232] Compound (38) can be obtained by subjecting compound (37) to a deprotection reaction.

[0233] Any of known reactions may be used as the deprotection reaction, for example, when P^2 is tert-butoxycarbonyl group (Boc), compound (37) can be deprotected in an inert solvent or in the absence of solvent in the presence of an acid (such as hydrochloric acid and trifluoroacetic acid) to give compound (38).

[0234] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

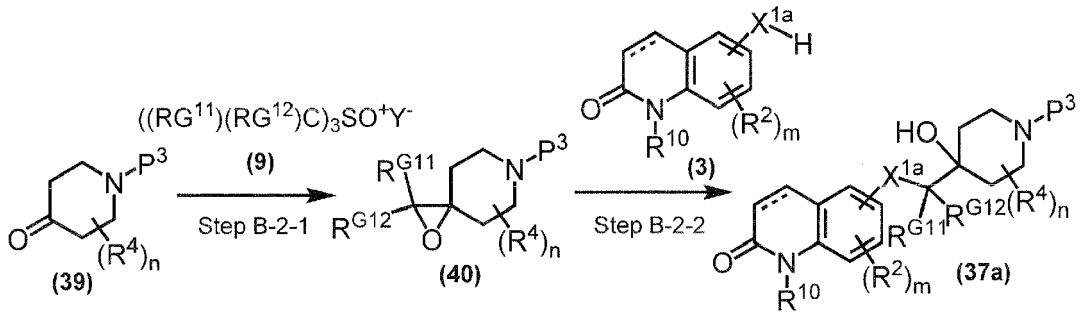
[0235] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-1-3: (38) + (5) -> (1e))

[0236] Among the compounds represented as formula (1), compound (1e) can be obtained, for example, by reacting compound (38) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

Scheme B-2

[Chem.37]



wherein each symbol is as defined above.

(Step B-2-1: (39) + (9) -> (40))

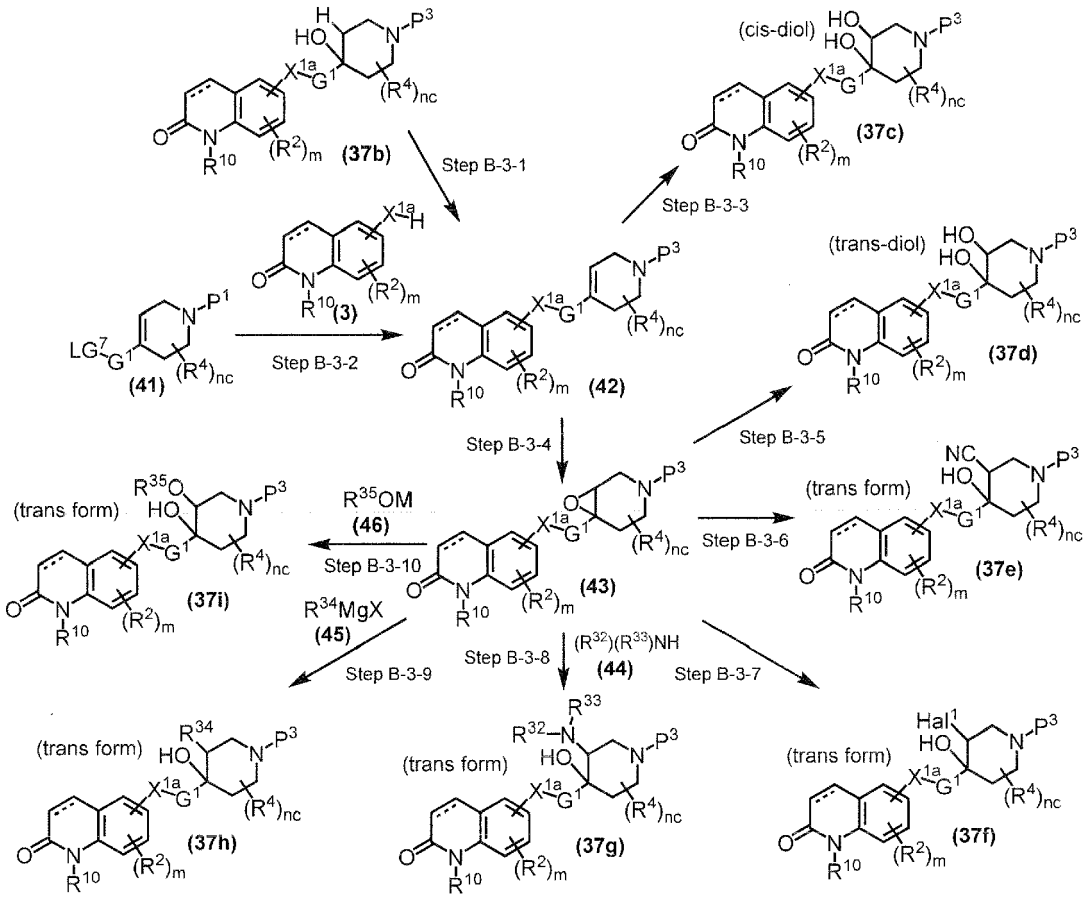
[0237] Compound (40) can be obtained, for example, by reacting compound (39) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

(Step B-2-2: (40) + (3) -> (37a))

[0238] Among the compounds represented as formula (37), compound (37a) can be obtained, for example, by reacting compound (40) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-3-2.

Scheme B-3

[Chem.38]



wherein LG^7 represents a leaving group; Hal^1 represents halogen; R^{32} and R^{33} each independently represents hydrogen or lower alkyl; R^{34} represents lower alkyl; R^{35} represents lower alkyl; M represents an alkali metal atom; X represents halogen; nc is an integer of 0 to 7; and other symbols are as defined above.

(Step B-3-1: (37b) -> (42))

[0239] Compound (42) can be obtained, for example, by transforming hydroxy in compound (37b) to a leaving group by using any known method followed by olefination reaction. Said reaction can be performed under the conditions similar to above step A-10-1.

(Step B-3-2: (41) + (3) -> (42))

[0240] Compound (42) can be obtained, for example, by reacting compound (41) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

(Step B-3-3: (42) -> (37c))

[0241] Among the compounds represented as formula (37), compound (37c) can be obtained, for example, by reacting compound (42) in an inert solvent, in the presence of osmium tetraoxide and a reoxidizing agent.
The amount of osmium tetraoxide used is typically 0.01 to 0.5 molar equivalents relative to compound (42). Also, potassium osmate ($K_2OsO_2(OH)_4$) may be used as an alternative to osmium tetraoxide. In addition, it is possible to use an immobilized catalyst in which osmium tetraoxide is support on a solvent resistant polymer. Example of immobilized catalyst includes "Osmium Oxide, Immobilized Catalyst I (Os IC-I)" (trade name) (Wako Pure Chemical Industries, Ltd.). Examples of the reoxidizing agent include, for example, N-methylmorpholine oxide, trimethylamine oxide, tert-butyl hydroperoxide and potassium ferricyanide ($K_3Fe(CN)_6$), and it is also possible to use any two or more of them in an

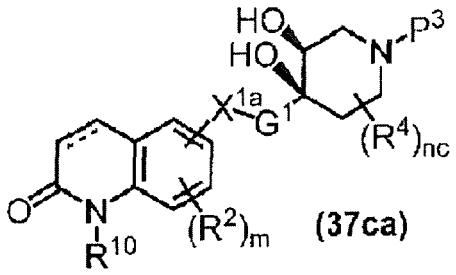
appropriate ratio. The amount of the reoxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (42).

In addition, Sharpless asymmetric dihydroxylation reaction can be done by using an asymmetric amine ligand.

Examples of the asymmetric amine ligand include, for example, hydroquinine ethers such as hydroquinine anthraquinone-1,4-diyl diether [$(DHQ)_2AQN$], hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQ)_2PYR$] and hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$] and; hydroquinidine ethers such as hydroquinidine anthraquinone-1,4-diyl diether [$(DHQD)_2AQN$], hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2PYR$] and hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$]. The amount of the asymmetric amine ligand used is typically 0.001 to 1 molar equivalent relative to compound (42).

For example, when employing a hydroquinine ether, typically, it is possible to obtain mainly, a compound represented as formula (37ca):

[Chem.39]

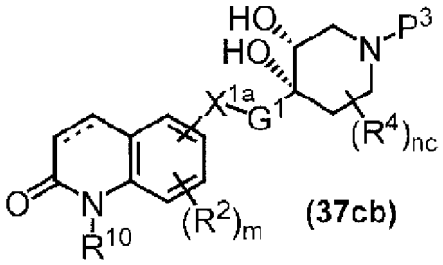


(37ca)

wherein each symbol is as defined above
as compound (37c).

For example, when using a hydroquinidine ether, typically, it is possible to obtain mainly, a compound represented as formula (37cb):

[Chem.40]



(37cb)

wherein each symbol is as defined above
as compound (37c).

In addition, it is possible to add a base, as necessary. Examples of the base include alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydroxides, aromatic amines and tertiary amines. The amount of the base used is typically 0.001 to 3 molar equivalents relative to compound (42).

In addition, an additive agent can be added, as necessary. Example of the additive agent includes methanesulfonamide. The amount of the additive agent used is typically 0.001 to 3 molar equivalents relative to compound (42).

In addition, a commercially available reagent kit such as AD-mix-α (comprising $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$ and K_2CO_3) or AD-mix-β (comprising $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$ and K_2CO_3) can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-3-4: (42) -> (43))

[0242] Compound (43) can be obtained, for example, by reacting compound (42) in an inert solvent in the presence of an oxidizing agent. Said reaction can be performed under the conditions similar to above step A-4-4.

(Step B-3-5: (43) -> (37d))

[0243] Among the compounds represented as formula (37), compound (37d) can be obtained, for example, by treating compound (43) with an acid.

[0244] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (43).
The acid can be used as a solvent, or an additional inert solvent can be used. Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-3-6: (43) -> (37e))

[0245] Among the compounds represented as formula (37), compound (37e) can be obtained, for example, treating compound (43) with a cyane source and a base.

[0246] Examples of the cyane source include, for example, α-cyanohydrins such as α-hydroxyisobutyronitrile. The amount of the cyane source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (43).

[0247] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (43).

[0248] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0249] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-3-7: (43) -> (37f))

[0250] Among the compounds represented as formula (37), compound (37f) can be obtained, by reacting for example, compound (43) with hydrogen halide in an inert solvent or in the absence of solvent.

[0251] When Hal^1 is fluorine, tetrabutylammonium dihydrogen trifluoride can be used as the hydrogen halide.

[0252] The amount of the hydrogen halide used is typically 1 molar equivalent to excessive amounts relative to compound (43).

[0253] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0254] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-3-8: (43) + (44) -> (37g))

[0255] Among the compounds represented as formula (37), compound (37g) can be obtained, for example, by reacting compound (43) with compound (44).
The amount of compound (44) used is typically 1 molar equivalent to excessive amounts relative to compound (43).
Compound (44) can be used as a solvent, or an additional inert solvent can be used. Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-3-9: (43) + (45) -> (37h))

[0256] Among the compounds represented as formula (37), compound (37h) can be obtained, for example, by reacting compound (43) with compound (45) in an inert solvent.

[0257] The amount of compound (45) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (43).

[0258] In addition, a copper compound can be used as a catalyst, as necessary.

[0259] Examples of the copper compound include for example, copper (I) chloride, copper (II) chloride, copper (I) bromide, copper (II) bromide, copper (I) iodide, copper (I) oxide, copper (II) oxide, copper (I) acetate, copper (II) acetate, copper (I) cyanide, copper (II) sulfate, or a dimethyl sulfide complex thereof. The amount of the copper compound used is typically 0.001 to 3 molar equivalents relative to compound (43).

[0260] Examples of the inert solvent include, for example, hydrocarbons, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0261] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-3-10: (43) + (46) -> (37i))

[0262] Among the compounds represented as formula (37), compound (37i) can be obtained, for example, by reacting compound (43) with compound (46) in an inert solvent.

[0263] The amount of compound (46) used is typically 1 molar equivalent to excessive amounts relative to compound (43).

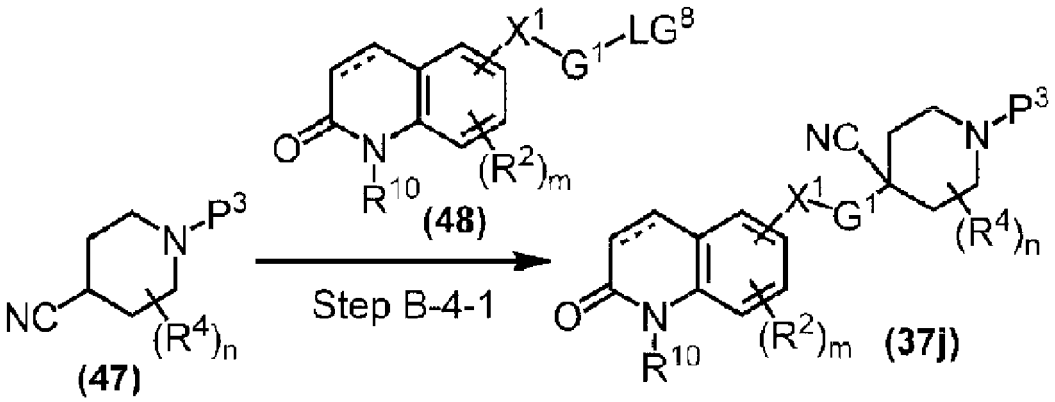
[0264] Examples of the alkali metal represented as M include potassium, sodium and cesium.

[0265] Examples of the inert solvent include, for example, alcohols corresponding to compound (46), or hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme B-4

[Chem.41]



wherein LG^8 represents a leaving group; and other symbols are as defined above.

(Step B-4-1: (47) + (48) -> (37j))

[0266] Among the compounds represented as formula (37), compound (37j) can be obtained, for example, by reacting compound (47) with compound (48) in an inert solvent in the presence of a base.

[0267] The amount of compound (48) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (47).

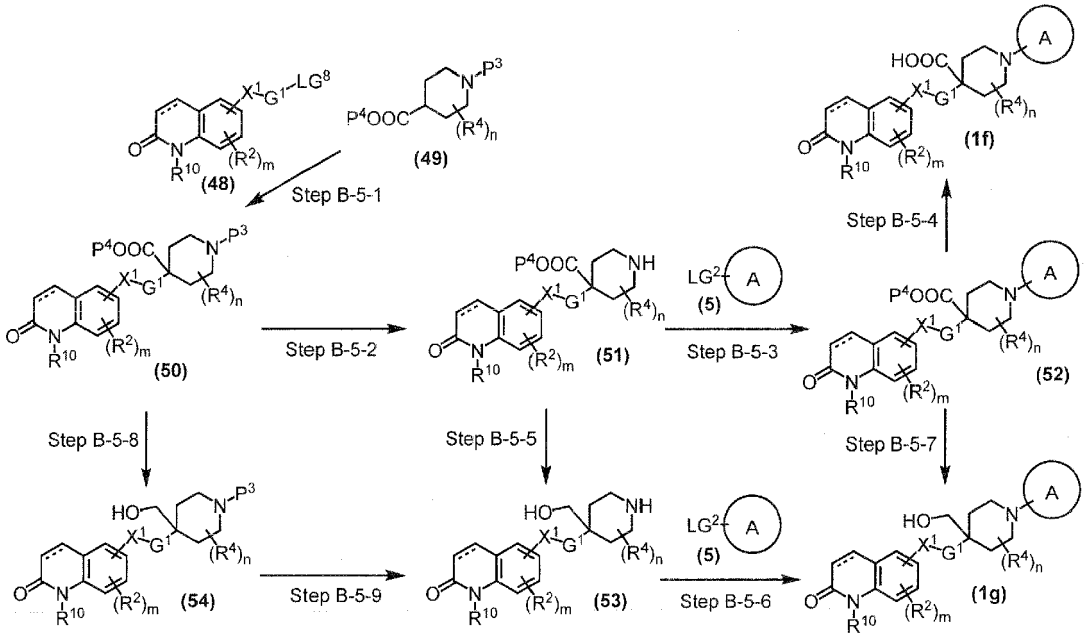
[0268] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (47).

[0269] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0270] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme B-5

[Chem.42]



wherein P^4 represents a carboxy protecting group; and other symbols are as defined above.

(Step B-5-1: (49) + (48) -> (50))

[0271] Compound (50) can be obtained, for example, by reacting compound (49) with compound (48) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step B-4-1.

(Step B-5-2: (50) -> (51))

[0272] Compound (51) can be obtained by subjecting compound (50) to a deprotection reaction. For example, said reaction can be performed under the conditions similar to above step B-1-2.

(Step B-5-3: (51) + (5) -> (52))

[0273] Compound (52) can be obtained, for example, by reacting compound (51) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

(Step B-5-4: (52) -> (1f))

[0274] Among the compounds represented as formula (1), compound (1f) can be obtained by subjecting compound (52) to a deprotection reaction.

[0275] Any of known reactions may be used as the deprotection reaction, for example, when P^4 is lower alkyl, said group can be deprotected by reacting the compound in an inert solvent in the presence of a base.

[0276] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen phosphates and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (50).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio. The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-5-5: (51) -> (53))

[0277] Compound (53) can be obtained by subjecting P^4 of compound (51) to the deprotection reaction by using similar

reaction to those of the above step B-5-4 to give carboxylic acid, and then subjecting the obtained compound to a reduction reaction in an inert solvent, in the presence of a reducing agent, alternatively, subjecting compound (51) directly to a reduction reaction in an inert solvent in the presence of a reducing agent.

[0278] Examples of the reducing agent include sodium borohydride, lithium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, sodium triethylborohydride, lithium triethylborohydride, lithium aluminum hydride, sodium dihydridobis(2-methoxyethoxy)-aluminate, borane-tetrahydrofuran complex and diisobutylaluminium hydride. The amount of the reducing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (51).

[0279] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, alcohols, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0280] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step B-5-6: (53) + (5) -> (1g))

[0281] Compound (1g) can be obtained, for example, by reacting compound (53) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

(Step B-5-7: (52) -> (1g))

[0282] Among the compounds represented as formula (1), compound (1g) can be obtained by subjecting P^4 of compound (52) to the deprotection reaction by using similar reaction to those of the above step B-5-4 to give carboxylic acid, and then subjecting the obtained compound to a reduction reaction in an inert solvent, in the presence of a reducing agent, alternatively, subjecting compound (52) directly to a reduction reaction in an inert solvent in the presence of a reducing agent. Said reaction can be performed under the conditions similar to above step B-5-5.

(Step B-5-8: (50) -> (54))

[0283] Compound (54) can be obtained by subjecting P^4 of compound (50)) to the deprotection reaction by using similar reaction to those of the above step B-5-4 to give carboxylic acid, and then subjecting the obtained compound to a reduction reaction in an inert solvent, in the presence of a reducing agent, alternatively, subjecting compound (50) directly to a reduction reaction in an inert solvent, in the presence of a reducing agent. Said reaction can be performed under the conditions similar to above step B-5-5.

(Step B-5-9: (54) -> (53))

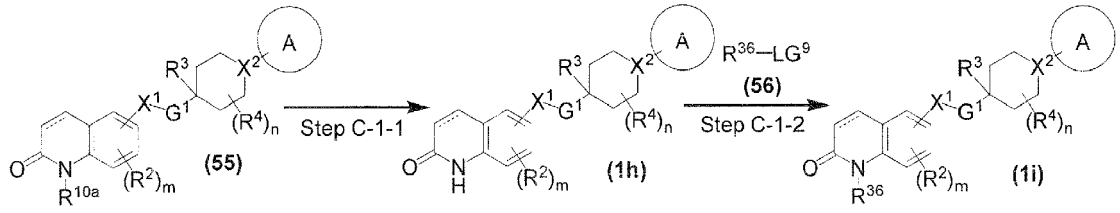
[0284] Compound (53) can be obtained by subjecting compound (54) to a deprotection reaction. For example, said reaction can be performed under the conditions similar to above step B-1-2.

Preparation method C: Various derivatizations

[0285]

Scheme C-1

[Chem.43]



wherein R^{10a} represents an amino protecting group; LG^9 represents a leaving group; R^{36} represents amino optionally having one or more lower alkyl or lower alkyl; and other symbols are as defined above.

(Step C-1-1: (55) -> (1h))

[0286] Among the compounds represented as formula (1), compound (1h) can be obtained by subjecting compound (55) to a deprotection reaction.

[0287] Any of known reactions may be used as the deprotection reaction, for example, when R^{10a} is 4-methoxybenzyl (PMB), compound (1h) can be obtained by hydrogenation in the presence of a hydrogen source and a metal catalyst, treatment with an oxidizing agent, or treatment under strong acid conditions.

[0288] When a subformula of the above formula (aa) is the formula represented as above formula (aa1), namely, compound (55) is protected as the imidic acid (lower alkyl protection), compound (1h) can be obtained by treating it under a strong acid condition.

[0289] Examples of the hydrogen source include, for example, hydrogen gas, formic acid, sodium formate, ammonium formate, cyclohexene, phosphinic acid salt and hydrazine. When using hydrogen gas as the hydrogen source, the reaction can be done under the hydrogen pressure of about 1 to 10 atm. The amount of another hydrogen source used is typically 1 molar equivalent to excessive amounts, preferably 1 to 10 molar equivalents relative to compound (55).
Examples of the metal catalyst include, for example, palladium on carbon, palladium black, palladium chloride, palladium hydroxide on carbon, platinum oxide, platinum black, platinum-palladium, platinum-carbon, Raney nickel and Raney cobalt. The amount of the metal catalyst used is typically 0.001 to 1000 molar equivalents, preferably 0.01 to 100 molar equivalents relative to compound (55).
Examples of the oxidizing agent include quinone oxidizing agents such as 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and; metalic oxidizing agents such as ammonium hexanitratocerate (IV) (CAN). The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (55).
Examples of the strong acid include inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid and; organic acids such as trifluoroacetic acid and trifluoromethanesulfonic acid. The amount of the strong acid used is typically 1 molar equivalent to excessive amounts relative to compound (55).
In addition, when using the strong acid, it is possible to use a cation scavenger, as necessary. Examples of the cation scavenger include, for example, anisole, thioanisole, phenol, m-cresol, p-cresol and dimethyl sulfide. The amount of the cation scavenger used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (55).
The strong acid can be used as a solvent, or an inert solvent can be used.
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-1-2: (1h) + (56) -> (1i))

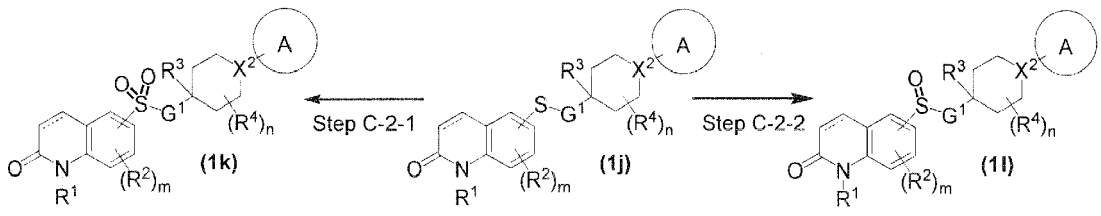
[0290] Among the compounds represented as formula (1), compound (1i) can be obtained, for example, by reacting compound (1h) with compound (56) in an inert solvent in the presence of a base.

[0291] The amount of compound (56) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1h).

[0292] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1h).
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme C-2

[Chem.44]



wherein each symbol is as defined above.

(Step C-2-1: (1j) -> (1k))

[0293] Compound (1k) can be obtained, for example, by reacting compound (1j) in an inert solvent in the presence of an oxidizing agent.

[0294] Examples of the oxidizing agent include for example, inorganic peroxides (such as hydrogen peroxide, sodium hypochlorite and sodium periodate), organic peroxides (such as m-chloroperbenzoic acid, perbenzoic acid, peracetic acid and trifluoroperacetic acid) and dioxiranes (such as dimethyldioxirane). The amount of the oxidizing agent used is typically 2 to 10 molar equivalents, preferably 2 to 5 molar equivalents relative to compound (1j).

[0295] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

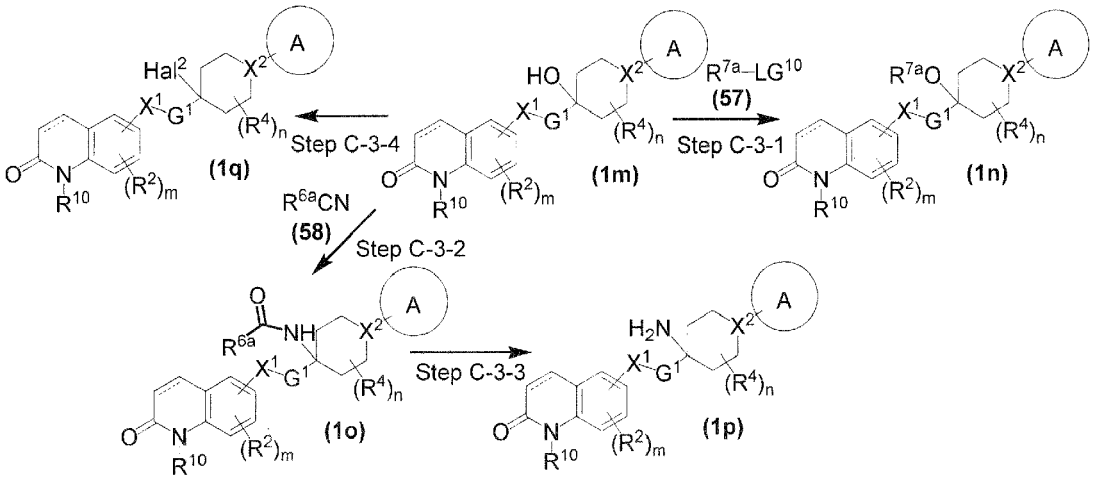
[0296] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-2-2: (1j) -> (1l))

[0297] Compound (1l) can be obtained, for example, by reacting compound (1j) in an inert solvent in the presence of an oxidizing agent. Said reaction can be performed under the conditions similar to above step C-2-1. The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 1.5 molar equivalents relative to compound (1j).

Scheme C-3

[Chem.45]



wherein R^{6a} represents lower alkyl optionally having one or more amino which optionally having one or more lower alkyl; R^{7a} represents amino, lower alkanoyl or lower alkyl; Hal^2 represents halogen; LG^{10} represents a leaving group; and other symbols are as defined above.

(Step C-3-1: (1m) + (57) -> (1n))

[0298] Compound (1n) can be obtained, for example, by reacting compound (1m) with compound (57) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

[0299] In addition, when R^{7a} is lower alkanoyl, it is possible to use carboxylic acid anhydride such as $(R^{7a})_2O$ in place of compound (57).

(Step C-3-2: (1m) + (58) -> (1o))

[0300] Compound (1o) can be obtained, for example, reacting compound (1m) with compound (58) in the presence of an acid.

[0301] The amount of compound (58) used is typically 1 molar equivalent to excessive amounts relative to compound (1m).

[0302] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid and; organic acids such as trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (1m).

[0303] The acid or compound (58) can be used as a solvent, or an additional inert solvent can be used.

[0304] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, sulfoxides and nitriles, and it is also possible to use any two or more of them in an appropriate ratio.

[0305] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-3-3: (1o) -> (1p))

[0306] Compound (1p) can be obtained, for example, by treating compound (1o) with an acid.

[0307] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid and; organic acids such as trifluoroacetic acid and trifluoromethanesulfonic acid and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (1o).

[0308] The acid can be used as a solvent, or an additional inert solvent can be used. Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0309] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-3-4: (1m) -> (1q))

[0310] Compound (1q) can be obtained, for example, by reacting compound (1m) with a halogenating agent in an inert solvent.

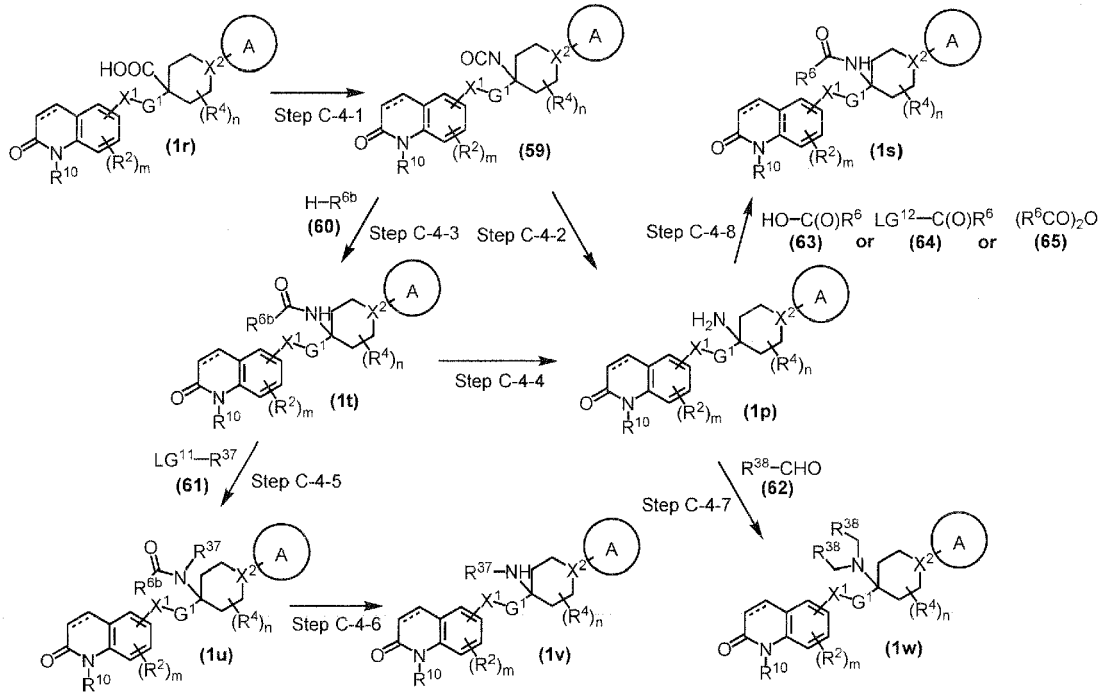
[0311] Examples of the halogenating agent include, for example, thionyl chloride, oxalyl chloride, phosgene, phosphorus oxychloride and phosphorus pentachloride, phosphorus trichloride for chlorination; thionyl bromide and phosphorus tribromide for • bromination; and bis(2-methoxyethyl)aminosulfur trifluoride and diethylaminosulfur trifluoride for fluorination. The amount of the halogenating agent used is typically 1 to 10 molar equivalents relative to compound (1m).

[0312] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0313] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme C-4

[Chem.46]



wherein R^{6b} represents lower alkoxy; R^{37} represents lower alkyl; R^{38} represents hydrogen or alkyl having 1 to 5 carbon atoms; LG^{11} or LG^{12} each independently represents a leaving group; and other symbols are as defined above.

(Step C-4-1: (1r) -> (59))

[0314] Compound (59) can be obtained, for example, by reacting compound (1r) with a phosphoryl azide compound in an inert solvent in the presence of a base.

[0315] Examples of the phosphoryl azide compound include, for example, diphenylphosphoryl azide, bis(p-nitrophenyl)phosphoryl azide and diethylphosphoryl azide. The amount of the phosphoryl azide compound used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1r).

[0316] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, preferably, tertiary amines, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1r).

[0317] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0318] The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-4-2: (59) -> (1p))

[0319] Among the compounds represented as formula (1), compound (1p) can be obtained, for example, by treating compound (59) with an acid.

[0320] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (59).

[0321] The acid can be used as a solvent, or an additional inert solvent can be used.

[0322] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0323] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-4-3: (59) + (60) -> (1t))

[0324] Among the compounds represented as formula (1), compound (It) can be obtained, for example, by reacting compound (59) with compound (60).

[0325] The amount of compound (60) used is typically 1 molar equivalent to excessive amounts relative to compound (59).

[0326] Compound (60) can be used as a solvent, or an inert solvent can be used in addition to compound (60).

[0327] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0328] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-4-4: (It) -> (1p))

[0329] Among the compounds represented as formula (1), compound (1p) can be obtained, for example, by treating compound (1t) with an acid.

[0330] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, • sulfuric acid, nitric acid and hydrobromic acid; and organic acids such as acetic acid, trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (It).

[0331] The acid can be used as a solvent, or an additional inert solvent can be used.

[0332] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, water, alcohols, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-4-5: (1t) + (61) -> (1u))

[0333] Among the compounds represented as formula (1), compound (1u) can be obtained, for example, by reacting compound (It) with compound (61) in an inert solvent in the presence of a base.

[0334] The amount of compound (61) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (It).

[0335] Examples of the base include, for example, alkali metal hydrides and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (It).

[0336] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0337] The reaction temperature is typically -40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-4-6: (1u) -> (1v))

[0338] Among the compounds represented as formula (1), compound (1v) can be obtained, for example, by treating compound (1u) with an acid. Said reaction can be performed under the conditions similar to above step C-4-4.

(Step C-4-7: (1p) + (62) -> (1w))

[0339] Among the compounds represented as formula (1), compound (1w) can be obtained by reacting compound (1p) with compound (62) in an inert solvent, in the presence of a reducing agent (reductive amination reaction).

[0340] The amount of compound (62) used is typically 2 molar equivalents to excessive amounts relative to compound (1p).

[0341] Examples of the reducing agent include sodium borohydride, lithium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, sodium triethylborohydride, lithium triethylborohydride, lithium aluminum hydride, sodium dihydridobis(2-methoxyethoxy)-aluminate, borane-tetrahydrofuran complex, diisobutylaluminium hydride, formic acid, sodium formate and ammonium formate. The amount of the reducing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

[0342] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, alcohols, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-4-8: (1p) + (63) or (64) or (65) -> (1s))

[0343] Among the compounds represented as formula (1), compound (1s) can be obtained by the condensation reaction of compound (1p) with compound (63), (64) or (65) in an inert solvent.

[0344] The respective amount of compound (63), (64) or (65) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

[0345] In addition, it is possible to add a base, as necessary. Example of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

[0346] In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 0.01 molar equivalents to excessive amounts relative to compound (1p).

[0347] In addition, especially when condensation reaction is performed with compound (63), it is preferred to use a condensation agent in the condensation. Examples of the condensation agent include, for example, carbodiimides such as • 1,3-dicyclohexylcarbodiimide, 1-cyclohexyl-3-morpholinoethylcarbodiimide, 1-cyclohexyl-3-(4-diethylaminocyclohexyl)carbodiimide, 1,3-diethylcarbodiimide, 1,3-diisopropylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or salts thereof. The amount of the condensation agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

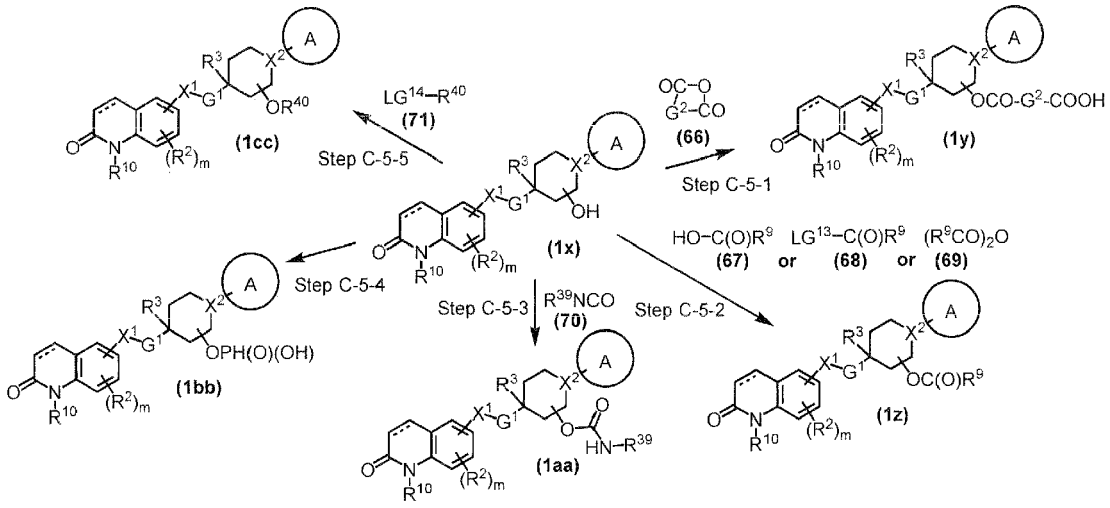
[0348] In addition, a condensation accelerator can be added in addition to the condensation agent. Examples of the condensation accelerator include, for example, 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), 1-hydroxy-7-azabenzotriazole (HOAt) and hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOOBt). The amount of the condensation accelerator used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

[0349] In addition, tertiary amines such as pyridine can be used as a solvent, or an inert solvent can be used.

[0350] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme C-5

[Chem.47]



wherein R^{39} represents alkyl; R^{40} represents benzyl optionally having one or more lower alkoxy, or lower alkyl; LG^{13} or LG^{14} each independently represents a leaving group; and other symbols are as defined above.

(Step C-5-1: (1x) + (66) -> (1y))

[0351] Among the compounds represented as formula (1), compound (1y) can be obtained by reacting compound (1x) with compound (66) in an inert solvent.

[0352] The amount of compound (66) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

[0353] In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include, N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 1 molar equivalent to excessive amounts relative to compound (1x).

[0354] In addition, pyridine etc. can be used as a solvent, or an inert solvent can be used.

[0355] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0356] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-5-2: (1x) + (67) or (68) or (69) -> (1z))

[0357] Among the compounds represented as formula (1), compound (1z) can be obtained by the condensation reaction of compound (1x) with compound (67), (68) or (69) in an inert solvent.
The respective amount of compound (67), (68) or (69) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x). In addition, it is possible to add a base, as necessary. Example of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x). In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include, N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 0.01 molar equivalents to excessive amounts relative to compound (1x).
In addition, especially when condensation reaction is performed with compound (67), it is preferred to use a condensation agent in the condensation. Examples of the condensation agent include, for example, carbodiimides such as • 1,3-dicyclohexylcarbodiimide, 1-cyclohexyl-3-morpholinoethylcarbodiimide, 1-cyclohexyl-3-(4-diethylaminocyclohexyl)-carbodiimide, 1,3-diethylcarbodiimide, 1,3-diisopropylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or salts thereof. The amount of the condensation agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).
In addition, a condensation accelerator can be added in addition to the condensation agent. Examples of the condensation accelerator include, for example, 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), 1-hydroxy-7-azabenzotriazole (HOAt) and hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOOBt). The amount of the condensation accelerator used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).
In addition, tertiary amines such as pyridine can be used as a solvent, or an inert solvent can be used.
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-5-3: (1x) + (70) -> (1aa))

[0358] Among the compounds represented as formula (1), compound (laa) can be obtained, for example, by reacting compound (1x) with compound (70) in an inert solvent.

[0359] The amount of compound (70) used is typically 1 molar equivalent to excessive amounts relative to compound (1x).
In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include, N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 1 molar equivalent to excessive amounts relative to compound (1x).
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-5-4: (1x) -> (1bb))

[0360] Among the compounds represented as formula (1), compound (1bb) can be obtained, for example, reacting compound (1x) with diphenyl phosphite in an inert solvent in the presence of a base.

[0361] The amount of diphenyl phosphite used is typically 1 molar equivalent to excessive amounts relative to compound (1x).

[0362] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal

amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

[0363] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

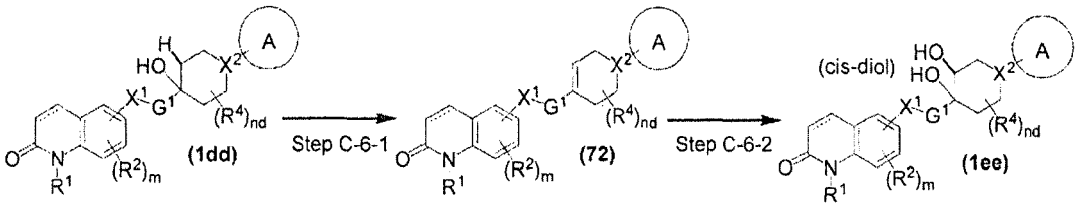
[0364] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step C-5-5: (1x) + (71) -> (1cc))

[0365] Among the compounds represented as formula (1), compound (1cc) can be obtained, for example, by reacting compound (1x) with compound (71) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

Scheme C-6

[Chem.48]



wherein nd is an integer of 0 to 7; and other symbols are as defined above.

(Step C-6-1: (1dd) -> (72))

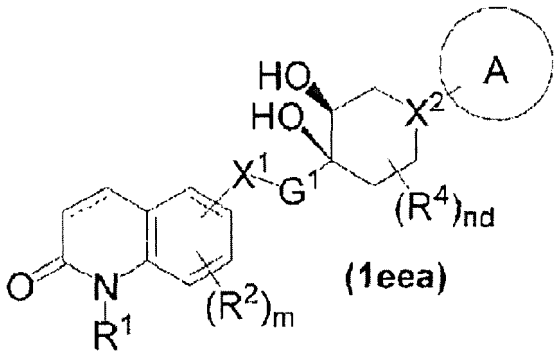
[0366] Compound (72) can be obtained, for example, by transforming hydroxy in compound (1dd) to a leaving group by using any known method followed by olefination reaction. Said reaction can be performed under the conditions similar to above step A-10-1.

(Step C-6-2: (72) -> (1ee))

[0367] Among the compounds represented as formula (1), compound (lee) can be obtained, for example, reacting compound (72) in an inert solvent in the presence of osmium tetraoxide and a reoxidizing agent. Said reaction can be performed under the conditions similar to above step B-3-3.

[0368] Similar to the above step B-3-3, when, for example, a hydroquinine ether is used as a catalyst, typically, it is possible to obtain, mainly, a compound represented as formula (1eea):

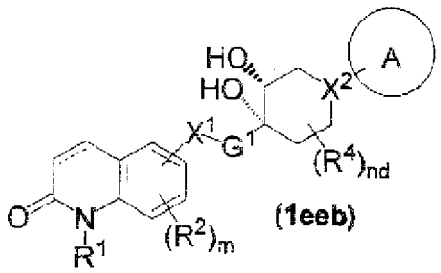
[Chem.49]



wherein each symbol is as defined above
as compound (1ee).

[0369] For example, when using a hydroquinidine ether, typically, it is possible to obtain, mainly, a compound represented as formula (1eeb):

[Chem.50]

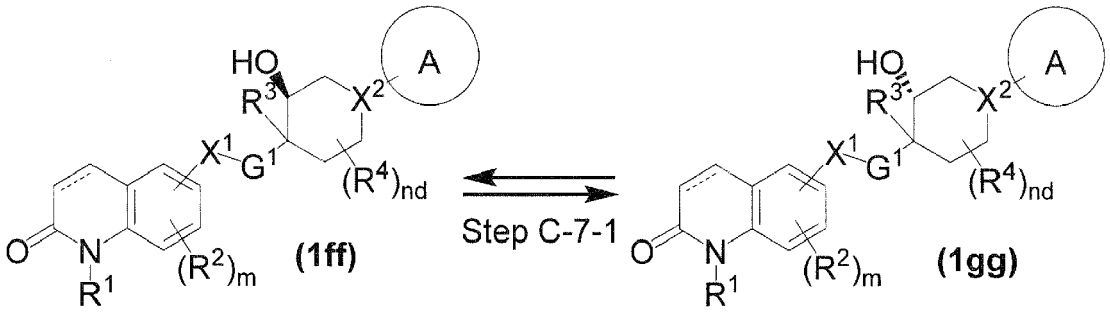


(1eeb)

wherein each symbol is as defined above as compound (1ee).

Scheme C-7

[Chem.51]



(1ff) Step C-7-1 (1gg)

wherein each symbol is as defined above

(Step C-7-1: (1ff) <--> (1gg))

[0370] Among the compounds represented as formula (1), compound (1gg) can be obtained from compound (1ff) by Mitsunobu reaction followed by a hydrolysis reaction.

[0371] Mitsunobu reaction can be performed, for example, by reacting compound (1ff) with carboxylic acid in an inert solvent, in the presence of azodicarboxylic acid ester and phosphine.

[0372] Examples of the azodicarboxylic acid ester include, for example, dimethyl azodicarboxylate, diethyl azodicarboxylate, diisopropyl azodicarboxylate, dibenzyl azodicarboxylate, di-tert-butyl azodicarboxylate and 1,1'-(azodicarbonyl)dipiperidine. The amount of the azodicarboxylic acid ester used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1ff).

[0373] Examples of the phosphine include, for example, triphenylphosphine, tricyclohexylphosphine and tributylphosphine. The amount of the phosphine used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1ff).

[0374] Examples of the carboxylic acid include benzoic acid, p-nitrobenzoic acid and p-methoxybenzoic acid. The amount of the carboxylic acid used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1ff).

In addition, hydrolysis reaction after Mitsunobu reaction can be done, for example, by reacting the compound in an inert solvent in the presence of a base.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen phosphates and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 molar equivalent to excessive amounts relative to compound (1ff).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

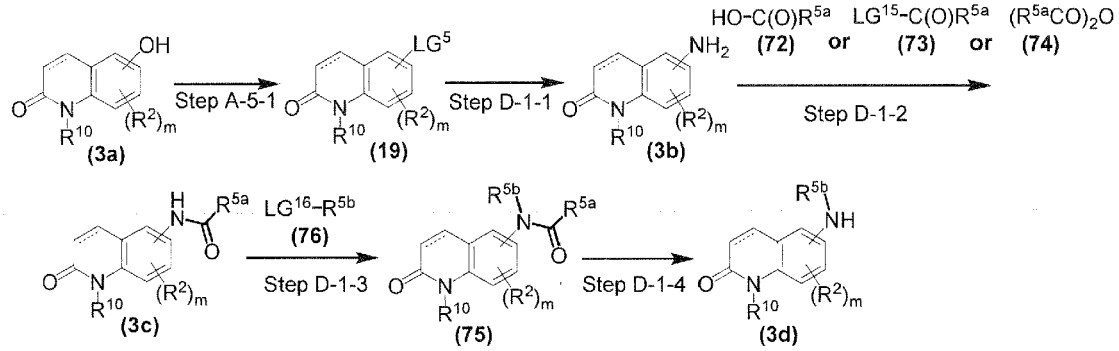
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.
In addition, compound (1ff) can be obtained from compound (1gg) by using a similar method.

Preparation method D: Synthesis of starting materials

[0375]

Scheme D-1

[Chem.52]



wherein R^{5a} represents hydrogen or lower alkyl; R^{5b} represents lower alkyl; LG^{15} and LG^{16} each independently represents a leaving group; and other symbols are as defined above.

(Step D-1-1: (19) -> (3b))

[0376] Among the compounds represented as formula (3), compound (3b) can be obtained from compound (19) by using any known method for introducing amino, for example, by reacting compound (19) with benzophenone imine or hexamethyldisilazane in an inert solvent, in the presence of base and transition metal catalyst, followed by the hydrolysis of the obtained compound.

[0377] Examples of the benzophenone imine include, for example, benzophenone imine and 4,4' -dimethoxybenzophenone imine.

[0378] The amount of the benzophenone imine or hexamethyldisilazane used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (19).
Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (19).
Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(tert-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (19).
In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(tert-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2' ,4' ,6' -triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (19).
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio. The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step D-1-2: (3b) + (72) or (73) or (74) -> (3c))

[0379] Among the compounds represented as formula (3), compound (3c) can be obtained by the condensation reaction of compound (3b) with compound (72), (73) or (74) in an inert solvent. Said reaction can be performed under the conditions similar to above step C-4-8.

(Step D-1-3: (3c) + (76) -> (75))

[0380] Compound (75) can be obtained, for example, by reacting compound (3c) with compound (76) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step C-4-5.

(Step D-1-4: (75) -> (3d))

[0381] Among the compounds represented as formula (3), compound (3d) can be obtained, for example, by treating compound (75) with an acid.

[0382] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, • sulfuric acid, nitric acid and hydrobromic acid ; and organic acids such as acetic acid, trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (75).

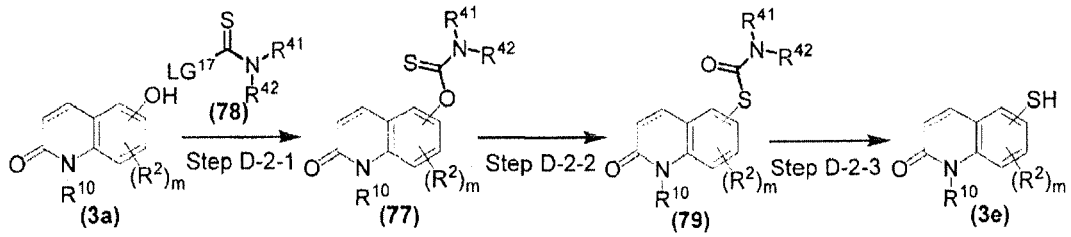
[0383] The acid can be used as a solvent, or an additional inert solvent can be used.

[0384] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, water, alcohols, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0385] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme D-2

[Chem.53]



wherein R^{41} and R^{42} each independently represents lower alkyl; LG^{17} represents a leaving group; and other symbols are as defined above.

(Step D-2-1: (3a) + (78) -> (77))

[0386] Compound (77) can be obtained, for example, by reacting compound (3a) with compound (78) in an inert solvent in the presence of a base.

[0387] The amount of compound (78) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (3a).

[0388] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (3a).

[0389] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step D-2-2: (77) -> (79))

[0390] Compound (79) can be obtained by heat treatment of compound (77) in an inert solvent.

[0391] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0392] The reaction temperature is typically 100 to 300 °C. The reaction time is typically 0.1 to 200 hours.

(Step D-2-3: (79) -> (3e))

[0393] Among the compounds represented as formula (3), compound (3e) can be obtained, for example, by treating compound (79) with a base followed by hydrolysis.

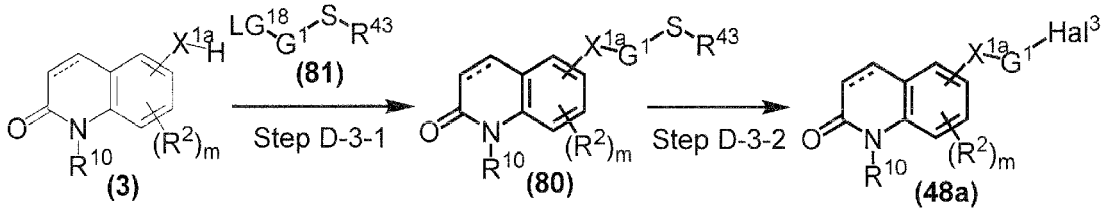
[0394] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (79).

[0395] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0396] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme D-3

[Chem.54]



wherein R^{43} represents lower alkyl; LG^{18} represents a leaving group; Hal^3 represents halogen; and other symbols are as defined above.

(Step D-3-1: (3) + (81) -> (80))

[0397] Compound (80) can be obtained, for example, by reacting compound (3) with compound (81) in an inert solvent in the presence of a base. Said reaction can be performed similar to the above step A-1-1.

(Step D-3-2: (80) -> (48a))

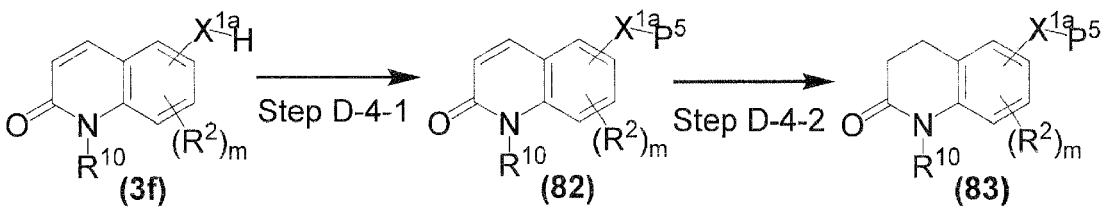
[0398] Among the compounds represented as formula (48), compound (48a) can be obtained, for example, by reacting compound (80) with a halogenating agent in an inert solvent. Examples of the halogenating agent include, For example, sulfuryl chloride, sulfuryl fluoride. The amount of the halogenating agent used is typically 1 to 10 molar equivalents relative to compound (80).

[0399] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

[0400] The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

Scheme D-4

[Chem.55]



wherein P^5 represents a protecting group; and other symbols are as defined above.

(Step D-4-1: (3f) -> (82))

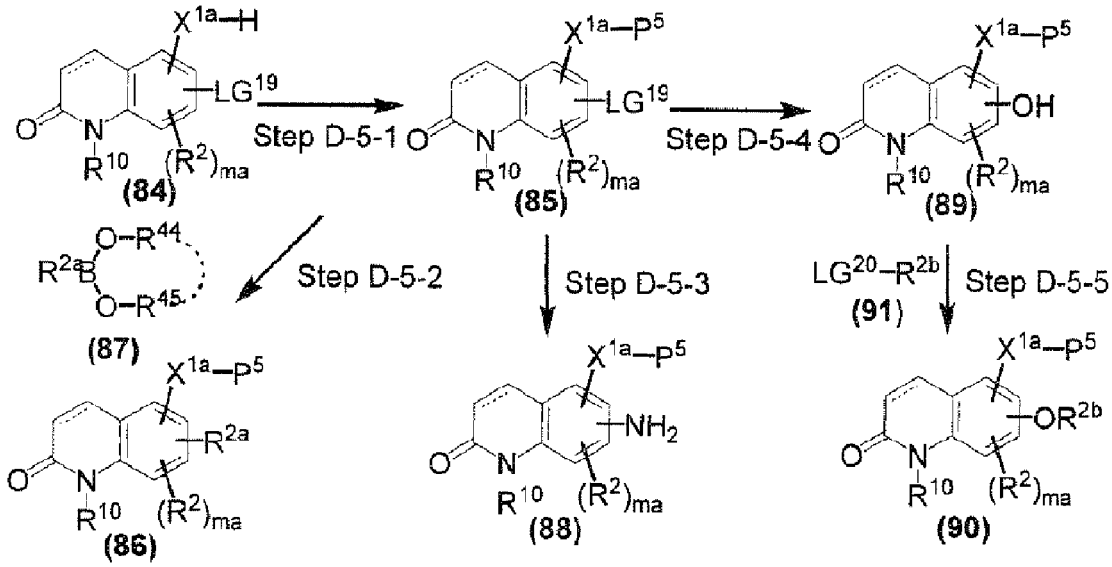
[0401] Compound (82) can be obtained by subjecting compound (3f) to any of known reaction for introducing a protecting group.

(Step D-4-2: (82) -> (83))

[0402] Compound (83) can be obtained, for example, by subjecting compound (82) to a reduction reaction in an inert solvent in the presence of a hydrogen source and a metal catalyst. Said reaction can be performed under the conditions similar to above step A-5-5.

Scheme D-5

[Chem.56]



wherein R^{2a} and R^{2b} each independently represents lower alkyl; R^{44} and R^{45} each independently represents hydrogen or lower alkyl, or R^{44} and R^{45} may unitedly form a ring; LG^{19} represents a leaving group; LG^{19} and LG^{20} each independently represents a leaving group; ma is an integer of 0 to 2; and other symbols are as defined above.

(Step D-5-1: (84) -> (85))

[0403] Compound (85) can be obtained by subjecting compound (84) to known reaction for introducing a protecting

group.

(Step D-5-2: (85) + (87) -> (86))

[0404] Compound (86) can be obtained, for example, by reacting compound (85) with compound (87) in an inert solvent in the presence of a base and a transition metal catalyst.

[0405] The amount of compound (87) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (85).

[0406] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (85).

[0407] Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(tert-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (85).
In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(tert-butyl)phosphine, 2,2' -bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2' ,4' ,6' -triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (85).
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step D-5-3: (85) -> (88))

[0408] Compound (88) can be obtained from compound (85) by using any known method for introducing amino, for example, by reacting compound (85) with benzophenone imine or hexamethyldisilazane in an inert solvent in the presence of base and transition metal catalyst followed by the hydrolysis of the obtained compound. Said reaction can be performed under the conditions similar to the above step D-1-1.

(Step D-5-4: (85) -> (89))

[0409] Compound (89) can be obtained from compound (85) by using any known method for introducing hydroxy, for example, reacting compound (85) with a diboronic acid diester, which is $((R^{B1}O)_2B)_2$ wherein R^{B1} each independently represents lower alkyl or may unitedly form a ring (such as bis(pinacolato)diboron), or a boronic acid ester, which is $B(OR^{B2})_3$ wherein R^{B2} each independently represents hydrogen or lower alkyl, in an inert solvent, followed by the hydrolysis of the obtained compound.

[0410] The hydrolysis reaction can be done by using Oxone (registered trade name), hydroxyamine and a base.

[0411] The amount of the diboronic acid diester or boronic acid ester used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (85).

[0412] When using the diboronic acid diester, it is preferred to react in the presence of base and transition metal catalyst.

[0413] Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal carboxylates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (85). Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(tert-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (85).

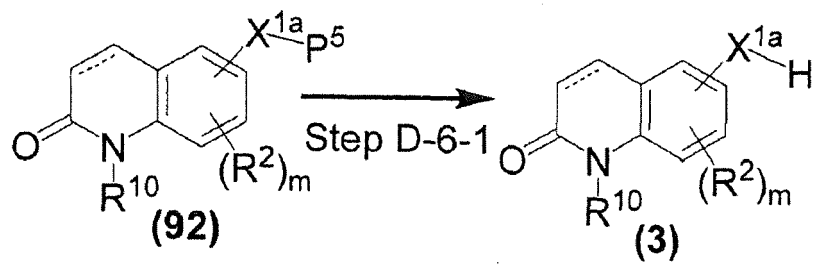
In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(tert-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2' ,4' ,6' -triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (85).
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.
The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

(Step D-5-5: (89) + (91) -> (90))

[0414] Compound (90) can be obtained, for example, by reacting compound (89) with compound (91) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step C-4-5.

Scheme D-6

[Chem.57]



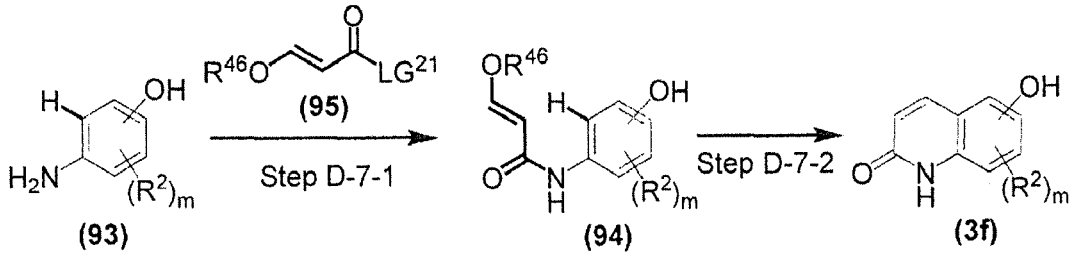
wherein each symbol is as defined above.

(Step D-6-1: (92) -> (3))

[0415] Compound (3) can be obtained by subjecting compound (92) to any known deprotection reaction.

Scheme D-7

[Chem.58]



wherein R^{46} represents lower alkyl; LG^{21} represents a leaving group; and other symbols are as defined above.

(Step D-7-1: (93) + (95) -> (94))

[0416] Compound (94) can be obtained by a condensation reaction of compound (93) with compound (95) in an inert solvent. Said reaction can be performed under the conditions similar to above step C-4-8.

(Step D-7-2: (94) -> (3f))

[0417] Among the compounds represented as formula (3), compound (3f) can be obtained, for example, by treating

compound (94) with an acid.

[0418] Examples of the acid include, for example, inorganic acids such as hydrochloric acid, • sulfuric acid, nitric acid and hydrobromic acid ; and organic acids such as acetic acid, trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (94).

[0419] The acid can be used as a solvent, or an additional inert solvent can be used.

[0420] Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, water, alcohols, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0421] The compound (1) of the present invention can be prepared by any synthetic method including the above respective steps or a method analogous to those described above. Further, the intermediates and the starting materials in the respective steps can be prepared by considering any synthetic method including the above respective steps or a method analogous to those described above, or a method in Reference Examples and Examples disclosed herein or a method analogous to those described in Examples, and a method known or publicly known at the filing date of the present application. When an intermediate or a starting material is commercially available, such a compound may be used as it is.

[0422] In addition, in the preparation of the compound (1), it is possible to further derivatize the obtained compound optionally by subjecting the compound to any of the known reactions such as various alkylation reaction, acylation reaction, amidation reaction, esterification reaction, etherification reaction, halogenation reaction, hydroxylation reaction, amination reaction, aryl coupling reaction, condensation reaction such as carbon extension reaction, addition reaction, substitution reaction, oxidation reaction, reduction reaction, dehydration reaction and hydrolysis reaction in addition to the above steps.

[0423] If necessary, a functional group in the starting materials and the intermediates for the above respective steps can be protected with any protecting group by using any known method before subjecting a specific reaction, and after the completion of said specific reaction, the protecting group can be deprotected by using any known method.

[0424] Each intermediate and the final compound in the above respective steps can be used in the next step as it is, or it is possible to isolate and purify the compound after the completion of the reaction. For example, when the compound should be isolated and purified, the reaction mixture may be cooled and subjected to a procedure for isolating the crude reaction product such as filtration, condensation or extraction, and then, the crude reaction product may be subjected to a procedure of common purification such as column chromatography or recrystallization to isolate and purify the product from the reaction mixture.

[0425] The starting materials, the intermediates and the final compounds and the compound (1) of the present invention include their solvates in which a solvent is added to the compound (for example, hydrates and ethanol solvate etc.).

[0426] The starting materials, the intermediates and the final compounds and the compound (1) of the present invention include their geometric isomers, stereoisomers and optical isomers. These isomers can be separated by any known separation method. For example, a racemic compound can be separated to a sterically pure isomer by using common method for optical resolution (for example, optical resolution by crystallization, directly resolving by a chromatography etc.). In addition, it is possible to prepare an optically active compound by using an appropriate optically active starting material.

[0427] The starting materials and the final compounds in the above respective steps can be used in a form of an appropriate salt. Examples of such salts include those exemplified below as the salt of compound (1) of the present invention.

[0428] When a compound obtained in the respective steps or a commercially available product is in a free form, it is possible to convert the compound to a desired salt by using a method known per se. Alternatively, when a compound obtained in the respective steps or a commercially available product is in a salt form, it is possible to convert the compound to a desired free form or a desired another salt form by using a method known per se.

[0429] Compound (1) in the present invention includes a pharmaceutically acceptable salt form thereof.

[0430] Among Compound (1) in the present invention, the compound with one or more basic groups may form a salt with a pharmaceutically acceptable acid. An example of the acid includes, for example, an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid, and an organic acid such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, and lactic acid.

[0431] Among Compound (1) in the present invention, the compound with one or more acidic groups may form a salt with a pharmaceutically acceptable base. An example of the base includes, for example, an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate, and an organic base such as methylamine, diethylamine, trimethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methyl-

amine, dicyclohexylamine, N,N'-dibenzylethylenediamine, guanidine, pyridine, picoline, and choline.

[0432] Compound (1) in the present invention includes the compound wherein one or more atoms are substituted with one or more isotopic atoms. An example of the isotopic atom includes, for example, deuterium (^{2}H), tritium (^{3}H), ^{13}C, ^{14}N, and ^{18}O.

[0433] A medical formulation/pharmaceutical composition comprising as the active ingredient Compound (1) in the present invention is illustrated as below.

[0434] The medical formulation is what Compound (1) in the present invention is formulated into the form of the usual medical formulation, which is prepared with Compound (1) in the present invention and a pharmaceutically acceptable carrier. The carrier includes a diluent or an excipient such as a filler, a bulking agent, a binder, a humidity adding agent, a disintegrant, a surface active agent, and a lubricant as commonly used.

[0435] Such a medical formulation may be selected from various forms depending on therapeutic purposes, and a typical example of the formulation includes, for example, a tablet, a pill, a powder, a liquid, a suspension, an emulsion, a granule, a capsule, a suppository, and an injection (such as a liquid and a suspension).

[0436] Any known carriers may be widely used as a carrier used in preparing a tablet formulation, and include, for example, an excipient such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, and crystalline cellulose, a binder such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, and polyvinylpyrrolidone, a disintegrant such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride stearate, and starch, lactose, a disintegration suppressant such as sucrose, stearin, cacao butter, and hydrogenated oil, an absorption promoter such as quaternary ammonium salt, and sodium lauryl sulfate, a humectant such as glycerin and starch, an adsorbent such as starch, lactose, kaolin, bentonite, and colloidal silica, a lubricant such as purified talc, stearate, boric acid powder, and polyethylene glycol.

[0437] The tablet may be also formulated, if needed, as a tablet with a common coating including, for example, a sugar-coated tablet, a gelatin-encapsulated tablet, an enteric coated tablet, a film coated tablet, a double tablet or a multi-layered tablet.

[0438] Any known carriers may be widely used as a carrier used in preparing a pill formulation, and include, for example, an excipient such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin, and talc, a binder such as gum arabic powder, tragacanth powder, gelatin, and ethanol, and a disintegrant such as laminaran, and agar.

[0439] Any known carriers may be widely used as a carrier used in preparing a suppository formulation, and include, for example, polyethylene glycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin, and semisynthetic glyceride.

[0440] It is preferable in the preparation of an injection that a liquid, an emulsion, and a suspension are sterilized and isotonic with blood. Any known diluents may be widely used as a diluent used in preparing the liquid, emulsion, and suspension, and include, for example, water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, poly-oxylated isostearyl alcohol, and polyoxyethylene sorbitan fatty acid esters. In this case, the medical formulation may comprise a sufficient amount of salt, glucose or glycerin to prepare the isotonic solution, and it may also comprise a common solubilizing agent, beffering agent, soothing agent, and the like as well as a colorant, preserving agent, perfume, flavoring agent, sweetening agent, and other medicinal products, if needed.

[0441] The amount of Compound (1) in the present invention contained in a medical formulation is not limited and may be optionally adjusted with a broad range; it is preferable that the medical formulation typically comprises 1 to 70% by weight of Compound (1) in the present invention.

[0442] A method of administering the medical formulation in the present invention is not limited and the medical formulation may be administered depending on various dosage forms, ages and genders of patients, disease states, and other conditions. For example, a tablet, pill, liquid, suspension, emulsion, granule, and capsule may be orally administered. An injection may be intravenously administered solely or in combination with a common replacement fluid such as glucose and amino acid, and if needed, may be solely administered intramuscularly, intradermally, subcutaneously or intraperitoneally. A suppository may be rectally administered.

[0443] A dosage amount of the medical formulation may be optionally adjusted depending on dosage regimens, ages and genders of patients, the extent of disease, and other conditions; it may be typically administered in 0.01 to 100 mg/kg, preferably 0.1 to 50 mg/kg, of body weight per day in a single dose or multiple doses.

[0444] The dosage amount may be varied on the basis of various conditions, and a lower dosage amount than the above may be sufficient in some cases and a higher dosage amount than the above may be necessary in other cases.

[0445] Compound (1) in the present invention has a specific efficacy in particular against tuberculosis bacteria such as mycobacteria, including tuberculosis bacteria genus, and non-tuberculous mycobacteria genus, and also has an excellent activity against multidrug-resistant tuberculosis bacteria. It not only shows an antibacterial activity in vitro but also expresses an antibacterial activity in oral administration in vivo due to its favorable distribution in lung tissues which are the primarily infected organ. Compound (1) in the present invention is thus useful as an agent for diagnosing,

preventing and/or treating tuberculosis.

[0446] Compound (1) in the present invention does not induce diarrhea as seen in known antibacterial agents with a wide spectrum for common bacteria such as gram-positive bacteria and gram-negative bacteria, and may become a medicinal substance which allows for a long-term administration.

[0447] Compound (1) in the present invention is effective for intracellular parasitic bacteria such as human-origin tuberculosis bacteria which is parasitic in macrophage and has in a bactericidal test a stronger bactericidal activity in a low concentration than existing antitubercular agents. It can be thus expected that the relapse rate in tuberculosis will be reduced, which eventually allows for a short-term chemotherapy.

[0448] Due to a lower toxicity than existing drugs, Compound (1) in the present invention can be also expected for long-term use in the treatment for latent tuberculosis.

[0449] Compound (1) in the present invention shows a low inhibitory activity against a drug-metabolizing enzyme and a low possibility for an enzyme induction of CYP3A. Due to limited concerns about drug interaction, it can be expected for a combination use with other therapeutic agents. The agents capable of the combination use include, for example, a first antituberculosis drug, a secondary antituberculosis drug, a quinolone antimicrobial, a macrolide antimicrobial, an oxazolidinone antimicrobial, a sufa drug, an anti-HIV drug, delamanid, bedaquiline, or PA-824, Sutezolid currently under development.

Examples

EXAMPLES

[0450] Hereinafter, the present invention is described in more detail with reference to Reference Examples, Examples and Test Examples. These Examples are not intended to limit the present invention, and they can be modified within the scope of the present invention.

[0451] The term "room temperature" in the following Examples is usually referred to a temperature between about 10 °C to about 35 °C. A ratio of mixed solvents is referred to a volume ratio, unless otherwise specified. % is referred to a weight %, unless otherwise specified.

[0452] ^{1}HNMR (proton nuclear magnetic resonance spectrum) was determined at room temperature by using a Fourier transform NMR (any one of Bruker AVANCE 300 (300 M Hz), Bruker AVANCE 500 (500 M Hz), Bruker AVANCE III 400 (400 M Hz) and Bruker AVANCE III 500 (500 M Hz)). In a silica gel column chromatography, when it is described as a basic, an aminopropylsilane-bonded silica gel was used.

Reference Example 1

(2E)-N-(2-Chloro-5-hydroxyphenyl)-3-ethoxyprop-2-enamide

[0453] To a solution of 3-amino-4-chlorophenol (10.35 g), pyridine (6.41 mL) in N,N-dimethylacetamide (90 mL), a solution of (2E)-3-ethoxyprop-2-enoyl chloride (10.9 g) in N,N-dimethylacetamide (10 mL) was added dropwise under ice-cooling, and the reaction mixture was stirred at the same temperature for 1 h. The reaction solution was poured into water, and the precipitate was collected on a filter to provide the title compound (10.7 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (3H, t, J = 7.1 Hz), 4.01 (2H, q, J = 7.1 Hz), 5.39 (1H, d, J = 12.1 Hz), 6.58 (1H, dd, J = 8.8 Hz, 2.9 Hz), 7.20 (1H, d, J = 8.9 Hz), 7.52 (1H, brs), 7.68 (1H, d, J = 12.1 Hz), 8.13 (1H, brs), 8.33 (1H, d, J = 2.9 Hz).

Reference Example 2

(2E)-3-Ethoxy-N-(2-fluoro-5-hydroxyphenyl)prop-2-enamide

[0454] Synthesized analogous to Reference Example 1.
^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (3H, t, J = 7.0 Hz), 3.99 (2H, q, J = 7.0 Hz), 5.36 (1H, d, J = 12.1 Hz), 6.49-6.55 (1H, m), 6.94 (1H, dd, J = 9.0 Hz, 8.9 Hz), 7.22 (1H, brs), 7.67 (1H, d, J = 12.1 Hz), 8.08 (1H, brs), 8.23-8.29 (1H, m).

Reference Example 3

(2E)-N-(2,3-Difluoro-5-methoxyphenyl)-3-ethoxyprop-2-enamide

[0455] Synthesized analogous to Reference Example 1.
^{1}HNMR ($CDCl_3$) δ ppm: 1.37 (3H, t, J = 6.9 Hz), 3.78 (3H, s), 3.97 (2H, q, J = 6.9 Hz), 5.35 (1H, d, J = 12.0 Hz), 6.38-6.46 (1H, m), 7.13 (1H, s), 7.66 (1H, d, J = 12.0 Hz), 7.82-7.87 (1H, m).

Reference Example 4

(2E)-N-(2,4-Dibromo-3-fluoro-5-methoxyphenyl)-3-ethoxyprop-2-enamide

[0456] Synthesized analogous to Reference Example 1.
^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (3H, t, J = 7.2 Hz), 3.93 (3H, s), 4.00 (2H, q, J = 7.2 Hz), 5.36 (1H, d, J = 12.0 Hz), 7.47 (1H, s), 7.67 (1H, d, J = 12.0 Hz), 8.19 (1H, d, J = 2.1 Hz).

Reference Example 5

8-Fluoro-5-hydroxyquinolin-2(1H)-one

[0457] To conc. hydrochloric acid (270 mL), a solution of (2E)-3-ethoxy-N-(2-fluoro-5-hydroxyphenyl)prop-2-enamide (27.0 g) in methanol (135 mL) was added dropwise at 65 °C, then the reaction mixture was stirred at 85 °C for 30 min. The reaction solution was poured into water, and the precipitate was collected on a filter to provide the title compound (19.2 g).
^{1}HNMR (DMSO-d6) δ ppm: 6.46 (1H, d, J = 9.8 Hz), 6.52 (1H, dd, J = 8.8 Hz, 3.7 Hz), 7.21 (1H, dd, J = 10.9 Hz, 8.8 Hz), 8.02 (1H, dd, J = 9.8 Hz, 1.6 Hz), 10.33 (1H, brs), 11.60 (1H, brs).

Reference Example 6

8-Chloro-5-hydroxyquinolin-2(1H)-one

[0458] Synthesized analogous to Reference Example 5.
^{1}HNMR (DMSO-d6) δ ppm: 6.47 (1H, d, J = 9.7 Hz), 6.62 (1H, d, J = 8.6 Hz), 7.42 (1H, d, J = 8.6 Hz), 8.05 (1H, d, J = 9.8 Hz), 10.68 (1H, s), 10.75 (1H, brs).

Reference Example 7

7,8-Difluoro-5-methoxyquinolin-2(1H)-one

[0459] To conc. sulfuric acid (17 mL) was added (2E)-N-(2,3-difluoro-5-methoxyphenyl)-3-ethoxyprop-2-enamide (1.66 g) at 70-80 °C, and the reaction mixture was stirred for 5 min. After the reaction solution was added to ice water, the precipitate was collected on a filter to provide the title compound (1.0 g). ^{1}HNMR (DMSO-d6) δ ppm: 3.90 (3H, s), 6.45 (1H, d, J = 9.9 Hz), 6.90 (1H, dd, J = 12.9 Hz, 6.0 Hz), 7.97 (1H, dd, J = 9.9 Hz, 1.5 Hz), 12.00 (1H, s).

Reference Example 8

6,8-Dibromo-7-fluoro-5-methoxyquinolin-2(1H)-one

[0460] Synthesized analogous to Reference Example 7.
^{1}HNMR (DMSO-d6) δ ppm: 3.91 (3H, s), 6.61 (1H, d, J = 9.5 Hz), 8.02 (1H, d, J = 9.5 Hz), 10.96-11.10 (1H, brs).

Reference Example 9

7-Fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0461] Under hydrogen atmosphere, a suspension of 7-fluoro-5-methoxyquinolin-2(1H)-one (29.0 g) and 10 % palladium on carbon (10 g) in acetic acid (600 mL) was stirred at 105 °C for 2.5 h. Insoluble materials were filtered off and the filtrate was concentrated. The residue was washed with water and dried to provide the title compound (25.7 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.62 (2H, m), 2.89 (2H, t, J = 7.5 Hz), 3.82 (3H, s), 6.15 (1H, dd, J = 9.0 Hz, 2.1 Hz), 6.32 (1H, dd, J = 10.8 Hz, 2.1 Hz), 7.92 (1H, brs).

Reference Example 10

7,8-Difluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0462] Synthesized analogous to Reference Example 9.

^{1}HNMR ($CDCl_3$) δ ppm: 2.58-2.64 (2H, m), 2.90-2.96 (2H, m), 3.79 (3H, s), 6.37 (1H, dd, J = 12.0 Hz, 6.3 Hz), 7.51 (1H, brs).

Reference Example 11

7-Amino-8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0463] A mixture of 7-amino-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (0.90 g) and 48 % hydrogen bromide in water (18 mL) was heated to reflux for 20 h. The precipitate was collected on a filter, and washed with 48 % hydrogen bromide in water. The obtained solid was stirred in saturated aqueous sodium hydrogencarbonate, and the precipitated crystal was collected on a filter to provide the title compound (0.68 g).
^{1}HNMR (DMSO-d6) δ ppm: 2.30-2.36 (2H, m), 2.61-2.66 (2H, m), 4.90 (2H, brs), 5.90 (1H, d, J = 7.5 Hz), 8.90 (1H, brs), 9.60 (1H, brs).

Reference Example 12

7-Fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0464] Synthesized analogous to Reference Example 11.
^{1}HNMR (DMSO-d6) δ ppm: 2.37-2.42 (2H, m), 2.71 (2H, t, J = 7.5 Hz), 6.14 (1H, dd, J = 10.2 Hz, 2.4 Hz), 6.23 (1H, dd, J = 10.8 Hz, 2.4 Hz), 9.01-11.2 (2H, m).

Reference Example 13

7,8-Difluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0465] Synthesized analogous to Reference Example 11.
^{1}HNMR (DMSO-d6) δ ppm: 2.39-2.44 (2H, m), 2.71-2.77 (2H, m), 6.37 (1H, dd, J = 12.3 Hz, 6.6 Hz), 9.86 (1H, brs), 10.16 (1H, s).

Reference Example 14

8-Fluoro-5-hydroxy-7-methyl-3,4-dihydroquinolin-2(1H)-one

[0466] Synthesized analogous to Reference Example 11.
^{1}HNMR (DMSO-d6) δ ppm: 2.11 (3H, d, J = 1.8 Hz), 2.36-2.44 (2H, m), 2.75 (2H, t, J = 7.2 Hz), 6.28 (1H, d, J = 6.3 Hz), 9.25 (1H, s), 9.77 (1H, s).

Reference Example 15

8-Chloro-7-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0467] Synthesized analogous to Reference Example 11.
^{1}HNMR (DMSO-d6) δ ppm: 2.41-2.50 (2H, m), 2.72-2.82 (2H, m), 6.47 (1H, d, J = 11.1 Hz), 9.48 (1H, brs), 10.22 (1H, brs).

Reference Example 16

7-Fluoro-5-hydroxy-8-methyl-3,4-dihydroquinolin-2(1H)-one

[0468] Synthesized analogous to Reference Example 11.
^{1}HNMR (DMSO-d6) δ ppm: 1.99 (3H, d, J = 1.8 Hz), 2.34-2.40 (2H, m), 2.68-2.74 (2H, m), 6.27 (1H, d, J = 11.4 Hz), 9.45 (1H, s), 9.69 (1H, s).

Reference Example 17

8-Ethyl-7-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0469] To a solution of 8-ethyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (150 mg) in dichloromethane (5 mL), a solution of 1 N boron tribromide in dichloromethane (2.02 mL) was added dropwise under ice-cooling, and the reaction

mixture was stirred at room temperature overnight. Methanol (1 mL) was added to the reaction solution, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (ethyl acetate) to provide the title compound (100 mg).
^{1}HNMR (DMSO-d6) δ ppm: 0.96 (3H, t, J = 7.5 Hz), 2.34-2.39 (2H, m), 2.53-2.57 (2H, m), 2.67-2.73 (2H, m), 6.25 (1H, d, J = 11.7 Hz), 9.50 (1H, s), 9.71 (1H, s).

Reference Example 18

6,8-Difluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0470] To a solution of 5-hydroxy-3,4-dihydroquinolin-2(1H)-one (0.50 g) in 1,2-dichloroethane (10 mL) was added fluoropyridinium triflate (2.27 g), and the reaction mixture was heated to reflux overnight. The reaction solution was concentrated, the water was added to the residue, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (38 mg).
^{1}HNMR (DMSO-d6) δ ppm: 2.44 (2H, t, J = 8.0 Hz), 2.86 (2H, t, J = 7.5 Hz), 7.10 (1H, t, J = 10.7 Hz), 9.57 (1H, brs), 9.97 (1H, brs).

Reference Example 19

8-Chloro-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

[0471] A solution of 8-chloro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (2.00 g), 3,4-dihydro-2H-pyran (2.55 g) and pyridinium p-toluenesulfonate (0.51 g) in dichloromethane (40 mL) was stirred at room temperature overnight. The reaction solution was washed with brine, dried over sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.74 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.48-1.78 (3H, m), 1.79-2.08 (3H, m), 2.62 (2H, t, J = 7.7 Hz), 2.91-3.13 (2H, m), 3.56-3.67 (1H, m), 3.79-3.90 (1H, m), 5.34-5.45 (1H, m), 6.78 (1H, d, J = 9.0 Hz), 7.15 (1H, d, J = 9.0 Hz), 7.38 (1H, brs).

Reference Example 20

8-Fluoro-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

[0472] Synthesized analogous to Reference Example 19.
^{1}HNMR ($CDCl_3$) δ ppm: 1.57-1.75 (3H, m), 1.82-1.93 (2H, m), 1.93-2.03 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.96-3.10 (2H, m), 3.58-3.66 (1H, m), 3.82-3.90 (1H, m), 5.35 (1H, t, J = 3.3 Hz), 6.74 (1H, dd, J = 9.1 Hz, 4.2 Hz), 6.89 (1H, t, J = 9.6 Hz), 7.90 (1H, brs).

Reference Example 21

7-Bromo-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0473] To a solution of 8-fluoro-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinol in-2(1H)-one (29.8 g) in methanol/water (3/1) (900 mL), copper (II) bromide (62.1 g) was added, and the reaction mixture was heated to reflux for 3 h. Water was added to the reaction solution, then which was ice-cooled to collect the precipitate on a filter. To the resultant precipitate was added ethyl acetate (1000 mL), and after refluxing for a while, insoluble materials were filtered off. The filtrate was concentrated and the precipitate was collected on a filter to provide the title compound (21.4 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.59-2.67 (2H, m), 2.90-2.95 (2H, m), 3.81 (3H, s), 6.67 (1H, d, J = 5.1 Hz), 7.71 (1H, brs).

Reference Example 22

7-Amino-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0474] Under nitrogen atmosphere, a solution of benzophenone imine (31.3 mL), 7-bromo-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (21.4 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (3.65 g), sodium tert-butoxide (19.5 g) and tris(dibenzylideneacetone)dipalladium (1.79 g) in toluene (250 mL) was heated to reflux for 2 h. The reaction solution was filtered over Celite, water (150 mL) and 6 N hydrochloric acid (75 mL) were added to the filtrate and the reaction

mixture was stirred at 80 °C for 30 min. The reaction solution was cooled to room temperature, poured into aqueous sodium hydroxide, and the precipitate was collected on a filter to provide the title compound (13.0 g).
^{1}HNMR (DMSO-d6) δ ppm: 2.36 (2H, t, J = 7.5 Hz), 2.67 (2H, t, J = 7.5 Hz), 3.66 (3H, s), 5.04 (2H, brs), 6.05 (1H, d, J = 6.9 Hz), 9.76 (1H, brs).

Reference Example 23

8-Fluoro-5-methoxy-7-methyl-3,4-dihydroquinolin-2(1H)-one

[0475] Under nitrogen atmosphere, a solution of 7-bromo-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (50 mg), methylboronic acid (16.4 mg), 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane adduct (14.9 mg) and tripotassium phosphate (77 mg) in 1,4-dioxane (2 mL) was stirred at 100 °C for 15 h. To the reaction solution was added ethyl acetate, and insoluble materials were filtered off. The filtrate was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane -> dichloromethane/methanol) to provide the title compound (34 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.26 (3H, d, H = 1.8 Hz), 2.55-2.65 (2H, m), 2.93 (2H, t, J = 7.7 Hz), 3.79 (3H, s), 6.32 (1H, d, J = 5.7 Hz), 8.14 (1H, brs).

Reference Example 24

8-Fluoro-7-hydroxy-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0476] To a solution of 8-fluoro-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinol in-2(1H)-one (98 mg) in ethanol (7 mL), hydroxylamine hydrochloride (32.8 mg) and sodium hydroxide (24.4 mg) were added, and the reaction mixture was stirred at 40 °C for 72 h. After the solvent of the reaction solution was distilled off, to the residue was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (20 mg).
^{1}HNMR (DMSO-d6) δ ppm: 2.36-2.41 (2H, m), 2.68-2.73 (2H, m), 3.69 (3H, s), 6.20 (1H, d, J = 6.6 Hz), 9.72 (1H, brs), 9.90 (1H, brs).

Reference Example 25

8-Fluoro-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroqui nolin-2(1H)-one

[0477] Under nitrogen atmosphere, a solution of 8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (50 g), bis(pinacolato)diboron (98 g), 4,4'-di-tert-butyl-2,2'-dipyridyl (5.50 g) and di-μ-methoxobis(1,5-cyclooctadiene)diiridium (I) (6.79 g) in tetrahydrofuran (900 mL) was heated to reflux for 2.5 h. After cooling to room temperature, the reaction solution was concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (44.5 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.35 (12H, s), 2.57-2.63 (2H, m), 2.94-3.00 (2H, m), 3.84 (3H, s), 6.79 (1H, d, J = 3.9 Hz), 7.50 (1H, brs).

Reference Example 26

7-Ethoxy-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0478] To a solution of 8-fluoro-7-hydroxy-5-methoxy-3,4-dihydroquinolin-2(1H)-one (1.1 g) in N,N-dimethylformamide (20 mL) was added potassium carbonate (0.864 g) and ethyl iodide (0.505 mL), and the reaction mixture was stirred at room temperature for 3 h. The reaction solution was poured into water, and the solid was collected on a filter to provide the title compound (1.05 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.33 (3H, t, J = 6.9 Hz), 2.40 (2H, t, J = 7.5 Hz), 2.75 (2H, t, J = 7.5 Hz), 3.77 (3H, s), 4.10 (2H, q, J = 6.9 Hz), 6.43 (1H, d, J = 6.9 Hz), 10.00 (1H, brs).

Reference Example 27

7-Ethoxy-8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0479] Synthesized analogous to Reference Example 17.
^{1}HNMR (DMSO-d6) δ ppm: 1.31 (3H, t, J = 6.9 Hz), 2.37-2.42 (2H, m), 2.70-2.74 (2H, m), 3.98 (2H, q, J = 6.9 Hz), 6.20 (1H, d, J = 6.9 Hz), 9.34 (1H, s), 9.82 (1H, brs).

Reference Example 28

8-Bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0480] To a solution of 7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (10 g) in acetic acid (600 mL), bromine (2.76 mL) was added dropwise, and then the reaction mixture was stirred at room temperature for 20 min. The reaction solution was poured into water, and the precipitate was collected on a filter to provide the title compound (8.31 g).
^{1}HNMR (DMSO-d6) δ ppm: 2.42-2.53 (2H, m), 2.76-2.86 (2H, m), 3.81 (3H, s), 6.82 (1H, d, J = 11.1 Hz), 9.17 (1H, brs).

Reference Example 29

8-Chloro-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0481] Under argon atmosphere, a solution of 8-bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (11.3 g) and copper (I) chloride (8.56 g) in N-methyl-2-pyrrolidone (300 mL) was stirred at 130 °C for 20 h. After cooling to room temperature, the reaction mixture was poured into 5 % ammonium chloride aqueous solution, and the precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (basic silica gel; dichloromethane) to provide the title compound (7.31 g).
^{1}HNMR (DMSO-d6) δ ppm: 2.41-2.53 (2H, m), 2.76-2.86 (2H, m), 3.80 (3H, s), 6.82 (1H, d, J = 11.7 Hz), 9.60 (1H, brs).

Reference Example 30

7-Fluoro-5-methoxy-8-methyl-3,4-dihydroquinolin-2(1H)-one

[0482] Under nitrogen atmosphere, a solution of 8-bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (1.23 g), methylboronic acid (0.81 g), potassium phosphate (2.86 g) and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane adduct (0.73 g) in 1,4-dioxane (25 mL) was stirred at 110 °C for 1 h. The reaction solution was cooled to room temperature, concentrated, and then purified by silica gel column chromatography (dichloromethane/methanol). The obtained material was treated with activated charcoal, filtrated and concentrated to provide the title compound (410 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.06 (3H, d, J = 1.5 Hz), 2.54-2.60 (2H, m), 2.87-2.93 (2H, m), 3.80 (3H, s), 6.34 (1H, d, J = 11.4 Hz), 7.30-7.40 (1H, brs).

Reference Example 31

7-Fluoro-5-methoxyquinolin-2(1H)-one

[0483] Under hydrogen atmosphere, a suspension of 6,8-dibromo-7-fluoro-5-methoxyquinolin-2(1H)-one (40.6 g), sodium hydroxide (9.13 g) and 20 % palladium hydroxide on carbon (4 g) in N,N-dimethylacetamide (800 mL) was stirred at 45 °C for 2 h. Insoluble materials were filtered off by using Celite, the filtrate was poured into water and neutralized with 6 N hydrochloric acid (57.1 mL). The precipitate was collected on a filter to provide the title compound (18.2 g).
^{1}HNMR (DMSO-d6) δ ppm: 3.92 (3H, s), 6.37 (1H, d, J = 10.0 Hz), 6.63-6.72 (2H, m), 7.96 (1H, d, J = 10.0 Hz), 11.81 (1H, s).

Reference Example 32

8-Ethenyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0484] Under nitrogen atmosphere, a solution of 8-bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (100 mg), 4,4,5,5-tetramethyl-2-vinyl-1,3,3-dioxaborolane (112 mg), sodium carbonate (116 mg) and tetrakis(triphenylphosphine)palladium (42.2 mg) in 1,4-dioxane/water (5/1) (2 mL) was stirred at 100 °C overnight. The reaction solution was

cooled to room temperature, concentrated, and then the residue was purified by silica gel chromatography (hexane/ethyl acetate) to provide the title compound (50 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.61 (2H, m), 2.86-2.92 (2H, m), 3.82 (3H, s), 5.56-5.65 (2H, m), 6.36 (1H, d, J = 12.0 Hz), 6.45-6.55 (1H, m), 7.66 (1H, s).

Reference Example 33

8-Ethyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

[0485] Under nitrogen atmosphere, to a solution of 8-ethenyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (200 mg) in acetic acid (4 mL) was added 10 % palladium on carbon (50 mg), and the reaction mixture was stirred at room temperature for 10 min under hydrogen atmosphere. The reaction solution was filtered over Celite and the solvents of the filtrate were distilled off. Water was added to the obtained residue, and the precipitate was collected on a filter to provide the title compound (150 mg).
^{1}HNMR (CDC13) δ ppm: 1.13 (3H, t, J = 7.6 Hz), 2.51-2.60 (4H, m), 2.87-2.92 (2H, m), 3.79 (3H, s), 6.34 (1H, d, J = 11.6 Hz), 7.39 (1H, brs).

Reference Example 34

5-(Benzyloxy)-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[0486] A solution of 7-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (500 mg), potassium carbonate (496 mg) and benzyl bromide (0.39 mL) in N,N-dimethylformamide (5 mL) was stirred at room temperature for 1 h. The reaction solution was poured into cold-water, and the precipitate was collected on a filter, washed with water, ethanol and diethyl ether to provide the title compound (748 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.62 (2H, m), 2.92-2.97 (2H, m), 5.05 (2H, s), 6.17 (1H, dd, J = 9.0 Hz, 2.1 Hz), 6.39 (1H, dd, J = 10.8 Hz, 2.1 Hz), 7.30-7.45 (5H, m), 7.99 (1H, s).

Reference Example 35

5-(Benzyloxy)-8-bromo-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[0487] Synthesized analogous to Reference Example 28.
^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.61 (2H, m), 2.95-3.00 (2H, m), 5.04 (2H, s), 6.49 (1H, d, J = 10.2 Hz), 7.30-7.45 (5H, m), 7.44 (1H, s).

Reference Example 36

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0488] Synthesized analogous to Reference Example 34.
^{1}HNMR (DMSO-d6) δ ppm: 2.28 (6H, s), 2.42-2.49 (2H, m), 2.85-2.91 (2H, m), 4.99 (2H, s), 6.66 (1H, dd, J = 9.0 Hz, 3.9 Hz), 6.95-7.04 (4H, m), 10.01 (1H, s).

Reference Example 37

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-7-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0489] Under nitrogen atmosphere, a solution of 5-[(3,5-dimethylbenzyl)oxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one (1.0 g), bis(pinacolato)diboron (1.27 g), 4,4'-di-tert-butyl-2,2'-dipyridyl (0.07 g) and di-μ-methoxobis(1,5-cyclooctadiene)diiridium (I) (0.09 g) in tetrahydrofuran (20 mL) was heated to reflux for 10 h. After the reaction solution was allowed to cool to room temperature, methanol (20 mL) followed by Oxone (Registered trade mark) (2.46 g) in water (20 mL) were added, and the reaction mixture was stirred at room temperature for 10 min. To the reaction solution was added water, and the precipitated crystal was collected on a filter, then washed with water, ethanol and diethyl ether to provide the title compound (500 mg).
^{1}HNMR (DMSO-d6) δ ppm: 2.28 (6H, s), 2.38-2.43 (2H, m), 2.74-2.79 (2H, m), 4.91 (2H, s), 6.28 (1H, d, J = 7.2 Hz), 6.96 (1H, s), 7.02 (2H, s), 9.72 (1H, s), 9.91 (1H, s).

Reference Example 38

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydro quinolin-2(1H)-one

[0490] A mixture of 5-[(3,5-dimethylbenzyl)oxy]-8-fluoro-7-hydroxy-3,4-dihydroquinolin-2(1H)-one (100 mg), 3,4-dihydro-2H-pyran (1 mL) and p-toluenesulfonic acid (10.9 mg) was stirred at room temperature for 30 min, and was extracted with saturated aqueous sodium hydrogencarbonate and ethyl acetate. The solvent of the organic layer was distilled off, and then the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (106 mg, 84 %).
^{1}HNMR (DMSO-d6) δ ppm: 1.50-1.90 (6H, m), 2.27 (6H, s), 2.39-2.43 (2H, m), 2.77-2.82 (2H, m), 3.31-3.54 (1H, m), 3.75-3.83 (1H, m), 4.95 (2H, s), 5.48 (1H, s),m 6.65 (1H, d, J = 6.7 Hz), 6.95 (1H, s), 7.03 (2H, s), 10.00 (1H, s).

Reference Example 39

5-(Benzyloxy)-7-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro quinolin-2(1H)-one

[0491] Under nitrogen atmosphere, a solution of 5-(benzyloxy)-8-bromo-7-fluoro-3,4-dihydroquinolin-2(1H)-one (1.0 g), bis(pinacolato)diboron (1.45 g), potassium acetate (0.84 g) and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex (0.12 g) in DMSO (10 mL) was stirred at 110 °C for 3.5 h. The reaction solution was allowed to cool to room temperature, and was extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (850 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.31 (12H, s), 2.41-2.50 (2H, m), 2.78-2.84 (2H, m), 5.18 (2H, s), 6.65 (1H, d, J = 12.0 Hz), 7.33-7.46 (5H, m), 9.19 (1H, s).

Reference Example 40

5-(Benzyloxy)-7-fluoro-8-hydroxy-3,4-dihydroquinolin-2(1H)-one

[0492] To a solution of 5-(benzyloxy)-7-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroqui nolin-2(1H)-one (800 mg) in methanol (6 mL) was added Oxone (Registered trade mark) (1.86 g) in water (6 mL) under water-cooling and the reaction mixture was stirred at room temperature for 5min. To the reaction solution was added water, the precipitate was collected on a filter, and washed with water. The obtained crude crystal was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (300 mg).
^{1}HNMR (CD_3CN) δ ppm: 2.46-2.52 (2H, m), 2.87-2.93 (2H, m), 5.04 (2H, s), 6.49-6.56 (1H, m), 6.32 (1H, s), 7.34-7.46 (5H, m), 7.80 (1H, s).

Reference Example 41

5-(Benzyloxy)-7-fluoro-8-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H) -one

[0493] Synthesized analogous to Reference Example 38.
^{1}HNMR ($CDCl_3$) δ ppm: 1.5-2.0 (4H, m), 2.45-2.55 (2H, m), 2.80-2.90 (1H, m), 2.95-3.05 (1H, m), 3.45-3.55 (2H, m), 4.00-4.10 (2H, m), 4.90-4.92 (1H, m), 5.00 (2H, s), 6.39 (1H, d, J = 12.3 Hz), 7.40-7.45 (5H, m), 8.18 (1H, s).

Reference Example 42

8-Fluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0494] To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-[(4-methoxybenzyl)oxy]-3,4-dihydroquinolin-2(1H)-one (2.17 g) in ethanol/ethyl acetate (1:1) (40 mL) was added 20 % palladium hydroxide on carbon (wetted with 50 % water) (0.2 g) and stirred at room temperature for 1.5 h under hydrogen atmosphere. The reaction solution was filtered and the solvents of the filtrate were distilled off. The residue was washed with hexane to provide the title compound (1.39 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.61-2.69 (2H, m), 2.81-2.88 (2H, m), 3.74 (3H, s), 5.21 (2H, brs), 5.31 (1H, s), 6.43 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.71-6.78 (3H, m), 7.09-7.14 (2H, m).

Reference Example 43

8-Fluoro-1-(4-methoxybenzyl)-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin -2(1H)-one

[0495] To a stirred solution of 8-fluoro-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one (8.8 g) in N,N-dimethylformamide (100 mL) was added 60 % sodium hydride (1.46 g) at 0 °C and stirred at the same temperature for 20 min. 4-Methoxybenzyl chloride (5.40 mL) was added at room temperature and stirred for 5 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (12.7 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.56-1.72 (3H, m), 1.80-1.91 (2H, m), 1.91-2.03 (1H, m), 2.64 (2H, t, J = 7.2 Hz), 2.82-2.98 (2H, m), 3.57-3.63 (1H, m), 3.74 (3H, s), 3.80-3.88 (1H, m), 5.18 (1H, d, J = 15.3 Hz), 5.26 (1H, d, J = 15.3 Hz), 5.27-5.30 (1H, m), 6.73-6.84 (4H, m), 7.10-7.15 (2H, m).

Reference Example 44

8-Chloro-1-(4-methoxybenzyl)-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinoli n-2(1H)-one

[0496] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.52-2.03 (6H, m), 2.50-2.60 (2H, m), 2.67-2.87 (2H, m), 3.54-3.65 (1H, m), 3.73 (3H, s), 3.75-3.88 (1H, m), 5.30-5.44 (3H, m), 6.68-6.76 (2H, m), 6.82 (1H, d, J = 9.0 Hz), 7.03-7.15 (3H, m).

Reference Example 45

8-Chloro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0497] To a solution of 8-chloro-1-(4-methoxybenzyl)-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2 (1H)-one (43.7 g) in ethanol (450 mL) was added p-toluenesulfonic acid pyridinium (5.47 g) and the reaction mixture was stirred at 80 °C for 1 h. The reaction solution was poured into ice water, the solution was extracted with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (33.75 g, quant.).
^{1}HNMR (DMSO-d6) δ ppm: 2.42-2.54 (2H, m), 2.62-2.72 (2H, m), 3.67 (3H, s), 5.26 (2H, brs), 6.58 (1H, d, J = 8.7 Hz), 6.76 (2H, d, J = 8.7 Hz), 6.98-7.05 (3H, m), 9.79 (1H, brs).

Reference Example 46

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-1-(4-methoxybenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

[0498] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.67 (4H, m), 1.81-1.88 (2H, m), 2.31 (6H, s), 2.56-2.61 (2H, m), 2.80-2.85 (2H, m), 3.54-3.59 (1H, m), 3.74 (3H, s), 3.84-3.92 (1H, m), 4.87 (2H, s), 5.20 (2H, s), 5.28-5.30 (1H, m), 6.60 (1H, d, J = 6.3 Hz), 6.74-6.77 (2H, m), 6.95-6.99 (3H, m), 7.12 (2H, d, J = 8.7 Hz).

Reference Example 47

2,8-Dichloroquinolin-5-ol

[0499] To a solution of 8-chloro-5-hydroxyquinolin-2(1H)-one (13.0 g) in N,N-dimethylformamide (150 mL), thionyl chloride (14.52 mL) was added dropwise, and the reaction mixture was stirred at 80 °C for 2 h. The reaction solution was allowed to cool to room temperature, poured into ice water, the precipitate was collected on a filter and washed with water. The obtained crystal was dissolved in ethyl acetate, dried over anhydrous sodium sulfate, and then the solvent was distilled of to provide the title compound (9.8 g).
^{1}HNMR ($CDCl_3$) δ ppm: 6.97 (1H, d, J = 8.3 Hz), 7.60 (1H, d, J = 8.8 Hz), 7.79 (1H, d, J = 8.3 Hz), 8.57 (1H, d, J = 8.8 Hz), 11.03 (1H, brs).

Reference Example 48

2-Chloro-8-fluoroquinolin-5-ol

[0500] Synthesized analogous to Reference Example 47.
^{1}HNMR (DMSO-d6) δ ppm: 6.88-6.94 (1H, m), 7.45-7.52 (1H, m), 7.56 (1H, d, J = 8.5 Hz), 8.47-8.55 (1H, m), 10.74 (1H, brs).

Reference Example 49

2-Chloro-8-fluoro-5-(tetrahydro-2H-pyran-2-yloxy)quinoline

[0501] Synthesized analogous to Reference Example 19.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.83 (3H, m), 1.93-2.15 (3H, m), 3.64-3.69 (1H, m), 3.84-3.91 (1H, m), 5.57 (1H, t, J = 3.1 Hz), 7.13 (1H, dd, J = 8.7 Hz, 3.7 Hz), 7.33 (1H, dd, J = 10.2 Hz, 8.7 Hz), 7.43 (1H, d, J = 8.8 Hz), 8.53 (1H, dd, J = 8.8 Hz, 1.6 Hz).

Reference Example 50

8-Fluoro-2-methoxyquinolin-5-ol

[0502] To a solution of 2-chloro-8-fluoro-5-(tetrahydro-2H-pyran-2-yloxy)quinoline (2.65 g) in N,N-dimethylformamide (25 mL), sodium methoxide (5M methanol solution) (5.6 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 10 h. The reaction solution was poured into water, neutralized with acetic acid, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was dissolved into methanol (25 mL), 5 N hydrochloric acid (2 mL) was added thereto and the reaction mixture was stirred at room temperature for 5 h. To the mixture were added saturated aqueous sodium hydrogencarbonate (150 mL) and water (150 mL), the reaciton mixture was stirred at room temperature for 1 h, and the precipitate was collected on a filter to provide the title compound (1.61 g).
^{1}HNMR ($CDCl_3$) δ ppm: 4.11 (3H, s), 5.38 (1H, brs), 6.60 (1H, dd, J = 8.4 Hz, 3.5 Hz), 6.93 (1H, d, J = 9.1 Hz), 7.16 (1H, dd, J = 10.6 Hz, 8.4 Hz), 8.34 (1H, dd, J = 9.1 Hz, 1.7 Hz).

Reference Example 51

2,8-Dichloro-5-(tetrahydro-2H-pyran-2-yloxy)quinoline

[0503] Synthesized analogous to Reference Example 19.
^{1}HNMR ($CDCl_3$) δ ppm: 1.72-1.81 (2H, m), 1.93-2.14 (4H, m), 3.63-3.68 (1H, m), 3.82-3.87 (1H, m), 5.62 (1H, t, J = 3.0 Hz), 7.15 (1H, d, J = 8.5 Hz), 7.43 (1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 8.5 Hz), 8.56 (1H, d, J = 8.7 Hz).

Reference Example 52

8-Chloro-2-methoxyquinolin-5-ol

[0504] Synthesized analogous to Reference Example 50.
^{1}HNMR ($CDCl_3$) δ ppm: 4.14 (3H, s), 5.70 (1H, brs), 6.65 (1H, d, J = 8.2 Hz), 6.93 (1H, d, J = 9.0 Hz), 7.54 (1H, d, J = 8.2 Hz), 8.37 (1H, d, J = 9.0 Hz).

Reference Example 53

8-Fluoro-1-(4-methoxybenzyl)-5-[(4-methoxybenzyl)oxy]-3,4-dihydroquinolin-2(1H)-one

[0505] Under argon atmosphere, to a solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (10.0 g) in N,N-dimethylformamide (100 mL) was added sodium hydride (55 % in oil) (5.14 g) at 0 °C, the reaction mixture was stirred at the same temperature for 30 min, and 4-methoxybenzyl chloride (16.0 mL) was added thereto dropwise. The reaction mixture was stirred at the same temperature for 1.5 h, then at room temperature for 7 h. To the reaction solution was added ammonium chloride aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled of to provide the

title compound (23.2 g, quant.).
^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.63 (2H, m), 2.82-2.89 (2H, m), 3.74 (3H, s), 3.82 (3H, s), 4.92 (2H, s), 5.22 (2H, brs), 6.59 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 6.88-6.93 (2H, m), 7.09-7.14 (2H, m), 7.27-7.32 (2H, m).

Reference Example 54

7,8-Difluoro-1-(4-methoxybenzyl)-5-[(4-methoxybenzyl)oxy]-3,4-dihydroquinolin-2 (1H)-one

[0506] Synthesized analogous to Reference Example 53.
^{1}HNMR ($CDCl_3$) δ ppm: 2.57-2.63 (2H, m), 2.79-2.85 (2H, m), 3.75 (3H, s), 3.82 (3H, s), 4.88 (2H, s), 5.23 (2H, brs), 6.51 (1H, dd, J = 11.7 Hz, 6.1 Hz), 6.75-6.80 (2H, m), 6.88-6.93 (2H, m), 7.09-7.15 (2H, m), 7.27-7.31 (2H, m).

Reference Example 55

7,8-Difluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0507] Synthesized analogous to Reference Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 2.61-2.68 (2H, m), 2.78-2.83 (2H, m), 3.75 (3H, s), 5.22 (2H, brs), 5.40-6.20 (1H, broad signal), 6.34-6.42 (1H, m), 6.74-6.80 (2H, m), 7.08-7.14 (2H, m).

Reference Example 56

8-Fluoro-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[0508] Under argon atmosphere, to a suspension of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (5.0 g) and potassium carbonate (5.72 g) in N,N-dimethylformamide (50 mL), chloromethyl methyl sulfide (3.32 mL) was added dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 36 h. To the reaction solution was added water, and the precipitate was collected on a filter to provide the title compound (4.95 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.26 (3H, s), 2.60-2.25 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 5.15 (2H, s), 6.54 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.93 (1H, dd, J = 9.7 Hz, 9.2 Hz), 7.54 (1H, brs).

Reference Example 57

8-Fluoro-1-(4-methoxybenzyl)-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[0509] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 2.22 (3H, s), 2.61-2.67 (2H, m), 2.86-2.92 (2H, m), 3.74 (3H, s), 5.10 (2H, s), 5.22 (2H, brs), 6.59 (1H, dd, J = 9.1 Hz, 3.5 Hz), 6.73-6.78 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

Reference Example 58

5-(Chloromethoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0510] To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one (5.48 g) in dichloromethane (100 mL), sulfuryl chloride (1.22 mL) was added dropwise under ice-cooling, and the reaction mixture was stirred at the same temperature for 1 h. The solvent was distilled off to provide the title compound (5.3 g, quant.).
^{1}HNMR ($CDCl_3$) δ ppm: 2.60-2.66 (2H, m), 2.84-2.91 (2H, m), 3.74 (3H, s), 5.22 (2H, brs), 5.84 (2H, s), 6.74-6.78 (2H, m), 6.82 (1H, dd, J = 9.2 Hz, 3.5 Hz), 6.90 (1H, dd, J = 12.4 Hz, 9.2 Hz), 7.09-7.14 (2H, m).

Reference Example 59

1-tert-Butyl 4-ethyl 4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-1,4-dicarboxylate

[0511] Under argon atmosphere, to a solution of piperidine-1,4-dicarboxylic acid 4-ethyl 1-tert-butyl (9.75 g) in tetrahydrofuran (90 mL), lithium diisopropylamide (2 M heptane/tetrahydrofuran/ethylbenzene solution) (19.7 mL) was added

dropwise at -70 °C, the reaction mixture was stirred at the same temperature for 1 h, a solution of 5-(chloromethoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (5.3 g) in tetrahydrofuran (50 mL) was added dropwise, and the reaction mixture was stirred at -40 °C for 7 h. To the reaction solution was added aqueous saturated ammonium chloride solution, the reaction was allowed to warm to room temperature, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (6.31 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.46 (9H, s), 1.48-1.58 (2H, m), 2.17-2.24 (2H, m), 2.57-2.63 (2H, m), 2.76-2.83 (2H, m), 2.83-3.15 (2H, m), 3.74 (3H, s), 3.79-4.04 (4H, m), 4.17 (2H, q, J = 7.1 Hz), 5.21 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.77 (2H, m), 6.81 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.14 (2H, m).

Reference Example 60

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) piperidine-4-carboxylate

[0512] To a solution of 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) piperidine-1,4-dicarboxylic acid 4-ethyl 1-tert-butyl (6.31 g) in ethyl acetate (60 mL) was added 4 N hydrochloric acid/ethyl acetate (60 mL), and the reaction mixture was stirred at room temperature for 3 h. The solvent was distilled off and to the residue was added ethyl acetate and water, the reaction mixture was made basic with aqueous sodium hydroxide, and then extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (5.37 g, quant.).
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.51-1.59 (2H, m), 1.87 (1H, brs), 2.19-2.27 (2H, m), 2.57-2.63 (2H, m), 2.74-2.84 (4H, m), 2.96-3.03 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 5.21 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.81 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.15 (2H, m).

Reference Example 61

8-Chloro-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[0513] Synthesized analogous to Reference Example 56.
^{1}HNMR ($CDCl_3$) δ ppm: 2.26 (3H, s), 2.62 (2H, t, J = 7.7 Hz), 3.01 (2H, t, J = 7.7 Hz), 5.17 (2H, s), 6.59 (1H, d, J = 8.9 Hz), 7.19 (1H, d, J = 8.9 Hz), 7.74 (1H, brs).

Reference Example 62

8-Chloro-1-(4-methoxybenzyl)-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[0514] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 2.21 (3H, s), 2.55 (2H, t, J = 6.8 Hz), 2.77 (2H, t, J = 6.8 Hz), 3.73 (3H, s), 5.12 (2H, s), 5.36 (2H, s), 6.64 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 7.05-7.08 (2H, m), 7.16 (1H, d, J = 9.0 Hz).

Reference Example 63

8-Chloro-5-(chloromethoxy)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0515] Synthesized analogous to Reference Example 58.
^{1}HNMR ($CDCl_3$) δ ppm: 2.55 (2H, t, J = 6.8 Hz), 2.76 (2H, t, J = 6.8 Hz), 3.73 (3H, s), 5.37 (2H, s), 5.85 (2H, s), 6.70-6.73 (2H, m), 6.87 (1H, d, J = 9.0 Hz), 7.04-7.07 (2H, m), 7.22 (1H, d, J = 9.0 Hz).

Reference Example 64

4-({[8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)piperidine-1,4-dicarboxylic acid 4-ethyl 1-tert-butyl

[0516] Synthesized analogous to Reference Example 59.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.46 (9H, s), 1.52 (2H, br), 2.19-2.22 (2H, m), 2.52 (2H, t, J = 6.8 Hz), 2.66-2.69 (2H, m), 3.00 (2H, brs), 3.73 (3H, s), 3.92 (4H, brs), 4.16 (2H, q, J = 7.1 Hz), 5.36 (2H, s), 6.51 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 7.04-7.07 (2H, m), 7.12 (1H, d, J = 8.9 Hz).

Reference Example 65

Ethyl 4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0517] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.64-1.69 (2H, m), 2.25-2.28 (2H, m), 2.52 (2H, t, J = 6.7 Hz), 2.67-2.70 (2H, m), 2.81-2.86 (2H, m), 3.07-3.12 (2H, m), 3.73 (3H, s), 3.93 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 5.36 (2H, s), 6.51 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 7.04-7.07 (2H, m), 7.12 (1H, d, J = 8.8 Hz).

Reference Example 66

Ethyl 1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahy droquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0518] A solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) piperidine-4-carboxylate (5.37 g), 2,3,5-trichloropyridine (2.50 g) and potassium carbonate (2.37 g) in N-methyl-2-pyrrolidone (50 mL) was stirred at 100 °C for 3 days. To the reaction solution was added ammonium chloride aqueous solution, and the reaction mixture was stirred and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (3.17 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.74-1.83 (2H, m), 2.32-2.39 (2H, m), 2.58-2.64 (2H, m), 2.78-2.84 (2H, m), 3.02-3.10 (2H, m), 3.60-3.68 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, brs), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.15 (2H, m), 7.59 (1H, d, J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

Reference Example 67

Ethyl 1-(3,5-difluoropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahyd roquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0519] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.72-1.80 (2H, m), 2.31-2.37 (2H, m), 2.60 (2H, t, J = 7.1 Hz), 2.80 (2H, t, J = 7.1 Hz), 3.05-3.12 (2H, m), 3.69-3.77 (2H, m), 3.75 (3H, s), 3.95 (2H, s), 4.16 (2H, q, J = 7.1 Hz), 5.23 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.79 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.14 (3H, m), 7.92 (1H, d, J = 2.5 Hz).

Reference Example 68

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-(5-fluoro-3-methylpyridin-2-yl)piperidine-4-carboxylate

[0520] Under nitrogen atmosphere, a solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) piperidine-4-carboxylate (2.69 g), 2-chloro-5-fluoro-3-methylpyridine (1 g), tris(dibenzylideneacetone)dipalladium (0) (0.105 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.178 g) and sodium tert-butoxide (1.10 g) in toluene (20 mL) was stirred at 100 °C overnight. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.36 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.2 Hz), 1.77-1.82 (2H, m), 2.28 (3H, s), 2.34-2.37 (2H, m), 2.60-2.62 (2H, m), 2.81-2.83 (2H, m), 2.93-2.99 (2H, m), 3.19-3.23 (2H, m), 3.74 (3H, s), 4.00 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11-7.14 (2H, m), 7.18 (1H, dd, J = 8.6 Hz, 2.9 Hz), 7.99 (1H, d, J = 3.0 Hz).

Reference Example 69

Ethyl 1-(2,4-dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroqu inolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0521] Synthesized analogous to Reference Example 68.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.85 (2H, m), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.79-2.84 (4H, m), 3.20-3.24 (2H, m), 3.74 (3H, s), 3.98 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.94 (1H, d, J = 8.6 Hz), 7.11-7.13 (2H, m), 7.17 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

Reference Example 70

Ethyl 1-(2,5-dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroqu inolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0522] Under nitrogen atmosphere, a solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) piperidine-4-carboxylate (300 mg), 1,4-dichloro-2-iodobenzene (0.103 mL), tris(dibenzylideneacetone)dipalladium (0) (11.7 mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (19.85 mg) and cesium carbonate (415 mg) in toluene (6 mL) was stirred at 110 °C overnight. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (240 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.86 (2H, m), 2.38-2.40 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H, m), 3.24-3.28 (2H, m), 3.74 (3H, s), 3.98 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.83 (1H, dd, J = 12.8 Hz, 9.1 Hz), 6.94 (1H, dd, J = 8.5 Hz, 2.4 Hz), 6.99 (1H, d, J = 2.4 Hz), 7.11-7.13 (2H, m), 7.26-7.27 (1H, m).

Reference Example 71

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylate

[0523] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.74-1.80 (2H, m), 2.35-2.38 (2H, m), 2.60-2.62 (2H, m), 2.80-2.82 (2H, m), 2.92-2.98 (2H, m), 3.48-3.52 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.88-6.91 (2H, m), 7.09-7.13 (4H, m).

Reference Example 72

Ethyl 1-(2,4-dichloro-5-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetr ahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0524] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.38-2.40 (2H, m), 2.60-2.63 (2H, m), 2.78-2.83 (4H, m), 3.23-3.26 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.81-6.85 (2H, m), 7.12 (2H, d, J = 8.6 Hz), 7.39 (1H, d, J = 7.6 Hz).

Reference Example 73

Ethyl 1-(2,5-dichloro-4-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetr ahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0525] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.77-2.84 (4H, m), 3.17-3.19 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.04 (1H, d, J = 7.2 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.19 (1H, d, J = 8.6 Hz).

Reference Example 74

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-(2,4,5-trichlorophenyl)piperidine-4-carboxylate

[0526] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.79-2.83 (4H, m), 3.22-3.25 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 8.9 Hz), 7.07 (1H, s), 7.12 (2H, d, J = 8.6 Hz), 7.44 (1H, s).

Reference Example 75

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-[5-fluoro-2-(trifluoromethyl)phenyl]piperidine-4-carboxylate

[0527] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.24 (3H, t, J = 7.1 Hz), 1.77-1.83 (2H, m), 2.34-2.36 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H, m), 3.01-3.03 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.0 Hz), 6.87-6.91 (1H, m), 6.99 (1H, dd, J = 10.1 Hz, 2.3 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.60 (1H, dd, J = 8.7 Hz, 6.4 Hz).

Reference Example 76

Ethyl 1-(2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroqui nolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0528] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.84 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.81-2.88 (4H, m), 3.32-3.35 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.56-6.66 (2H, m), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.92-6.97 (1H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 77

Ethyl 1-(4-chloro-2,6-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetr ahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0529] Synthesized analogous to Reference Example 68.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.72-1.78 (2H, m), 2.30-2.32 (2H, m), 2.60-2.63 (2H, m), 2.80-2.83 (2H, m), 3.13-3.19 (4H, m), 3.74 (3H, s), 3.96 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.80-6.88 (3H, m), 7.12 (2H, d,J = 8.6 Hz).

Reference Example 78

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-(2,4,6-trifluorophenyl)piperidine-4-carboxylate

[0530] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.73-1.79 (2H, m), 2.30-2.33 (2H, m), 2.60-2.63 (2H, m), 2.80-2.83 (2H, m), 3.08-3.20 (4H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.61 (2H, t, J = 8.9 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 79

Ethyl 1-(4-chloro-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetr ahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0531] Under nitrogen atmosphere, a solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) piperidine-4-carboxylate (0.85 g), 1-bromo-4-chloro-2,5-difluorobenzene (0.616 g), tris(dibenzyli-

deneacetone)dipalladium (0) (0.033 g), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) (0.063 g) and cesium carbonate (1.177 g) in toluene (12 mL) was stirred at 110 °C overnight. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (555 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.77-1.83 (2H, m), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.80-2.87 (4H, m), 3.29-3.32 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.70-6.77 (3H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.06 (1H, dd, J = 11.6 Hz, 6.8 Hz), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 80

Ethyl 1-(4-chloro-2-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahyd roquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0532] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.78-1.84 (2H, m), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.80-2.87 (4H, m), 3.27-3.29 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.80-6.88 (2H, m), 7.02-7.06 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 81

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-(2,4,5-trifluorophenyl)piperidine-4-carboxylate

[0533] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.78-1.84 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.79-2.83 (4H, m), 3.23-3.25 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.93 (5H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 82

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-[2-fluoro-4-(trifluoromethyl)phenyl]piperidine-4-carboxylate

[0534] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.84 (2H, m), 2.38-2.41 (2H, m), 2.60-2.63 (2H, m), 2.81-2.83 (2H, m), 2.91-2.97 (2H, m), 3.41-3.43 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.98 (1H, t, J = 8.4 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.25-7.28 (1H, m), 7.31 (1H, d, J = 8.5 Hz).

Reference Example 83

Ethyl 1-[2-chloro-4-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3 ,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0535] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.81-1.87 (2H, m), 2.40-2.42 (2H, m), 2.60-2.63 (2H, m), 2.81-2.91 (4H, m), 3.33-3.35 (2H, m), 3.74 (3H, s), 3.99 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.07 (1H, t, J = 8.4 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.45-7.46 (1H, m), 7.61 (1H, d, J = 1.9 Hz).

Reference Example 84

Ethyl 1-(2,4-difluorophenyl)-4-([8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroqui nolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0536] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H,

m), 3.22-3.24 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.75-6.84 (6H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 85

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-(2-fluoro-4-methylphenyl)piperidine-4-carboxylate

[0537] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.28 (3H, s), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H, m), 3.26-3.28 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.80-6.86 (4H, m), 7.12 (2H, d, J = 8.5 Hz).

Reference Example 86

Ethyl 1-[4-chloro-2-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3 ,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0538] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.75-1.81 (2H, m), 2.33-2.35 (2H, m), 2.60-2.63 (2H, m), 2.81-2.86 (4H, m), 2.95-2.97 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.0 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.26-7.28 (1H, m), 7.46 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.59 (1H, d, J = 2.4 Hz).

Reference Example 87

Ethyl 1-(4-bromo-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetr ahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0539] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.77-1.83 (2H, m), 2.36-2.39 (2H, m), 2.60-2.63 (2H, m), 2.80-2.87 (4H, m), 3.30-3.33 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.71 (1H, dd, J = 10.2 Hz, 7.5 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz),7.12 (2H, d, J = 8.6 Hz), 7.19 (1H, dd, J = 11.4 Hz, 6.4 Hz).

Reference Example 88

Ethyl 1-(2',4'-dichloro-2,5-difluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0540] Under nitrogen atmosphere, to a solution of ethyl 1-(4-bromo-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetr ahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (287 mg), 2,4-dichlorophenylboronic acid (108 mg) and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane adduct (17.7 mg) in 1,2-dimethoxyethane (4 mL) was added 2 M sodium carbonate aqueous solution (0.651 mL), and the reaction mixture was stirred under reflux for 20 h. The reaction solution was poured into water, and and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (213 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.86 (2H, m), 2.39-2.42 (2H, m), 2.61-2.64 (2H, m), 2.81-2.84 (2H, m), 2.90-2.95 (2H, m), 3.40-3.43 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.71 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.75-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.96 (1H, dd, J = 12.5 Hz, 6.7 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.23 (1H, d, J = 8.3 Hz), 7.30 (1H, dd, J = 8.3 Hz, 2.0 Hz), 7.49 (1H, d, J = 2.1 Hz).

Reference Example 89

Ethyl 1-(4'-chloro-2,2',5-trifluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1, 2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0541] Synthesized analogous to Reference Example 88.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.86 (2H, m), 2.39-2.41 (2H, m), 2.60-2.63 (2H, m), 2.81-2.84 (2H, m), 2.90-2.94 (2H, m), 3.40-3.42 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.71-6.77 (3H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.03 (1H, dd, J = 12.7 Hz, 6.7 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.17-7.21 (2H, m), 7.26-7.31 (1H, m).

Reference Example 90

Ethyl 4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4-dichlorophenyl)piperidine-4-carboxylate

[0542] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.39 (2H, m), 2.51-2.54 (2H, m), 2.69-2.72 (2H, m), 2.79-2.84 (2H, m), 3.21-3.23 (2H, m), 3.73 (3H, s), 4.00 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.37 (2H, s), 6.54 (1H, d, J = 8.9 Hz), 6.71-6.73 (2H, m), 6.95 (1H, d, J = 8.7 Hz),7.05-7.07 (2H, m), 7.14 (1H, d, J = 8.9 Hz), 7.18 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.36 (1H, d, J = 2.4 Hz).

Reference Example 91

Ethyl 1-(4-chloro-2-fluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahy droquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0543] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.78-1.84 (2H, m), 2.36-2.39 (2H, m), 2.51-2.54 (2H, m), 2.69-2.71 (2H, m), 2.82-2.87 (2H, m), 3.26-3.29 (2H, m), 3.73 (3H, s), 3.98 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 5.37 (2H, s), 6.54 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 6.84-6.88 (1H, m),7.02-7.07 (4H, m), 7.13 (1H, d, J = 8.9 Hz).

Reference Example 92

Ethyl 1-(4-chloro-2,6-difluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetr ahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

[0544] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.72-1.79 (2H, m), 2.29-2.32 (2H, m), 2.51-2.54 (2H, m), 2.69-2.71 (2H, m), 3.13-3.21 (4H, m), 3.73 (3H, s), 3.99 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.37 (2H, s), 6.54 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 6.84-6.89 (2H, m),7.05-7.08 (2H, m), 7.13 (1H, d, J = 8.9 Hz).

Reference Example 93

1-(3,5-Dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrah ydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0545] To a solution of ethyl 1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahy droquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (3.17 g) in methanol/ tetrahydrofuran (1:1) (60 mL) was added 5 N aqueous sodium hydroxide (10.3 mL), and the reaction mixture was stirred at 60 °C for 5.5 h. The solvent was distilled off and to the residue were added water and 5 N hydrochloric acid to make the reaction residue acidic, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (3.15 g, quant.).
^{1}HNMR ($CDCl_3$) δ ppm: 1.75-1.84 (2H, m), 2.34-2.43 (2H, m), 2.58-2.66 (2H, m), 2.79-2.87 (2H, m), 3.09-3.18 (2H, m), 3.61-3.69 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.22 (2H, brs), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.70-6.76 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.14 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

Reference Example 94

1-(3,5-Difluoropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrah ydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0546] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.71-1.80 (2H, m), 2.33-2.40 (2H, m), 2.60 (2H, t, J = 7.0 Hz), 2.81 (2H, t, J = 7.0 Hz), 3.13-3.22 (2H, m), 3.71 (3H, s), 3.69-3.78 (2H, m), 3.99 (2H, s), 5.22 (2H, brs), 6.48 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.70-6.74 (2H, m), 6.81 (1H, dd, J = 13.0 Hz, 9.0 Hz), 7.08-7.14 (3H, m), 7.93 (1H, d J = 2.5 Hz), 10.77 (1H, brs).

Reference Example 95

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-(5-fluoro-3-methylpyridin-2-yl)piperidine-4-carboxylic acid

[0547] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.70-2.00 (2H, br), 2.31-2.47 (2H, m), 2.59-2.62 (2H, m), 2.82-2.85 (2H, m), 3.10-3.47 (4H, br), 3.73 (3H, s), 4.02 (2H, s), 5.22 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.31-7.37 (1H, m), 8.01 (1H, s).

Reference Example 96

1-(2,4-Dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydro quinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0548] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.85 (2H, m), 2.40-2.42 (2H, m), 2.61-2.64 (2H, m), 2.82-2.91 (4H, m), 3.22-3.25 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 2.9 Hz), 6.73 (2H, d, J = 8.7 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.95-6.97 (1H, m), 7.11 (2H, d, J = 8.4 Hz), 7.17-7.19 (1H, m), 7.35-7.36 (1H, m).

Reference Example 97

1-(2,5-Dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydro quinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0549] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.86 (2H, m), 2.40-2.43 (2H, m), 2.61-2.64 (2H, m), 2.83-2.92 (4H, m), 3.26-3.29 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.74 (2H, d, J = 8.6 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.94 (1H, dd, J = 8.5 Hz, 2.4 Hz), 7.01 (1H, d, J = 2.2 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.27 (1H, d, J = 8.4 Hz).

Reference Example 98

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylic acid

[0550] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.70-1.85 (2H, br), 2.39-2.42 (2H, m), 2.61-2.64 (2H, m), 2.81-2.84 (2H, m), 2.98-3.09 (2H, br), 3.50-3.53 (2H, m), 3.71 (3H, s), 3.99 (2H, s), 5.22 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.71-6.74 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.0 Hz), 6.87-6.94 (2H, m), 7.07-7.14 (4H, m).

Reference Example 99

1-(2,4-Dichloro-5-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-te trahydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0551] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.86 (2H, m), 2.41-2.43 (2H, m), 2.62-2.65 (2H, m), 2.83-2.89 (4H, m), 3.25-3.27 (2H, m), 3.73 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.82-6.86 (2H, m), 7.12

(2H, d, J = 8.6 Hz), 7.39 (1H, d, J = 7.6 Hz).

Reference Example 100

1-(2,5-Dichloro-4-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-te trahydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0552] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.85 (2H, m), 2.41-2.44 (2H, m), 2.62-2.65 (2H, m), 2.83-2.90 (4H, m), 3.19-3.21 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.2 Hz, 3.1 Hz), 6.72-6.74 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.06 (1H, d, J = 7.2 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.20 (1H, d, J = 8.6 Hz).

Reference Example 101

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-(2,4,5-trichlorophenyl)piperidine-4-carboxylic acid

[0553] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.84 (2H, m), 2.41-2.44 (2H, m), 2.62-2.65 (2H, m), 2.83-2.92 (4H, m), 3.24-3.26 (2H, m), 3.72 (3H, s), 4.02 (2H, s), 5.23 (2H, s), 6.50-6.52 (1H, m), 6.73 (2H, d, J = 8.7 Hz), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.09-7.12 (3H, m), 7.44 (1H, s).

Reference Example 102

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-[5-fluoro-2-(trifluoromethyl)phenyl]piperidine-4-carboxylic acid

[0554] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.77-1.82 (2H, m), 2.38-2.41 (2H, m), 2.63-2.66 (2H, m), 2.83-2.86 (2H, m), 2.89-2.94 (2H, m), 3.03-3.05 (2H, m), 3.72 (3H, s), 4.02 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.72-6.75 (2H, m), 6.83-6.91 (2H, m), 7.03 (1H, dd, J = 10.1 Hz, 2.3 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.60 (1H, dd, J = 8.8 Hz, 6.3 Hz).

Reference Example 103

1-(2,5-Difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydro quinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0555] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.85 (2H, m), 2.40-2.42 (2H, m), 2.61-2.64 (2H, m), 2.82-2.85 (2H, m), 2.91-2.96 (2H, m), 3.34-3.36 (2H, m), 3.72 (3H, s), 4.00 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.57-6.62 (1H, m), 6.64-6.70 (1H, m), 6.74 (2H, d, J = 8.5 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.92-6.98 (1H, m), 7.11 (2H, d, J = 8.5 Hz).

Reference Example 104

1-(4-Chloro-2,6-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-te trahydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0556] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.80 (2H, m), 2.33-2.35 (2H, m), 2.61-2.64 (2H, m), 2.82-2.85 (2H, m), 3.15-3.18 (2H, m), 3.22-3.27 (2H, m), 3.73 (3H, s), 4.00 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.81-6.89 (3H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 105

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-(2,4,6-trifluorophenyl)piperidine-4-carboxylic acid

[0557] Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.75-1.80 (2H, m), 2.33-2.36 (2H, m), 2.61-2.64 (2H, m), 2.82-2.85 (2H, m), 3.10-3.13 (2H, m), 3.22-3.27 (2H, m), 3.73 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.62 (2H, t, J = 8.9 Hz), 6.72-6.75 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 106

1-(4-Chloro-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-te trahydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0558] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.77-1.83 (2H, m), 2.40-2.43 (2H, m), 2.62-2.65 (2H, m), 2.82-2.85 (2H, m), 2.90-2.95 (2H, m), 3.31-3.34 (2H, m), 3.72 (3H, s), 3.99 (2H, s), 5.23 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.71-6.77 (3H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.07 (1H, dd, J = 11.6 Hz, 6.9 Hz), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 107

1-(4-Chloro-2-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrah ydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0559] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.84 (2H, m), 2.40-2.43 (2H, m), 2.62-2.65 (2H, m), 2.82-2.85 (2H, m), 2.90-2.94 (2H, m), 3.29-3.31 (2H, m), 3.72 (3H, s), 4.00 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.71-6.73 (2H, m), 6.82-6.89 (2H, m), 7.02-7.06 (2H, m), 7.11 (2H, d, J = 8.5 Hz).

Reference Example 108

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-(2,4,5-trifluorophenyl)piperidine-4-carboxylic acid

[0560] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.99 (2H, br), 2.43-2.46 (2H, m), 2.62-2.65 (2H, m), 2.82-2.84 (2H, m), 2.96-3.12 (2H, br), 3.31-3.34 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.72-6.73 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.92-7.08 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 109

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-[2-fluoro-4-(trifluoromethyl)phenyl]piperidine-4-carboxylic acid

[0561] Synthesized analogous to Reference Example 93.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.78 (2H, m), 2.19-2.21 (2H, m), 2.57-2.60 (2H, m), 2.79-2.82 (2H, m), 2.92-2.96 (2H, m), 3.38-3.41 (2H, m), 3.68 (3H, s), 4.03 (2H, s), 5.09 (2H, s), 6.73 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.79-6.82 (2H, m), 6.98 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.06 (2H, d, J = 8.7 Hz), 7.21 (1H, t, J = 8.6 Hz), 7.44-7.46 (1H, m), 7.53 (1H, dd, J = 13.2 Hz, 1.8 Hz).

Reference Example 110

1-[2-Chloro-4-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1, 2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0562] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.89 (2H, m), 2.43-2.46 (2H, m), 2.63-2.65 (2H, m), 2.83-2.86 (2H, m), 2.93-3.04 (2H, br), 3.35-3.38 (2H, m), 3.72 (3H, s), 4.03 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.11-7.12 (3H, m), 7.45-7.48 (1H, m), 7.62 (1H, d, J = 1.8 Hz).

Reference Example 111

1-(2,4-Difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydro quinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0563] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 2.40-2.84 (8H, m), 3.48-3.74 (7H, m), 4.08 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.2 Hz, 3.21 Hz), 6.73-6.75 (2H, m), 6.84-6.99 (4H, m), 7.11 (2H, d, J = 8.5 Hz).

Reference Example 112

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-(2-fluoro-4-methylphenyl)piperidine-4-carboxylic acid

[0564] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.97 (2H, br), 2.29 (3H, s), 2.40-2.44 (2H, m), 2.61-2.65 (2H, m), 2.81-3.05 (4H, m), 3.21-3.39 (2H, br), 3.71 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.72-6.73 (2H, m), 6.82-6.92 (4H, m), 7.11 (2H, d, J = 8.5 Hz).

Reference Example 113

1-[4-Chloro-2-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1, 2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0565] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.97 (2H, m), 2.37-2.39 (2H, m), 2.62-2.65 (2H, m), 2.83-2.86 (2H, m), 2.89-2.99 (4H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.74 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.29 (1H, d, J = 8.6 Hz), 7.47 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.60 (1H, d, J = 2.5 Hz).

Reference Example 114

1-(2',4'-Dichloro-2,5-difluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-ox o-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0566] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.95-2.08 (2H, br), 2.45-2.48 (2H, m), 2.63-2.66 (2H, m), 2.83-2.86 (2H, m), 3.10-3.24 (2H, br), 3.48-3.50 (2H, m), 3.72 (3H, s), 4.03 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.0 Hz), 6.73-6.74 (2H, m), 6.85 (1H, dd, J = 12.5 Hz, 9.1 Hz), 6.99-7.08 (2H, m), 7.12 (2H, d, J = 8.6 Hz), 7.23 (1H, d, J = 8.3 Hz), 7.31 (1H, dd, J = 8.3 Hz, 2.1 Hz), 7.50 (1H, d, J = 2.1 Hz).

Reference Example 115

1-(4'-Chloro-2,2',5-trifluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo -1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0567] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.88 (2H, m), 2.42-2.45 (2H, m), 2.63-2.65 (2H, m), 2.83-2.86 (2H, m), 2.99-3.04 (2H, m), 3.42-3.45 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.80 (3H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.04 (1H, dd, J = 12.7 Hz, 6.7 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.17-7.21 (2H, m), 7.26-7.32 (1H, m).

Reference Example 116

4-({[8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-(2,4-dichlorophenyl)piperidine-4-carboxylic acid

[0568] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.85 (2H, m), 2.41-2.43 (2H, m), 2.51-2.54 (2H, m), 2.70-2.73 (2H, m), 2.87-2.91 (2H, m),

3.23-3.25 (2H, m), 3.70 (3H, s), 4.03 (2H, s), 5.39 (2H, s), 6.57 (1H, d, J = 9.0 Hz), 6.67-6.68 (2H m), 6.96 (1H, d, J = 8.6 Hz), 7.04-7.06 (2H, m), 7.15 (1H, d, J = 8.9 Hz), 7.18 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.36 (1H, d, J = 2.4 Hz).

Reference Example 117

1-(4-Chloro-2-fluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetra hydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0569] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.84 (2H, m), 2.39-2.42 (2H, m), 2.51-2.54 (2H, m), 2.70-2.72 (2H, m), 2.89-2.94 (2H, m), 3.29-3.31 (2H, m), 3.70 (3H, s), 4.01 (2H, s), 5.38 (2H, s), 6.56 (1H, d, J = 9.0 Hz), 6.67-6.69 (2H m), 6.86-6.89 (1H, m), 7.02-7.06 (4H, m), 7.15 (1H, d, J = 8.9 Hz).

Reference Example 118

1-(4-Chloro-2,6-difluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-t etrahydroquinolin-5-yl]oxy }methyl)piperidine-4-carboxylic acid

[0570] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.75-1.82 (2H, m), 2.32-2.35 (2H, m), 2.51-2.54 (2H, m), 2.70-2.72 (2H, m), 3.14-3.28 (4H, m), 3.72 (3H, s), 4.03 (2H, s), 5.38 (2H, s), 6.56 (1H, d, J = 8.9 Hz), 6.70 (2H, d, J = 8.6 Hz), 6.84-6.90 (2H, m), 7.06 (2H, d, J = 8.5 Hz), 7.14 (1H, d, J = 8.9 Hz).

Reference Example 119

1-(5-Fluoro-3-methylpyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

[0571] A solution of 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -1-(5-fluoro-3-methylpyridin-2-yl)piperidine-4-carboxylic acid (1.33 g) and anisole (0.527 mL) in trifluoroacetic acid (10 mL) was stirred at 65 °C for 3 h. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (1.00 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.75 (2H, m), 2.18-2.21 (2H, m), 2.26 (3H, s), 2.43-2.46 (2H, m), 2.80-2.89 (4H, m), 3.17-3.20 (2H, m), 4.03 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.03 (1H, m), 7.05-7.52 (1H, m), 8.06-8.07 (1H, m), 10.03 (1H, s), 12.28-13.00 (1H, br).

Reference Example 120

1-(2,4-Dichlorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]met hyl}piperidine-4-carboxylic acid

[0572] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.78 (2H, m), 2.20-2.23 (2H, m), 2.43-2.46 (2H, m), 2.78-2.83 (4H, m), 3.15-3.17 (2H, m), 4.05 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.04 (1H, m), 7.17 (1H, d, J = 8.8 Hz), 7.34 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.53 (1H, d, J = 2.5 Hz), 10.02 (1H, s), 12.59-12.79 (1H, br).

Reference Example 121

1-(2,5-Dichlorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]met hyl}piperidine-4-carboxylic acid

[0573] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.79 (2H, m), 2.19-2.22 (2H, m), 2.43-2.46 (2H, m), 2.80-2.86 (4H, m), 3.18-3.21 (2H, m), 4.07 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.00-7.04 (1H, m), 7.09 (1H, dd, J = 8.5 Hz, 2.4 Hz), 7.17 (1H, d J = 2.4 Hz), 7.43 (1H, d, J = 8.5 Hz), 10.03 (1H, s), 12.54-12.81 (1H, br).

Reference Example 122

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-[4-(trifluoromet hoxy)phenyl]piperidine-4-carboxylic acid

[0574] Synthesized analogous to Reference Example 119.
^{1}HNMR ($CDCl_3$) δ ppm: 2.34-2.41 (2H, m), 2.51-2.58 (4H, m), 2.89-2.91 (2H, m), 3.46-3.51 (2H, m), 3.72-3.75 (2H, m), 3.86 (2H, s), 6.53 (1H, dd, J = 9.2 Hz, 3.8 Hz), 6.90-6.96 (1H, m), 7.34-7.35 (2H, m), 7.57-7.59 (2H, m), 8.57-8.63 (1H, br).

Reference Example 123

1-(2,4-Dichloro-5-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

[0575] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.78 (2H, m), 2.20-2.22 (2H, m), 2.43-2.46 (2H, m), 2.80-2.85 (4H, m), 3.19-3.23 (2H, m), 4.05 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.04 (1H, m), 7.24 (1H, d, J = 11.2 Hz), 7.71 (1H, d, J = 7.8 Hz), 10.03 (1H, s), 12.60-12.81 (1H, br).

Reference Example 124

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-[5-fluoro-2-(trifl uoromethyl)phenyl]piperidine-4-carboxylic acid

[0576] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.77 (2H, m), 2.15-2.18 (2H, m), 2.43-2.46 (2H, m), 2.80-2.84 (4H, m), 2.98-3.01 (2H, m), 4.09 (2H, s), 6.64 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.12-7.16 (1H, m), 7.38-7.41 (1H, m), 7.73 (1H, dd, J = 8.7 Hz, 6.4 Hz), 10.03 (1H, s), 12.58-12.73 (1H, br).

Reference Example 125

1-(2,5-Difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]met hyl}piperidine-4-carboxylic acid

[0577] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.77 (2H, m), 2.18-2.20 (2H, m), 2.43-2.46 (2H, m), 2.80-2.87 (4H, m), 3.27-3.29 (2H, m), 4.04 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.71-6.76 (1H, m), 6.86-6.90 (1H, m), 7.02 (1H, t, J = 9.7 Hz), 7.12-7.17 (1H, m), 10.03 (1H, s), 12.71 (1H, brs).

Reference Example 126

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-(2,4,5-trichlorop henyl)piperidine-4-carboxylic acid

[0578] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.79 (2H, m), 2.18-2.22 (2H, m), 2.43-2.46 (2H, m), 2.80-2.87 (4H, m), 3.18-3.20 (2H, m), 4.06 (2H, s), 6.62 (1H, dd, J = 9.2 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.37 (1H, s), 7.76 (1H, s), 10.03 (1H, s), 12.70 (1H, brs).

Reference Example 127

1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

[0579] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.71 (2H, m), 2.14-2.17 (2H, m), 2.43-2.46 (2H, m), 2.79-2.82 (2H, m), 3.11-3.12 (4H, m), 4.02 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.25-7.31 (2H, m), 10.03 (1H, s), 12.70 (1H, brs).

Reference Example 128

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-(2,4,6-trifluorop henyl)piperidine-4-carboxylic acid

[0580] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.71 (2H, m), 2.14-2.17 (2H, m), 2.43-2.46 (2H, m), 2.79-2.82 (2H, m), 3.04-3.12 (4H, m), 4.02 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.00-7.03 (1H, m), 7.13 (2H, t, J = 9.3 Hz), 10.03 (1H, s), 12.68 (1H, brs).

Reference Example 129

1-(2,5-Dichloro-4-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

[0581] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.78 (2H, m), 2.19-2.21 (2H, m), 2.43-2.46 (2H, m), 2.79-2.83 (4H, m), 3.11-3.14 (2H, m), 4.06 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.35 (1H, d, J = 7.4 Hz), 7.66 (1H, d, J = 9.1 Hz), 10.04 (1H, s), 12.69 (1H, brs).

Reference Example 130

1-(4-Chloro-2,5-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

[0582] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.77 (2H, m), 2.17-2.20 (2H, m), 2.43-2.46 (2H, m), 2.80-2.88 (4H, m), 3.27-3.30 (2H, m), 4.03 (2H, s), 6.57-6.64 (1H, m), 7.02 (1H, t, J = 9.7 Hz), 7.12 (1H, dd, J = 11.3 Hz, 7.9 Hz), 7.50 (1H, dd, J = 12.0 Hz, 7.1 Hz), 10.04 (1H, s), 12.72 (1H, brs).

Reference Example 131

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ox y]methyl}piperidine-4-carboxylic acid

[0583] Synthesized analogous to Reference Example 119.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.77 (2H, m), 2.18-2.21 (2H, m), 2.43-2.46 (2H, m), 2.80-2.84 (4H, m), 3.22-3.24 (2H, m), 4.03 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.03 (1H, m), 7.07 (1H, t, J = 9.1 Hz), 7.16 (1H, dd, J = 8.7 Hz, 2.0 Hz), 7.32 (1H, dd, J = 12.4 Hz, 2.4 Hz), 10.03 (1H, s), 12.70 (1H, brs).

Reference Example 133

1-(3,5-Difluoropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

[0584] Synthesized analogous to Reference Example 119.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.75 (2H, m), 2.12-1.19 (2H, m), 2.42 (2H, t, J = 7.5 Hz), 2.78 (2H, t, J = 7.5 Hz), 3.02-3.10 (2H, m), 3.62-3.69 (2H, m), 4.02 (2H, s), 6.59 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.99 (1H, t, J = 9.5 Hz), 7.75-7.81 (1H, m), 8.09 (1H, d, J = 2.5 Hz), 10.03 (1H, s), 12.72 (1H, brs).

Reference Example 134

5-{[1-(3,5-Dichloropyridin-2-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0585] To a suspension of 1-(3,5-dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy] methyl}piperidine-4-carboxylic acid (1.46 g) in 1,4-dioxane (15 mL) were added triethylamine (0.456 mL) and diphenylphosphoryl azide (0.705 mL), and the reaction mixture was heated to reflux for 2 h. The solvent was distilled off and to the residue was added water, and insoluble materials were filtered off to provide the title compound (1.41 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-2.02 (4H, m), 2.62-2.69 (2H, m), 3.06 (2H, t, J = 7.7 Hz), 3.17-3.26 (2H, m), 3.71-3.78 (2H, m), 3.95 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.54 (1H, brs), 7.62 (1H, d, J = 2.3 Hz), 8.14 (1H, d, J = 2.3 Hz).

Reference Example 135

5-{[1-(3,5-Difluoropyridin-2-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0586] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.92 (2H, m), 1.92-1.98 (2H, m), 2.64 (2H, t, J = 7.5 Hz), 3.04 (2H, t, J = 7.5 Hz), 3.20-3.28 (2H, m), 3.82-3.88 (2H, m), 3.93 (2H, s), 6.42 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.5 Hz), 7.11-7.17 (1H, m), 7.49 (1H, brs), 7.95 (1H, d, J = 2.5 Hz).

Reference Example 136

8-Fluoro-5-{[1-(5-fluoro-3-methylpyridin-2-yl)-4-isocyanatopiperidin-4-yl]methoxy }-3,4-dihydroquinolin-2(1H)-one

[0587] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.98 (4H, m), 2.29 (3H, s), 2.65-2.68 (2H, m), 3.05-3.08 (2H, m), 3.15-3.20 (2H, m), 3.25-3.28 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.20 (1H, dd, J = 8.5 Hz, 2.7 Hz), 7.51 (1H, brs), 8.02 (1H, d, J = 2.9 Hz).

Reference Example 137

5-{[1-(2,4-Dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihyd roquinolin-2(1H)-one

[0588] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.93-2.00 (4H, m), 2.64-2.68 (2H, m), 2.99-3.08 (4H, m), 3.26-3.28 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.03 (1H, d, J = 8.7 Hz), 7.22 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.5 Hz), 7.53 (1H, brs).

Reference Example 138

5-{[1-(2,5-Dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihyd roquinolin-2(1H)-one

[0589] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-2.00 (4H, m), 2.65-2.68 (2H, m), 3.00-3.08 (4H, m), 3.31-3.33 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.94 (1H, t, J = 9.4 Hz), 7.08 (1H, d, J = 2.3 Hz), 7.17-7.22 (1H, m), 7.28-7.30 (1H, m), 7.69 (1H, brs).

Reference Example 139

8-Fluoro-5-({4-isocyanato-1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}methoxy)-3 ,4-dihydroquinolin-2(1H)-one

[0590] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.98-2.08 (4H, m), 2.61-2.66 (2H, m), 2.94-2.98 (2H, m), 3.02-3.06 (2H, m), 3.54-3.57 (2H, m), 3.94 (2H, s), 6.41-6.44 (1H, m), 6.86-7.46 (5H, m), 7.56 (1H, brs).

Reference Example 140

5-{[1-(2,4-Dichloro-5-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0591] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.01 (4H, m), 2.64-2.67 (2H, m), 2.97-3.02 (2H, m), 3.04-3.07 (2H, m), 3.29-3.31 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.89-6.96 (2H, m), 7.41 (1H, d, J = 7.6 Hz), 7.56 (1H, brs).

Reference Example 141

8-Fluoro-5-({1-[5-fluoro-2-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}met hoxy)-3,4-dihydroquinoli-2(1H)-one

[0592] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-1.95 (4H, m), 2.64-2.67 (2H, m), 3.05-3.08 (6H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz,

3.8 Hz), 6.92-6.96 (2H, m), 7.11 (1H, dd, J = 9.9 Hz, 2.3 Hz), 7.51 (1H, brs), 7.63 (1H, dd, J = 8.8 Hz, 6.1 Hz).

Reference Example 142

tert-Butyl (4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-[5-fluoro-2-(triflu oromethyl)phenyl]piperidin-4-yl)carbamate

[0593] Synthesized analogous to Reference Example 134. In place of 1,4-dioxane, tert-butanol was used as the solvent. ^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (9H, s), 1.92-1.98 (2H, m), 2.22-2.24 (2H, m), 2.63-2.66 (2H, m), 2.93-3.06 (6H, m), 4.13 (2H, s), 4.46 (1H, brs), 6.51 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.89-6.93 (2H, m), 7.06 (1H, dd, J = 10.1 Hz, 2.4 Hz), 7.54-7.63 (2H, m).

Reference Example 143

5-{[1-(2,5-Difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihyd roquinolin-2(1H)-one

[0594] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.00 (4H, m), 2.65-2.68 (2H, m), 3.02-3.07 (4H, m), 3.38-3.41 (2H, m), 3.95 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.61-6.65 (1H, m), 6.69-6.73 (1H, m), 6.92-7.00 (2H, m), 7.50 (1H, brs).

Reference Example 144

8-Fluoro-5-{[4-isocyanato-1-(2,4,5-trichlorophenyl)piperidin-4-yl]methoxy}-3,4-dih ydroquinolin-2(1H)-one

[0595] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.01 (4H, m), 2.63-2.68 (2H, m), 2.97-3.07 (4H, m), 3.28-3.30 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.94 (1H, t, J = 9.5 Hz), 7.16 (1H, s), 7.47 (1H, s), 7.50 (1H, brs).

Reference Example 145

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0596] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.93 (4H, m), 2.64-2.67 (2H, m), 3.04-3.07 (2H, m), 3.13-3.15 (2H, m), 3.40-3.45 (2H, m), 3.93 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.88-6.94 (2H, m), 7.39 (1H, t, J = 7.9 Hz), 7.54 (1H, brs).

Reference Example 146

8-Fluoro-5-{[4-isocyanato-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dih ydroquinolin-2(1H)-one

[0597] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.94 (4H, m), 2.64-2.67 (2H, m), 3.00-3.09 (4H, m), 3.40-3.45 (2H, m), 3.93 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.63-6.66 (2H, m), 6.93 (1H, t, J = 9.4 Hz), 7.52 (1H, brs).

Reference Example 147

5-{[1-(2,5-Dichloro-4-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0598] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.00 (4H, m), 2.65-2.68 (2H, m), 2.98-3.03 (2H, m), 3.05-3.08 (2H, m), 3.22-3.24 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.94 (1H, t, J = 9.4 Hz), 7.13 (1H, d, J = 7.2 Hz), 7.22 (1H, d, J = 8.5 Hz), 7.53 (1H, brs).

Reference Example 148

5-{[1-(4-Chloro-2,5-difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0599] Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90-2.00 (4H, m), 2.64-2.68 (2H, m), 3.02-3.07 (4H, m), 3.35-3.37 (2H, m), 3.95 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.79 (1H, dd, J = 10.5 Hz, 7.6 Hz), 6.94 (1H, d, J = 9.4 Hz), 7.09 (1H, dd, J = 11.5 Hz, 6.9 Hz), 7.58 (1H, brs).

Reference Example 149

5-{[1-(4-Chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0600] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-2.00 (4H, m), 2.64-2.68 (2H, m), 3.02-3.07 (4H, m), 3.32-3.34 (2H, m), 3.94 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92-6.95 (2H, m), 7.05-7.08 (2H, m), 7.57 (1H, brs).

Reference Example 150

8-Fluoro-5-{[4-isocyanato-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-1-(4-me thoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0601] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89-1.98 (4H, m), 2.65-2.68 (2H, m), 2.91-2.94 (2H, m), 2.98-3.03 (2H, m), 3.27-3.29 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.78 (2H, m), 6.81-6.87 (2H, m), 6.90-6.95 (1H, m), 7.13 (2H, d, J = 8.6 Hz).

Reference Example 151

8-Fluoro-5-({1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}met hoxy)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0602] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.90-1.99 (4H, m), 2.65-2.68 (2H, m), 2.91-2.94 (2H, m), 3.09-3.14 (2H, m), 3.45-3.48 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.78 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.04 (1H, t, J = 8.5 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.27-7.30 (1H, m), 7.35 (1H, d, J = 8.7 Hz).

Reference Example 152

5-({1-[2-Chloro-4-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}methoxy)-8-f luoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0603] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.01 (4H, m), 2.65-2.68 (2H, m), 2.92-2.95 (2H, m), 3.05-3.10 (2H, m), 3.37-3.40 (2H, m), 3.74 (3H, s), 3.92 (2H, s), 5.24 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.76-6.78 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.13-7.16 (3H, m), 7.48-7.51 (1H, m), 7.63 (1H, d, J = 1.8 Hz).

Reference Example 153

5-{[1-(2,4-Difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-1-(4-meth oxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0604] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.90-1.95 (4H, m), 2.65-2.68 (2H, m), 2.92-2.94 (2H, m), 2.99-3.05 (2H, m), 3.26-3.28 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.75-6.78 (2H, m), 6.80-6.87 (3H, m), 6.96-7.00 (1H, m), 7.13 (2H, d, J = 8.6 Hz).

Reference Example 154

8-Fluoro-5-{[1-(2-fluoro-4-methylphenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4 -methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0605] Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.93-1.96 (4H, m), 2.65-2.68 (2H, m), 2.92-2.95 (2H, m), 2.98-3.04 (2H, m), 3.30-3.32 (2H, m), 3.74 (3H, s), 3.89 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.82-6.93 (4H, m), 7.13 (2H, d, J = 8.6 Hz).

Reference Example 155

5-({1-[4-Chloro-2-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}methoxy)-8-flu oro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0606] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.94 (4H, m), 2.65-2.68 (2H, m), 2.91-2.97 (4H, m), 3.04-3.09 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.38 (1H, d, J = 8.6 Hz), 7.51 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.61 (1H, d, J = 2.5 Hz).

Reference Example 156

5-{[1-(2',4'-Dichloro-2,5-difluorobiphenyl-4-yl)-4-isocyanatopiperidin-4-yl]methoxy }-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0607] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-2.00 (4H, m), 2.66-2.69 (2H, m), 2.92-2.95 (2H, m), 3.08-3.13 (2H, m), 3.45-3.48 (2H, m), 3.75 (3H, s), 3.91 (2H, s), 5.24 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.79 (3H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.98 (1H, dd, J = 12.4 Hz, 6.8 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.24 (1H, d, J = 8.3 Hz), 7.31 (1H, dd, J = 8.3 Hz, 2.2 Hz), 7.50 (1H, d, J = 2.1 Hz).

Reference Example 157

5-{[1-(4'-Chloro-2,2',5-trifluorobiphenyl-4-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0608] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-2.00 (4H, m), 2.66-2.68 (2H, m), 2.92-2.95 (2H, m), 3.07-3.12 (2H, m), 3.45-3.47 (2H, m), 3.75 (3H, s), 3.91 (2H, s), 5.24 (2H, s), 6.50 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.76-6.87 (4H, m), 7.03-7.07 (1H, m), 7.14 (2H, d, J = 8.6 Hz), 7.18-7.22 (2H, m), 7.28-7.32 (1H, m).

Reference Example 158

8-Chloro-5-{[1-(2,4-dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4-met hoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0609] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-1.96 (4H, m), 2.57-2.59 (2H, m), 2.81-2.83 (2H, m), 2.97-3.02 (2H, m), 3.24-3.27 (2H, m), 3.73 (3H, s), 3.93 (2H, s), 5.39 (2H, s), 6.56 (1H, d, J = 8.9 Hz), 6.73 (2H, d, J = 8.6 Hz), 7.03 (1H, d, J = 8.6 Hz), 7.08 (2H, d, J = 8.6 Hz), 7.16 (1H, d, J = 8.9 Hz), 7.22 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.5 Hz).

Reference Example 159

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4 -methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0610] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.90-1.97 (4H, m), 2.57-2.59 (2H, m), 2.80-2.83 (2H, m), 3.00-3.05 (2H, m), 3.31-3.34 (2H, m), 3.73 (3H, s), 3.92 (2H, s), 5.39 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.72-6.74 (2H, m), 6.91-6.95 (1H, m), 7.05-7.08 (4H, m), 7.16 (1H, d, J = 8.9 Hz).

Reference Example 160

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0611] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83-1.91 (4H, m), 2.56-2.59 (2H, m), 2.80-2.83 (2H, m), 3.12-3.14 (2H, m), 3.39-3.44 (2H, m), 3.73 (3H, s), 3.91 (2H, s), 5.38 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.71-6.75 (2H, m), 6.86-6.92 (2H, m), 7.06-7.09 (2H, m), 7.15 (1H, d, J = 8.9 Hz).

Reference Example 161

5-{[4-Amino-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methox ybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0612] To 8-fluoro-5-{[4-isocyanato-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-1-(4-meth oxybenzyl)-3,4-dihydroquinolin-2(1H)-one (364 mg) were added acetic acid (4 mL) and 2 N hydrochloric acid (3.2 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution, aqueous sodium hydroxide was added to make the reaction residue basic, and the solution was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/ethyl acetate) to provide the title compound (305 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.68 (2H, m), 1.90-1.95 (2H, m), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.06-3.16 (4H, m), 3.71 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.80-6.94 (3H, m), 7.13 (2H, d, J = 8.6 Hz).

Reference Example 162

5-({4-Amino-1-[2-chloro-4-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluor o-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0613] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.68-1.71 (2H, m), 1.93-1.98 (2H, m), 2.65-2.67 (2H, m), 2.89-2.92 (2H, m), 3.14-3.18 (2H, m), 3.23-3.25 (2H, m), 3.73-3.75 (5H, m), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, 12.7 Hz, 9.1 Hz), 7.13-7.15 (3H, m), 7.45-7.48 (1H, m), 7.61 (1H, d, J = 1.8 Hz).

Reference Example 163

5-({4-Amino-1-[2-fluoro-4-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0614] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.69 (2H, m), 1.91-1.97 (2H, m), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.19-3.24 (2H, m), 3.30-3.33 (2H, m), 3.72 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, 12.7 Hz, 9.1 Hz), 7.03 (1H, t, 8.5 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.25-7.28 (1H, m), 7.32 (1H, d, J = 8.5 Hz).

Reference Example 164

5-{[4-Amino-1-(2,4-difluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxy benzyl)-3,4-dihydroquinolin-2(1H)-one

[0615] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.69 (2H, m), 1.91-1.97 (2H, m), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.06-3.15 (4H, m), 3.72 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.86 (5H, m), 6.94-6.99 (1H, m), 7.13 (2H, d, J = 8.6 Hz).

Reference Example 165

5-{[4-Amino-1-(2-fluoro-4-methylphenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-me thoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0616] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.70 (2H, m), 1.93-1.98 (2H, m), 2.28 (3H, s), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.05-3.19 (4H, m), 3.73 (2H, s), 3.74 (3H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.75-6.77 (2H, m), 6.81-6.92 (4H, m), 7.13 (2H, d, J = 8.6 Hz).

Reference Example 166

5-({4-Amino-1-[4-chloro-2-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluor o-1-(4-methoxybenzyl)-3,4-dihydro-quinolin-2(1H)-one

[0617] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.64 (2H, m), 1.88-1.93 (2H, m), 2.64-2.67 (2H, m), 2.86-2.91 (4H, m), 3.07-3.11 (2H, m), 3.73 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.2 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.36 (1H, d, J = 8.6 Hz), 7.47-7.49 (1H, m), 7.60 (1H, d, J = 2.5 Hz).

Reference Example 167

5-{[4-Amino-1-(2',4'-dichloro-2,5-difluorobiphenyl-4-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihyd-roquinolin-2(1H)-one

[0618] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.70 (2H, m), 1.93-1.98 (2H, m), 2.65-2.68 (2H, m), 2.89-2.92 (2H, m), 3.17-3.22 (2H, m), 3.30-3.33 (2H, m), 3.73 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (3H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.0 Hz), 6.96 (1H, dd, J = 12.5 Hz, 6.8 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.24 (1H, d, J = 8.3 Hz), 7.30 (1H, dd, J = 8.3 Hz, 2.1 Hz), 7.50 (1H, d, J = 2.1 Hz).

Reference Example 168

5-{[4-Amino-1-(4'-chloro-2,2',5-trifluorobiphenyl-4-yl)piperidin-4-yl]methoxy}-8-fl uoro-1-(4-methoxybenzyl)-3,4-dihyd-roquinolin-2(1H)-one

[0619] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.70 (2H, m), 1.92-1.98 (2H, m), 2.65-2.68 (2H, m), 2.89-2.91 (2H, m), 3.17-3.22 (2H, m), 3.30-3.32 (2H, m), 3.72 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.86 (4H, m), 7.04 (1H, dd, J = 12.5 Hz, 6.9 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.18-7.22 (2H, m), 7.29-7.32 (1H, m).

Reference Example 169

5-{[4-Amino-1-(2,4-dichlorophenyl)piperidin-4-yl]methoxy}-8-chloro-1-(4-methoxy benzyl)-3,4-dihydroquinolin-2(1H)-one

[0620] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.69 (2H, m), 1.91-1.97 (2H, m), 2.56-2.58 (2H, m), 2.77-2.79 (2H, m), 3.06-3.14 (4H, m), 3.74 (3H, s), 3.76 (2H, s), 5.38 (2H, s), 6.58 (1H, d, J = 9.0 Hz), 6.71-6.73 (2H, m), 7.01 (1H, d, J = 8.6 Hz), 7.08 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 8.9 Hz), 7.19 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.37 (1H, d, J = 2.4 Hz).

Reference Example 170

5-{[4-Amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-1-(4-met hoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0621] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.68 (2H, m), 1.90-1.96 (2H, m), 2.55-2.58 (2H, m), 2.76-2.79 (2H, m), 3.08-3.13 (2H, m),

3.16-3.20 (2H, m), 3.74 (3H, s), 3.74 (2H, s), 5.38 (2H, s), 6.58 (1H, d, J = 9.0 Hz), 6.71-6.74 (2H, m), 6.90-6.94 (1H, m), 7.03-7.09 (4H, m), 7.15 (1H, d, J = 8.9 Hz).

Reference Example 171

5-{[4-Amino-1-(4-chloro-2,6-difluorophenyl)piperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0622] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.63 (2H, m), 1.84-1.90 (2H, m), 2.55-2.58 (2H, m), 2.76-2.79 (2H, m), 3.06-3.09 (2H, m), 3.36-3.41 (2H, m), 3.74 (3H, s), 3.75 (2H, s), 5.38 (2H, s), 6.58 (1H, d, J = 9.0 Hz), 6.72-6.74 (2H, m), 6.85-6.90 (2H, m), 7.08 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 8.9 Hz).

Reference Example 172

1-(tert-Butoxycarbonyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroq uinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

[0623] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.47 (11H, m), 2.11-2.13 (2H, m), 2.53-2.56 (2H, m), 2.76-2.78 (2H, m), 3.02 (2H, brs), 3.69 (3H, s), 3.84 (4H, brs), 5.17 (2H, s), 6.41 (1H, dd, J = 9.2 Hz, 2.7 Hz), 6.70-6.77 (3H, m), 7.07 (2H, d, J = 8.5 Hz).

Reference Example 173

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy]methyl) -4-isocyanatopiperidine-1-carboxylate

[0624] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.57-1.64 (2H, m), 1.81-1.83 (2H, m), 2.64-2.67 (2H, m), 2.89-2.91 (2H, m), 2.99-3.14 (2H, br), 3.74 (3H, s), 3.84 (2H, s), 3.95-4.19 (2H, br), 5.23 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.13 (2H, d, J = 8.6 Hz).

Reference Example 174

5-[(4-Aminopiperidin-4-yl)methoxy]-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquin olin-2(1H)-one

[0625] A mixture of tert-butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -4-isocyanatopiperidine-1-carboxylate (1.18 g), acetic acid (10 mL) and 2 N hydrochloric acid (10 mL) was stirred at room temperature overnight. The reaction solution was concentrated, water was added to the residue, and the reaction mixture was made basic with aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/methanol) to provide the title compound (683 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.50-1.53 (2H, m), 1.69-1.77 (2H, m), 2.63-2.66 (2H, m), 2.87-2.92 (4H, m), 2.98-3.03 (2H, br), 3.67 (2H, s), 3.74 (3H, s), 5.23 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.13 (2H, d, J = 8.5 Hz).

Reference Example 175

5-{[4-Amino-1-(2-chloro-4-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-met hoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0626] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.69 (2H, m), 1.92-1.98 (2H, m), 2.64-2.67 (2H, m), 2.89-2.92 (2H, m), 3.02-3.10 (4H, m), 3.74-3.74 (5H, m), 5.24 (2H, s), 6.52 (1H, dd, J = 9.0 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.92-6.96 (1H, m), 7.04-7.07 (1H, m), 7.12-7.14 (3H, m).

Reference Example 176

Ethyl 1-(2,4-dichlorophenyl)piperidine-4-carboxylate

[0627] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.28 (3H, t, J = 7.1 Hz), 1.91-2.07 (4H, m), 2.04-2.46 (1H, m), 2.66-2.71 (2H, m), 3.30-3.33 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 6.94 (1H, d, J = 8.7 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

Reference Example 177

Ethyl 1-(4-chloro-2-fluorophenyl)piperidine-4-carboxylate

[0628] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.28 (3H, t, J = 7.1 Hz), 1.89-2.05 (4H, m), 2.39-2.45 (1H, m), 2.69-2.75 (2H, m), 3.36-3.39 (2H, m), 4.16 (2H, q, J = 7.1 Hz), 6.84-6.88 (1H, m), 7.01-7.05 (2H, m).

Reference Example 178

8-Fluoro-2-methoxy-5-[(methylsulfanyl)methoxy]quinoline

[0629] Synthesized analogous to Reference Example 56.
^{1}HNMR ($CDCl_3$) δ ppm: 2.29 (3H, s), 4.11 (3H, s), 5.29 (2H, s), 6.71 (1H, dd, J = 8.6 Hz, 3.4 Hz), 6.94 (1H, d, J = 9.1 Hz), 7.23-7.27 (1H, m), 8.39 (1H, dd, J = 9.1 Hz, 1.7 Hz).

Reference Example 179

8-Chloro-2-methoxy-5-[(methylsulfanyl)methoxy]quinoline

[0630] Synthesized analogous to Reference Example 56.
^{1}HNMR ($CDCl_3$) δ ppm: 2.29 (3H, s), 4.14 (3H, s), 5.30 (2H, s), 6.74 (1H, d, J = 8.5 Hz), 6.93 (1H, d, J = 9.0 Hz), 7.64 (1H, d, J = 8.4 Hz), 8.41 (1H, d, J = 9.0 Hz).

Reference Example 180

Ethyl 1-(2,4-dichlorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4 -carboxylate

[0631] Synthesized analogous to Reference Example 59.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.89-1.94 (2H, m), 2.48-2.50 (2H, m), 2.84-2.89 (2H, m), 3.25-3.27 (2H, m), 4.10 (3H, s), 4.16 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.58 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.92 (1H, d, J = 9.1 Hz), 6.97 (1H, d, J = 8.6 Hz), 7.18-7.24 (2H, m), 7.37 (1H, d, J = 2.4 Hz), 8.32 (1H, d, J = 9.1 Hz).

Reference Example 181

Ethyl 1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperi dine-4-carboxylate

[0632] Synthesized analogous to Reference Example 59.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.87-1.93 (2H, m), 2.47-2.50 (2H, m), 2.87-2.93 (2H, m), 3.30-3.34 (2H, m), 4.10 (3H, s), 4.14 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.58 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.87-6.93 (2H, m), 7.03-7.07 (2H, m), 7.22 (1H, dd, J = 10.6 Hz, 8.6 Hz), 8.32 (1H, dd, J = 9.0 Hz, 1.6 Hz).

Reference Example 182

Ethyl 4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}-1-(2,4-dichlorophenyl)piperidine-4-carboxylate

[0633] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.89-1.94 (2H, m), 2.48-2.50 (2H, m), 2.84-2.89 (2H, m), 3.25-3.27 (2H, m), 4.13 (3H, s), 4.17 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.64 (1H, d, J = 8.5 Hz), 6.92 (1H, d, J = 9.0 Hz), 6.97 (1H, d, J = 8.7 Hz), 7.19 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.37 (1H, d, J = 2.5 Hz), 7.61 (1H, d, J = 8.4 Hz), 8.34 (1H, d, J = 9.1 Hz).

Reference Example 183

Ethyl 1-(4-chloro-2-fluorophenyl)-4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}piperi dine-4-carboxylate

[0634] Synthesized analogous to Reference Example 79.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.87-1.93 (2H, m), 2.47-2.50 (2H, m), 2.88-2.93 (2H, m), 3.30-3.34 (2H, m), 4.13 (3H, s), 4.16 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.63 (1H, d, J = 8.5 Hz), 6.87-6.93 (2H, m), 7.03-7.07 (2H, m), 7.61 (1H, d, J = 8.4 Hz), 8.34 (1H, d, J = 9.1 Hz).

Reference Example 184

1-(2,4-Dichlorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidin e-4-carboxylic acid

[0635] Synthesized analogous to Reference Example 93.
^{1}HNMR (DMSO-d6) δ ppm: 1.80-1.86 (2H, m), 2.29-2.32 (2H, m), 2.88-2.86 (2H, m), 3.19-3.21 (2H, m), 4.00 (3H, s), 4.25 (2H, s), 6.90 (1H, dd, J = 8.7 Hz, 3.3 Hz), 7.11 (1H, d, J = 9.1 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.44 (1H, dd, J = 10.9 Hz, 8.7 Hz), 7.54 (1H, d, J = 2.5 Hz), 8.31 (1H, dd, J = 9.1 Hz, 1.5 Hz), 12.77 (1H, brs).

Reference Example 185

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}pipe ridine-4-carboxylic acid

[0636] Synthesized analogous to Reference Example 93.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89-1.95 (2H, m), 2.47-2.50 (2H, m), 2.90-2.94 (2H, m), 3.31-3.33 (2H, m), 4.09 (3H, s), 4.16 (2H, s), 6.55 (1H, dd, J = 8.6 Hz, 3.2 Hz), 6.78 (1H, d, J = 9.1 Hz), 7.84-6.87 (1H, m), 7.03-7.06 (2H, m), 7.20 (1H, dd, J = 10.5 Hz, 8.7 Hz), 8.22 (1H, d, J = 9.1 Hz).

Reference Example 186

4-{[(8-Chloro-2-methoxyquinolin-5-yl)oxy]methyl}-1-(2,4-dichlorophenyl)piperidin e-4-carboxylic acid

[0637] Synthesized analogous to Reference Example 93.
^{1}HNMR (DMSO-d6) δ ppm: 1.81-1.86 (2H, m), 2.29-2.32 (2H, m), 2.82-2.86 (2H, m), 3.19-3.21 (2H, m), 4.04 (3H, s), 4.28 (2H, s), 6.98 (1H, dd, J = 8.6 Hz), 7.12 (1H, d, J = 9.0 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.54 (1H, d, J = 2.5 Hz), 7.76 (1H, d, J = 8.5 Hz), 8.34 (1H, d, J = 9.0 Hz), 12.79 (1H, brs).

Reference Example 187

1-(4-Chloro-2-fluorophenyl)-4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}pipe ridine-4-carboxylic acid

[0638] Synthesized analogous to Reference Example 93.
^{1}HNMR (DMSO-d6) δ ppm: 1.80-1.85 (2H, m), 2.28-2.30 (2H, m), 2.84-2.88 (2H, m), 3.26-3.30 (2H, m), 4.04 (3H, s), 4.25 (2H, s), 6.97 (1H, d, J = 8.6 Hz), 7.07-7.18 (3H, m), 7.33 (1H, dd, J = 12.4 Hz, 2.4 Hz), 7.76 (1H, d, J = 8.5 Hz), 8.34 (1H, d, J = 9.0 Hz), 12.80 (1H, brs).

Reference Example 188

5-{[1-(2,4-Dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-2-methox yquinoline

[0639] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 2.03-2.08 (4H, m), 3.03-3.08 (2H, m), 3.29-3.31 (2H, m), 4.10 (2H, s), 4.12 (3H, s), 6.62 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.97 (1H, d, J = 9.1 Hz), 7.05 (1H, d, J = 8.6 Hz), 7.22-7.24 (2H, m), 7.39 (1H, d, J = 2.5 Hz), 8.42 (1H, dd, J = 9.1 Hz, 1.5 Hz).

Reference Example 189

5-{[1-(4-Chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-2-m ethoxyquinoline

[0640] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.99-2.07 (4H, m), 3.06-3.11 (2H, m), 3.35-3.38 (2H, m), 4.09 (2H, s), 4.12 (3H, s), 6.61 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.94-6.98 (2H, m), 7.06-7.09 (2H, m), 7.22-7.26 (1H, m), 8.41 (1H, dd, J = 9.1 Hz, 1.6 Hz).

Reference Example 190

8-Chloro-5-{[1-(2,4-dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-2-methox yquinoline

[0641] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 2.00-2.08 (4H, m), 3.03-3.08 (2H, m), 3.29-3.31 (2H, m), 4.12 (2H, s), 4.15 (3H, s), 6.67 (1H, d, J = 8.5 Hz), 6.97 (1H, d, J = 9.0 Hz), 7.05 (1H, d, J = 8.6 Hz), 7.23 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.39 (1H, d, J = 2.4 Hz), 7.64 (1H, d, J = 8.4 Hz), 8.44 (1H, d, J = 9.0 Hz).

Reference Example 191

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-2-m ethoxyquinoline

[0642] Synthesized analogous to Reference Example 134.
^{1}HNMR ($CDCl_3$) δ ppm: 1.99-2.07 (4H, m), 3.06-3.11 (2H, m), 3.35-3.38 (2H, m), 4.10 (2H, s), 4.15 (3H, s), 6.67 (1H, d, J = 8.5 Hz), 6.94-6.98 (2H, m), 7.06-7.09 (2H, m), 7.64 (1H, d, J = 8.4 Hz), 8.44 (1H, d, J = 9.0 Hz).

Reference Example 192

4-{[(8-Chloro-2-methoxyquinolin-5-yl)oxy]methyl}-1-(2,4-dichlorophenyl)piperidin e-4-amine

[0643] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (2H, brs), 1.76-1.78 (2H, m), 2.02-2.08 (2H, m), 3.10-3.18 (4H, m), 3.94 (2H, s), 4.15 (3H, s), 6.69 (1H, d, J = 8.5 Hz), 6.94 (1H, d, J = 9.0 Hz), 7.04 (1H, d, J = 8.7 Hz), 7.20 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz), 7.63 (1H, d, J = 8.6 Hz), 8.42 (1H, d, J = 9.0 Hz).

Reference Example 193

1-(4-Chloro-2-fluorophenyl)-4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}pipe ridine-4-amine

[0644] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (2H, brs), 1.75-1.77 (2H, m), 2.02-2.07 (2H, m), 3.14-3.25 (4H, m), 3.92 (2H, s), 4.15 (3H, s), 6.68 (1H, d, J = 8.5 Hz), 6.93-6.96 (2H, m), 7.04-7.07 (2H, m), 7.63 (1H, d, J = 8.4 Hz), 8.41 (1H, d, J = 9.0 Hz).

Reference Example 194

1-(2,4-Dichlorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidin e-4-amine

[0645] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (2H, brs), 1.75-1.78 (2H, m), 2.02-2.08 (2H, m), 3.09-3.18 (4H, m), 3.93 (2H, s), 4.12 (3H, s), 6.63 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.94 (1H, d, J = 9.1 Hz), 7.03 (1H, d, J = 8.6 Hz), 7.19-7.26 (2H, m), 7.38 (1H, d, J = 2.4 Hz), 8.40 (1H, dd, J = 9.0 Hz).

Reference Example 195

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}pipe ridine-4-amine

[0646] Synthesized analogous to Reference Example 161.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (2H, brs), 1.75-1.77 (2H, m), 2.02-2.07 (2H, m), 3.14-3.25 (4H, m), 3.91 (2H, s), 4.12 (3H, s), 6.62 (1H, dd, J = 8.6 Hz, 3.4 Hz), 6.93-6.96 (2H, m), 7.04-7.07 (2H, m), 7.23 (1H, dd, J = 10.6 Hz, 8.6 Hz), 8.39 (1H,

dd, J = 9.1 Hz, 1.5 Hz).

Reference Example 196

[0647] 8-(2,5-Dichloro-4-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane To a microwave reaction tube were added 1-bromo-2,5-dichloro-4-fluorobenzene (1.00 g), sodium tert-butoxide (0.473 g), tris(dibenzylideneacetone)dipalladium (0.038 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.077 g), 1,4-dioxa-8-azaspiro[4.5]decane (0.590 mL) and toluene (3 mL). The tube was sealed, and then irradiated with microwave at 130 °C for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (845 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.05 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 7.07 (1H, d, J = 7.5 Hz), 7.19 (1H, d, J = 8.5 Hz).

Reference Example 197

8-(4-Chloro-2-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0648] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88 (4H, t, J = 5.5 Hz), 3.14 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.88 (1H, t, J = 9.0 Hz), 7.01-7.05 (2H, m).

Reference Example 198

8-(2,4-Dichloro-5-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0649] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 6.0 Hz), 3.09 (4H, t, J = 6.0 Hz), 4.00 (4H, s), 6.84 (1H, d, J = 10.5 Hz), 7.38 (1H, d, J = 8.0 Hz).

Reference Example 199

8-(4-Chloro-2,6-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0650] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.23 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 6.83-6.89 (2H, m).

Reference Example 200

8-(2-Chloro-6-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0651] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86 (4H, t, J = 5.5 Hz), 3.24 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 6.91-6.95 (2H, m), 7.13-7.16 (1H, m).

Reference Example 201

8-(4-Chloro-2,5-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0652] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.87 (4H, t, J = 6.0 Hz), 3.15 (4H, t, J = 6.0 Hz), 4.00 (4H, s), 6.73 (1H, dd, J = 10.5 Hz, 7.5 Hz), 7.06 (1H, dd, J = 11.5 Hz, 7.0 Hz).

Reference Example 202

8-(2-Chloro-5-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0653] Under nitrogen atmosphere, to a mixture of 3-bromo-4-chloronitrobenzene (3.05 g), sodium tert-butoxide (1.49 g), tris(dibenzylideneacetone)dipalladium (0.118 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.241 g), and 1,4-di-

oxa-8-azaspiro[4.5]decane (1.86 mL) was added toluene (24 mL), and the reaction mixture was stirred at 90-110 °C for 18 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (346 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.93 (4H, t, J = 5.5 Hz), 3.20 (4H, t, J = 5.5 Hz), 4.02 (4H, s), 7.50 (1H, d, J = 8.5 Hz), 7.82 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.91 (1H, d, J = 2.5 Hz).

Reference Example 203

8-(2,4-Dichloro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0654] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.86 (4H, m), 2.31 (3H, s), 2.93-2.97 (2H, m), 3.41-3.46 (2H, m), 3.99-4.02 (4H, m), 7.05 (1H, d, J = 2.5 Hz), 7.16 (1H, d, J = 2.5 Hz).

Reference Example 204

8-[2-Chloro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0655] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91 (4H, t, J = 5.5 Hz), 3.13 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 6.82 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.89 (1H, d, J = 2.5 Hz), 7.35 (1H, d, J = 9.0 Hz).

Reference Example 205

8-(4-Chloro-3-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0656] Under nitrogen atmosphere, to a mixture of 5-bromo-2-chlorotoluene (2.19 mL), sodium tert-butoxide (1.85 g), tris(dibenzylideneacetone)dipalladium (0.147 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.300 g) and 1,4-dioxa-8-azaspiro[4.5]decane (2.31 mL) was added toluene (24 mL), and the reaction mixture was heated to reflux for 3 h. After the reaction mixture was allowed to cool to room temperature, to the reaction solution was added water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (4.28 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 2.32 (3H, s), 3.28 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 6.70 (1H, dd, J = 8.5 Hz, 3.0 Hz), 6.80 (1H, d, J = 3.0 Hz), 7.17 (1H, d, J = 8.5 Hz).

Reference Example 206

Ethyl 2-chloro-5-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)benzoate

[0657] Under nitrogen atmosphere, to a mixture of ethyl 5-bromo-2-chlorobenzoate (2.12 mL), cesium carbonate (12.2 g), tris(dibenzylideneacetone)dipalladium (0.114 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.233 g) and 1,4-dioxa-8-azaspiro[4.5]decane (1.79 mL) was added toluene (24 mL), and the reaction mixture was heated to reflux for 5 h. To the reaction solution was added aqueous saturated ammonium chloride solution, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (852 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.5 Hz), 1.83 (4H, t, J = 5.5 Hz), 3.33 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.39 (2H, q, J = 7.5 Hz), 6.95 (1H, dd, J = 8.5 Hz, 3.5 Hz), 7.27 (1H, d, J = 8.5 Hz), 7.32 (1H, d, J = 3.5 Hz).

Reference Example 207

8-(4-Ethoxy-2-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0658] Into an eggplant flask were added 1-bromo-4-ethoxy-2-fluorobenzene (758 mg), tris(dibenzylideneacetone)dipalladium (31.7 mg), 2',4',6'-triisopropyl-2-(dicyclohexylphosphino)-1,1'-biphenyl (X-PHOS) (39.6 mg), sodium tert-butoxide (499 mg) and 1,4-dioxa-8-azaspiro[4.5]decane (0.50 mL), the flask was purged with nitrogen, and then toluene

(3.8 mL) was added thereto and the mixture was stirred at 100 °C for 3 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (310 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.5 Hz), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.97 (2H, q, J = 7.5 Hz), 4.00 (4H, s), 6.59 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.63 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

Reference Example 208

8-[2-Chloro-4-(propan-2-yl)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0659] To a solution of 8-[4-(propan-2-yl)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane (803 mg) in N,N-dimethylformamide (6.5 mL) was added N-chlorosuccinimide (451 mg), and the reaction mixture was stirred at room temperature for 45 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (726 mg). ^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 1.90 (4H, t, J = 5.5 Hz), 2.83 (1H, sep, J = 7.0 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.99 (1H, d, J = 8.5 Hz), 7.05 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.22 (1H, d, J = 2.0 Hz).

Reference Example 209

8-(2-Fluoro-4-propoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0660] Synthesized analogous to Reference Example 207.
^{1}HNMR ($CDCl_3$) δ ppm: 1.02 (3H, t, J = 7.0 Hz), 1.74-1.81 (2H, m), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.85 (2H, t, J = 6.5 Hz), 3.99 (4H, s), 6.59 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.64 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

Reference Example 210

8-(2-Chloro-4-ethylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0661] Synthesized analogous to Reference Example 208.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 1.90 (4H, t, J = 5.5 Hz), 2.57 (2H, q, J = 7.5 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.98 (1H, d, J = 8.0 Hz), 7.03 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.20 (1H, d, J = 2.0 Hz).

Reference Example 211

8-(2-Chloro-4-propylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0662] Synthesized analogous to Reference Example 208.
^{1}HNMR ($CDCl_3$) δ ppm: 0.92 (3H, t, J = 7.5 Hz), 1.60 (2H, sext, J = 7.5 Hz), 1.90 (4H, t, J = 5.5 Hz), 2.50 (2H, t, J = 7.5 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.97 (1H, d, J = 8.0 Hz), 7.00 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.18 (1H, d, J = 2.0 Hz).

Reference Example 212

8-(2,4-Dichloro-6-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0663] Synthesized analogous to Reference Example 208.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84 (4H, t, J = 5.5 Hz), 3.21 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.98 (1H, dd, J = 11.0 Hz, 2.0 Hz), 7.18 (1H, dd, J = 2.0 Hz, 1.5 Hz).

Reference Example 213

8-(4-Butoxy-2-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0664] Synthesized analogous to Reference Example 207.
^{1}HNMR ($CDCl_3$) δ ppm: 0.96 (3H, t, J = 7.5 Hz), 1.43-1.51 (2H, m), 1.71-1.76 (2H, m), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.89 (2H, t, J = 6.5 Hz), 4.00 (4H, s), 6.59 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.64 (1H, dd, J = 13.5

Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

Reference Example 214

8-[2-Fluoro-4-(propan-2-yloxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0665] Synthesized analogous to Reference Example 207.
^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (6H, d, J = 6.0 Hz), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.43 (1H, sep, J = 6.0 Hz), 6.58 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.62 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.90 (1H, t, J = 9.0 Hz).

Reference Example 215

8-[2-Chloro-4-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0666] Synthesized analogous to Reference Example 208.
^{1}HNMR ($CDCl_3$) δ ppm: 1.90 (4H, t, J = 5.5 Hz), 3.10 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 7.04 (1H, d, J = 9.0 Hz), 7.07-7.09 (1H, m), 7.26 (1H, d, J = 2.5 Hz).

Reference Example 216

8-[2-Fluoro-4-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0667] Synthesized analogous to Reference Example 207.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.16 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.92-6.97 (3H, m).

Reference Example 217

8-(2-Fluoro-4-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0668] Synthesized analogous to Reference Example 207.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.76 (3H, s), 4.00 (4H, s), 6.60 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 218

8-[2,4-Dichloro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0669] Synthesized analogous to Reference Example 208.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.92 (4H, m), 3.09-3.12 (4H, m), 4.01 (4H, s), 6.98 (1H, d, J = 1.0 Hz), 7.46 (1H, s).

Reference Example 219

8-[2-Fluoro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0670] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.19 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.75-6.80 (2H, m), 7.00 (1H, dd, J = 12.0 Hz, 9.0 Hz).

Reference Example 220

8-[4-(Benzyloxy)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0671] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 5.00 (2H, s), 6.60 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.72 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 7.31-7.34 (1H, m), 7.37-7.42 (4H, m).

Reference Example 221

8-[2-Fluoro-4-(2-methoxyethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0672] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.44 (3H, s), 3.71-3.73 (2H, m), 3.99 (4H, s), 4.05-4.07 (2H, m), 6.63 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.91 (1H, t, J = 9.0 Hz).

Reference Example 222

8-(2-Bromo-5-ethoxy-4-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0673] Synthesized analogous to Reference Example 207.
^{1}HNMR ($CDCl_3$) δ ppm: 1.49 (3H, t, J = 7.5 Hz), 1.92 (4H, t, J = 5.5 Hz), 3.22 (4H, t, J = 5.5 Hz), 4.02 (4H, s), 4.15 (2H, q, J = 7.5 Hz), 6.61 (1H, s), 8.18 (1H, s).

Reference Example 223

8-[4-Chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0674] Synthesized analogous to Reference Example 208.
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.89 (4H, m), 3.15-3.18 (4H, m), 4.01 (4H, s), 6.87 (1H, d, J = 9.0 Hz), 7.13 (1H, d, J = 11.5 Hz).

Reference Example 224

8-(4-Ethoxy-2,5-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0675] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 1.88 (4H, t, J = 5.5 Hz), 3.07 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.04 (2H, q, J = 7.0 Hz), 6.71 (1H, dd, J = 13.0 Hz, 7.5 Hz), 6.76 (1H, dd, J = 13.0 Hz, 8.0 Hz).

Reference Example 225

8-[4-(Ethoxymethyl)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0676] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.24 (3H, t, J = 7.0 Hz), 1.89 (4H, t, J = 5.5 Hz), 3.16 (4H, t, J = 5.5 Hz), 3.52 (2H, q, J = 7.0 Hz), 4.00 (4H, s), 4.41 (2H, s), 6.93 (1H, t, J = 8.0 Hz), 7.00-7.05 (2H, m).

Reference Example 226

8-(2,6-Difluoro-4-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0677] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.18 (4H, t, J = 5.5 Hz), 3.74 (3H, s), 3.99 (4H, s), 6.38-6.44 (2H, m).

Reference Example 227

2-[4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-2,5-difluorophenoxy]-N,N-dimethylethane amine

[0678] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88 (4H, t, J = 5.5 Hz), 2.33 (6H, s), 2.72 (2H, t, J = 6.0 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.06 (2H, t, J = 6.0 Hz), 6.72-6.78 (2H, m).

Reference Example 228

8-(2-Fluoro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0679] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.84 (4H, m), 2.32 (3H, s), 3.14 (4H, brs), 4.00 (4H, s), 6.81-6.88 (1H, m), 6.93-6.98 (2H, m).

Reference Example 229

8-(4-Ethoxy-2,3,5,6-tetrafluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0680] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.84 (4H, t, J = 5.5 Hz), 3.26 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.19 (2H, q, J = 7.0 Hz).

Reference Example 230

8-{2-Fluoro-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-1,4-dioxa-8-azaspiro[4.5]decan e

[0681] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.39 (3H, s), 3.56-3.58 (2H, m), 3.70-3.72 (2H, m), 3.83 (2H, t, J = 5.0 Hz), 3.99 (4H, s), 4.08 (2H, t, J = 5.0 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.91 (1H, t, J = 9.0 Hz).

Reference Example 231

8-(4-Chloro-2-fluoro-5-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0682] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88 (4H, t, J = 5.5 Hz), 2.29 (3H, s), 3.13 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.80 (1H, d, J = 9.0 Hz), 7.02 (1H, d, J = 12.0 Hz).

Reference Example 232

8-(4-Ethoxy-2-fluoro-5-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0683] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.43 (3H, t, J = 7.0 Hz), 1.90 (4H, t, J = 5.5 Hz), 3.11 (4H, t, J = 5.5 Hz), 3.83 (3H, s), 4.00 (4H, s), 4.02 (2H, q, J = 7.0 Hz), 6.61 (1H, d, J = 8.5 Hz), 6.65 (1H, d, J = 13.5 Hz).

Reference Example 233

8-(4-Ethoxy-2,6-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

[0684] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (3H, t, J = 7.0 Hz), 1.83 (4H, t, J = 5.5 Hz), 3.17 (4H, t, J = 5.5 Hz), 3.94 (2H, q, J = 7.0 Hz), 3.99 (4H, s), 6.36-6.42 (2H, m).

Reference Example 234

8-[2-Fluoro-4-(2-fluoroethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0685] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.12-4.19 (2H, m), 4.67-4.78 (2H, m), 6.63 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 235

2-[4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-3-fluorophenoxy]-N,N-dimethylethaneami ne

[0686] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 2.32 (6H, s), 2.70 (2H, t, J = 6.0 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.00 (2H, t, J = 6.0 Hz), 6.62 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.91 (1H, t, J = 9.0 Hz).

Reference Example 236

8-[2-Fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0687] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.10 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.29 (2H, q, J = 8.0 Hz), 6.65 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.71 (1H, dd, J = 13.0 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 237

8-(1-Benzofuran-5-yl)-1,4-dioxa-8-azaspiro[4.5]decane

[0688] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.90 (4H, t, J = 5.5 Hz), 3.27 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 6.68 (1H, d, J = 2.0 Hz), 7.02 (1H, dd, J = 9.0 Hz, 2.0 Hz), 7.14 (1H, d, J = 2.0 Hz), 7.38 (1H, d, J = 9.0 Hz), 7.56 (1H, d, J = 2.0 Hz).

Reference Example 238

6-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)quinoxaline

[0689] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.57 (4H, t, J = 5.5 Hz), 4.02 (4H, s), 7.30 (1H, d, J = 3.0 Hz), 7.55 (1H, dd, J = 9.5 Hz, 3.0 Hz), 7.92 (1H, d, J = 9.5 Hz), 8.58 (1H, d, J = 2.0 Hz), 8.68 (1H, d, J = 2.0 Hz).

Reference Example 239

8-[4-(Difluoromethoxy)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0690] Synthesized analogous to Reference Example 206.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.13 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.43 (1H, t, J = 74.0 Hz), 6.78-6.88 (2H, m), 6.94 (1H, t, J = 9.0 Hz).

Reference Example 240

8-[4-(Difluoromethoxy)-2,6-difluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0691] Synthesized analogous to Reference Example 206.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.23 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.44 (1H, t, J = 73.0 Hz), 6.64-6.70 (2H, m).

Reference Example 241

8-[2-Chloro-4-(methylsulfanyl)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0692] Synthesized analogous to Reference Example 208.
^{1}HNMR ($CDCl_3$) δ ppm: 1.90 (4H, t, J = 5.5 Hz), 2.45 (3H, s), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.99 (1H, d, J = 8.5 Hz), 7.12 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.20 (1H, d, J = 2.0 Hz).

Reference Example 242

8-[4-(Ethylsulfanyl)-2,6-difluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0693] Synthesized analogous to Reference Example 196.
^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (3H, t, J = 7.5 Hz), 1.83 (4H, t, J = 5.5 Hz), 2.89 (2H, q, J = 7.5 Hz), 3.24 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 6.77-6.83 (2H, m).

Reference Example 243

8-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

[0694] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.19 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.27 (2H, q, J = 8.0 Hz), 6.45-6.50 (2H, m).

Reference Example 244

1-(2,5-Dichloro-4-fluorophenyl)piperidin-4-one

[0695] To a solution of 8-(2,5-dichloro-4-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (845 mg) in acetone (20 mL) was added 5 N hydrochloric acid (10 mL), and the reaction mixture was heated to reflux for 3 h. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (556 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.64 (4H, t, J = 6.0 Hz), 3.29 (4H, t, J = 6.0 Hz), 7.08 (1H, d, J = 7.0 Hz), 7.25 (1H, d, J = 8.5 Hz).

Reference Example 245

1-(2,4-Dichloro-5-fluorophenyl)piperidin-4-one

[0696] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.65 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 6.86 (1H, d, J = 10.0 Hz), 7.44 (1H, d, J = 7.5 Hz).

Reference Example 246

1-(4-Chloro-2,6-difluorophenyl)piperidin-4-one

[0697] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.58 (4H, t, J = 6.0 Hz), 3.46 (4H, t, J = 6.0 Hz), 6.89-6.95 (2H, m).

Reference Example 247

1-(2-Chloro-6-fluorophenyl)piperidin-4-one

[0698] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.46 (4H, dt, J = 1.5 Hz, 6.0 Hz), 6.92-7.04 (2H, m), 7.20-7.22 (1H, m).

Reference Example 248

1-(4-Chloro-2,5-difluorophenyl)piperidin-4-one

[0699] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 6.77 (1H, dd, J = 10.5 Hz, 7.5 Hz), 7.12 (1H, dd, J = 11.5 Hz, 7.0 Hz).

Reference Example 249

1-[2-Chloro-5-(trifluoromethoxy)phenyl]piperidin-4-one

[0700] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.66 (4H, t, J = 6.0 Hz), 3.36 (4H, t, J = 6.0 Hz), 6.89 (1H, d, J = 1.0 Hz), 6.90 (1H, dd, J = 9.0 Hz, 1.0 Hz), 7.41 (1H, d, J = 9.0 Hz).

Reference Example 250

1-(2-Chloro-5-nitrophenyl)piperidin-4-one

[0701] To a solution of 8-(2-chloro-5-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (346 mg) in tetrahydrofuran (4 mL) was added 5 N hydrochloric acid (2 mL), and the reaction mixture was stirred at room temperature for 13 h. The reaction solution was concentrated, neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (229 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.69 (4H, t, J = 6.0 Hz), 3.43 (4H, t, J = 6.0 Hz), 7.57 (1H, d, J = 9.0 Hz), 7.90 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.92 (1H, d, J = 2.5 Hz).

Reference Example 251

1-(4-Chloro-3-methylphenyl)piperidin-4-one

[0702] To a solution of 8-(4-chloro-3-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (2.26 g) in tetrahydrofuran (46 mL) was added 5 N hydrochloric acid (23 mL), and the reaction mixture was stirred at room temperature for 14 h, then at 70 °C for 3 h. The reaction solution was concentrated, neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.58 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.35 (3H, s), 2.55 (4H, t, J = 6.0 Hz), 3.56 (4H, t, J = 6.0 Hz), 6.74 (1H, dd, J = 8.5 Hz, 3.0 Hz), 6.83 (1H, d, J = 3.0 Hz), 7.23 (1H, d, J = 8.5 Hz).

Reference Example 252

Ethyl 2-chloro-5-(4-oxopiperidin-1-yl)benzoate

[0703] Synthesized analogous to Reference Example 250.
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 2.57 (4H, t, J = 6.0 Hz), 3.61 (4H, t, J = 6.0 Hz), 4.41 (2H, q, J = 7.0 Hz), 6.99 (1H, dd, J = 9.0 Hz, 3.0 Hz), 7.33 (1H, d, J = 9.0 Hz), 7.35 (1H, d, J = 3.0 Hz).

Reference Example 253

1-[2-Chloro-4-(propan-2-yl)phenyl]piperidin-4-one

[0704] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 7.0 Hz), 2.64 (4H, t, J = 6.0 Hz), 2.86 (1H, sep, J = 7.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 6.99 (1H, d, J = 8.0 Hz), 7.09 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.27 (1H, d, J = 2.0 Hz).

Reference Example 254

1-(2,4-Dichloro-6-methylphenyl)piperidin-4-one

[0705] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.37 (3H, s), 2.53-2.63 (4H, m), 3.22-3.27 (2H, m), 3.59-3.64 (2H, m), 7.10-7.12 (1H, m), 7.21 (1H, d, J = 2.5 Hz).

Reference Example 255

1-(4-Ethoxy-2-fluorophenyl)piperidin-4-one

[0706] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.98 (2H, q, J = 7.0 Hz), 6.62 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 256

1-(2-Fluoro-4-propoxyphenyl)piperidin-4-one

[0707] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 1.03 (3H, t, J = 7.5 Hz), 1.76-1.83 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.87 (2H, t, J = 6.5 Hz), 6.62 (1H, ddd, J = 8.5 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 8.5 Hz).

Reference Example 257

1-(2-Chloro-4-ethylphenyl)piperidin-4-one

[0708] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.5 Hz), 2.59 (2H, q, J = 7.5 Hz), 2.64 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 6.98 (1H, d, J = 8.0 Hz), 7.06 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.25 (1H, d, J = 2.0 Hz).

Reference Example 258

1-(2-Chloro-4-propylphenyl)piperidin-4-one

[0709] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 0.94 (3H, t, J = 7.5 Hz), 1.62 (2H, sext, J = 7.5 Hz), 2.52 (2H, t, J = 7.5 Hz), 2.64 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 6.97 (1H, d, J = 8.0 Hz), 7.03 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.23 (1H, d, J = 2.0 Hz).

Reference Example 259

1-(2,4-Dichloro-6-fluorophenyl)piperidin-4-one

[0710] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.60 (4H, t, J = 6.0 Hz), 3.43 (4H, dt, J = 1.0 Hz, 6.0 Hz), 7.02 (1H, dd, J = 11.0 Hz, 2.0 Hz), 7.24 (1H, t, J = 2.0 Hz).

Reference Example 260

1-(4-Butoxy-2-fluorophenyl)piperidin-4-one

[0711] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.44-1.52 (2H, m), 1.72-1.78 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.90 (2H, t, J = 6.5 Hz), 6.62 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 261

1-[2-Fluoro-4-(propan-2-yloxy)phenyl]piperidin-4-one

[0712] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 1.32 (6H, d, J = 6.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.45 (1H, sep, J = 6.0 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.66 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

Reference Example 262

1-[2-Chloro-4-(trifluoromethoxy)phenyl]piperidin-4-one

[0713] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.65 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 7.06 (1H, d, J = 9.0 Hz), 7.12 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.32 (1H, d, J = 2.5 Hz).

Reference Example 263

1-[2,4-Dichloro-5-(trifluoromethoxy)phenyl]piperidin-4-one

[0714] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.65 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 6.98 (1H, d, J = 1.0 Hz), 7.53 (1H, s).

Reference Example 264

1-[2-Fluoro-4-(trifluoromethoxy)phenyl]piperidin-4-one

[0715] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 6.96-7.02 (3H, m).

Reference Example 265

1-(2-Fluoro-4-methoxyphenyl)piperidin-4-one

[0716] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.77 (3H, s), 6.63 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.95 (1H, t, J = 9.0 Hz).

Reference Example 266

1-[4-(Benzyloxy)-2-fluorophenyl]piperidin-4-one

[0717] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 5.02 (2H, s), 6.70 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.76 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.32-7.36 (1H, m), 7.37-7.43 (4H, m).

Reference Example 267

1-[2-Fluoro-4-(2-methoxyethoxy)phenyl]piperidin-4-one

[0718] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.45 (3H, s), 3.73-3.74 (2H, m), 4.06-4.08 (2H, m), 6.66 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.72 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 268

1-[4-Chloro-2-fluoro-5-(trifluoromethoxy)phenyl]piperidin-4-one

[0719] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.42 (4H, t, J = 6.0 Hz), 6.91 (1H, dd, J = 8.0 Hz, 1.0 Hz), 7.20 (1H, d, J = 11.5 Hz).

Reference Example 269

1-(2-Bromo-5-ethoxy-4-nitrophenyl)piperidin-4-one

[0720] To a solution of 8-(2-bromo-5-ethoxy-4-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (2.70 g) in tetrahydrofuran (54 mL) was added 2 N hydrochloric acid (54 mL), and the reaction mixture was stirred at room temperature for 64 h, then at 70 °C for 6 h. To the reaction mixture were added acetone (80 mL) and 5 N hydrochloric acid (40 mL), and the reaction mixture was heated to reflux for 5 h. The reaction solution was concentrated, neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (662 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.50 (3H, t, J = 7.0 Hz), 2.69 (4H, t, J = 6.0 Hz), 3.44 (4H, t, J = 6.0 Hz), 4.17 (2H, q, J = 7.0 Hz), 6.63 (1H, s), 8.21 (1H, s).

Reference Example 270

1-(4-Ethoxy-2,5-difluorophenyl)piperidin-4-one

[0721] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 1.43 (3H, t, J = 7.0 Hz), 2.61 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.06 (2H, q, J = 7.0 Hz), 6.75 (1H, dd, J = 13.0 Hz, 8.0 Hz), 6.76 (1H, dd, J = 12.5 Hz, 8.0 Hz).

Reference Example 271

1-[4-(Ethoxymethyl)-2-fluorophenyl]piperidin-4-one

[0722] To a solution of 8-[4-(ethoxymethyl)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane (1.19 g) in ethanol/water (12-1.2 mL) was added oxalic acid (1.81 g), and the reaction mixture was heated to reflux for 6 h. To the reaction solution was added water, the mixture was neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (756 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.25 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 3.54 (2H, q, J = 7.0 Hz), 4.43 (2H, s), 6.95 (1H, t, J = 8.5 Hz), 7.05 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.09 (1H, dd, J = 13.0 Hz, 2.0 Hz).

Reference Example 272

1-(2,6-Difluoro-4-methoxyphenyl)piperidin-4-one

[0723] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.57 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 3.76 (3H, s), 6.42-6.48 (2H, m).

Reference Example 273

1-{4-[2-(Dimethylamino)ethoxy]-2,5-difluorophenyl}piperidin-4-one

[0724] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.34 (6H, s), 2.61 (4H, t, J = 6.0 Hz), 2.74 (2H, t, J = 5.5 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.08 (2H, t, J = 5.5 Hz), 6.74-6.81 (2H, m).

Reference Example 274

1-(4-Ethoxy-2,3,5,6-tetrafluorophenyl)piperidin-4-one

[0725] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 2.59 (4H, t, J = 6.0 Hz), 3.48 (4H, t, J = 6.0 Hz), 4.23 (2H, q, J = 7.0 Hz).

Reference Example 275

1-(4-Chloro-2-fluoro-6-methylphenyl)piperidin-4-one

[0726] To a solution of 8-(2-fluoro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (3.46 g) in N,N-dimethylformamide (28 mL) was added N-chlorosuccinimide (2.57 g), and the reaction mixture was stirred at room temperature for 77 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give a mixture of 8-(2-fluoro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane and the title compound (1.9 g). To the mixture were added tetrahydrofuran (40 mL) and 2 N hydrochloric acid (20L), and the reaction mixture was stirred at room temperature for 13 h, then at 70 °C for 6 h. The reaction solution was concentrated and neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (307 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.38 (3H, s), 2.53-2.59 (4H, m), 3.32-3.37 (4H, m), 6.92 (1H, dd, J = 11.5 Hz, 2.0 Hz), 7.00-7.02 (1H, m).

Reference Example 276

1-{2-Fluoro-4-[2-(2-methoxyethoxy)ethoxy]phenyl}piperidin-4-one

[0727] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.40 (3H, s), 3.57-3.59 (2H, m), 3.71-3.72 (2H, m), 3.84 (2H, t, J = 5.0 Hz), 4.10 (2H, t, J = 5.0 Hz), 6.64 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.71 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

Reference Example 277

1-(4-Chloro-2-fluoro-5-methylphenyl)piperidin-4-one

[0728] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.31 (3H, s), 2.62 (4H, t, J = 6.0 Hz), 3.37 (4H, t, J = 6.0 Hz), 6.82 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 12.0 Hz).

Reference Example 278

1-(4-Ethoxy-2-fluoro-5-methoxyphenyl)piperidin-4-one

[0729] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 3.85 (3H, s), 4.04 (2H, q, J = 7.0 Hz), 6.60 (1H, d, J = 8.5 Hz), 6.69 (1H, d, J = 13.0 Hz).

Reference Example 279

1-(4-Ethoxy-2,6-difluorophenyl)piperidin-4-one

[0730] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 2.57 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 3.96 (2H, q, J = 7.0 Hz), 6.40-6.46 (2H, m).

Reference Example 280

1-[2-Fluoro-4-(2-fluoroethoxy)phenyl]piperidin-4-one

[0731] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 4.14-4.21 (2H, m), 4.68-4.79 (2H, m), 6.66 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.72 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

Reference Example 281

1-{4-[2-(Dimethylamino)ethoxy]-2-fluorophenyl}piperidin-4-one

[0732] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.33 (6H, s), 2.62 (4H, t, J = 6.0 Hz), 2.71 (2H, t, J = 5.5 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.01 (2H, t, J = 5.5 Hz), 6.65 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.71 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 282

1-[2-Fluoro-4-(2,2,2-trifluoroethoxy)phenyl]piperidin-4-one

[0733] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 4.31 (2H, q, J = 8.0 Hz), 6.68 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.75 (1H, dd, J = 13.0 Hz, 3.0 Hz), 6.96 (1H, t, J = 9.0 Hz).

Reference Example 283

1-(Quinoxalin-6-yl)piperidin-4-one

[0734] Synthesized analogous to Reference Example 271.
^{1}HNMR ($CDCl_3$) δ ppm: 2.64 (4H, t, J = 6.0 Hz), 3.84 (4H, t, J = 6.0 Hz), 7.36 (1H, d, J = 3.0 Hz), 7.57 (1H, dd, J = 9.5 Hz, 3.0 Hz), 8.00 (1H, d, J = 9.5 Hz), 8.63 (1H, d, J = 2.0 Hz), 8.72 (1H, d, J = 2.0 Hz).

Reference Example 284

1-(1-Benzofuran-5-yl)piperidin-4-one

[0735] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.54 (4H, t, J = 6.0 Hz), 6.70 (1H, dd, J = 2.5 Hz, 0.5 Hz), 7.05 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.17 (1H, dd, J = 2.5 Hz, 0.5 Hz), 7.43 (1H, d, J = 9.0 Hz), 7.60 (1H, d, J = 2.5 Hz).

Reference Example 285

1-[4-(Difluoromethoxy)-2-fluorophenyl]piperidin-4-one

[0736] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.37 (4H, t, J = 6.0 Hz), 6.46 (1H, t, J = 73.5 Hz), 6.88 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.92 (1H, dd, J = 12.5 Hz, 2.5 Hz), 6.97 (1H, t, J = 9.0 Hz).

Reference Example 286

1-[4-(Difluoromethoxy)-2,6-difluorophenyl]piperidin-4-one

[0737] Synthesized analogous to Reference Example 244.
^{1}HNMR ($CDCl_3$) δ ppm: 2.59 (4H, t, J = 6.0 Hz), 3.45 (4H, t, J = 6.0 Hz), 6.47 (1H, t, J = 72.5 Hz), 6.70-6.76 (2H, m).

Reference Example 287

1-[2-Chloro-4-(methylsulfanyl)phenyl]piperidin-4-one

[0738] Synthesized analogous to Reference Example 271.
^{1}HNMR ($CDCl_3$) δ ppm: 2.47 (3H, s), 2.64 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.00 Hz), 6.99 (1H, d, J = 8.5 Hz), 7.15 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.32 (1H, d, J = 2.0 Hz).

Reference Example 288

1-[4-(Ethylsulfanyl)-2,6-difluorophenyl]piperidin-4-one

[0739] Synthesized analogous to Reference Example 271.
^{1}HNMR ($CDCl_3$) δ ppm: 1.33 (3H, t, J = 7.5 Hz), 2.58 (4H, t, J = 6.0 Hz), 2.92 (2H, q, J = 7.5 Hz), 3.45 (4H, t, J = 6.0 Hz), 6.80-6.86 (2H, m).

Reference Example 289

1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]piperidin-4-one

[0740] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.58 (4H, t, J = 6.0 Hz), 3.41 (4H, t, J = 6.0 Hz), 4.30 (2H, q, J = 8.0 Hz), 6.49-6.55 (2H, m).

Reference Example 290

1-Bromo-4-ethoxy-2-fluoro-5-nitrobenzene

[0741] To a suspension of 4-bromo-5-fluoro-2-nitrophenol (5.14 g) and potassium carbonate (6.02 g) in acetonitrile (100 mL) was added ethyl iodide (2.29 mL), and the reaction mixture was heated to reflux for 4 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (4.73 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.50 (3H, t, J = 7.0 Hz), 4.16 (2H, q, J = 7.0 Hz), 6.86 (1H, d, J = 10.0 Hz), 8.14 (1H, d, J = 7.0 Hz).

Reference Example 291

4-Bromo-2,5-difluorophenyl ethyl ether

[0742] Synthesized analogous to Reference Example 290.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (3H, t, J = 7.0 Hz), 4.07 (2H, q, J = 7.0 Hz), 6.76 (1H, dd, J = 9.5 Hz, 7.0 Hz), 7.25 (1H, dd, J = 10.5 Hz, 7.0 Hz).

Reference Example 292

1-Bromo-4-(ethoxymethyl)-2-fluorobenzene

[0743] To a solution of (4-bromo-3-fluorophenyl)methanol (2.19 g) in N,N-dimethylformamide (22 mL) was added sodium hydride (55 % in oil) (0.282 g), and the reaction mixture was stirred at room temperature for 1.5 h. Then ethyl iodide (1.12 mL) was added thereto and the mixture was stirred at 60 °C for 5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with 5 N aqueous sodium hydroxide and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.28 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.25 (3H, t, J = 7.0 Hz), 3.54 (2H, q, J = 7.0 Hz), 4.45 (2H, s), 7.00 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.13 (1H, dd, J = 9.5 Hz, 1.5 Hz), 7.50 (1H, dd, J = 8.0 Hz, 7.0 Hz).

Reference Example 293

2-(4-Bromo-2,5-difluorophenoxy)-N,N-dimethylethaneamine

[0744] To a suspension of 4-bromo-2,5-difluorophenol (4.44 g) and potassium carbonate (9.69 g) in acetonitrile (90 mL) were added sodium iodide (4.14 g) and 2-chloro-N,N-dimethylethylamine hydrochloride (3.98 g), and the reaction mixture was heated to reflux for 5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with 5 N aqueous sodium hydroxide and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to provide the title compound (2.11 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.39 (6H, s), 2.83 (2H, t, J = 5.5 Hz), 4.13 (2H, t, J = 5.5 Hz), 6.75-6.80 (1H, m), 7.21-7.27 (1H, m).

Reference Example 294

1-Bromo-4-ethoxy-2-fluoro-5-methoxybenzene

[0745] Synthesized analogous to Reference Example 290.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (3H, t, J = 7.0 Hz), 3.84 (3H, s), 4.05 (2H, q, J = 7.0 Hz), 6.70 (1H, d, J = 10.0 Hz), 6.96 (1H, d, J = 6.5 Hz).

Reference Example 295

4-Bromo-3,5-difluorophenyl ethyl ether

[0746] Synthesized analogous to Reference Example 290.
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 3.99 (2H, q, J = 7.0 Hz), 6.50-6.54 (2H, m).

Reference Example 296

4-Bromo-3,5-difluorophenyl ethyl sulfide

[0747] Synthesized analogous to Reference Example 290.
^{1}HNMR ($CDCl_3$) δ ppm: 1.35 (3H, t, J = 7.5 Hz), 2.96 (2H, q, J = 7.5 Hz), 6.84-6.87 (2H, m).

Reference Example 297

4-Bromo-3,5-difluorophenyl 2,2,2-trifluoroethyl ether

[0748] Synthesized analogous to Reference Example 290.
^{1}HNMR ($CDCl_3$) δ ppm: 4.33 (2H, q, J = 8.0 Hz), 6.59-6.62 (2H, m).

Reference Example 298

4-Chloro-2-fluoro-5-(2-fluoroethoxy)aniline

[0749] Synthesized analogous to Reference Example 292.
^{1}HNMR ($CDCl_3$) δ ppm: 3.73 (2H, brs), 4.15-4.23 (2H, m), 4.69-4.81 (2H, m), 6.41 (1H, d, J = 8.0 Hz), 7.02 (1H, d, J = 10.5 Hz).

Reference Example 299

4-Chloro-2-fluoro-5-(2,2,2-trifluoroethoxy)aniline

[0750] Synthesized analogous to Reference Example 290.
^{1}HNMR ($CDCl_3$) δ ppm: 3.78 (2H, brs), 4.32 (2H, q, J = 8.0 Hz), 6.46 (1H, d, J = 8.0 Hz), 7.04 (1H, d, J = 10.5 Hz).

Reference Example 300

4-Chloro-5-[2-(dimethylamino)ethoxy]-2-fluoroaniline

[0751] Synthesized analogous to Reference Example 292.
^{1}HNMR ($CDCl_3$) δ ppm: 2.36 (6H, s), 2.76 (2H, t, J = 6.0 Hz), 3.72 (2H, brs), 4.03 (2H, t, J = 6.0 Hz), 6.39 (1H, d, J = 8.0 Hz), 7.01 (1H, d, J = 10.5 Hz).

Reference Example 301

4-Chloro-5-[(4-chlorobenzyl)oxy]-2-fluoroaniline

[0752] Synthesized analogous to Reference Example 292.
^{1}HNMR ($CDCl_3$) δ ppm: 3.70 (2H, brs), 5.02 (2H, s), 6.37 (1H, d, J = 8.0 Hz), 7.04 (1H, d, J = 10.5 Hz), 7.34-7.39 (4H, m).

Reference Example 302

4-Chloro-2-fluoro-5-(2-methoxyethoxy)aniline

[0753] Synthesized analogous to Reference Example 292.
^{1}HNMR ($CDCl_3$) δ ppm: 3.47 (3H, s), 3.72 (2H, brs), 3.76 (2H, t, J = 5.0 Hz), 4.09 (2H, t, J = 5.0 Hz), 6.42 (1H, d, J = 8.0 Hz), 7.01 (1H, d, J = 10.0 Hz).

Reference Example 303

4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethoxy]aniline

[0754] Synthesized analogous to Reference Example 292.
^{1}HNMR ($CDCl_3$) δ ppm: 3.73 (2H, brs), 4.26-4.31 (4H, m), 6.45 (1H, d, J = 8.0 Hz), 6.90-6.92 (2H, m), 6.96-7.01 (2H, m), 7.02 (1H, d, J = 10.0 Hz).

Reference Example 304

4-Chloro-2-fluoro-5-propylaniline

[0755] Under nitrogen atmosphere, a solution of 1-bromo-2-chloro-4-fluoro-5-nitrobenzene (1.40 g), tetrakis(triphenylphosphine)palladium (0) (0.318 g), sodium carbonate (1.75 g) and trans-propenylboronic acid (0.945 g) in 1,4-dioxane-water (30-6 mL) was stirred at 100 °C for 5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give (E)-4-chloro-2-fluoro-5-(1-propenyl)aniline. Under nitrogen atmosphere, to platinum on carbon (wetted with 56 % water) (140 mg) was added a solution of the obtained compound in ethanol (14 mL) and the reaction mixture was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction solution was filtrated with Celite, the filter was washed with ethanol, and the solvent of the filtrate was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (405 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 0.95 (3H, t, J = 7.0 Hz), 1.55-1.63 (2H, m), 2.56 (2H, t, J = 7.5 Hz), 3.64 (2H, brs), 6.61 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 11.0 Hz).

Reference Example 305

1-Chloro-2-ethenyl-5-fluoro-4-nitrobenzene

[0756] Under nitrogen atmosphere, a solution of 1-bromo-2-chloro-4-fluoro-5-nitrobenzene (4.14 g), tetrakis(triphenylphosphine)palladium (0) (0.941 g), sodium carbonate (5.18 g) and vinylboronic acid pinacol ester (5.95 mL) in 1,4-dioxane-water (80-16 mL) was stirred at 100 °C for 3 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (3.20 g).
^{1}HNMR ($CDCl_3$) δ ppm: 5.57 (1H, d, J = 11.0 Hz), 5.85 (1H, d, J = 17.0 Hz), 7.00 (1H, J = 17.0 Hz, 11.0 Hz), 7.35 (1H, dd, J = 10.0 Hz), 8.28 (1H, d, J = 8.0 Hz).

Reference Example 306

4-Chloro-5-ethyl-2-fluoroaniline

[0757] Under nitrogen atmosphere, to a suspension of platinum on carbon (wetted with 56 % water) (150 mg) in ethanol was added a solution of 1-chloro-2-ethenyl-5-fluoro-4-nitrobenzene (1.49 g) in ethanol, and the reaction mixture was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction solution was filtered with Celite, the filtrate was washed with ethanol, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (929 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.17 (3H, t, J = 7.5 Hz), 2.62 (2H, q, J = 7.5 Hz), 3.65 (2H, brs), 6.63 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 10.5 Hz).

Reference Example 307

2-(2-Chloro-4-fluoro-5-nitrophenyl)ethanol

[0758] Under nitrogen atmosphere, to a solution of 1-chloro-2-ethenyl-5-fluoro-4-nitrobenzene (3.69 g) in tetrahydrofuran (70 mL) was added a solution of 1 M borane-tetrahydrofuran complex solution (18.3 mL), and the reaction mixture was stirred at room temperature for 10 h. To the reaction solution were added 10 % aqueous sodium hydroxide (0.925 g) and 30 % hydrogen peroxide water (2.26 mL), and the reaction mixture was stirred at room temperature for 14 h. To the reaction solution was added aqueous saturated ammonium chloride solution, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.08 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.51 (1H, t, J = 5.0 Hz), 3.05 (2H, t, J = 6.5 Hz), 3.93-3.96 (2H, m), 7.36 (1H, J = 10.0 Hz), 8.08 (1H, d, J = 8.0 Hz).

Reference Example 308

5-Ethoxy-2,4-difluoroaniline

[0759] Synthesized analogous to Reference Example 292.
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 3.54 (2H, brs), 4.02 (2H, q, J = 7.0 Hz), 6.41 (1H, t, J = 8.5 Hz), 6.80 (1H, t, J = 10.5 Hz).

Reference Example 309

4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy)ethyl]aniline

[0760] Synthesized analogous to Reference Example 306.
^{1}HNMR ($CDCl_3$) δ ppm: 3.08 (2H, t, J = 7.0 Hz), 3.70 (2H, brs), 4.10 (2H, t, J = 7.0 Hz), 6.73 (1H, d, J = 9.0 Hz), 6.83 (2H, dd, J = 9.5 Hz, 4.0 Hz), 6.96 (2H, t, J = 9.5 Hz), 7.03 (1H, d, J = 10.5 Hz).

Reference Example 310

4-Chloro-2-fluoro-5-(2-methoxyethyl)aniline

[0761] Synthesized analogous to Reference Example 292.
^{1}HNMR ($CDCl_3$) δ ppm: 2.88 (2H, t, J = 7.0 Hz), 3.36 (3H, s), 3.56 (2H, t, J = 7.0 Hz), 3.67 (2H, brs), 6.68 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 10.5 Hz).

Reference Example 311

1-Chloro-5-fluoro-2-[2-(4-fluorophenoxy)ethyl]-4-nitrobenzene

[0762] Under nitrogen atmosphere, to a solution of 2-(2-chloro-4-fluoro-5-nitrophenyl)ethanol (507 mg), 4-fluorophenol (259 mg) and triphenylphosphine (666 mg) in dichloromethane (10 mL) was added a solution of 2.2 M diethyl azodicarboxylate in toluene (1.26 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. To the reaction solution was added 1 N hydrochloric acid, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (260 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 3.25 (2H, t, J = 6.5 Hz), 4.18 (2H, t, J = 6.5 Hz), 6.82 (2H, dd, J = 9.0 Hz, 4.5 Hz), 6.97 (2H, dd, J = 9.0 Hz, 8.5 Hz), 7.37 (1H, J = 10.0 Hz), 8.13 (1H, d, J = 7.5 Hz).

Reference Example 312

5-Ethenyl-2,4-difluoroaniline

[0763] Under nitrogen atmosphere, a solution of 5-bromo-2,4-difluoroaniline (2.04 g), vinylboronic acid pinacol ester

(3.44 mL), potassium fluoride (1.81 g), tri-tert-butylphosphine-tetrafluoroborate (0.137 g) and tris(dibenzylideneacetone)dipalladium (0.172 g) in tetrahydrofuran/water (4: 1) (25 mL) was heated to reflux for 9 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.09 g).
^{1}HNMR ($CDCl_3$) δ ppm: 3.58 (2H, brs), 5.29 (1H, d, J = 11.5 Hz), 5.67 (1H, d, J = 17.5 Hz), 6.72-6.78 (2H, m), 6.87 (1H, dd, J = 9.5 Hz, 7.5 Hz).

Reference Example 313

2,4-Difluoro-5-[(1E)-prop-1-en-1-yl]aniline

[0764] Synthesized analogous to Reference Example 312.
^{1}HNMR ($CDCl_3$) δ ppm: 1.87 (3H, dd, J = 6.5 Hz, 1.0 Hz), 3.54 (2H, brs), 6.15 (1H, dq, J = 16.0 Hz, 6.5 Hz), 6.42 (1H, dd, J = 16.0 Hz, 1.0 Hz), 6.72 (1H, t, J = 10.5 Hz), 6.79 (1H, dd, J = 9.5 Hz, 7.5 Hz).

Reference Example 314

5-Ethyl-2,4-difluoroaniline

[0765] Under nitrogen atmosphere, to 10 % palladium on carbon (wetted with 50 % water) (110 mg) was added a solution of 5-ethenyl-2,4-difluoroaniline (1.09 g) in ethanol (11 mL), and the reaction mixture was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction solution was filtrated with Celite, the filter was washed with ethanol, and the solvent of the filtrate was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (692 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.17 (3H, t, J = 7.5 Hz), 2.55 (2H, q, J = 7.5 Hz), 3.51 (2H, brs), 6.59 (1H, dd, J = 9.5 Hz, 7.5 Hz), 6.71 (1H, dd, J = 11.0 Hz, 10.0 Hz).

Reference Example 315

2,4-Difluoro-5-propylaniline

[0766] Synthesized analogous to Reference Example 314.
^{1}HNMR ($CDCl_3$) δ ppm: 0.93 (3H, t, J = 7.5 Hz), 1.58 (2H, sext, J = 7.5 Hz), 2.49 (2H, t, J = 7.5 Hz), 3.49 (2H, brs) 6.57 (1H, dd, J = 10.0 Hz, 7.5 Hz), 6.71 (1H, dd, J = 11.0 Hz, 9.5 Hz).

Reference Example 316

2-(5-Amino-2-chloro-4-fluorophenyl)ethanol

[0767] Synthesized analogous to Reference Example 306.
^{1}HNMR ($CDCl_3$) δ ppm: 1.43 (1H, brs), 2.88 (2H, t, J = 6.5 Hz), 3.70 (2H, brs), 3.84 (2H, t, J = 6.5 Hz), 6.69 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 10.5 Hz).

Reference Example 317

1-Methyl-1-(2-nitrobenzyl)-4-oxopiperidinium bromide

[0768] To a solution of 1-methyl-4-piperidone (29.1 mL) in acetone (300 mL) was added 2-nitrobenzyl bromide (48.8 g), and the reaction mixture was stirred at room temperature. After 2 h, the precipitate was collected on a filter, and washed with acetone and ethanol to provide the title compound (63.2 g).
^{1}HNMR (DMSO-d6) δ ppm: 2.52-2.60 (2H, m), 2.81-2.96 (2H, m), 3.22 (3H, s), 3.63-3.72 (2H, m), 3.73-3.89 (2H, m), 5.11 (2H, s), 7.80-7.95 (3H, m), 8.18 (1H, d, J = 7.2 Hz).

Reference Example 318

1-(4-Chloro-5-ethoxy-2-fluorophenyl)piperidin-4-one

[0769] To a solution of 4-chloro-5-ethoxy-2-fluoroaniline (2.60 g) in ethanol-water (27-18 mL) was added 1-benzyl-1-methyl-4-oxopiperidinium bromide (3.90 g), and the reaction mixture was stirred at 100 °C for 14 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.42 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 4.06 (2H, q, J = 7.0 Hz), 6.56 (1H, d, J = 8.0 Hz), 7.11 (1H, d, J = 11.5 Hz).

Reference Example 319

1-[4-Chloro-2-fluoro-5-(2-fluoroethoxy)phenyl]piperidin-4-one

[0770] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 4.25 (2H, dt, J = 28.0 Hz, 4.0 Hz), 4.77 (2H, dt, J = 47.5 Hz, 4.0 Hz), 6.64 (1H, d, J = 8.0 Hz), 7.12 (1H, d, J = 11.5 Hz).

Reference Example 320

1-[4-Chloro-2-fluoro-5-(propan-2-yloxy)phenyl]piperidin-4-one

[0771] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 1.35 (6H, d, J = 6.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.38 (4H, t, J = 6.0 Hz), 4.43 (1H, sep, J = 6.0 Hz), 6.59 (1H, d, J = 8.0 Hz), 7.10 (1H, d, J = 11.5 Hz).

Reference Example 321

1-[4-Chloro-2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl]piperidin-4-one

[0772] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 4.37 (2H, q, J = 8.0 Hz), 6.66 (1H, d, J = 7.5 Hz), 7.14 (1H, d, J = 11.5 Hz).

Reference Example 322

1-{4-Chloro-5-[(4-chlorobenzyl)oxy]-2-fluorophenyl}piperidin-4-one

[0773] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.60 (4H, t, J = 6.0 Hz), 3.35 (4H, t, J = 6.0 Hz), 5.06 (2H, s), 6.55 (1H, d, J = 7.5 Hz), 7.13 (1H, d, J = 11.5 Hz), 7.36-7.40 (4H, m).

Reference Example 323

1-[4-Chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]piperidin-4-one

[0774] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 3.47 (3H, s), 3.76-3.78 (2H, m), 4.14-4.16 (2H, m), 6.66 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 11.5 Hz).

Reference Example 324

1-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy)ethoxy]phenyl}piperidin-4-one

[0775] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.37 (4H, t, J = 6.0 Hz), 4.30-4.35 (4H, m), 6.66 (1H, d, J = 7.5 Hz),

6.88-6.92 (2H, m), 6.97-7.01 (2H, m), 7.12 (1H, d, J = 11.5 Hz).

Reference Example 325

1-(4-Chloro-2-fluoro-5-propoxyphenyl)piperidin-4-one

[0776] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 1.07 (3H, t, J = 7.5 Hz), 1.81-1.88 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 3.94 (2H, t, J = 6.5 Hz), 6.55 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 11.5 Hz).

Reference Example 326

1-(5,6-Dimethylpyridin-2-yl)piperidin-4-one

[0777] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.17 (3H, s), 2.38 (3H, s), 2.48 (4H, t, J = 6.0 Hz), 3.87 (4H, t, J = 6.0 Hz), 6.52 (1H, d, J = 8.5 Hz), 7.26 (1H, d, J = 8.5 Hz).

Reference Example 327

1-(4-Chloro-2-fluoro-5-propylphenyl)piperidin-4-one

[0778] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.57-1.65 (2H, m), 2.61-2.64 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.38 (4H, t, J = 6.0 Hz), 6.79 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 12.0 Hz).

Reference Example 328

1-[4-Chloro-2-fluoro-5-(propan-2-yl)phenyl]piperidin-4-one

[0779] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.33 (1H, sep, J = 7.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 6.86 (1H, d, J = 9.5 Hz), 7.07 (1H, d, J = 12.0 Hz).

Reference Example 329

1-(2,4-Difluoro-5-methylphenyl)piperidin-4-one

[0780] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.22 (3H, s), 2.62 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 6.77-6.81 (2H, m).

Reference Example 330

1-(4-Chloro-5-ethyl-2-fluorophenyl)piperidin-4-one

[0781] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 2.62 (4H, t, J = 6.0 Hz), 2.68 (2H, q, J = 7.5 Hz), 3.38 (4H, t, J = 6.0 Hz), 6.82 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

Reference Example 331

1-(4-Chloro-2-fluoro-5-methoxyphenyl)piperidin-4-one

[0782] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.41 (4H, t, J = 6.0 Hz), 3.88 (3H, s), 6.55 (1H, d, J = 8.0 Hz), 7.12 (1H, d, J = 11.5 Hz).

Reference Example 332

1-(2,2,6-Trifluoro-1,3-benzodioxol-5-yl)piperidin-4-one

[0783] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 6.80 (1H, d, J = 7.0 Hz), 6.90 (1H, d, J = 10.5 Hz).

Reference Example 333

1-(5-Ethoxy-2,4-difluorophenyl)piperidin-4-one

[0784] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 4.08 (2H, q, J = 7.0 Hz), 6.63 (1H, t, J = 8.0 Hz), 6.88 (1H, t, J = 11.0 Hz).

Reference Example 334

1-(2,4-Difluoro-5-methoxyphenyl)piperidin-4-one

[0785] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.35 (4H, t, J = 6.0 Hz), 3.87 (3H, s), 6.63 (1H, t, J = 8.0 Hz), 6.89 (1H, t, J = 11.5 Hz).

Reference Example 335

1-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy)ethyl]phenyl}piperidin-4-one

[0786] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.14 (2H, t, J = 6.5 Hz), 3.38 (4H, t, J = 6.0 Hz), 4.12 (2H, t, J = 6.5 Hz), 6.79-6.84 (1H, m), 6.91-6.98 (4H, m), 7.11 (1H, d, J = 11.5 Hz).

Reference Example 336

1-(5-Ethyl-2,4-difluorophenyl)piperidin-4-one

[0787] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 2.62 (2H, q, J = 7.5 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 6.79 (1H, dd, J = 11.5 Hz, 9.5 Hz), 6.81 (1H, dd, J = 9.5 Hz, 8.0 Hz).

Reference Example 337

1-(2,4-Difluoro-5-propylphenyl)piperidin-4-one

[0788] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 0.94 (3H, t, J = 7.5 Hz), 1.60 (2H, sext, J = 7.5 Hz), 2.55 (2H, t, J = 7.5 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 6.76-6.82 (2H, m).

Reference Example 338

1-[4-Chloro-2-fluoro-5-(2-methoxyethyl)phenyl]piperidin-4-one

[0789] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 2.94 (2H, t, J = 7.0 Hz), 3.36 (3H, s), 3.39 (4H, t, J = 6.0 Hz), 3.58 (2H, t, J = 7.0 Hz), 6.88 (1H, d, J = 9.0 Hz), 7.09 (1H, d, J = 12.0 Hz).

Reference Example 339

1-(2-Bromo-4-chloro-6-fluorophenyl)piperidin-4-one

[0790] Synthesized analogous to Reference Example 318.
^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, brs), 3.34-3.51 (4H, m), 7.07 (1H, dd, J = 11.2 Hz, 2.4 Hz), 7.43 (1H, t, 2.0 Hz).

Reference Example 340

6-(3,5-Dichloropyridin-2-yl)-1-oxa-6-azaspiro[2.5]octane

[0791] A solution of 1-(3,5-dichloropyridin-2-yl)piperidin-4-one (3.0 g), trimethylsulfoxonium iodide (2.69 g) and potassium tert-butoxide (1.37 g) in 1,2-dimethoxyethane (60 mL) was refluxed for 21 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.01 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.69 (2H, m), 1.96-2.04 (2H, m), 2.73 (2H, s), 3.38-3.46 (2H, m), 3.50-3.58 (2H, m), 7.60 (1H, d, J = 2.2 Hz), 8.12 (1H, d, J = 2.2 Hz).

Reference Example 341

6-(2,4-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0792] To a solution of trimethylsulfoxonium iodide (550 mg) in dimethyl sulfoxide (6.8 mL) was added sodium hydride (55 % in oil) (109 mg), and the reaction mixture was stirred at room temperature for 30 min. To the reaction mixture was added a solution of 1-(2,4-dichlorophenyl)piperidin-4-one (555 mg) in dimethyl sulfoxide (3 mL), and the reaction mixture was stirred at room temperature for 2.5 h. Under ice-cooling, to the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed sequentially with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (442 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.06-2.11 (2H, m), 2.73 (2H, s), 3.08-3.13 (2H, m), 3.15-3.20 (2H, m), 7.00 (1H, d, J = 8.5 Hz), 7.19 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.38 (1H, d, J = 2.5 Hz).

Reference Example 342

6-(2,5-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0793] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.67 (2H, m), 2.04-2.10 (2H, m), 2.73 (2H, s), 3.10-3.16 (2H, m), 3.18-3.22 (2H, m), 6.95 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.03 (1H, d, J = 2.5 Hz), 7.28 (1H, d, J = 8.5 Hz).

Reference Example 343

6-(2,5-Dichloro-4-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0794] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 2.05-2.11 (2H, m), 2.73 (2H, s), 3.06-3.16 (4H, m), 7.09 (1H, d, J = 7.0 Hz), 7.21 (1H, d, J = 8.5 Hz).

Reference Example 344

6-(2-Chloro-4-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0795] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 2.06-2.11 (2H, m), 2.73 (2H, s), 3.05-3.16 (4H, m), 6.94 (1H, ddd, J = 8.5 Hz, 8.0 Hz, 3.0 Hz), 7.04 (1H, dd, J = 8.5 Hz, 5.5 Hz), 7.14 (1H, dd, J = 8.0 Hz, 3.0 Hz).

Reference Example 345

6-Phenyl-1-oxa-6-azaspiro[2.5]octane

[0796] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 1.95-2.00 (2H, m), 2.72 (2H, s), 3.32-3.37 (2H, m), 3.40-3.44 (2H, m), 6.86 (1H, t, J = 7.0 Hz), 6.97 (2H, d, J = 8.0 Hz), 7.27 (2H, dd, J = 8.0 Hz, 7.0 Hz).

Reference Example 346

N,N-Dimethyl-4-(1-oxa-6-azaspiro[2.5]oct-6-yl)aniline

[0797] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.68 (2H, m), 1.95-2.00 (2H, m), 2.70 (2H, s), 2.87 (6H, s), 3.16-3.24 (4H, m), 6.74 (2H, d, J = 9.5 Hz), 6.95 (2H, d, J = 9.5 Hz).

Reference Example 347

6-(3-Chlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0798] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.58-1.62 (2H, m), 1.94-1.99 (2H, m), 2.72 (2H, s), 3.32-3.37 (2H, m), 3.42-3.47 (2H, m), 6.79-6.83 (2H, m), 6.91 (1H, t, J = 2.0 Hz), 7.16 (1H, t, J = 8.5 Hz).

Reference Example 348

6-(Pyridin-3-yl)-1-oxa-6-azaspiro[2.5]octane

[0799] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 1.98-2.04 (2H, m), 2.74 (2H, s), 3.35-3.40 (2H, m), 3.45-3.50 (2H, m), 7.17 (1H, dd, J = 8.5 Hz, 4.5 Hz), 7.23 (1H, ddd, J = 8.5 Hz, 3.0 Hz, 1.5 Hz), 8.10 (1H, dd, J = 4.5 Hz, 1.5 Hz), 8.35 (1H, d, J = 3.0 Hz).

Reference Example 349

6-(Thiophen-3-yl)-1-oxa-6-azaspiro[2.5]octane

[0800] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 1.95-2.00 (2H, m), 2.72 (2H, s), 3.23-3.33 (4H, m), 6.22-6.24 (1H, m), 6.88-6.90 (1H, m), 7.23-7.26 (1H, m).

Reference Example 350

6-(4-Chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0801] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.03-2.09 (2H, m), 2.73 (2H, s), 3.14-3.18 (2H, m), 3.21-3.25 (2H, m), 6.89-6.23 (1H, m), 7.03-7.07 (2H, m).

Reference Example 351

6-(2,4-Dichloro-5-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0802] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.64 (2H, m), 2.07-2.12 (2H, m), 2.74 (2H, s), 3.08-3.13 (2H, m), 3.17-3.21 (2H, m), 6.86 (1H, d, J = 10.5 Hz), 7.40 (1H, d, J = 7.5 Hz).

Reference Example 352

6-(2,3-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0803] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.08-2.13 (2H, m), 2.74 (2H, s), 3.11-3.16 (2H, m), 3.18-3.22 (2H, m), 6.99 (1H, dd, J = 7.0 Hz, 2.5 Hz), 7.13-7.17 (2H, m).

Reference Example 353

6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0804] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.19-3.23 (2H, m), 3.34-3.39 (2H, m), 6.85-6.91 (2H, m).

Reference Example 354

6-[4-Chloro-2-(trifluoromethyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0805] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.53-1.57 (2H, m), 2.05-2.10 (2H, m), 2.72 (2H, s), 2.96-3.01 (2H, m), 3.05-3.09 (2H, m), 7.33 (1H, d, J = 8.5 Hz), 7.48 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.61 (1H, d, J = 2.5 Hz).

Reference Example 355

6-(3,4-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0806] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.57-1.61 (2H, m), 1.95-2.00 (2H, m), 2.73 (2H, s), 3.30-3.35 (2H, m), 3.40-3.45 (2H, m), 6.78 (1H, dd, J = 9.0 Hz, 3.0 Hz), 7.00 (1H, d, J = 3.0 Hz), 7.27 (1H, d, J = 9.0 Hz).

Reference Example 356

6-(4-Chloro-2-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0807] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.68 (2H, m), 1.96-2.01 (2H, m), 2.30 (3H, s), 2.72 (2H, s), 2.94-2.99 (2H, m), 3.01-3.06 (2H, m), 6.97 (1H, d, J = 8.0 Hz), 7.12 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.16 (1H, d, J = 2.5 Hz).

Reference Example 357

6-[2-(Trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0808] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.14-3.24 (4H, m), 6.99 (1H, ddd, J = 8.0 Hz, 7.5 Hz, 1.5 Hz), 7.06 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.19-7.26 (2H, m).

Reference Example 358

6-(2-Chloro-6-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0809] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67 (2H, brs), 1.94 (2H, brs), 2.71 (2H, s), 3.19-3.26 (2H, m), 3.36-3.41 (2H, m), 6.92-6.99 (2H, m), 7.14-7.19 (1H, m).

Reference Example 359

6-(4-Chloro-2,5-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0810] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.03-2.09 (2H, m), 2.74 (2H, s), 3.14-3.19 (2H, m), 3.23-3.27 (2H, m), 6.76 (1H, dd, J = 11.0 Hz, 8.0 Hz), 7.08 (1H, dd, J = 11.5 Hz, 7.0 Hz).

Reference Example 360

6-(2-Bromo-4-chlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0811] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.07-2.12 (2H, m), 2.73 (2H, s), 3.07-3.12 (2H, m), 3.14-3.18 (2H, m), 7.00 (1H, d, J = 8.5 Hz), 7.24 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.57 (1H, d, J = 2.5 Hz).

Reference Example 361

6-(2,4,6-Trichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0812] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.68 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.16-3.20 (2H, m), 3.41-3.46 (2H, m), 7.27-7.30 (2H, m).

Reference Example 362

6-(2,6-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0813] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.71 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.20-3.25 (2H, m), 3.43-3.48 (2H, m), 6.97 (1H, t, J = 8.0 Hz), 7.25-7.29 (2H, m).

Reference Example 363

6-(4-Chloro-3-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0814] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.97-2.02 (2H, m), 2.73 (2H, s), 3.29-3.34 (2H, m), 3.38-3.43 (2H, m), 3.89 (3H, s), 6.50 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.54 (1H, d, J = 3.0 Hz), 7.21 (1H, d, J = 9.0 Hz).

Reference Example 364

6-(3-Ethoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0815] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 1.59-1.64 (2H, m), 1.93-1.99 (2H, m), 2.71 (2H, s), 3.32-3.37 (2H, m), 3.40-3.45 (2H, m), 4.02 (2H, q, J = 7.0 Hz), 6.41 (1H, dd, J = 8.0 Hz, 2.5 Hz), 6.51 (1H, t, J = 2.5 Hz), 6.57 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.16 (1H, t, J = 8.0 Hz).

Reference Example 365

6-(4-Ethoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0816] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.64-1.68 (2H, m), 1.96-2.02 (2H, m), 2.72 (2H, s), 3.17-3.29 (4H, m), 3.99 (2H, q, J = 7.0 Hz), 6.84 (2H, d, J = 9.0 Hz), 6.94 (2H, d, J = 9.0 Hz).

Reference Example 366

6-[3-(Propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0817] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.25 (6H, d, J = 7.0 Hz), 1.63-1.68 (2H, m), 1.95-2.01 (2H, m), 2.72 (2H, s), 2.86 (1H, sep, J = 7.0 Hz), 3.30-3.34 (2H, m), 3.35-3.43 (2H, m), 6.76 (1H, dd, J = 7.5 Hz, 1.0 Hz), 6.79 (1H, dd, J = 7.5 Hz, 2.5 Hz), 6.85 (1H, dd, J = 2.5 Hz, 1.0 Hz), 7.20 (1H, t, J = 7.5 Hz).

Reference Example 367

6-[4-(Propan-2-yl)phenyl]-1-oxa-6-azaspiro [2.5]octane

[0818] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 7.0 Hz), 1.62-1.67 (2H, m), 1.94-2.00 (2H, m), 2.71 (2H, s), 2.84 (1H, sep, J = 7.0 Hz), 3.26-3.38 (4H, m), 6.92 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.5 Hz).

Reference Example 368

6-(3,5-Dichloropyridin-4-yl)-1-oxa-6-azaspiro[2.5]octane

[0819] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.00-2.06 (2H, m), 2.74 (2H, s), 3.35-3.40 (2H, m), 3.54-3.59 (2H, m), 8.35 (2H, s).

Reference Example 369

4-(1-Oxa-6-azaspiro[2.5]oct-6-yl)benzonitrile

[0820] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.59 (2H, m), 1.95-2.01 (2H, m), 2.74 (2H, s), 3.46-3.51 (2H, m), 3.63-3.68 (2H, m), 6.89 (2H, d, J = 9.0 Hz), 7.50 (2H, d, J = 9.0 Hz).

Reference Example 370

3-(1-Oxa-6-azaspiro[2.5]oct-6-yl)benzonitrile

[0821] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.58-1.63 (2H, m), 1.97-2.02 (2H, m), 2.74 (2H, s), 3.35-3.40 (2H, m), 3.48-3.52 (2H, m), 7.09 (1H, dd, J = 7.5 Hz, 1.0 Hz), 7.14-7.16 (2H, m), 7.32 (1H, dd, J = 9.0 Hz, 7.5 Hz).

Reference Example 371

6-(4-Phenoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0822] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.68 (2H, m), 1.98-2.03 (2H, m), 2.73 (2H, s), 3.26-3.31 (2H, m), 3.34-3.38 (2H, m), 6.94-6.97 (6H, m), 7.04 (1H, t, J = 7.5 Hz), 7.28-7.31 (2H, m).

Reference Example 372

6-(Biphenyl-2-yl)-1-oxa-6-azaspiro[2.5]octane

[0823] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39-1.44 (2H, m), 1.67-1.73 (2H, m), 2.61 (2H, s), 2.90-3.02 (4H, m), 7.08 (2H, t, J = 7.5 Hz), 7.25-7.31 (3H, m), 7.40 (2H, t, J = 7.5 Hz), 7.64-7.66 (2H, m).

Reference Example 373

6-[2-Chloro-5-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0824] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.07-2.12 (2H, m), 2.74 (2H, s), 3.12-3.17 (2H, m), 3.21-3.25 (2H, m), 6.85 (1H, ddd, J = 8.5 Hz, 2.5 Hz, 1.0 Hz), 6.90 (1H, d, J = 2.5 Hz), 7.37 (1H, d, J = 8.5 Hz).

Reference Example 374

6-[2-(Propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0825] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 7.0 Hz), 1.68 (2H, brs), 1.98 (2H, brs), 2.72 (2H, s), 2.93-2.98 (2H, m), 3.04-3.09 (2H, m), 3.52 (1H, sep J = 7.0 Hz), 7.08-7.18 (3H, m), 7.24-7.28 (1H, m).

Reference Example 375

6-(2-Chloro-5-nitrophenyl)-1-oxa-6-azaspiro[2.5]octane

[0826] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.70 (2H, m), 2.09-2.14 (2H, m), 2.76 (2H, s), 3.18-3.31 (4H, m), 7.52 (1H, d, J = 8.5 Hz), 7.84 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.92 (1H, d, J = 2.5 Hz).

Reference Example 376

6-(2-Ethylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0827] To a solution of trimethylsulfoxonium iodide (1.48 g) in dimethyl sulfoxide (10 mL) was added sodium tert-butoxide (0.65 g), and the reaction mixture was stirred at room temperature for 30 min. To the reaction solution was added a solution of 1-(2-ethylphenyl)-piperidin-4-one (1.24 g) in dimethyl sulfoxide (4 mL), and the reaction mixture was stirred at room temperature for 8.5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (880 mg) as a colorless oil.
^{1}HNMR ($CDCl_3$) δ ppm: 1.26 (3H, t, J = 7.5 Hz), 1.65-1.69 (2H, m), 1.96-1.99 (2H, m), 2.72 (2H, s), 2.73 (2H, q, J = 7.5 Hz), 2.96-3.00 (2H, m), 3.05-3.10 (2H, m), 7.02-7.19 (3H, m), 7.21-7.28 (1H, m).

Reference Example 377

6-[3-(Trifluoromethyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0828] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.97-2.02 (2H, m), 2.74 (2H, s), 3.36-3.41 (2H, m), 3.47-3.52 (2H, m), 7.08 (1H, d, J = 8.0 Hz), 7.10 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.15 (1H, d, J = 2.5 Hz), 7.35 (1H, t, J = 8.0 Hz).

Reference Example 378

6-(4-Chloro-3-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0829] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.64 (2H, m), 1.94-2.00 (2H, m), 2.33 (3H, s), 2.72 (2H, s), 3.27-3.32 (2H, m), 3.36-3.40 (2H, m), 6.73 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.82 (1H, d, J = 3.0 Hz), 7.19 (1H, d, J = 9.0 Hz).

Reference Example 379

Ethyl 4-(1-oxa-6-azaspiro[2.5]oct-6-yl)benzoate

[0830] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.37 (3H, t, J = 7.0 Hz), 1.56-1.60 (2H, m), 1.95-2.00 (2H, m), 2.74 (2H, s), 3.46-3.51 (2H, m), 3.62-3.66 (2H, m), 4.33 (2H, q, J = 7.0 Hz), 6.90 (2H, d, J = 9.0 Hz), 6.93 (2H, d, J = 9.0 Hz).

Reference Example 380

Ethyl 2-chloro-5-(1-oxa-6-azaspiro[2.5]oct-6-yl)benzoate

[0831] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 1.59-1.63 (2H, m), 1.96-2.01 (2H, m), 2.73 (2H, s), 3.32-3.37 (2H, m), 3.43-3.47 (2H, m), 4.40 (2H, q, J = 7.0 Hz), 6.98 (1H, dd, J = 9.0 Hz, 3.0 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.34 (1H, d, J = 3.0 Hz).

Reference Example 381

6-(2-Chloro-4-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0832] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.05-2.10 (2H, m), 2.28 (3H, s), 2.72 (2H, s), 3.07-3.17 (4H, m), 6.98 (1H, d, J = 8.5 Hz), 7.02 (1H, dd, J = 8.5 Hz, 1.5 Hz), 7.20 (1H, d, J = 1.5 Hz).

Reference Example 382

6-(4-Methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0833] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 1.95-2.00 (2H, m), 2.28 (3H, s), 2.72 (2H, s), 3.26-3.31 (2H, m), 3.33-3.37 (2H, m), 6.89 (2H, d, J = 8.5 Hz), 7.08 (2H, d, J = 8.5 Hz).

Reference Example 383

6-(4-Chloro-2-nitrophenyl)-1-oxa-6-azaspiro[2.5]octane

[0834] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.53-1.57 (2H, m), 2.10-2.15 (2H, m), 2.74 (2H, s), 3.17-3.23 (4H, m), 7.14 (1H, d, J = 8.5 Hz), 7.45 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.80 (1H, d, J = 2.5 Hz).

Reference Example 384

6-[2-Chloro-4-(propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0835] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 1.62-1.65 (2H, m), 2.05-2.10 (2H, m), 2.72 (2H, s), 2.84 (1H, sep, J = 7.0 Hz), 3.09-3.16 (4H, m), 7.00 (1H, d, J = 8.5 Hz), 7.07 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.24 (1H, d, J = 2.0 Hz).

Reference Example 385

6-(4-Bromo-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0836] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.21-3.25 (2H, m), 6.86 (1H, t, J = 9.0 Hz), 7.17-7.21 (2H, m).

Reference Example 386

6-(4-Ethoxy-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0837] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.63-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.08-3.17 (4H, m), 3.97 (2H, q, J = 7.0 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

Reference Example 387

6-(2-Fluoro-4-propoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0838] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.02 (3H, t, J = 7.5 Hz), 1.63-1.67 (2H, m), 1.75-1.82 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.09-3.17 (4H, m), 3.86 (2H, t, J = 6.5 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.94 (1H, t, J = 9.0 Hz).

Reference Example 388

6-(2,4-Dichloro-6-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0839] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.43-1.46 (1H, m), 1.67-1.71 (1H, m), 1.85-1.90 (1H, m), 2.05-2.11 (1H, m), 2.33 (1.5H, s), 2.34 (1.5H, s), 2.70 (1H, s), 2.72 (1H, s), 2.90-2.94 (1H, m), 3.10-3.15 (1H, m), 3.34-3.39 (1H, m), 3.58-3.63 (1H, m), 7.06-7.09 (1H, m), 7.17-7.19 (1H, m).

Reference Example 389

6-(2-Chloro-4-ethylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0840] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 1.62-1.66 (2H, m), 2.05-2.10 (2H, m), 2.58 (2H, q, J = 7.5 Hz), 2.72 (2H, s), 3.09-3.17 (4H, m), 7.00 (1H, d, J = 8.5 Hz), 7.05 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.22 (1H, d, J = 2.0 Hz).

Reference Example 390

6-(2-Chloro-4-propylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0841] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 0.93 (3H, t, J = 7.5 Hz), 1.57-1.65 (4H, m), 2.05-2.10 (2H, m), 2.51 (2H, t, J = 7.5 Hz), 2.72 (2H, s), 3.09-3.20 (4H, m), 6.99 (1H, d, J = 8.0 Hz), 7.02 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.20 (1H, d, J = 2.0 Hz).

Reference Example 391

6-(2,4-Dichloro-6-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0842] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.65 (2H, brs), 1.95 (2H, brs), 2.71 (2H, s), 3.15-3.22 (2H, m), 3.33-3.38 (2H, m), 6.99 (1H, dd, J = 11.5 Hz, 2.5 Hz), 7.20 (1H, dd, J = 2.5 Hz, 2.0 Hz).

Reference Example 392

6-(2-Chloro-4,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0843] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.64 (2H, brs), 1.95 (2H, brs), 2.71 (2H, s), 3.12-3.18 (2H, m), 3.30-3.38 (2H, m), 6.74 (1H, ddd, J = 11.5 Hz, 8.5 Hz, 3.0 Hz), 6.96 (1H, ddd, J = 8.0 Hz, 3.0 Hz, 2.0 Hz).

Reference Example 393

6-(4-Butoxy-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0844] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.44-1.51 (2H, m), 1.63-1.67 (2H, m), 1.71-1.77 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.16 (4H, m), 3.90 (2H, t, J = 6.5 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

Reference Example 394

6-[2-Fluoro-4-(propan-2-yloxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0845] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (6H, d, J = 6.0 Hz), 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.18 (4H, m), 4.44 (1H, sep, J = 6.0 Hz), 6.61 (1H, ddd, J = 8.5 Hz, 3.0 Hz, 1.0 Hz), 6.64 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, dd, J = 9.5 Hz, 8.5 Hz).

Reference Example 395

6-[2-Chloro-4-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0846] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.08-2.13 (2H, m), 2.74 (2H, s), 3.10-3.15 (2H, m), 3.18-3.22 (2H, m), 7.07 (1H, d, J = 8.5 Hz), 7.11 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.28 (1H, d, J = 2.5 Hz).

Reference Example 396

6-[2,4-Dichloro-5-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0847] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.07-2.12 (2H, m), 2.74 (2H, s), 3.10-3.15 (2H, m), 3.18-3.23 (2H, m), 7.00 (1H, d, J = 1.0 Hz), 7.48 (1H, s).

Reference Example 397

6-(2-Fluoro-4-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0848] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.67 (2H, m), 2.03-2.08 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 3.77 (3H, s), 6.62 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.66 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.96 (1H, t, J = 9.0 Hz).

Reference Example 398

6-(2,4,6-Trifluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0849] To a solution of trimethylsulfoxonium iodide (4.89 g) in dimethyl sulfoxide (50 mL) was added sodium tert-butoxide (1.93 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. To the reaction mixture was added a solution of 1-(2,4,6-trifluorophenyl)piperidin-4-one (4.85 g) in dimethyl sulfoxide (10 mL) dropwise, and the reaction mixture was stirred at room temperature for 2 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (4.3 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.68 (2H, m), 1.89-1.99 (2H, m), 2.71 (2H, s), 3.13-3.23 (2H, m), 3.30-3.38 (2H, m), 6.58-6.68 (2H, m).

Reference Example 399

6-[2-Fluoro-4-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0850] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.05-2.10 (2H, m), 2.74 (2H, s), 3.15-3.20 (2H, m), 3.23-3.27 (2H, m), 6.94-7.00 (3H, m).

Reference Example 400

6-[4-(Benzyloxy)-2-fluorophenyl]-1-oxa-6-azaspiro[2.5]octane

[0851] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 5.01 (2H, s), 6.69 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.73 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 7.31-7.35 (1H, m), 7.36-7.43 (4H, m).

Reference Example 401

6-[2-Fluoro-4-(2-methoxyethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0852] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.18 (4H, m), 3.45 (3H, s), 3.72-3.74 (2H, m), 4.05-4.07 (2H, m), 6.65 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.69 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

Reference Example 402

6-[4-Chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0853] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.03-2.09 (2H, m), 2.74 (2H, s), 3.16-3.21 (2H, m), 3.24-3.28 (2H, m), 6.90 (1H, dd, J = 8.0 Hz, 1.0 Hz), 7.15 (1H, d, J = 11.5 Hz).

Reference Example 403

6-(2-Bromo-5-ethoxy-4-nitrophenyl)-1-oxa-6-azaspiro[2.5]octane

[0854] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.50 (3H, t, J = 7.0 Hz), 1.58-1.63 (2H, m), 2.14-2.20 (2H, m), 2.76 (2H, s), 3.17-3.22 (2H, m), 3.34-3.38 (2H, m), 4.17 (2H, q, J = 7.0 Hz), 6.63 (1H, s), 8.19 (1H, s).

Reference Example 404

6-(4-Ethoxy-2,5-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0855] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 1.62-1.66 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.06-3.17 (4H, m), 4.04 (2H, q, J = 7.0 Hz), 6.73 (1H, dd, J = 13.0 Hz, 7.5 Hz), 6.79 (1H, dd, J = 13.0 Hz, 8.0 Hz).

Reference Example 405

6-[4-(Ethoxymethyl)-2-fluorophenyl]-1-oxa-6-azaspiro[2.5]octane

[0856] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.24 (3H, t, J = 7.0 Hz), 1.63-1.67 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.15-3.20 (2H, m), 3.22-3.26 (2H, m), 3.53 (2H, q, J = 7.0 Hz),4.42 (2H, s), 6.93-6.98 (1H, m), 7.02-7.07 (2H, m).

Reference Example 406

6-(2,6-Difluoro-4-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0857] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.68 (2H, m), 1.89-1.94 (2H, m), 2.70 (2H, s), 3.12-3.19 (2H, m), 3.29-3.34 (2H, m), 3.75 (3H, s), 6.39-6.45 (2H, m).

Reference Example 407

2-[2,5-Difluoro-4-(1-oxa-6-azaspiro[2.5]oct-6-yl)phenoxy]-N,N-dimethylethaneamin e

[0858] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.01-2.07 (2H, m), 2.34 (6H, s), 2.72 (2H, s), 2.73 (2H, t, J = 6.0 Hz), 3.06-3.18 (4H, m), 4.07 (2H, t, J = 6.0 Hz), 6.75 (1H, dd, J = 13.0 Hz, 8.0 Hz), 6.78 (1H, dd, J = 12.5 Hz, 8.0 Hz).

Reference Example 408

6-(4-Ethoxy-2,3,5,6-tetrafluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0859] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 1.60-1.65 (2H, m), 1.94-1.99 (2H, m), 2.72 (2H, s), 3.21-3.26 (2H, m), 3.37-3.42 (2H, m), 4.21 (2H, q, J = 7.0 Hz), 6.73 (1H, dd, J = 13.0 Hz, 7.5 Hz), 6.79 (1H, dd, J = 13.0 Hz, 8.0 Hz).

Reference Example 409

6-(4-Chloro-5-ethoxy-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0860] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 1.60-1.64 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.14-3.18 (2H, m), 3.22-3.26 (2H, m), 4.06 (2H, q, J = 7.0 Hz), 6.57 (1H, d, J = 8.0 Hz), 7.07 (1H, d, J = 11.5 Hz).

Reference Example 410

6-{2-Fluoro-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-1-oxa-6-azaspiro[2.5]octane

[0861] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 3.39 (3H, s), 3.57-3.59 (2H, m), 3.70-3.72 (2H, m), 3.83-3.85 (2H, m), 4.08-4.10 (2H, m), 6.63 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

Reference Example 411

6-(4-Chloro-2-fluoro-6-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0862] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.80 (4H, brs), 2.32 (3H, s), 2.71 (2H, s), 3.08 (2H, brs), 3.24 (2H, brs), 6.89 (1H, dd, J = 11.5 Hz, 2.0 Hz), 6.96-6.98 (1H, m).

Reference Example 412

6-(4-Chloro-2-fluoro-5-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0863] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 2.02-2.08 (2H, m), 2.30 (3H, s), 2.73 (2H, s), 3.13-3.17 (2H, m), 3.20-3.24 (2H, m), 6.82 (1H, d, J = 9.5 Hz), 7.04 (1H, d, J = 12.0 Hz).

Reference Example 413

6-(4-Ethoxy-2-fluoro-5-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0864] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.44 (3H, t, J = 7.0 Hz), 1.62-1.67 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.09-3.20 (4H, m), 3.85 (3H, s), 4.03 (2H, q, J = 7.0 Hz), 6.62 (1H, d, J = 8.0 Hz), 6.67 (1H, d, J = 13.0 Hz).

Reference Example 414

6-[2-Fluoro-4-(2-fluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0865] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.03-2.08 (2H, m), 2.72 (2H, s), 3.08-3.18 (4H, m), 4.16 (2H, dt, J = 28.0 Hz, 4.0 Hz), 4.73 (2H, dt, J = 47.5 Hz, 4.0 Hz), 6.65 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.70 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.95 (1H, t, J = 9.0 Hz).

Reference Example 415

6-(4-Ethoxy-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0866] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.63-1.68 (2H, m), 1.88-1.94 (2H, m), 2.70 (2H, s), 3.12-3.18 (2H, m), 3.28-3.33 (2H, m), 3.95 (2H, q, J = 7.0 Hz), 6.38-6.43 (2H, m).

Reference Example 416

2-[3-Fluoro-4-(1-oxa-6-azaspiro[2.5]oct-6-yl)phenoxy]-N,N-dimethylethaneamine

[0867] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.33 (6H, s), 2.68-2.72 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 3.99-4.02 (2H, m), 6.64 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

Reference Example 417

6-(1-Benzothiophen-5-yl)-1-oxa-6-azaspiro[2.5]octane

[0868] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.71 (2H, m), 2.01-2.07 (2H, m), 2.74 (2H, s), 3.33-3.38 (2H, m), 3.42-3.46 (2H, m), 7.12 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.23 (1H, d, J = 5.0 Hz), 7.35 (1H, d, J = 2.5 Hz), 7.41 (1H, d, J = 5.0 Hz), 7.74 (1H, d, J = 9.0 Hz).

Reference Example 418

6-[2-Fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0869] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.66 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.10-3.20 (4H, m), 4.30 (2H, q, J = 8.0 Hz), 6.67 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.72 (1H, dd, J = 13.0 Hz, 2.5 Hz), 6.96 (1H, t, J = 9.0 Hz).

Reference Example 419

6-(1-Oxa-6-azaspiro[2.5]oct-6-yl)quinoxaline

[0870] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.68 (2H, m), 2.03-2.08 (2H, m), 2.77 (2H, s), 3.54-3.59 (2H, m), 3.69-3.74 (2H, m), 7.33 (1H, d, J = 2.5 Hz), 7.56 (1H, dd, J = 9.5 Hz, 2.5 Hz), 7.94 (1H, d, J = 9.5 Hz), 8.60 (1H, d, J = 2.0 Hz), 8.69 (1H, d, J = 2.0 Hz).

Reference Example 420

6-(1-Benzofuran-5-yl)-1-oxa-6-azaspiro[2.5]octane

[0871] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.71 (2H, m), 2.00-2.06 (2H, m), 2.73 (2H, s), 3.26-3.36 (4H, m), 6.69 (1H, d, J = 2.0 Hz), 7.03 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.16 (1H, d, J = 2.5 Hz), 7.40 (1H, d, J = 9.0 Hz), 7.57 (1H, d, J = 2.0 Hz).

Reference Example 421

6-[4-(Difluoromethoxy)-2-fluorophenyl]-1-oxa-6-azaspiro[2.5]octane

[0872] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.66 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.20-3.24 (2H, m), 6.44 (1H, t, J = 73.5 Hz), 6.86 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.89 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.97 (1H, t, J = 9.0 Hz).

Reference Example 422

6-(1-Oxa-6-azaspiro[2.5]oct-6-yl)quinoline

[0873] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.71 (2H, m), 2.03-2.08 (2H, m), 2.76 (2H, s), 3.43-3.48 (2H, m), 3.57-3.61 (2H, m), 7.07-7.09 (1H, m), 7.30-7.32 (1H, m), 7.51-7.53 (1H, m), 7.94-8.00 (2H, m), 8.69-8.73 (1H, m).

Reference Example 423

6-(5-Chloro-3-fluoropyridin-2-yl)-1-oxa-6-azaspiro[2.5]octane

[0874] Synthesized analogous to Reference Example 398.
^{1}HNMR ($CDCl_3$) δ ppm: 1.56-1.65 (2H, m), 1.91-2.01 (2H, m), 2.73 (2H, s), 3.52-3.59 (2H, m), 3.70-3.77 (2H, m), 7.27 (1H, dd, J = 12.2 Hz, 2.2 Hz), 7.95-7.99 (1H, m).

Reference Example 424

6-(2,4-Difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0875] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.11-3.21 (4H, m), 6.78-6.84 (2H, m), 6.93-6.98 (1H, m).

Reference Example 425

6-[4-Chloro-2-fluoro-5-(2-fluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0876] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.04-2.10 (2H, m), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.22-3.27 (2H, m), 4.25 (2H, dt, J = 28.0 Hz, 4.5 Hz), 4.76 (2H, dt, J = 47.5 Hz, 4.5 Hz), 6.64 (1H, d, J = 8.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

Reference Example 426

6-[4-Chloro-2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0877] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.74 (2H, s), 3.14-3.19 (2H, m), 3.22-3.27 (2H, m), 4.36 (2H, q, J = 8.5 Hz), 6.67 (1H, d, J = 8.0 Hz), 7.09 (1H, d, J = 11.5 Hz).

Reference Example 427

6-[4-Chloro-2-fluoro-5-(propan-2-yloxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0878] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.35 (6H, d, J = 6.5 Hz), 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.21-3.25 (2H, m), 4.43 (1H, sep, J = 6.5 Hz), 6.61 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 12.0 Hz).

Reference Example 428

6-{4-Chloro-5-[(4-chlorobenzyl)oxy]-2-fluorophenyl}-1-oxa-6-azaspiro[2.5]octane

[0879] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.57-1.62 (2H, m), 2.03-2.09 (2H, m), 2.73 (2H, s), 3.09-3.14 (2H, m), 3.18-3.22 (2H, m), 5.06 (2H, s), 6.57 (1H, d, J = 7.5 Hz), 7.09 (1H, d, J = 11.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 7.39 (2H, d, J = 8.5 Hz).

Reference Example 429

6-[4-Chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0880] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.64 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.22-3.26 (2H, m), 3.47 (3H, s), 3.77 (2H, t, J = 5.0 Hz), 4.14 (2H, t, J = 5.0 Hz), 6.66 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 11.5 Hz).

Reference Example 430

2-[2-Chloro-4-fluoro-5-(1-oxa-6-azaspiro[2.5]oct-6-yl)phenoxy]-N,N-dimethylethan eamine

[0881] To a solution of 4-chloro-5-[2-(dimethylamino)ethoxy]-2-fluoroaniline (4.46 g) in ethanol-water (45-30 mL) was added 1-benzyl-1-methyl-4-oxopiperidinium bromide (5.45 g), and the reaction mixture was stirred at 100 °C for 23 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off to give 1-(4-chloro-5-(2-(dimethylamino)ethoxy)-2-fluorophenyl)piperidin-4-one (ketone compound). To a solution of trimethylsulfoxonium iodide (4.22 g) in dimethyl sulfoxide (55 mL) was added sodium hydride (55 % in oil) (0.84 g), and the reaction mixture was stirred at room temperature for 30 min. The solution of the obtained ketone compound in dimethyl sulfoxide (8 mL) was added thereto, and the reaction mixture was stirred at room temperature for 2.5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (NH silica gel; hexane/ethyl acetate) to provide the title compound (2.10 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.36 (6H, s), 2.73 (2H, s), 2.77 (2H, t, J = 6.0 Hz), 3.13-3.18 (2H, m), 3.22-3.26 (2H, m), 4.08 (2H, t, J = 6.0 Hz), 6.61 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 11.5 Hz).

Reference Example 431

6-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethoxy]phenyl}-1-oxa-6-azaspiro[2.5]octane

[0882] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.63 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.17 (2H, m), 3.21-3.25 (2H, m), 4.29-4.31 (2H, m), 4.33-4.35 (2H, m), 6.67 (1H, d, J = 7.5 Hz), 6.90 (2H, dd, J = 9.0 Hz, 2.5 Hz), 6.99 (2H, t, J = 9.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

Reference Example 432

6-(4-Chloro-2-fluoro-5-propoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0883] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.06 (3H, t, J = 7.5 Hz), 1.60-1.64 (2H, m), 1.81-1.88 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.22-3.26 (2H, m), 3.94 (2H, t, J = 6.5 Hz), 6.57 (1H, d, J = 7.5 Hz), 7.07 (1H, d, J = 11.5 Hz).

Reference Example 433

6-[4-Chloro-2-fluoro-5-(propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0884] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 6.5 Hz), 1.62-1.66 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.16-3.26 (4H, m), 3.32 (1H, sep, J = 6.5 Hz), 6.88 (1H, d, J = 9.5 Hz), 7.04 (1H, d, J = 11.5 Hz).

Reference Example 434

6-(4-Chloro-2-fluoro-5-propylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0885] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 0.96 (3H, t, J = 7.5 Hz), 1.56-1.65 (4H, m), 2.03-2.08 (2H, m), 2.62 (2H, t, J = 7.5 Hz), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.20-3.25 (2H, m), 6.80 (1H, d, J = 9.5 Hz), 7.04 (1H, d, J = 12.0 Hz).

Reference Example 435

6-[4-(Difluoromethoxy)-2,6-difluorophenyl]-1-oxa-6-azaspiro[2.5]octane

[0886] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.17-3.24 (2H, m), 3.34-3.39 (2H, m), 6.45 (1H, t, J = 73.5 Hz), 6.66-6.72 (2H, m).

Reference Example 436

6-(5,6-Dimethylpyridin-2-yl)-1-oxa-6-azaspiro[2.5]octane

[0887] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.92 (2H, m), 1.85-1.93 (2H, m), 2.15 (3H, s), 2.37 (3H, s), 2.72 (2H, s), 3.55-3.62 (2H, m), 3.76-3.84 (2H, m), 6.45 (1H, d, J = 8.5 Hz), 7.21 (1H, d, J = 8.5 Hz).

Reference Example 437

6-(2,4-Difluoro-5-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0888] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.03-2.08 (2H, m), 2.21 (3H, s), 2.72 (2H, s), 3.10-3.19 (4H, m), 6.76 (1H, dd, J = 12.0 Hz, 9.5 Hz), 6.80 (1H, t, J = 8.5 Hz).

Reference Example 438

6-(4-Chloro-2-fluoro-5-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0889] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 2.05-2.11 (2H, m), 2.74 (2H, s), 3.15-3.20 (2H, m), 3.24-3.28 (2H, m), 3.87 (3H, s), 6.57 (1H, d, J = 8.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

Reference Example 439

6-(4-Chloro-5-ethyl-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0890] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.5 Hz), 1.61-1.66 (2H, m), 2.03-2.08 (2H, m), 2.68 (2H, q, J = 7.5 Hz), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.21-3.25 (2H, m), 6.83 (1H, d, J = 9.0 Hz), 7.04 (1H, d, J = 12.0 Hz).

Reference Example 440

6-(2,2,6-Trifluoro-1,3-benzodioxol-5-yl)-1-oxa-6-azaspiro[2.5]octane

[0891] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.09-3.18 (4H, m), 6.80 (1H, d, J = 7.0 Hz), 6.86 (1H, d, J = 10.0 Hz).

Reference Example 441

6-[2-Chloro-4-(methylsulfanyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0892] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.64 (2H, m), 2.04-2.10 (2H, m), 2.46 (3H, s), 2.73 (2H, s), 3.09-3.18 (4H, m), 6.99-7.01 (1H, m), 7.12-7.15 (1H, m), 7.26-7.30 (1H, m).

Reference Example 442

6-(5-Ethoxy-2,4-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0893] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.10-3.15 (2H, m), 3.16-3.21 (2H, m), 4.07 (2H, q, J = 7.0 Hz), 6.65 (1H, t, J = 9.0 Hz), 6.85 (1H, t, J = 11.5 Hz).

Reference Example 443

6-(2,4-Difluoro-5-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

[0894] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.12-3.16 (2H, m), 3.18-3.22 (2H, m), 3.87 (3H, s), 6.65 (1H, t, J = 8.5 Hz), 6.86 (1H, t, J = 11.5 Hz).

Reference Example 444

6-(4-Bromo-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0895] Synthesized analogous to Reference Example 398.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.91-1.97 (2H, m), 2.71 (2H, s), 3.19-3.23 (2H, m), 3.35-3.39 (2H, m), 7.00-7.05 (2H, m).

Reference Example 445

6-(5-Ethyl-2,4-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0896] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.5 Hz), 1.62-1.66 (2H, m), 2.03-2.08 (2H, m), 2.60 (2H, q, J = 7.5 Hz), 2.73 (2H, s), 3.11-3.20 (4H, m), 6.76 (1H, dd, J = 12.0 Hz, 10.0 Hz), 6.82 (1H, t, J = 9.0 Hz).

Reference Example 446

6-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethyl]phenyl}-1-oxa-6-azaspiro[2.5]octane

[0897] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.11-3.18 (2H, m), 3.13 (2H, t, J = 7.0 Hz), 3.21-3.25 (2H, m), 4.12 (2H, t, J = 7.0 Hz), 6.80-6.84 (2H, m), 6.92 (1H, d, J = 9.0 Hz), 6.96 (2H, t, J = 8.5 Hz), 7.07 (1H, d, J = 12.0 Hz).

Reference Example 447

6-(2,4-Difluoro-5-propylphenyl)-1-oxa-6-azaspiro[2.5]octane

[0898] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 0.94 (3H, t, J = 7.5 Hz), 1.55-1.66 (4H, m), 2.03-2.08 (2H, m), 2.55 (2H, t, J = 7.5 Hz), 2.73 (2H, s), 3.11-3.19 (4H, m), 6.76 (1H, dd, J = 11.5 Hz, 9.5 Hz), 6.79 (1H, dd, J = 9.0 Hz, 8.0 Hz).

Reference Example 448

6-[4-(Ethylsulfanyl)-2,6-difluorophenyl]-1-oxa-6-azaspiro[2.5]octane

[0899] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (3H, t, J = 7.5 Hz), 1.62-1.66 (2H, m), 1.90-1.96 (2H, m), 2.70 (2H, s), 2.90 (2H, q, J = 7.5 Hz), 3.19-3.25 (2H, m), 3.34-3.38 (2H, m), 6.78-6.84 (2H, m).

Reference Example 449

6-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0900] Synthesized analogous to Reference Example 398.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.66 (2H, m), 1.91-1.96 (2H, m), 2.71 (2H, s), 3.14-3.18 (2H, m), 3.31-3.35 (2H, m), 4.28 (2H, q, J = 8.0 Hz), 6.46-6.52 (2H, m).

Reference Example 450

6-[4-Chloro-2-fluoro-5-(2-methoxyethyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

[0901] Synthesized analogous to Reference Example 341.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.02-2.08 (2H, m), 2.73 (2H, s), 2.94 (2H, t, J = 7.0 Hz), 3.14-3.19 (2H, m), 3.21-3.25 (2H, m), 3.36 (3H, s), 3.58 (2H, t, J = 7.0 Hz), 6.88 (1H, d, J = 9.5 Hz), 7.05 (1H, d, J = 12.0 Hz).

Reference Example 451

6-(2,2-Difluoro-1,3-benzodioxol-5-yl)-1-oxa-6-azaspiro[2.5] octane

[0902] Synthesized analogous to Reference Example 398.
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.98-2.03 (2H, m), 2.73 (2H, s), 3.22-3.27 (2H, m), 3.29-3.34 (2H, m), 6.62 (1H, dd, J = 8.5 Hz, 2.0 Hz), 6.74 (1H, d, J = 2.0 Hz), 6.93 (1H, d, J = 8.5 Hz).

Reference Example 452

6-(2-Bromo-4-chloro-6-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

[0903] Synthesized analogous to Reference Example 398.
^{1}HNMR (DMSO-d6) δ ppm: 0.86-2.41 (4H, m), 2.71 (2H, s), 3.03 (2H, m), 3.27-3.44 (2H, m), 7.04 (1H, dd, J = 11.3 Hz, 2.4 Hz), 7.39 (1H, t, J = 2.0 Hz).

Reference Example 453

tert-Butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidine -1-carboxylate

[0904] Under argon atmosphere, a solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (1.0 g), tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (1.30 g) and tripotassium phosphate (0.234 g) in N,N-dimethylformamide/2-propanol (1:1) (10 mL) was stirred at 70 °C for 48 h. To the reaction solution was added water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was washed with diethyl ether to provide the title compound (1.15 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.56-1.78 (4H, m), 1.99-2.08 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.99 (2H, t, J = 7.7 Hz), 3.12-3.30 (2H, m), 3.79 (2H, s), 3.82-4.10 (2H, m), 6.46 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.56 (1H, brs).

Reference Example 454

8-Fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[0905] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.44-1.73 (5H, m), 2.02 (1H, brs), 2.61-2.68 (2H, m), 2.87-2.94 (2H, m), 2.97-3.09 (4H, m), 3.79 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.59 (1H, brs).

Reference Example 455

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -4-hydroxypiperidine-1-carboxylate

[0906] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.58-1.67 (2H, m), 1.67-1.74 (2H, m), 1.99 (1H, brs), 2.61-2.67 (2H, m), 2.83-2.89 (2H, m), 3.11-3.30 (2H, m), 3.74 (3H, s), 3.75 (2H, s), 3.79-4.05 (2H, m), 5.23 (2H, brs), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

Reference Example 456

8-Fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroqu inolin-2(1H)-one hydrochloride

[0907] To a solution of tert-butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -4-hydroxypiperidine-1-carboxylate (6.35 g) in ethyl acetate (60 mL) was added 4 N hydrochloric acid/ethyl acetate (60 mL), and the reaction mixture was stirred at room temperature for 4 h. The solvent was distilled off, and the residue was crystallized from ethyl acetate/ethanol to provide the title compound (5.15 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.73 (2H, m), 1.85-1.94 (2H, m), 2.57-2.66 (2H, m), 2.86-2.94 (2H, m), 3.04-3.13 (2H, m), 3.13-3.21 (2H, m), 3.68 (3H, s), 3.75 (2H, s), 5.10 (2H, brs), 5.14 (1H, s), 6.69 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.78-6.83 (2H, m), 6.98 (1H, dd, J = 13.1 Hz, 9.2 Hz), 7.04-7.09 (2H, m), 8.45-8.71 (2H, m).

Reference Example 457

8-Fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroqu inolin-2(1H)-one

[0908] To a suspension of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroquin olin-2(1H)-one hydrochloride (1.10 g) in ethyl acetate were added water and 5 N aqueous sodium hydroxide to make the reaction residue weakly basic, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was distilled of to provide the title compound (1.03 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.74 (4H, m), 1.95 (2H, brs), 2.62-2.67 (2H, m), 2.84-2.93 (4H, m), 3.00-3.07 (2H, m), 3.74 (3H, s), 3.75 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.76 (2H, d, J = 8.0 Hz), 6.83 (1H, dd, J = 12.5 Hz, 9.0 Hz), 7.12 (2H, d, J = 8.0 Hz).

Reference Example 458

tert-Butyl 4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidine -1-carboxylate

[0909] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.58-1.70 (2H, m), 1.70-1.76 (2H, m), 1.97 (1H, brs), 2.59-2.67 (2H, m), 2.99 (2H, t, J = 7.7 Hz), 3.12-3.30 (2H, m), 3.81 (2H, s), 3.82-4.10 (2H, m), 6.52 (1H, d, J = 8.9 Hz), 7.18 (1H, d, J = 8.9 Hz), 7.74 (1H, brs).

Reference Example 459

8-Chloro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[0910] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.55-2.20 (6H, m), 2.62 (2H, t, J = 7.7 Hz), 2.84-2.96 (2H, m), 2.96-3.11 (4H, m), 3.81 (2H, s), 6.53 (1H, d, J = 8.9 Hz), 7.18 (1H, d, J = 8.9 Hz), 7.78 (1H, brs).

Reference Example 460

8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate

[0911] To a suspension of 8-fluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (10 g) in dichloromethane (100 mL) was added pyridine (4.03 mL), and to the mixture trifluoromethanesulfonic anhydride (6.70 mL) was added dropwise under ice-cooling and then the reaction mixture was stirred at the same temperature for 4 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (12.8 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.68-2.73 (2H, m), 2.93-2.98 (2H, m), 3.75 (3H, s), 5.23 (2H, brs), 6.75-6.79 (2H, m), 6.92-7.00 (2H, m), 7.07-7.12 (2H, m).

Reference Example 461

5-Amino-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0912] Under argon atmosphere, a solution of 8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate (17.5 g), benzophenone imine (9.44 mL), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.89 g), palladium (II) acetate (0.453 g) and cesium carbonate (13.16 g) in toluene (170 mL) was heated to reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, to the reaction solution was added basic silica gel (80 g), and the reaction mixture was filtered. The filtrate was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was dissolved in tetrahydrofuran (170 mL), and 1 N hydrochloric acid (80 mL) was added thereto. The mixture was stirred at room temperature for 1 h, 1 N aqueous sodium hydroxide (80 mL) and water was added thereto, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/ethyl acetate) to provide the title compound (9.74 g). ^{1}HNMR ($CDCl_3$) δ ppm: 2.60-2.70 (4H, m), 3.44 (2H, brs), 3.74 (3H, s), 5.20 (2H, brs), 6.36 (1H, dd, J = 8.8 Hz, 3.8 Hz), 6.70-6.78 (3H, m), 7.10-7.14 (2H, m).

Reference Example 462

N-[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide

[0913] To acetic anhydride (7 mL) was added 5-amino-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (782 mg), and the reactoin mixture was stirred at room temperature for 15 min. To the reaction solution was added diethyl ether, and the precipitate was collected on a filter to provide the title compound (760 mg).
^{1}HNMR (DMSO-d6) δ ppm: 2.02 (3H, s), 2.47-2.62 (2H, m), 2.66-2.78 (2H, m), 3.68 (3H, s), 5.08 (2H, brs), 6.73-6.85 (2H, m), 6.95-7.13 (4H, m), 9.55 (1H, brs).

Reference Example 463

8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate

[0914] Synthesized analogous to Reference Example 460.
^{1}HNMR (DMSO-d6) δ ppm: 2.58-2.68 (2H, m), 2.81-2.89 (2H, m), 3.66 (3H, s), 5.27 (2H, brs), 6.70-6.79 (2H, m), 6.98-7.08 (2H, m), 7.22 (1H, d, J = 9.0 Hz), 7.46 (1H, d, J = 9.0 Hz).

Reference Example 464

5-Amino-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0915] Synthesized analogous to Reference Example 461.
^{1}HNMR ($CDCl_3$) δ ppm: 2.47-2.63 (4H, m), 3.58 (2H, brs), 3.73 (3H, s), 5.34 (2H, brs), 6.41 (1H, d, J = 8.7 Hz), 6.67-6.76 (2H, m), 7.01 (1H, d, J = 8.7 Hz), 7.03-7.10 (2H, m).

Reference Example 465

N-[8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide

[0916] Synthesized analogous to Reference Example 462.
^{1}HNMR (DMSO-d6) δ ppm: 2.02 (3H, brs), 2.42-2.54 (2H, m), 2.58-2.67 (2H, m), 3.67 (3H, s), 5.25 (2H, s), 6.71-6.79 (2H, m), 6.96-7.04 (2H, m), 7.15 (1H, d, J = 8.9 Hz), 7.23 (1H, d, J = 8.9 Hz), 9.58 (1H, brs).

Reference Example 466

7,8-Difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate

[0917] Synthesized analogous to Reference Example 460.
^{1}HNMR ($CDCl_3$) δ ppm: 2.68-2.73 (2H, m), 2.89-2.97 (2H, m), 3.76 (3H, s), 5.24 (2H, brs), 6.76-6.81 (2H, m), 6.86 (1H, dd, J = 9.3 Hz, 6.1 Hz), 7.07-7.12 (2H, m).

Reference Example 467

5-Amino-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0918] Synthesized analogous to Reference Example 461.
^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.63 (2H, m), 2.63-2.71 (2H, m), 3.51 (2H, brs), 3.75 (3H, s), 5.21 (2H, brs), 6.24 (1H, dd, J = 11.3 Hz, 6.4 Hz), 6.71-6.81 (2H, m), 7.07-7.16 (2H, m).

Reference Example 468

N-[7,8-Difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetami de

[0919] Synthesized analogous to Reference Example 462.
^{1}HNMR ($CDCl_3$) δ ppm: 2.18 (3H, s), 2.58-2.68 (2H, m), 2.68-2.76 (2H, m), 3.74 (3H, s), 5.22 (2H, s), 6.71-6.80 (2H, m), 6.90 (1H, brs), 7.07-7.14 (2H, m), 7.17 (1H, dd, J = 11.0 Hz, 6.9 Hz).

Reference Example 469

2,2,2-Trifluoro-N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5 -yl]acetamide

[0920] To a solution of 5-amino-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.7 g) in dichloromethane (7 mL), trifluoroacetic anhydride (0.389 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was distilled off, and the residue was washed with diisopropyl ether to provide the title compound (0.87 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.63-2.70 (2H, m), 2.70-2.76 (2H, m), 3.73 (3H, s), 5.23 (2H, brs), 6.73-6.78 (2H, m), 6.97 (1H, dd, J = 12.3 Hz, 8.9 Hz), 7.08-7.12 (2H, m), 7.15 (1H, dd, J = 8.9 Hz, 4.1 Hz), 7.69 (1H, brs).

Reference Example 470

8-Fluoro-1-(4-methoxybenzyl)-5-(methylamino)-3,4-dihydroquinolin-2(1H)-one

[0921] Under argon atmosphere, to a solution of 2,2,2-trifluoro-N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (0.87 g) in N-methyl-2-pyrrolidone (8 mL) was added sodium hydride (55 % in oil) (0.105 g) under ice-cooling. The reaction mixture was stirred at the same temperature for 15 min, and methyl iodide (0.273 mL)

was added dropwise thereto. The reaction mixture was stirred at room temperature for 15 h. To the reaction solution was added aqueous saturated ammonium chloride solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was dissolved in methanol/tetrahydrofuran (1:1) (16 mL), 5 N aqueous sodium hydroxide (1.32 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 2 h. The solvent was distilled off, and to the residue was added aqueous saturated ammonium chloride solution, and then the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.60 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.58-2.63 (2H, m), 2.63-2.68 (2H, m), 2.82 (3H, brs), 3.33 (1H, brs), 3.73 (3H, s), 5.21 (2H, brs), 6.32 (1H, dd, J = 9.0 Hz, 3.4 Hz), 6.72-6.77 (2H, m), 6.83 (1H, dd, J = 12.9 Hz, 9.0 Hz), 7.09-7.14 (2H, m).

Reference Example 471

5-[{[1-(2,4-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methyl} (methyl)amino]-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0922] To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-(methylamino)-3,4-dihydroquinolin-2(1H)-one (0.61 g) in acetic acid (3 mL) was added a solution of 6-(2,4-dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane (3.00 g) in acetic acid (3 mL), and the reaction mixture was stirred at 60 °C for 13 h. The solvent was distilled off and to the residue was added saturated aqueous sodium hydrogencarbonate, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.53 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.50 (2H, m), 1.60-1.69 (2H, m), 2.51 (1H, s), 2.60-2.67 (2H, m), 2.69 (3H, s), 2.87-2.95 (2H, m), 2.95-3.00 (2H, m), 3.00-3.06 (2H, m), 3.07 (2H, s), 3.69 (3H, s), 5.21 (2H, brs), 6.71-6.76 (2H, m), 6.84-6.95 (2H, m), 6.97 (1H, d, J = 8.6 Hz), 7.03-7.13 (2H, m), 7.17 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.34 (1H, d, J = 2.5 Hz).

Reference Example 472

5-({[1-(2,4-Dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0923] Synthesized analogous to Reference Example 471.

^{1}HNMR (DMSO-d6) δ ppm: 1.71 (4H, brs), 2.58-2.61 (2H, m), 2.69-2.72 (2H, m), 2.90-3.10 (6H, m), 3.68 (3H, s), 4.50-4.60 (1H, m), 4.69 (1H, s), 5.08 (2H, brs), 6.41 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.78-6.89 (3H, m), 7.06 (2H, d, J = 8.7 Hz), 7.25 (1H, d, J = 11.1 Hz), 7.70 (1H, d, J = 7.8 Hz).

Reference Example 473

5-({[1-(4-Chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0924] Synthesized analogous to Reference Example 471.

^{1}HNMR ($CDCl_3$) δ ppm: 1.68 (1H, s), 1.75-2.00 (4H, m), 2.68 (4H, s), 2.95-3.15 (4H, m), 3.15-3.30 (2H, m), 3.55-3.70 (1H, brs), 3.74 (3H, s), 5.22 (2H, brs), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.71-6.87 (4H, m), 7.03-7.18 (3H, m).

Reference Example 474

5-({[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0925] Synthesized analogous to Reference Example 471.

^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.95 (5H, m), 2.68 (4H, s), 3.00-3.15 (4H, m), 3.28-3.44 (2H, m), 3.60-3.71 (1H, brs), 3.74 (3H, s), 5.21 (2H, brs), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.71-6.94 (5H, m), 7.13 (2H, d, J = 8.4 Hz).

Reference Example 475

5-({[1-(2,4-Dichloro-6-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-1-(4-methoxybenzyl)-3,4-dihydro-quinolin-2(1H)-one

[0926] Synthesized analogous to Reference Example 471.
^{1}HNMR ($CDCl_3$) δ ppm: 1.68-1.94 (5H, m), 2.68 (4H, s), 2.95-3.15 (4H, m), 3.30-3.45 (2H, m), 3.60-3.70 (1H, brs), 3.74 (3H, s), 5.21 (2H, brs), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.72-6.88 (3H, m), 6.96-7.02 (1H, m), 7.10-7.21 (3H, m).

Reference Example 476

5-({[1-(2-Chloro-4,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-1-(4-methoxybenzyl)-3,4-dihydro-quinolin-2(1H)-one

[0927] Synthesized analogous to Reference Example 471.
^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.94 (5H, m), 2.68 (4H, m), 2.93-3.04 (2H, m), 3.11 (2H, brs), 3.29-3.43 (2H, m), 3.60-3.72 (1H, brs), 3.74 (3H, s), 5.21 (2H, brs), 6.41 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.69-6.88 (4H, m), 6.91-7.00 (1H, m), 7.08-7.17 (2H, m).

Reference Example 477

5-[({1-[2-Chloro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methyl)amin o]-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0928] Synthesized analogous to Reference Example 471.
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.96 (4H, m), 2.68 (4H, s), 2.98-3.19 (7H, m), 3.73 (3H, s), 5.21 (2H, s), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.73-6.86 (3H, m), 7.04-7.11 (5H, m).

Reference Example 478

5-({[1-(4-Ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquin-olin-2(1H)-one

[0929] Synthesized analogous to Reference Example 471.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 6.9 Hz), 1.75-1.99 (5H, m), 2.60-2.75 (4H, m), 2.92-3.20 (6H, m), 3.60-3.80 (4H, m), 3.97 (2H, q, J = 6.9 Hz), 5.21 (2H, brs), 6.36-6.43 (1H, m), 6.57-6.68 (2H, m), 6.70-6.87 (3H, m), 6.89-6.99 (1H, m), 7.08-7.17 (2H, m).

Reference Example 479

5-({[1-(2-Chloro-4-ethylphenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquino-lin-2(1H)-one

[0930] Synthesized analogous to Reference Example 471.
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.8 Hz), 1.68-2.00 (5H, m), 2.58 (2H, q, H = 7.8 Hz), 2.68 (4H, brs), 2.94-3.07 (2H, m), 3.08-3.12 (4H, m), 3.62-3.89 (4H, m), 5.21 (2H, brs), 6.41 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.70-6.88 (3H, m), 6.96-7.25 (5H, m).

Reference Example 480

8-Fluoro-5-[({1-[2-fluoro-4-(propan-2-yloxy)phenyl]-4-hydroxypiperidin-4-yl}meth yl)amino]-1-(4-methoxybenzyl)-3,4-di-hydroquinolin-2(1H)-one

[0931] Synthesized analogous to Reference Example 471.
^{1}HNMR ($CDCl_3$) δ ppm: 1.30 (6H, d, J = 6 Hz), 1.75-1.98 (4H, m), 2.25-2.50 (1H, brs), 2.55-2.75 (4H, m), 2.90-3.18 (6H, m), 3.50-3.80 (4H, m), 4.36-4.50 (1H, m), 5.19 (2H, brs), 6.37 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.54-6.98 (6H, m), 7.04-7.16 (2H, m).

Reference Example 481

5-({[1-(2-Chloro-4-propylphenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0932] Synthesized analogous to Reference Example 471.
^{1}HNMR ($CDCl_3$) δ ppm: 0.92 (3H, t, J = 7.4 Hz), 1.60 (2H, sex, J = 7.4 Hz), 1.77-1.99 (4H, m), 2.22 (1H, brs), 2.50 (2H, t, J = 7.4 Hz), 2.58-2.73 (4H, m), 2.92-3.20 (6H, m), 3.60-3.80 (4H, m), 5.20 (2H, brs), 6.39 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.67-6.88 (3H, m), 6.94-7.05 (2H, m), 7.06-7.15 (2H, m), 7.16-7.20 (1H, m).

Reference Example 482

8-Fluoro-5-({[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0933] Synthesized analogous to Reference Example 471.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.92 (4H, m), 2.60-2.76 (4H, m), 2.98-3.05 (4H, m), 3.31-3.42 (2H, m), 3.65-3.80 (1H, m), 3.73 (3H, s), 5.16-5.28 (2H, m), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.58-6.67 (2H, m), 6.72-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.0 Hz), 7.10-7.16 (2H, m).

Reference Example 483

8-Chloro-5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0934] To a solution of N-[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (200 mg) and 6-(4-chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (202 mg) in N,N-dimethylformamide/2-propanol (1:1) (2 mL) was added tripotassium phosphate (59.2 mg), and the mixture was stirred at 90 °C for 18 h. To the mixture was added sodium hydroxide (11.2 mg), and the mixture was stirred at 90 °C for 18 h. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (279 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.93 (4H, m), 2.33 (1H, brs), 2.53 (4H, brs), 2.97-3.25 (6H, m), 3.68 (3H, s), 3.92 (1H, brs), 5.31 (2H, brs), 6.43 (1H, d, J = 8.7 Hz), 6.63-6.72 (2H, m), 6.83-6.93 (1H, m), 6.98-7.11 (5H, m).

Reference Example 484

8-Chloro-5-({[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}ami no)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0935] Synthesized analogous to Reference Example 483.
^{1}HNMR ($CDCl_3$) δ ppm: 1.70-1.89 (4H, m), 2.32 (1H, brs), 2.54 (4H, m), 3.00-3.16 (4H, m), 3.30-3.44 (2H, m), 3.69 (3H, s), 3.96 (1H, brs), 5.32 (2H, brs), 6.43 (1H, d, J = 8.7 Hz), 6.65-6.72 (2H, m), 6.81-6.93 (2H, m), 7.01-7.13 (3H, m).

Reference Example 485

8-Chloro-5-({[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}ami no)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0936] To a solution of N-[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (200 mg) and 6-(2,4-dichloro-5-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (200 mg) in N,N-dimethylformamide/2-propanol (1:1) (2 mL) was added tripotassium phosphate (59.2 mg), and the reaction mixture was stirred at 90 °C for 16 h. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (324 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.76-1.94 (4H, m), 2.30 (1H, brs), 2.53 (4H, brs), 2.92-3.20 (6H, m), 3.68 (3H, s), 3.92 (1H, brs), 5.32 (2H, s), 6.44 (1H, d, J = 9.0 Hz), 6.66-6.70 (2H, m), 6.85 (1H, d, J = 10.5 Hz), 7.00-7.13 (3H, m), 7.37 (1H, d, J = 7.8 Hz).

Reference Example 486

8-Chloro-5-({[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0937] Synthesized analogous to Reference Example 483.
^{1}HNMR (DMSO-d6) δ ppm: 1.29 (3H, t, J = 6.9 Hz), 1.60-1.78 (4H, m), 2.55-2.65 (2H, m), 2.89-2.98 (4H, m), 3.04 (2H, d, J = 5.7 Hz), 3.17-3.23 (2H, m), 3.67 (3H, s), 3.96 (2H
,q, J = 6.9 Hz), 4.50 (1H, brs), 4.72-4.75 (1H, m), 5.23 (2H, brs), 6.50 (1H, d, J = 8.7 Hz), 6.62-6.71 (2H, m), 6.72-6.79 (2H, m), 6.94-7.08 (4H, m).

Reference Example 487

8-Chloro-5-({[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methyl}amino)-1-(4 -methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0938] Synthesized analogous to Reference Example 483.
^{1}HNMR ($CDCl_3$) δ ppm: 1.71-1.89 (4H, m), 2.38 (1H, brs), 2.54 (4H, brs), 2.93-3.06 (2H, m), 3.11 (2H, brs), 3.30-3.44 (2H, m), 3.69 (3H, s), 3.97 (1H, brs), 5.32 (2H, s), 6.43 (1H, d, J = 9.0 Hz), 6.55-6.72 (4H, m), 7.01-7.12 (3H, m).

Reference Example 488

8-Chloro-5-({[1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}ami no)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0939] Synthesized analogous to Reference Example 485.
^{1}HNMR ($CDCl_3$) δ ppm: 1.72-1.92 (4H, m), 2.10 (1H, brs), 2.54 (4H, brs), 2.98-3.28 (6H, m), 3.70 (3H, s), 3.90 (1H, brs), 5.32 (2H, brs), 6.44 (1H, d, J = 8.7 Hz), 6.66-6.80 (3H, m), 7.01-7.12 (4H, m).

Reference Example 489

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-7,8-difluo ro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0940] Synthesized analogous to Reference Example 485.
^{1}HNMR ($CDCl_3$) δ ppm: 1.77-1.86 (2H, m), 1.86-1.97 (2H, m), 2.56-2.72 (4H, m), 2.98-3.10 (2H, m), 3.15-3.26 (2H, m), 3.75 (3H, s), 3.77-3.83 (1H, m), 5.22 (1H, brs), 6.27 (1H, dd, J = 12.4 Hz, 6.3 Hz), 6.71-6.81 (2H, m), 6.87-6.95 (1H, m), 7.01-7.08 (2H, m), 7.09-7.17 (2H, m).

Reference Example 490

5-({[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-7,8-difluo ro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0941] Synthesized analogous to Reference Example 485.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.95 (4H, m), 2.57-2.74 (4H, m), 2.97-3.09 (4H, m), 3.16-3.26 (2H, m), 3.75 (3H, s), 3.77-3.83 (1H, m), 5.22 (2H, brs), 6.27 (1H, dd, J = 12.4 Hz, 6.3 Hz), 6.73-6.79 (2H, m), 6.86 (1H, t, J = 8.6 Hz), 7.09-7.16 (2H, m), 7.17-7.22 (2H, m).

Reference Example 491

5-{[1-(2-Chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybe nzyl)-3,4-dihydroquinolin-2(1H)-one

[0942] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.88 (2H, m), 1.93-1.99 (2H, m), 2.06 (1H, brs), 2.65-2.68 (2H, m), 2.89-2.92 (2H, m), 3.07-3.12 (2H, m), 3.21-3.23 (2H, m), 3.74 (3H, s), 3.83 (2H, s), 5.24 (2H, brs), 6.54 (1H, dd, J = 9.0, 3.0 Hz), 6.76 (2H, d, J = 8.5 Hz), 6.85 (1H, dd, J = 12.5H, 9.0 Hz), 6.97 (1H, dt, J = 1.5 Hz, 8.0 Hz), 7.10 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.23 (1H, dt, J = 1.5 Hz, 8.0 Hz), 7.37 (1H, dd, J = 8.0 Hz, 1.5 Hz).

Reference Example 492

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-m ethoxybenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

[0943] A solution of 5-[(3,5-dimethylbenzyl)oxy]-8-fluoro-1-(4-methoxybenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one (630 mg), potassium carbonate (335 mg) and 10 % palladium on carbon (300 mg) in 2-propanol (15ml) was stirred at room temperature for 1 h under hydrogen atmosphere. The reaction solution was filtrated and to the filtrate were added sodium hydroxide (445 mg), N,N-dimethylformamide (15 mL) and 6-(4-chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (740 mg), then the solution was stirred at 70 °C for 19.5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (370 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.70 (4H, m), 1.80-2.00 (6H), 2.60-2.65 (2H, m), 2.79-2.84 (2H, m), 3.04-3.13 (2H, m), 3.20-3.24 (3H, m), 3.52-3.62 (1H, m), 3.70-3.90 (6H,m), 5.21 (2H, s), 5.33 (1H, s), 6.51 (1H, d, J = 6.0 Hz), 6.74-6.79 (2H, m), 6.88-6.95 (1H, m), 7.01-7.07 (2H, m), 7.11-7.15 (2H, m).

Reference Example 493

1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl} piperidin-4-ol

[0944] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.93 (2H, m), 1.93-2.02 (2H, m), 2.10 (1H, s), 3.07-3.15 (2H, m), 3.47-3.56 (2H, m), 4.00 (2H, s), 4.12 (3H, s), 6.65 (1H, dd, J = 8.7 Hz, 3.4 Hz), 6.85-6.93 (2H, m), 6.95 (1H, d, J = 9.1 Hz), 7.24 (1H, dd, J = 10.6 Hz, 8.7 Hz), 8.37 (1H, dd, J = 9.1 Hz, 1.6 Hz).

Reference Example 494

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}pipe ridin-4-ol

[0945] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-1.98 (2H, m), 1.98-2.06 (2H, m), 2.08 (1H, s), 3.11-3.19 (2H, m), 3.23-3.31 (2H, m), 4.00 (2H, s), 4.12 (3H, s), 6.65 (1H, dd, J = 8.6 Hz, 3.4 Hz), 6.92-6.98 (2H, m), 7.03-7.09 (2H, m), 7.24 (1H, dd, J = 10.5 Hz, 8.6 Hz), 8.37 (1H, dd, J = 9.1 Hz, 1.6 Hz).

Reference Example 495

tert-Butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate

[0946] A solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (4.66 g), tert-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate (5.95 g) and potassium carbonate (3.55 g) in N-methyl-2-pyrrolidone (100 mL) was stirred at 80 °C for 4 h. To the reaction solution were added water (400 mL) and ethyl acetate (100 mL) and the solution was stirred at room temperature for 20 min. The precipitated crystal was collected on a filter and washed with ethyl acetate to provide the title compound (8.48 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.41 (9H, s), 2.08-2.15 (2H, m), 2.42-2.48 (2H, m), 2.82-2.89 (2H, m), 3.40-3.48 (2H, m), 3.81-3.91 (2H), 4.41-4.47 (2H, m), 5.65-5.82 (1H, m), 6.60 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.2 Hz), 10.01 (1H, brs).

Reference Example 496

tert-Butyl 4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl }-3,6-dihydropyridine-1(2H)-carboxylate

[0947] To a solution of tert-butyl 4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidine -1-carboxylate (13.7 g) in acetonitrile (180 mL) were added N,N,N',N'-tetramethyl-1,3-diaminopropane (31.8 mL) and methanesulfonyl chloride (7.74 mL), and the solution was stirred at room temperature overnight. The reaction solution was poured into water, and the precipitate was collected on a filter. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (10.7 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.48 (9H, s), 2.14-2.24 (2H, m), 2.59-2.64 (2H, m), 2.97-3.02 (2H, m), 3.52-3.59 (2H, m),

3.92-3.98 (2H), 4.42-4.48 (2H, m), 5.76-5.84 (1H, m), 6.51 (1H, d, J = 9.0 Hz), 7.16 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Reference Example 497

tert-Butyl 4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydro pyridine-1(2H)-carboxylate

[0948] Synthesized analogous to Reference Example 495.
^{1}HNMR ($CDCl_3$) δ ppm: 1.48 (9H, s), 2.15-2.22 (2H, m), 2.60-2.63 (2H, m), 2.93-2.97 (2H, m), 3.55-3.57 (2H, m), 3.93-3.99 (2H, m), 4.40 (2H, brs), 5.72-5.84 (1H, m), 6.43 (1H, d, J = 10.9 Hz), 7.75 (1H, brs).

Reference Example 498

tert-Butyl 4-{[(7,8-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyrid ine-1(2H)-carboxylate

[0949] Synthesized analogous to Reference Example 495.
^{1}HNMR ($CDCl_3$) δ ppm: 1.48 (9H, s), 2.13-2.24 (2H, m), 2.60-2.64 (2H, m), 2.93-2.96 (2H, m), 3.52-3.60 (2H, m), 3.92-3.99 (2H, m), 4.37 (2H, brs), 5.71-5.87 (1H, m), 6.37 (1H, dd, J = 12.0 Hz, 6.3 Hz), 7.58 (1H, brs).

Reference Example 499

tert-Butyl(3S*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiper idine-1-carboxylate

[0950] To a solution of tert-butyl 4-[[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (0.38 g) in acetone (3 mL)-water (1 mL) were added aqueous solution of 4.8 M N-methylmorpholine-N-oxide (0.42 mL) and aqueous solution of 4 • % osmium tetraoxide (0.01 mL) and the reaction mixture was stirred at room temperature for 6 days. The solvent was distilled off, and the obtained crude crystal was washed with ethyl acetate to provide the title compound (0.36 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.40 (9H, s), 1.54-1.73 (2H, m), 2.44 (2H, t, J = 7.6 Hz), 2.74-3.09 (4H, m), 3.46-3.55 (1H, m), 3.62 (1H, d, J = 8.8 Hz), 3.66-3.85 (2H, m), 3.98 (1H, d, J = 8.8 Hz), 4.58 (1H, brs), 4.92-5.01 (1H, m), 6.54 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.4 Hz), 10.01 (1H, brs).

Reference Example 500

tert-Butyl (3R,4R)-4-[[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydro xypiperidine-1-carboxylate

[0951] To a suspension of tert-butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (0.753 g) and AD-Mix-beta (2.8 g) in acetone (25 mL) was added water (15 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added aqueous saturated sodium sulfite under ice-cooling, and the solution was stirred for 10 min. Then the solution was extracted with ethyl acetate, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate), and recrystallized from ethanol to provide the title compound (347 mg, over 99 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.69-1.75 (1H, m), 1.83-1.86 (1H, m), 2.36-2.37 (1H, m), 2.51-2.60 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.91-3.00 (3H, m), 3.01-3.20 (1H, m), 3.68-4.17 (5H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.51 (1H, brs).

Reference Example 501

tert-Butyl (3S,4S)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydro xypiperidine-1-carboxylate

[0952] A solution of tert-butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (200 mg) and AD-Mix-alpha (743 mg) in acetone/water = (2: 1) (10 mL) was stirred at room temperature overnight, and the reaction solution was treated in a manner analogous to Reference Example 500 to provide the title compound (131 mg, 90 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.69-1.75 (1H, m), 1.83-1.86 (1H, m), 2.26-2.39 (1H, m), 2.52-2.60 (1H, m), 2.64 (2H, t, J = 7.6 Hz), 2.91-3.20 (4H, m), 3.71-4.19 (5H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.50 (1H, brs).

Reference Example 502

tert-Butyl (3R,4R)-4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydro xypiperidine-1-carboxylate

[0953] Synthesized analogous to Reference Example 500.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.86 (1H, m), 2.37-2.69 (4H, m), 2.87-3.02 (3H, m), 3.03-3.20 (1H, m), 3.69-4.17 (5H, m), 6.55 (1H, d, J = 8.9 Hz), 7.19 (1H, t, J = 8.9 Hz), 7.76 (1H, brs).

Reference Example 503

tert-Butyl (3S,4S)-4-{[(8-chloro-2-oxo-l,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydro xypiperidine-1-carboxylate

[0954] Synthesized analogous to Reference Example 501.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.86 (1H, m), 2.36-2.68 (4H, m), 2.86-3.02 (3H, m), 3.03-3.20 (1H, m), 3.67-4.19 (5H, m), 6.55 (1H, d, J = 9.0 Hz), 7.18 (1H, t, J = 8.9 Hz), 7.74 (1H, brs).

Reference Example 504

tert-Butyl (3R*,4R*)-4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihyd roxypiperidine-1-carboxylate

[0955] To a solution of tert-butyl 4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydro pyridine-1(2H)-carboxylate (250 mg) in tetrahydrofuran/water (3: 1) (4 mL) were added Osmium Oxide, Immobilized Catalyst I (content: 7 %) (110 mg) and N-methylmorpholine N-oxide (0.254 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added aqueous saturated sodium sulfite under ice-cooling, insoluble materials were filtered off, and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (249 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.85 (1H, m), 2.20-2.57 (2H, m), 2.62 (2H, t, J = 7.7 Hz), 2.88-3.01 (3H, m), 3.02-3.19 (1H, m), 3.69-4.17 (5H, m), 6.47 (1H, d, J = 10.6 Hz), 7.75 (1H, brs).

Reference Example 505

tert-Butyl (3R,4R)-4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3, 4-dihydroxypiperidine-1-carboxylate

[0956] Synthesized analogous to Reference Example 500.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.85 (1H, m), 2.20-2.57 (2H, m), 2.60-2.63 (2H, m), 2.88-3.01 (3H, m), 3.02-3.19 (1H, m), 3.69-4.17 (5H, m), 6.47 (1H, d, J = 10.6 Hz), 7.75 (1H, brs).

Reference Example 506

tert-Butyl (3R,4R)-4-{[(7,8-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihy droxypiperidine-1-carboxylate

[0957] Synthesized analogous to Reference Example 500.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.70-1.76 (1H, m), 1.82-1.85 (1H, m), 2.28-2.69 (4H, m), 2.85-3.21 (4H, m), 3.68-4.20 (5H, m), 6.41 (1H, dd, J = 11.8 Hz, 6.3 Hz), 7.61 (1H, brs).

Reference Example 507

tert-Butyl (3R*,4R*)-4-{[(7,8-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxyp iperidine-1-carboxylate

[0958] Synthesized analogous to Reference Example 504.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.70-1.77 (1H, m), 1.82-1.85 (1H, m), 2.28-2.79 (4H, m), 2.83-3.21 (4H, m), 3.68-4.20 (5H, m), 6.41 (1H, dd, J = 11.8 Hz, 6.3 Hz), 7.71 (1H, brs).

Reference Example 508

5-{[(3S*,4S*)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2 (1H)-one hydrochloride

[0959] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.80 (1H, m), 1.95-2.07 (1H, m), 2.47 (2H, t, J = 8.0 Hz), 2.83-3.16 (6H, m), 3.66 (1H, d, J = 8.8 Hz), 3.85-3.95 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 5.07 (1H, brs), 5.34-5.44 (1H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.5 Hz), 8.63-8.83 (2H, m), 10.04 (1H, brs).

Reference Example 509

5-{[(3R,4R)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one hydrochloride

[0960] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.99-2.05 (1H, m), 2.45-2.48 (2H, m), 2.85-3.12 (6H, m), 3.66 (1H, d, J = 8.8 Hz), 3.90-3.93 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.97-5.22 (1H, m), 5.28-5.51 (1H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.03 (1H, t, J = 9.7 Hz), 8.73-8.96 (2H, m), 10.06 (1H, brs).

Reference Example 510

5-{[(3R,4R)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[0961] Synthesized analogous to Reference Example 60.
^{1}HNMR (DMSO-d6) δ ppm: 1.49-1.55 (1H, m), 1.62-1.72 (1H, m), 1.80-2.10 (1H, broad signal), 2.43-2.49 (2H, m), 2.54-2.62 (2H, m), 2.62-2.75 (2H, m), 2.82-2.95 (2H, m), 3.47-3.54 (1H, m), 3.54 (1H, d, J = 8.7 Hz), 3.96 (1H, d, J = 8.7 Hz), 4.20 (1H, s), 4.50 (1H, d, J = 6.5 Hz), 6.54 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.7 Hz), 10.02 (1H, brs).

Reference Example 511

5-{[(3S,4S)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one hydrochloride

[0962] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.99-2.05 (1H, m), 2.45-2.48 (2H, m), 2.85-3.12 (6H, m), 3.66 (1H, d, J = 8.8 Hz), 3.90-3.93 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.41-5.77 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.6 Hz), 7.02 (1H, t, J = 9.7 Hz), 8.76-9.00 (2H, m), 10.05 (1H, brs).

Reference Example 512

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -3,6-dihydropyridine-1(2H)-carboxylate

[0963] Synthesized analogous to Reference Example 495.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 2.13-2.23 (2H, m), 2.59-2.67 (2H, m), 2.83-2.92 (2H, m), 3.49-3.60 (2H, m), 3.74 (3H, s), 3.89-3.99 (2H, m), 4.32-4.39 (2H, m), 5.22 (2H, brs), 5.70-5.80 (1H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.71-6.78 (2H, m), 6.81 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

Reference Example 513

tert-Butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-3,4-dihydroxypiperidine-1-carboxylate

[0964] Synthesized analogous to Reference Example 499.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.64-1.75 (1H, m), 1.78-1.87 (1H, m), 2.26-2.35 (1H, m), 2.48-2.56 (1H, m), 2.61-2.68 (2H, m), 2.76-3.00 (3H, m), 3.01-3.18 (1H, m), 3.74 (3H, s), 3.75-3.83 (1H, m), 3.84-3.98 (3H, m), 3.99-4.16 (1H, m), 5.16-5.30 (2H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.79 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.09-7.16 (2H, m).

Reference Example 514

tert-Butyl (3R,4R)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy }methyl)-3,4-dihydroxypiperidine-1-carboxylate

[0965] Synthesized analogous to Reference Example 500.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.67-1.73 (1H, m), 1.81-1.84 (1H, m), 2.38-2.39 (1H, m), 2.51-2.68 (3H, m), 2.78-3.18 (4H, m), 3.71-3.82 (4H, m), 3.85-4.18 (4H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 515

tert-Butyl (3S,4S)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy }methyl)-3,4-dihydroxypiperidine-1-carboxylate

[0966] Synthesized analogous to Reference Example 501.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.67-1.74 (1H, m), 1.81-1.84 (1H, m), 2.35-2.68 (4H, m), 2.78-3.19 (4H, m), 3.71-4.18 (8H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 516

tert-Butyl (3R,4R)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]ox y}methyl)-3,4-dihydroxypiperidine-1-carboxylate

[0967] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.68-1.74 (1H, m), 1.81-1.84 (1H, m), 2.29 (1H, d, J = 6.2 Hz), 2.46-2.78 (5H, m), 2.84-3.19 (2H, m), 3.65-4.17 (8H, m), 5.34-5.41 (2H, m), 6.59 (1H, d, J = 9.0 Hz), 6.71-6.74 (2H, m), 7.07 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 8.9 Hz).

Reference Example 517

tert-Butyl (3S,4S)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy }methyl)-3,4-dihydroxypiperidine-1-carboxylate

[0968] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.67-1.74 (1H, m), 1.81-1.84 (1H, m), 2.27 (1H, d, J = 6.2 Hz), 2.46-2.78 (5H, m), 2.84-3.19 (2H, m), 3.65-4.17 (8H, m), 5.34-5.41 (2H, m), 6.59 (1H, d, J = 9.0 Hz), 6.71-6.74 (2H, m), 7.05-7.08 (2H, m), 7.15 (1H, d, J = 8.9 Hz).

Reference Example 518

tert-Butyl (3R,4R)-4-({[8-chloro-7-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin -5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

[0969] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.69-1.75 (1H, m), 1.81-1.84 (1H, m), 2.19-2.74 (6H, m), 2.84-3.21 (2H, m),

3.63-4.19 (8H, m), 5.35-5.42 (2H, m), 6.53 (1H, d, J = 10.5 Hz), 6.72-6.75 (2H, m), 7.06 (2H, d, J = 8.6 Hz).

Reference Example 519

tert-Butyl (3R*,4R*)-4-({[8-chloro-7-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]o xy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

[0970] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.68-1.75 (1H, m), 1.81-1.83 (1H, m), 2.18-2.24 (1H, m), 2.40-2.73 (5H, m), 2.84-3.21 (2H, m), 3.63-4.19 (8H, m), 5.35-5.42 (2H, m), 6.53 (1H, d, J = 10.5 Hz), 6.72-6.75 (2H, m), 7.05-7.07 (2H, m).

Reference Example 520

tert-Butyl (3R,4R)-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

[0971] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.68-1.74 (1H, m), 1.80-1.83 (1H, m), 2.21-2.70 (4H, m), 2.73-2.86 (2H, m), 2.86-3.22 (2H, m), 3.63-4.19 (8H, m), 5.19-5.27 (2H, m), 6.46 (1H, dd, J = 11.4 Hz, 5.9 Hz), 6.76-6.79 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 521

tert-Butyl (3R*,4R*)-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}m ethyl)-3,4-dihydroxypiperidine-1-carboxylate

[0972] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.68-1.74 (1H, m), 1.80-1.83 (1H, m), 2.21-2.70 (4H, m), 2.73-2.86 (2H, m), 2.86-3.22 (2H, m), 3.63-4.19 (8H, m), 5.19-5.27 (2H, m), 6.46 (1H, dd, J = 11.5 Hz, 5.9 Hz), 6.76-6.79 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 522

5-{[(3S*,4S*)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

[0973] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.80 (1H, m), 1.95-2.07 (1H, m), 2.56-2.65 (2H, m), 2.81-3.16 (6H, m), 3.65 (1H, d, J = 8.8 Hz), 3.68 (3H, s), 3.86-3.95 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 5.00-5.20 (3H, m), 5.40 (1H, brs), 6.67 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.77-6.84 (2H, m), 6.99 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.04-7.11 (2H, m), 8.91 (2H, brs).

Reference Example 523

5-{[(3S*,4S*)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0974] Synthesized analogous to Reference Example 457.
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.76 (1H, m), 1.78-1.87 (1H, m), 1.96-2.44 (2H, br), 2.59-2.68 (2H, m), 2.75-3.02 (6H, m), 3.73 (3H, s), 3.74-3.80 (1H, m), 3.85-3.93 (2H, m), 5.15-5.30 (2H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.78 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.16 (2H, m).

Reference Example 524

5-{[(3R,4R)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3 ,4-dihydroquinolin-2(1H)-one

[0975] To a solution of tert-butyl (3R,4R)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy }methyl)-3,4-dihydroxypiperidine-1-carboxylate (2.89 g) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL), and the reaction mixture was stirred at room temperature for 3 h. To the reaction solution was added 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine,

dried over anhydrous magnesium sulfate, and the solvent was distilled off to provide the title compound (1.84 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.69-1.78 (1H, m), 1.82-1.86 (1H, m), 2.62-2.65 (2H, m), 2.80-3.02 (6H, m), 3.71-3.95 (6H, m), 5.17-5.26 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.76 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.12 (2H, d, J = 8.5 Hz).

Reference Example 525

5-{[(3S,4S)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3 ,4-dihydroquinolin-2(1H)-one

[0976] Synthesized analogous to Reference Example 524.
^{1}HNMR ($CDCl_3$) δ ppm: 1.73-1.78 (1H, m), 1.82-1.86 (1H, m), 2.56-2.66 (2H, m), 2.79-3.06 (6H, m), 3.71-3.92 (6H, m), 5.17-5.26 (2H, m), 6.52 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.74-6.76 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11 (2H, d, J = 8.5 Hz).

Reference Example 526

5-{[(3S*,4S*)-1-(2,4-Dichlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor o-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0977] Under argon atmosphere, to a solution of 5-{[(3S*,4S*)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroqui nolin-2(1H)-one hydrochloride (0.37 g), 1-bromo-2,4-dichlorobenzene (0.20 g), triethylamine (0.27 mL) and sodium tert-butoxide (0.18 g) in toluene (3 mL) were added 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (15 mg) and tris(dibenzylideneacetone)dipalladium (0) (7 mg), and the reaction mixture was stirred while heating at 100 °C overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (40 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.94-2.00 (2H, m), 2.44-2.51 (1H, m), 2.61-2.71 (3H, m), 2.80-2.96 (3H, m), 2.97-3.14 (2H, m), 3.24-3.33 (1H, m), 3.74 (3H, s), 3.94 (1H, d, J = 9.2 Hz), 4.00-4.08 (2H, m), 5.15-5.34 (2H, m), 6.56 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.67-6.80 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.00 (1H, d, J = 8.6 Hz), 7.09-7.16 (2H, m), 7.20 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz).

Reference Example 527

5-{[(3S*,4S*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fl uoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0978] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: 1.93-2.00 (2H, m), 2.42-2.50 (1H, m), 2.58-2.70 (3H, m), 2.79-2.97 (3H, m), 3.00-3.10 (1H, m), 3.12-3.22 (1H, m), 3.30-3.39 (1H, m), 3.74 (3H, s), 3.94 (1H, d, J = 9.1 Hz), 3.97-4.07 (2H, m), 5.14-5.32 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.81-6.95 (2H, m), 7.02-7.09 (2H, m), 7.10-7.16 (2H, m).

Reference Example 528

2-[(3R,4R)-4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-y l]oxy}methyl)-3,4-dihydroxypiperidin-1-yl]-5-iodopyridine-3-carbonitrile

[0979] A solution of 2-chloro-5-iodopyridine-3-carbonitrile (0.675 g), 5-{[(3R,4R)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4 -dihydroquinolin-2(1H)-one (1 g) and potassium carbonate (0.642 g) in N-methyl-2-pyrrolidone (20 mL) was stirred at 100 °C overnight. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (678 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.92 (1H, m), 1.96-2.00 (1H, m), 2.62-2.65 (2H, m), 2.77-2.87 (2H, m), 2.89-3.04 (2H, m), 3.26-3.30 (1H, m), 3.43-3.48 (1H, m), 3.74 (3H, s), 3.90-4.00 (3H, m), 4.15-4.20 (1H, m), 4.25-4.29 (1H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.98 (1H, d, J = 2.4 Hz), 8.46 (1H, d, J = 2.3 Hz).

Reference Example 529

2-[(3S,4S)-4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-y l]oxy}methyl)-3,4-dihydroxypiperidin-1-yl]-5-iodopyridine-3-carbonitrile

[0980] Synthesized analogous to Reference Example 528.
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.91 (1H, m), 1.95-1.99 (1H, m), 2.62-2.65 (2H, m), 2.77-2.87 (2H, m), 2.89-3.04 (2H, m), 3.26-3.30 (1H, m), 3.42-3.48 (1H, m), 3.74 (3H, s), 3.90-4.00 (3H, m), 4.15-4.20 (1H, m), 4.25-4.29 (1H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.98 (1H, d, J = 2.3 Hz), 8.46 (1H, d, J = 2.3 Hz).

Reference Example 530

tert-Butyl (3S*,4S*)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0981] To a solution of tert-butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-3,4-dihydroxypiperidine-1-carboxylate (5.31 g) in N,N-dimethylformamide (10 mL) were added imidazole (2.72 g) and tert-butyl dimethylchlorosilane (3.01 g) at 0 °C, and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water, 2 M citric acid solution and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (5.5 g).
^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.08 (3H, s), 0.83 (9H, s), 1.48 (9H, s), 1.67-1.75 (1H, m), 1.82-1.99 (1H, m), 2.42-2.68 (3H, m), 2.70-3.18 (4H, m), 3.55 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.77-4.15 (4H, m), 5.14-5.32 (2H, m), 6.45 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.08-7.15 (2H, m).

Reference Example 531

tert-Butyl (3R,4R)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0982] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.08 (3H, s), 0.83 (9H, s), 1.48 (9H, s), 1.67-1.76 (1H, m), 1.82-2.00 (1H, m), 2.42-2.68 (3H, m), 2.70-3.18 (4H, m), 3.55 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.78-4.16 (4H, m), 5.16-5.29 (2H, m), 6.45 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.07-7.15 (2H, m).

Reference Example 532

tert-Butyl (3S,4S)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1 ,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0983] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.08 (3H, s), 0.83 (9H, s), 1.48 (9H, s), 1.67-1.76 (1H, m), 1.81-1.99 (1H, m), 2.42-2.69 (3H, m), 2.70-3.18 (4H, m), 3.55 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.77-4.16 (4H, m), 5.14-5.31 (2H, m), 6.45 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.07-7.16 (2H, m).

Reference Example 533

tert-Butyl (3R,4R)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0984] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.18 (3H, s), 0.07 (3H, brs), 0.83 (9H, s), 1.47 (9H, s), 1.69-1.72 (1H, m), 1.80-1.98 (1H, m), 2.42-3.15 (7H, m), 3.56 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.77-4.17 (4H, m), 5.32 (1H, d, J = 15.3 Hz), 5.43 (1H, d, J = 15.2 Hz), 6.52 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.05 (2H, d, J = 8.6 Hz), 7.14 (1H, d, J = 8.9 Hz).

Reference Example 534

tert-Butyl (3S,4S)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0985] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.18 (3H, s), 0.07 (3H, brs), 0.83 (9H, s), 1.47 (9H, s), 1.69-1.72 (1H, m), 1.80-1.98 (1H, m), 2.42-3.15 (7H, m), 3.56 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.77-4.17 (4H, m), 5.32 (1H, d, J = 14.7 Hz), 5.43 (1H, d, J = 15.2 Hz), 6.52 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.05 (2H, d, J = 8.7 Hz), 7.14 (1H, d, J = 8.9 Hz).

Reference Example 535

tert-Butyl (3R,4R)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-7-fluoro-1-(4-methoxybenzy l)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxyl ate

[0986] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.07 (3H, brs), 0.84 (9H, s), 1.47 (9H, s), 1.70-1.73 (1H, m), 1.78-1.97 (1H, m), 2.42-3.18 (7H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.76-4.16 (4H, m), 5.32 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 15.2 Hz), 6.45 (1H, d, J = 10.5 Hz), 6.71 (2H, d, J = 8.6 Hz), 7.04 (2H, d, J = 8.6 Hz).

Reference Example 536

tert-Butyl (3R*,4R*)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-7-fluoro-1-(4-methoxybenzyl)-2-ox o-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0987] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.07 (3H, brs), 0.84 (9H, s), 1.47 (9H, s), 1.70-1.73 (1H, m), 1.77-1.95 (1H, m), 2.42-3.18 (7H, m), 3.54 (1H, d, J = 8.4 Hz), 3.73 (3H, s), 3.76-4.16 (4H, m), 5.32 (1H, d, J = 15.8 Hz), 5.44 (1H, d, J = 15.1 Hz), 6.45 (1H, d, J = 10.4 Hz), 6.71 (2H, d, J = 8.7 Hz), 7.04 (2H, d, J = 8.6 Hz).

Reference Example 537

tert-Butyl (3R,4R)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-o xo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0988] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.09 (3H, brs), 0.84 (9H, s), 1.48 (9H, s), 1.70-1.73 (1H, m), 1.77-1.97 (1H, m), 2.38-3.20 (7H, m), 3.51 (1H, d, J = 8.4 Hz), 3.71-4.16 (7H, m), 5.23 (2H, brs), 6.38 (1H, dd, J = 11.5 Hz, 5.8 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 538

tert-Butyl (3R,4R)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-o xo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[0989] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.09 (3H, brs), 0.84 (9H, s), 1.48 (9H, s), 1.70-1.73 (1H, m), 1.77-1.97 (1H, m), 2.41-3.18 (7H, m), 3.51 (1H, d, J = 8.4 Hz), 3.71-4.16 (7H, m), 5.23 (2H, brs), 6.38 (1H, dd, J = 11.5 Hz, 5.9 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 539

5-({(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-y l}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0990] To a solution of tert-butyl (3S*,4S*)-3-t[tert-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate (1.82 g) and 2,6-lutidine (1.31 mL) in dichloromethane (1 mL), trimethylsilyl trifluoromethanesulfonate (2.04 mL) was added dropwise under cooling with water-

bath, and the reaction mixture was stirred at room temperature for 4 h. To the reaction solution was added saturated aqueous sodium hydrogencarbonate, and the solution was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound. The compound was used for the next step without further purification.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.03 (3H, s), 0.14 (9H, s), 0.83 (9H, s), 1.68-1.88 (2H, m), 2.58-2.66 (2H, m), 2.77-3.04 (6H, m), 3.70 (1H, d, J = 8.2 Hz), 3.73 (3H, s), 3.77-3.83 (1H, m), 3.97 (1H, d, J = 8.2 Hz), 5.16-5.30 (2H, m), 6.40 (1H, d, J = 9.0 Hz, 3.2 Hz), 6.71-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.08-7.15 (2H, m).

Reference Example 540

5-({(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl }methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0991] Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.02 (3H, s), 0.13 (9H, s), 0.83 (9H, s), 1.68-1.88 (2H, m), 2.58-2.66 (2H, m), 2.77-3.02 (6H, m), 3.69 (1H, d, J = 8.2 Hz), 3.73 (3H, s), 3.74-3.80 (1H, m), 3.97 (1H, d, J = 8.2 Hz), 5.16-5.29 (2H, m), 6.41 (1H, d, J = 9.0 Hz, 3.2 Hz), 6.71-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.08-7.15 (2H, m).

Reference Example 541

5-({(3S,4S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl} methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0992] Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.02 (3H, s), 0.13 (9H, s), 0.82 (9H, s), 1.68-1.86 (2H, m), 2.59-2.66 (2H, m), 2.76-3.01 (6H, m), 3.69 (1H, d, J = 8.2 Hz), 3.73 (3H, s), 3.74-3.80 (1H, m), 3.97 (1H, d, J = 8.2 Hz), 5.16-5.29 (2H, m), 6.41 (1H, d, J = 9.0 Hz, 3.2 Hz), 6.71-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.08-7.16 (2H, m).

Reference Example 542

5-({(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl }methoxy)-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0993] Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.00 (3H, s), 0.12 (9H, s), 0.83 (9H, s), 1.69-1.78 (2H, m), 2.54 (2H, t, J = 6.7 Hz), 2.69-2.97 (6H, m), 3.69-3.71 (5H, m), 3.98 (1H, d, J = 8.2 Hz), 5.34 (1H, d, J = 15.3 Hz), 5.41 (1H, d, J = 15.2 Hz), 6.48 (1H, d, J = 8.9 Hz), 6.68-6.71 (2H, m), 7.04-7.07 (2H, m), 7.15 (1H, d, J = 8.9 Hz).

Reference Example 543

5-({(3S,4S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl} methoxy)-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0994] Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.02 (3H, s), 0.13 (9H, s), 0.83 (9H, s), 1.75-1.78 (1H, m), 1.86-1.94 (1H, m), 2.52-2.55 (2H, m), 2.67-3.04 (6H, m), 3.54-3.56 (1H, m),3.72 (3H, s), 3.83-3.85 (1H, m), 3.90-3.99 (2H, m), 5.34-5.41 (2H, m), 6.46 (1H, d, J = 9.0 Hz), 6.68-6.70 (2H, m), 7.04-7.07 (2H, m), 7.13-7.15 (1H, m).

Reference Example 544

5-({(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl }methoxy)-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0995] Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.03 (3H, s), 0.15 (9H, s), 0.84 (9H, s), 1.77-1.80 (1H, m), 1.92-1.98 (1H, m), 2.52-2.56 (2H, m), 2.65-2.78 (2H, m), 2.97-3.09 (4H m), 3.15-3.56 (1H, m), 3.69-3.72 (4H, m), 3.87-3.90 (1H, m), 3.97 (1H, d, J = 8.1 Hz), 5.35 (1H, d, J = 15.1 Hz), 5.42 (1H, d, J = 15.1 Hz), 6.37 (1H, d, J = 10.4 Hz), 6.70 (2H, d, J = 8.6 Hz), 7.04 (2H, d, J = 8.6 Hz).

Reference Example 545

5-({(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-y l}methoxy)-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[0996] Synthesized analogous to Reference Example 539.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.01 (3H, s), 0.13 (9H, s), 0.84 (9H, s), 1.67-1.77 (1H, m), 2.52-2.55 (2H, m), 2.64-2.81 (4H, m), 2.86-2.96 (2H, m), 3.66-3.72 (5H, m), 3.95 (1H, d, J = 8.1 Hz), 5.34 (1H, d, J = 15.2 Hz), 5.42 (1H, d, J = 15.2 Hz), 6.40 (1H, d, J = 10.6 Hz), 6.69-6.72 (2H, m), 7.03-7.06 (2H, m).

Reference Example 546

5-({(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl }methoxy)-7,8-difluoro-1-(4-methoxy-benzyl)-3,4-dihydroquinolin-2(1H)-one

[0997] Synthesized analogous to Reference Example 539.
^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.06 (3H, s), 0.17 (9H, s), 0.84 (9H, s), 1.83-1.86 (1H, m), 2.08-2.15 (2H, m), 2.58-2.68 (2H, m), 2.82-2.84 (2H, m), 3.05-3.25 (4H, m), 3.69 (1H, d, J = 8.1 Hz), 3.75 (3H, s), 3.97 (1H, d, J = 8.1 Hz), 4.04 (1H, dd, J = 10.7 Hz, 4.8 Hz), 5.23 (2H, s), 6.29 (1H, dd, J = 11.4 Hz, 5.8 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 547

5-({(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-y l}methoxy)-7,8-difluoro-1-(4-methoxy-benzyl)-3,4-dihydroquinolin-2(1H)-one

[0998] Synthesized analogous to Reference Example 539.
^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.03 (3H, s), 0.14 (9H, s), 0.83 (9H, s), 1.81-1.87 (2H, m), 2.58-2.67 (2H, m), 2.82-3.02 (6H, m), 3.65 (1H, d, J = 8.0 Hz), 3.74 (3H, s), 3.77-3.80 (1H, m), 3.94 (1H, d, J = 8.0 Hz), 5.23 (2H, s), 6.32 (1H, dd, J = 11.6 Hz, 5.7 Hz), 6.75-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 548

5-{[(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy} -8-fluoro-1-(4-methoxybenzyl)-3,4-di-hydroquinolin-2(1H)-one

[0999] A solution of 5-({(3R*,4R*)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (1.74 g) and potassium carbonate (1.95 g) in methanol (45 mL) was stirred at 50 °C for 18 h. To the reaction solution was added water and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.17 g).
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.03 (3H, s), 0.82 (9H, s), 1.71-1.79 (1H, m), 1.84-1.95 (1H, m), 2.46-2.70 (3H, m), 2.74-3.02 (6H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.82 (1H, d, J = 8.5 Hz), 3.87-3.94 (1H, m), 5.22 (2H, brs), 6.47 (1H, d, J = 9.0 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.15 (2H, m).

Reference Example 549

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8 -fluoro-1-(4-methoxybenzyl)-3,4-dihyd-roquinolin-2(1H)-one

[1000] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.03 (3H, s), 0.82 (9H, s), 1.71-1.79 (1H, m), 1.84-1.95 (1H, m), 2.44-2.70 (3H, m), 2.74-3.02 (6H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 3.87-3.95 (1H, m), 5.22 (2H, brs), 6.47 (1H, d, J = 9.1 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.15 (2H, m).

Reference Example 550

5-{[(3S,4S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8 -fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1001] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.03 (3H, s), 0.82 (9H, s), 1.71-1.79 (1H, m), 1.85-1.95 (1H, m), 2.42-2.70 (3H, m), 2.74-3.02 (6H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 3.88-3.95 (1H, m), 5.22 (2H, brs), 6.47 (1H, d, J = 9.1 Hz, 3.3 Hz), 6.72-6.79 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.16 (2H, m).

Reference Example 551

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8 -chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1002] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.19 (3H, s), 0.02 (3H, s), 0.82 (9H, s), 1.73-1.76 (1H, m), 1.85-1.90 (1H, m), 2.52-2.55 (3H, m), 2.63-2.85 (4H, m), 2.91-2.98 (2H, m), 3.55 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.84 (1H, d, J = 8.5 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.1 Hz), 5.43 (1H, d, J = 15.1 Hz), 6.54 (1H, d, J = 8.9 Hz), 6.68-6.71 (2H, m), 7.06 (2H, d, J = 8.6 Hz), 7.14 (1H, d, J = 8.9 Hz).

Reference Example 552

5-{[(3S,4S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8 -chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1003] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.19 (3H, s), 0.02 (3H, s), 0.82 (9H, s), 1.72-1.76 (1H, m), 1.85-1.92 (1H, m), 2.52-2.55 (3H, m), 2.63-2.85 (4H, m), 2.91-2.98 (2H, m), 3.55 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.84 (1H, d, J = 8.5 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.33 (1H, d, J = 15.1 Hz), 5.43 (1H, d, J = 15.1 Hz), 6.54 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.04-7.07 (2H, m), 7.14 (1H, d, J = 8.9 Hz).

Reference Example 553

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8 -chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1004] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.18 (3H, s), 0.03 (3H, s), 0.83 (9H, s), 1.74-1.77 (1H, m), 1.83-1.89 (1H, m), 2.53-2.55 (3H, m), 2.63-2.69 (1H, m), 2.76-2.82 (3H, m), 2.92-2.98 (2H, m), 3.53 (1H, d, J = 8.4 Hz), 3.72 (3H, s), 3.81 (1H, d, J = 8.4 Hz), 3.87 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.2 Hz), 5.44 (1H, d, J = 15.2 Hz), 6.47 (1H, d, J = 10.6 Hz), 6.69-6.72 (2H, m), 7.03-7.06 (2H, m).

Reference Example 554

5-{[(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy} -8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1005] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.18 (3H, s), 0.03 (3H, s), 0.83 (9H, s), 1.74-1.77 (1H, m), 1.83-1.89 (1H, m), 2.52-2.55 (3H, m), 2.63-2.69 (1H, m), 2.76-2.82 (3H, m), 2.92-2.98 (2H, m), 3.53 (1H, d, J = 8.4 Hz), 3.72 (3H, s), 3.80 (1H, d, J = 8.4 Hz), 3.86 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.3 Hz), 5.44 (1H, d, J = 15.4 Hz), 6.47 (1H, d, J = 10.6 Hz), 6.69-6.72 (2H, m), 7.03-7.06 (2H, m).

Reference Example 555

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-7 ,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1006] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.04 (3H, s), 0.83 (9H, s), 1.73-1.76 (1H, m), 1.83-1.89 (1H, m), 2.53-2.67 (3H, m), 2.76-2.98 (6H, m), 3.50 (1H, d, J = 8.4 Hz), 3.74 (3H, s), 3.78 (1H, d, J = 8.5 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.23 (2H, s), 6.40 (1H, dd, J = 11.6 Hz, 5.9 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 556

5-{[(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy} -7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1007] Synthesized analogous to Reference Example 548.
^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.04 (3H, s), 0.83 (9H, s), 1.73-1.77 (1H, m), 1.83-1.89 (1H, m), 2.53-2.67 (3H, m), 2.76-2.98 (6H, m), 3.50 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.78 (1H, d, J = 8.4 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.23 (2H, s), 6.40 (1H, dd, J = 11.6 Hz, 5.9 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

Reference Example 557

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}1-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1008] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.83-1.91 (1H, m), 2.10-2.22 (1H, m), 2.50-2.54 (1H, m), 2.57-2.70 (2H, m), 2.80-2.96 (3H, m), 3.02-3.19 (2H, m), 3.26-3.34 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.12-4.18 (1H, m), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.72-6.78 (2H, m), 6.79-6.94 (2H, m), 7.03-7.09 (2H, m), 7.10-7.16 (2H, m).

Reference Example 558

5-{[(3S,4S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}1-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1009] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.82-1.91 (1H, m), 2.10-2.22 (1H, m), 2.50-2.56 (1H, m), 2.57-2.71 (2H, m), 2.79-2.96 (3H, m), 3.02-3.19 (2H, m), 3.26-3.34 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.12-4.18 (1H, m), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.79-6.94 (2H, m), 7.02-7.09 (2H, m), 7.10-7.16 (2H, m).

Reference Example 559

5-{[(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-(2,2,6-trifluoro-1,3-be nzodioxol-5-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroqui nolin-2(1H)-one

[1010] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.13-2.20 (1H, m), 2.52 (1H, d, J = 2.5 Hz), 2.59-2.69 (2H, m), 2.80-2.96 (3H, m), 3.03-3.06 (2H, m), 3.17-3.20 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.12-4.16 (1H, m), 5.23 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.74 (2H, d, J = 8.5 Hz), 6.79 (1H, d, J = 7.0 Hz), 6.83 (1H, dd, J = 12.5 Hz, 9.0 Hz), 6.87 (1H, d, J = 10.0 Hz), 7.11 (2H, d, J = 8.5 Hz).

Reference Example 560

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-(2,2,6-trifluoro-1,3-ben zodioxol-5-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquin olin-2(1H)-one

[1011] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.85-1.89 (1H, m), 2.13-2.20 (1H, m), 2.51 (1H, d, J = 2.3 Hz), 2.59-2.69 (2H, m), 2.81-2.95 (3H, m), 3.03-3.06 (2H, m), 3.18 (1H, dd, J = 10.8 Hz, 5.2 Hz), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.12-4.16 (1H, m), 5.23 (2H, m), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.79 (1H, d, J = 7.0 Hz), 6.82-6.88 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 561

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1012] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.13-2.19 (1H, m), 2.55-2.59 (3H, m), 2.68-2.89 (3H, m), 2.99-3.22 (3H, m), 3.66 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.17 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.33 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 15.1 Hz), 6.56 (1H, d, J = 9.0 Hz), 6.70 (2H, d, J = 8.6 Hz), 6.93-6.97 (1H, m), 7.02-708 (3H, m), 7.13-7.16 (2H, m).

Reference Example 562

5-{[(3S,4S)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1013] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.14-2.20 (1H, m), 2.55-2.59 (3H, m), 2.68-2.89 (3H, m), 2.99-3.22 (3H, m), 3.66 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.17 (1H, dd, J = 10.2 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.0 Hz), 5.44 (1H, d, J = 15.0 Hz), 6.56 (1H, d, J = 9.0 Hz), 6.70 (2H, d, J = 8.6 Hz), 6.93-6.97 (1H, m), 7.02-7.08 (3H, m), 7.13-7.16 (2H, m).

Reference Example 563

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinoli n-2(1H)-one

[1014] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.86-1.88 (1H, m), 2.11-2.17 (1H, m), 2.55-2.59 (3H, m), 2.63-2.85 (3H, m), 2.99-3.22 (3H, m), 3.63 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 4.14 (1H, dd, J = 10.2 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.2 Hz), 5.45 (1H, d, J = 15.2 Hz), 6.49 (1H, d, J = 10.5 Hz), 6.70-6.72 (2H, m), 6.93-6.97 (1H, m), 7.02-7.07 (3H, m), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

Reference Example 564

5-{[(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydr oxypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquino lin-2(1H)-one

[1015] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.86-1.88 (1H, m), 2.11-2.18 (1H, m), 2.55-2.84 (6H, m), 2.99-3.22 (3H, m), 3.63 (1H, d, J = 8.4 Hz), 3.72 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 4.14 (1H, dd, J = 10.2 Hz, 5.3 Hz), 5.33 (1H, d, J = 14.9 Hz), 5.45 (1H, d, J = 14.6 Hz), 6.49 (1H, d, J = 10.5 Hz), 6.70-6.72 (2H, m), 6.93-6.97 (1H, m), 7.02-7.07 (3H, m), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

Reference Example 565

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-hy droxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1016] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.12-2.18 (1H, m), 2.51 (1H, d, J = 2.3 Hz), 2.59-2.69 (2H, m), 2.81-2.93 (3H, m), 3.03-3.33 (3H, m), 3.62 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.13 (1H, dd, J = 10.4 Hz, 5.2 Hz), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.73-6.77 (3H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.07-7.12 (3H, m).

Reference Example 566

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichlorophenyl)-4-hydroxypip eridin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1017] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.14-2.20 (1H, m), 2.58 (1H, d, J = 2.4 Hz), 2.61-2.70 (2H, m), 2.76 (1H, t, J = 10.7 Hz), 2.84-2.97 (2H, m), 3.05-3.12 (2H, m), 3.25-3.28 (1H, m), 3.64 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.17 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.17-5.28 (2H, m), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.99 (1H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.20 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.39 (1H, d, J = 2.5 Hz).

Reference Example 567

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichloro-5-fluorophenyl)-4-hy droxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1018] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.90 (1H, m), 2.14-2.20 (1H, m), 2.57 (1H, d, J = 2.4 Hz), 2.63-2.66 (2H, m), 2.75 (1H, t, J = 10.7 Hz), 2.83-2.96 (2H, m), 3.06-3.08 (2H, m), 3.28 (1H, dd, J = 11.1 Hz, 5.2 Hz), 3.64 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.17 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.19-5.27 (2H, m), 6.48 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.73-6.76 (2H, m), 6.82-6.87 (2H, m), 7.12 (2H, d, J = 8.5 Hz), 7.42 (1H, d, J = 7.6 Hz).

Reference Example 568

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,5-dichloro-4-fluorophenyl)-4-hy droxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1019] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.14-2.20 (1H, m), 2.56 (1H, d, J = 2.3 Hz), 2.62-2.66 (2H, m), 2.75 (1H, t, J = 10.6 Hz),2.83-3.11 (4H, m), 3.18-3.21 (1H, m), 3.64 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.16 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.19-5.27 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08 (1H, d, J = 7.1 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.21 (1H, d, J = 4.4 Hz).

Reference Example 569

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-ethoxy-2-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1020] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.40 (3H, t, J = 7.0 Hz), 1.84-1.88 (1H, m), 2.12-2.21 (1H, m), 2.53-3.23 (9H, m), 3.63 (1H, d, J = 8.8 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.3 Hz), 3.98 (2H, q, J = 7.1 Hz), 4.16 (1H, dd, J = 10.0 Hz, 5.2 Hz), 5.23 (2H, brs), 6.47-6.50 (1H, m), 6.61-6.67 (2H, m), 6.74-6.76 (2H, m), 6.81-6.94 (2H, m), 7.11-7.13 (2H, m).

Reference Example 570

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1021] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.12-2.17 (1H, m), 2.58-2.93 (6H, m), 2.99-3.23 (3H, m), 3.60 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.81 (1H, d, J = 8.5 Hz), 4.15 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.24 (2H, brs), 6.41 (1H, dd, J = 11.5 Hz, 5.9 Hz), 6.75-6.78 (2H, m), 6.94-6.97 (1H, m), 7.03 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.11-7.16 (3H, m).

Reference Example 571

5-{[(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydr oxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1022] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.11-2.18 (1H, m), 2.58-2.92 (6H, m), 2.99-3.23 (3H, m), 3.60 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.81 (1H, d, J = 8.5 Hz), 4.15 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.24 (2H, brs), 6.41 (1H, dd, J = 11.6 Hz, 5.9 Hz), 6.75-6.78 (2H, m), 6.94-6.97 (1H, m), 7.03 (1H, dd, J = 9.0 Hz, 5.5 Hz), 7.11-7.16 (3H, m).

Reference Example 572

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichlorophenyl)-4-hydroxypip eridin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1023] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.13-2.19 (1H, m), 2.54-2.58 (3H, m), 2.69-2.86 (3H, m), 3.02-3.12 (2H, m), 3.24-3.27 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.14-4.18 (1H, m), 5.33 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 14.8 Hz), 6.55 (1H, d, J = 8.9 Hz), 6.68-6.71 (2H, m), 6.99 (1H, d, J = 8.7 Hz), 7.07 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 9.0 Hz), 7.20 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz).

Reference Example 573

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,5-dichloro-4-fluorophenyl)-4-hy droxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1024] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.12-2.19 (1H, m), 2.55-2.57 (3H, m), 2.67-2.86 (3H, m), 2.98-3.20 (3H, m), 3.65 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.14-4.17 (1H, m), 5.33 (1H, d, J = 15.2 Hz), 5.44 (1H, d, J = 15.2 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.06-7.09 (3H, m), 7.16 (1H, d, J = 8.9 Hz), 7.22 (1H, d, J = 8.5 Hz).

Reference Example 574

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichloro-5-fluorophenyl)-4-hy droxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1025] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.13-2.17 (1H, m), 2.54-2.57 (3H, m), 2.67-2.86 (3H, m), 3.05-3.07 (2H, m), 3.26-3.29 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.14-4.17 (1H, m), 5.33 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 15.1 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 6.86 (1H, d, J = 10.5 Hz), 7.05-7.08 (2H, m), 7.16 (1H, d, J = 8.9 Hz), 7.41 (1H, d, J = 7.6 Hz).

Reference Example 575

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1026] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.14-2.21 (1H, m), 2.58 (1H, d, J = 2.2 Hz), 2.59-2.69 (2H, m), 2.76 (1H, t, J = 10.6 Hz), 2.84-3.13 (4H, m), 3.18-3.25 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.18 (1H, dd, J = 10.3 Hz, 5.3 Hz),5.19-5.27 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.0 Hz), 6.93-6.97 (1H, m), 7.04 (1H, dd, J = 8.8 Hz, 5.4 Hz), 7.11-7.16 (3H, m).

Reference Example 576

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-hy droxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1027] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.85-1.87 (1H, m), 2.12-2.17 (1H, m), 2.51-2.85 (6H, m), 3.03-3.17 (2H, m), 3.29-3.32 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.10-4.13 (1H, m), 5.33 (1H, d, J = 15.2 Hz), 5.44 (1H, d, J = 14.8 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.54-6.56 (2H, m), 6.74 (1H, dd, J = 10.5 Hz, 7.6 Hz), 7.05-7.10 (3H, m), 7.15 (1H, d, J = 8.7 Hz).

Reference Example 577

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-hy droxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1028] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.08-2.15 (1H, m), 2.51 (1H, d, J = 2.3 Hz), 2.58-2.69 (2H, m), 2.78-2.89 (3H, m), 3.03-3.33 (3H, m), 3.58 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.81 (1H, d, J = 8.5 Hz), 4.10-4.14 (1H, m), 5.23 (2H, brs), 6.41 (1H, dd, J = 11.5 Hz, 6.0 Hz), 6.73-6.77 (3H, m), 7.07-7.12 (3H, m).

Reference Example 578

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chlorophenyl)-4-hydroxypiperid in-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1029] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.10 (3H, s), 0.85 (9H, s), 1.81-1.85 (1H, m), 2.09-2.15 (1H, m), 2.53-2.64 (3H, m), 2.72-2.83 (2H, m), 2.89-2.93 (1H, m), 3.07-3.13 (1H, m), 3.39-3.48 (2H, m), 3.60 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.83 (1H, d, J = 8.6 Hz), 4.07-4.10 (1H, m), 5.22 (2H, brs), 6.46 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.81-6.87 (3H, m), 7.11 (2H, d, J = 8.5 Hz), 7.20-7.24 (2H, m).

Reference Example 579

5-({(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-[2-fluoro-4-(trifluoromethoxy)phe nyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroqui nolin-2(1H)-one

[1030] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.86-1.89 (1H, m), 2.13-2.19 (1H, m), 2.53 (1H, d, J = 2.3 Hz), 2.61-2.66 (2H, m), 2.84-2.91 (3H, m), 3.06-3.32 (3H, m), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.15 (1H, dd, J = 10.4 Hz, 5.3 Hz), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75 (2H, d, J = 8.6 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.96-7.00 (3H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 580

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-fluorophenyl)-4-hydroxypiperid in-4-yl]methoxyl-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1031] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 1.86-1.89 (1H, m), 2.15-2.20 (1H, m), 2.55 (1H, d, J = 2.3 Hz), 2.59-2.69 (2H, m), 2.83-2.95 (3H, m), 3.06-3.38 (3H, m), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.17 (1H, dd, J = 10.4 Hz, 5.3 Hz), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.93-7.09 (4H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 581

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2-chlorophenyl)-4-hydroxypiperid in-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1032] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.87-1.90 (1H, m), 2.16-2.22 (1H, m), 2.60 (1H, d, J = 2.4 Hz), 2.63-2.67 (2H, m), 2.79 (1H, t, J = 10.7 Hz), 2.85-2.98 (2H, m), 3.10-3.13 (2H, m), 3.32-3.35 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.20 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.19-5.27 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.99 (1H, dt, J = 1.4 Hz, 7.6 Hz), 7.08 (1H, dd, J = 8.0 Hz, 1.4 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.22-7.25 (1H, m), 7.38 (1H, dd, J = 7.9 Hz, 1.5 Hz).

Reference Example 582

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,4-difluorophenyl)-4-hydroxypip eridin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1033] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.13-2.20 (1H, m), 2.53 (1H, d, J = 2.3 Hz), 2.59-3.25 (8H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.14-4.17 (1H, m), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.79-6.86 (3H, m), 6.94-6.97 (1H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 583

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,6-difluorophenyl)-4-hydroxypiper idin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1034] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.78-1.81 (1H, m), 2.08-2.15 (1H, m), 2.58 (1H, d, J = 2.3 Hz), 2.59-2.70 (2H, m), 2.84-3.05 (3H, m), 3.14 (1H, dd, 11.7 Hz, 5.3 Hz), 3.25-3.29 (1H, m), 3.46-3.50 (1H, m), 3.62 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.10 (1H, dd, J = 10.3 Hz, 5.5 Hz), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.81-6.94 (4H, m), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 584

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-phenylpiperidin-4-yl]m ethoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1035] Synthesized analogous to Reference Example 70.
^{1}HNMR (DMSO-d6) δ ppm: -0.17 (3H, s), 0.05 (3H, s), 0.80 (9H, s), 1.67-1.70 (1H, m), 1.93-1.99 (1H, m), 2.50-3.00 (6H, m), 3.40-3.50 (2H, m), 3.61 (1H, d, J = 8.7 Hz), 3.67 (3H, s), 3.91-3.95 (2H, m), 4.43 (1H, s), 5.02-5.16 (2H, m), 6.60 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.76-6.79 (3H, m), 6.92-704 (5H, m), 7.22-7.25 (2H, m).

Reference Example 585

5-({(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-[4-(trifluoromethoxy)p henyl]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1036] Synthesized analogous to Reference Example 70.
^{1}HNMR (DMSO-d6) δ ppm: -0.17 (3H, s), 0.06 (3H, s), 0.80 (9H, s), 1.68-1.70 (1H, m), 1.93-1.99 (1H, m), 2.45-3.03 (6H, m), 3.40-3.51 (2H, m), 3.61 (1H, d, J = 8.7 Hz), 3.67 (3H, s), 3.91-3.94 (2H, m), 4.48 (1H, s), 5.02-5.16 (2H, m), 6.60 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.76-6.78 (2H, m), 6.92-7.04 (5H, m), 7.21 (2H, d, J = 8.9 Hz).

Reference Example 586

5-({(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-[4-(difluoromethoxy)phenyl]-4-hy droxypiperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1 H)-one

[1037] Synthesized analogous to Reference Example 70.
^{1}HNMR (DMSO-d6) δ ppm: -0.17 (3H, s), 0.05 (3H, s), 0.80 (9H, s), 1.67-1.70 (1H, m), 1.93-1.98 (1H, m), 2.50-3.00 (6H, m), 3.41-3.51 (2H, m), 3.61 (1H, d, J = 8.7 Hz), 3.67 (3H, s), 3.91-3.95 (2H, m), 4.44 (1H, s), 5.01-5.17 (2H, m), 6.60 (1H, dd, J = 9.4 Hz, 3.1 Hz), 6.78 (2H, d, J = 8.7 Hz), 6.91-7.07 (7H, m).

Reference Example 587

5-{[(3R*,4R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydr oxypiperidin-4-yl]methoxy]-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1038] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 1.82-1.89 (1H, m), 2.08-2.18 (1H, m), 2.53 (1H, d, J = 2.5 Hz), 2.58-2.69 (2H, m), 2.78-2.91 (3H, m), 3.02-3.10 (1H, m), 3.11-3.17 (1H, m), 3.26-3.32 (1H, m), 3.58 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.80 (1H, d, J = 8.5 Hz), 4.09-4.15 (1H, m), 5.24 (2H, brs), 6.39 (1H, dd, J = 12.0 Hz, 6.0 Hz), 6.74-6.79 (2H, m), 6.87-6.92 (1H, m), 7.04-7.09 (2H, m), 7.09-7.14 (2H, m).

Reference Example 588

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinoli n-2(1H)-one

[1039] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.09-2.16 (1H, m), 2.53-2.57 (3H, m), 2.63-2.86 (3H, m), 3.03-3.30 (3H, m), 3.61 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 4.09-4.13 (1H, m), 5.33 (1H, d, J = 15.2 Hz), 5.45 (1H, d, J = 15.2 Hz), 6.48 (1H, d, J = 10.5 Hz), 6.69-6.72 (2H, m), 6.87-6.91 (1H, m), 7.04-7.08 (4H, m).

Reference Example 589

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydro xypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1040] Synthesized analogous to Reference Example 70.
HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.82-1.89 (1H, m), 2.10-2.20 (1H, m), 2.51-2.58 (3H, m), 2.65-2.64 (1H, m), 2.78-2.87 (2H, m), 3.03-3.09 (1H, m), 3.11-3.18 (1H, m), 3.25-3.31 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.10-4.16 (1H, m), 5.32 (1H, d, J = 15.0 Hz), 5.43 (1H, d, J = 15.0 Hz), 6.54 (1H, d, J = 9.0 Hz), 6.68-6.72 (2H, m), 6.88 (1H, t, J = 9.0 Hz), 7.03-7.09 (4H, m), 7.14 (1H, d, J = 9.0 Hz).

Reference Example 590

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluoro-5-methoxyphen yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquin olin-2(1H)-one

[1041] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.072 (3H, s), 0.84 (9H, s), 1.86-1.90 (1H, m), 2.12-2.20 (1H, m), 2.52 (1H, d, J = 2.3 Hz), 2.58-2.70 (2H, m), 2.82-2.96 (3H, m), 3.07-3.19 (2H, m), 3.31-3.36 (1H, m), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 3.87 (3H, s), 4.12-4.17 (1H, m), 5.23 (2H, s), 6.48 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.55 (1H, d, J = 7.7 Hz), 6.74 (2H, d, J = 8.6 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.08 (1H, d, J = 11.6 Hz), 7.12 (2H, d, J = 8.6 Hz).

Reference Example 591

5-{[(3R,4R)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluoro-5-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinol in-2(1H)-one

[1042] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.072 (3H, s), 0.84 (9H, s), 1.84-1.88 (1H, m), 2.11-2.20 (1H, m), 2.30 (3H, s), 2.53 (1H, d, J = 2.4 Hz), 2.59-2.70 (2H, m), 2.80-2.96 (3H, m), 3.03-3.09 (1H, m), 3.12-3.17 (1H, m), 3.27-3.32 (1H, m), 3.62 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.12-4.17 (1H, m), 5.23 (2H, s), 6.48 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.74 (2H, d, J = 8.8 Hz), 6.81 (1H, d, J = 8.8 Hz), 6.83 (1H, dd, J = 12.8 Hz, 9.2 Hz), 7.05 (1H, d, J = 11.8 Hz), 7.12 (2H, d, J = 8.8 Hz).

Reference Example 592

5-{[1-(4-Chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1043] Under nitrogen atmosphere, to a solution of 5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-d ihydroquinolin-2(1H)-one (441 mg) in tetrahydrofuran (8 mL), Burgess reagent (597 mg) was added under ice-cooling, and the reaction mixture was stirred at room temperature for 16.5 h, then at 60 °C for 2 h. To the reaction solution was added water, and the precipitate was collected on a filter to provide the title compound (380 mg). The compound was used for the next step without further purification.
^{1}HNMR ($CDCl_3$) δ ppm: 2.29-2.34 (2H, m), 2.63 (2H, t, J = 8.0 Hz), 3.02 (2H, t, J = 8.0 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs), 4.43 (2H, s), 5.85 (1H, brs), 6.48 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.87-6.93 (3H, m), 7.49 (1H, brs).

Reference Example 593

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methox y]-3,4-dihydroquinolin-2(1H)-one

[1044] Synthesized analogous to Reference Example 592.
^{1}HNMR ($CDCl_3$) δ ppm: 2.23-2.32 (2H, m), 2.60-2.66 (2H, m), 3.02 (2H, t, J = 8.1 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs), 4.46 (2H, s), 5.85 (1H, brs), 6.54 (1H, d, J = 8.9 Hz), 6.87-6.92 (2H, m), 7.16-7.19 (1H, m), 7.74 (1H, brs).

Reference Example 594

5-{[1-(4-Chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-7,8-di fluoro-3,4-dihydroquinolin-2(1H)-one

[1045] Synthesized analogous to Reference Example 592.
^{1}HNMR ($CDCl_3$) δ ppm: 2.28-2.32 (2H, m), 2.60-2.65 (2H, m), 2.95-2.99 (2H, m), 3.33-3.35 (2H, m), 3.73 (2H, brs), 4.41 (2H, s), 5.86 (1H, brs), 6.40 (1H, dd, J = 12.1 Hz, 6.3 Hz), 6.86-6.93 (2H, m), 7.67 (1H, brs).

Reference Example 595

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3 ,4-dihydroquinolin-2(1H)-one

[1046] To a solution of 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one (8 g) in N-methyl-2-pyrrolidone (60 mL) was added N,N,N',N'-tetramethyl-1,3-diaminopropane (13.59 mL),

then methanesulfonyl chloride (5.30 mL) was added dropwise under ice-cooling. The reaction mixture was stirred at room temperature for 16 h. To the reaction solution were added water and tert-butyl methyl ether, and the precipitate was collected on a filter. The obtained solid was washed with water and diisopropyl ether to provide the title compound (7.27 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.33-2.37 (2H, m), 2.61-2.65 (2H, m), 3.00-3.05 (2H, m), 3.29 (2H, t, J = 5.6 Hz), 3.65 (2H, brs), 4.44 (2H, s), 5.88 (1H, brs), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.83 (1H, t, J = 9.1 Hz), 6.90 (1H, t, J = 9.4 Hz), 7.16-7.22 (2H, m), 7.49 (1H, brs).

Reference Example 596

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one

[1047] Synthesized analogous to Reference Example 592.
^{1}HNMR (DMSO-d6) δ ppm: 2.25 (2H, brs), 2.44-2.48 (2H, m), 2.86-2.90 (2H, m), 3.20-3.22 (2H, m), 3.57-3.60 (2H, m), 4.52 (2H, s), 5.91 (1H, brs), 6.72 (1H, d, J = 9.0 Hz), 6.98-7.02 (1H, m), 7.23-7.30 (2H, m), 7.42-7.45 (1H, m), 9.37 (1H, brs).

Reference Example 597

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-7,8-difluo ro-3,4-dihydroquinolin-2(1H)-one

[1048] Synthesized analogous to Reference Example 592.
^{1}HNMR (DMSO-d6) δ ppm: 2.25 (2H, brs), 2.42-2.47 (2H, m), 2.81-2.85 (2H, m), 3.21 (2H, t, J = 5.6 Hz), 3.59 (2H, brs), 4.49 (2H, s), 5.92 (1H, brs), 6.79 (1H, dd, J = 12.8 Hz, 6.3 Hz), 7.00 (1H, t, J = 9.1 Hz), 7.27-7.30 (1H, m), 7.43 (1H, dd, J = 12.2 Hz, 2.3 Hz), 10.31 (1H, brs).

Reference Example 598

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methox y}-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1049] Synthesized analogous to Reference Example 595.
^{1}HNMR (DMSO-d6) δ ppm: 2.23 (2H, brs), 2.45-2.49 (2H, m), 2.83-2.87 (2H, m), 3.25-3.29 (2H, m), 3.64 (2H, brs), 4.53 (2H, s), 5.89 (1H, brs), 6.87 (1H, d, J = 11.6 Hz), 7.23-7.33 (2H, m), 9.70 (1H, brs).

Reference Example 599

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-chloro-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1050] Synthesized analogous to Reference Example 595.
^{1}HNMR (DMSO-d6) δ ppm: 2.25 (2H, brs), 2.45-2.49 (2H, m), 2.82-2.86 (2H, m), 3.21 (2H, t, J = 5.6 Hz), 3.59 (2H, brs), 4.54 (2H, s), 5.93 (1H, brs), 6.87 (1H, d, J = 11.6 Hz), 7.00 (1H, t, J = 9.1 Hz), 7.27-7.30 (1H, m), 7.43 (1H, dd, J = 12.3 Hz, 2.3 Hz), 9.69 (1H, brs).

Reference Example 600

5-{[1-(2-Chloro-4,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1051] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.32 (2H, brs), 2.62-2.66 (2H, m), 3.03 (2H, t, J = 8.1 Hz), 3.27-3.29 (2H, m), 3.66 (2H, brs), 4.45 (2H, s), 5.86 (1H, brs), 6.49 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.73-6.78 (1H, m), 6.89-6.98 (2H, m), 7.52 (1H, brs).

Reference Example 601

5-{[1-(4-Bromo-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1052] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.31 (2H, brs), 2.61-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs),

4.43 (2H, s), 5.85 (1H, brs), 6.48 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.3 Hz), 7.01-7.06 (2H, m), 7.51 (1H, brs).

Reference Example 602

8-Fluoro-5-{[1-(2,4,6-trifluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1053] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.28-2.35 (2H, m), 2.60-2.66 (2H, m), 3.03 (2H, t, J = 7.7 Hz), 3.31 (2H, t, J = 5.5 Hz), 3.65-3.3.70 (2H, m), 4.44 (2H, brs), 5.83-5.88 (1H, m), 6.49 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.60-6.69 (2H, m), 6.90 (1H, t, J = 9.5 Hz), 7.49 (1H, brs).

Reference Example 603

5-{[1-(2,4-Dichloro-6-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1054] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.32 (2H, brs), 2.62-2.65 (2H, m), 3.03 (2H, t, J = 7.7 Hz), 3.29-3.32 (2H, m), 3.69 (2H, brs), 4.44 (2H, s), 5.86 (1H, brs), 6.49 (1H, dd, J = 9.3 Hz, 3.9 Hz), 6.91 (1H, t, J = 9.3 Hz), 7.00 (1H, dd, J = 11.3 Hz, 2.4 Hz), 7.20-7.21 (1H, m), 7.52 (1H, brs).

Reference Example 604

5-({1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1,2,3,6-tetrahydropyridin-4-yl} methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1055] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.30-2.34 (2H, m), 2.62-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.28-3.31 (2H, m), 3.66 (2H, brs), 4.29 (2H, q, J = 8.0 Hz), 4.43 (2H, s), 5.85 (1H, brs), 6.47-6.54 (3H, m), 6.91 (1H, t, J = 9.5 Hz), 7.52 (1H, brs).

Reference Example 605

5-({1-[4-(Difluoromethoxy)-2,6-difluorophenyl]-1,2,3,6-tetrahydropyridin-4-yl}meth oxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1056] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.30-2.35 (2H, m), 2.62-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.31-3.34 (2H, m), 3.71 (2H, brs), 4.44 (2H, s), 5.86 (1H, brs), 6.46 (1H, t, J = 73.2 Hz), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.68-6.73 (2H, m), 6.91 (1H, t, J = 9.5 Hz), 7.57 (1H, brs).

Reference Example 606

5-{[1-(4-Ethoxy-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yllmethoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1057] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 6.8 Hz), 2.30-2.34 (2H, m), 2.60-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.26-3.29 (2H, m), 3.64 (2H, brs), 3.96 (2H, q, J = 6.8 Hz), 4.43 (2H, s), 5.85 (1H, brs), 6.39-6.46 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.56 (1H, brs).

Reference Example 607

5-{[1-(4-Chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-7,8-difluo ro-3,4-dihydroquinolin-2(1H)-one

[1058] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.31-2.38 (2H, m), 2.61 (2H, t, J = 7.6 Hz), 2.95 (2H, t, J = 7.6 Hz), 3.28 (2H, t, J = 5.6 Hz), 3.63-3.68 (2H, m), 4.45 (2H, s), 5.90 (1H, brs), 6.38 (1H, dd, J = 11.7 Hz, 6.3 Hz), 6.87 (1H, t, J = 8.9 Hz), 7.02-7.09 (2H, m), 7.57 (1H, brs).

Reference Example 608

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1059] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.32-2.39 (2H, m), 2.58 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 3.28 (2H, t, J = 5.5 Hz), 3.66 (2H, s), 4.47 (2H, s), 5.90 (1H, s), 6.54 (1H, d, J = 9.0 Hz), 6.86-6.91 (1H, m), 7.02-7.10 (2H, m), 7.16 (1H, d, J = 9.0 Hz), 7.79 (1H, s).

Reference Example 609

5-{[1-(4-Bromo-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-chlo ro-3,4-dihydroquinolin-2(1H)-one

[1060] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 2.31 (2H, brs), 2.60-2.64 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs), 4.46 (2H, s), 5.85 (1H, brs), 6.54 (1H, d, J = 8.9 Hz), 7.01-7.06 (2H, m), 7.17 (1H, d, J = 8.9 Hz), 7.73 (1H, brs).

Reference Example 610

5-{[1-(2-Bromo-4-chloro-6-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxyl-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1061] Synthesized analogous to Reference Example 595.
^{1}HNMR (DMSO-d6) δ ppm: 2.15-2.37 (2H, m), 2.42-2.49 (2H, m), 2.88 (2H, t, J = 7,6 Hz), 3.17-3.29 (2H, m), 3.59 (2H, brs), 4.48 (2H, s), 5.89 (1H, brs), 6.63 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.52 (1H, dd, J = 11.8 Hz, 2.4 Hz), 7.62-7.69 (1H, m), 10.03 (1H, brs).

Reference Example 611

5-{[1-(4-Chloro-2,5-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1062] Synthesized analogous to Reference Example 592.
^{1}HNMR ($CDCl_3$) δ ppm: 2.29-2.40 (2H, m), 2.46-2.72 (2H, m), 3.01 (2H, t, J = 7.6 Hz), 3.30 (2H, t, J = 5.7 Hz), 3.60-3.72 (2H, m), 4.44 (2H, brs), 5.82-5.92 (1H, m), 6.47 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.67-6.76 (1H, m), 6.91 (1H, t, J = 9.4 Hz), 7.08 (1H, dd, J = 11.7 Hz, 6.9 Hz), 7.52 (1H, brs).

Reference Example 612

5-{[1-(4-Chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3, ,4-dihydroquinolin-2(1H)-one

[1063] Synthesized analogous to Reference Example 592.
^{1}HNMR ($CDCl_3$) δ ppm: 2.32-2.38 (2H, m), 2.61-2.67 (2H, m), 3.00-3.05 (2H, m), 3.28-3.30 (2H, m), 3.65 (2H, brs), 4.44 (2H, s), 5.89 (1H, brs), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.86-6.93 (2H, m), 7.03-7.09 (2H, m), 7.52 (1H, brs).

Reference Example 613

4-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydr opyridine

[1064] Under nitrogen atmosphere, to a solution of potassium hexamethyldisilazide (2.05 g) in tetrahydrofuran (10 mL) was added a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (2.00 g) in tetrahydrofuran (10 mL) at - 78 °C, and the reaction mixture was stirred for 30 min. Then tert-butyldimethylsilyl chloride (1.35 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1.5 h. To the reaction solution were added hexane and water to extract the product. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled of to provide the title compound (2.89 g).
^{1}HNMR ($CDCl_3$) δ ppm: 0.17 (6H, s), 0.93 (9H, s), 2.20-2.24 (2H, m), 3.29-3.32 (2H, m), 3.64-3.66 (2H, m), 4.87-4.89 (1H, m), 6.84-6.89 (2H, m).

Reference Example 614

1-(4-Bromo-2-fluorophenyl)-4-{[tert-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydropyr idine

[1065] To a solution of 1-(4-bromo-2-fluorophenyl)piperidin-4-one (20 g) in acetonitrile (60 mL), triethylamine (12.81 mL), tert-butyl dimethylchlorosilane (12.74 g) and sodium iodide (12.67 g) were addedunder ice-cooling. Under nitrogen atmosphere, the reaction mixture was stirred at reflux for 1 h. The reaction solution was allowed to cool to room temperature, and hexane was added thereto, filtered with Celite, and the filtrate was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to provide the title compound (28.8 g).
^{1}HNMR ($CDCl_3$) δ ppm: 0.16 (6H, s), 0.93 (9H, s), 2.03-2.09 (2H, m), 3.11 (2H, t, J = 5.7 Hz), 3.43 (2H, dd, J = 5.7 Hz, 2.5 Hz), 4.73-4.76 (1H, m), 6.65 (1H, t, J = 8.9 Hz), 6.97-7.05 (2H, m).

Reference Example 615

4-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyr idine

[1066] Synthesized analogous to Reference Example 614.
^{1}HNMR ($CDCl_3$) δ ppm: 0.16 (6H, s), 0.93 (9H, s), 2.19-2.26 (2H, m), 3.28 (2H, t, J = 5.7 Hz), 3.60 (2H, dd, J = 5.7 Hz, 2.5 Hz), 4.89-4.92 (1H, m), 6.88 (1H, t, J = 8.9 Hz), 6.99-7.06 (2H, m).

Reference Example 616

1-(4-Bromo-2,6-difluorophenyl)-4-{[tert-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydr opyridine

[1067] Synthesized analogous to Reference Example 614.
^{1}HNMR ($CDCl_3$) δ ppm: 0.17 (6H, s), 0.93 (9H, s), 2.18-2.24 (2H, m), 3.27-3.33 (2H, m), 3.62-3.68 (2H, m), 4.86-4.89 (1H, m), 6.98-7.04 (2H, m).

Reference Example 617

(1R,6R)-3-(4-Bromo-2-fluorophenyl)-6-{[tert-butyl(dimethyl)silyl]oxy}-7-oxa-3-aza bicyclo[4.1.0]heptane

[1068] To a solution of potassium carbonate (9.44 g) in 32 mL of 4 x 10^{-4} M aqueous ethylenediamine tetraacetic acid disodium salt was added a solution of 1-(4-bromo-2-fluorophenyl)-4-{[tert-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydropyrid ine (8.8 g) in acetonitrile/1-propanol/toluene (1:1:2) (95 mL). After the addition of Shi epoxidizing catalyst (1.765 g) under ice-cooling, 30 % hydrogen peroxide aqueous solution (9.31 mL) was added dropwise thereto at an internal temperature of 2 °C, and the reaction mixture was stirred at the same temperature for 12 h. To the reaction solution were added hexane and water to extract the product. The organic layer was washed with water, brine and sodium sulfite, dried over anhydrous sodium sulfate, and the solvent was distilled off to provide the title compound (8.79 g).
^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.19-2.25 (1H, m), 2.29-2.36 (1H, m), 2.81-2.89 (1H, m), 3.08-3.14 (1H, m), 3.17 (1H, d, J = 13.7 Hz), 3.37 (1H, d, J = 4.5 Hz), 3.56-3.63 (1H, m), 6.72 (1H, t, J = 9.0 Hz), 7.13-7.19 (2H, m).

Reference Example 618

(1R,6R)-6-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-chloro-2,6-difluorophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane

[1069] Synthesized analogous to Reference Example 617.
^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.13-2.19 (1H, m), 2.23-2.31 (1H, m), 2.91-2.97 (1H, m), 3.07-3.14 (1H, m), 3.33-3.40 (2H, m), 3.51 (1H, dd, 13.7 Hz, 4.0 Hz), 6.83-6.90 (2H, m).

Reference Example 619

(1R*,6R*)-3-(4-Bromo-2,6-difluorophenyl)-6-{[tert-butyl(dimethyl)silyl]oxy}-7-oxa-3-azabicyclo[4.1.0]heptane

[1070] To a solution of 1-(4-bromo-2,6-difluorophenyl)-4-{[tert-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydrop yridine (7.0 g) and 1,1,1-trifluoroacetone (0.93 mL) in acetonitrile/toluene/1-propanol (1: 2: 1) (84 mL) was added a solution of

potassium carbonate (7.18 g) and ethylenediamine tetraacetic acid disodium salt (3.9 mg) in water (26 mL) at 0 °C. To the reaction mixture, 30 % hydrogen peroxide aqueous solution (7.07 mL) was added dropwise at an internal temperature of 3-5 °C, and the mixture was stirred at the same temperature for 9.5 h. To the reaction solution were added toluene and aqueous 1 M sodium thiosulfate to extract the product. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (6.58 g).
^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.17 (3H, s), 0.90 (9H, s), 2.12-2.19 (1H, m), 2.22-2.30 (1H, m), 2.91-2.98 (1H, m), 3.06-3.14 (1H, m), 3.34 (1H, d, J = 4.1 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.53 (1H, dd, J = 14.1 Hz, 4.1 Hz), 6.97-7.03 (2H, m).

Reference Example 620

(1R,6R)-3-(4-Bromo-2,6-difluorophenyl)-6-{[tert-butyl(dimethyl)silyl]oxy}-7-oxa-3-azabicyclo[4.1.0]heptane

[1071] Synthesized analogous to Reference Example 617.
^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.14-2.18 (1H, m), 2.23-2.29 (1H, m), 2.92-2.97 (1H, m), 3.07-3.13 (1H, m), 3.35 (1H, d, J = 4.0 Hz), 3.37 (1H, d, J = 14.0 Hz), 3.53 (1H, dd, J = 14.0 Hz, 4.0 Hz), 6.98-7.03 (2H, m).

Reference Example 621

(1R,6R)-6-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-chloro-2-fluorophenyl)-7-oxa-3-aza bicyclo[4.1.0]heptane

[1072] Synthesized analogous to Reference Example 617.
^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.20-2.24 (1H, m), 2.29-2.34 (1H, m), 2.82-2.88 (1H, m), 3.07-3.11 (1H, m), 3.17 (1H, d, J = 14.0 Hz), 3.37 (1H, d, J = 4.3), 3.57-3.62 (1H, m), 6.79 (1H, t, J = 9.2 Hz), 6.99-7.04 (2H, m).

Reference Example 622

(1R*,6R*)-6-{[tert-Butyl(dimethyl)silyl]oxy}-3-(4-chloro-2,6-difluorophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane

[1073] Synthesized analogous to Reference Example 619.
^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.12-2.19 (1H, m), 2.22-2.31 (1H, m), 2.90-2.97 (1H, m), 3.06-3.15 (1H, m), 3.33-3.40 (2H, m), 3.53 (1H, dd, J = 14.0 Hz, 3.2 Hz), 6.83-6.90 (2H, m).

Reference Example 623

(3R,4R)-6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1074] To a suspension of trimethylsulfoxonium iodide (3.44 g) in dimethyl sulfoxide (37 mL) was added sodium tert-butoxide (1.50 g), and the reaction mixture was stirred at room temperature for 30 min. Then a solution of (3R)-1-(4-chloro-2,6-difluorophenyl)-3-hydroxypiperidin-4-one (3.72 g, 81.7 % ee) in dimethyl sulfoxide (37 mL) was added to the mixture, and the reaction mixture was stirred at room temperature for 10 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallization from ethanol to provide the title compound (1.49 g, 98 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 9.5 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.13-3.18 (1H, m), 3.26-3.32 (1H, m), 3.39-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 6.87-6.92 (2H, m).

Reference Example 624

(3R*,4R*)-6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1075] Synthesized analogous to Reference Example 623.
^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 9.5 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.13-3.18 (1H, m), 3.26-3.32 (1H, m), 3.39-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 6.87-6.92 (2H, m).

Reference Example 625

(3R*,4R*)-6-(4-Chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1076] To a suspension of 1-(4-chloro-2-fluorophenyl)piperidin-4-one (3.00 g) and DL-proline (0.455 g) in N,N-dimethylformamide (20 mL) was added a solution of nitrosobenzene (1.41 g) in N,N-dimethylformamide (40 mL) at 0 °C over 6 h, and the reaction mixture was stirred at the same temperature for 1 h. The reaction solution was poured into aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved in methanol (30 mL), copper (II) sulfate (0.631 g) was added to the solution and the mixture was stirred at 0 °C for 2 h. To the reaction solution was added brine and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtrated. To the filtrate was added dimethyl sulfoxide (30 mL) and the mixture was concentrated to give a solution of 1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-one (a-hydroxyketone compound) in dimethyl sulfoxide. To a suspension of trimethylsulfoxonium iodide (3.19 g) in dimethyl sulfoxide (30 mL) was added sodium tert-butoxide (1.39 g), and the reaction mixture was stirred at room temperature for 30 min. To the obtained mixture a solution of α-hydroxyketone compound in dimethyl sulfoxide was added, and the mixture was stirred at room temperature for 30 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate). The product was recrystallized from ethyl acetate/hexane to provide the title compound (647 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.97 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.99-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.47-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.91 (1H, t, J = 9.0 Hz), 7.04-7.08 (2H, m).

Reference Example 626

(3R*,4R*)-6-(4-Bromo-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1077] Synthesized analogous to Reference Example 625.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.96 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 11.0 Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.98-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.48-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.85 (1H, t, J = 9.0 Hz), 7.18-7.20 (2H, m).

Reference Example 627

(3R,4R)-6-(4-Bromo-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1078] To a solution of 1-(4-bromo-2-fluorophenyl)-4-{[tert-butyl(diphenyl)silyl]oxy}-1,2,3,6-tetrahydropyrid ine (34.2 g) in acetonitrile-dimethoxymethane (240-240 mL) were added at 0 °C, 240 mL of buffer (0.05 M aqueous sodium tetraborate decahydrate in 4 x 10^{-4} M aqueous ethylenediamine tetraacetic acid disodium salt), Shi epoxidizing catalyst (6.86 g), and tetrabutylammonium hydrogensulfate (0.910 g). Thereafter, a solution of Oxone (Registered trade mark) (56.8 g) in 300 mL of 4 x 10^{-4} M aqueous ethylenediamine tetraacetic acid disodium salt and a solution of potassium carbonate (53.7 g) in water (300 mL) were added dropwise through two separate addition funnels over 2 h, and then the mixture was stirred at 0 °C for 2 h. To the reaction solution were added ice-cooled hexane and ice-cooled water to extract the product. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved in tetrahydrofuran-water (175-140 mL), 5 N hydrochloric acid (35 mL) was added to the solution, and the mixture was stirred at room temperature for 1 h. To the reaction solution was added water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtrated. To the filtrate was added dimethyl sulfoxide (160 mL) and the solution was concentrated to give a solution of (R)-1-(4-bromo-2-fluorophenyl)-3-hydroxypiperidin-4-one (a-hydroxyketone compound) in dimethyl sulfoxide. To a suspension of trimethylsulfonium iodide (16.2 g) in dimethyl sulfoxide (160 mL) was added sodium tert-butoxide (7.08 g), and the reaction mixture was stirred at room temperature for 30 min. The solution of α-hydroxyketone compound in dimethyl sulfoxide was added to the mixture, and the obtained mixture was stirred at room temperature for 15 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallized from ethyl acetate/hexane to provide the title compound (3.27 g, 99 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.96 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 11.0

Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.98-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.48-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.85 (1H, t, J = 9.0 Hz), 7.18-7.20 (2H, m).

Reference Example 628

(3R*,4R*)-6-(4-Bromo-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1079] Synthesized analogous to Reference Example 625.
^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 10.0 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.14-3.19 (1H, m), 3.26-3.32 (1H, m), 3.40-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 7.02-7.07 (2H, m).

Reference Example 629

(3R,4R)-6-(4-Bromo-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1080] Synthesized analogous to Reference Example 627.
^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 10.0 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.14-3.19 (1H, m), 3.26-3.32 (1H, m), 3.40-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 7.02-7.07 (2H, m).

Reference Example 630

(3R,4R)-6-(4-Chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1081] Synthesized analogous to Reference Example 627.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.97 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.99-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.47-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.91 (1H, t, J = 9.0 Hz), 7.04-7.08 (2H, m).

Reference Example 631

(3R*,4R*)-6-(4-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1082] Synthesized analogous to Reference Example 625.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 4.0 Hz), 1.94 (1H, d, J = 11.0 Hz), 2.17 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.71 (1H, d, J = 4.5 Hz), 2.83 (1H, dd, J = 11.5 Hz, 9.0 Hz), 3.04-3.09 (1H, m), 3.09 (1H, d, J = 4.5 Hz), 3.34-3.38 (1H, m), 3.60-3.63 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.5 Hz, 4.5 Hz), 6.91-7.00 (4H, m).

Reference Example 632

(3R,4R)-6-(4-Fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

[1083] To a suspension of 1-(4-fluorophenyl)piperidin-4-one (10.3 g) and (S)-5-(pyrrolidin-2-yl)-1H-tetrazole (0.371 g) in N,N-dimethylformamide (100 mL) was added a solution of nitrosobenzene (5.71 g) in N,N-dimethylformamide (100 mL) over 6.5 h at -20 °C, and the reaction mixture was stirred at the same temperature for 1 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved in methanol (100 mL), copper (II) sulfate (2.55 g) was added to the solution and the mixture was stirred at 0 °C for 2 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtrated. To the filtrate was added dimethyl sulfoxide (100 mL) and the mixture was concentrated to give a solution of (R)-1-(4-fluorophenyl)-3-hydroxypiperidin-4-one (a-hydroxyketone compound) in dimethyl sulfoxide. To a suspension of trimethylsulfonium iodide (12.9 g) in dimethyl sulfoxide (100 mL) was added sodium tert-butoxide (5.64 g), and the mixture was stirred at 1 h. To the mixture was added the solution of α-hydroxyketone compound in dimethyl sulfoxide and the reaction mixture was stirred at room temperature for 15 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallized from ethyl ace-

tate/hexane to provide the title compound (1.01 g, > 99 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 4.0 Hz), 1.94 (1H, d, J = 11.0 Hz), 2.17 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.71 (1H, d, J = 4.5 Hz), 2.83 (1H, dd, J = 11.5 Hz, 9.0 Hz), 3.04-3.09 (1H, m), 3.09 (1H, d, J = 4.5 Hz), 3.34-3.38 (1H, m), 3.60-3.63 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.5 Hz, 4.5 Hz), 6.91-7.00 (4H, m).

Reference Example 633

tert-Butyl (1S*,6S*)-6-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-7-oxa-3-azabicyclo [4.1.0]heptane-3-carboxylate

[1084] To a solution of tert-butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (3.06 g) in chloroform (30 mL) was added 75 % meta-chloroperoxybenzoic acid (2.81 g) and the reaction mixture was stirred at room temperature overnight. After insoluble materials were filtered off, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.8 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.96-2.06 (1H, m), 2.07-2.20 (1H, m), 2.59-2.67 (2H, m), 2.96-3.03 (2H, m), 3.06-3.22 (1H, m), 3.25-3.37 (1H, m), 3.51-3.80 (2H, m), 3.82-4.16 (3H, m), 6.42 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.90 (1H, t, J = 9.3 Hz), 7.59 (1H, brs).

Reference Example 634

tert-Butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate

[1085] Synthesized analogous to Reference Example 633.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.94-2.04 (1H, m), 2.06-2.18 (1H, m), 2.58-2.68 (2H, m), 2.81-2.91 (2H, m), 3.06-3.20 (1H, m), 3.24-3.39 (1H, m), 3.51-3.79 (2H, m), 3.74 (3H, s), 3.82-4.18 (3H, m), 5.17-5.27 (2H, m), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.72-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.15 (2H, m).

Reference Example 635

tert-Butyl (3R*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiper idine-1-carboxylate

[1086] To a solution of tert-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (9.3 g) in anisole (0.4 mL) was added trifluoroacetic acid (40 mL) dropwise, the reaction mixture was stirred while heating at 60 °C for 3 h, and the solvent was distilled off. To the residue, methanol (40 mL) and triethylamine (7.6 mL) followed by di-tert-butyl dicarbonate (4.6 mL) were added, and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added 5 N aqueous sodium hydroxide and the reaction mixture was stirred at 60 °C for 15 h. After the reaction mixture was allowed to cool to room temperature, the precipitate was collected on a filter and purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (2.0 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.32-1.39 (1H, m), 1.39 (9H, s), 1.66-1.79 (1H, m), 2.40-2.48 (2H, m), 2.86-3.00 (2H, m), 3.38-3.43 (1H, m), 3.52-3.82 (5H, m), 3.86-3.94 (1H, m), 4.82 (1H, brs), 4.86-4.96 (1H, m), 6.54 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.98 (1H, t, J = 9.2 Hz), 9,98 (1H, brs).

Reference Example 636

tert-Butyl (3R*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-3,4-dihydroxypiperidine-1-carboxylate

[1087] Synthesized analogous to Reference Example 43.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.50-1.57 (1H, m), 1.83-1.92 (1H, m), 2.38 (1H, brs), 2.65 (2H, t, J = 7.1 Hz), 2.80-2.91 (2H, m), 3.12-3.24 (1H, m), 3.34-3.51 (1H, m), 3.71-3.79 (2H, m), 3.74 (3H, s), 3.86-4.09 (3H, m), 5.23 (2H, brs), 6.55 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.74-6.78 (2H, m), 6.83 (1H, dd, J = 12.3 Hz, 9.2 Hz), 7.10-7.14 (2H, m).

Reference Example 637

tert-Butyl (3R*,4S*)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

[1088] Synthesized analogous to Reference Example 530.
^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.09-0.17 (3H, m), 0.76-0.86 (9H, m), 1.46 (9H, s), 1.47-1.55 (1H, m), 1.86-1.97 (1H, m), 2.28 (1H, brs), 2.57-2.70 (2H, m), 2.82-2.90 (2H, m), 3.07-3.39 (2H, m), 3.62-3.72 (2H, m), 3.73 (3H, s), 3.79-3.92 (1H, m), 3.93-4.08 (2H, m), 5.23 (2H, brs), 6.46 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.78 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.09-7.14 (2H, m).

Reference Example 638

5-({(3R*,4S*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-y l}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1089] Synthesized analogous to Reference Example 539.
^{1}HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.04 (3H, s), 0.05 (9H, s), 0.81 (9H, s), 1.39-1.45 (1H, m), 1.69-1.77 (1H, m), 2.62 (2H, t. J = 7.0 Hz), 2.65-2.71 (1H, m), 2.79-2.98 (4H, m), 3.12-3.17 (1H, m), 3.61-3.66 (2H, m), 3.73 (3H, s), 3.91 (1H, d, J = 9.4 Hz), 5.12-5.32 (2H, m), 6.41 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.76 (2H, m), 6.82 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.08-7.13 (2H, m).

Reference Example 639

5-{[(3R*,4S*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydr oxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H) -one

[1090] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.02 (3H, s), 0.78 (9H, s), 1.60-1.68 (1H, m), 2.19-2.27 (1H, m), 2.30 (1H, brs), 2.59-2.70 (2H, m), 2.83-2.92 (2H, m), 3.11-3.27 (3H, m), 3.32-3.37 (1H, m), 3.73 (3H, s), 3.77-3.81 (1H, m), 3.82-3.86 (1H, m), 4.03-4.09 (1H, m), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.81-6.90 (2H, m), 6.98-7.05 (2H, m), 7.09-7.16 (2H, m).

Reference Example 640

5-{[(3R*,4S*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichlorophenyl)-4-hydroxypi peridin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1091] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.06 (3H, s), 0.01 (3H, s), 0.81 (9H, s), 1.64-1.71 (1H, m), 2.26-2.32 (2H, m), 2.61-2.72 (2H, m), 2.87-2.92 (2H, m), 2.93-2.99 (1H, m), 3.03-3.10 (1H, m), 3.13-3.19 (1H, m),3.40-3.46 (1H, m), 3.76 (3H, s), 3.89 (1H, d, J = 9.0 Hz), 3.92-3.95 (1H, m), 4.10 (1H, d, = 9.0 Hz), 5.26 (2H, brs), 6.53 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.75-6.80 (2H, m), 6.87 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.97 (1H, d, J = 8.7 Hz), 7.12-7.16 (2H, m), 7.19 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.37 (1H, d, J = 2.5 Hz).

Reference Example 641

5-{[(3R*,4S*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-h ydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1092] Synthesized analogous to Reference Example 70.
^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.01 (3H, s), 0.75 (9H, s), 1.59-1.64 (1H, m), 2.16-2.24 (1H, m), 2.30 (1H, s), 2.59-2.70 (2H, m), 2.83-2.89 (2H, m), 3.17-3.31 (3H,m), 3.36 (1H, dd,J = 12.7 Hz, 2.2 Hz), 3.73 (3H, s), 3.75 (1H, d, J = 8.9 Hz), 3.79-3.83 (1H, m), 4.04 (1H, d, J = 8.9 Hz), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.71 (1H, dd, J = 10.9 Hz, 7.7 Hz), 6.73-6.77 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.03 (1H, dd, J = 11.9 Hz, 7.0 Hz), 7.09-7.14 (2H, m).

Reference Example 642

8-Fluoro-1-(4-methoxybenzyl)-5-[(trimethylsilyl)ethinyl]-3,4-dihydroquinolin-2(1H) -one

[1093] Under nitrogen atmosphere, to a solution of 8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate (433 mg), trimethylsilylacetylene (0.166 mL), bis(triphenylphosphine)palladium (II) dichloride (70 mg) and copper (I) iodide (38 mg) in N-methyl-2-pyrrolidone (3 mL) was added triethylamine (0.697 mL), and the mixture was stirred at 50 °C for 18 h. The reaction solution was poured into 1 N hydrochloric acid, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (222 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 0.25 (9H, s), 2.66-2.69 (2H, m), 3.03-3.06 (2H, m), 3.74 (3H, s), 5.22 (2H, brs), 6.73-6.79 (2H, m), 6.80-6.85 (1H, m), 7.08-7.12 (3H, m).

Reference Example 643

5-Ethinyl-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1094] To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-[(trimethylsilyl)ethinyl]-3,4-dihydroquinolin-2(1H)-one (220 mg) in tetrahydrofuran (2 mL) was added tetrabutylammonium fluoride (1 M tetrahydrofuran solution) (0.692 mL), and the mixture was stirred at room temperature for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (16 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.66-2.70 (2H, m), 3.06-3.09 (2H, m), 3.24 (1H, s), 3.74 (3H, s), 5.22 (2H, brs), 6.74-6.76 (2H, m), 6.83-6.88 (1H, m), 7.09-7.15 (3H, m).

Reference Example 644

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethinyl}-8-fluoro-1-(4-m ethoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1095] To a solution of 5-ethinyl-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (166 mg) in tetrahydrofuran (2 mL), n-butyllithium (1.6 M hexane solution) (0.351 mL) was added dropwise at -60 °C, and the reaction mixture was stirred at the same temperature for 1 h. To the mixture was added a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (120 mg) in tetrahydrofuran (1 mL) dropwise, and the reaction mixture was stirred at -60 °C for 2 h, then at room temperature for 18 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (110 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.97-2.04 (2H, m), 2.08-2.12 (3H, m), 2.67-2.71 (2H, m), 3.04-3.07 (2H, m), 3.21-3.31 (4H, m), 3.74 (3H, s), 5.23 (2H, brs), 6.72-6.77 (2H, m), 6.84-6.89 (3H, m), 7.08-7.12 (3H, m).

Reference Example 645

5-{2-[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1096] To a solution of 5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethinyl}-8-fluoro-1-(4-m ethoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.105 g) in ethanol (2 mL) was added palladium-carbon ethylenediamine complex (palladium 3.5-6.5 %) (50 mg), and the reaction mixture was stirred at room temperature for 1 h under hydrogen atmosphere. The catalyst was filtered off with Celite, and the filtrate was concentrated to provide the title compound (99 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.69 (4H, m), 1.77-1.85 (2H, m), 2.63-2.70 (4H, m), 2.82-2.85 (2H, m), 3.02-3.06 (2H, m), 3.33-3.38 (2H, m), 3.74 (3H, s), 5.21 (2H, s), 6.74-6.77 (2H, m), 6.81-6.90 (4H, m), 7.12 (2H, d, J = 8.5 Hz).

Reference Example 646

O-[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]dimethyl-carbamothioate

[1097] Under argon atmosphere, to a solution of 8-fluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (5.0 g) in N,N-dimethylformamide (50 mL) was added sodium hydride (55 % in oil) (0.796 g) under ice-cooling, and the reaction mixture was stirred at room temperature for 45 min. To the reaction mixture, a solution of dimethylthiocarbamoyl chloride (3.28 g) in N,N-dimethylformamide (5 mL) was added dropwise, and the mixture was stirred at 60 °C for 2.5 h. The reaction solution was poured into cold ammonium chloride aqueous solution, and hexane was added to the mixture and the obtained solution was stirred. The precipitate was collected on a filter to provide the title compound (6.40 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.63-2.68 (2H, m), 2.68-2.73 (2H, m), 3.34 (3H, s), 3.45 (3H, s), 3.74 (3H, s), 5.22 (2H, brs), 6.67 (1H, dd, J = 9.0 Hz, 3.9 Hz), 6.74-6.79 (2H, m), 6.91 (1H, dd, J = 12.4 Hz, 9.0 Hz), 7.09-7.15 (2H, m).

Reference Example 647

S-[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]dimethyl-carbamothioate

[1098] Under argon atmosphere, a suspension of O-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] dimethylcarbamothioate (3.0 g) in diphenyl ether (15 mL) was stirred at 200 °C for 5 days. To the reaction solution was added hexane, and after stirring the mixture, the supernatant thereof was removed by decantation. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.15 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.63-2.70 (2H, m), 2.93-3.06 (5H, m), 3.10 (3H, brs), 3.74 (3H, s), 5.20 (2H, brs), 6.75-6.79 (2H, m), 6.90 (1H, dd, J = 12.6 Hz, 8.6 Hz), 7.10-7.14 (2H, m), 7.16 (1H, dd, J = 8.6 Hz, 4.7 Hz).

Reference Example 648

8-Fluoro-1-(4-methoxybenzyl)-5-sulfanyl-3,4-dihydroquinolin-2(1H)-one

[1099] Under argon atmosphere, to a suspension of S-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] dimethylcarbamothioate (1.15 g) in methanol/water (1:1) (20 mL) was added 5 N aqueous sodium hydroxide (2.96 mL) and the reaction mixture was heated to reflux for 3 h. The reaction solution was poured into ice water and was made weak acidic with 5 N hydrochloric acid, and the precipitate was collected on a filter. The obtained solid was dissolved into dichloromethane, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was washed with hexane/diisopropyl ether to provide the title compound (0.83 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.63-2.70 (2H, m), 2.90-2.97 (2H, m), 3.24 (1H, s), 3.74 (3H, s), 5.21 (2H, brs), 6.73-6.77 (2H, m), 6.80 (1H, dd, J = 12.7 Hz, 8.7 Hz), 6.98 (1H, dd, J = 8.7 Hz, 4.4 Hz), 7.07-7.12 (2H, m).

Reference Example 649

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro -1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1100] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.81 (4H, m), 1.99 (1H, s), 2.63-2.69 (2H, m), 2.97-3.04 (4H, m), 3.06-3.11 (2H, m), 3.11-3.17 (2H, m), 3.71 (3H, s), 5.21 (2H, brs), 6.72-6.76 (2H, m), 6.84-6.91 (2H, m), 7.01-7.06 (2H, m), 7.07-7.12 (2H, m), 7.16 (1H, dd, J = 8.7 Hz, 4.5 Hz).

Reference Example 650

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxy-1-oxidepiperidin-4-yl]methyl}sulfonyl) -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1101] To a suspension of 5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3 ,4-dihydroquinolin-2(1H)-one (0.25 g) in chloroform (10 mL) was added m-chloroperoxybenzoic acid (contain 25 % water) (0.419 g) and the reaction mixture was stirred at room temperature for 7.5 h. The solvent was distilled off, the residue was washed with saturated aqueous sodium hydrogencarbonate and ethyl acetate, and crystalized from ethyl acetate to provide the title compound (0.25 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.85 (2H, m), 2.51-2.60 (2H, m), 2.63-2.75 (2H, m), 2.76-2.86 (2H, m), 3.30-3.45 (2H, m), 3.57 (2H, s), 4.10-4.21 (2H, m), 4.70-5.50 (1H, broad signal), 7.37 (1H, t, J = 9.4 Hz), 7.48 (1H, dd, J = 8.9 Hz, 2.2 Hz), 7.58 (1H, dd, J = 8.9 Hz, 5.1 Hz), 7.64 (1H, dd, J = 12.4 Hz, 2.2 Hz), 8.71 (1H, t, J = 9.2 Hz), 10.41 (1H, brs).

Reference Example 651

tert-Butyl (3R*,4R*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxy-3-(meth ylamino)piperidine-1-carboxylate

[1102] To tert-butyl (1S*,6S*)-6-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-7-oxa-3-azabicyclo [4.1.0]heptane-3-carboxylate (0.39 g) was added 40 % methylamine in methanol (30 mL) and the reaction mixture was heated to reflux for 6 h. The reaction solvent was distilled off to provide the title compound. The compound was used for the next step without further purification.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.49-1.82 (4H, m), 2.42 (3H, s), 2.47-2.57 (1H, m), 2.64 (2H, t, J = 7.9 Hz), 2.99 (2H, t, J = 7.9 Hz), 3.13-3.52 (2H, m), 3.62-4.02 (3H, m), 4.06-4.18 (1H, m), 6.52 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.3 Hz), 7.66 (1H, brs).

Reference Example 652

8-Fluoro-5-{[(3R*,4R*)-4-hydroxy-3-(methylamino) piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one dihydrochloride

[1103] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.81-1.93 (1H, m), 2.30-2.40 (1H, m), 2.42-2.49 (2H, m), 2.70 (3H, brs), 2.89-2.98 (2H, m), 3.10-3.30 (3H, m), 3.46-3.55 (1H, m), 3.56-3.68 (1H, m), 4.09-4.25 (3H, m), 6.63-6.72 (1H, m), 7.03-7.12 (1H, m), 8.91 (1H, brs), 9.51 (1H, brs), 9.59 (1H, brs), 9.83 (1H,brs), 10.05 (1H, brs).

Reference Example 653

tert-Butyl (3R*,4R*)-3-amino-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxy piperidine-1-carboxylate

[1104] Synthesized analogous to Reference Example 651.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.49-1.74 (3H, m), 1.79-1.91 (1H, m), 2.26-2.42 (1H, m), 2.64 (2H, t, J = 7.9 Hz), 2.93-3.06 (3H, m), 3.18-3.34 (1H, m), 3.47-3.79 (2H, m), 3.80-3.98 (2H, m), 4.09-4.19 (1H, m), 6.51 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.57 (1H, brs).

Reference Example 654

5-{[(3R*,4R*)-3-Amino-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquin olin-2(1H)-one dihydrochloride

[1105] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.79-1.89 (1H, m), 2.29-2.39 (1H, m), 2.41-2.49 (2H, m), 2.87-2.98 (2H, m), 3.09-3.29 (2H, m), 3.30-3.62 (3H, m), 3.90-3.90 (1H, m), 4.01-4.07 (1H, m), 4.11-4.18 (1H, m), 6.60-6.80 (1H, m), 7.01-7.11 (1H, m), 8.72 (3H, brs), 9.47 (1H, brs), 9.69 (1H, brs), 10.04 (1H, brs).

Reference Example 655

tert-Butyl (3S*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxy-3-methy lpiperidine-1-carboxylate

[1106] Under argon atmosphere, to a suspension of tert-butyl (1S*,6S*)-6-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-7-oxa-3-azabicyclo [4.1.0]heptane-3-carboxylate (0.5 g) and copper (I) bromide-dimethylsulfide complex (0.026 g) in tetrahydrofuran (10 mL) was added dropwise methylmagnesium chloride (3M tetrahydrofuran solution) (1.27 mL) at 0 °C, and the reaction mixture was heated to reflux for 3.5 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.25 g).

^{1}HNMR ($CDCl_3$) δ ppm: 0.99 (3H, d, J = 7.1 Hz), 1.47 (9H, s), 1.50-1.57 (1H, m), 1.77-1.86 (1H, m), 1.86-2.01 (1H, m), 2.17 (1H, brs), 2.65 (2H, t, J = 7.7 Hz), 2.95-3.03 (2H, m), 3.14-3.42 (1H, m), 3.45-3.53 (1H, m), 3.59-3.66 (1H, m), 3.68-4.02 (3H, m), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.51 (1H, brs).

Reference Example 656

8-Fluoro-5-{[(3S*,4S*)-4-hydroxy-3-methylpiperidin-4-yl]methoxy}-3,4-dihydroquinol in-2(1H)-one

[1107] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.05 (3H, d, J = 7.2 Hz), 1.48-1.56 (1H, m), 1.56-1.70 (1H, broad signal), 1.83-1.96 (2H, m), 2.20 (1H, brs), 2.60 (1H, dd, J = 12.7 Hz, 5.6 Hz), 2.63-2.67 (2H, m), 2.79-2.86 (1H, m), 3.00 (2H, t, J = 7.7 Hz), 3.03-3.10 (1H, m), 3.21 (1H, dd, J = 12.7 Hz, 3.8 Hz), 3.84-3.93 (2H, m), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.57 (1H, brs).

Reference Example 657

tert-Butyl (3S*,4R*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate

[1108] To a suspension of tert-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.4 g) in methanol (5 mL) was added sodium methoxide (5M methanol solution) (1.56 mL), and the reaction mixture was stirred at 60 °C for 32 h. To the reaction solution was added acetic acid (0.45 mL) and the solvent was distilled off. Water was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.29 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.52 (10H, m), 1.77-1.86 (1H, m), 2.32 (1H, brs), 2.60-2.68 (2H, m), 2.79-2.89 (2H, m), 3.03-3.27 (3H, m), 3.33 (3H, brs), 3.69-4.07 (3H, m), 3.74 (3H,s), 4.08-4.32 (1H, m), 5.16-5.28 (2H, m), 6.55 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

Reference Example 658

8-Fluoro-5-{[(3S*,4R*)-4-hydroxy-3-methoxypiperidin-4-yl]methoxy}-1-(4-methoxy benzyl)-3,4-dihydroquinolin-2(1H)-one

[1109] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.44-1.51 (1H, m), 1.51-1.70 (1H, broad signal), 1.70-1.79 (1H, m), 2.27 (1H, brs), 2.62-2.67 (2H, m), 2.82-2.90 (3H, m), 2.94-3.02 (1H, m), 3.02-3.09 (2H, m), 3.09-3.14 (1H, m), 3.31 (3H, s), 3.73 (1H, d, J = 9.0 Hz), 3.74 (3H, s), 4.03 (1H, d, J = 9.0 Hz), 5.17-5.28 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.74-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

Reference Example 659

5-{[(3S*,4R*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-methoxypiperidin-4-yl]meth oxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1110] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.68 (1H, m), 2.16-2.25 (1H, m), 2.37 (1H, s), 2.62-2.69 (2H, m), 2.85-2.91 (2H, m), 3.28 (3H, s), 3.31-3.40 (2H, m), 3.42-3.48 (1H, m), 3.60-3.67 (1H, m), 3.74 (3H, s), 3.85 (1H, d, J = 9.1 Hz), 3.89-3.97 (1H, m), 4.10 (1H, d, J = 9.1 Hz), 5.16-5.28 (2H, m), 6.57 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.58 (1H, d, J = 2.3 Hz), 8.10 (1H, d, J = 2.3 Hz).

Reference Example 660

tert-Butyl (3R*,4S*)-3-cyano-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]o xy}methyl)-4-hydroxypiperidine-1-carboxylate

[1111] Under argon atmosphere, to a solution of acetonecyanohydrin (0.342 mL) in tetrahydrofuran (4 mL) was added

lithium hydride (0.028 g) and the reaction mixture was stirred at room temperature for 2 h. Then, to the mixture was added tert-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.6 g) and the reaction mixture was heated to reflux for 7 h. After the reaction solution was allowed to cool to room temperature, water was added thereto, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.53 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.50 (9H, s), 1.62-1.70 (1H, m), 1.86-1.95 (1H, m), 2.50 (1H, s), 2.62-2.69 (2H, m), 2.77-3.03 (3H, m), 3.03-3.31 (1H, m), 3.31-3.60 (1H, m), 3.74 (3H, s), 3.90 (1H, d, J = 9.4 Hz), 3.93-4.49 (3H, m), 5.14-5.31 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.87 (1H, dd, J = 12.5 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

Reference Example 661

(3R*,4S*)-4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] oxy}methyl)-4-hydroxypiperidine-3-carbonitrile

[1112] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.68 (2H, m), 1.79-1.88 (1H, m), 2.42 (1H, brs), 2.66 (2H, t, J = 7.0 Hz), 2.79-2.92 (3H, m), 2.95-3.02 (1H, m), 3.02-3.11 (1H, m), 3.17 (1H, dd, J = 13.1 Hz, 2.2 Hz), 3.34 (1H, dd, J = 13.1 Hz, 3.1 Hz), 3.74 (3H, s), 3.88 (1H, d, J = 9.4 Hz), 4.10 (1H, d, J = 9.4 Hz), 5.17-5.29 (2H, m), 6.57 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.86 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

Reference Example 662

(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2 ,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-3-carbonitrile

[1113] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.85 (1H, m), 2.19-2.26 (1H, m), 2.48 (1H, s), 2.68 (2H, t, J = 7.1 Hz), 2.82-2.94 (2H, m), 3.09-3.12 (1H, m), 3.25-3.33 (1H, m), 3.52 (1H, dd, J = 12.9 Hz, 2.8 Hz), 3.65-3.72 (1H, m), 3.74 (3H, s), 3.91-3.97 (1H, m), 3.98 (1H, d, J = 9.4 Hz), 4.20 (1H, d, J = 9.4 Hz), 5.16-5.30 (2H, m), 6.60 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.80 (2H, m), 6.88 (1H, dd, J = 12.5 Hz, 9.1 Hz), 7.10-7.15 (2H, m), 7.65 (1H, d, J = 2.3 Hz), 8.15 (1H, d, J = 2.3 Hz).

Reference Example 663

tert-Butyl (3R*,4S*)-3-fluoro-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]o xy}methyl)-4-hydroxypiperidine-1-carboxylate

[1114] To tert-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.51 g) was added tetrabutylammonium dihydrogen trifluoride (2.0 g, excess), and the reaction mixture was stirred at 120 °C for 2 days. To the reaction solution was added water and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.36 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.57-1.62 (1H, m), 1.78-1.91 (1H, m), 2.42-2.48 (1H, m), 2.61-2.69 (2H, m), 2.79-2.93 (2H, m), 3.03-3.49 (2H, m), 3.75 (3H, m), 3.75-3.79 (1H, m), 3.90-4.06 (2H, m), 4.21-4.79 (2H, m), 5.16-5.29 (2H, m), 6.54 (1H, dd, J = 9.0 Hz, 3.3 Hz), 6.72-6.79 (2H, m), 6.85 (1H, dd, J = 12.6 Hz. 9.1 Hz), 7.05-7.16 (2H, m).

Reference Example 664

8-Fluoro-5-{[(3R*,4S*)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-1-(4-methoxybe nzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

[1115] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.80 (1H, m), 1.83-1.92 (1H, m), 2.56-2.65 (2H, m), 2.81-3.02 (2H, m), 3.06-3.20 (2H, m), 3.44-3.56 (1H, m), 3.68 (3H, s), 3.81-3.90 (1H, m), 3.92-4.00 (1H, m), 4.77-4.83 (1H, m), 4.88-4.94 (1H, m), 5.05-5.16 (2H, m), 5.81 (1H, brs), 6.72 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.77-6.85 (2H, m), 6.99 (1H, dd, J = 9.1 Hz, 4.2 Hz), 7.03-7.11 (2H, m), 8.66 (1H, brs), 9.27 (1H, brs).

Reference Example 665

5-{[(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3-fluoro-4-hydroxypiperidin-4-yl]methox y}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1116] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.68-1.77 (1H, m), 2.17-2.28 (1H, m), 2.48-2.58 (1H, m), 2.61-2.70 (2H, m), 2.81-2.94 (2H, m), 3.21-3.31 (1H, m), 3.44-3.61 (1H, m), 3.74 (3H, s), 3.75-3.86 (2H, m), 4.02-4.13 (2H, m), 4.56-4.72 (1H, m), 5.16-5.30 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.80 (2H, m), 6.85 (1H, dd, J = 12.6 Hz. 9.1 Hz), 7.09-7.16 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.10 (1H, d, J = 2.3 Hz).

Reference Example 666

4-[(Acetyloxy)methyl]-1-(4-methoxybenzyl)-3-methylpyridinium chloride

[1117] A solution of (3-methylpyridin-4-yl)methyl acetate (20.4 g) and 4-methoxybenzyl chloride (15.6 mL) in acetonitrile (120 mL) was stirred at 100 °C for 8 h. The reaction solution was allowed to cool to room temperature, and the precipitate was collected on a filter which was washed with ethyl acetate to provide the title compound (23.1 g).
^{1}HNMR (DMSO-d6) δ ppm: 2.20 (3H, s), 2.43 (3H, s), 3.75 (3H, s), 5.36 (2H, s), 5.73 (2H, s), 6.96-7.02 (2H, m), 7.52-7.58 (2H, m), 8.01 (1H, d, J = 8.0 Hz), 9.08 (1H, d, J = 8.0 Hz), 9.16 (1H, s).

Reference Example 667

[1-(4-Methoxybenzyl)-5-methyl-1,2,3,6-tetrahydropyridin-4-yl]methyl acetate

[1118] To a solution of 4-[(acetyloxy)methyl]-1-(4-methoxybenzyl)-3-methylpyridinium chloride (23.1 g) in methanol (200 mL) was added at -20 °C sodium borohydride (8.86 g), and the reaction mixture was stirred at the same temperature for 30 min. To the reaction solution was added water, the mixture was stirred overnight, the solvent was distilled off, ethyl acetate was added to the residue, and insoluble materials were filtered off. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (6.8 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.66 (3H, s), 2.05 (3H, s), 2.13-2.22 (2H, m), 2.53 (2H, t, J = 7.2 Hz), 2.84-2.90 (2H, m), 3.49-3.54 (2H, m), 3.81 (3H, s), 4.57-4.61 (2H, m), 6.83-6.89 (2H, m), 7.22-7.29 (2H, m).

Reference Example 668

tert-Butyl 4-(hydroxymethyl)-5-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[1119] To a solution of [1-(4-methoxybenzyl)-5-methyl-1,2,3,6-tetrahydropyridin-4-yl]methyl acetate (0.33 g) in dichloromethane (10 mL) was added 2-chloroethyl chloroformate (0.19 mL) and the reaction mixture was stirred at 50 °C for 5 h. The solvent was distilled off and to the residue was added methanol (10 mL) and the reaction mixture was stirred at 70 °C for 2 h. After the reaction was completed, the solvent was distilled off, and the residue was dissolved in methanol (10 mL). To the solution were added triethylamine (0.48 mL) and di-tert-butyl dicarbonate (0.39 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added 2 N aqueous sodium hydroxide (10 mL), the reaction mixture was stirred at 1 h, to which an aqueous solution of 2 M citric acid was added and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.20 g). ^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.50-1.65 (2H, m), 1.71 (3H, s), 2.20-2.30 (2H, m), 3.45-3.55 (2H, m), 4.16 (2H, brs).

Reference Example 669

tert-Butyl 4-(chloromethyl)-5-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[1120] To a solution of tert-butyl 4-(hydroxymethyl)-5-methyl-3,6-dihydropyridine-1(2H)-carboxylate (3.57 g) in acetonitrile (50 mL) were added triethylamine (3.06 mL) and methanesulfonyl chloride (1.46 mL) at 0 °C, and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate,

and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.53 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.74 (3H, s), 2.15-2.28 (2H, m), 3.45-3.55 (2H, m), 3.73-3.86 (2H, m), 4.07-4.12 (2H, m).

Reference Example 670

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -5-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[1121] Synthesized analogous to Reference Example 495.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.69 (3H, brs), 2.16-2.26 (2H, m), 2.58-2.66 (2H, m), 2.81-2.89 (2H, m), 2.44-2.54 (2H, m), 3.74 (3H, s), 3.76-3.84 (2H, m), 4.42-4.47 (2H, m), 5.18-5.26 (2H, m), 6.51 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

Reference Example 671

tert-Butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-methyl-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate

[1122] Synthesized analogous to Reference Example 633.
^{1}HNMR ($CDCl_3$) δ ppm: 1.37 (3H, s), 1.46 (9H, s), 2.02-2.20 (2H, m), 2.60-2.69 (2H, m), 2.81-2.95 (2H, m), 3.14-3.47 (2H, m), 3.48-3.76 (2H, m), 3.74 (3H, s), 3.93-4.08 (2H, m), 5.17-5.29 (2H, brs), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.82 (1H, dd, J = 12.4 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

Reference Example 672

tert-Butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-3,4-dihydroxy-3-methylpiperidine-1-carboxylate

[1123] Synthesized analogous to Reference Example 499.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.64 (3H, s), 1.66-1.75 (1H, m), 1.77-1.85 (1H, m), 2.58-2.71 (2H, m), 2.73-2.92 (3H, m), 2.93-3.00 (1H, m), 3.02-3.26 (2H, m), 3.65-3.84 (2H, m), 3.74 (3H, s), 3.96-4.09 (1H, m), 4.13-4.18 (1H, m), 5.12-5.33 (2H, m), 6.55 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

Reference Example 673

5-{[(3S*,4S*)-3,4-Dihydroxy-3-methylpiperidin-4-yl]methoxy}-8-fluoro-1-(4-methox ybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

[1124] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.22 (3H, s), 1.93-2.08 (2H, m), 2.55-2.65 (2H, m), 2.77-3.12 (6H, m), 3.38-3.50 (2H, m), 3.68 (3H, s), 3.78-3.85 (1H, m), 4.11-4.19 (1H, m), 5.10 (2H, brs), 6.77 (1H, dd, J = 9.4 Hz, 3.3 Hz), 6.78-6.86 (2H, m), 6.99 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.04-7.12 (2H, m), 8.81 (1H, brs), 8.95 (1H, brs).

Reference Example 674

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxy-3-methylpiperidin-4-yl]me thoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1125] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.37 (3H, s), 1.86-1.96 (1H, m), 2.02-2.12 (1H, m), 2.61-2.69 (2H, m), 2.84-2.93 (2H, m), 3.05 (1H, brs), 3.31-3.51 (4H, m), 3.60-3.74 (1H, m), 3.75 (3H, s), 3.93 (1H, d, J = 9.4 Hz), 4.14 (1H, d, J = 9.4 Hz), 5.14-5.32 (2H, m), 6.58 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.86 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.09-7.17 (2H, m), 7.63 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Reference Example 675

5-{[(3S*,4S*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxy-3-methylpiperidin-4-yl]me thoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1126] Under nitrogen atmosphere, to a solution of 5-{[(3S*,4S*)-3,4-dihydroxy-3-methylpiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride (0.36 g), 1-bromo-4-chloro-2-fluorobenzene (0.19 g), triethylamine (0.16 mL) and cesium carbonate (0.72 g) in toluene (6 mL) were added 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (41 mg) and tris(dibenzylideneacetone)dipalladium (0) (20 mg), and the reaction mixture was stirred at 100 °C overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (42 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, s), 1.89-2.05 (2H, m), 2.59-2.72 (2H, m), 2.79-3.08 (6H, m), 3.09-3.15 (2H, m), 3.74 (3H, s), 3.89 (1H, d, J = 9.2 Hz), 4.17 (1H, d, J = 9.2 Hz), 5.14-5.32 (2H, m), 6.58 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.82-6.93 (2H, m), 7.01-7.08 (2H, m), 7.09-7.17 (2H, m).

Reference Example 676

1-(2-Chloro-4-fluorophenyl)-3-fluoro-4,4-dimethoxypiperidine

[1127] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-1.98 (1H, m), 2.10-2.18 (1H, m), 2.80-2.88 (1H, m), 3.06-3.22 (2H, m), 3.30 (3H, s), 3.34 (3H, s), 3.39-3.49 (1H, m), 4.57-4.71 (1H, m), 6.90-6.95 (1H, m), 7.02 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.12 (1H, dd, J = 8.3 Hz, 2.9 Hz).

Reference Example 677

1-(2-Chloro-4-fluorophenyl)-3-fluoropiperidin-4-one

[1128] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.58-2.66 (1H, m), 2.81-2.91 (1H, m), 3.03-3.16 (2H, m), 3.49-3.56 (1H, m), 3.85-3.92 (1H, m), 5.18 (1H, ddd, J = 48.0 Hz, 10.3 Hz, 6.9 Hz), 6.95-7.01 (1H, m), 7.05 (1H, dd, J = 8.9 Hz, 5.4 Hz), 7.19 (1H, dd, J = 8.2 Hz, 2.9 Hz).

Reference Example 678

1-(4-Chloro-2-fluorophenyl)-3-fluoro-4,4-dimethoxypiperidine

[1129] Synthesized analogous to Reference Example 205.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-1.98 (1H, m), 2.06-2.15 (1H, m), 2.86-2.93 (1H, m), 3.11-3.26 (2H, m), 3.28 (3H, s), 3.33 (3H, s), 3.55-3.63 (1H, m), 4.56-4.69 (1H, m), 6.84-6.90 (1H, m), 7.00-7.07 (2H, m).

Reference Example 679

1-(4-Chloro-2-fluorophenyl)-3-fluoropiperidin-4-one

[1130] Synthesized analogous to Reference Example 251.
^{1}HNMR ($CDCl_3$) δ ppm: 2.61-2.68 (1H, m), 2.77-2.86 (1H, m), 3.09-3.22 (2H, m), 3.60-3.67 (1H, m), 3.93-4.01 (1H, m), 5.05-5.20 (1H, m), 6.90-6.95 (1H, m), 7.06-7.14 (2H, m).

Reference Example 680

(3R*,4S*)-6-(4-Chloro-2-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1131] Under argon atmosphere, to a solution of trimethylsulfoxonium iodide (2.00 g) in dimethyl sulfoxide (20 mL) was added sodium tert-butoxide (0.834 g), and the reaction mixture was stirred at room temperature for 30 min. To the mixture was added a solution of 1-(4-chloro-2-fluorophenyl)-3-fluoropiperidin-4-one (2.03 g) in dimethyl sulfoxide (10

mL), and the mixture was stirred at room temperature for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and the title compound (1.03 g) was obtained from lower polarity fractions.
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.71 (1H, m), 2.26-2.35 (1H, m), 2.80 (1H, dd, J = 4.6 Hz, 1.9 Hz), 3.00 (1H, d, J = 4.6 Hz), 3.16-3.29 (2H, m), 3.31-3.50 (2H, m), 4.32 (1H, ddd, J = 48.0 Hz, 5.1 Hz, 3.1 Hz), 6.88-6.94 (1H, m), 7.03-7.10 (2H, m).

Reference Example 681

(3R*,4R*)-6-(4-Chloro-2-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1132] From higher polarity fractions of Reference Example 680, the title compound (0.48 g) was obtained.
^{1}HNMR ($CDCl_3$) δ ppm: 1.90-2.03 (2H, m), 2.78 (1H, dd, J = 4.6 Hz, 3.4 Hz), 3.03 (1H, d, J = 4.6 Hz), 3.16-3.28 (2H, m), 3.32-3.47 (2H, m), 4.65 (1H, ddd, J = 48.0 Hz, 7.3 Hz, 3.9 Hz), 6.89-6.94 (1H, m), 7.04-7.10 (2H, m).

Reference Example 682

(3R*,4S*)-6-(2-Chloro-4-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1133] The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from lower polarity fractions.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.83 (1H, m), 2.16-2.26 (1H, m), 2.78 (1H, dd, J = 4.7 Hz, 2.1 Hz), 3.03 (1H, d, J = 4.7 Hz), 3.08-3.19 (2H, m), 3.24-3.43 (2H, m), 4.41 (1H, ddd, J = 48.5 Hz, 5.7 Hz, 3.4 Hz), 6.93-6.98 (1H, m), 7.04 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

Reference Example 683

(3R*,4R*)-6-(2-Chloro-4-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1134] The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from higher polarity fractions.
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.90 (1H, m), 2.02-2.13 (1H, m), 2.78 (1H, dd, J = 4.8 Hz, 2.6 Hz), 3.07 (1H, d, J = 4.8 Hz), 3.08-3.17 (2H, m), 3.18-3.27 (1H, m), 3.37-3.46 (1H, m), 4.75 (1H, ddd, J = 47.9 Hz, 8.3 Hz, 4.1 Hz), 6.93-6.99 (1H, m), 7.05 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

Reference Example 684

1-(4-Chloro-2,6-difluorophenyl)-4-[(trimethylsilyl)oxy]-1,2,3,6-tetrahydropyridine

[1135] Under argon atmosphere, a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one(1 g), chlorotrimethylsilane (1.55 mL) and triethylamine (2.84 mL) in N,N-dimethylformamide (5 mL) was stirred at 70 °C for 15 h, and the solvent was distilled off. To the residue was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (1.28 g).
^{1}HNMR ($CDCl_3$) δ ppm: 0.21 (9H, s), 2.18-2.25 (2H, m), 3.27-3.34 (2H, m), 3.62-3.68 (2H, m), 4.86-4.90 (1H, m), 6.83-6.91 (2H, m).

Reference Example 685

1-(4-Chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one

[1136] Under argon atmosphere, to a solution of 1-(4-chloro-2,6-difluorophenyl)-4-[(trimethylsilyl)oxy]-1,2,3,6-tetrahydropyridine (1.28 g) in acetonitrile (15 mL) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1.57 g) under ice-cooling, and the mixture was stirred at the same temperature for 1 h, then at room temperature for 1.5 h. To the reaction solution was added saturated aqueous sodium hydrogencarbonate, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.76 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.65 (1H, m), 2.74-2.84 (1H, m), 3.38-3.50 (3H, m), 3.78-3.86 (1H, m), 5.08 (1H, ddd, J = 48.3 Hz, 10.1 Hz, 6.8 Hz), 6.90-6.99 (2H, m).

Reference Example 686

(3R*,4S*)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1137] The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from lower polarity fractions.
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.72 (1H, m), 2.18-2.26 (1H, m), 2.77 (1H, dd, J = 4.7 Hz, 2.0 Hz), 2.99 (1H, d, J = 4.7 Hz), 3.20-3.28 (1H, m), 3.30-3.44 (2H, m), 3.52-3.63 (1H, m), 4.29 (1H, ddd, J = 48.5 Hz, 5.6 Hz, 3.2 Hz), 6.86-6.93 (2H, m).

Reference Example 687

(3R*,4R*)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1138] The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from higher polarity fractions.
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.90 (1H, m), 1.97-2.05 (1H, m), 2.76 (1H, dd, J = 4.7 Hz, 3.7 Hz), 3.00 (1H, d, J = 4.7 Hz), 3.15-3.22 (1H, m), 3.34-3.54 (3H, m), 4.56 (1H, ddd, J = 48.3 Hz, 6.9 Hz, 3.9 Hz), 6.86-6.94 (2H, m).

Reference Example 688

(3R)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one

[1139] Under argon atmosphere, to a suspension of N-fluorobenzenesulfonimide (2.0 g) and sodium carbonate (1.01 g) in tetrahydrofuran (10 mL) was added a solution of 9-epi-9-amino-9-deoxydihydroquinidine (9-epi-DHQDA) (0.413 g), trichloroacetic acid (0.218 g) and water (0.023 mL) in tetrahydrofuran (15 mL) at -20 °C, and the mixture was stirred for 10 min. To the mixture was added 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (3.12 g), and the reaction mixture was stirred at the same temperature for 16 h, then at -10 °C for 24 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.26 g). ^{1}HNMR ($CDCl_3$) δ ppm: 2.57-2.65 (1H, m), 2.75-2.84 (1H, m), 3.38-3.50 (3H, m), 3.78-3.86 (1H, m), 5.00-5.16 (1H, m), 6.92-6.98 (2H, m).

Reference Example 689

(3S)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one

[1140] By the procedure analogous to Reference Example 688, with 9-epi-9-amino-9-deoxydihydroquinine (9-epi-DHQA) as catalyst, the title compound was obtained.
^{1}HNMR ($CDCl_3$) δ ppm: 2.57-2.65 (1H, m), 2.75-2.84 (1H, m), 3.38-3.50 (3H, m), 3.78-3.86 (1H, m), 5.00-5.16 (1H, m), 6.92-6.98 (2H, m).

Reference Example 690

(3S,4R)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1141] The reaction and purification analogous to Reference Examples 680 and 681 with (3R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one (1.20 g) were done. The material obtained from lower polarity fractions was recrystallized from ethanol/water to provide the title compound (0.47 g, 97 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.72 (1H, m), 2.18-2.26 (1H, m), 2.77 (1H, dd, J = 4.7 Hz, 2.0 Hz), 2.99 (1H, d, J = 4.7 Hz), 3.20-3.28 (1H, m), 3.30-3.44 (2H, m), 3.52-3.63 (1H, m), 4.29 (1H, ddd, J = 48.5 Hz, 5.6 Hz, 3.2 Hz), 6.86-6.93 (2H, m).

Reference Example 691

(3R,4R)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1142] The material obtained from higher polarity fractions of Reference Example 690 was recrystallized from hexane to provide the title compound (0.24 g, 91 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.90 (1H, m), 1.97-2.05 (1H, m), 2.76 (1H, dd, J = 4.7 Hz, 3.7 Hz), 3.00 (1H, d, J = 4.7 Hz), 3.15-3.22 (1H, m), 3.34-3.54 (3H, m), 4.56 (1H, ddd, J = 48.3 Hz, 6.9 Hz, 3.9 Hz), 6.86-6.94 (2H, m).

Reference Example 692

(3R,4S)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1143] The reaction and purification analogous to Reference Example 680 and 681 with (3S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one (1.19 g) were done. The material obtained from lower polarity fractions was recrystallized from ethanol/water to provide the title compound (0.43 g, 96 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.72 (1H, m), 2.18-2.26 (1H, m), 2.77 (1H, dd, J = 4.7 Hz, 2.0 Hz), 2.99 (1H, d, J = 4.7 Hz), 3.20-3.28 (1H, m), 3.30-3.44 (2H, m), 3.52-3.63 (1H, m), 4.29 (1H, ddd, J = 48.5 Hz, 5.6 Hz, 3.2 Hz), 6.86-6.93 (2H, m).

Reference Example 693

(3S,4S)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

[1144] The material obtained from higher polarity fractions of Reference Example 692 was recrystallized from ethanol/water to provide the title compound (0.22 g, 86 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.90 (1H, m), 1.97-2.05 (1H, m), 2.76 (1H, dd, J = 4.7 Hz, 3.7 Hz), 3.00 (1H, d, J = 4.7 Hz), 3.15-3.22 (1H, m), 3.34-3.54 (3H, m), 4.56 (1H, ddd, J = 48.3 Hz, 6.9 Hz, 3.9 Hz), 6.86-6.94 (2H, m).

Reference Example 694

(3R*,4R*)-4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)piperidin-3-ol

[1145] To a solution of (3R*,4R*)-1-benzyl-4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-piperidin-3-ol (11.6 g) in ethanol (100 mL) was added 20 % palladium hydroxide on carbon (1.16 g, 10wt %), and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 2 h. After the reaction solution was allowed to cool to room temperature, palladium hydroxide was filtered off with Celite, and the solvent of the filtrate was distilled off to provide the title compound (8.66 g).
^{1}HNMR ($CDCl_3$) δ ppm: 0.09 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.00-1.13 (1H, m), 1.45-1.72 (3H, m), 2.42 (1H, dd, J = 11.7 Hz, 10.0 Hz), 2.56 (1H, dt, J = 2.8 Hz, 12.3 Hz), 2.97-3.04 (1H, m), 3.17-3.24 (1H, m), 3.50-3.58 (1H, m), 3.62 (1H, t, J = 9.6 Hz), 3.69-3.77 (1H, m), 3.94-4.30 (1H, m).

Reference Example 695

(3R*,4R*)-4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-1-(2,4-dichlorophenyl)piperidi n-3-ol

[1146] Synthesized analogous to Reference Example 68.
^{1}HNMR ($CDCl_3$) δ ppm: 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 1.35-1.48 (1H, m), 1.59-1.76 (2H, m), 2.50 (1H, dd, J = 10.8 Hz, 9.8 Hz), 2.59 (1H, dt, J = 2.6 Hz, 11.8 Hz), 3.26-3.35 (1H, m), 3.43-3.51 (1H, m), 3.71 (1H, t, J = 9.6 Hz), 3.79-3.90 (2H, m), 4.16-4.20 (1H, m), 6.96 (1H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 8.6 Hz, 2.3 Hz), 7.35 (1H, d, J = 2.3 Hz).

Reference Example 696

(3R*,4R*)-1-(2,4-Dichlorophenyl)-4-(hydroxymethyl)piperidin-3-ol

[1147] To a solution of (3R*,4R*)-4-({[tert-butyl(dimethyl)silyl]oxy }methyl)-1-(2,4-dichlorophenyl)piperidin-3-ol (1.67 g) in tetrahydrofuran (12 mL) was added a solution of 1 M tetrabutylammonium fluoride in tetrahydrofuran (5.1 mL), and the reaction mixture was stirred at room temperature overnight. After the solvent was distilled off, water was added to the residue and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column

chromatography (hexane/ethyl acetate) to provide the title compound (1.11 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.40-1.54 (1H, m), 1.66-1.79 (2H, m), 2.36-2.34 (1H, m), 2.53 (1H, dd, J = 10.8 Hz, 9.7 Hz), 2.62 (1H, dt, J = 2.5 Hz, 11.7 Hz), 3.12-3.19 (1H, m), 3.26-3.34 (1H, m), 3.42-3.49 (1H, m), 3.75-3.93 (3H, m), 6.96 (1H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

Reference Example 697

[(3R*,4R*)-1-(2,4-Dichlorophenyl)-3-hydroxypiperidin-4-yl]methyl 4-methylbenzenesulfonate

[1148] To a solution of (3R*,4R*)-1-(2,4-dichlorophenyl)-4-(hydroxymethyl)piperidin-3-ol (1.11 g) in dichloromethane (12 mL) were added para-toluenesulfonyl chloride (0.84 g) and N,N,N',N'-tetramethyl-1,3-diaminopropane (0.94 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. To the reaction solution was added water and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.0 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.77 (2H, m), 1.81-1.87 (1H, m), 2.05-2.10 (1H, m), 2.46 (3H, m), 2.48-2.64 (2H, m), 3.21-3.29 (1H, m), 3.40-3.48 (1H, m), 3.71-3.81 (1H, m), 4.14-4.20 (1H, m), 4.23-4.30 (1H, m), 6.92 (1H, d, J = 8.6 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.35 (1H, d, J = 2.4 Hz), 7.36-7.40 (2H, m), 7.80-7.85 (2H, m).

Reference Example 698

(3R*,4R*)-4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-1-(4-chloro-2-fluorophenyl)pip eridin-3-ol

[1149] Synthesized analogous to Reference Example 68.
^{1}HNMR ($CDCl_3$) δ ppm: 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 1.33-1.45 (1H, m), 1.58-1.75 (2H, m), 2.52 (1H, t, J = 10.5 Hz), 2.63 (1H, dt, J = 2.5 Hz, 12.0 Hz), 3.34-3.41 (1H, m), 3.49-3.56 (1H, m), 3.69 (1H, t, J = 9.7 Hz), 3.78-3.87 (2H, m), 4.17-4.20 (1H, m), 6.83-6.91 (1H, m), 7.00-7.07 (2H, m).

Reference Example 699

(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-4-(hydroxymethyl)piperidin-3-ol

[1150] Synthesized analogous to Reference Example 696.
^{1}HNMR ($CDCl_3$) δ ppm: 1.37-1.51 (1H, m), 1.65-1.77 (2H, m), 2.18-2.29 (1H, m), 2.55 (1H, t, J = 10.5 Hz), 2.65 (1H, dt, J = 2.6 Hz, 12.0 Hz), 3.05-3.08 (1H, m), 3.33-3.40 (1H, m), 3.48-3.56 (1H, m), 3.73-3.91 (3H, m), 6.84-6.91 (1H, m), 7.05-7.08 (2H, m).

Reference Example 700

4-methylbenzenesulfonic acid [(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methyl ester

[1151] Synthesized analogous to Reference Example 697.
^{1}HNMR ($CDCl_3$) δ ppm: 1.57-1.75 (2H, m), 1.78-1.85 (1H, m), 2.06-2.11 (1H, m), 2.46 (3H, m), 2.47-2.66 (2H, m), 3.28-3.36 (1H, m), 3.47-3.53 (1H, m), 3.69-3.79 (1H, m), 4.13-4.19 (1H, m), 4.24-4.30 (1H, m), 6.80-6.87 (1H, m), 7.00-7.07 (2H, m), 7.34-7.39 (2H, m), 7.78-7.84 (2H, m).

Reference Example 701

(3R*,4R*)-4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-1-(4-chloro-2,5-difluorophenyl)piperidin-3-ol

[1152] Synthesized analogous to Reference Example 68.
^{1}HNMR ($CDCl_3$) δ ppm: 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 1.31-1.44 (1H, m), 1.58-1.75 (2H, m), 2.50 (1H, t, J = 10.6 Hz), 2.64 (1H, dt, J = 2.5 Hz, 12.0 Hz), 3.35-3.43 (1H, m), 3.52-3.59 (1H, m), 3.68 (1H, t, J = 9.6 Hz), 3.77-3.85 (2H, m), 4.16-4.19 (1H, m), 6.73 (1H, dd, J = 10.7 Hz, 7.6 Hz), 7.05 (1H, dd, J = 11.6 Hz, 6.9 Hz).

Reference Example 702

(3R*,4R*)-1-(4-Chloro-2,5-difluorophenyl)-4-(hydroxymethyl)piperidin-3-ol

[1153] Synthesized analogous to Reference Example 696.
^{1}HNMR ($CDCl_3$) δ ppm: 1.37-1.50 (1H, m), 1.66-1.78 (2H, m), 2.15-2.24 (1H, m), 2.53 (1H, t, J = 10.5 Hz), 2.65 (1H, dt, J = 2.6 Hz, 12.1 Hz), 3.16-3.23 (1H, m), 3.35-3.43 (1H, m), 3.51-3.59 (1H, m), 3.73-3.90 (3H, m), 6.73 (1H, dd, J = 10.6 Hz, 7.6 Hz), 7.06 (1H, d, J = 11.6 Hz, 6.9 Hz).

Reference Example 703

[(3R',4R')-1-(4-Chloro-2,5-difluorophenyl)-3-hydioxypiperidin-4-yl]methyl 4-methylbenzenesulfonate

[1154] Synthesized analogous to Reference Example 697.
^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.75 (2H, m), 1.78-1.86 (1H, m), 2.04-2.08 (1H, m), 2.46 (3H, m), 2.47-2.64 (2H, m), 3.31-3.39 (1H, m), 3.50-3.57 (1H, m), 3.69-3.78 (1H, m), 4.11-4.18 (1H, m), 4.26-4.32 (1H, m), 6.70 (1H, dd, J = 10.6 Hz, 7.6 Hz), 7.06 (1H, dd, J = 11.5 Hz, 6.8 Hz), 7.33-7.40 (2H, m), 7.78-7.84 (2H, m).

Reference Example 704

tert-Butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-1-carboxyl ate

[1155] Synthesized analogous to Reference Example 495.
^{1}HNMR ($CDCl_3$) δ ppm: 1.23-1.35 (2H, m), 1.47 (9H, s), 1.75-1.83 (2H, m), 1.90-2.03 (1H, m), 2.59-2.66 (2H, m), 2.69-2.83 (2H, m), 2.98 (2H, t, J = 7.7 Hz), 3.78 (2H, d, J = 6.3 Hz), 4.05-4.28 (2H, m), 6.43 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.51 (1H, brs).

Reference Example 705

8-Fluoro-5-(piperidin-4-ylmethoxy)-3,4-dihydroquinolin-2(1H)-one

[1156] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.24-1.36 (2H, m), 1.49-1.77 (1H, broad signal), 1.77-1.84 (2H, m), 1.87-1.99 (1H, m), 2.58-2.70 (4H, m), 2.99 (2H, t, J = 7.7 Hz), 3.09-3.17 (2H, m), 3.77 (2H, d, J = 6.3 Hz), 6.43 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.89 (1H, t, J = 9.5 Hz), 7.53 (1H, brs).

Reference Example 706

tert-Butyl (3S*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3-hydroxypiperidin e-1-carboxylate

[1157] Synthesized analogous to Reference Example 495.
^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.46 (1H, m), 1.47 (9H, s), 1.77-1.85 (1H, m), 1.86-1.95 (1H, m), 2.41-2.52 (1H, m), 2.53-2.83 (4H, m), 2.89-3.03 (2H, m), 3.57-3.67 (1H, m), 4.00-4.42 (4H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.59 (1H, brs).

Reference Example 707

8-Fluoro-5-{[(3S*,4S*)-3-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one hydrochloride

[1158] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.79 (1H, m), 1.83-1.91 (1H, m), 1.92-1.99 (1H, m), 2.42-2.49 (2H, m), 2.58-2.69 (1H, m), 2.81-2.94 (3H, m), 3.19-3.30 (2H, m), 3.42-3.46 (1H, m), 3.72-3.80 (1H, m), 4.00-4.07 (2H, m), 6.60 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.4 Hz), 8.83-8.95 (1H, m), 8.97-9.08 (1H, m), 10.04 (1H, brs).

Reference Example 708

(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinoli n-5-yl)oxy]methyl}piperidin-3-yl 4-nitrobenzoate

[1159] To a solution of 5-{[(3S*,4S*)-1-(3,5-dichloropyridin-2-yl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one (1.0 g) in tetrahydrofuran (20 mL) were added 4-nitrobenzoic acid (0.49 g), triphenylphosphine (0.89 g) and diethyl azodicarboxylate (1.55 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was distilled off, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) and further purified by basic silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.0 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.92 (1H, m), 2.12-2.22 (1H, m), 2.41-2.50 (1H, m), 2.61 (2H, d, J = 7.7 Hz), 2.92-3.03 (2H, m), 3.05-3.12 (1H, m), 3.13-3.18 (1H, m), 3.91-3.96 (2H, m), 4.00-4.07 (1H, m), 4.32-4.39 (1H, m), 5.53-5.56 (1H, m), 6.39 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.84 (1H, t, J = 9.5 Hz), 7.46 (1H, d, J = 2.3 Hz), 7.59 (1H, brs), 8.04-8.08 (3H, m), 8.22-8.26 (2H, m).

Reference Example 709

tert-Butyl (3R*,4R*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-3-hydroxypiperidine-1-carboxylate

[1160] Synthesized analogous to Reference Example 495.
^{1}HNMR ($CDCl_3$) δ ppm: 1.36-1.45 (1H, m), 1.46 (9H, s), 1.74-1.93 (2H, m), 2.36-2.48 (1H, m), 2.50-2.92 (6H, m), 3.55-3.66 (1H, m), 3.74 (3H, s), 3.96-4.39 (4H, m), 5.15-5.31 (2H, m), 6.53 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.2 Hz), 7.09-7.16 (2H, m).

Reference Example 710

8-Fluoro-5-{[(3R*,4R*)-3-hydroxypiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4 -dihydroquinolin-2(1H)-one hydrochloride

[1161] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.98 (3H, m), 2.55-2.69 (3H, m), 2.79-2.93 (3H, m), 3.18-3.28 (2H, m), 3.68 (3H, s), 3.70-3.81 (1H, m), 3.97-4.03 (2H, m), 5.04-5.16 (2H, m), 5.45-5.55 (1H, m), 6.71 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.78-6.84 (2H, m), 6.98 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.03-7.10 (2H, m), 8.86-9.26 (2H, m).

Reference Example 711

5-{[(3R*,4R*)-1-(2,4-Dichlorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1 -(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1162] Synthesized analogous to Reference Example 526.
^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.78 (1H, m), 1.87-1.98 (2H, m), 2.41-2.45 (1H, m), 2.54-2.73 (4H, m), 2.79-2.95 (2H, m), 3.28-3.36 (1H, m), 3.47-3.54 (1H, m), 3.74 (3H, s), 3.86-3.95 (1H, m), 4.01-4.16 (2H, m), 5.15-5.32 (2H, m), 6.56 (1H, dd, J = 9.2 Hz, 3.4H), 6.73-6.80 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.94 (1H, d, J = 8.6 Hz), 7.10-7.16 (2H, m), 7.19 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.37 (1H, d, J = 2.4 Hz).

Reference Example 712

5-{[(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-flu oro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1163] Synthesized analogous to Reference Example 526.
^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.77 (1H, m), 1.85-1.96 (2H, m), 2.31-2.35 (1H, m), 2.55-2.75 (4H, m), 2.81-2.93 (2H, m), 3.36-3.43 (1H, m), 3.53-3.60 (1H, m), 3.74 (3H, s), 3.84-3.94 (1H, m), 4.02-4.12 (2H, m), 5.18-5.30 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4H), 6.73-6.79 (2H, m), 6.80-6.92 (2H, m), 7.02-7.09 (2H, m), 7.10-7.16 (2H, m).

Reference Example 713

5-{[(3R*,4R*)-1-(4-Chloro-2,5-difluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8 -fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1164] Synthesized analogous to Reference Example 526.
^{1}HNMR ($CDCl_3$) δ ppm: 1.55-1.76 (2H, m), 1.86-1.95 (1H, m), 2.41-2.49 (1H, m), 2.56-2.73 (3H, m), 2.80-2.89 (2H, m), 3.33-3.39 (1H, m), 3.46-3.62 (2H, m), 3.68 (3H, s), 3.96-4.04 (1H, m), 4.06-4.13 (1H, m), 5.04-5.16 (3H, m), 6.70 (1H, dd, J = 9.2 Hz, 3.4H), 6.77-6.84 (2H, m), 6.98 (1H, dd, J = 13.2 Hz, 9.1 Hz), 7.02-7.13 (3H, m), 7.50 (1H, dd, J = 12.1 Hz, 7.1 Hz).

Reference Example 714

5-{[1-(3,5-Dichloropyridin-2-yl)-4-methoxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1165] Under argon atmosphere, to a solution of 5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-met hoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.35 g) and methyl iodide (0.078 mL) in N,N-dimethylformamide (7 mL)was added sodium hydride (55 % in oil) (0.030 g) under ice-cooling, and the reaction mixture was stirred at the same temperature for 2 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate, the organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.33 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.89 (2H, m), 1.98-2.04 (2H, m), 2.61-2.68 (2H, m), 2.87-2.94 (2H, m), 3.16-3.26 (2H, m), 3.32 (3H, s), 3.54-3.61 (2H, m), 3.74 (3H, s), 3.87 (2H, s), 5.23 (2H, brs), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.17 (2H, m), 7.59 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Reference Example 715

8-Fluoro-5-{[4-(hydroxymethyl)piperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-d ihydroquinolin-2(1H)-one

[1166] Under argon atmosphere at -70 °C, to a solution of 1-tert-butyl 4-ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) piperidine-1,4-dicarboxylate (1.50 g) in tetrahydrofuran (15 mL) was added sodium triethylborohydride (1 M tetrahydrofuran solution) (6.05 mL) dropwise, and the reaction mixture was stirred for 9 h while allowing to warm to room temperature slowly. Then, brine was added to the mixture, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give 1-tert-butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -4-(hydroxymethyl)piperidine-1-carboxylate (alcohol compound). The obtained alcohol compound was dissolved into ethyl acetate (4 mL), and 4 N hydrochloric acid/ ethyl acetate (4 mL) was added to the mixture. After stirring the mixture at room temperature for 2 h, the solvent was distilled off. The residue was dissolved into water, the reaction mixture was made basic with aqueous sodium hydroxide, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off, the residue was purified by silica gel column chromatography (basic silica gel: dichloromethane/methanol) to provide the title compound (0.15 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.63 (4H, m), 1.63-1.74 (2H, m), 2.61-2.67 (2H, m), 2.81-2.91 (6H, m), 3.71 (2H, s), 3.74 (3H, s), 3.84 (2H, s), 5.23 (2H, brs), 6.55 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11-7.15 (2H, m).

Reference Example 716

5-{[1-(3,5-Dichloropyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl]methoxy}-8-fluor o-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1167] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.73 (1H, m), 1.75-1.82 (4H, m), 2.60-2.68 (2H, m), 2.82-2.89 (2H, m), 3.28-3.35 (4H, s), 3.74 (3H, s), 3.77 (2H, brs), 3.91 (2H, s), 5.23 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.74-6.79 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11-7.16 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

Reference Example 717

Methyl [1-(3,5-Dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrah ydroquinolin-5-yl]oxy}methyl)piperidin-4-yl]carbamate

[1168] To a solution of 1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahy droquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid (0.86 g) in 1,4-dioxane (8 mL) were added triethylamine (0.214 mL) and diphenylphosphoryl azide (0.331 mL), and the mixture was refluxed for 2 h. The solvent was distilled off and to the residue was added methanol (20 mL), and the reaction mixture was refluxed for 15 h. The solvent was distilled off, the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.82 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-2.00 (2H, m), 2.22-2.30 (2H, m), 2.61-2.67 (2H, m), 2.83-2.89 (2H, m), 3.09-3.17 (2H, m), 3.56-3.60 (2H, m), 3.61 (3H, s), 3.74 (3H, s), 4.08 (2H, s), 4.64 (1H, s), 5.22 (2H, brs), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.61 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Reference Example 718

Methyl [1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahy droquinolin-5-yl]oxy}methyl)piperidin-4-yl]methylcarbamate

[1169] To a solution of methyl [1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahy droquinolin-5-yl]oxy}methyl)piperidin-4-yl]carbamate (0.3 g) in N,N-dimethylformamide (3 mL) was added methyl iodide (0.061 mL), then sodium hydride (55 % in oil) (0.032 g) was added under ice-cooling, and the reaction mixture was stirred at room temperature for 4 h. To the reaction solution was added ammonium chloride aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.31 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.08-2.18 (2H, m), 2.60-2.68 (4H, m), 2.81-2.87 (2H, m), 3.07 (3H, s), 3.18-3.26 (2H, m), 3.44-3.51 (2H, m), 3.64 (3H, s), 3.74 (3H, s), 4.18 (2H, s), 5.22 (2H, brs), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Reference Example 719

Methyl [1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidin-4-yl]methylcarbamate

[1170] Synthesized analogous to Reference Example 119.
^{1}HNMR ($CDCl_3$) δ ppm: 2.10-2.19 (2H, m), 2.61-2.71 (4H, m), 2.97 (2H, t, J = 7.7 Hz), 3.10 (3H, s), 3.18-3.27 (2H, m), 3.46-3.53 (2H, m), 3.66 (3H, s), 4.23 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.48 (1H, brs), 7.61 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Reference Example 720

5-{[4-(Aminooxy)-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1171] Under argon atmosphere, to a solution of 5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-met hoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.694 g) in N,N-dimethylformamide (7 mL) was added sodium hydride (55 % in oil) (0.059 g) under ice-cooling, and the mixture was stirred at room temperature for 30 min. To the reaction solution was added O-mesitylenesulfonylhydroxylamine (0.32 g) under ice-cooling, and the mixture was stirred at the same temperature for 30 min, and then at room temperature for 18 h. To the reaction solution was added ammonium chloride aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.30 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.87 (2H, m), 2.06-2.13 (2H, m), 2.61-2.68 (2H, m), 2.88-2.94 (2H, m), 3.11-3.19 (2H, m), 3.53-3.61 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.95 (2H, s), 5.23 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.83 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.59 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Reference Example 721

5-Fluoro-2-[4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-y l]oxy}methyl)-4-hydroxypiperidin-1-yl]benzonitrile

[1172] To a solution of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroquin olin-2(1H)-one hydrochloride (1.0 g) in water (10 mL) was added 5 N aqueous sodium hydroxide (1 mL) to make the reaction residue basic, and the solution was extracted with dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. To the residue were added 2,5-difluorobenzonitrile (0.463 g), potassium carbonate (0.460 g) and N-methyl-2-pyrrolidone (5 mL), and the mixture was stirred at 100 °C for 24 h. To the reaction solution was added ammonium chloride aqueous solution and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.83 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-2.01 (4H, m), 2.02 (1H, s), 2.63-2.69 (2H, m), 2.86-2.92 (2H, m), 3.16-3.25 (2H, m), 3.28-3.34 (2H, m), 3.74 (3H, s), 3.82 (2H, s), 5.24 (2H, brs), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.06 (1H, dd, J = 9.1 Hz, 4.6 Hz), 7.11-7.16 (2H, m), 7.20-7.25 (1H, m), 7.28 (1H, dd, J = 7.8 Hz, 3.0 Hz).

Reference Example 722

5-Fluoro-2-[4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] oxy}methyl)-4-hydroxypiperidin-1-yl]pyridine-3-carbonitrile

[1173] Synthesized analogous to Reference Example 721.
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.91 (4H, m), 2.05 (1H, s), 2.63-2.69 (2H, m), 2.84-2.91 (2H, m), 3.42-3.51 (2H, m), 3.74 (3H, s), 3.80 (2H, s), 3.99-4.07 (2H, m), 5.23 (2H, brs), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m), 7.54 (1H, dd, J = 7.3 Hz, 3.1 Hz), 8.24 (1H, d, J = 3.1 Hz).

Reference Example 723

2-[4-(Aminooxy)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinol in-5-yl]oxy}methyl)piperidin-1-yl]-5-fluorobenzonitrile

[1174] Synthesized analogous to Reference Example 720.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.94 (2H, m), 2.13-2.20 (2H, m), 2.62-2.68 (2H, m), 2.88-2.95 (2H, m), 3.02-3.10 (2H, m), 3.24-3.30 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.95 (2H, s), 5.24 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.74-6.79 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.03 (1H, dd, J = 9.1 Hz, 4.6 Hz), 7.11-7.16 (2H, m), 7.19-7.24 (1H, m), 7.28 (1H, dd, J = 7.8 Hz, 3.0 Hz).

Reference Example 724

2-[4-(Aminooxy)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinol in-5-yl]oxy}methyl)piperidin-1-yl]-5-fluoropyridine-3-carbonitrile

[1175] Synthesized analogous to Reference Example 720.
^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.84 (2H, m), 2.09-2.17 (2H, m), 2.61-2.67 (2H, m), 2.86-2.93 (2H, m), 3.28-3.38 (2H, m), 3.74 (3H, s), 3.94 (2H, s), 3.94-4.01 (2H, m), 4.97 (2H, s), 5.23 (2H, brs), 6.54 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.53 (1H, dd, J = 7.3 Hz, 3.1 Hz), 8.24 (1H, d, J = 3.1 Hz).

Reference Example 725

tert-Butyl 4-cyano-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy }methyl)piperidine-1-carboxylate

[1176] Synthesized analogous to Reference Example 59.
^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.55-1.63 (2H, m), 2.04-2.09 (2H, m), 2.63-2.69 (2H, m), 2.86-2.94 (2H, m), 3.00-3.20 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 4.05-4.40 (2H, m), 5.23 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79

(2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

Reference Example 726

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carbo nitrile

[1177] To a mixture of tert-butyl 4-cyano-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy }methyl)piperidine-1-carboxylate (0.92 g) and anisole (0.382 mL) was added trifluoroacetic acid (10 mL), and the mixture was stirred at 65-70 °C for 2 h, and then the solvent was distilled off. To the residue was added ethyl acetate, and the insoluble precipitate was collected on a filter. The obtained solid was suspended in water (20 mL), to which 5 N aqueous sodium hydroxide (0.35 mL) was added and insoluble crystal was collected on a filter to provide the title compound (0.46 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.55-1.69 (3H, m), 2.06-2.12 (2H, m), 2.65 (2H, t, J = 7.7 Hz), 2.99-3.08 (4H, m), 3.11-3.18 (2H, m), 3.94 (2H, s), 6.42 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.51 (1H, brs).

Reference Example 727

5-{[1-(2,4-Dichlorophenyl)-4-(hydroxymethyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1178] To a suspension of 1-(2,4-dichlorophenyl)-4-([8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroqu inolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid (397 mg) in tetrahydrofuran (8 mL) was added triethylamine (0.104 mL), then ethyl chlorocarbonate (0.068 mL) was added dropwise under ice-cooling, and the reaction mixture was stirred for 1 h. The precipitate was filtered off, and to the filtrate was added a solution of sodium borohydride (77 mg) in water (3 mL), and the solution was stirred at room temperature for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off to provide the title compound (304 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.70 (1H, t, J = 5.6 Hz), 1.77-1.86 (4H, m), 2.63-2.66 (2H, m), 2.84-2.87 (2H, m), 3.01 (4H, t, J = 5.5 Hz), 3.74 (3H, s), 3.77 (2H, d, J = 5.5 Hz), 3.91 (2H, s), 5.23 (2H, brs), 6.57 (1H, dd, 9.2 Hz, 3.2 Hz), 6.77 (2H, d, 8.7 Hz), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.96 (1H, d, J = 8.6 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

Reference Example 728

tert-Butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-4-hydroxy-3-methoxypiperidine-1-carboxylate

[1179] To a solution of tert-butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-3,4-dihydroxypiperidine-1-carboxylate (1.06 g) in tetrahydrofuran (10 mL) was added sodium tert-butoxide (0.23 g) and the mixture was stirred at room temperature for 30 min. At the same temperature methyl iodide (0.15 mL) and N-methyl-2-pyrrolidone (2 mL) were added to the mixture and the solution was stirred at room temperature overnight. The solvent was distilled off, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.40 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.48 (9H, s), 1.68-1.76 (1H, m), 1.77-1.89 (1H, m), 2.36-2.42 (1H, m), 2.60-2.68 (2H, m), 2.78-3.02 (3H, m), 3.08-3.19 (1H, m), 3.33-3.40 (1H, m), 3.38 (3H, m), 3.64-3.71 (1H, m), 3.74 (3H, s), 3.78-3.90 (1H, m), 3.91-3.96 (1H, m), 4.16-4.40 (1H, m), 5.16-5.28 (2H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.09-7.16 (2H, m).

Reference Example 729

8-Fluoro-5-{[(3S*,4S*)-4-hydroxy-3-methoxypiperidin-4-yl]methoxy}-1-(4-methoxy benzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

[1180] Synthesized analogous to Reference Example 456.
^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.79 (1H, m), 1.93-2.06 (1H, m), 2.59-2.60 (2H, m), 2.83-3.06 (4H, m), 3.09-3.19 (1H, m), 3.25 (3H, s), 3.56-3.61 (1H, m), 3.68 (3H, s), 3.70-3.76 (1H, m), 3.99-4.20 (2H, m), 5.04-5.15 (2H, m), 5.22 (1H, brs), 6.70 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.77-6.84 (2H, m), 7.00 (1H, dd, J = 13.0 Hz, 9.1 Hz), 7.04-7.10 (2H, m), 8.76 (1H, brs), 8.93 (1H, brs).

Reference Example 730

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-methoxypiperidin-4-yl]meth oxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1181] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.87 (1H, m), 2.03-2.12 (1H, m), 2.42-2.46 (1H, m), 2.61-2.68 (2H, m), 2.81-2.94 (2H, m), 2.98-3.05 (1H, m), 3.15-3.23 (1H, m), 3.39 (3H, s), 3.62-3.69 (2H, m), 3.72-3.77 (1H, m), 3.74 (3H, s), 3.91-4.02 (2H, m), 5.18-5.28 (2H, m), 6.55 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.84 (1H, dd, J = 12.8 Hz, 9.0 Hz), 7.10-7.17 (2H, m), 7.62 (1H, d, J = 2.3 Hz), 8.13 (1H, d, J = 2.3 Hz).

Reference Example 731

1-(4-Chloro-2,6-difluorophenyl)-4-ethylidenepiperidine

[1182] To a solution of ethyltriphenylphosphonium bromide (1.81 g) in tetrahydrofuran (12 mL), n-butyllithium (1.6 M hexane solution) (3.05 mL) was added dropwise at 0 °C, and the reaction mixture was stirred for 10 min. To the mixture was added a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (1 g) in tetrahydrofuran (4 mL), and the mixture was stirred at room temperature for 1 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (852 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.61 (3H, d, J = 6.9 Hz), 2.26-2.36 (4H, m), 3.09-3.21 (4H, m), 5.25-5.30 (1H, m), 6.82-6.89 (2H, m).

Reference Example 732

1-(4-Chloro-2,6-difluorophenyl)-4-[1-hydroxyethyl]piperidin-4-ol

[1183] Synthesized analogous to Reference Example 504.
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, d, J = 6.6 Hz), 1.57-1.62 (1H, m), 1.67-1.81 (3H, m), 1.86-1.89 (2H, m), 3.06 (2H, d, J = 11.8 Hz), 3.36-3.44 (2H, m), 3.60-3.66 (1H, m), 6.83-6.90 (2H, m).

Reference Example 733

1-[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl 4-methylbenzenesulfonate

[1184] Synthesized analogous to Reference Example 697.
^{1}HNMR ($CDCl_3$) δ ppm: 1.26 (3H, d, J = 6.4 Hz), 1.50-1.57 (1H, m), 1.62-1.67 (4H, m), 2.46 (3H, s), 2.95-3.03 (2H, m), 3.31-3.39 (2H, m), 4.51 (1H, q, J = 6.4 Hz), 6.82-6.89 (2H, m), 7.36 (2H, d, J = 8.0 Hz), 7.81 (2H, d, J = 8.0 Hz).

Reference Example 734

(3R*,5R*)-1-(4-Chloro-2,6-difluorophenyl)-3,5-dihydroxypiperidin-4-one

[1185] To a suspension of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (5.00 g) and DL-proline (0.703 g) in N,N-dimethylformamide (50 mL), a solution of nitrosobenzene (2.18 g) in N,N-dimethylformamide (50 mL) was added over 5 h at 0 °C, and the mixture was stirred at the same temperature for 2 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved into methanol (50 mL), and copper (II) sulfate (0.975 g) was added to the solution at 0 °C, and the mixture was stirred at the same temperature for 2 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound. The compound was used for the next step without further purification.
^{1}HNMR ($CDCl_3$) δ ppm: 3.26-3.30 (2H, m), 3.59-3.63 (2H, m), 4.57-4.59 (2H, m), 6.95-7.00 (2H, m).

Reference Example 735

(4R*,8R*)-6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane-4,8-diol

[1186] Synthesized analogous to Reference Example 623.
^{1}HNMR ($CDCl_3$) δ ppm: 2.01 (1H, d, J = 10.5 Hz), 2.74 (1H, d, J = 8.0 Hz), 2.94 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.08-3.16 (2H, m), 3.38-3.43 (1H, m), 3.50-3.52 (1H, m), 3.65-3.70 (1H, m), 4.12-4.17 (1H, m), 6.90-6.98 (2H, m).

Reference Example 736

8-(4-Chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol

[1187] To a solution of 4-chloro-2-fluoro-1-iodobenzene (1.01 mL) in tetrahydrofuran (20 ml), a solution of 2 M isopropylmagnesium chloride tetrahydrofuran (4.29 mL) was added dropwise under argon atmosphere at -30 °C, and the mixture was stirred at from -30 to -20 °C for 5 min, then at room temperature for 2 h. To the reaction solution at -5 °C was added 1,4-dioxaspiro[4.5]decan-8-one (1.47 g), and the reaction mixture was stirred at room temperature overnight. The reaction solution was poured into aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.16 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.74 (2H, m,), 1.80-1.91 (2H, m), 1.97 (1H, d, J = 4.2 Hz), 2.04-2.16 (2H, m), 2.26-2.39 (2H, m), 3.99 (4H, t, J = 2.3 Hz), 7.07 (1H, dd, J = 12.0 Hz, 2.1 Hz), 7.12 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.48 (1H, t, J = 8.7 Hz).

Reference Example 737

4-(4-Chloro-2-fluorophenyl)-4-[(4-methoxybenzyl)oxy]cyclohexanone

[1188] Under argon atmosphere, to a solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (6.51 g) in N,N-dimethylformamide (65ml) was added sodium hydride (50 % in oil) (2.18 g) under ice-cooling, and the mixture was stirred at the same temperature for 30 min. To the mixture was added α-chloro-4-methoxytoluene (6.16 mL) and the solution was stirred at room temperature for 3 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography to provide 8-(4-chloro-2-fluorophenyl)-8-[(4-methoxybenzyl)oxy]-1,4-dioxaspiro[4.5]decane as oil (9.06 g). The oil was dissolved into tetrahydrofuran (130 mL), and to the solution was added 5 N hydrochloric acid (33 mL), and the mixture was stirred at room temperature for 5 h. The reaction solution was poured into potassium carbonate aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (7.64 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.21-2.42 (4H, m), 2.55-2.66 (2H, m), 2.76-2.90 (2H, m), 3.81 (3H, s), 4.23 (2H, s), 6.85-6.93 (2H, m), 7.13 (1H, dd, J = 11.7 Hz, 2.1 Hz), 7.17 (1H, m), 7.22-7.29 (2H, m), 7.40 (1H, t, J = 8.5 Hz).

Reference Example 738

6-(4-Chloro-2-fluorophenyl)-6-[(4-methoxybenzyl)oxy]-1-oxaspiro[2.5]octane

[1189] Synthesized analogous to Reference Example 623.
^{1}HNMR ($CDCl_3$) δ ppm: 1.15-1.23 (2H, m), 2.15-2.26 (2H, m), 2.29-2.38 (2H, m), 2.38-2.50 (2H, m), 2.71 (2H, s), 3.81 (3H, s), 4.12 (2H, s), 6.84-6.93 (2H, m), 7.05-7.13 (1H, dd, J = 11.7 Hz, 2.1 Hz), 7.13-7.18 (1H, dd, J = 8.4 Hz, 2.1 Hz), 7.22-7.30 (2H, m), 7.38 (1H, t, J = 8.5 Hz).

Reference Example 739

4-Chloro-2-fluoro-1-{1-[(4-methoxybenzyl)oxy]-4-methylidenecyclohexyl}benzene

[1190] To a suspension of methyltriphenylphosphonium bromide (5.59 g) in tetrahydrofuran (42 mL) was added potassium tert-butoxide (1.55 g) under argon atmosphere, and the mixture was stirred at room temperature for 1 h. To the mixture was added a solution of 4-(4-chloro-2-fluorophenyl)-4-[(4-methoxybenzyl)oxy]cyclohexanone (4.36 g) in tetrahy-

drofuran (10 mL), and the reaction mixture was stirred at room temperature overnight. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (3.90 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-2.00 (2H, m), 2.17-2.27 (2H, m), 2.30-2.40 (2H, m), 2.52-2.64 (2H, m), 3.80 (3H, s), 4.16 (2H, s), 4.65-4.71 (2H, m), 6.83-6.90 (2H, m), 7.08 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.10-7.16 (1H, m), 7.21-7.28 (2H, m), 7.36 (1H, t, J = 8.5 Hz).

Reference Example 740

4-(4-Chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-[(4-methoxybenzyl)oxy]cyclohex anol

[1191] To a solution of 4-chloro-2-fluoro-1-{1-[(4-methoxybenzyl)oxy]-4-methylidenecyclohexyl}benzene (0.30 g) in acetone/water (6 mL/1.5 mL) were added N-methylmorpholine (0.24 g) and Osmium Oxide, Immobilized Catalyst I (content: 7 %) (0.030 g, 8.31 μM), and the reaction mixture was stirred at room temperature overnight. Insoluble materials were filtered off, and the filtrate was concentrated. Water was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.28 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.51-1.68 (2H, m), 1.69-1.86 (2H, m), 1.86-2.30 (6H, m), 3.49 (0.6H, d, J = 5.1 Hz), 3.63 (1.4H, d, J = 5.4 Hz), 3.80 (3H, s), 4.09 (0.6H, s), 4.14 (1.4H, s), 6.83 (2H, m), 7.09 (1H, dd, J = 11.9 Hz, 2.1 Hz), 7.13 (1H, dd, J = 8.4 Hz, 2.1 Hz), 7.17-7.28 (2H, m), 7.32-7.42 (1H, m).

Reference Example 741

{cis-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-[(4-methoxybenzyl)oxy]cyclohexyl} methyl 4-methylbenzenesulfonate

[1192] Synthesized analogous to Reference Example 697.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.71 (2H, m), 1.80-2.00 (4H, m), 2.11 (1H, s), 2.12-2.23 (2H, m), 2.45 (3H, s), 3.80 (3H, s), 4.04 (2H, s), 4.10 (2H, s), 6.82-6.89 (2H, m), 7.05-7.15 (2H, m), 7.18-7.22 (2H, m), 7.31 (1H, t, J = 8.5 Hz), 7.36 (2H, d, J = 8.0 Hz), 7.76-7.84 (2H, m).

Reference Example 742

(3s,6s)-6-(4-Chloro-2-fluorophenyl)-6-[(4-methoxybenzyl)oxy]-1-oxaspiro[2.5]octan e

[1193] A solution of {cis-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-[(4-methoxybenzyl)-oxy]cyclohexyl}m ethyl 4-methylbenzenesulfonate (1.09 g) and 1,8-diazabicyclo[5.4.0]undecene (0.36 mL) in ethyl acetate (11 mL) was stirred at room temperature overnight. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.68 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.21-1.34 (2H, m), 2.07-2.19 (2H, m), 2.32-2.47 (4H, m), 2.67 (2H, s), 3.81 (3H, s), 4.16 (2H, s), 6.83-6.92 (2H, m), 7.11 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.13-7.20 (1H, m), 7.22-7.30 (2H, m), 7.40 (1H, t, J = 8.5 Hz).

Reference Example 743

8-(4-Chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

[1194] A solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (0.30 g) and (methoxycarbonylsulfamoyl)triethylammonium hydroxide (0.50 g) in tetrahydrofuran (6 mL) was stirred, under argon atmosphere, at room temperature for 1 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.25 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.90 (2H, t, J = 6.5 Hz), 2.44-2.49 (2H, m), 2.57-2.63 (2H, m), 3.99-4.05 (4H, m), 5.83-5.87 (1H, m), 7.03-7.09 (2H, m), 7.19 (1H, t, J = 8.4 Hz).

Reference Example 744

8-(4-Chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decane

[1195] To a solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (1.18 g) in ethyl acetate (12 mL) was added platinum oxide (60 mg) under argon atmosphere, and the reaction mixture was stirred at room temperature for 7 h under hydrogen atmosphere. Insoluble materials were filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.60 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.92 (8H, m), 2.82-2.94 (1H, m), 3.98 (4H, s), 7.04 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.07 (1H, dd, J = 8.3 Hz, 2.0 Hz), 7.19 (1H, t, J = 8.2 Hz).

Reference Example 745

4-(4-Chloro-2-fluorophenyl)cyclohexanone

[1196] A solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decane (2.95 g) and 5 N hydrochloric acid (15 mL) in tetrahydrofuran (59 mL) was stirred at room temperature for 5 h, then under heated to reflux for 5 h. The reaction solution was concentrated, and potassium carbonate aqueous solution was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.95 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-2.02 (2H, m), 2.13-2.27 (2H, m), 2.45-2.60 (4H, m), 3.26-3.39 (1H, m), 7.02-7.20 (3H, m).

Reference Example 746

4-Chloro-2-fluoro-1-(4-methylidenecyclohexyl)benzene

[1197] Synthesized analogous to Reference Example 739.
^{1}HNMR ($CDCl_3$) δ ppm: 1.44-1.59 (2H, m), 1.83-1.99 (2H, m), 2.09-2.24 (2H, m), 2.38-2.47 (2H, m), 2.94-3.05 (1H, m), 4.68 (2H, t, J = 1.7 Hz), 7.03 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.06 (1H, dd, J = 8.3 Hz, 2.1 Hz), 7.12 (1H, t, J = 8.1 Hz).

Reference Example 747

4-(4-Chloro-2-fluorophenyl)-1-(hydroxymethyl)cyclohexanol

[1198] Synthesized analogous to Reference Example 740.
^{1}HNMR ($CDCl_3$) δ ppm: 1.40-1.65 (4H, m), 1.68-1.78 (0.5H, m), 1.78-1.91 (2.5H, m), 1.91-1.99 (1.5H, m), 1.99-2.11 (1.5H, m), 2.76-2.99 (1H, m), 3.48 (0.5H, d, J = 5.9 Hz), 3.70 (1.5H, d, J = 5.9 Hz), 7.00-7.25 (3H, m).

Reference Example 748

[cis-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methyl 4-methylbenzenesulfonate

[1199] To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)cyclohexanol (1.96 g) in dichloromethane (20 mL) were added p-toluenesulfonyl chloride (1.74 g) and N,N,N',N'-tetramethyl-1,3-propanediamine (2.52 mL) under ice-cooling, and the mixture was stirred at the same temperature for 3 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.45 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.39-1.52 (2H, m), 1.63-1.73 (2H, m), 1.75-1.92 (5H, m), 2.46 (3H, s), 2.71-2.87 (1H, m), 3.87 (2H, s), 7.02 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.07 (1H, dd, J = 8.4 Hz, 1.9 Hz), 7.18 (1H, t, J = 8.2 Hz), 7.37 (2H, d, J = 8.1 Hz), 7.77-7.85 (2H, m).

Reference Example 749

[trans-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methyl 4-methylbenzenesulfonate

[1200] To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)cyclohexanol (1.96 g) in dichloromethane (20

mL) were added p-toluenesulfonyl chloride (1.74 g) and N,N,N',N'-tetramethyl-1,3-propanediamine (2.52 mL) under ice-cooling, and the reaction mixture was stirred at the same temperature for 3 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.97 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.29-1.44 (2H, m), 1.51-1.68 (2H, m), 1.71-1.85 (2H, m), 1.88-2.02 (2H, m), 2.17 (1H, s), 2.46 (3H, s), 2.72-2.83 (1H, m), 4.12 (2H, s), 6.96-7.11 (3H, m), 7.38 (2H, d, J = 8.0 Hz), 7.79-7.89 (2H, m).

Reference Example 750

(3r,6r)-6-(4-Chloro-2-fluorophenyl)-1-oxaspiro[2.5]octane

[1201] Synthesized analogous to Reference Example 742.
^{1}HNMR ($CDCl_3$) δ ppm: 1.33-1.48 (2H, m), 1.62-1.77 (2H, m), 1.94-2.15 (4H, m), 2.66 (2H, s), 2.85-2.97 (1H, m), 7.03 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.07 (1H, dd, J = 8.4 Hz, 1.9 Hz), 7.16 (1H, t, J = 8.1 Hz).

Reference Example 751

(3s,6s)-6-(4-Chloro-2-fluorophenyl)-1-oxaspiro[2.5]octane

[1202] Synthesized analogous to Reference Example 742.
^{1}HNMR ($CDCl_3$) δ ppm: 1.32-1.43 (2H, m), 1.77-1.95 (4H, m), 2.01-2.16 (2H, m), 2.71 (2H, s), 2.88-3.00 (1H, m), 7.05 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.10 (1H, dd, J = 8.4 Hz, 2.3 Hz), 7.21 (1H, t, J = 8.2 Hz).

Reference Example 752

5-{[cis-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1203] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.56-1.66 (2H, m), 1.70-1.79 (2H, m), 1.85-1.99 (5H, m), 2.62-2.70 (2H, m), 2.81-2.93 (3H, m), 3.74 (3H, s), 3.77 (2H, s), 5.24 (2H, brs), 6.52 (1H, dd, J = 7.3 Hz, 3.4 Hz), 6.73-6.79 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.05 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.10 (1H, dd, J = 8.5 Hz, 1.9 Hz), 7.12-7.15 (2H, m), 7.23 (1H, t, J = 8.0 Hz).

Reference Example 753

5-{[4-(4-Chloro-2-fluorophenyl)cyclohex-1-en-1-yl]methoxy}-8-fluoro-1-(4-methox ybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1204] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 1.76-1.90 (1H, m), 1.90-2.00 (1H, m), 2.10-2.31 (3H, m), 2.31-2.41 (1H, m), 2.60-2.69 (2H, m), 2.83-2.97 (2H, m), 3.05-3.19 (1H, m), 3.73 (3H, s), 4.35 (2H, s), 5.23 (2H, brs), 5.82-5.90 (1H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.71-6.79 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.00-7.11 (2H, m), 7.10-7.18 (3H, m).

Reference Example 754

5-{[(1R*,2R*,4R*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1205] Synthesized analogous to Reference Example 740.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.74 (2H, m), 1.77-1.93 (2H, m), 1.93-2.08 (2H, m), 2.20 (1H, d, J = 5.8 Hz), 2.48 (1H, d, J = 0.7 Hz), 2.61-2.71 (2H, m), 2.81-3.00 (3H, m), 3.74 (3H, s), 3.88-3.93 (1H, m), 3.94 (2H, s), 5.14-5.34 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.79 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.06 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.09-7.16 (3H, m), 7.21 (1H, t, J = 8.1 Hz).

Reference Example 755

5-{[(1R*,2R*,4S*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1206] Synthesized analogous to Reference Example 740.
^{1}HNMR ($CDCl_3$) δ ppm: 1.58-1.67 (1H, m), 1.78-1.94 (3H, m), 1.98-2.15 (2H, m), 2.56-2.69 (4H, m), 2.83-2.92 (2H, m), 3.31-3.42 (1H, m), 3.74 (3H, s), 4.04 (2H, s), 4.08 (1H, brs), 5.24 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.86 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.00-7.09 (2H, m), 7.09-7.17 (3H, m).

Reference Example 756

5-({4-(4-Chloro-2-fluorophenyl)-4-[(4-methoxybenzyl)oxy]cyclohex-1-en-1-yl}meth oxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1207] Synthesized analogous to Reference Example 595.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-2.01 (1H, m), 2.25-2.44 (3H, m), 2.54-2.62 (2H, m), 2.63-2.82 (2H, m), 2.96 (2H, t, J = 7.7 Hz), 3.79 (3H, s), 4.17 (2H, s), 4.39 (2H, brs), 5,78 (1H, brs), 6.42 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.77-6.94 (3H, m), 7.05-7.15 (2H, m), 7.15-7.20 (2H, m), 7.29 (1H, t, J = 8.6 Hz), 7.51 (1H, brs).

Reference Example 757

5-({(1R*,2R*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxy-4-[(4-methoxybenzyl)oxy] -cyclohexyl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1208] Synthesized analogous to Reference Example 740.
^{1}HNMR ($CDCl_3$) δ ppm: 1.77-2.46 (6H, m), 2.48-2.69 (4H, m), 2.78-2.95 (2H, m), 3.81 (3H, s), 3.93 (1H, d, J = 8.9 Hz), 4.00 (1H, d, J = 8.9 Hz), 4.10 (2H, s), 4.19-4.33 (1H, m), 6.49 (1H, dd, J = 9.0 Hz, 3.9 Hz), 6.80-6.95 (3H, m), 7.09-7.24 (4H, m), 7.33-7.42 (1H, m), 7.51 (1H, brs).

Reference Example 758

(1R*,2R*,5S*)-5-(4-Chloro-2-fluorophenyl)-2-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroqui nolin-5-yl)oxy]methyl}-2-hydroxy-5-[(4-methoxybenzyl)oxy]cyclohexyl acetate

[1209] To a solution of 5-({(1R*,2R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxy-4-[(4-methoxybenzyl)oxy]cyclohexyl}me thoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (1.39 g) in pyridine (14 mL) was added acetic anhydride(0.28 mL), and the reaction mixture was stirred at 50-60 °C for 4 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (0.67 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.70-1.80 (1H, m), 2.07 (3H, s), 2.14-2.22 (2H, m), 2.23-2.25 (1H, m), 2.27-2.37 (1H, m), 2.38-2.52 (3H, m), 2.58 (1H, dd, J = 12.9 Hz, 4.3 Hz), 2.72-2.91 (2H, m), 3.73-3.88 (5H, m), 4.06 (1H, d, J = 10.3 Hz), 4.39 (1H, d, J = 10.3 Hz), 5.49 (1H, dd, J = 11.6 Hz, 4.4 Hz), 6.41 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.81-6.92 (3H, m), 7.12 (1H, dd, J = 11.6 Hz, 2.0 Hz), 7.15 (1H, dd, J = 8.4 Hz, 2.1 Hz), 7.27-7.32 (2H, m), 7.38 (1H, t, J = 8.4 Hz), 7.54 (1H, brs).

Reference Example 759

(1R*,2R*,5R*)-5-(4-Chloro-2-fluorophenyl)-2-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroqu inolin-5-yl)oxy]methyl}-2-hydroxy-5-[(4-methoxybenzyl)oxy]cyclohexyl acetate

[1210] To a solution of 5-({(1R*,2R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxy-4-[(4-methoxybenzyl)oxy]cyclohexyl}me thoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (1.39 g) in pyridine (14 mL) was added acetic anhydride (0.28 mL), and the reaction mixture was stirred at 50-60 °C for 4 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (0.29 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.50-1.64 (1H, m), 1.81-1.92 (1H, m), 2.08 (3H, s), 2.15-2.34 (3H, m), 2.48-2.73 (5H, m),

2.84-2.94 (1H, m), 3.73 (2H, s), 3.78 (3H, s), 4.04 (1H, d, J = 10.4 Hz), 4.19 (1H, d, J = 10,.4 Hz), 5.10 (1H, dd, J = 12.0 Hz, 4.4 Hz), 6.34 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.79 (3H, m), 7.08-7.15 (2H, m), 7.17 (1H, dd, J = 11.9 Hz, 2.1 Hz), 7.24 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.48 (1H, brs), 7.71 (1H, t, J = 8.5 Hz).

Reference Example 760

Dimethyl 4-(4-chloro-2-fluorophenyl)-4-cyanoheptanedioate

[1211] A solution of 4-chloro-2-fluorophenylacetonitrile (10.00 g), methyl acrylate (53.1 mL) and Triton B (2.68 mL) in acetonitrile (200 mL) was heated to reflux for 8 h. The reaction solution was concentrated, and 2 N hydrochloric acid was added to the residue. The solution was extracted with diethyl ether, the organic layer was washed with water and potassium carbonate aqueous solution, and dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (20.2 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.10-2.23 (2H, m), 2.29-2.43 (2H, m), 2.46-2.66 (4H, m), 3.62 (6H, s), 7.06-7.30 (2H, m), 7.50 (1H, t, J = 8.5 Hz).

Reference Example 761

Methyl 5-(4-chloro-2-fluorophenyl)-5-cyano-2-oxocyclohexanecarboxylate

[1212] To a solution of dimethyl 4-(4-chloro-2-fluorophenyl)-4-cyanoheptanedioate (20.15 g) in 1,2-dimethoxyethane (202 mL) was added sodium hydride (50 % in oil) (8.49 g) under argon atmosphere at 0 °C, and the mixture was stirred at the same temperature for 5 min, then at room temperature for 10 min, and then heated to reflux for 1 h. The reaction solution was poured into aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (14.04 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.23-2.54 (3H, m), 2.66-2.89 (2H, m), 3.01-3.17 (1H, m), 3.79 (3H, s), 7.15-7.26 (2H, m), 7.38-7.50 (1H, m), 12.25 (1H, s).

Reference Example 762

1-(4-Chloro-2-fluorophenyl)-4-oxocyclohexanecarbonitrile

[1213] To a solution of methyl 5-(4-chloro-2-fluorophenyl)-5-cyano-2-oxocyclohexanecarboxylate (14.04 g) in dimethyl sulfoxide (112 mL) were added sodium chloride (14.04 g) and water (18 mL), and the reaction mixture was stirred at 140-150 °C for 8 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (10.2 g). ^{1}HNMR ($CDCl_3$) δ ppm: 2.34-2.45 (2H, m), 2.51-2.65 (4H, m), 2.84-2.98 (2H, m), 7.18-7.25 (2H, m), 7.48 (1H, t, J = 8.5 Hz).

Reference Example 763

(3r,6r)-6-(4-Chloro-2-fluorophenyl)-1-oxaspiro[2.5]octane-6-carbonitrile

[1214] Synthesized analogous to Reference Example 623.
^{1}HNMR ($CDCl_3$) δ ppm: 1.35-1.49 (2H, m), 2.23-2.34 (4H, m), 2.45-2.60 (2H, m), 2.78 (2H, s), 7.13-7.24 (2H, m), 7.41 (1H, t, J = 8.6 Hz).

Reference Example 764

8-(4-Chloro-2-fluorophenyl)-8-methoxy-1,4-dioxaspiro[4.5]decane

[1215] To a solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (2.00 g) in N,N-dimethylformamide (20 mL) was added sodium hydride (50 % in oil) (0.670 g) under argon atmosphere at 0 °C, and the reaction mixture was stirred at the same temperature for 30 min. Then to the mixture was added iodomethane (0.868 mL) and the solution was stirred at room temperature for 1 h. The reaction solution was poured into water, and the solution was extracted

with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.98 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.70 (2H, m), 1.93-2.05 (2H, m), 2.05-2.21 (4H, m), 3.07 (3H, s), 3.88-4.04 (4H, m), 7.00-7.09 (1H, dd, J = 11.8 Hz, 2.2 Hz), 7.11 (1H, m), 7.31 (1H, t, J = 8.5 Hz).

Reference Example 765

4-(4-Chloro-2-fluorophenyl)-4-methoxycyclohexanone

[1216] Synthesized analogous to Reference Example 745.
^{1}HNMR ($CDCl_3$) δ ppm: 2.20-2.39 (4H, m), 2.42-2.55 (2H, m), 2.70-2.84 (2H, m), 3.19 (3H, s), 7.11 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.15-7.20 (1H, m), 7.34 (1H, t, J = 8.5 Hz).

Reference Example 766

4-Chloro-2-fluoro-1-(1-methoxy-4-methylidenecyclohexyl)benzene

[1217] Synthesized analogous to Reference Example 739.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83-1.99 (2H, m), 2.12-2.28 (4H, m), 2.41-2.56 (2H, m), 3.11 (3H, s), 4.68 (2H, t, J = 1.7 Hz), 7.06 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.09-7.15 (1H, m), 7.30 (1H, t, J = 8.5 Hz).

Reference Example 767

4-(4-Chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-methoxycyclohexanol

[1218] Synthesized analogous to Reference Example 740.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46-1.64 (1H, m), 1.67-2.25 (9H, m), 3.05 (1H, s), 3.10 (2H, s), 3.51 (0.6H, d, J = 5.2 Hz), 3.63 (1.4H, d, J = 5.6 Hz), 7.00-7.17 (2H, m), 7.28-7.36 (1H, m).

Reference Example 768

[trans-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methyl 4-methylbenzenesulfonate

[1219] To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-methoxycyclohexanol (1.48 g) in dichloromethane (15 mL) were added N,N,N',N'-tetramethyl-1,3-propanediamine (1.704 mL) and p-toluenesulfonyl chloride (1.17 g), and the reaction mixture was stirred at room temperature for 1 h. To the reaction solution was added brine, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.53 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.49-1.62 (2H, m), 1.65-1.78 (2H, m), 1.80 (1H, s), 1.97-2.03 (2H, m), 2.09-2.22 (2H, m), 2.46 (3H, s), 3.00 (3H, s), 3.89 (2H, s), 7.06 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.09-7.15 (1H, m), 7.28 (1H, t, J = 7.9 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.77-7.85 (2H, m).

Reference Example 769

[cis-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methyl 4-methylbenzenesulfonate

[1220] To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-methoxycyclohexanol (1.48 g) in dichloromethane (15 mL) were added N,N,N',N'-tetramethyl-1,3-propanediamine (1.704 mL) and p-toluenesulfonyl chloride (1.173 g), and the reaction mixture was stirred at room temperature for 1 h. To the reaction solution was added brine, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.41 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.69 (2H, m), 1.73-1.93 (4H, m), 1.98-2.08 (2H, m), 2.11 (1H, s), 2.45 (3H, s), 3.06 (3H, s), 4.04 (2H, s), 7.06 (1H, dd, J = 12.2 Hz, 2.2 Hz), 7.12 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.25 (1H, t, J = 8.5 Hz), 7.33-7.40 (2H, m), 7.76-7.85 (2H, m).

Reference Example 770

(3r,6r)-6-(4-Chloro-2-fluorophenyl)-6-methoxy-1-oxaspiro[2.5]octane

[1221] Synthesized analogous to Reference Example 742.
^{1}HNMR ($CDCl_3$) δ ppm: 1.11-1.22 (2H, m), 2.09-2.26 (4H, m), 2.31-2.43 (2H, m), 2.72 (2H, s), 3.09 (3H, s), 7.09 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.13 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.31 (1H, t, J = 8.5 Hz).

Reference Example 771

(3s,6s)-6-(4-Chloro-2-fluorophenyl)-6-methoxy-1-oxaspiro[2.5]octane

[1222] Synthesized analogous to Reference Example 742.
^{1}HNMR ($CDCl_3$) δ ppm: 1.12-1.30 (2H, m), 1.97-2.13 (2H, m), 2.18-2.35 (4H, m), 2.66 (2H, s), 3.12 (3H, s), 7.08 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.14 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.34 (1H, t, J = 8.5 Hz).

Reference Example 772

8-(4-Chloro-2,6-difluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol

[1223] Synthesized analogous to Reference Example 736.
^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.70 (2H, m), 2.08-2.14 (4H, m), 2.29-2.43 (2H, m), 2.53 (1H, t, J = 5.5 Hz), 3.93-4.01 (4H, m), 6.86-6.95 (2H, m).

Reference Example 773

4-(4-Chloro-2,6-difluorophenyl)-4-hydroxycyclohexanone

[1224] Synthesized analogous to Reference Example 745.
^{1}HNMR ($CDCl_3$) δ ppm: 2.27-2.40 (2H, m), 2.40-2.55 (4H, m), 2.86-2.98 (3H, m), 6.94-7.00 (2H, m).

Reference Example 774

1-(4-Chloro-2,6-difluorophenyl)-4-methylidenecyclohexanol

[1225] Synthesized analogous to Reference Example 739.
^{1}HNMR ($CDCl_3$) δ ppm: 2.02-2.25 (6H, m), 2.54-2.70 (3H, m), 4.68 (2H, t, J = 1.7 Hz), 6.81-6.96 (2H, m).

Reference Example 775

1-(4-Chloro-2,6-difluorophenyl)-4-(hydroxymethyl)cyclohexane-1,4-diol

[1226] Synthesized analogous to Reference Example 740.
^{1}HNMR (DMSO-d6) δ ppm: 1.22-1.31 (0.5H, m), 1.40-1.52 (1.5H, m), 1.56-1.72 (1.5H, m), 1.75-1.96 (2.5H, m), 2.01-2.11 (1.5H, m), 2.17-2.33 (0.5H, m), 3.15 (0.5H, d, J = 5.6 Hz), 3.28 (1.5H, d, J = 5.9 Hz), 3.86 (0.25H, s), 4.06 (0.75H, s), 4.38 (0.75H, t, J = 5.9 Hz), 4.47 (0.25H, t, J = 5.6 Hz), 5.00 (0.25H, s), 5.20 (0.75H, s), 7.15-7.29 (2H, m).

Reference Example 776

[trans-4-(4-Chloro-2,6-difluorophenyl)-1,4-dihydroxycyclohexyl]methyl 4-methylbenzenesulfonate

[1227] To a solution of 1-(4-chloro-2,6-difluorophenyl)-4-(hydroxymethyl)cyclohexane-1,4-diol (1.59 g) in dichloromethane (32 mL) were added N,N,N',N'-tetramethyl-1,3-propanediamine (1.81 mL) and p-toluenesulfonyl chloride (1.24 g), and the reaction mixture was stirred at room temperature for 3 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.72 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.52-1.63 (2H, m), 1.79 (1H, s), 1.81-1.92 (2H, m), 1.92-2.00 (2H, m), 2.22-2.32 (1H, m),

2.35-2.50 (5H, m), 3.88 (2H, s), 6.84-6.97 (2H, m), 7.37 (2H, d, J = 8.0 Hz), 7.81 (2H, m).

Reference Example 777

[cis-4-(4-Chloro-2,6-difluorophenyl)-1,4-dihydroxycyclohexyl]methyl 4-methylbenzenesulfonate

[1228] To a solution of 1-(4-chloro-2,6-difluorophenyl)-4-(hydroxymethyl)cyclohexane-1,4-diol (1.59 g) in dichloromethane (32 mL) were added N,N,N',N'-tetramethyl-1,3-propanediamine (1.81 mL) and p-toluenesulfonyl chloride (1.24 g), and the reaction mixture was stirred at room temperature for 3 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.35 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.74 (2H, m), 1.94-2.04 (6H, m), 2.14 (1H, s), 2.45 (3H, s), 2.51 (1H, t, J = 4.9 Hz), 4.06 (2H, s), 6.83-6.97 (2H, m), 7.36 (2H, d, J = 8.0 Hz), 7.76-7.86 (2H, m).

Reference Example 778

(3r,6r)-6-(4-Chloro-2,6-difluorophenyl)-1-oxaspiro[2.5]octan-6-ol

[1229] Synthesized analogous to Reference Example 742.
^{1}HNMR ($CDCl_3$) δ ppm: 1.14-1.22 (1.6H, m), 1.22-1.28 (0.4H, m), 2.11-2.19 (1.6H, m), 2.23-2.33 (0.4H, m), 2.35-2.55 (4H, m), 2.57-2.64 (1H, m), 2.67 (0.4H, s), 2.72 (1.6H, s), 6.85-6.99 (2H, m).

Reference Example 779

(3s,6s)-6-(4-Chloro-2,6-difluorophenyl)-1-oxaspiro[2.5]octan-6-ol

[1230] Synthesized analogous to Reference Example 742.
^{1}HNMR ($CDCl_3$) δ ppm: 1.17-1.32 (2H, m), 2.16-2.34 (4H, m), 2.40-2.53 (2H, m), 2.61 (1H, t, J = 5.5 Hz), 2.66 (2H, s), 6.87-6.99 (2H, m).

Reference Example 780

1-(4-Chloro-2,6-difluorophenyl)-3-[(phenylamino)oxy]piperidin-4-one

[1231] Under nitrogen atmosphere, to a suspension of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (3.00 g) and DL-proline (0.070 g) in dimethyl sulfoxide (8 mL) was added a solution of nitrosobenzene (0.436 g) in dimethyl sulfoxide (8 mL), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (807 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.57-2.59 (1H, m), 2.77-2.83 (1H, m), 3.43-3.47 (2H, m), 3.49-3.54 (1H, m), 3.81-3.85 (1H, m), 4.63-4.67 (1H, m), 6.91-6.98 (5H, m), 7.24-7.27 (2H, m), 7.76 (1H, brs).

Reference Example 781

1-(4-Chloro-2,6-difluorophenyl)-3-hydroxypiperidin-4-one

[1232] To a solution of 1-(4-chloro-2,6-difluorophenyl)-3-[(phenylamino)oxy]piperidin-4-one (807 mg) in methanol (8 mL) was added copper (II) sulfate (110 mg) at 0 °C, and the reaction mixture was stirred for 4 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (342 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.60 (1H, m), 2.84-2.90 (1H, m), 3.09-3.14 (1H, m), 3.37-3.43 (1H, m), 3.49-3.54 (1H, m), 3.63 (1H, d, J = 4.0 Hz), 3.76-3.81 (1H, m), 4.38-4.43 (1H, m), 6.91-6.96 (2H, m).

Reference Example 782

(3R)-1-(4-Chloro-2,6-difluorophenyl)-3-hydroxypiperidin-4-one

[1233] To a suspension of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (2.00 g) and L-proline (0.187 g) in N,N-dimethylformamide (8 mL) was added a solution of nitrosobenzene (0.581 g) in N,N-dimethylformamide (8 mL), and the reaction mixture was stirred at room temperature for 1 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved into methanol (16 mL), to the obtained solution copper (II) sulfate (0.260 g) was added at 0 °C, and the mixture was stirred for 4 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (545 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.60 (1H, m), 2.84-2.90 (1H, m), 3.09-3.14 (1H, m), 3.37-3.43 (1H, m), 3.49-3.54 (1H, m), 3.63 (1H, d, J = 3.5 Hz), 3.76-3.81 (1H, m), 4.38-4.43 (1H, m), 6.91-6.96 (2H, m).

Reference Example 783

(3R)-1-(4-Chloro-2-fluorophenyl)-3-hydroxypiperidin-4-one

[1234] To a suspension of 1-(4-chloro-2-fluorophenyl)piperidin-4-one (3.00 g) and (S)-5-(pyrrolidin-2-yl)-1H-tetrazole (0.183 g) in N,N-dimethylformamide (20 mL), 3/4 of a solution of nitrosobenzene (1.41 g) in N,N-dimethylformamide (40 mL) was added dropwise at -40 °C. After stirring the mixture at -30 °C for 4 h, the remaining 1/4 of the solution was added dropwise, and the reaction mixture was stirred for 12 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved into methanol (30 mL), copper (II) sulfate (0.631 g) was added to the solution at 0 °C, and the mixture was stirred for 2 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.25 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.59-2.63 (1H, m), 2.81 (1H, t, J = 11.0 Hz), 2.85-2.92 (1H, m), 3.04-3.09 (1H, m), 3.62 (1H, d, J = 3.5 Hz), 3.71-3.76 (1H, m), 3.95-3.99 (1H, m), 4.43-4.47 (1H, m), 6.91 (1H, t, J = 9.0 Hz), 7.07 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 7.10 (1H, dd, J = 11.5 Hz, 2.5 Hz).

Reference Example 784

(3S)-1-(4-Chloro-2,6-difluorophenyl)-3-hydroxypiperidin-4-one

[1235] To a suspension of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (31.6 g) and D-proline (4.44 g) in N,N-dimethylformamide (300 mL), a solution of nitrosobenzene (14.06 g) in N,N-dimethylformamide (300 mL) was added dropwise at 0 °C over 10 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved into methanol (300 mL), copper (II) sulfate (6.16 g) was added to the solution at 0 °C, and the mixture was stirred for 2 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (11.5 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.60 (1H, m), 2.84-2.90 (1H, m), 3.09-3.14 (1H, m), 3.37-3.43 (1H, m), 3.49-3.54 (1H, m), 3.63 (1H, d, J = 3.5 Hz), 3.76-3.81 (1H, m), 4.38-4.43 (1H, m), 6.91-6.96 (2H, m).

Reference Example 785

(3S)-1-(4-Chloro-2-fluorophenyl)-3-hydroxypiperidin-4-one

[1236] Synthesized analogous to Reference Example 784.
^{1}HNMR ($CDCl_3$) δ ppm: 2.59-2.63 (1H, m), 2.81 (1H, t, J = 11.0 Hz), 2.85-2.92 (1H, m), 3.04-3.09 (1H, m), 3.62 (1H, d, J = 3.5 Hz), 3.71-3.76 (1H, m), 3.95-3.99 (1H, m), 4.43-4.47 (1H, m), 6.91 (1H, t, J = 9.0 Hz), 7.07 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 7.10 (1H, dd, J = 11.5 Hz, 2.5 Hz).

Reference Example 786

(3R)-1-(4-Bromo-2-fluorophenyl)-3-hydroxypiperidin-4-one

[1237] To a solution of (1R,6R)-3-(4-bromo-2-fluorophenyl)-6-{[tert-butyl(dimethyl)silyl]oxy}-7-oxa-3-azabi cyclo[4.1.0]heptane (0.28 g) in tetrahydrofuran/water (15: 1) (3 mL) was added p-toluenesulfonic acid monohydrate (13.2 mg), and the reaction mixture was stirred at room temperature for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off to provide the title compound (0.3 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.59-2.65 (1H, m), 2.79 (1H, t, J = 11.1 Hz), 2.84-2.93 (1H, m), 3.04 (1H, dt, J = 12.2 Hz, 9.4 Hz), 3.61 (1H, d, J = 3.8 Hz), 3.73-3.78 (1H, m), 3.95-4.01 (1H, m), 4.41-4.48 (1H, m), 6.84 (1H, t, J = 8.8 Hz), 7.13-7.27 (2H, m).

Reference Example 787

1-(4-Bromo-2,6-difluorophenyl)-3-hydroxypiperidin-4-one

[1238] To a solution of (1R*,6R*)-3-(4-bromo-2,6-difluorophenyl)-6-{[tert-butyl(dimethyl)silyl]oxy}-7-oxa-3-azabicycl o[4.1.0]heptane (6.58 g) in dichloromethane (65 mL) was added 5 N hydrochloric acid (15.65 mL), and the reaction mixture was stirred at room temperature for 30 min. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (3.90 g).
^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.61 (1H, m), 2.82-2.91 (1H, m), 3.07-3.14 (1H, m), 3.35-3.43 (1H, m), 3.48-3.56 (1H, m), 3.61-3.66 (1H, m), 3.75-3.83 (1H, m), 4.37-4.44 (1H, m), 7.04-7.11 (2H, m).

Reference Example 788

(3R)-1-(4-Chloro-2,6-difluorophenyl)-3-[(4-methoxybenzyl)oxy]piperidin-4-one

[1239] To a solution of 4-methoxybenzyl2,2,2-trichloroethaneimidate (1.58 g) in hexane (9.4 mL) was added a solution of (3R)-1-(4-chloro-2,6-difluorophenyl)-3-hydroxypiperidin-4-one (976 mg) in dichloromethane (4.7 mL), then boron trifluoride-diethylether complex (0.014 mL) was added to the mixture at 0 °C, and the reaction mixture was stirred for 14 h. The reaction solution was filtered with Celite, the filtrate was washed with hexane/ dichloromethane (2/1), then the organic layer was washed with aqueous saturated sodium bicarbonate, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (663 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 2.53-2.57 (1H, m), 2.68-2.75 (1H, m), 3.31-3.45 (3H, m), 3.60-3.64 (1H, m), 3.80 (3H, s), 4.12-4.15 (1H, m), 4.50 (1H, d, J = 11.5 Hz), 4.78 (1H, d, J = 11.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 6.88-6.94 (2H, m), 7.30 (2H, d, J = 8.5 Hz).

Reference Example 789

1-(4-Chloro-2,6-difluorophenyl)-3-[(4-methoxybenzyl)oxy]piperidin-4-one

[1240] Synthesized analogous to Reference Example 788.
^{1}HNMR ($CDCl_3$) δ ppm: 2.53-2.57 (1H, m), 2.68-2.75 (1H, m), 3.31-3.45 (3H, m), 3.60-3.64 (1H, m), 3.80 (3H, s), 4.12-4.15 (1H, m), 4.50 (1H, d, J = 11.5 Hz), 4.78 (1H, d, J = 11.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 6.88-6.94 (2H, m), 7.30 (2H, d, J = 8.5 Hz).

Reference Example 790

(3S)-1-(4-Chloro-2,6-difluorophenyl)-3-[(4-methoxybenzyl)oxy]piperidin-4-one

[1241] Synthesized analogous to Reference Example 788.
^{1}HNMR ($CDCl_3$) δ ppm: 2.53-2.57 (1H, m), 2.68-2.75 (1H, m), 3.31-3.45 (3H, m), 3.60-3.64 (1H, m), 3.80 (3H, s), 4.12-4.15 (1H, m), 4.50 (1H, d, J = 11.5 Hz), 4.78 (1H, d, J = 11.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 6.88-6.94 (2H, m), 7.30 (2H, d, J = 8.5 Hz).

Reference Example 791

(3S)-1-(4-Chloro-2-fluorophenyl)-3-[(4-methoxybenzyl)oxy]piperidin-4-one

[1242] Synthesized analogous to Reference Example 788.
^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.60 (1H, m), 2.69-2.75 (1H, m), 3.02-3.13 (2H, m), 3.57-3.62 (1H, m), 3.70-3.79 (1H, m), 3.80 (3H, s), 4.14-4.18 (1H, m), 4.51 (1H, d, J = 11.5 Hz), 4.80 (1H, d, J = 11.5 Hz), 6.84 (1H, t, J = 9.0 Hz), 6.88 (2H, d, J = 8.5 Hz), 7.03 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 7.07 (1H, dd, J = 11.5 Hz, 2.5 Hz), 7.30 (2H, d, J = 8.5 Hz).

Reference Example 792

(3S,4R)-6-(4-Chloro-2,6-difluorophenyl)-4-[(4-methoxybenzyl)oxy]-1-oxa-6-azaspir o[2.5]octane

[1243] Synthesized analogous to Reference Example 398.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.94 (2H, m), 2.65 (1H, d, J = 5.0 Hz), 3.04 (1H, d, J = 5.0 Hz), 3.16-3.23 (2H, m), 3.27-3.32 (1H, m), 3.40-3.43 (1H, m), 3.49-3.51 (1H, m), 3.79 (3H, s), 4.50 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 11.5 Hz), 6.86 (2H, d, J = 8.5 Hz), 6.85-6.90 (2H, m), 7.23 (2H, d, J = 8.5 Hz).

Reference Example 793

(3S*,4R*)-6-(4-Chloro-2,6-difluorophenyl)-4-[(4-methoxybenzyl)oxy]-1-oxa-6-azasp iro[2.5]octane

[1244] Synthesized analogous to Reference Example 398.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.94 (2H, m), 2.65 (1H, d, J = 5.0 Hz), 3.04 (1H, d, J = 5.0 Hz), 3.16-3.23 (2H, m), 3.27-3.32 (1H, m), 3.40-3.43 (1H, m), 3.49-3.51 (1H, m), 3.79 (3H, s), 4.50 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 11.5 Hz), 6.86 (2H, d, J = 8.5 Hz), 6.85-6.90 (2H, m), 7.23 (2H, d, J = 8.5 Hz).

Reference Example 794

(3R,4S)-6-(4-Chloro-2,6-difluorophenyl)-4-[(4-methoxybenzyl)oxy]-1-oxa-6-azaspir o[2.5]octane

[1245] Synthesized analogous to Reference Example 340.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.94 (2H, m), 2.65 (1H, d, J = 5.0 Hz), 3.04 (1H, d, J = 5.0 Hz), 3.16-3.23 (2H, m), 3.27-3.32 (1H, m), 3.40-3.43 (1H, m), 3.49-3.51 (1H, m), 3.79 (3H, s), 4.50 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 11.5 Hz), 6.86 (2H, d, J = 8.5 Hz), 6.85-6.90 (2H, m), 7.23 (2H, d, J = 8.5 Hz).

Reference Example 795

(3R,4S)-6-(4-Chloro-2-fluorophenyl)-4-[(4-methoxybenzyl)oxy]-1-oxa-6-azaspiro[2. 5]octane

[1246] Synthesized analogous to Reference Example 340.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.89 (1H, m), 1.98-2.02 (1H, m), 2.68 (1H, d, J = 5.0 Hz), 3.00 (1H, d, J = 5.0 Hz), 3.03-3.08 (1H, m), 3.10-3.14 (1H, m), 3.24-3.34 (2H, m), 3.47-3.49 (1H, m), 3.80 (3H, s), 4.54 (1H, d, J = 11.5 Hz), 4.60 (1H, d, J = 11.5 Hz), 6.84-6.91 (3H, m), 7.00-7.07 (2H, m), 7.24 (2H, d, J = 8.5 Hz).

Reference Example 796

(3R*,4S*)-6-(4-Bromo-2,6-difluorophenyl)-4-[(4-methoxybenzyl)oxy]-1-oxa-6-azasp iro[2.5]octane

[1247] A solution of 1-(4-bromo-2,6-difluorophenyl)-3-hydroxypiperidin-4-one (2 g), 4-methoxybenzyl 2,2,2-trichloroacetimidate (5.16 g) and lanthanum (III) trifluoromethanesulfonate (0.191 g) in toluene (25 mL) was stirred at room temperature for 16.5 h. After insoluble materials were filtered off, the solvent was distilled off, and the residue was purified by silica gel column chromatography (dichloromethane) to give the mixture of 1-(4-bromo-2,6-difluorophenyl)-3-hydroxypiperidin-4-one and 1-(4-bromo-2,6-difluorophenyl)-3-[(4-methoxybenzyl)oxy]piperidin-4-one. To a suspension of trimethylsulfoxonium iodide (0.898 g) in dimethyl sulfoxide (7.5 mL) was added sodium t-butoxide (0.392 g), the mixture was stirred at room temperature for 30 min, to which the solution of the mixture in dimethyl sulfoxide (7.5 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. To the reaction mixture was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous

sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.44 g). ^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.94 (2H, m), 2.65 (1H, d, J = 5.2 Hz), 3.03 (1H, d, J = 5.2 Hz), 3.15-3.24 (2H, m), 3.26-3.33 (1H, m), 3.39-3.45 (1H, m), 3.50 (1H, dd, J = 7.6 Hz, 4.0 Hz), 3.80 (3H, s), 4.50 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 11.5 Hz), 6.83-6.88 (2H, m), 6.98-7.05 (2H, m), 7.21-7.25 (2H, m).

Reference Example 797

5-([(3R,4S)-1-(4-Chloro-2,6-difluorophenyl)-4-hydroxy-3-[(4-methoxybenzyl)oxy]p iperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1248] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.65 (1H, m), 2.15-2.21 (1H, m), 2.41 (1H, brs), 2.59 (2H, t, J = 7.5 Hz), 2.74-2.80 (1H, m), 2.87-2.93 (1H, m), 3.08-3.12 (1H, m), 3.33-3.36 (1H, m), 3.47-3.55 (3H, m), 3.73 (3H, s), 3.79 (1H, d, J = 9.0 Hz), 4.15 (1H, d, J = 9.0 Hz), 4.33 (1H, d, J = 11.5 Hz), 4.62 (1H, d, J = 11.5 Hz), 6.44 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.70 (2H, d, J = 8.5 Hz), 6.86-6.91 (2H, m), 6.92 (1H, t, J = 9.0 Hz), 7.11 (2H, d, J = 8.5 Hz), 7.75 (1H, brs).

Reference Example 798

5-({(3R*,4S*)-1-(4-Chloro-2,6-difluorophenyl)-4-hydroxy-3-[(4-methoxybenzyl)oxy] piperidin-4-yl]methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1249] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.65 (1H, m), 2.15-2.21 (1H, m), 2.35 (1H, brs), 2.59 (2H, t, J = 7.5 Hz), 2.74-2.80 (1H, m), 2.87-2.93 (1H, m), 3.08-3.12 (1H, m), 3.33-3.36 (1H, m), 3.47-3.55 (3H, m), 3.73 (3H, s), 3.79 (1H, d, J = 9.0 Hz), 4.15 (1H, d, J = 9.0 Hz), 4.33 (1H, d, J = 11.5 Hz), 4.62 (1H, d, J = 11.5 Hz), 6.44 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.70 (2H, d, J = 8.5 Hz), 6.86-6.91 (2H, m), 6.92 (1H, t, J = 9.0 Hz), 7.11 (2H, d, J = 8.5 Hz), 7.60 (1H, brs).

Reference Example 799

5-([(3S,4R)-1-(4-Chloro-2,6-difluorophenyl)-4-hydroxy-3-[(4-methoxybenzyl)oxy]p iperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1250] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.65 (1H, m), 2.15-2.21 (1H, m), 2.45 (1H, brs), 2.59 (2H, t, J = 7.5 Hz), 2.74-2.80 (1H, m), 2.87-2.93 (1H, m), 3.08-3.12 (1H, m), 3.33-3.36 (1H, m), 3.47-3.55 (3H, m), 3.73 (3H, s), 3.79 (1H, d, J = 9.0 Hz), 4.15 (1H, d, J = 9.0 Hz), 4.33 (1H, d, J = 11.5 Hz), 4.62 (1H, d, J = 11.5 Hz), 6.44 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.70 (2H, d, J = 8.5 Hz), 6.86-6.91 (2H, m), 6.92 (1H, t, J = 9.0 Hz), 7.11 (2H, d, J = 8.5 Hz), 7.82 (1H, brs).

Reference Example 800

5-({(3S,4R)-1-(4-Chloro-2-fluorophenyl)-4-hydroxy-3-[(4-methoxybenzyl)oxy]piper idin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1251] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.68-1.72 (1H, m), 2.17-2.23 (1H, m), 2.37 (1H, brs), 2.59 (2H, t, J = 7.5 Hz), 2.71-2.77 (1H, m), 2.85-2.91 (1H, m), 3.10-3.17 (2H, m), 3.22-3.27 (1H, m), 3.50-3.52 (1H, m), 3.52-3.63 (1H, m), 3.73 (3H, s), 3.76 (1H, d, J = 9.0 Hz), 4.16 (1H, d, J = 9.0 Hz), 4.39 (1H, d, J = 11.5 Hz), 4.70 (1H, d, J = 11.5 Hz), 6.43 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.69 (2H, d, J = 8.5 Hz), 6.90-6.94 (2H, m), 7.02-7.08 (2H, m), 7.11 (2H, d, J = 8.5 Hz), 7.67 (1H, brs).

Reference Example 801

5-({(3S*,4R*)-1-(4-Bromo-2,6-difluorophenyl)-4-hydroxy-3-[(4-methoxybenzyl)oxy] piperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1252] Synthesized analogous to Reference Example 453.
^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.67 (1H, m), 2.13-2.22 (1H, m), 2.34 (1H, s), 2.60 (2H, t, J = 7.7 Hz), 2.73-2.81 (1H, m), 2.85-2.94 (1H, m), 3.07-3.14 (1H, m), 3.31-3.38 (1H, m), 3.44-3.56 (3H, m), 3.74 (3H, s), 3.78 (1H, d, J = 8.9 Hz), 4.15

(1H, d, J = 8.9 Hz), 4.33 (1H, d, J = 11.7 Hz), 4.61 (1H, d, J = 11.7 Hz), 6.44 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.68-6.73 (2H, m), 6.92 (1H, t, J = 9.5 Hz), 6.99-7.07 (2H, m), 7.09-7.13 (2H, m), 7.55 (1H, brs).

Reference Example 802

5-(Chloromethoxy)-8-fluoro-2-methoxyquinoline

[1253] Synthesized analogous to Reference Example 58.
^{1}HNMR ($CDCl_3$) δ ppm: 4.11 (3H, s), 6.03 (2H, s), 6.96 (1H, d, J = 9.1 Hz), 7.01 (1H, dd, J = 8.7 Hz, 3.5 Hz), 7.30 (1H, dd, J = 10.3 Hz, 8.7 Hz), 8.32 (1H, dd, J = 9.1 Hz, 1.6 Hz).

Reference Example 803

8-Chloro-5-(chloromethoxy)-2-methoxyquinoline

[1254] Synthesized analogous to Reference Example 58.
^{1}HNMR ($CDCl_3$) δ ppm: 4.14 (3H, s), 6.04 (2H, s), 6.96 (1H, d, J = 9.1 Hz), 7.03 (1H, d, J = 8.5 Hz), 7.70 (1H, d, J = 8.5 Hz), 8.35 (1H, d, J = 9.1 Hz).

Reference Example 804

1-tert-butyl 4-ethyl 4-{[(8-Chloro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-1,4-dicarboxylate

[1255] Synthesized analogous to Reference Example 59.
^{1}HNMR ($CDCl_3$) δ ppm: 1.19 (3H, t, J = 7.1 Hz), 1.47 (9H, s), 1.57-1.64 (2H, m), 2.30-2.33 (2H, m), 2.94-3.16 (2H, br), 3.85-4.06 (2H, br), 4.10 (2H, brs), 4.13 (3H, s), 4.20 (2H, q, J = 7.1 Hz), 6.61 (1H, d, J = 8.4 Hz), 6.91 (1H, d, J = 8.9 Hz), 7.60 (1H, d, J = 8.4 Hz), 8.30 (1H, d, J = 8.9 Hz).

Reference Example 805

Ethyl 4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-carboxylate

[1256] Synthesized analogous to Reference Example 60.
^{1}HNMR ($CDCl_3$) δ ppm: 1.19 (3H, t, J = 7.2 Hz), 1.65-1.70 (2H, m), 2.33-2.36 (2H, m), 2.82-2.88 (2H, m), 3.05-3.08 (2H, m), 4.10 (2H, s), 4.13 (3H, s), 4.19 (2H, q, J = 7.1 Hz), 6.62 (1H, d, J = 8.6 Hz), 6.91 (1H, d, J = 9.0 Hz), 7.60 (1H, d, J = 8.4 Hz), 8.33 (1H, d, J = 9.0 Hz).

Reference Example 806

2,4-Dibromo-3-fluoro-5-methoxyaniline

[1257] To a solution of 4-bromo-3-fluoro-5-methoxyaniline (456 mg) in acetonitrile (5 mL) was added N-bromosuccinimide (369 mg) under ice-cooling, and the mixture was stirred at the same temperature for 3 min. To the reaction solution was added water, the precipitate was collected on a filter, and washed with water to give the title compound (530 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 3.83 (3H, s), 4.26 (2H, brs), 6.15 (1H, d, J = 1.8 Hz).

Reference Example 807

5-Bromo-2,2,6-trifluoro-1,3-benzodioxole

[1258] To a solution of 2,2,6-trifluoro-1,3-benzodioxol-5-amine (5.38 g) in acetonitrile (90 mL) was added tert-butyl nitrite (5.02 mL) at 0 °C, and the mixture was stirred at the same temperature for 15 min. To the mixture was added copper (II) bromide (9.43 g), and the reaction mixture was stirred at room temperature for 3 h. To the reaction solution were added water, hexane and ethyl acetate, and the precipitate was filtered off by using Celite. The organic layer of the filtrate was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (4.89 g).
^{1}HNMR ($CDCl_3$) δ ppm: 6.95 (1H, d, J = 7.0 Hz), 7.27 (1H, d, J = 5.5 Hz).

Reference Example 808

1-(4-Bromo-2-fluorophenyl)-4-{[tert-butyl(diphenyl)silyl]oxy}-1,2,3,6-tetrahydropyr idine

[1259] Synthesized analogous to Reference Example 613.
^{1}HNMR ($CDCl_3$) δ ppm: 1.04 (9H, s), 2.21-2.25 (2H, m), 3.23-3.25 (2H, m), 3.42-3.43 (2H, m), 4.64-4.69 (1H, m), 6.62 (1H, t, J = 9.0 Hz), 7.07 (1H, ddd, J = 9.0 Hz, 2.0 Hz, 1.0 Hz), 7.14 (1H, dd, J = 12.0 Hz, 2.0 Hz), 7.37-7.40 (4H, m), 7.43-7.46 (2H, m), 7.71-7.73 (4H, m).

Reference Example 809

5-{[1-(3,5-Dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-m ethoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

[1260] Synthesized analogous to Reference Example 66.
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.95 (4H, m), 2.01 (1H, s), 2.62-2.69 (2H, m), 2.85-2.92 (2H, m), 3.23-3.34 (2H, m), 3.59-3.67 (2H, m), 3.74 (3H, s), 3.81 (2H, s), 5.23 (2H, brs), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 1

5-{[4-Amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one

[1261] To a suspension of 5-{[1-(3,5-dichloropyridin-2-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one (0.44 g) in acetic acid (4 mL) was added conc. hydrochloric acid (3 mL), and the reaction mixture was stirred at 80 °C for 2 h. The solvent was distilled off, aqueous sodium hydroxide was added to the residue, and the insoluble precipitate was collected on a filter. The obtained solid was dissolved into dichloromethane, the solution was washed with 1 N aqueous sodium hydroxide and brine, and the organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography (basic silica gel: dichloromethane -> dichloromethane/ethyl acetate), and the obtained product was recrystallized from ethanol. The crystal was collected on a filter and air-dried (60 °C) to provide the title compound (0.32 g).
m.p. 173-174 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (2H, brs), 1.62-1.71 (2H, m), 1.88-1.98 (2H, m), 2.65 (2H, t, J = 8.0 Hz)), 3.02 (2H, t, J = 8.0 Hz), 3.24-3.36 (2H, m), 3.49-3.60 (2H, m), 3.78 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.52 (1H, brs), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 2

2-(4-Amino-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperid in-1-yl)-5-fluorobenzonitrile

[1262] To N-[1-(2-cyano-4-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy] methyl}piperidin-4-yl]acetamide (68.0 mg) were added acetic acid (2 mL) and 6 N hydrochloric acid (12 mL) and the mixture was refluxed for 36 h. After the reaction mixture was allowed to cool to room temperature, 3 N aqueous sodium hydroxide was added to make the reaction solution alkaline, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/methanol), and the obtained solid was recrystallized from hexane/ethyl acetate to provide the title compound (30 mg).
m.p. 223.9-225.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.20-1.70 (2H, brs), 1.68-1.75 (2H, m), 1.95-2.04 (2H, m), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.20-3.30 (4H), 3.77 (2H, s), 6.45 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.05 (1H, dd, J = 9.0 Hz, 4.5 Hz), 7.19-7.25 (1H, m), 7.25-7.31 (1H, m), 7.50 (1H, brs).

Example 3

5-{[4-Amino-1-(2,5-difluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroqu inolin-2(1H)-one

[1263] Synthesized analogous to Example 1.
^{1}HNMR (DMSO-d6) δ ppm: 1.51-1.54 (2H, m), 1.79-1.84 (2H, m), 2.46 (2H, t, J = 7.7 Hz), 2.90 (2H, t, J = 7.7 Hz),

3.11-3.14 (4H, m), 3.71 (2H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.6 Hz), 6.69-6.74 (1H, m), 6.88 (1H, ddd, J = 10.7 Hz, 7.4 Hz, 3.2 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.13 (1H, ddd, J = 12.6 Hz, 8.9 Hz, 5.4 Hz), 10.02 (1H, s).

Example 4

5-{[4-Amino-1-(2,4,5-trichlorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1264] Synthesized analogous to Example 1.
^{1}HNMR (DMSO-d6) δ ppm: 1.53-1.58 (4H, m), 1.79-1.85 (2H, m), 2.47 (2H, t, J = 7.6 Hz), 2.92 (2H, t, J = 7.6 Hz), 3.04-3.14 (4H, m), 3.74 (2H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.37 (1H, s), 7.75 (1H, s), 10.02 (1H, s).

Example 5

5-{[4-Amino-1-(4-chloro-2,6-difluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-d ihydroquinolin-2(1H)-one

[1265] Synthesized analogous to Example 1.
^{1}HNMR (DMSO-d6) δ ppm: 1.47-1.65 (4H, m), 1.73-1.79 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.91 (2H, t, J = 7.7 Hz), 2.95-2.97 (2H, m), 3.38-3.47 (2H, m), 3.71 (2H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.22-7.30 (2H, m), 10.01 (1H, s).

Example 6

5-{[4-Amino-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroqu inolin-2(1H)-one

[1266] A solution of 5-{[4-amino-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxy benzyl)-3,4-dihydroquinolin-2(1H)-one (305 mg) and anisole (0.123 mL) in trifluoroacetic acid (3 mL) was stirred at 65 °C for 1 h. The reaction solution was concentrated, 5 N aqueous sodium hydroxide was added to the residue, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography (dichloromethane/methanol). The obtained product was crystallized from ethanol, the precipitate was collected on a filter and dried under reduced pressure to provide the title compound (195 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.40-1.62 (4H, m), 1.78-1.84 (2H, m), 2.46 (2H, t, J = 7.6 Hz), 2.91 (2H, t, J = 7.6 Hz), 3.04-3.12 (4H, m), 3.72 (2H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.16 (1H, dt, J = 12.7 Hz, 8.4 Hz), 7.45 (1H, dt, J = 7.7 Hz, 11.4 Hz), 10.02 (1H, s).

Example 7

5-({4-Amino-1-[2-fluoro-4-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1267] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.52-1.57 (4H, m), 1.80-1.86 (2H, m), 2.45 (2H, t, J = 7.6 Hz), 2.89 (2H, t, J = 7.6 Hz), 3.22-3.29 (4H, m), 3.72 (2H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.22 (1H, t, J = 8.7 Hz), 7.45 (1H, d, J = 8.6 Hz), 7.51 (1H, dd, J = 13.3 Hz, 1.7 Hz), 10.02 (1H, s).

Example 8

5-({4-Amino-1-[2-chloro-4-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1268] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.56-1.58 (4H, m), 1.81-1.87 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.92 (2H, t, J = 7.6 Hz), 3.17-3.21 (4H, m), 3.74 (2H, s), 6.59 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.34 (1H, d, J = 8.5 Hz), 7.63 (1H, dd, J = 8.6 Hz, 1.8 Hz), 7.75 (1H, d, J = 1.9 Hz), 10.02 (1H, s).

Example 9

5-{[4-Amino-1-(2,4-dichlorophenyl)piperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H) -one

[1269] A solution of 1-(2,4-dichlorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4 -amine (144 mg) in 1 M hydrogen chloride/ethanol (4 mL) was stirred under reflux for 6 h. The reaction solution was concentrated, aqueous sodium hydroxide was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was crystallized from ethanol, and the precipitate was collected on a filter and dried under reduced pressure to provide the title compound (40 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.64 (2H, m), 1.80-1.85 (2H, m), 3.01-3.04 (2H, m), 3.09-3.14 (2H, m), 3.86 (2H, s), 6.52 (1H, d, J = 9.8 Hz), 6.68 (1H, dd, J = 8.9 Hz, 3.3 Hz), 7.22 (1H, d, J = 8.7 Hz), 7.32-7.37 (2H, m), 7.53 (1H, d, J = 2.5 Hz), 8.22 (1H, dd, J = 9.8 Hz, 1.5 Hz).

Example 10

5-{[4-Amino-1-(2',4'-dichloro-2,5-difluorobiphenyl-4-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1270] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.53-1.56 (4H, m), 1.81-1.87 (2H, m), 2.46 (2H, t, J = 7.6 Hz), 2.91 (2H, t, J = 7.6 Hz), 3.18-3.26 (4H, m), 3.73 (2H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.98-7.04 (2H, m), 7.19 (1H, dd, J = 13.0 Hz, 7.0 Hz), 7.44 (1H, d, J = 8.3 Hz), 7.52 (1H, dd, J = 8.3 Hz, 2.1 Hz), 7.76 (1H, d, J = 2.1 Hz), 10.02 (1H, s).

Example 11

5-{[4-amino-1-(4'-chloro-2,2',5-trifluorobiphenyl-4-yl)piperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1271] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.56-1.58 (2H, m), 1.82-1.88 (2H, m), 2.46 (2H, t, J = 7.6 Hz), 2.91 (2H, t, J = 7.6 Hz), 3.22-3.27 (4H, m), 3.76 (2H, s), 6.59 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.00-7.04 (2H, m), 7.27 (1H, dd, J = 13.1 Hz, 7.0 Hz), 7.40 (1H, dd, J = 8.3 Hz, 2.0 Hz), 7.49 (1H, t, J = 8.2 Hz), 7.57 (1H, dd, J = 10.0 Hz, 2.0 Hz), 10.02 (1H, s).

Example 12

5-{[4-Amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one

[1272] Synthesized analogous to Example 9.
^{1}HNMR (DMSO-d6) δ ppm: 1.78-1.87 (2H, m), 1.91-1.96 (2H, m), 3.08-3.11 (2H, m), 3.19-3.23 (2H, m), 4.07 (2H, s), 6.53 (1H, d, J = 9.8 Hz), 6.73 (1H, dd, J = 9.0 Hz, 3.3 Hz), 7.10 (1H, t, J = 9.1 Hz), 7.19 (1H, dd, J = 8.6 Hz, 2.0 Hz), 7.31-7.38 (2H, m), 8.36 (1H, d, J = 9.8 Hz).

Example 13

5-{[4-Amino-1-(2,4-dichlorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroq uinolin-2(1H)-one

[1273] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.54-1.56 (4H, m), 1.79-1.84 (2H, m), 2.48 (2H, t, J = 7.6 Hz), 2.93 (2H, J = 7.6 Hz), 3.00-3.03 (2H, m), 3.07-3.11 (2H, m), 3.77 (2H, s), 6.69 (1H, d, J = 9.0 Hz), 7.20 (1H, d, J = 8.7 Hz), 7.24 (1H, d, J = 8.9 Hz), 7.35 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.52 (1H, d, J = 2.5 Hz), 9.36 (1H, s).

Example 14

5-{[4-Amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihy droquinolin-2(1H)-one

[1274] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.52-1.55 (4H, m), 1.79-1.84 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.91 (2H, t, J = 7.6 Hz), 3.08-3.15 (4H, m), 3.75 (2H, s), 6.68 (1H, d, J = 9.0 Hz), 7.09 (1H, t, J = 9.1 Hz), 7.17 (1H, dd, J = 8.7 Hz, 2.2 Hz), 7.24 (1H, d, J = 8.9 Hz), 7.30 (1H, dd, J = 12.5 Hz, 2.4 Hz), 9.36 (1H, s).

Example 15

5-{[4-Amino-1-(4-chloro-2,6-difluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one

[1275] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.48-1.53 (4H, m), 1.73-1.78 (2H, m), 2.48 (2H, t, J = 7.3 Hz), 2.91-2.97 (4H, m), 3.40-3.45 (2H, m), 3.74 (2H, s), 6.68 (1H, d, J = 9.0 Hz), 7.23-7.28 (3H, m), 9.36 (1H, s).

Example 16

5-{[4-Amino-1-(2,4-dichlorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one

[1276] Synthesized analogous to Example 9.
^{1}HNMR (DMSO-d6) δ ppm: 1.62-1.65 (2H, m), 1.79-1.85 (2H, m), 3.02-3.14 (4H, m), 3.90 (2H, s), 6.55 (1H, d, J = 9.8 Hz), 6.80 (1H, d, J = 8.9 Hz), 7.22 (1H, d, J = 8.8 Hz), 7.36 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.53 (1H, d, J = 2.5 Hz), 7.58 (1H, d, J = 8.7 Hz), 8.28 (1H, d, J = 9.8 Hz).

Example 17

5-{[4-Amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one

[1277] Synthesized analogous to Example 9.
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.62 (2H, m), 1.79-1.85 (2H, m), 3.10-3.17 (4H, m), 3.88 (2H, s), 6.54 (1H, d, J = 9.7 Hz), 6.79 (1H, d, J = 8.8 Hz), 7.10 (1H, t, J = 9.1 Hz), 7.18 (1H, dd, J = 8.7 Hz, 2.2 Hz), 7.31 (1H, dd, J = 12.5 Hz, 2.4 Hz), 7.58 (1H, d, J = 8.7 Hz), 8.25 (1H, d, J = 9.8 Hz).

Example 18

5-{[4-Amino-1-(3,5-difluoropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one

[1278] Synthesized analogous to Example 1.
(Ethanol) m.p. 160.9-163.1 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.43-1.50 (2H, m), 1.57 (2H, brs), 1.71-1.82 (2H, m), 2.43 (2H, t, J = 7.5 Hz), 2.84 (2H, t, J = 7.5 Hz), 3.27-3.37 (2H, m), 3.53-3.61 (2H, m), 3.69 (2H, s), 6.54 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.98 (1H, t, J = 9.8 Hz), 7.71-7.78 (1H, m), 8.08 (1H, d, J = 2.5 Hz), 10.01 (1H, s).

Example 19

5-{[4-Amino-1-(5-fluoro-3-methylpyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1279] Synthesized analogous to Example 1.
^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (2H, brs), 1.68-1.72 (2H, m), 1.90-1.96 (2H, m), 2.30 (3H, s), 2.65 (2H, t, J = 7.7 Hz), 3.03 (2H, t, J = 7.7 Hz), 3.10-3.19 (4H, m), 3.82 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.19-7.21 (1H, m), 7.65 (1H, brs), 8.01 (1H, d, J = 2.9 Hz).

Example 20

5-{[4-Amino-1-(2,4-dichlorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroqu inolin-2(1H)-one

[1280] Synthesized analogous to Example 1.
^{1}HNMR ($CDCl_3$) δ ppm: 1.34 (2H, brs), 1.68-1.70 (2H, m), 1.94-1.99 (2H, m), 2.65 (2H, t, J = 7.7 Hz), 3.02-3.15 (6H, m), 3.78 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.02 (1H, d, J = 8.7 Hz), 7.19 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.37 (1H, d, J = 2.4 Hz), 7.55 (1H, brs).

Example 21

5-{[4-Amino-1-(2,5-dichlorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroqu inolin-2(1H)-one

[1281] Synthesized analogous to Example 1.
^{1}HNMR ($CDCl_3$) δ ppm: 1.68-1.71 (2H, m), 1.94-2.00 (2H, m), 2.67 (2H, dd, J = 7.1 Hz, 8.3 Hz), 3.03 (2H, t, J = 7.7 Hz), 3.08-3.19 (4H, m), 3.78 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.91 (1H, d, J = 9.6 Hz), 6.95 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.07 (1H, d, J = 2.4 Hz), 7.28 (1H, d, J = 8.5 Hz), 7.61 (1H, brs).

Example 22

5-({4-Amino-1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}methoxy)-8-fluoro-3,4-d ihydroquinolin-2(1H)-one

[1282] Synthesized analogous to Example 1.
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.69 (2H, m), 1.89-1.95 (2H, m), 2.64 (2H, t, J = 7.7 Hz), 3.01 (2H, t, J = 7.7 Hz), 3.19-3.24 (2H, m), 3.39-3.43 (2H, m), 3.76 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.89-6.95 (3H, m), 7.11 (2H, d, J = 9.1 Hz), 7.55 (1H, brs).

Example 23

5-{[4-Amino-1-(2,4-dichloro-5-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-d ihydroquinolin-2(1H)-one

[1283] Synthesized analogous to Example 1.
^{1}HNMR (DMSO-d6) δ ppm: 1.54-1.56 (4H, m), 1.79-1.85 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.92 (2H, t, J = 7.6 Hz), 3.04-3.13 (4H, m), 3.74 (2H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.24 (1H, d, J = 11.3 Hz), 7.70 (1H, d, J = 7.9 Hz), 10.02 (1H, s).

Example 24

5-({4-Amino-1-[5-fluoro-2-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1284] Synthesized analogous to Example 1.
^{1}HNMR (DMSO-d6) δ ppm: 1.51-1.54 (2H, m), 1.63 (2H, brs), 1.77-1.83 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.81-2.83 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 3.12 (2H, t, J = 10.0 Hz), 3.75 (2H, s), 6.60 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.13 (1H, dt, J = 2.4 Hz, 8.3 Hz), 7.44 (1H, dd, J = 10.8 Hz, 2.3 Hz), 7.72 (1H, dd, J = 8.8 Hz, 6.4 Hz), 10.02 (1H, s).

Example 25

5-{[4-Amino-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1285] Synthesized analogous to Example 1.
^{1}HNMR (DMSO-d6) δ ppm: 1.48-1.50 (4H, m), 1.73-1.79 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.87-2.93 (4H, m), 3.38-3.43 (2H, m), 3.71 (2H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.11 (2H, t, J = 9.4 Hz), 10.01 (1H, s).

Example 26

5-{[4-Amino-1-(2,5-dichloro-4-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-d ihydroquinolin-2(1H)-one

[1286] To a solution of 5-{[1-(2,5-dichloro-4-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydro-quinolin-2(1H)-one (144 mg) in acetic acid (4 mL) was added 2 N hydrochloric acid (1.5 mL), and the reaction mixture was stirred at room temperature for 3 h. The solvent was distilled off, aqueous sodium hydroxide was added to the residue, and the solution was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (basic silica gel: dichloromethane -> dichloromethane/ethyl acetate), and the obtained product was recrystallized from dichloromethane/ethanol. The crystal was collected on a filter, and air-dried (60 °C) to provide the title compound (60 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.53-1.56 (4H, m), 1.79-1.84 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.92 (2H, t, J = 7.6 Hz), 2.97-3.11 (4H, m), 3.74 (2H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.36 (1H, d, J = 7.4 Hz), 7.65 (1H, d, J = 9.1 Hz), 10.01 (1H, s).

Example 27

5-{[4-Amino-1-(4-chloro-2,5-difluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-d ihydroquinolin-2(1H)-one

[1287] Synthesized analogous to Example 26.
^{1}HNMR (DMSO-d6) δ ppm: 1.50-1.55 (4H, m), 1.78-1.84 (2H, m), 2.46 (2H, t, J = 7.6 Hz), 2.90 (2H, t, J = 7.6 Hz), 3.15-3.16 (4H, m), 3.71 (2H, s), 6.56 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.11 (1H, dd, J = 11.4 Hz, 7.9 Hz), 7.48 (1H, dd, J = 12.2 Hz, 7.1 Hz), 10.01 (1H, s).

Example 28

5-{[4-Amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one

[1288] Synthesized analogous to Example 26.
^{1}HNMR (DMSO-d6) δ ppm: 1.51-1.54 (4H, m), 1.79-1.84 (2H, m), 2.46 (2H, t, J = 7.6 Hz), 2.90 (2H, t, J = 7.6 Hz), 3.08-3.14 (4H, m), 3.71 (2H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.09 (1H, t, J = 9.1 Hz), 7.17 (1H, dd, J = 8.8 Hz, 2.2 Hz), 7.30 (1H, dd, J = 12.5 Hz, 2.4 Hz), 10.01 (1H, s).

Example 29

5-{[4-Amino-1-(2-chloro-4-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one

[1289] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.54-1.56 (4H, m), 1.79-1.85 (2H, m), 2.47 (2H, t, J = 7.6 Hz), 2.92-2.97 (4H, m), 3.05-3.08 (2H, m), 3.74 (2H, s), 6.59 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.17 (1H, dt, J = 2.9 Hz, 8.5 Hz), 7.24 (1H, dd, J = 9.0 Hz, 5.7 Hz), 7.38 (1H, dd, J = 8.6 Hz, 3.0 Hz), 10.02 (1H, s).

Example 30

5-{[4-Amino-1-(2,4-difluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroqu inolin-2(1H)-one

[1290] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.52-1.54 (4H, m), 1.79-1.85 (2H, m), 2.46 (2H, t, J = 7.7 Hz), 2.91 (2H, t, J = 7.6 Hz), 3.01-3.11 (4H, m), 3.72 (2H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.96-7.03 (2H, m), 7.09-7.19 (2H, m), 10.01 (1H, s).

Example 31

5-{[4-Amino-1-(2-fluoro-4-methylphenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one

[1291] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.52-1.53 (4H, m), 1.79-1.84 (2H, m), 2.23 (3H, s), 2.46 (2H, t, J = 7.7 Hz), 2.91 (2H, t, J = 7.6 Hz), 3.02-3.09 (4H, m), 3.71 (2H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.89-7.03 (4H, m), 10.01 (1H, s).

Example 32

5-({4-Amino-1-[4-chloro-2-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1292] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.51-1.59 (4H, m), 1.76-1.82 (2H, m), 2.47 (2H, t, J = 7.7 Hz), 2.75-2.77 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 3.10-3.15 (2H, m), 3.74 (2H, s), 6.59 (1H, dd, J = 9.0 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.64 (1H, d, J = 8.6 Hz), 7.68 (1H, d, J = 2.4 Hz), 7.72 (1H, dd, J = 8.6 Hz, 2.4 Hz), 10.02 (1H, s).

Example 33

5-{[1-(3,5-Dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1293] A solution of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one (0.25 g), 2,3,5-trichloropyridine (0.186 g) and potassium carbonate (0.176 g) in N-methyl-2-pyrrolidone (NMP) (3 mL) was stirred at

100 °C for 12 h. To a solution were added ammonium chloride aqueous solution and diethyl ether, and the insoluble precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (dichloromethane -> dichloromethane/methanol) and recrystallized from ethanol/water. The precipitate was collected on a filter, and air-dried (60 °C) to provide the title compound (0.29 g).
m.p. 176-178 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.97 (4H, m), 2.05 (1H, s), 2.62-2.69 (2H, m), 3.02 (2H, t, J = 8.0 Hz), 3.24-3.35 (2H, m), 3.61-3.68 (2H, m), 3.86 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.52 (1H, brs), 7.60 (1H, d, J = 2.3 Hz), 8.13 (1H, d, J = 2.3 Hz).

Example 34

5-Fluoro-2-(4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydr oxypiperidin-1-yl)pyridine-3-carbonitrile

[1294] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83-1.93 (4H, m), 2.07 (1H, s), 2.65 (2H, t, J = 7.7 Hz), 3.01 (2H, t, J = 7.7 Hz), 3.41-3.3.52 (2H, m), 3.85 (2H, s), 4.00-4.08 (2H, m), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.50 (1H, brs), 7.54 (1H, dd, J = 7.3 Hz, 3.1 Hz), 8.25 (1H, d, J = 3.1 Hz).

Example 35

5-{[1-(2,5-Difluoropyridin-3-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1295] A solution of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one (0.2 g), 2,3,5-trifluoropyridine (0.078 mL) and potassium carbonate (0.141 g) in N-methyl-2-pyrrolidone (NMP) (3 mL) was stirred at room temperature for 12 h, then at 60 °C for 8 h. To a solution was added ammonium chloride aqueous solution, and insoluble precipitate was collected on a filter. The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate), and further purified by thin layer chromatography (dichloromethane/ethyl acetate). The product obtained from lower polarity fractions was washed with diethyl ether to provide the title compound (60 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.98 (4H, m), 2.05 (1H, s), 2.64-2.69 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.12-3.21 (2H, m), 3.35-3.42 (2H, m), 3.86 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.02-7.08 (1H, m), 7.52-7.58 (2H, m).

Example 36

5-{[1-(3,5-Difluoropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1296] The product obtained from higher polarity fractions of Example 35 was washed with diethyl ether to provide the title compound (68 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.93 (4H, m), 2.04 (1H, s), 2.62-2.69 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.30-3.39 (2H, m), 3.71-3.79 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.09-7.15 (1H, m), 7.52 (1H, s), 7.94 (1H, d, J = 2.5 Hz).

Example 37

5-Fluoro-2-(4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydr oxypiperidin-1-yl)benzonitrile

[1297] Synthesized analogous to Example 33.
(Ethanol/diethyl ether) m.p. 206.0-206.9 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.76 (2H, m), 1.83-1.92 (2H, m), 2.46 (2H, t, J = 7.5 Hz), 2.93 (2H, t, J = 7.5 Hz), 3.08-3.17 (2H, m), 3.18-3.25 (2H, m), 3.81 (2H, s), 4.76 (1H, s), 6.59 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.99 (1H, t, J = 9.8 Hz), 7.24 (1H, dd, J = 9.3 Hz, 4.8 Hz), 7.47 (1H, dt, J = 3.0 Hz, 8.8 Hz), 7.69 (1H, dd, J = 8.5 Hz, 3.0 Hz), 10.02 (1H, s).

Example 38

8-Fluoro-5-{[4-hydroxy-1-(quinolin-2-yl)piperidin-4-yl]methoxy}-3,4-dihydroquinol in-2(1H)-one

[1298] Synthesized analogous to Example 33.

(Ethanol/ethyl acetate) m.p. 198-199 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.90 (4H, m), 2.09 (1H, s), 2.60-2.65 (2H, m), 2.98 (2H, t, J = 7.7 Hz), 3.47-3.55 (2H, m), 3.82 (2H, s), 4.33-4.41 (2H, m), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.04 (1H, d, J = 9.2 Hz), 7.20-7.25 (1H, m), 7.50-7.56 (2H, m), 7.60 (1H, dd, J = 8.0 Hz, 1.2 Hz), 7.69 (1H, d, J = 8.1 Hz), 7.89 (1H, d, J = 9.1 Hz).

Example 39

8-Fluoro-5-{[4-hydroxy-1-(isoquinolin-1-yl)piperidin-4-yl]methoxy}-3,4-dihydroqui nolin-2(1H)-one

[1299] Synthesized analogous to Example 33.
(Ethanol/ethyl acetate) m.p. 198-199 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-1.99 (2H, m), 2.05-2.14 (3H, m), 2.64-2.69 (2H, m), 3.05 (2H, t, J = 7.7 Hz), 3.44-3.51 (2H, m), 3.64-3.71 (2H, m), 3.93 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.94 (1H, t, J = 9.4 Hz), 7.23-7.27 (1H, overlapping with solvent signal), 7.49-7.54 (1H, m), 7.55 (1H, brs), 7.59-7.64 (1H, m), 7.76 (1H, d, J = 8.1 Hz), 8.08 (1H, d, J = 8.5 Hz), 8.15 (1H, d, J = 5.8 Hz).

Example 40

1-Amino-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1300] Under argon atmosphere, to a suspension of 5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one (0.5 g) in N,N-dimethylformamide (5 mL) was added sodium hydride (55 % in oil) (0.050 g), and the mixture was stirred at room temperature for 15 min. To the mixture was added 2-[(aminooxy)sulfonyl]-1,3,5-trimethylbenzene (0.293 g) at 0 °C, and the reaction mixture was stirred at the same temperature for 1 h. To the reaction solution was added water, the precipitate was collected on a filter and purified by silica gel column chromatography (dichloromethane/ethyl acetate -> dichloromethane/methanol), and recrystallized from ethanol/ethyl acetate. The precipitate was collected on a filter, and air-dried (60 °C) to provide the title compound (0.3 g).
(Ethyl acetate/ethanol) m.p. 187-189 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.96 (4H, m), 2.02 (1H, s), 2.66-2.71 (2H, m), 2.91-2.97 (2H, m), 3.26-3.34 (2H, m), 3.61-3.68 (2H, m), 3.86 (2H, s), 5.00 (2H, d, J = 2.3 Hz), 6.61 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.98 (1H, dd, J = 12.1 Hz, 9.1 Hz), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 41

5-{[1-(2,5-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1301] To a microwave reaction tube were added 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one (384 mg), 1-bromo-2,5-dichlorobenzene (295 mg), sodium tert-butoxide (151 mg), tris(dibenzylideneacetone)dipalladium (0) (11.96 mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (24.39 mg) and toluene (3 mL) and the tube was sealed. Then the tube was irradiated with microwave at 130 °C for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallized form methanol/ethyl acetate to provide the title compound (7.5 mg).
(Ethyl acetate/methanol) m.p. 191.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.90 (2H, m), 1.93-1.99 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.07-3.12 (2H, m), 3.22-3.24 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.95 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.07 (1H, d, J = 2.5 Hz), 7.28 (1H, d, J = 8.5 Hz), 7.54 (1H, brs).

Example 42

5-{[1-(2,4-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1302] Under argon atmosphere, a solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (355 mg), 6-(2,4-dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane (442 mg) and tripotassium phosphate (72.7 mg) in N,N-dimethylformamide:2-propanol (1:1) (3.6 mL) was stirred ad 70 °C for 22 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was recrystallized form ethyl acetate, and the precipitate was collected on a filter and dried to provide the title compound (427 mg).

(Ethyl acetate) m.p. 209.1 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.71 (2H, m), 1.84-1.89 (2H, m), 2.47 (2H, t, J = 7.5 Hz), 2.93 (2H, t, J = 7.5 Hz), 2.99-3.08 (4H, m), 3.80 (2H, s), 4.74 (1H, brs), 6.60 (1H, dd, J = 9.0 Hz, 3.5 Hz), 7.01 (1H, t, J = 9.0 Hz), 7.21 (1H, d, J = 8.5 Hz), 7.35 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.52 (1H, d, J = 2.5 Hz), 10.01 (1H, brs).

Example 43

5-{[1-(2-Chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquin olin-2(1H)-one

[1303] Synthesized analogous to Example 6.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.90 (2H, m), 1.95-2.01 (2H, m), 2.05 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.22-3.25 (2H, m), 3.88 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.98 (1H, t, J = 8.0 Hz), 7.11 (1H, d, J = 8.0 Hz), 7.23 (1H, t, J = 8.0 Hz), 7.37 (1H, d, J = 8.0 Hz), 7.56 (1H, brs).

Example 44

5-{[1-(2,5-Dichloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1304] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 207.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.92-1.98 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.09 (2H, m), 3.13-3.15 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.12 (1H, d, J = 7.5 Hz), 7.21 (1H, d, J = 9.0 Hz), 7.54 (1H, brs).

Example 45

5-{[1-(2-Chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1305] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 208 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 2.04 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.07-3.09 (2H, m), 3.13-3.15 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.91-6.97 (2H, m), 7.07 (1H, dd, J = 9.0 Hz, 5.5 Hz), 7.14 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.56 (1H, brs).

Example 46

8-Fluoro-5-[(4-hydroxy-1-phenylpiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H) -one

[1306] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 177.0-177.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.94 (4H, m), 2.05 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.19-3.24 (2H, m), 3.49-3.53 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.85-6.89 (1H, m), 6.92 (1H, t, J = 9.0 Hz), 6.98-6.99 (2H, m), 7.25-7.29 (2H, m), 7.58 (1H, brs).

Example 47

8-Fluoro-5-({4-hydroxy-1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}methoxy)-3,4 -dihydroquinolin-2(1H)-one

[1307] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 200.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.93 (4H, m), 2.06 (1H, brs), 2.65 (2H, t, J = 8.0 Hz), 3.01 (2H, t, J = 8.0 Hz), 3.19-3.24 (2H, m), 3.46-3.49 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.92 (1H, dd, J = 9.0 Hz, 1.0 Hz), 6.94 (2H, d, J = 9.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.60 (1H, brs).

Example 48

8-Fluoro-5-({4-hydroxy-1-[4-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-3,4-d ihydroquinolin-2(1H)-one

[1308] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 216.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.87 (4H, m), 2.09 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 3.29-3.35 (2H, m), 3.63-3.66 (2H, m), 3.83 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.92 (1H, dd, J = 9.0 Hz, 1.0 Hz), 6.97 (2H, d, J = 9.0 Hz), 7.48 (2H, d, J = 9.0 Hz), 7.56 (1H, brs).

Example 49

5-{[1-(4-Chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquin olin-2(1H)-one

[1309] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.92 (4H, m), 2.05 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.17-3.22 (2H, m), 3.45-3.47 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.89 (2H, d, J = 9.0 Hz), 6.92 (1H, dd, J = 9.0 Hz, 1.0 Hz), 7.21 (2H, d, J = 9.0 Hz), 7.57 (1H, brs).

Example 50

5-{[1-(3-Chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquin olin-2(1H)-one

[1310] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 169-170 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.83-1.91 (4H, m), 2.05 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 3.21-3.27 (2H, m), 3.50-3.53 (2H, m), 3.84 (2H, s), 6.47 (1H, dd,J = 9.0 Hz, 4.0 Hz), 6.79-6.84 (2H, m), 6.90-6.93 (2H, m), 7.17 (1H, t, J = 8.5 Hz), 7.56 (1H, brs).

Example 51

8-Fluoro-5-{[4-hydroxy-1-(pyridin-3-yl)piperidin-4-yl]methoxy}-3,4-dihydroquinoli n-2(1H)-one

[1311] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 178.2-178.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.91 (4H, m), 2.11 (1H, brs), 2.65 (2H, t, J = 8.0 Hz), 3.01 (2H, t, J = 8.0 Hz), 3.24-3.29 (2H, m), 3.52-3.56 (2H, m), 3.85 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.16-7.18 (1H, m), 7.23-7.25 (1H, m), 7.56 (1H, brs), 8.09-8.10 (1H, m), 8.36-8.37 (1H, m).

Example 52

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1312] Synthesized analogous to Example 42.
(Methanol/dichloromethane) m.p. 190.6-190.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.92-1.98 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.23-3.26 (2H, m), 3.85 (2H, s), 6.48 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.91-6.95 (2H, m), 7.05-7.07 (2H, m), 7.56 (1H, brs).

Example 53

5-{[1-(2,4-Dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1313] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 198.7-198.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.90 (2H, m), 1.92-1.98 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.09 (2H, m), 3.20-3.22 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.89 (1H, d, J = 10.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.40 (1H, d, J = 7.5 Hz), 7.52 (1H, brs).

Example 54

5-{[1-(2,3-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1314] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 228.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.90 (2H, m), 1.94-2.00 (2H, m), 2.04 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.20-3.23 (2H, m), 3.88 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 7.01-7.03 (1H, m), 7.16-7.17 (2H, m), 7.53 (1H, brs).

Example 55

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1315] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 225.5-225.6 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.63-1.65 (2H, m), 1.78-1.81 (2H, m), 2.47 (2H, t, J = 7.5 Hz), 2.92 (2H, t, J = 7.5 Hz), 2.96-2.99 (2H, m), 3.35-3.40 (2H, m), 3.77 (2H, s), 4.81 (1H, brs), 6.59 (1H, dd, J = 9.0 Hz, 4.0 Hz), 7.02 (1H, dd, J = 9.0 Hz, 1.0 Hz), 7.23-7.29 (2H, m), 10.03 (1H, brs).

Example 56

5-({1-[4-Chloro-2-(trifluoromethyl)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1316] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 211.3-211.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.85 (2H, m), 1.88-1.94 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.89-2.91 (2H, m), 3.02 (2H, t, J = 7.5 Hz), 3.11-3.14 (2H, m), 3.86 (2H, s), 6.49 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.37 (1H, d, J = 8.5 Hz), 7.49 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.56 (1H, brs), 7.61 (1H, d, J = 2.5 Hz).

Example 57

5-{[1-(3,4-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1317] Synthesized analogous to Example 42.
(Acetic acid-dimethyl sulfoxide) m.p. 230.9-231.2 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.62 (2H, m), 1.77-1.81 (2H, m), 2.43 (2H, t, J = 7.5 Hz), 2.82 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.47-3.68 (2H, m), 3.75 (2H, s), 4.89 (1H, brs), 6.57 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.96 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.01 (1H, dd, J = 9.0 Hz, 1.0 Hz), 7.14 (1H, d, J = 2.5 Hz), 7.38 (1H, d, J = 9.0 Hz), 10.02 (1H, brs).

Example 58

8-Fluoro-5-{[4-hydroxy-1-(thiophen-3-yl)piperidin-4-yl]methoxy}-3,4-dihydroquino lin-2(1H)-one

[1318] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 200.4-200.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.87 (2H, m), 1.90-1.95 (2H, m), 2.03 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.12-3.17 (2H, m), 3.37-3.40 (2H, m), 3.84 (2H, s), 6.25 (1H, dd, J = 3.0 Hz, 1.5 Hz), 6.47 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.90 (1H, dd, 5.0 Hz, 1.5 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.24 (1H, dd, J = 5.0 Hz, 3.0 Hz), 7.57 (1H, brs).

Example 59

5-{[1-(4-Chloro-2-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1319] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 214-215 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.94 (4H, m), 2.02 (1H, brs), 2.28 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 2.90-2.93 (2H, m), 3.03 (2H, t, J = 7.5 Hz), 3.01-3.07 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.00 (1H,

d, J = 8.5 Hz), 7.13 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.16 (1H, d, J = 2.5 Hz), 7.53 (1H, brs).

Example 60

8-Fluoro-5-({4-hydroxy-1-[2-(trifluoromethoxy)phenyl]piperidin-4-yl}methoxy)-3,4 -dihydroquinolin-2(1H)-one

[1320] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 168 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.88 (2H, m), 1.90-1.96 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.10-3.15 (2H, m), 3.23-3.25 (2H, m), 3.86 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.99 (1H, dt, J = 1.5 Hz, 8.0 Hz), 7.08 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.19-7.24 (2H, m), 7.55 (1H, brs).

Example 61

5-{[1-(2-Chloro-6-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1321] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 212-213 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.84 (2H, m), 1.90-1.96 (2H, m), 2.06 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.09 (2H, m), 3.47-3.52 (2H, m), 3.88 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.95-6.97 (2H, m), 7.16-7.18 (1H, m), 7.53 (1H, brs).

Example 62

5-{[1-(4-Chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1322] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 185.1-185.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.90-1.96 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.26-3.28 (2H, m), 3.85 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.79 (1H, dd, J = 10.5 Hz, 7.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.08 (1H, dd, J = 11.5 Hz, 7.0 Hz), 7.54 (1H, brs).

Example 63

5-{[1-(2-Bromo-4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1323] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 204.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 2.04 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.15-3.17 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.03 (1H, d, J = 8.5 Hz), 7.25 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.55 (1H, brs), 7.57 (1H, d, J = 2.5 Hz).

Example 64

5-{[1-(4-Chloro-3-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1324] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 222.6-222.7 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.63 (2H, m), 1.79-1.85 (2H, m), 2.43 (2H, t, J = 7.5 Hz), 2.85 (2H, t, J = 7.5 Hz), 3.07-3.12 (2H, m), 3.51-3.53 (2H, m), 3.75 (2H, s), 3.82 (3H, s), 4.74 (1H, brs), 6.52 (1H, dd, J = 8.5 Hz, 2.5 Hz), 6.57 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.66 (1H, d, J = 2.5 Hz), 7.00 (1H, t, J = 9.0 Hz), 7.16 (1H, d, J = 8.5 Hz), 10.01 (1H, brs).

Example 65

5-{[1-(2,6-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1325] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 203.6-203.8 °C^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.83 (2H, m), 1.93-1.99 (2H, m), 2.06 (1H,

brs), 2.66 (2H, t, J = 7.5 Hz), 2.97-3.02 (2H, m), 3.04 (2H, t, J = 7.5 Hz), 3.63-3.68 (2H, m), 3.89 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.97 (1H, t, J = 8.0 Hz), 7.24 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 8.0 Hz), 7.53 (1H, brs).

Example 66

5-{[1-(3-Ethoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroqui nolin-2(1H)-one

[1326] Synthesized analogous to Example 42.
(ethyl acetate/hexane) m.p. 128.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 1.82-1.84 (2H, m), 1.86-1.92 (2H, m), 2.01 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.19-3.24 (2H, m), 3.50-3.52 (2H, m), 3.83 (2H, s), 4.02 (2H, q, J = 7.0 Hz), 6.41 (1H, dd, J = 8.0 Hz, 2.0 Hz), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.52 (1H, t, J = 2.0 Hz), 6.58 (1H, dd, J = 8.0 Hz, 2.0 Hz), 6.92 (1H, dd, J = 9.0 Hz, 1.0 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.51 (1H, brs).

Example 67

5-{[1-(4-Ethoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroqui nolin-2(1H)-one

[1327] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 198.8-199.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.85-1.88 (2H, m), 1.90-1.96 (2H, m), 2.02 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.14 (2H, m), 3.31-3.34 (2H, m), 3.85 (2H, s), 3.99 (2H, q, J = 7.0 Hz), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.84 (2H, d, J = 9.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 6.96 (2H, d, J = 9.0 Hz), 7.57 (1H, brs).

Example 68

8-Fluoro-5-{[4-hydroxy-1-(2,4,6-trichlorophenyl)piperidin-4-yl]methoxy}-3,4-dihyd roquinolin-2(1H)-one

[1328] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 239.4-239.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.83 (2H, m), 1.90-1.96 (2H, m), 2.06 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.93-2.96 (2H, m), 3.03 (2H, t, J = 7.5 Hz), 3.61-3.66 (2H, m), 3.87 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.26 (1H, s), 7.32 (1H, s), 7.56 (1H, brs).

Example 69

8-Fluoro-5-({4-hydroxy-1-[3-(propan-2-yl)phenyl]piperidin-4-yl}methoxy)-3,4-dihy droquinolin-2(1H)-one

[1329] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 131.1-131.3 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.25 (6H, d, J = 7.0 Hz), 1.85-1.87 (2H, m), 1.89-1.95 (2H, m), 2.01 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 2.86 (1H, sep, J = 7.0 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.18-3.23 (2H, m), 3.48-3.51 (2H, m), 3.85 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.75 (1H, dd, J = 8.0 Hz, 1.0 Hz), 6.81 (1H, dd, 8.0 Hz, 2.0 Hz), 6.86 (1H, dd, J = 2.0 Hz, 1.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 7.20 (1H, t, J = 8.0 Hz), 7.52 (1H, brs).

Example 70

8-Fluoro-5-({4-hydroxy-1-[4-(propan-2-yl)phenyl]piperidin-4-yl}methoxy)-3,4-dihy droquinolin-2(1H)-one

[1330] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 194.9-195.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 7.0 Hz), 1.84-1.87 (2H, m), 1.88-1.94 (2H, m), 2.00 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 2.85 (1H, sep, J = 7.0 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.14-3.20 (2H, m), 3.43-3.47 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 6.93 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.5 Hz), 7.52 (1H, brs).

Example 71

5-{[1-(3,5-Dichloropyridin-4-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1331] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 225.8-225.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.86 (2H, m), 1.91-1.97 (2H, m), 2.07 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.23-3.25 (2H, m), 3.67-3.72 (2H, m), 3.88 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.51 (1H, brs), 8.34 (2H, s).

Example 72

4-(4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiper idin-1-yl)benzonitrile

[1332] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 216 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.84 (2H, m), 1.86-1.88 (2H, m), 2.12 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 3.35-3.40 (2H, m), 3.69-3.72 (2H, m), 3.83 (2H, s), 6.46 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.90 (2H, d, J = 9.5 Hz), 6.92 (1H, t, J = 9.0 Hz), 7.50 (2H, d, J = 9.5 Hz), 7.57 (1H, brs).

Example 73

3-(4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiper idin-1-yl)benzonitrile

[1333] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 175-177 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.88 (4H, m), 2.07 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.25-3.30 (2H, m), 3.54-3.56 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.08-7.10 (1H, m), 7.15-7.17 (2H, m), 7.31-7.34 (1H, m), 7.55 (1H, brs).

Example 74

8-Fluoro-5-{[4-hydroxy-1-(4-phenoxyphenyl)piperidin-4-yl]methoxy}-3,4-dihydroq uinolin-2(1H)-one

[1334] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 186.9-187.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.96 (4H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.15-3.21 (2H, m), 3.41-3.44 (2H, m), 3.86 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.95-6.98 (6H, m), 7.04 (1H, t, J = 7.5 Hz), 7.28-7.31 (2H, m), 7.53 (1H, brs).

Example 75

5-({1-[2-Chloro-5-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1335] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 190.4-190.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.91 (2H, m), 1.94-2.00 (2H, m), 2.04 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.24-3.26 (2H, m), 3.88 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.85 (1H, dd, J = 8.5 Hz, 1.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 6.94 (1H, d, J = 1.0 Hz), 7.37 (1H, d, J = 8.5 Hz), 7.52 (1H, brs).

Example 76

8-Fluoro-5-({4-hydroxy-1-[2-(propan-2-yl)phenyl]piperidin-4-yl}methoxy)-3,4-dihy droquinolin-2(1H)-one

[1336] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 163.0-163.3 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 1.86-1.95 (4H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.86-2.89 (2H, m), 3.04 (2H, t, J = 7.5 Hz), 3.10-3.13 (2H, m), 3.48 (1H, sep, J = 7.0 Hz), 3.89 (2H, s), 6.50 (1H, dd, J = 9.0 Hz,

4.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 7.09-7.12 (1H, m), 7.15-7.19 (2H, m), 7.26-7.28 (1H, m), 7.51 (1H, brs).

Example 77

5-{[1-(2-Chloro-5-nitrophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one

[1337] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 204.8-205.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-1.94 (2H, m), 1.95-2.01 (2H, m), 2.06 (1H, brs), 2.67 (2H, t, J = 7.5 Hz), 3.04 (2H, t, J = 7.5 Hz), 3.17-3.23 (2H, m), 3.29-3.31 (2H, m), 3.89 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 7.52 (1H, d, J = 9.0 Hz), 7.53 (1H, brs), 7.84 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.95 (1H, d, J = 2.5 Hz).

Example 78

5-{[1-(2-Ethylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquino lin-2(1H)-one

[1338] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 178.6-179.3 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.25 (3H, t, J = 7.5 Hz), 1.86-1.95 (4H, m), 2.05 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.71 (2H, q, J = 7.5 Hz), 2.91-2.93 (2H, m), 3.04 (2H, t, J = 7.5 Hz), 3.07-3.12 (2H, m), 3.88 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.05-7.13 (1H, m), 7.13-7.18 (2H, m), 7.23-7.25 (1H, m), 7.61 (1H, brs).

Example 79

8-Fluoro-5-({4-hydroxy-1-[3-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-3,4-d ihydroquinolin-2(1H)-one

[1339] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 159.4-159.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.90 (4H, m), 2.06 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 3.25-3.31 (2H, m), 3.55-3.58 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 7.07 (1H, d, J = 8.0 Hz), 7.11 (1H, d, J = 8.0 Hz), 7.16 (1H, s), 7.35 (1H, t, J = 8.0 Hz), 7.57 (1H, brs).

Example 80

5-{[1-(4-Chloro-3-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1340] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 216.1-216.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.59-1.61 (2H, m), 1.77-1.83 (2H, m), 2.26 (3H, s), 2.42 (2H, t, J = 7.5 Hz), 2.83 (2H, t, J = 7.5 Hz), 3.04-3.09 (2H, m), 3.47-3.49 (2H, m), 3.74 (2H, s), 4.72 (1H, brs), 6.56 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.80 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.94 (1H, d, J = 2.5 Hz), 7.00 (1H, t, J = 9.0 Hz), 7.17 (1H, d, J = 9.0 Hz), 10.01 (1H, brs).

Example 81

Ethyl 2-chloro-5-(4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydro xypiperidin-1-yl)benzoate

[1341] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 148 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 1.86-1.88 (4H, m), 2.04 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.21-3.27 (2H, m), 3.50-3.52 (2H, m), 3.84 (2H, s), 4.40 (2H, q, J = 7.0 Hz), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 6.99 (1H, dd, J = 9.0 Hz, 3.0 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.32 (1H, d, J = 3.0 Hz), 7.53 (1H, brs).

Example 82

5-{[1-(2-Chloro-4-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1342] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.94-2.00 (2H, m), 2.03 (1H, brs), 2.28 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 3.03

(2H, t, J = 7.5 Hz), 3.04-3.09 (2H, m), 3.17-3.19 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.01 (1H, d, J = 8.5 Hz), 7.03 (1H, dd, J = 8.5 Hz, 1.5 Hz), 7.20 (1H, d, J = 1.5 Hz), 7.54 (1H, brs).

Example 83

8-Fluoro-5-{[4-hydroxy-1-(4-methylphenyl)piperidin-4-yl]methoxy}-3,4-dihydroqui nolin-2(1H)-one

[1343] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 181 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.87 (2H, m), 1.89-1.95 (2H, m), 2.00 (1H, brs), 2.28 (3H, s), 2.65 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.13-3.19 (2H, m), 3.42-3.45 (2H, m), 3.84 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.90 (1H, d, J = 8.5 Hz), 6.92 (2H, t, J = 9.0 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.51 (1H, brs).

Example 84

5-{[1-(4-Chloro-2-nitrophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinoli-2(1H)-one

[1344] Synthesized analogous to Example 42.
(Methanol/dichloromethane) m.p. 188-189 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.84-1.86 (2H, m), 1.91-1.97 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.12 (2H, m), 3.23-3.28 (2H, m), 3.86 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.15 (1H, d, J = 8.5 Hz), 7.45 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.51 (1H, brs), 7.80 (1H, d, J = 2.5 Hz).

Example 85

5-{[1-(4-Ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1345] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 196.0-196.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.04-3.10 (2H, m), 3.15-3.17 (2H, m), 3.85 (2H, s), 3.98 (2H, q, J = 7.0 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.61-6.67 (2H, m), 6.91-6.99 (2H, m), 7.52 (1H, brs).

Example 86

8-Fluoro-5-{[1-(2-fluoro-4-propoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-d ihydroquinolin-2(1H)-one

[1346] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 185.1-185.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.5 Hz), 1.75-1.82 (2H, m), 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.04-3.10 (2H, m), 3.15-3.17 (2H, m), 3.85 (2H, s), 3.85-3.88 (2H, m), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.62-6.67 (2H, m), 6.91-6.99 (2H, m), 7.52 (1H, brs).

Example 87

5-{[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1347] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 204.8-205.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.92-1.97 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.24-3.26 (2H, m), 3.85 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.87-6.95 (2H, m), 7.18-7.20 (2H, m), 7.57 (1H, brs).

Example 88

5-([1-[2-Chloro-4-(propan-2-yl)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1348] Synthesized analogous to Example 42.

(Ethyl acetate) m.p. 176.5-176.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 6.5 Hz), 1.86-1.89 (2H, m), 1.94-2.00 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.84 (1H, sep, J = 6.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.18-3.21 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.04 (1H, d, J = 8.5 Hz), 7.09 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.24 (1H, d, J = 2.0 Hz), 7.51 (1H, brs).

Example 89

5-{[1-(2,4-Dichloro-6-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1349] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 251.6-251.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.86 (3.2H, m), 1.94-2.00 (0.8H, m), 2.02 (0.6H, brs), 2.15 (0.4H, brs), 2.31 (1.8H, s), 2.35 (1.2H, s), 2.65 (2H, t, J = 7.5 Hz), 2.72-2.74 (1.2H, m), 3.03 (2H, t, J = 7.5 Hz), 3.07-3.10 (0.8H, m), 3.28-3.33 (0.8H, m), 3.75-3.80 (1.2H, m), 3.85 (1.2H, s), 3.93 (0.8H, s), 6.48-6.52 (1H, m), 6.91-6.95 (1H, m), 7.05 (0.4H, d, J = 2.5 Hz), 7.10 (0.6H, d, J = 2.5 Hz), 7.17 (0.6H, d, J = 2.5 Hz), 7.21 (0.4H, d, J = 2.5 Hz), 7.58 (1H, brs).

Example 90

5-{[1-(2-Chloro-4-propylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1350] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 197.5-197.6 °C
^{1}HNMR ($CDCl_3$) δ ppm: 0.93 (3H, t, J = 7.5 Hz), 1.59-1.64 (2H, m), 1.86-1.89 (2H, m), 1.94-2.00 (2H, m), 2.04 (1H, brs), 2.51 (2H, t, J = 7.5 Hz), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.18-3.20 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.01-7.05 (2H, m), 7.20 (1H, s), 7.57 (1H, brs).

Example 91

5-{[1-(2-Chloro-4-ethylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1351] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 167.8-168.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.5 Hz), 1.87-1.89 (2H, m), 1.94-2.00 (2H, m), 2.03 (1H, brs), 2.58 (2H, q, J = 7.5 Hz), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.18-3.20 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.03 (1H, d, J = 8.0 Hz), 7.06 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.22 (1H, d, J = 2.0 Hz), 7.54 (1H, brs).

Example 92

5-{[1-(4-Butoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1352] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 193.2-193.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.44-1.50 (2H, m), 1.72-1.77 (2H, m), 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.04-3.10 (2H, m), 3.15-3.17 (2H, m), 3.85 (2H, s), 3.90 (2H, t, J = 6.5 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.61-6.67 (2H, m), 6.91-6.98 (2H, m), 7.57 (1H, brs).

Example 93

8-Fluoro-5-({1-[2-fluoro-4-(propan-2-yloxy)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-3,4-dihydroquinolin-2(1H)-one

[1353] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 191.9-192.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.32 (6H, d, J = 6.0 Hz), 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.04-3.10 (2H, m), 3.15-3.18 (2H, m), 3.85 (2H, s), 4.44 (1H, sep, J = 6.0 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.60-6.66 (2H, m), 6.91-6.96 (2H, m), 7.54 (1H, brs).

Example 94

5-{[1-(2,4-Dichloro-6-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1354] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 238.8-239.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.84 (2H, m), 1.88-1.94 (2H, m), 2.06 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.01-3.04 (2H, m), 3.02 (2H, t, J = 7.5 Hz), 3.45-3.50 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.00 (1H, dd, J = 11.5 Hz, 2.0 Hz), 7.20 (1H, dd, J = 2.0 Hz, 0.5 Hz), 7.56 (1H, brs).

Example 95

5-{[1-(2-Chloro-4,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1355] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 239.3-239.6 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.84 (2H, m), 1.88-1.94 (2H, m), 2.05 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.97-3.01 (2H, m), 3.03 (2H, t, J = 7.5 Hz), 3.44-3.49 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.75 (1H, ddd, J = 11.5 Hz, 8.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.96 (1H, ddd, J = 8.5 Hz, 5.0 Hz, 3.0 Hz), 7.55 (1H, brs).

Example 96

5-({1-[2-Chloro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fl uoro-3,4-dihydroquinolin-2(1H)-one

[1356] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 181.8-181.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.90 (2H, m), 1.93-1.99 (2H, m), 2.05 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.19-3.21 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.03-7.13 (2H, m), 7.28 (1H, s), 7.58 (1H, brs).

Example 97

5-([1-[2,4-Dichloro-5-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy) -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1357] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 254.8-254.9 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.71 (2H, m), 1.84-1.90 (2H, m), 2.46 (2H, t, J = 7.5 Hz), 2.92 (2H, t, J = 7.5 Hz), 3.02-3.07 (2H, m), 3.12-3.15 (2H, m), 3.80 (2H, s), 4.76 (1H, brs), 6.59 (1H, dd, J = 9.5 Hz, 4.0 Hz), 7.01 (1H, t, J = 9.5 Hz), 7.26 (1H, s), 7.84 (1H, s), 10.02 (1H, brs).

Example 98

8-Fluoro-5-({1-[2-fluoro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}meth oxy)-3,4-dihydroquinolin-2(1H)-one

[1358] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 174.2-174.3 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.90 (2H, m), 1.92-1.98 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.11-3.16 (2H, m), 3.25-3.27 (2H, m), 3.86 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.91-7.02 (4H, m), 7.53 (1H, brs).

Example 99

8-Fluoro-5-{[1-(2-fluoro-4-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1359] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 201.3-201.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J =

7.5 Hz), 3.04-3.10 (2H, m), 3.15-3.18 (2H, m), 3.77 (3H, s), 3.85 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.62-6.68 (2H, m), 6.91-7.00 (2H, m), 7.53 (1H, brs).

Example 100

8-Fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydr oquinolin-2(1H)-one

[1360] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.85 (2H, m), 1.86-1.94 (2H, m), 2.07 (1H, brs), 2.66 (2H, t, J = 8.0 Hz), 2.99-3.06 (4H, m), 3.42-3.50 (2H, m), 3.85 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.59-6.67 (2H, m), 6.93 (1H, t, J = 9.4 Hz), 7.64 (1H, brs).

Example 101

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-di hydroquinolin-2(1H)-one

[1361] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 222.9-223.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.92-1.98 (2H, m), 2.00 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.24-3.26 (2H, m), 3.88 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 7.05-7.07 (2H, m), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 102

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4 -dihydroquinolin-2(1H)-one

[1362] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 181.0-181.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.83 (2H, m), 1.86-1.92 (2H, m), 1.99 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.07-3.09 (2H, m), 3.45-3.49 (2H, m), 3.87 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.85-6.91 (2H, m), 7.19 (1H, d, J = 9.0 Hz), 7.74 (1H, brs).

Example 103

5-({1-[4-(Benzyloxy)-2-fluorophenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-3 ,4-dihydroquinolin-2(1H)-one

[1363] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 193 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.15-3.17 (2H, m), 3.85 (2H, s), 5.01 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.69-6.75 (2H, m), 6.91-6.99 (2H, m), 7.31-7.43 (5H, m), 7.54 (1H, brs).

Example 104

8-Fluoro-5-({1-[2-fluoro-4-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}met hoxy)-3,4-dihydroquinolin-2(1H)-one

[1364] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 174 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.04-3.10 (2H, m), 3.15-3.18 (2H, m), 3.45 (3H, s), 3.72-3.74 (2H, m), 3.85 (2H, s), 4.06-4.08 (2H, m), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.65-6.71 (2H, m), 6.91-6.98 (2H, m), 7.56 (1H, brs).

Example 105

5-({1-[4-Chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}meth oxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1365] Synthesized analogous to Example 42.

(Ethyl acetate/hexane) m.p. 208 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.97 (4H, m), 2.04 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.12-3.17 (2H, m), 3.27-3.29 (2H, m), 3.86 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.91-6.95 (2H, m), 7.15 (1H, d, J = 11.5 Hz), 7.55 (1H, brs).

Example 106

5-{[1-(4-Ethoxy-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1366] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 174.1-174.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.43 (3H, t, J = 7.0 Hz), 1.86-1.88 (2H, m), 1.92-1.98 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.03-3.09 (2H, m), 3.14-3.19 (2H, m), 3.85 (2H, s), 4.05 (2H, q, J = 7.0 Hz), 6.48 (1H, dd, J = 9.5 Hz, 3.5 Hz), 6.73 (1H, dd, J = 13.0 Hz, 8.0 Hz), 6.82 (1H, dd, J = 13.0 Hz, 8.0 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.56 (1H, brs).

Example 107

5-{[1-(2-Bromo-5-ethoxy-4-nitrophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1367] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.36 (3H, t, J = 7.0 Hz), 1.71-1.73 (2H, m), 1.87-1.92 (2H, m), 2.47 (2H, t, J = 7.5 Hz), 2.93 (2H, t, J = 7.5 Hz), 3.14-3.18 (2H, m), 3.29-3.37 (2H, m), 3.82 (2H, s), 4.27 (2H, q, J = 7.0 Hz), 4.80 (1H, brs), 6.60 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.87 (1H, s), 7.01 (1H, t, J = 9.0 Hz), 8.14 (1H, s), 10.02 (1H, brs).

Example 108

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4 -dihydroquinolin-2(1H)-one

[1368] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.70 (2H, m), 1.79-1.87 (2H, m), 2.44-2.50 (2H, m), 2.88 (2H, t, J = 7.2 Hz), 2.98-3.22 (4H, m), 3.79 (2H, s), 4.77 (1H, s), 6.75 (1H, dd, J = 12.9 Hz, 6.3 Hz), 7.07-7.20 (2H, m), 7.32 (1H, dd, J = 12.6 Hz, 2.4 Hz), 10.31 (1H, s).

Example 109

5-({1-[4-(Ethoxymethyl)-2-fluorophenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1369] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 154.2-154.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.24 (3H, t, J = 7.0 Hz), 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.06 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.26-3.28 (2H, m), 3.53 (2H, q, J = 7.0 Hz), 3.85 (2H, s), 4.42 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.99-7.07 (3H, m), 7.63 (1H, brs).

Example 110

5-{[1-(2,6-Difluoro-4-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1370] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 195.7-196.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.83 (2H, m), 1.87-1.93 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.98-3.01 (2H, m), 3.03 (2H, t, J = 7.5 Hz), 3.41-3.45 (2H, m), 3.75 (3H, s), 3.85 (2H, s), 6.40-6.46 (2H, m), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.51 (1H, brs).

Example 111

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquin olin-2(1H)-one

[1371] Synthesized analogous to Example 42.
(Methanol/ethyl acetate) m.p. 231.6-232.9 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.75 (2H, m), 1.84-1.93 (2H, m), 1.41 (2H, t, J = 7.7 Hz), 2.87 (2H, t, J = 7.7 Hz), 3.00-3.70 (2H, m), 3.08-3.15 (2H, m), 3.75 (2H, s), 4.06 (1H, s), 6.41-6.46 (2H, m), 6.84-6.89 (1H, m), 6.91-6.99 (3H, m), 9.54 (1H, s).

Example 112

7-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}1-3,4-dihydroquin olin-2(1H)-one

[1372] Synthesized analogous to Example 42.
(Methanol/ethyl acetate) m.p. 207.8-208.7 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.67 (2H, m), 1.79-1.88 (2H, m), 2.40 (2H, t, J = 7.5 Hz), 2.77 (2H, t, J = 7.5 Hz), 2.98-3.05 (2H, m), 3.09-3.15 (2H, m), 3.73 (2H, s), 4.73 (1H, s), 6.47 (1H, d, J = 2.5 Hz), 6.50 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.04-7.12 (2H, m), 7.16 (1H, dd, J = 9.0, 2.0 Hz), 7.29 (1H, dd, J = 12.5 Hz, 2.5 Hz), 10.01 (1H, s).

Example 113

8-Fluoro-5-({1-[2-fluoro-4-(hydroxymethyl)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-3,4-dihydroquinolin-2(1H)-one

[1373] To a solution of 5-({1-[4-(ethoxymethyl)-2-fluorophenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (591 mg) in tetrahydrofuran (THF) (12 mL) was added 5 N hydrochloric acid (6 mL) and the reaction mixture was stirred at 70 °C for 16 h. Then, to the reaction solution were added water and ethyl acetate, the mixture was stirred, and the precipitate was collected on a filter. The obtained solid was recrystallized from ethyl acetate. The precipitate was collected on a filter and dried to provide the title compound (165 mg).
(Ethyl acetate) m.p. 202.4-202.6 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.68 (2H, m), 1.84-1.90 (2H, m), 2.46 (2H, t, J = 7.5 Hz), 2.92 (2H, t, J = 7.5 Hz), 2.99-3.03 (2H, m), 3.11-3.14 (2H, m), 3.78 (2H, s), 4.41 (2H, d, J = 5.5 Hz), 4.69 (1H, brs), 5.15 (1H, t, J = 5.5 Hz), 6.58 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.99-7.04 (4H, m), 10.02 (1H, brs).

Example 114

8-Chloro-5-{[1-(4-ethoxy-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1374] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 169.0-169.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.43 (3H, t, J = 7.0 Hz), 1.86-1.88 (2H, m), 1.92-1.99 (2H, m), 1.99 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.04-3.09 (2H, m), 3.16-3.18 (2H, m), 3.87 (2H, s), 4.05 (2H, q, J = 7.0 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.73 (1H,dd, J = 13.0 Hz, 8.0 Hz), 6.82 (1H, dd, J = 13.0 Hz, 8.0 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 115

8-Chloro-5-({1-[2-fluoro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}meth oxy)-3,4-dihydroquinolin-2(1H)-one

[1375] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 149.7-149.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.90 (2H, m), 1.93-1.98 (2H, m), 1.99 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.11-3.16 (2H, m), 3.25-3.28 (2H, m), 3.88 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.95-7.02 (3H, m), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 116

8-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquin olin-2(1H)-one

[1376] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.77 (2H, m), 1.77-1.85 (2H, m), 2.42-2.52 (2H, m), 2.86 (2H, t, J = 7.3 Hz), 3.00-3.09 (2H, m), 3.11-3.19 (2H, m), 3.80 (2H, s), 5.18 (1H, brs), 6.75-6.85 (2H, m), 6.85-6.91 (1H, m), 7.09 (1H, t, J = 9.3 Hz), 7.16-7.20 (1H, m), 7.28-7.35 (1H, m), 9.71 (1H, brs).

Example 117

8-Chloro-5-{[1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4 -dihydroquinolin-2(1H)-one

[1377] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 190.3-190.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.91-1.97 (2H, m), 1.99 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.26-3.29 (2H, m), 3.87 (2H, s), 6.54 (1H, d, J = 9.0 Hz), 6.79 (1H, dd, J = 11.0 Hz, 7.5 Hz), 7.08 (1H, dd, J = 12.0 Hz, 7.0 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 118

8-Chloro-5-{[1-(2,6-difluoro-4-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy]-3,4-dihydroquinolin-2(1H)-one

[1378] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 171.1-171.3 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.83 (2H, m), 1.87-1.93 (2H, m), 2.00 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 2.98-3.02 (2H, m), 3.02 (2H, t, J = 7.5 Hz), 3.41-3.45 (2H, m), 3.75 (3H, s), 3.88 (2H, s), 6.43 (2H, d, J = 11.0 Hz), 6.55 (1H, d, J = 9.0 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.74 (1H, brs).

Example 119

6-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquin olin-2(1H)-one

[1379] Synthesized analogous to Example 42.
(Methanol/ethyl acetate) m.p. 219.1-220.0 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.66 (2H, m), 1.81-1.89 (2H, m), 2.37-2.42 (2H, m), 2.82 (2H, t, J = 7.5 Hz), 2.98-3.05 (2H, m), 3.09-3.15 (2H, m), 3.74 (2H, s), 4.68 (1H, s), 6.72-6.78 (2H, m), 6.80-6.83 (1H, m), 7.07 (1H, t, J = 9.0 Hz), 7.15 (1H, dd, J = 9.0 Hz, 2.0 Hz), 7.29 (1H, dd, J = 12.5 Hz, 2.5 Hz), 9.92 (1H, s).

Example 120

5-{[1-(4-Ethoxy-2,3,5,6-tetrafluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1380] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 208.9-209.3 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 1.82-1.84 (2H, m), 1.86-1.92 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.12 (2H, m), 3.49-3.53 (2H, m), 3.85 (2H, s), 4.21 (2H, q, J = 7.0 Hz), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.54 (1H, brs).

Example 121

8-Chloro-5-{[1-(4-ethoxy-2,3,5,6-tetrafluorophenyl)-4-hydroxypiperidin-4-yl]metho xy}-3,4-dihydroquinolin-2(1H)-one

[1381] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 174.4-174.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 1.82-1.84 (2H, m), 1.87-1.93 (2H, m), 2.01 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.12 (2H, m), 3.49-3.53 (2H, m), 3.87 (2H, s), 4.21 (2H, q, J = 7.0 Hz), 6.55 (1H, d, J = 9.0 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 122

5-{[1-(4-Chloro-5-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1382] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 239.8-239.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 1.87-1.89 (2H, m), 1.92-1.98 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.25-3.27 (2H, m), 3.86 (2H, s), 4.07 (2H, q, J = 7.0 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.61 (1H, d, J = 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.06 (1H, d, J = 11.5 Hz), 7.54 (1H, brs).

Example 123

8-Fluoro-5-[(1-{2-fluoro-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-4-hydroxypiperidi n-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[1383] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 128.7-130.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.04-3.10 (2H, m), 3.15-3.17 (2H, m), 3.40 (3H, s), 3.57-3.59 (2H, m), 3.71-3.72 (2H, m), 3.83-3.85 (2H, m), 3.85 (2H, s), 4.08-4.10 (2H, m), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.64-6.70 (2H, m), 6.91-6.98 (2H, m), 7.53 (1H, brs).

Example 124

8-Chloro-5-{[1-(4-chloro-5-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methox y}-3,4-dihydroquinolin-2(1H)-one

[1384] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 228.1-229.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 1.99 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.25-3.27 (2H, m), 3.88 (2H, s), 4.07 (2H, q, J = 7.0 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.60 (1H, d, J = 8.0 Hz), 7.07 (1H, d, J = 11.5 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 125

5-{[1-(4-Chloro-2-fluoro-5-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1385] Synthesized analogous to Example 42.
(dichloromethane) m.p. 208.6-208.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.92-1.98 (2H, m), 2.01 (1H, brs), 2.31 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.23-3.25 (2H, m), 3.85 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.85 (1H, d, J = 9.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.04 (1H, d, J = 12.0 Hz), 7.55 (1H, brs).

Example 126

8-Chloro-5-{[1-(4-chloro-2-fluoro-5-methylphenyl)-4-hydroxypiperidin-4-yl]methox y}-3,4-dihydroquinolin-2(1H)-one

[1386] Synthesized analogous to Example 42.
(dichloromethane/methanol) m.p. 212.2-213.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.92-1.98 (2H, m), 1.98 (1H, brs), 2.31 (3H, s), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.23-3.25 (2H, m), 3.87 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.85 (1H, d, J = 9.0 Hz), 7.04 (1H, d, J = 12.0), 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 127

5-{[1-(4-Chloro-2-fluoro-6-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1387] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 258.8-259.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.88 (4H, m), 2.06 (1H, brs), 2.29 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 2.86-2.87 (2H, m), 3.03

(2H, t, J = 7.5 Hz), 3.36-3.47 (2H, m), 3.88 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.90 (1H, dd, J = 11.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.97 (1H, d, J = 2.5 Hz), 7.53 (1H, brs).

Example 128

5-{[1-(4-Ethoxy-2-fluoro-5-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1388] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 190.8-191.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.44 (3H, t, J = 7.0 Hz), 1.86-1.89 (2H, m), 1.94-1.99 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.17-3.19 (2H, m), 3.85 (3H, s), 3.86 (2H, s), 4.03 (2H, q, J = 7.0 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.65 (1H, d, J = 7.5 Hz), 6.67 (1H, d, J = 13.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.52 (1H, brs).

Example 129

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoroqui nolin-2(1H)-one

[1389] A solution of 1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}pip eridin-4-ol (0.34 g) in 1 N hydrogen chloride/ethanol (14 mL) was refluxed for 9 h. After the reaction mixture was allowed to cool to room temperature, the solvent was distilled off and to the residue was added ethanol-water, the insoluble precipitate was collected on a filter, and the obtained solid was recrystallized form acetic acid/water. The precipitate was collected on a filter, dried (60 °C air) to provide the title compound (0.27 g).
m.p. 297 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.75 (2H, m), 1.75-1.85 (2H, m), 2.95-3.04 (2H, m), 3.35-3.44 (2H, m), 3.90 (2H, s), 4.86 (1H, s), 6.54 (1H, d, J = 9.8 Hz), 6.68 (1H, dd, J = 9.0 Hz, 3.4 Hz), 7.23-7.31 (2H, m), 7.33 (1H, dd, J = 10.8 Hz, 9.0 Hz), 8.23 (1H, dd, J = 9.8 Hz, 1.5 Hz), 11.73 (1H, s).

Example 130

5-{[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4 -dihydroquinolin-2(1H)-one

[1390] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.63-1.67 (2H, m), 1.77-1.84 (2H, m), 2.42-2.49 (2H, m), 2.86 (2H, t, J = 7.8 Hz), 2.96-3.03 (2H, m), 3.10-3.14 (2H, m), 3.78 (2H, s), 4.75 (1H, s), 6.75 (1H, dd, J = 12.9 Hz, 6.3 Hz), 6.99-7.05 (1H, m), 7.25-7.29 (1H, m), 7.40 (1H, m), 10.30 (1H, s).

Example 131

5-{[1-(2,4-Dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro -3,4-dihydroquinolin-2(1H)-one

[1391] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.71 (2H, m), 1.78-1.82 (2H, m), 2.42-2.49 (2H, m), 2.88-2.92 (2H, m), 2.96-3.12 (4H, m), 3.80 (2H, s), 4.78 (1H, s), 6.76 (1H, dd, J = 12.6 Hz, 6.3 Hz), 7.25 (1H, d, J = 11.4 Hz), 7.71 (1H, d, J = 6.9 Hz), 10.32 (1H, s).

Example 132

5-{[1-(4-Ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4 -dihydroquinolin-2(1H)-one

[1392] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.28 (3H, t, J = 7.2 Hz), 1.63-1.67 (2H, m), 1.76-1.83 (2H, m), 2.42-2.49 (2H, m), 2.84-2.98 (6H, m), 3.78 (2H, s), 3.96 (2H, q, J = 7.2 Hz), 4.62 (1H, s), 6.65-6.77 (3H, m), 6.96-7.03 (1H, m), 10.21 (1H, s).

Example 133

8-Fluoro-5-{[1-(2-fluoro-4-hydroxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-d ihydroquinolin-2(1H)-one

[1393] A solution of 5-({1-[4-(benzyloxy)-2-fluorophenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-3,4 -dihydroquin-

olin-2(1H)-one (5.14 g) and 10 % palladium on carbon (containing water) (1 g) in ethanol (100 mL) was stirred at room temperature for 1.5 h under hydrogen atmosphere. Insoluble materials were filtered off with Celite, and the solvent of the filtrate was distilled off. The residue was washed with ethyl acetate/methanol and dried to provide the title compound (590 mg).

^{1}HNMR (DMSO-d6) δ ppm: 1.62-1.65 (2H, m), 1.80-1.86 (2H, m), 2.45 (2H, t, J = 7.5 Hz), 2.91 (2H, t, J = 7.5 Hz), 2.92-2.94 (4H, m), 3.75 (2H, s), 4.62 (1H, brs), 6.49-6.53 (2H, m), 6.57 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.89-6.93 (1H, m), 6.99 (1H, t, J = 9.0 Hz), 9.36 (1H, brs), 10.00 (1H, brs).

Example 134

4-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one

[1394] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.82 (2H, m), 1.82-1.92 (2H, m), 3.02-3.20 (4H, m), 3.96 (2H, s), 4.92 (1H, brs), 7.08-7.14 (2H, m), 7.16-7.21 (2H, m), 7.26-7.30 (1H, m), 7.30-7.34 (1H, m), 7.49-7.54 (1H, m), 7.93-7.97 (1H, m), 11.35 (1H, brs).

Example 135

5-{[1-(4-Ethoxy-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1395] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 207.9-208.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.80-1.83 (2H, m), 1.87-1.93 (2H, m), 2.02 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 2.98-3.03 (2H, m), 3.03 (2H, t, J = 7.5 Hz), 3.41-3.45 (2H, m), 3.85 (2H, s), 3.95 (2H, q, J = 7.0 Hz), 6.38-6.44 (2H, m), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.52 (1H, brs).

Example 136

8-Fluoro-5-({1-[2-fluoro-4-(2-fluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-3,4-dihydroquinolin-2(1H)-one

[1396] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 186.5-186.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.11 (2H, m), 3.16-3.18 (2H, m), 3.85 (2H, s), 4.13-4.20 (2H, m), 4.68-4.79 (2H, m), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.65-6.71 (2H, m), 6.93 (1H, t, J = 9.0 Hz), 6.98 (1H, t, J = 9.0 Hz), 7.55 (1H, brs).

Example 137

8-Chloro-5-{[1-(4-ethoxy-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1397] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 180.6-181.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.80-1.83 (2H, m), 1.87-1.93 (2H, m), 2.00 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 2.97-3.01 (2H, m), 3.02 (2H, t, J = 7.5 Hz), 3.41-3.45 (2H, m), 3.87 (2H, s), 3.95 (2H, q, J = 7.0 Hz), 6.38-6.44 (2H, m), 6.55 (1H, d, J = 9.0 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.74 (1H, brs).

Example 138

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one

[1398] Synthesized analogous to Example 42.
(Methanol/ethyl acetate) m.p. 275.7-277.0 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.79 (2H, m), 1.82-1.91 (2H, m), 3.02-3.10 (2H, m), 3.13-3.21 (2H, m), 3.92 (2H, s), 4.87 (1H, s), 6.44 (1H, d, J = 9.5 Hz), 6.71 (1H, d, J = 8.5 Hz), 6.87 (1H, d, J = 8.5 Hz), 7.10 (1H, t, J = 8.5 Hz), 7.17 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.31 (1H, dd, J = 12.5 Hz, 2.0 Hz), 7.39 (1H, t, J = 8.5 Hz), 8.20 (1H, d, J = 10.0 Hz), 11.72 (1H, s).

Example 139

8-Chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-di hydroquinolin-2(1H)-one

[1399] Synthesized analogous to Example 33.
(Acetic acid/water) m.p. 218 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.89 (2H, m), 1.89-1.97 (2H, m), 2.02 (1H, brs), 2.61-2.67 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.26-3.35 (2H, m), 3.61-3.68 (2H, m), 3.88 (2H, s), 6.54 (1H, d, J = 8.9 Hz), 7.19 (1H, d, J = 8.9 Hz), 7.60 (1H, d, J = 2.3 Hz), 7.75 (1H, brs), 8.13 (1H, d, J = 2.3 Hz).

Example 140

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoroquinoli n-2(1H)-one

[1400] Synthesized analogous to Example 129.
(Acetic acid/water) m.p. 255-256 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.80 (2H, m), 1.80-1.91 (2H, m), 3.01-3.10 (2H, m), 3.12-3.20 (2H, m), 3.91 (2H, s), 4.87 (1H, s), 6.54 (1H, d, J = 9.8 Hz), 6.67 (1H, dd, J = 9.0 Hz, 3.4 Hz), 7.11 (1H, t, J = 9.1 Hz), 7.18 (1H, dd, J = 8.6 Hz, 2.1 Hz), 7.29-7.36 (2H, m), 8.22 (1H, dd, J = 1.5 Hz, 9.8 Hz), 11.73 (1H, s).

Example 141

5-{[1-(1-Benzothiophen-5-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihyd roquinoli-2(1H)-one

[1401] Synthesized analogous to Example 42.
(Ethyl acetate/methanol/dichloromethane) m.p. 209.5-210.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.91 (2H, m), 1.94-2.00 (2H, m), 2.04 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.22-3.27 (2H, m), 3.50-3.53 (2H, m), 3.86 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.13 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.23 (1H, d, J = 5.5 Hz), 7.36 (1H, d, J = 2.5 Hz), 7.41 (1H, d, J = 5.5 Hz), 7.54 (1H, brs), 7.74 (1H, d, J = 8.5 Hz).

Example 142

5-{[1-(1-Benzothiophen-5-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihyd roquinoli-2(1H)-one

[1402] Synthesized analogous to Example 42.
(Ethyl acetate/dichloromethane) m.p. 193.8-194.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.91 (2H, m), 1.95-2.00 (2H, m), 2.00 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.22-3.27 (2H, m), 3.51-3.53 (2H, m), 3.88 (2H, s), 6.54 (1H, d, J = 9.0 Hz), 7.13 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.24 (1H, d, J = 5.5 Hz), 7.36 (1H, d, J = 2.5 Hz), 7.41 (1H, d, J = 5.5 Hz), 7.74 (1H, d, J = 8.5 Hz), 7.75 (1H, brs).

Example 143

8-Fluoro-5-({1-[2-fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl} methoxy)-3,4-dihydroquinoli-2(1H)-one

[1403] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.11 (2H, m), 3.18-3.20 (2H, m), 3.86 (2H, s), 4.28-4.33 (2H, m), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.66-6.69 (1H, m), 6.73 (1H, dd, J = 13.0 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.99 (1H, t, J = 9.0 Hz), 7.51 (1H, brs).

Example 144

8-Fluoro-5-{[4-hydroxy-1-(quinoxalin-6-yl)piperidin-4-yl]methoxy}-3,4-dihydroqui nolin-2(1H)-one

[1404] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-1.94 (4H, m), 2.13 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.41-3.47

(2H, m), 3.79-3.81 (2H, m), 3.86 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 7.34 (1H, d, J = 2.5 Hz), 7.53 (1H, brs), 7.57 (1H, dd, J = 9.5 Hz, 2.5 Hz), 7.94 (1H, d, J = 9.5 Hz), 8.60 (1H, d, J = 2.0 Hz), 8.69 (1H, d, J = 2.0 Hz).

Example 145

7-Amino-5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one hydrochloride

[1405] A solution of 7-amino-8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (310 mg), 6-(4-chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (764 mg) and sodium hydroxide (63.2 mg) in N,N-dimethylformamide/2-propanol (1:1) (4 mL) was stirred at 70 °C-80 °C for 30 min. After the reaction mixture was allowed to cool to room temperature, water and ethyl acetate were added to the mixture, and the insoluble precipitate was collected on a filter. The obtained solid was dissolved in ethanol/6 N hydrochloric acid. The solution was treated with activated charcoal, insoluble materials were filtered off, and the solvent in the filtrate was distilled off. The residue was washed with ethanol and dried under reduced pressure to provide the title compound (120 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.66 (2H, m), 1.82-1.91 (2H, m), 2.39 (2H, t, J = 6.9 Hz), 2.78 (2H, t, J = 6.9 Hz), 2.99-3.16 (4H, m), 3.67 (2H, s), 4.16-4.22 (4H, brs), 6.19 (1H, d, J = 6.3 Hz), 7.06-7.18 (2H, m), 7.30 (1H, dd, J = 12.6 Hz, 2.4 Hz), 9.84 (1H, s).

Example 146

5-{[1-(1-Benzofuran-5-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroq uinolin-2(1H)-one

[1406] Synthesized analogous to Example 42.
(Ethyl acetate/dichloromethane) m.p. 215.7-216.0 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.68 (2H, m), 1.85-1.91 (2H, m), 2.42 (2H, t, J = 7.5 Hz), 2.87 (2H, t, J = 7.5 Hz), 3.04-3.08 (2H, m), 3.37-3.39 (2H, m), 3.77 (2H, s), 4.69 (1H, brs), 6.58 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.82 (1H, d, J = 2.0 Hz), 7.00 (1H, t, J = 9.0 Hz), 7.03 (1H, dd, J = 9.0 Hz, 2.0 Hz), 7.15 (1H, d, J = 2.0 Hz), 7.42 (1H, d, J = 9.0 Hz), 7.87 (1H, d, J = 2.0 Hz), 10.01 (1H, brs).

Example 147

5-({1-[4-(Difluoromethoxy)-2-fluorophenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1407] Synthesized analogous to Example 42.
(Ethyl acetate/dichloromethane) m.p. 201.6-202.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.90 (2H, m), 1.93-1.98 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.22-3.25 (2H, m), 3.86 (2H, s), 6.45 (1H, t, J = 73.8 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.86-6.90 (2H, m), 6.93 (1H, t, J = 9.0 Hz), 6.99 (1H, t, J = 9.0 Hz), 7.51 (1H, brs).

Example 148

5-[(1-{4-[(4-Chlorobenzyl)oxy]-2-fluorophenyl}-4-hydroxypiperidin-4-yl)methoxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1408] Under nitrogen atmosphere, a suspension of 8-fluoro-5-{[1-(2-fluoro-4-hydroxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dih ydroquinolin-2(1H)-one (182 mg), potassium carbonate (124 mg) and 4-chlorobenzyl bromide (120 mg) in N,N-dimethylformamide (2.7 mL) was stirred at room temperature for 3 h, then at 60 °C for 1.5 h. To the reaction solution were added water and ethyl acetate, the precipitate was collected on a filter, and the obtained solid was recrystallized from ethyl acetate. The precipitate was collected on a filter, and dried to provide the title compound (126 mg).
(Ethyl acetate) m.p. 200.0-200.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 1.99 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.16-3.18 (2H, m), 3.85 (2H, s), 4.98 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.66-6.69 (1H, m), 6.71 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.99 (1H, t, J = 9.0 Hz), 7.33-7.37 (4H, m), 7.49 (1H, brs).

Example 149

8-Chloro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihyd roquinoli-2(1H)-one

[1409] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 175.6-176.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.83 (2H, m), 1.87-1.93 (2H, m), 1.99 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.00-3.04 (2H, m), 3.02 (2H, t, J = 7.5 Hz), 3.44-3.48 (2H, m), 3.87 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.60-6.66 (2H, m), 7.19 (1H, d, J = 9.0 Hz), 7.74 (1H, brs).

Example 150

8-Fluoro-5-[(1-{2-fluoro-4-[(4-fluorobenzyl)oxy]phenyl}-4-hydroxypiperidin-4-yl)m ethoxy]-3,4-dihydroquinolin-2(1H)-one

[1410] Synthesized analogous to Example 148.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.10 (2H, m), 3.16-3.18 (2H, m), 3.85 (2H, s), 4.97 (2H, s), 6.49 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.67-6.70 (1H, m), 6.72 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.5 Hz), 6.97 (1H, t, J = 9.5 Hz), 7.07 (2H, t, J = 8.5 Hz), 7.39 (2H, dd, J = 8.5 Hz, 5.5 Hz), 7.52 (1H, brs).

Example 151

8-Chloro-5-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-hydroxypiperidin-4-yl} methoxy)-3,4-dihydroquinolin-2(1H)-one

[1411] Synthesized analogous to Example 33.
(Ethyl acetate/hexane) m.p. 193.0-194.7 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.72 (2H, m), 1.80-1.88 (2H, m), 2.44 (2H, t, J = 7.5 Hz), 2.88 (2H, t, J = 7.5 Hz), 3.27-3.34 (2H, m), 3.78-3.90 (2H, m), 3.82 (2H, s), 4.85 (1H, s), 6.68 (1H, d, J = 9.0 Hz), 7.22 (1H, d, J = 9.0 Hz), 8.15 (1H, d, J = 2.0 Hz), 8.43-8.46 (1H, m), 9.36 (1H, s).

Example 152

8-Fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypip eridin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1412] Synthesized analogous to Example 148.
(Ethyl acetate/hexane) m.p. 199.9-200.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 1.99 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.04-3.11 (2H, m), 3.16-3.18 (2H, m), 3.85 (2H, s), 5.01 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.68-6.70 (1H, m), 6.73 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.98 (1H, t, J = 9.0 Hz), 7.24 (2H, d, J = 8.5 Hz), 7.45 (2H, d, J = 8.5 Hz), 7.49 (1H, brs).

Example 153

8-Chloro-5-{[1-(5-chloro-3-fluoropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3 ,4-dihydroquinolin-2(1H)-one

[1413] Synthesized analogous to Example 33.
(Ethyl acetate) m.p. 174.4-175.8 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.67 (2H, m), 1.75-1.85 (2H, m), 2.43 (2H, t, J = 7.5 Hz), 2.85 (2H, t, J = 7.5 Hz), 3.22-3.31 (2H, m), 3.73-3.82 (2H, m), 3.78 (2H, s), 4.82 (1H, s), 6.66 (1H, d, J = 8.5 Hz), 7.21 (1H, d, J = 8.5 Hz), 7.77 (1H, dd, J = 12.5 Hz, 2.0 Hz), 8.07 (1H, d, J = 2.0 Hz), 9.35 (1H, s).

Example 154

8-Fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethyl)benzyl]oxy}phenyl)-4-hydroxypiper idin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1414] Synthesized analogous to Example 148.
(Ethyl acetate/hexane) m.p. 207.4-210.3 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.11 (2H, m), 3.16-3.18 (2H, m), 3.85 (2H, s), 5.08 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.67-6.70 (1H, m), 6.73 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.98 (1H, t, J = 9.0 Hz), 7.53 (1H, brs), 7.53 (2H, d, J = 8.0 Hz), 7.65 (2H, d, J = 8.0 Hz).

Example 155

5-[(1-{4-[(2,4-Dichlorobenzyl)oxy]-2-fluorophenyl}-4-hydroxypiperidin-4-yl)metho xy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1415] Synthesized analogous to Example 148.
(Ethyl acetate/hexane) m.p. 175.9-177.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.11 (2H, m), 3.16-3.19 (2H, m), 3.85 (2H, s), 5.07 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.68-6.70 (1H, m), 6.74 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.98 (1H, t, J = 9.0 Hz), 7.28 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.42 (1H, d, J = 2.0 Hz), 7.47 (1H, d, J = 8.5 Hz), 7.52 (1H, brs).

Example 156

8-Fluoro-5-{[4-hydroxy-1-(quinolin-6-yl)piperidin-4-yl]methoxy}-3,4-dihydroquinol in-2(1H)-one

[1416] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-1.99 (4H, m), 2.05 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.31-3.36 (2H, m), 3.67-3.69 (2H, m), 3.87 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.09 (1H, d, J = 2.5 Hz), 7.31 (1H, dd, J = 8.5 Hz, 4.5 Hz), 7.52-7.54 (2H, m), 7.97-8.00 (2H, m), 8.71-8.72 (1H, m).

Example 157

5-{[1-(2,4-Difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydro quinolin-2(1H)-one

[1417] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 201.7-201.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.07-3.12 (2H, m), 3.18-3.20 (2H, m), 3.86 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.79-6.84 (2H, m), 6.93 (1H, t, J = 9.0 Hz), 6.96-7.01 (1H, m), 7.57 (1H, brs).

Example 158

8-Chloro-5-{[1-(2,4-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydro quinolin-2(1H)-one

[1418] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 200.0-200.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.69 (2H, m), 1.83-1.89 (2H, m), 2.48 (2H, t, J = 7.5 Hz), 2.93 (2H, t, J = 7.5 Hz), 2.97-3.03 (2H, m), 3.06-3.08 (2H, m), 3.81 (2H, s), 4.73 (1H, brs), 6.69 (1H, d, J = 9.0 Hz), 6.98-7.00 (1H, m), 7.09-7.19 (2H, m), 7.23 (1H, d, J = 9.0 Hz), 9.36 (1H, brs).

Example 159

5-({1-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1419] Synthesized analogous to Example 33.
(Ethyl acetate) m.p. 172.5-172.7 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.71 (2H, m), 1.80-1.99 (2H, m), 2.43 (2H, t, J = 7.5 Hz), 2.86 (2H, t, J = 7.5 Hz), 3.25-3.34 (2H, m), 3.78 (2H, s), 3.80-3.87 (2H, m), 4.00 (1H, s), 6.57 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.98 (1H, t, J = 9.9 Hz), 8.15 (1H, d, J = 2.5 Hz), 8.54 (1H, d, J = 1.0 Hz), 10.01 (1H, s).

Example 160

5-({1-[4-Chloro-2-fluoro-5-(2-fluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1420] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.68 (2H, m), 1.83-1.89 (2H, m), 2.46 (2H, t, J = 7.5 Hz), 2.91 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.18-3.20 (2H, m), 3.78 (2H, s), 4.30-4.38 (2H, m), 4.68-4.80 (2H, m), 4.74 (1H, brs), 6.58 (1H, dd, J = 9.5 Hz, 4.0 Hz), 6.80 (1H, d, J = 8.0 Hz), 7.01 (1H, t, J = 9.5 Hz), 7.31 (1H, d, J = 12.5 Hz), 10.02 (1H, brs).

Example 161

8-Chloro-5-({1-[4-chloro-2-fluoro-5-(2-fluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

[1421] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 223.0-223.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.69 (2H, m), 1.83-1.89 (2H, m), 2.47 (2H, t, J = 7.5 Hz), 2.93 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.18-3.20 (2H, m), 3.82 (2H, s), 4.30-4.38 (2H, m), 4.68-4.80 (2H, m), 4.76 (1H, brs), 6.69 (1H, d, J = 9.0 Hz), 6.80 (1H, d, J = 8.0 Hz), 7.24 (1H, d, J = 9.0 Hz), 7.31 (1H, d, J = 12.0 Hz), 9.36 (1H, brs).

Example 162

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-7-meth yl-3,4-dihydroquinolin-2(1H)-one

[1422] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.72 (2H, m), 1.78-1.93 (2H, m), 2.19 (3H, d, J = 1.8 Hz), 2.43 (2H, t, J = 7.6 Hz), 2.86 (2H, t, J = 7.6 Hz), 2.97-3.20 (4H, m), 3.76 (2H, s), 4.66 (1H, s), 6.50 (1H, d, J = 5.7 Hz), 7.06-7.18 (2H, m), 7.26-7.31 (1H, m), 9.89 (1H, s).

Example 163

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-ethoxy-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1423] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.32 (3H, t, J = 7.0 Hz), 1.61-1.73 (2H, m), 1.78-1.92 (2H, m), 2.39-2.47 (2H, m), 2.79-2.88 (2H, m), 2.98-3.20 (4H, m), 3.80 (2H, s), 4.10 (2H, q, J = 7.0 Hz), 4.67 (1H, s), 6.42 (1H, d, J = 6.6 Hz), 7.06-7.18 (2H, m), 7.27-7.32 (1H, m), 9.93 (1H, s).

Example 164

5-({1-[4-Chloro-2-fluoro-5-(propan-2-yloxy)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1424] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 216.7-217.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.36 (6H, d, J = 6.0 Hz), 1.87-1.89 (2H, m), 1.92-1.98 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J =

7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.24-3.26 (2H, m), 3.85 (2H, s), 4.43 (1H, sep, J = 6.0 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.64 (1H, d, J = 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.06 (1H, d, J = 11.5 Hz), 7.53 (1H, brs).

Example 165

5-[(1-{4-Chloro-5-[(4-chlorobenzyl)oxy]-2-fluorophenyl}-4-hydroxypiperidin-4-yl)me thoxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1425] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 205.1-205.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.88 (2H, m), 1.89-1.95 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.06-3.11 (2H, m), 3.20-3.22 (2H, m), 3.84 (2H, s), 5.06 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.60 (1H, d, J = 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.09 (1H, d, J = 11.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 7.39 (2H, d, J = 8.5 Hz), 7.52 (1H, brs).

Example 166

8-Chloro-5-({1-[4-chloro-2-fluoro-5-(propan-2-yloxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

[1426] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 173.3-173.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.36 (6H, d, J = 6.0 Hz), 1.86-1.89 (2H, m), 1.92-1.99 (2H, m), 1.99 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.07-3.13 (2H, m), 3.24-3.26 (2H, m), 3.88 (2H, s), 4.43 (1H, sep, J = 6.0 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.64 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 12.0 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 167

5-({1-[4-Chloro-2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl} methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1427] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 200.6-201.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.91-1.97 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.10-3.15 (2H, m), 3.25-3.27 (2H, m), 3.85 (2H, s), 4.34-4.39 (2H, m), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.70 (1H, d, J = 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.09 (1H, d, J = 12.0 Hz), 7.55 (1H, brs).

Example 168

7-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1428] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.90 (4H, m), 2.41-2.55 (2H, m), 2.93 (2H, t, J = 7.7 Hz), 2.98-3.20 (4H, m), 3.82 (2H, s), 4.70 (1H, s), 6.80 (1H, d, J = 5.7 Hz), 7.05-7.20 (2H, m), 7.29 (1H, dd, J = 12.6 Hz, 2.4 Hz), 10.19 (1H, s).

Example 169

5-{[1-(5-Chloro-3-fluoropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1429] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.59-1.66 (1H, m), 1.75-1.85 (1H, m), 2.43 (2H, t, J = 7.8 Hz), 2.85 (2H, t, J = 7.8 Hz), 3.23-3.31 (2H, m), 3.34 (2H, s), 3.73-3.81 (4H, m), 4.80 (1H, brs), 6.56 (1H, dd, J = 9.2 Hz, 3.5 Hz), 6.99 (1H, t, J = 9.6 Hz), 7.76-7.81 (1H, m), 8.05-8.08 (1H, m), 10.01 (1H, brs).

Example 170

5-{[1-(3,5-Dichloro-1-oxidopyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1430] To a solution of 5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-

2(1H)-one (403 mg) in chloroform (30 mL) was added m-chloroperoxybenzoic acid (75 %) (660 mg), and the reaction mixture was stirred at room temperature for 3 days. To the reaction solution was added sodium hydrogen carbonate aqueous solution, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was recrystallized from dichloromethane/methanol, the precipitate was collected on a filter and dried under reduced pressure to provide the title compound (120 mg).
m.p. 141.0-141.7 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.79 (2H, m), 1.80-1.95 (2H, m), 2.40-2.57 (2H, m), 2.83-2.95 (2H, m), 3.05-3.20 (3H, m), 3.74 (2H, s), 4.82 (2H, s), 6.50-6.63 (1H, m), 6.92-7.01 (1H, m), 8.16 (1H, s), 8.22 (1H, s), 10.01 (1H, s).

Example 171

5-({l-[4-Chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}met hoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1431] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 170.6-170.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.91-1.97 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.24-3.27 (2H, m), 3.47 (3H, s), 3.76-3.78 (2H, m), 3.85 (2H, s), 4.13-4.14 (2H, m), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.68 (1H, d, J = 7.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.06 (1H, d, J = 12.0 Hz), 7.54 (1H, brs).

Example 172

5-[(1-{4-Chloro-5-[2-(dimethylamino)ethoxy]-2-fluorophenyl}-4-hydroxypiperidin-4 -yl)methoxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1432] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 162.9-164.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.92-1.97 (2H, m), 2.02 (1H, brs), 2.37 (6H, s), 2.66 (2H, t, J = 7.5 Hz), 2.77 (2H, t, J = 6.0 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.24-3.27 (2H, m), 3.85 (2H, s), 4.09 (2H, t, J = 6.0 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.64 (1H, d, J = 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.06 (1H, d, J = 11.5 Hz), 7.51 (1H, brs).

Example 173

5-{[1-(4-Chloro-2-fluoro-5-propoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1433] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 200.7-201.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.07 (3H, t, J = 7.0 Hz), 1.81-1.89 (4H, m), 1.92-1.98 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.25-3.27 (2H, m), 3.86 (2H, s), 3.95 (2H, t, J = 6.5 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.60 (1H, d, J = 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.07 (1H, d, J = 12.0 Hz), 7.56 (1H, brs).

Example 174

5-[(1-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethoxy]phenyl}-4-hydroxypiperidin-4-yl)methoxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1434] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 159.2-160.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.91-1.97 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.23-3.25 (2H, m), 3.85 (2H, s), 4.30-4.36 (4H, m), 6.48 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.70 (1H, d, J = 8.0 Hz), 6.90-6.95 (3H, m), 6.97-7.01 (2H, m), 7.08 (1H, d, J = 11.5 Hz), 7.53 (1H, brs).

Example 175

8-Chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

[1435] Synthesized analogous to Example 42.

(Ethyl acetate/hexane) m.p. 143.5-145.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.92-1.98 (2H, m), 1.98 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.25-3.27 (2H, m), 3.48 (3H, s), 3.76-3.78 (2H, m), 3.87 (2H, s), 4.13-4.15 (2H, m), 6.55 (1H, d, J = 9.0 Hz), 6.68 (1H, d, J = 7.5 Hz), 7.06 (1H, d, J = 11.5 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 176

8-Fluoro-5-[(1-{2-fluoro-4-[2-(4-fluorophenoxy) ethoxy]phenyl}-4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one

[1436] Under nitrogen atmosphere, a suspension of 8-fluoro-5-{[1-(2-fluoro-4-hydroxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dih ydroquinolin-2(1H)-one (185 mg), potassium carbonate (126 mg), 1-(2-bromoethoxy)-4-fluorobenzene (110 mg) and sodium iodide (75 mg) in N,N-dimethylformamide (1.9 mL) was stirred at room temperature for 3 h, then at 60 °C for 10 h. To the reaction solution was added water and the solution was extracted with ethyl acetate/methanol, the organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/methanol), and the obtained product was recrystallized form ethyl acetate. The precipitate was collected on a filter and dried to provide the title compound (99 mg).
m.p. 199.3-199.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 1.99 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.11 (2H, m), 3.16-3.19 (2H, m), 3.86 (2H, s), 4.26 (4H, s), 6.49 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.67-6.69 (1H, m), 6.72 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.88-6.90 (2H, m), 6.93 (1H, t, J = 9.0 Hz), 6.96-7.00 (3H, m), 7.49 (1H, brs).

Example 177

5-{[1-(4-Chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro -3,4-dihydroquinolin-2(1H)-one

[1437] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.69 (2H, m), 1.78-1.82 (2H, m), 2.43-2.49 (2H, m), 2.84-2.89 (2H, m), 3.05-3.11 (2H, m), 3.18-3.22 (2H, m), 3.79 (2H, s), 4.75 (1H, s), 6.74 (1H, dd, J = 12.6 Hz, 6.3 Hz), 7.11 (1H, dd, J = 11.1 Hz, 7.5 Hz), 7.46 (1H, dd, J = 12.0 Hz, 6.9 Hz), 10.24 (1H, s).

Example 178

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro -3,4-dihydroquinolin-2(1H)-one

[1438] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.65 (2H, m), 1.72-1.78 (2H, m), 2.43-2.49 (2H, m), 2.85-2.90 (2H, m), 2.94-2.99 (2H, m), 3.18-3.25 (2H, m), 3.78 (2H, s), 4.70 (1H, s), 6.74 (1H, dd, J = 12.6 Hz, 6.3 Hz), 7.25 (2H, dd, J = 15 Hz, 5.4 Hz), 10.24 (1H, s).

Example 179

5-{[1-(4-Chloro-2-fluoro-5-propylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1439] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 196.5-196.6 °C
^{1}HNMR ($CDCl_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.58-1.66 (2H, m), 1.86-1.89 (2H, m), 1.92-1.98 (2H, m), 2.00 (1H, brs), 2.61-2.67 (4H, m), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.23-3.25 (2H, m), 3.85 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.83 (1H, d, J = 9.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.04 (1H, d, J = 11.5 Hz), 7.50 (1H, brs).

Example 180

5-({1-[4-Chloro-2-fluoro-5-(propan-2-yl)phenyl]-4-hydroxypiperidin-4-yl}methoxy) -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1440] Synthesized analogous to Example 42.
(Ethyl acetate/methanol/dichloromethane) m.p. 225.3-225.7 °C

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 1.87-1.90 (2H, m), 1.92-1.98 (2H, m), 2.04 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.10-3.16 (2H, m), 3.24-3.26 (2H, m), 3.33 (1H, sep, J = 7.0 Hz), 3.86 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.90 (1H, d, J = 9.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.04 (1H, d, J = 12.0 Hz), 7.55 (1H, brs).

Example 181

5-({1-[4-(Difluoromethoxy)-2,6-difluorophenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1441] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 172.6-172.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.84 (2H, m), 1.86-1.92 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.04-3.07 (2H, m), 3.45-3.50 (2H, m), 3.85 (2H, s), 6.45 (1H, t, J = 73.0 Hz), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.66-6.72 (2H, m), 6.93 (1H, t, J = 9.0 Hz), 7.52 (1H, brs).

Example 182

5-{[1-(2,4-Difluoro-5-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1442] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.92-1.98 (2H, m), 2.01 (1H, brs), 2.22 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.10 (2H, m), 3.17-3.19 (2H, m), 3.85 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.76 (1H, dd, J = 12.0 Hz, 9.5 Hz), 6.82 (1H, t, J = 9.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.54 (1H, brs).

Example 183

8-Chloro-5-{[1-(2,4-difluoro-5-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1443] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 195.0-195.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.93-1.99 (2H, m), 1.98 (1H, brs), 2.22 (3H, s), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.06-3.11 (2H, m), 3.17-3.19 (2H, m), 3.87 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.76 (1H, dd, J = 12.0 Hz, 9.5 Hz), 6.82 (1H, t, J = 9.0 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 184

8-Chloro-5-({1-[4-(difluoromethoxy)-2,6-difluorophenyl]-4-hydroxypiperidin-4-yl} methoxy)-3,4-dihydroquinoli-2(1H)-one

[1444] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 143.6-143.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.84 (2H, m), 1.87-1.93 (2H, m), 2.01 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.05-3.07 (2H, m), 3.45-3.49 (2H, m), 3.87 (2H, s), 6.45 (1H, t, J = 73.0 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.66-6.72 (2H, m),, 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 185

5-{[1-(4-Chloro-2-fluoro-5-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1445] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 232.4-232.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.90 (2H, m), 1.93-1.99 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.11-3.16 (2H, m), 3.26-3.29 (2H, m), 3.86 (2H, s), 3.88 (3H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.60 (1H, d, J = 7.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.08 (1H, d, J = 11.5 Hz), 7.54 (1H, brs).

Example 186

5-{[1-(5,6-Dimethylpyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1446] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 197.9-199.6 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.52-1.60 (2H, m), 1.63-1.71 (2H, m), 2.08 (3H, s), 2.25 (3H, s), 2.38 (2H, t, J = 7.5 Hz), 2.79 (2H, t, J = 7.5 Hz), 3.07-3.15 (2H, m), 3.72 (2H, s), 3.92-4.00 (2H, m), 4.70 (1H,s), 6.51-6.57 (2H, m), 6.96 (1H, t, J = 9.8 Hz), 7.22 (1H, d, J = 8.5 Hz), 9.99 (1H, s).

Example 187

8-Chloro-5-{[1-(5,6-dimethylpyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-di hydroquinolin-2(1H)-one

[1447] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 169.6-171.0 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.53-1.60 (2H, m), 1.63-1.71 (2H, m), 2.08 (3H, s), 2.25 (3H, s), 2.40 (2H, t, J = 7.5 Hz), 2.81 (2H, t, J = 7.5 Hz), 3.08-3.16 (2H, m), 3.76 (2H, s), 3.92-3.98 (2H, m), 4.73 (1H,s), 6.55 (1H, d, J = 8.5 Hz), 6.64 (1H, d, J = 8.5 Hz), 7.19 (1H, d, J = 8.5 Hz), 7.22 (1H, d, J = 8.5 Hz), 9.34 (1H, s).

Example 188

8-Chloro-5-{[1-(3-chloro-5-ethoxypyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1448] Synthesized analogous to Example 33.
(Ethyl acetate/hexane) m.p. 169.0-170.4 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.30 (3H, t, J = 7.0 Hz), 1.62-1.68 (2H, m), 1.77-1.86 (2H, m), 2.46 (2H, t, J = 7.5 Hz), 2.91 (2H, t, J = 7.5 Hz), 3.05-3.13 (2H, m), 3.23-3.37 (2H, m), 3.80 (2H, s), 4.03 (2H, q, J = 7.0 Hz), 4.69 (1H,s), 6.67 (1H, d, J = 9.0 Hz), 7.21 (1H, d, J = 9.0 Hz), 7.51 (1H, d, J = 2.5 Hz), 7.96 (1H, d, J = 2.5 Hz), 9.34 (1H, s).

Example 189

5-{[1-(4-Chloro-5-ethyl-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1449] Synthesized analogous to Example 42.
(Ethyl acetate/dichloromethane) m.p. 201.3-202.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 1.86-1.89 (2H, m), 1.92-1.98 (2H, m), 2.03 (1H, brs), 2.64-2.71 (4H, m), 3.03 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.24-3.26 (2H, m), 3.86 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.85 (1H, d, J = 9.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.04 (1H, d, J = 12.0 Hz), 7.56 (1H, brs).

Example 190

8-Chloro-5-{[1-(4-chloro-2-fluoro-5-methoxyphenyl)-4-hydroxypiperidin-4-yl]meth oxy}-3,4-dihydroquinolin-2(1H)-one

[1450] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 228.7-228.9 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.70 (2H, m), 1.83-1.89 (2H, m), 2.47 (2H, t, J = 7.5 Hz), 2.93 (2H, t, J = 7.5 Hz), 3.06-3.11 (2H, m), 3.18-3.21 (2H, m), 3.82 (2H, s), 3.85 (3H, s), 4.76 (1H, brs), 6.69 (1H, d, J = 9.0 Hz), 6.75 (1H, d, J = 8.0 Hz), 7.24 (1H, d, J = 9.0 Hz), 7.20 (1H, d, J = 12.0 Hz), 9.36 (1H, brs).

Example 191

5-{[1-(3-Chloro-5-ethoxypyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3 ,4-dihydroquinolin-2(1H)-one

[1451] Synthesized analogous to Example 33.
(Ethyl acetate/hexane) m.p. 187.9-190.2 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.30 (3H, t, J = 7.0 Hz), 1.62-1.68 (2H, m), 1.80-1.88 (2H, m), 2.44 (2H, t, J = 7.5 Hz), 2.90 (2H, t, J = 7.5 Hz), 3.06-3.14 (2H, m), 3.25-3.33 (2H, m), 3.77 (2H, s), 4.04 (2H, q, J = 7.0 Hz), 4.67 (1H,s), 6.57 (1H,

dd, J = 9.0 Hz, 4.0 Hz), 6.98 (1H, t, J = 9.5 Hz), 7.52 (1H, d, J = 2.5 Hz), 7.98 (1H, d, J = 2.5 Hz), 10.01 (1H, s).

Example 192

5-{[1-(5-Bromo-3-fluoropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1452] Synthesized analogous to Example 33.
(Ethyl acetate/methanol) m.p. 197.4-203.9 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.73 (2H, m), 1.82-1.90 (2H, m), 2.45 (2H, t, J = 7.5 Hz), 2.91 (2H, t, J = 7.5 Hz), 3.04-3.11 (2H, m), 3.13-3.20 (2H, m), 3.80 (2H, s), 4.77 (1H,s), 6.58 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.98 (1H, t, J = 9.5 Hz), 7.78 (1H, d, J = 2.0 Hz), 8.16 (1H, d, J = 2.0 Hz), 10.02 (1H, s).

Example 193

5-{[1-(5-Bromo-3-fluoropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-3 ,4-dihydroquinolin-2(1H)-one

[1453] Synthesized analogous to Example 33.
(Ethyl acetate/methanol) m.p. 231.2-233.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.74 (2H, m), 1.81-1.90 (2H, m), 2.43 (2H, t, J = 7.5 Hz), 2.92 (2H, t, J = 7.5 Hz), 3.04-3.11 (2H, m), 3.15-3.21 (2H, m), 3.84 (2H, s), 4.79 (1H,s), 6.65 (1H, d, J = 9.0 Hz), 7.23 (1H, d, J = 9.0 Hz), 7.77 (1H, d, J = 2.2 Hz), 8.16 (1H, d, J = 2.2 Hz), 9.37 (1H, s).

Example 194

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dih ydroquinolin-2(1H)-one

[1454] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.74 (2H, m), 1.75-1.92 (2H, m), 2.43 (2H, t, J = 7.7 Hz), 2.82 (2H, t, J = 7.7 Hz), 2.96-3.20 (4H, m), 3.81 (2H, s), 4.74 (1H, s), 6.29 (1H, dd, J = 9.9 Hz, 2.1 Hz), 6.52 (1H, dd, J = 9.9 Hz, 2.1 Hz), 7.05-7.19 (2H, m), 7.31 (1H, dd, J = 12.6 Hz, 2.1 Hz), 10.11 (1H, s).

Example 195

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluor o-3,4-dihydroquinolin-2(1H)-one

[1455] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.89 (4H, m), 2.42-2.53 (2H, m), 2.89 (2H, t, J = 7.4 Hz), 2.96-3.20 (4H, m), 3.84 (2H, s), 4.78 (1H, s), 6.84 (1H, d, J = 11.4 Hz), 7.04-7.20 (2H, m), 7.31 (1H, dd, J = 12.5 Hz, 2.3 Hz), 9.68 (1H, brs).

Example 196

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1456] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.58-1.87 (4H, m), 2.43 (2H, t, J = 7.9 Hz), 2.83 (2H, t, J = 7.9 Hz), 2.92-3.03 (2H, m), 3.28-3.46 (2H, m), 3.80 (2H, s), 4.73 (1H, s), 6.29 (1H, dd, J = 9.9 Hz, 2.4 Hz), 6.52 (1H, dd, J = 9.9 Hz, 2.4 Hz), 7.20-7.33 (2H, m), 10.11 (1H, brs).

Example 197

8-Chloro-5-{[4-hydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4-yl]meth oxy}-3,4-dihydroquinolin-2(1H)-one

[1457] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 213.4-213.5 °C^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 1.99 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.06-3.12 (2H, m), 3.15-3.17 (2H, m), 3.88 (2H, s), 6.55 (1H, d, J = 8.5 Hz), 6.83 (1H, d, J = 7.0 Hz), 6.86 (1H, d, J = 10.0 Hz), 7.20 (1H, d, J = 8.5 Hz), 7.75 (1H, brs).

Example 198

5-{[1-(5-Chloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydr oquinolin-2(1H)-one

[1458] Synthesized analogous to Example 33.
(Ethyl acetate) m.p. 192.0-192.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.55-1.62 (2H, m), 1.65-1.74 (2H, m), 2.40 (2H, t, J = 7.5 Hz), 2.80 (2H, t, J = 7.5 Hz), 3.17-3.27 (2H, m), 3.74 (2H, s), 4.00-4.07 (2H, m), 4.80 (1H, s), 6.54 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.89 (1H, d, J = 9.0 Hz), 6.97 (1H, t, J = 9.8 Hz), 7.55 (1H, dd, J = 9.0 Hz, 2.0 Hz), 8.09 (1H, d, J = 3.0 Hz), 10.01 (1H, s).

Example 199

8-Chloro-5-({1-[2-chloro-4-(methylsulfanyl)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-3,4-dihydroquinolin-2(1H)-one

[1459] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 160.7-160.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.94-2.00 (2H, m), 2.01 (1H, brs), 2.46 (3H, s), 2.65 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.18-3.20 (2H, m), 3.89 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 7.03 (1H, d, J = 8.5 Hz), 7.15 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.30 (1H, d, J = 2.0 Hz), 7.75 (1H, brs).

Example 200

5-{[1-(5-Chloro-1-oxidopyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1460] To a solution of 5-{[1-(5-chloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroq uinolin-2(1H)-one (183 mg) in chloroform (33 mL) was added m-chloroperoxybenzoic acid (75 %) (156 mg) and the reaction mixture was stirred at room temperature for 20 h. To the reaction solution was added sodium carbonate aqueous solution to extract the product. The organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off, the residue was recrystallized from ethyl acetate, and the precipitate was collected on a filter and dried under reduced pressure to provide the title compound (55 mg).
m.p. 189.0-189.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.56-1.67 (2H, m), 2.40-2.60 (2H, m), 2.57-2.67 (2H, m), 2.73-2.84 (2H, m), 2.94 (2H, t, J = 7.5 Hz), 3.84 (2H, s), 4.20-4.30 (2H, m), 5.01 (1H, s), 6.56-6.66 (1H, m), 6.97-7.06 (1H, m), 8.16-8.25 (1H, m), 8.51-8.59 (1H, m), 8.61 (1H, s), 10.04 (1H, s).

Example 201

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-f luoro-3,4-dihydroquinoli-2(1H)-one

[1461] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.85 (4H, m), 2.42-2.54 (2H, m), 2.82-3.04 (4H, m), 3.28-3.42 (2H, m), 3.83 (2H, s), 4.76 (1H, s), 6.84 (1H, d, J = 11.7 Hz), 7.20-7.33 (2H, m), 9.67 (1H, brs).

Example 202

8-Fluoro-5-{[4-hydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4-yl]meth oxy}-3,4-dihydroquinolin-2(1H)-one

[1462] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 226.6-226.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.92-1.98 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.12 (2H, m), 3.15-3.17 (2H, m), 3.85 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.84 (1H, d, J = 7.0 Hz), 6.86 (1H, d, J = 10.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.55 (1H, brs).

Example 203

5-({1-[2-Chloro-4-(methylsulfanyl)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1463] Synthesized analogous to Example 42.

(Ethyl acetate) m.p. 207.4-207.6 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 2.02 (1H, brs), 2.46 (3H, s), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.10 (2H, m), 3.18-3.20 (2H, m), 3.87 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.04 (1H, d, J = 8.5 Hz), 7.15 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.30 (1H, d, J = 2.5 Hz), 7.52 (1H, brs).

Example 204

8-Chloro-5-{[1-(5-ethoxy-2,4-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1464] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 182.1-182.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.00 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.06-3.12 (2H, m), 3.18-3.20 (2H, m), 3.88 (2H, s), 4.08 (2H, q, 7.0 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.68 (1H, t, J = 8.5 Hz), 6.85 (1H, t, J = 11.0 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.76 (1H, brs).

Example 205

8-Chloro-5-{[1-(2,4-difluoro-5-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1465] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 191.4-191.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.13 (2H, m), 3.19-3.22 (2H, m), 3.87 (3H, s), 3.88 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.68 (1H, t, J = 8.5 Hz), 6.86 (1H, t, J = 11.0 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.76 (1H, brs).

Example 206

5-{[1-(2,4-Dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one

[1466] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.72 (2H, m), 1.75-1.90 (2H, m), 2.03 (3H, s), 2.40 (2H, t, J = 7.2 Hz), 2.83 (2H, t, J = 7.2 Hz), 2.96-3.11 (4H, m), 3.79 (2H, s), 4.72 (1H, s), 6.54 (1H, d, J = 12.0 Hz), 7.23 (1H, d, J = 11.4 Hz), 7.68 (1H, d, J = 7.8 Hz), 9.54 (1H, s).

Example 207

5-{[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-meth yl-3,4-dihydroquinolin-2(1H)-one

[1467] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.63-1.71 (2H, m), 1.75-1.86 (2H, m), 2.03 (3H, s), 2.39 (2H, t, J = 7.2 Hz), 2.81 (2H, t, J = 7.2 Hz), 3.01-3.20 (4H, m), 3.77 (2H, s), 4.70 (1H, s), 6.54 (1H, d, J = 12.0 Hz), 6.99-7.05 (1H, m), 7.25-7.29 (1H, m), 7.36-7.41 (1H, m), 9.53 (1H, s).

Example 208

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one

[1468] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.72 (2H, m), 1.74-1.81 (2H, m), 1.99 (3H, s), 2.41 (2H, t, J = 7.2 Hz), 2.83 (2H, t, J = 7.2 Hz), 2.90-2.98 (2H, m), 3.25-3.45 (2H, m), 3.77 (2H, s), 4.69 (1H, s), 6.54 (1H, d, J = 12.0 Hz), 7.25 (2H, d, J = 9.0 Hz), 9.54 (1H, s).

Example 209

5-({1-[4-(Difluoromethoxy)-2,6-difluorophenyl]-4-hydroxypiperidin-4-yl}methoxy)-7, 8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1469] Synthesized analogous to Example 42.

^{1}HNMR (DMSO-d6) δ ppm: 1.59-1.65 (2H, m), 1.71-1.79 (2H, m), 2.42-2.48 (2H, m), 2.84-2.93 (4H, m), 3.30-3.38 (2H, m), 3.77 (2H, s), 4.70 (1H, s), 6.74 (1H, dd, J = 12.9 Hz, 6.3 Hz), 6.95-7.05 (2H, m), 7.22 (1H, s), 10.27 (1H, s).

Example 210

5-{[1-(4-Ethoxy-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro -3,4-dihydroquinolin-2(1H)-one

[1470] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.29 (3H, t, J = 7.2 Hz), 1.59-1.64 (2H, m), 1.72-1.79 (2H, m), 2.44-2.48 (2H, m), 2.79-2.91 (4H, m), 3.32-3.36 (2H, m), 3.78 (2H, s), 3.98 (2H, q, J = 7.2 Hz), 4.66 (1H, s), 6.65 (2H, d, J = 11.4 Hz), 6.75 (1H, dd, J = 12.9 Hz, 6.3 Hz), 10.28 (1H, s).

Example 211

8-Chloro-5-{[1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-f luoro-3,4-dihydroquinoli-2(1H)-one

[1471] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.73 (2H, m), 1.74-1.89 (2H, m), 2.41-2.53 (2H, m), 2.82-2.94 (2H, m), 2.97-3.12 (2H, m), 3.13-3.27 (2H, m), 3.84 (2H, s), 4.80 (1H, s), 6.83 (1H, d, J = 11.4 Hz), 7.12 (1H, dd, J = 11.4 Hz, 7.8 Hz), 7.48 (1H, dd, J = 12.0 Hz, 7.2 Hz), 9.66 (1H, brs).

Example 212

8-Chloro-5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-f luoro-3,4-dihydroquinoli-2(1H)-one

[1472] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.63-1.90 (4H, m), 2.42-2.53 (2H, m), 2.83-2.95 (2H, m), 2.96-3.18 (4H, m), 3.86 (2H, s), 4.79 (1H, s), 6.84 (1H, d, J = 11.7 Hz), 7.25 (1H, d, J = 13.8 Hz), 7.70 (1H, d, J = 7.8 Hz), 9.66 (1H, brs).

Example 213

5-{[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-7-fluor o-3,4-dihydroquinolin-2(1H)-one

[1473] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.90 (4H, m), 2.41-2.58 (2H, m), 2.83-2.94 (2H, m), 2.97-3.21 (4H, m), 3.84 (2H, s), 4.77 (1H, s), 6.84 (1H, d, J = 11.4 Hz), 6.99-7.10 (1H, m), 7.25-7.34 (1H, m), 7.35-7.46 (1H, m), 9.65 (1H, brs).

Example 214

8-Chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3 ,4-dihydroquinolin-2(1H)-one

[1474] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.58-1.84 (4H, m), 2.43-2.54 (2H, m), 2.82-2.98 (4H, m), 3.25-3.40 (2H, m), 3.83 (2H, s), 4.73 (1H, s), 6.84 (1H, d, J = 11.7 Hz), 7.03-7.20 (2H, m), 9.66 (1H, brs).

Example 215

7,8-Difluoro-5-({1-[2-fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

[1475] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.69 (2H, m), 1.79-1.83 (2H, m), 2.42-2.48 (2H, m), 2.85-2.91 (2H, m), 2.96-3.02 (4H, m), 3.79 (2H, s), 4.66-4.76 (3H, m), 6.72-6.84 (2H, m), 6.94-7.19 (2H, m), 10.28 (1H, s).

Example 216

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-1-methyl-3,4-dihydroquinolin-2(1H)-one

[1476] To a solution of 5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-d ihydroquinolin-2(1H)-one (135 mg) in N,N-dimethylformamide-tetrahydrofuran (1:1) (2 mL) was added sodium hydride (60 % in oil) (15 mg), and the reaction mixture was stirred at room temperature for 30 min, and methyl iodide (0.024 mL) was then added to the mixture, which was then stirred at room temperature. To the reaction solution was added water, and the solution was extracted with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (basic silica gel; hexane/ ethyl acetate) to provide the title compound (44 mg).
^{1}HNMR (Methanol-d4) δ ppm: 1.76-1.81 (2H, m), 1.92-2.02 (2H, m), 2.52-2.57 (2H, m), 2.89-2.94 (2H, m), 3.04-3.12 (2H, m), 3.17-3.22 (3H, m), 3.39 (3H, s), 4.07 (2H, s), 6.77 (1H, dd, J = 12.3 Hz, 6.3 Hz), 7.01-7.11 (3H, m).

Example 217

8-Chloro-5-({1-[2-fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl} methoxy)-3,4-dihydroquinoli-2(1H)-one

[1477] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 148.6-148.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 1.98 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.11 (2H, m), 3.18-3.20 (2H, m), 3.88 (2H, s), 4.28-4.33 (2H, m), 6.55 (1H, d, J = 9.0 Hz), 6.66-6.69 (1H, m), 6.73 (1H, dd, J = 13.0 Hz, 3.0 Hz), 6.99 (1H, t, J = 9.0 Hz), 7.20 (1H, t, J = 9.0 Hz), 7.75 (1H, brs).

Example 218

5-{[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihy droquinolin-2(1H)-one

[1478] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 223.1-223.2 °C^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.67 (2H, m), 1.81-1.86 (2H, m), 2.46 (2H, t, J = 7.5 Hz), 2.91 (2H, t, J = 7.5 Hz), 2.99-3.04 (2H, m), 3.12-3.14 (2H, m), 3.79 (2H, s), 4.76 (1H, brs), 6.67 (1H, d, J = 9.0 Hz), 7.03 (1H, t, J = 8.5 Hz), 7.22 (1H, d, J = 9.0 Hz), 7.27 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.39 (1H, dd, J = 12.0 Hz, 2.0 Hz), 9.35 (1H, brs).

Example 219

5-{[1-(4-Bromo-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1479] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 217.7-217.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.83 (2H, m), 1.85-1.91 (2H, m), 2.02 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.10 (2H, m), 3.45-3.49 (2H, m), 3.85 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.00-7.05 (2H, m), 7.53 (1H, brs).

Example 220

5-{[1-(4-Bromo-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-3,4 -dihydroquinolin-2(1H)-one

[1480] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 195.3-195.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.83 (2H, m), 1.86-1.92 (2H, m), 2.00 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.10 (2H, m), 3.45-3.49 (2H, m), 3.87 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 7.00-7.05 (2H, m), 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 221

5-[(1-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethyl]phenyl}-4-hydroxypiperidin-4-yl)methoxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1481] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 156.0-156.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.88 (2H, m), 1.91-1.97 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.15 (4H, m), 3.24-3.26 (2H, m), 3.85 (2H, s), 4.11-4.14 (2H, m), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.81-6.83 (2H, m), 6.91-6.97 (4H, m), 7.08 (1H, d, J = 12.0 Hz), 7.52 (1H, brs).

Example 222

5-{[1-(5-Ethyl-2,4-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1482] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 186.7-186.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 1.87-1.89 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.61 (2H, q, J = 7.5 Hz), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.07-3.12 (2H, m), 3.18-3.20 (2H, m), 3.86 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.76 (1H, dd, J = 12.0 Hz, 9.5 Hz), 6.84 (1H, dd, J = 9.0 Hz, 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.54 (1H, brs).

Example 223

5-{[1-(2,4-Difluoro-5-propylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1483] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 184.7-184.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 0.95 (3H, t, J = 7.0 Hz), 1.56-1.64 (2H, m), 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.02 (1H, brs), 2.55 (2H, t, J = 7.5 Hz), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.12 (2H, m), 3.17-3.20 (2H, m), 3.86 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.76 (1H, dd, J = 12.0 Hz, 9.5 Hz), 6.82 (1H, dd, J = 9.5 Hz, 8.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.55 (1H, brs).

Example 224

8-Chloro-5-{[1-(2,4-difluoro-5-propylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1484] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 156.9-157.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 0.94 (3H, t, J = 7.0 Hz), 1.54-1.64 (2H, m), 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 1.98 (1H, brs), 2.55 (2H, t, J = 7.5 Hz), 2.65 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.06-3.12 (2H, m), 3.17-3.20 (2H, m), 3.88 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.76 (1H, dd, J = 11.5 Hz, 9.5 Hz), 6.81 (1H, dd, J = 9.5 Hz, 8.0 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 225

8-Chloro-5-{[1-(5-ethyl-2,4-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1485] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 178.8-178.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 1.99 (1H, brs), 2.61 (2H, q, J = 7.5 Hz), 2.65 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.07-3.12 (2H, m), 3.18-3.20 (2H, m), 3.88 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.76 (1H, dd, J = 11.5 Hz, 9.5 Hz), 6.84 (1H, dd, J = 9.0 Hz, 8.0 Hz), 7.20 (1H, t, J = 9.0 Hz), 7.75 (1H, brs).

Example 226

8-Chloro-5-({1-[4-(ethylsulfanyl)-2,6-difluorophenyl]-4-hydroxypiperidin-4-yl}meth oxy)-3,4-dihydroquinolin-2(1H)-one

[1486] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 157.4-157.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.32 (3H, t, J = 7.5 Hz), 1.80-1.83 (2H, m), 1.87-1.93 (2H, m), 1.99 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 2.90 (2H, q, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.08-3.10 (2H, m), 3.44-3.49 (2H, m), 3.87 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.78-6.84 (2H, m), 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 227

8-Fluoro-5-{[1-(2-fluoro-4-{[5-(trifluoromethyl)pyridin-2-yl]methoxy}phenyl)-4-hy droxypiperidin-4-yl]methoxy}-3,4-dihy-droquinolin-2(1H)-one

[1487] Synthesized analogous to Example 148.
(Ethyl acetate) m.p. 194.9-195.1 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.93-1.99 (2H, m), 2.01 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.03 (2H, t, J = 7.5 Hz), 3.05-3.11 (2H, m), 3.16-3.19 (2H, m), 3.85 (2H, s), 5.22 (2H, s), 6.49 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.68-6.71 (1H, m), 6.76 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz), 6.98 (1H, t, J = 9.0 Hz), 7.53 (1H, d, J = 2.0 Hz), 7.66 (1H, d, J = 8.5 Hz), 7.96 (1H, dd, J = 8.5 Hz, 2.0 Hz), 8.86 (1H, brs).

Example 228

5-({1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1488] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 189.8-189.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.83 (2H, m), 1.87-1.92 (2H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 2.98-3.02 (2H, m), 3.02 (2H, t, J = 7.5 Hz), 3.42-3.47 (2H, m), 3.85 (2H, s), 4.26-4.31 (2H, m), 6.46-6.52 (3H, m), 6.93 (1H, t, J = 9.0 Hz), 7.52 (1H, brs).

Example 229

8-Chloro-5-({1-[2,6-difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

[1489] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 178.6-178.7 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.83 (2H, m), 1.87-1.93 (2H, m), 2.01 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 2.98-3.02 (2H, m), 3.02 (2H, t, J = 7.5 Hz), 3.42-3.47 (2H, m), 3.87 (2H, s), 4.26-4.31 (2H, m), 6.46-6.52 (2H, m), 6.55 (1H, d, J = 9.0 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 230

8-Chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethyl)phenyll-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

[1490] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.89 (2H, m), 1.92-1.98 (2H, m), 1.99 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 2.95 (2H, t, J = 7.0 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.09-3.14 (2H, m), 3.24-3.26 (2H, m), 3.37 (3H, s), 3.58 (2H, t, J = 7.0 Hz), 3.88 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.90 (1H, d, J = 9.0 Hz), 7.05 (1H, d, J = 11.5 Hz), 7.20 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 231

8-Chloro-7-fluoro-5-{[4-hydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4 -yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

[1491] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 249.4-250.5 °C (dec)
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.70 (2H, m), 1.80-1.86 (2H, m), 2.48 (2H, t, J = 7.5 Hz), 2.90 (2H, t, J = 7.5 Hz), 2.99-3.08 (4H, m), 3.84 (2H, s), 4.83 (1H, brs), 6.84 (1H, d, J = 11.5 Hz), 7.28 (1H, d, J = 7.5 Hz), 7.47 (1H, d, J = 10.5 Hz), 9.67 (1H, brs).

Example 232

7,8-Difluoro-5-{[4-hydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4-yl]m ethoxy}-3,4-dihydroquinolin-2(1H)-one

[1492] Synthesized analogous to Example 42.
White powder (Acetic acid/water) (5: 2) m.p. 258.9-259.0 °C (dec)
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.69 (2H, m), 1.80-1.86 (2H, m), 2.47 (2H, t, J = 7.5 Hz), 2.88 (2H, t, J = 7.5 Hz), 2.99-3.07 (4H, m), 3.80 (2H, s), 4.81 (1H, brs), 6.74 (1H, dd, J = 12.5 Hz, 6.0 Hz), 7.27 (1H, d, J = 7.5 Hz), 7.47 (1H, d, J = 11.0 Hz), 10.30 (1H, brs).

Example 233

5-1[1-(4-Bromo-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-7-f luoro-3,4-dihydroquinoli-2(1H)-one

[1493] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 200.5-200.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.82 (2H, m), 1.86-1.92 (2H, m), 1.94 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J = 7.5 Hz), 3.08-3.10 (2H, m), 3.44-3.49 (2H, m), 3.85 (2H, s), 6.46 (1H, d, J = 10.5 Hz), 7.00-7.06 (2H, m), 7.76 (1H, brs).

Example 234

5-{[1-(4-Bromo-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro -3,4-dihydroquinolin-2(1H)-one

[1494] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 233.1-233.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.82 (2H, m), 1.85-1.91 (2H, m), 1.96 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 2.97 (2H, t, J = 7.5 Hz), 3.08-3.10 (2H, m), 3.44-3.49 (2H, m), 3.81 (2H, s), 6.41 (1H, dd, J = 12.0 Hz, 6.5 Hz), 7.00-7.06 (2H, m), 7.58 (1H, brs).

Example 235

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-meth yl-3,4-dihydroquinolin-2(1H)-one

[1495] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.72 (2H, m), 1.79-1.87 (2H, m), 2.04 (3H, d, J = 1.5 Hz), 2.43 (2H, t, J = 7.2 Hz), 2.83 (2H, t, J = 7.2 Hz), 2.98-3.06 (2H, m), 3.11-3.20 (2H, m), 3.77 (2H, s), 4.72 (1H, s), 6.54 (1H, d, J = 12.0 Hz), 7.05-7.18 (2H, m), 7.30 (1H, dd, J = 12.0 Hz, 2.4 Hz), 9.56 (1H, s).

Example 236

5-{[1-(4-Chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl- 3,4-dihydroquinolin-2(1H)-one

[1496] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.74 (2H, m), 1.78-1.83 (2H, m), 2.04 (3H, d, J = 2.9 Hz), 2.40 (2H, t, J = 7.2 Hz), 2.82 (2H, t, J = 7.2 Hz), 3.04-3.08 (2H, m), 3.17-3.23 (2H, m), 3.77 (2H, s), 4.71 (1H, s), 6.54 (1H, d, J = 12.0 Hz), 7.12 (1H, dd, J = 9.0 Hz, 7.8 Hz), 7.48 (1H, dd, J = 12.0 Hz, 7.2 Hz), 9.56 (1H, s).

Example 237

5-({1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}metho xy)-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1497] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.82 (2H, m), 1.86-1.92 (2H, m), 1.96 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J = 7.5 Hz), 2.99-3.02 (2H, m), 3.42-3.46 (2H, m), 3.81 (2H, s), 4.26-4.31 (2H, m), 6.41 (1H, dd, J = 11.5 Hz, 6.0 Hz), 6.47-6.52 (2H, m), 7.56 (1H, brs).

Example 238

8-Chloro-5-({1-[2,6-difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1498] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.82 (2H, m), 1.87-1.93 (2H, m), 1.96 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 2.98 (2H, t, J = 7.5 Hz), 3.00-3.02 (2H, m), 3.42-3.46 (2H, m), 3.85 (2H, s), 4.26-4.31 (2H, m), 6.47 (1H, d, J = 10.5 Hz), 6.47-6.52 (2H, m), 7.77 (1H, brs).

Example 239

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-ethyl-7-fluoro -3,4-dihydroquinolin-2(1H)-one

[1499] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 0.98 (3H, t, J = 7.5 Hz), 1.66 (2H, m), 1.79-1.88 (2H, m), 2.37-2.43 (2H, m), 2.59-2.62 (2H, m), 2.82 (2H, t, J = 7.5 Hz), 3.01-3.06 (2H, m), 3.11-3.13 (2H, m), 3.77 (2H, s), 4.71 (12H, s), 6.53 (1H, d, J = 12.0 Hz), 7.08-7.15 (2H, m), 7.29 (1H, dd, J = 12.0 Hz, 2.4 Hz), 9.58 (1H, s).

Example 240

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-7-hydr oxy-3,4-dihydroquinolin-2(1H)-one

[1500] To a mixture of 5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-met hoxybenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one (350 mg) and anisole (0.12 mL) was added trifluoroacetic acid (10 mL), the reaction mixture was stirred at 60 °C for 30 min, and the reaction solution was concentrated. To the residue was added water, and the precipitate was collected on a filter. The product was crystallized from methanol, the obtained crystal was collected on a filter, and air-dried (60 °C) to provide the title compound (160 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.58-1.70 (2H, m), 1.80-1.87 (2H, m), 2.41 (2H, t, J = 6.9 Hz), 2.82 (2H, t, J = 7.8 Hz), 2.98-3.05 (2H, m), 3.10-3.15 (2H, m), 3.72 (2H, s), 4.68 (1H, s), 6.53 (1H, d, J = 12.0 Hz), 7.05-7.18 (2H, m), 7.30 (1H, dd, J = 12.0 Hz, 2.4 Hz), 9.6910 (12H, brs), 9.89 (1H, s).

Example 241

8-Bromo-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-f luoro-3,4-dihydroquinolin-2(1H)-one

[1501] To a suspension of 5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-d ihydroquinolin-2(1H)-one (400 mg) in acetic acid (10 mL) was added bromine (0.049 mL), and the reaction mixture was stirred at 50 °C for 40 min. The solvent was distilled off, the residue was purified by silica gel column chromatography (basic silica gel; dichloromethane), and washed with acetonitrile to provide the title compound (237 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.83 (4H, m), 2.42-2.56 (2H, m), 2.83-3.03 (4H, m), 3.27-3.42 (2H, m), 3.84 (2H, m), 4.76 (1H, brs), 6.84 (1H, d, J = 11.1 Hz), 7.20-7.32 (2H, m), 9.24 (1H, brs).

Example 242

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-i odo-3,4-dihydroquinolin-2(1H)-one

[1502] To a suspension of 5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-d ihydro-

quinolin-2(1H)-one (1.0 g) in acetic acid (25 mL) was added N-iodosuccinimide (0.536 g), and the reaction mixture was stirred at 60 °C for 1 h. The solvent was distilled off, the residue was purified by silica gel column chromatography (basic silica gel/dichloromethane), and washed with acetonitrile to provide the title compound (382 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.59-1.83 (4H, m), 2.42-2.53 (2H, m), 2.83-3.03 (4H, m), 3.25-3.41 (2H, m), 3.84 (2H, s), 4.76 (1H, s), 6.78 (1H, d, J = 10.5 Hz), 7.20-7.32 (2H, m), 8.58 (1H, brs).

Example 243

5-[[1-(2,2-Difluoro-1,3-benzodioxol-5-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1503] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 198.4-198.5 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.93 (4H, m), 2.03 (1H, brs), 2.66 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.13-3.19 (2H, m), 3.34-3.37 (2H, m), 3.84 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.63 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.75 (1H, d, J = 2.5 Hz), 6.91-6.95 (2H, m), 7.54 (1H, brs).

Example 244

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-hydr oxy-3,4-dihydroquinolin-2(1H)-one

[1504] A suspension of 5-(benzyloxy)-7-fluoro-8-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-o ne (290 mg), potassium carbonate (300 mg) and 20 % palladium hydroxide on carbon (300 mg) in 2-propanol (9 mL) was stirred at room temperature for 1 h under hydrogen atmosphere. After insoluble materials were filtered off, the solvent was distilled off. To a residue were added 6-(4-chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (377 mg), sodium hydroxide (156 mg) and N,N-dimethylformamide/2-propanol (1:1) (10 mL), and the reaction mixture was stirred at 70 °C for 7 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (basic silica gel; hexane/ethyl acetate -> ethyl acetate) to give 5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-(tetrah ydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one (110 mg). The obtained product was dissolved into trifluoroacetic acid (1 mL), the solution was stirred at room temperature for 3 min and the reaction solution was concentrated. Water was added to the residue, the precipitate was collected on a filter and washed with ethanol to provide the title compound (80 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.62-1.7568 (2H, m), 1.79-1.86 (2H, m), 2.41 (2H, m), 2.82 (2H, m), 2.97-3.16 (4H, m), 3.71 (2H, s), 6.53 (1H, d, J = 12.0 Hz), 7.05-7.18 (2H, m), 7.30 (1H, dd, J = 12.0 Hz, 2.4 Hz), 9.11 (2H, s).

Example 245

8-Fluoro-5-{[4-hydroxy-1-(1-methyl-1H-benzimidazol-2-yl)piperidin-4-yl]methoxy} -3,4-dihydroquinolin-2(1H)-one

[1505] A solution of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one (0.25 g), 2-chloro-1-methyl-1H-benzimidazole (0.156 g) and triethylamine (0.355 mL) in N-methyl-2-pyrrolidone (NMP) (0.3 mL) was stirred at 95 °C for 48 h. To the reaction solution were added water and ethyl acetate, and the insoluble precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (basic silica gel; dichloromethane/methanol) and recrystallized from ethanol/water. The precipitate was collected on a filter, and air-dried (60 °C) to provide the title compound (0.14 g).
(Ethanol/water) m.p. 229-230 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.72 (2H, m), 1.89-2.00 (2H, m), 2.44 (2H, t, J = 7.6 Hz), 2.91 (2H, t, J = 7.6 Hz), 3.24-3.36 (2H, m), 3.37-3.45 (2H, m), 3.60 (3H, s), 3.80 (2H, s), 4.80 (1H, s), 6.60 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.05-7.11 (2H, m), 7.29-7.34 (1H, m), 7.37-7.42 (1H, m), 10.02 (1H, s).

Example 246

5-{[1-(1,3-Benzoxazol-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydr oquinolin-2(1H)-one

[1506] A solution of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one (0.25 g), 2-chlorobenzoxazole (0.107 mL) and potassium carbonate (0.141 g) in N,N-dimethylformamide (3 mL) was stirred at room temperature for 24 h. To a solution were added water and ethyl acetate, and the insoluble precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (dichloromethane/methanol), and recrys-

tallized from ethanol/water. The precipitate was collected on a filter and dried under reduced pressure (100 °C) to provide the title compound (0.22 g).
(Ethanol/water) m.p. 207-208 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.73 (2H, m), 1.74-1.84 (2H, m), 2.40 (2H, t, J = 7.6 Hz), 2.86 (2H, t, J = 7.6 Hz), 3.41-3.50 (2H, m), 3.78 (2H, s), 3.97-4.04 (2H, m), 4.93 (1H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.97-7.04 (2H, m), 7.14 (1H, dt, J = 1.1 Hz, 7.7 Hz), 7.27 (1H, d, J = 7.1 Hz), 7.39 (1H, d, J = 7.8 Hz), 10.01 (1H, s).

Example 247

5-{[1-(6-Chloro-1,3-benzoxazol-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1507] Synthesized analogous to Example 246.
(Acetic acid/water) m.p. 249-250 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.74 (2H, m), 1.74-1.83 (2H, m), 2.41 (2H, t, J = 7.6 Hz), 2.87 (2H, t, J = 7.6 Hz), 3.41-3.51 (2H, m), 3.78 (2H, s), 3.95-4.04 (2H, m), 4.94 (1H, s), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.7 Hz), 7.19 (1H, dd, J = 8.3 Hz, 2.0 Hz), 7.26 (1H, d, J = 8.3 Hz), 7.56 (1H, d, J = 2.0 Hz), 10.01 (1H, s).

Example 248

5-1[1-(2-Bromo-4-chloro-6-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1508] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.63 (2H, d, J = 12.4 Hz), 1.82-1.88 (2H, m), 2.46 (2H, t, J = 7.7 Hz), 2.88-2.95 (4H, m), 3.38 (2H, t, J = 11.7 Hz), 3.77 (2H, s), 4.71 (1H, s), 6.59 (1H, dd, J = 9.1 Hz, 3.0 Hz), 7.01 (1H, t, J = 11.1 Hz), 7.48 (1H, dd, J = 11.9 Hz, 2.4 Hz), 7.61 (1H, m), 10.02 (1H, s).

Example 249

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1509] Synthesized analogous to Example 33.
(2-Propanol) m.p. 202.6-204.8 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.75 (1H, m), 1.88-1.99 (1H, m), 2.44 (2H, t, J = 7.7 Hz), 2.77-2.90 (2H, m), 2.93-3.05 (1H, m), 3.07-3.16 (1H, m), 3.53-3.64 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.76-3.84 (1H, m), 4.01 (1H, d, J = 8.8 Hz), 4.55 (1H, brs), 4.92 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.4 Hz), 8.02 (1H, d, J = 2.4 Hz), 8.26 (1H, d, J = 2.4 Hz), 10.00 (1H, brs).

Example 250

5-{[(3S*,4S*)-1-(2,4-Dichlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1510] To a mixture of 5-{[(3S*,4S*)-1-(2,4-dichlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methox ybenzyl)-3,4-dihydroquinolin-2(1H)-one (40 mg) and anisole (0.05 mL) was added trifluoroacetic acid (5 mL), the reaction mixture was stirred at 60 °C for 3 h, and the reaction solution was concentrated. The residue was dissolved into methanol, neutralized with aqueous sodium hydroxide, methanol was distilled off and insoluble precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (dichloromethane/ethyl acetate -> dichloromethane/methanol), and the obtained product was washed with dichloromethane/hexane to provide the title compound (14 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.79 (1H, m), 1.90-2.01 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.78-2.85 (1H, m), 2.86-2.95 (2H, m), 2.95-3.04 (2H, m), 3.07-3.14 (1H, m), 3.71 (1H, d, J = 8.9 Hz), 3.77-3.85 (1H, m), 4.02 (1H, d, J = 8.9 Hz), 4.52 (1H, brs), 4.91 (1H, d, J = 6.4 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.6 Hz), 7.18 (1H, d, J = 8.6 Hz), 7.35 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.54 (1H, d, J = 2.4 Hz), 10.01 (1H, brs).

Example 251

5-{[(3R,4R)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-f luoro-3,4-dihydroquinolin-2(1H)-one

[1511] Synthesized analogous to Example 33.

^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.73 (1H, m), 1.90-1.97 (1H, m), 2.44 (2H, t, J = 7.7 Hz), 2.80-2.87 (2H, m), 2.97 (1H, t, J = 11.3 Hz), 3.11 (1H, dt, J = 2.3 Hz, 12.6 Hz), 3.55-3.62 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.78-3.82 (1H, m), 4.02 (1H, d, J = 8.9 Hz), 4.57 (1H, s), 4.94 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 8.02 (1H, d, J = 2.3 Hz), 8.26 (1H, d, J = 2.3 Hz), 10.02 (1H, s).

Example 252

5-{[(3S,4S)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1512] Synthesized analogous to Example 33.
^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.73 (1H, m), 1.90-1.97 (1H, m), 2.44 (2H, t, J = 7.7 Hz), 2.80-2.87 (2H, m), 2.97 (1H, t, J = 11.3 Hz), 3.11 (1H, dt, J = 2.3 Hz, 12.6 Hz), 3.55-3.62 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.78-3.82 (1H, m), 4.02 (1H, d, J = 8.9 Hz), 4.57 (1H, s), 4.94 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 8.02 (1H, d, J = 2.3 Hz), 8.26 (1H, d, J = 2.3 Hz), 10.02 (1H, s).

Example 253

5-{[(3S*,4S*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1513] Synthesized analogous to Example 250.
(2-Propanol) m.p. 191.9-193.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.78 (1H, m), 1.88-2.00 (1H, m), 2.46 (2H, t, J = 7.5 Hz), 2.80-2.92 (3H, m), 2.93-3.03 (1H, m), 3.05-3.21 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.74-3.84 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.55 (1H, brs),4.90-4.95 (1H, m), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.5 Hz), 7.08 (1H, t, J = 9.5 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.0 Hz), 7.32 (1H, d, J = 12.5 Hz, 2.4 Hz), 10.01 (1H, brs).

Example 254

2-[(3R,4R)-4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-di hydroxypiperidin-1-yl]-5-iodopyridine-3-carbonitrile

[1514] Synthesized analogous to Example 6.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-2.01 (2H, m), 2.63 (2H, t, J = 7.8 Hz), 2.74 (1H, s), 2.79 (1H, d, J = 7.8 Hz), 2.91-3.00 (2H, m), 3.30 (1H, dd, J = 12.9 Hz, 10.2 Hz), 3.43-3.49 (1H, m), 3.96-4.02 (3H, m), 4.17-4.30 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.56 (1H, brs), 7.98 (1H, d, J = 2.3 Hz), 8.47 (1H, d, J = 2.3 Hz).

Example 255

2-[(3S,4S)-4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dih ydroxypiperidin-1-yl]-5-iodopyridine-3-carbonitrile

[1515] Synthesized analogous to Example 6.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-2.01 (2H, m), 2.63 (2H, t, J = 7.8 Hz), 2.74 (1H, s), 2.79 (1H, d, J = 7.8 Hz), 2.91-3.00 (2H, m), 3.30 (1H, dd, J = 12.9 Hz, 10.2 Hz), 3.43-3.49 (1H,m), 3.96-4.02 (3H, m), 4.17-4.30 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.56 (1H, brs), 7.98 (1H, d, J = 2.3 Hz), 8.47 (1H, d, J = 2.3 Hz).

Example 256

5-{[(3R*,4R*)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1516] To a solution of 5-{[1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro -3,4-dihydroquinolin-2(1H)-one (285 mg) in acetone-water (3: 1) (3 mL) were added • aqueous solution of 4 % osmium tetraoxide (428 mg) and aqueous solution of 4.8 M N-methylmorpholine N-oxide (NMO) (0.28 mL) under nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 18 h. To the reaction solution was added tetrahydrofuran (THF) (2 mL), and the mixture was stirred at 50 °C for 1 h. To the mixture was added saturated sodium thiosulfate aqueous solution, the mixture was stirred at room temperature for 30 min, and the precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (ethyl acetate) and recrystallized from ethyl acetate. The precipitate

was collected on a filter and dried to provide the title compound (157 mg).
(Ethyl acetate) m.p. 199-201 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (1H, d, J = 13.0 Hz), 1.91 (1H, dt, J = 4.3 Hz, 13.0 Hz), 2.45-2.50 (2H, m), 2.84-2.98 (4H, m), 3.21 (1H, t, J = 10.8 Hz), 3.30-3.35 (1H, m), 3.68 (1H, d, 8.8 Hz), 3.71-3.76 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.55 (1H, s), 4.88 (1H, d, J = 6.5 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.1 Hz), 7.25-7.30 (2H, m), 10.03 (1H, s).

Example 257

8-Chloro-5-{[(3S*,4S*)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy}-3,4-dihydroquinolin-2(1H)-one

[1517] To a solution of 8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy} -3,4-dihydroquinolin-2(1H)-one (415 mg) in tetrahydrofuran (8ml)/water (2ml) were added Osmium Oxide, Immobilized Catalyst I (content: 7 %) (172 mg) and aqueous solution of 4.8 M N-methylmorpholine-N-oxide (NMO) (0.394 mL), and the reaction mixture was stirred at room temperature for 16 h, then at 50 °C for 1 h. To the reaction solution was added saturated sodium thiosulfate aqueous solution, the solution was stirred at room temperature for 30 min, and the precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (ethyl acetate) and recrystallized from ethyl acetate. The precipitate was collected on a filter and dried to provide the title compound (145 mg).
m.p. 195-198 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70 (1H, d, J = 13.0 Hz), 1.90 (1H, dt, J = 4.5 Hz, 13.0 Hz), 2.47-2.51 (2H, m), 2.87-2.98 (4H, m), 3.21 (1H, t, J = 10.8 Hz), 3.29-3.35 (1H, m), 3.70-3.75 (2H, m), 4.05 (1H, d, J = 8.8 Hz), 4.57 (1H, s), 4.89 (1H, d, J = 6.4 Hz), 6.68 (1H, d, J = 9.0 Hz), 7.25 (1H, d, J = 9.0 Hz), 7.27-7.30 (2H, m), 9.38 (1H, s).

Example 258

5-{[(3S*,4S*)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1518] Synthesized analogous to Example 257.
(Ethyl acetate) m.p. 215-217 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (1H, d, J = 12.9 Hz), 1.87 (1H, dt, J = 4.7 Hz, 12.9 Hz), 2.45-2.50 (2H, m), 2.80-2.90 (3H, m), 2.96 (1H, dd, J = 10.8 Hz, 4.7 Hz), 3.20 (1H, t, J = 10.8 Hz), 3.30-3.34 (1H, m), 3.68-3.73 (2H, m), 4.02 (1H, d, J = 9.5 Hz), 4.56 (1H, s), 4.89 (1H, d, J = 6.4 Hz), 6.74 (1H, dd, J = 12.7 Hz, 6.2 Hz), 7.25-7.31 (2H, m), 10.31 (1H, s).

Example 259

5-{[(3R,4R)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-f luoro-3,4-dihydroquinolin-2(1H)-one

[1519] A solution of 5-{[(3R,4R)-3-{[tert-butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxy piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-on e (1.0 g), anisole (0.1 mL) in trifluoroacetic acid (10 mL) was stirred at 60 °C for 4 h, methanol (10 mL) was added thereto and the mixture was stirred at 60 °C overnight. The reaction solution was concentrated, the residue was purified by silica gel column chromatography (dichloromethane -> dichloromethane/ethyl acetate), and recrystallized from ethanol. The precipitate was collected on a filter and dried to provide the title compound (417 mg, > 99 % ee).
(Ethanol) m.p. 184-185 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.78 (1H, m), 1.88-2.00 (1H, m), 2.46 (2H, t, J = 7.6 Hz), 2.80-2.92 (3H, m), 2.93-3.03 (1H, m), 3.05-3.21 (2H, m), 3.69 (1H, d, J = 8.8 Hz), 3.75-3.84 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.56 (1H, brs), 4.90-4.96 (1H, m), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.5 Hz), 7.08 (1H, t, J = 9.5 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.0 Hz), 7.32 (1H, d, J = 12.8 Hz, 2.4 Hz), 10.01 (1H, brs).

Example 260

5-{[(3R,4R)-1-(4-Chloro-2,6-difluoropheny])-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1520] A solution of bis(dihydroquinidinyl)phthalazine ($(DHQD)_2PHAL$) (44.2 mg) and potassium osmate(VI) dihydrate (5.23 mg) in acetone-water (2: 1) (24 mL) was stirred at room temperature for 15 min, aqueous solution of 4.8 M N-

methylmorpholine-N-oxide (0.296 mL) and 5-{[1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro -3,4-dihydroquinolin-2(lH)-one (400 mg) were added thereto under ice-cooling, and the mixture was stirred at room temperature for 3 days. To the reaction solution was added saturated sodium sulfite aqueous solution, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with ethyl acetate. The extract was purified by silica gel column chromatography (ethyl acetate), and the residue was recrystallized form acetic acid/water. The precipitate was collected on a filter, and dried under reduced pressure (60 °C) to provide the title compound (210 mg, > 99 % ee).
m.p. 193-195 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (1H, d, J = 13.1 Hz), 1.91 (1H. dt, J = 4.7 Hz, 13.1 Hz), 2.45-2.51 (2H, m), 2.86-2.91 (3H, m), 2.96 (1H, dd, J = 10.7 Hz, 5.9 Hz), 3.21 (1H, t, J = 10.7 Hz), 3.30-3.34 (1H, m), 3.67 (1H, d, J = 8.8 Hz), 3.70-3.76 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.54 (1H, s), 4.88 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.2 Hz), 7.25-7.30 (2H, m), 10.03 (1H, s).

Example 261

5-{[(3S,4S)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1521] By the procedures analogous to Example 260, with $(DHQ)_2PHAL$ instead of $(DHQD)_2PHAL$, the title compound was obtained.
(Acetic acid) m.p. 190-193 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.1 Hz), 1.90 (1H, dt, J = 4.8 Hz, 13.1 Hz), 2.45-2.50 (2H, m), 2.84-2.91 (3H, m), 2.96 (1H, dd, J = 10.9 Hz, 5.8 Hz), 3.21 (1H, t, J = 10.9 Hz), 3.30-3.34 (1H, m), 3.67 (1H, d, 8.8 Hz), 3.72-3.74 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.55 (1H, s), 4.88 (1H, d, J = 5.6 Hz), 6.57 (1H, dd, J = 9.4 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.4 Hz), 7.25-7.31 (2H, m), 10.03 (1H, s).

Example 262

5-{[(3R*,4R*)-3,4-Dihydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4-yl] methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1522] Synthesized analogous to Example 259.
(Ethanol) m.p. 197.4-197.5 °C^{1}HNMR ($CDCl_3$) δ ppm: 1.96-2.04 (2H, m), 2.53 (1H, brs), 2.65 (2H, t, J = 7.5 Hz), 2.65 (1H, brs), 2.91 (1H, t, J = 10.0 Hz), 2.99-3.10 (4H, m), 3.26-3.30 (1H, m), 3.99 (1H, d, J = 9.0 Hz), 4.03-4.07 (1H, m), 4.04 (1H, d, J = 9.0 Hz), 6.52 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.82 (1H, d, J = 7.0 Hz), 6.87 (1H, d, J = 10.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 7.56 (1H, brs).

Example 263

8-Chloro-5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy}-3,4-dihydroquinolin-2(1H)-one

[1523] Synthesized analogous to Example 260.
(Acetic acid) m.p. 197-199 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70 (1H, d, J = 13.0 Hz), 1.90 (1H, dt, J = 4.8 Hz, 13.0 Hz), 2.47-2.52 (2H, m), 2.88-2.98 (4H, m), 3.21 (1H, t, J = 10.7 Hz), 3.31-3.35 (1H, m), 3.70-3.76 (2H, m), 4.05 (1H, d, J = 8.9 Hz), 4.58 (1H, s), 4.90 (1H, d, J = 6.0 Hz), 6.68 (1H, d, J = 9.0 Hz), 7.24-7.29 (3H, m), 9.38 (1H, s).

Example 264

5-{[(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1524] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 199-201 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (1H, d, J = 12.8 Hz), 1.87 (1H, dt, J = 4.8 Hz, 12.8 Hz), 2.46-2.51 (2H, m), 2.82-2.90 (3H, m), 2.96 (1H, dd, J = 10.6 Hz, 5.0 Hz), 3.20 (1H, t, J = 10.6 Hz), 3.29-3.34 (1H, m), 3.68-3.73 (2H, m), 4.01 (1H, d, J = 9.0 Hz), 4.57 (1H, s), 4.89 (1H, d, J = 6.4 Hz), 6.73 (1H, dd, J = 12.6 Hz, 6.1 Hz), 7.25-7.30 (2H, m), 10.31 (1H, s).

Example 265

5-{[(3S,4S)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1525] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.77 (1H, m), 1.89-2.00 (1H, m), 2.46 (2H, t, J = 7.6 Hz), 2.80-2.92 (3H, m), 2.93-3.03 (1H, m), 3.05-3.21 (2H, m), 3.69 (1H, d, J = 8.8 Hz), 3.75-3.84 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.54 (1H, brs), 4.88-4.95 (1H, m), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.5 Hz), 7.08 (1H, t, J = 9.5 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.0 Hz), 7.32 (1H, d, J = 12.8 Hz, 2.4 Hz), 10.00 (1H, brs).

Example 266

5-{[(3S*,4S*)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1526] Synthesized analogous to Example 257.
^{1}HNMR (DMSO-d6) δ ppm: 1.73 (1H, d, J = 13.1 Hz), 1.95 (1H, dt, J = 5.2 Hz, 13.1 Hz), 2.46 (2H, t, J = 7.7 Hz), 2.81-2.92 (3H, m), 2.97 (1H, t, J = 11.0 Hz), 3.09-3.19 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.79 (1H, brs), 4.02 (1H, d, J = 8.8 Hz), 4.57 (1H, brs), 4.94 (1H, brs), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00-7.05 (2H, m), 7.29 (1H, dd, J = 8.7 Hz, 1.6 Hz), 7.42 (1H, dd, J = 12.3 Hz, 2.3 Hz), 10.03 (1H, s).

Example 267

5-{[(3R,4R)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-f luoro-3,4-dihydroquinolin-2(1H)-one

[1527] A solution of bis(dihydroquinidinyl)phthalazine ($(DHQD)_2PHAL$) (30.3 mg), potassium osmate(VI) dihydrate (5.74 mg) and methanesulfonamide (111 mg) in acetone-water (1:1) (10 mL) was stirred at room temperature for 15 min, aqueous solution of 4.8 M N-methylmorpholine-N-oxide (43.4 mg) and 5-{[1-(4-bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one (350 mg) was added thereto under ice-cooling, and the reaction mixture was stirred at room temperature for 10 days. To the reaction solution was added saturated sodium sulfite aqueous solution, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with ethyl acetate. The obtained extract was filtered with silica gel, and the filtrate was concentrated. To the residue were added acetic acid and water, the precipitate was filtered off, water was added to the filtrate and the precipitate was collected on a filter. The resultant precipitate was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (35 mg, 97 % ee).
^{1}HNMR (DMSO-d6) δ ppm: 1.73 (1H, d, J = 13.1 Hz), 1.95 (1H, dt, J = 4.4 Hz, 13.1 Hz), 2.46 (2H, t, J = 7.7 Hz), 2.81-3.00 (4H, m), 3.08-3.12 (1H, m), 3.17 (1H, dd, J = 10.8 Hz, 4.5 Hz), 3.68 (1H, d, J = 8.7 Hz), 3.77-3.82 (1H, m), 4.02 (1H, d, J = 8.7 Hz), 4.57 (1H, s), 4.94 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.0 Hz, 3.7 Hz), 7.00-7.05 (2H, m), 7.29 (1H, dd, J = 8.3 Hz, 1.9 Hz), 7.42 (1H, dd, J = 12.3 Hz, 2.3 Hz), 10.03 (1H, s).

Example 268

5-{[(3R,4R)-3,4-Dihydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4-yl]m ethoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1528] Synthesized analogous to Example 259.
^{1}HNMR ($CDCl_3$) δ ppm: 1.98-2.01 (2H, m), 2.53-2.54 (1H, m), 2.63-2.66 (3H,m), 2.89-3.29 (5H, m), 3.26-3.29 (1H, m), 3.99 (1H, d, J = 9.1 Hz), 4.03-4.08 (2H, m), 6.52 (1H, dd, J = 3.9 Hz, 9.1 Hz), 6.82 (1H, t, J = 7.0 Hz), 6.87 (1H, d, J = 10.3 Hz), 6.94 (1H, t, J = 9.4 Hz), 7.55 (1H, brs).

Example 269

5-{[(3R*,4R*)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8 -chloro-3,4-dihydroquinolin-2(1H)-one

[1529] Synthesized analogous to Example 257.
(Acetic acid/water) m.p. 190-192 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74 (1H, d, J = 13.1 Hz), 1.94 (1H, dt, J = 4.9 Hz, 13.1 Hz), 2.45-2.50 (2H, m), 2.81-3.00

(4H, m), 3.10 (1H, d, J = 9.6 Hz), 3.17 (1H, dd, J = 10.7 Hz, 4.9 Hz), 3.73 (1H, d, J = 8.9 Hz), 3.78-3.80 (1H, m), 4.05 (1H, d, J = 8.9 Hz), 4.60 (1H, s), 4.96 (1H, brs), 6.68 (1H, d, J = 9.0 Hz), 7.02 (1H, t, J = 9.0 Hz), 7.25 (1H, d, J = 9.0 Hz), 7.29 (1H, dd, J = 8.6 Hz, 1.6 Hz), 7.42 (1H, dd, J = 12.2 Hz, 2.3 Hz), 9.37 (1H, s).

Example 270

5-{[(3R*,4R*)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-7, 8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1530] Synthesized analogous to Example 257.
(Acetic acid/water) m.p. 214-216 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.73 (1H, d, J = 12.9 Hz), 1.91 (1H, dt, J = 4.4 Hz, 12.9 Hz), 2.46 (2H, t, J = 7.7 Hz), 2.81-3.00 (4H, m), 3.10 (1H, d, J = 11.6 Hz), 3.17 (1H, dd, J = 10.6 Hz, 4.5 Hz), 3.73 (1H, d, J = 9.0 Hz), 3.74-3.79 (1H, m), 4.01 (1H, d, J = 9.0 Hz), 4.59 (1H, s), 4.96 (1H, d, J = 6.1 Hz), 6.73 (1H, dd, J = 12.7 Hz, 6.2 Hz), 7.02 (1H, t, J = 9.1 Hz), 7.29 (1H, dd, J = 8.6 Hz, 1.6 Hz), 7.42 (1H, dd, J = 12.3 Hz, 2.3 Hz), 10.31 (1H, s).

Example 271

5-{[(3R,4R)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-c hloro-3,4-dihydroquinolin-2(1H)-one

[1531] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 183-184 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74 (1H, d, J = 13.2 Hz), 1.94 (1H, dt, J = 4.6 Hz, 13.2 Hz), 2.45-2.49 (2H, m), 2.82-3.00 (4H, m), 3.10 (1H, d, J = 10.1 Hz), 3.17 (1H, dd, J = 11.0 Hz, 4.4 Hz), 3.73 (1H, d, J = 8.9 Hz), 3.78 (1H, brs), 4.05 (1H, d, J = 8.9 Hz), 4.60 (1H, brs), 4.96 (1H, brs), 6.68 (1H, d, J = 8.8 Hz), 7.02 (1H, t, J = 9.1 Hz), 7.25 (1H, d, J = 8.8 Hz), 7.29 (1H, dd, J = 8.6 Hz, 1.5 Hz), 7.42 (1H, dd, J = 12.2 Hz, 2.3 Hz), 9.37 (1H, s).

Example 272

5-{[(3R,4R)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-7,8 -difluoro-3,4-dihydroquinolin-2(1H)-one

[1532] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.75 (1H, m), 1.88-1.94 (1H, m), 2.46 (2H, t, J = 7.5 Hz), 2.78-2.89 (3H, m), 2.94-3.00 (1H, m), 3.09-3.11 (1H, m), 3.16-3.19 (1H, m), 3.72 (1H, d, J = 9.0 Hz), 3.75-3.79 (1H, m), 4.02 (1H, d, J = 9.0 Hz), 4.59 (1H, brs), 4.95 (1H, d, J = 6.5 Hz), 6.73 (1H, dd, J = 12.5 Hz, 5.5 Hz), 7.02 (1H, t, J = 9.0 Hz), 7.28-7.30 (1H, m), 7.42 (1H, dd, J = 12.0 Hz, 2.5 Hz), 10.31 (1H, brs).

Example 273

8-Chloro-5-{[(3R,4R)-1-(2-chloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]met hoxy}-3,4-dihydroquinolin-2(1H)-one

[1533] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.91-1.97 (1H, m), 2.47-2.50 (2H,m), 2.81 (1H, t, J = 10.5 Hz), 2.85-2.96 (4H, m), 3.04 (1H, dd, J = 10.4 Hz, 4.8 Hz), 3.76 (1H, d, J = 8.9 Hz), 3.79--3.83 (1H, m), 4.05 (1H, d, J = 9.0 Hz), 4.54 (1H, s), 4.91 (1H, d, J = 6.4 Hz), 6.69 (1H, d, J = 9.0 Hz), 7.15-7.26 (3H, m), 7.40 (1H, dd, J = 8.6 Hz, 2.9 Hz), 9.37 (1H, s).

Example 274

8-Chloro-5-{[(3S,4S)-1-(2-chloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]meth oxy}-3,4-dihydroquinolin-2(1H)-one

[1534] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.91-1.97 (1H, m), 2.47-2.50 (2H,m), 2.81 (1H, t, J = 10.5 Hz), 2.85-2.96 (4H, m), 3.04 (1H, dd, J = 10.4 Hz, 4.8 Hz), 3.76 (1H, d, J = 8.9 Hz), 3.79--3.83 (1H, m), 4.05 (1H, d, J = 9.0 Hz), 4.54 (1H, s), 4.91 (1H, d, J = 6.4 Hz), 6.69 (1H, d, J = 9.0 Hz), 7.15-7.26 (3H, m), 7.40 (1H, dd, J = 8.6 Hz, 2.9 Hz,), 9.37 (1H, s).

Example 275

8-Chloro-5-{[(3R,4R)-1-(2-chloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]met hoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1535] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 175.7-177.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.96-2.07 (2H, m), 2.61-2.64 (3H, m), 2.70 (1H, s), 2.93-3.07 (5H, m), 3.23-3.26 (1H, m), 4.02 (2H, s), 4.03-4.08 (1H, m), 6.51 (1H, d, J = 10.6 Hz), 6.94-6.98 (1H, m), 7.06 (1H, dd, J = 8.9 Hz, 5.4 Hz), 7.15 (1H, dd, J = 8.2 Hz, 2.9 Hz), 7.79 (1H, brs).

Example 276

8-Chloro-5-{[(3R*,4R*)-1-(2-chloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]me thoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1536] Synthesized analogous to Example 259.
^{1}HNMR ($CDCl_3$) δ ppm: 1.96-2.07 (2H, m), 2.30-2.40 (1H, m), 2.61-2.64 (3H,m), 2.93-3.07 (5H, m), 3.23-3.26 (1H, m), 4.02 (2H, s), 4.03-4.08 (1H, m), 6.51 (1H, d, J = 10.6 Hz), 6.94-6.98 (1H, m), 7.06 (1H, dd, J = 8.9 Hz, 5.4 Hz), 7.15 (1H, dd, J = 8.2 Hz, 2.9 Hz), 7.76 (1H, brs).

Example 277

8-Chloro-5-{[(3R*,4R*)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1537] Synthesized analogous to Example 257.
(Ethyl acetate) m.p. 201-204 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70 (1H, d, J = 13.0 Hz), 1.83-1.91 (1H, m), 2.47-2.50 (2H, m), 2.80-2.96 (4H, m), 3.21 (1H, t, J = 10.8 Hz), 3.29-3.34 (1H, m), 3.68-3.73 (1H, m), 3.76 (1H, d, J = 9.0 Hz), 4.05 (1H, d, J = 9.0 Hz), 4.59 (1H, s), 4.90 (1H, d, J = 6.4 Hz), 6.81 (1H, d, J = 11.5 Hz), 7.24-7.31 (2H, m), 9.70 (1H, s).

Example 278

8-Chloro-5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy }-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1538] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 192-194 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70 (1H, d, J = 13.5 Hz), 1.83-1.91 (1H, m), 2.47-2.51 (2H, m), 2.81-2.98 (4H, m), 3.21 (1H, t, J = 10.7 Hz), 3.30-3.36 (1H, m), 3.68-3.73 (1H, m), 3.76 (1H, d, J = 9.0 Hz), 4.05 (1H, d, J = 9.0 Hz), 4.60 (1H, s), 4.91 (1H, d, J = 6.2 Hz), 6.81 (1H, d, J = 11.4 Hz), 7.24-7.31 (2H, m), 9.69 (1H, s).

Example 279

5-{[(3R,4R)-1-(4-Chloro-2,5-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1539] Synthesized analogous to Example 259.
(Ethanol) m.p. 199.0-199.7 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.74 (1H, m), 1.91-1.99 (1H, m), 2.45 (2H, t, J = 7.7 Hz), 2.81-2.92 (3H, m), 2.98-3.03 (1H, m), 3.13-3.16 (1H, m), 3.22-3.25 (1H, m), 3.69 (1H, d, J = 8.8 Hz), 3.76-3.81 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.59 (1H, s), 4.96 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.11 (1H, dd, J = 11.3 Hz, 7.9 Hz), 7.50 (1H, dd, J = 12.2 Hz, 7.1 Hz), 10.02 (1H, s).

Example 280

5-{[(3R,4R)-1-(2,4-Dichlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1540] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.76 (1H, m), 1.92-1.98 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.79-3.11 (6H, m), 3.71 (1H, d, J = 8.9 Hz), 3.79-3.83 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.53 (1H, s), 4.92 (1H, d, J = 6.4 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.54 (1H, d, J = 2.5 Hz), 10.03 (1H, s).

Example 281

5-{[(3R,4R)-1-(2,4-Dichloro-5-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1541] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.76 (1H, m), 1.92-1.98 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.80-3.05 (5H, m), 3.15-3.18 (1H, m), 3.71 (1H, d, J = 8.9 Hz), 3.79-3.83 (1H, m), 4.03 (1H, d, J = 8.9 Hz), 4.56 (1H, s), 4.96 (1H, d, J = 6.4 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.24 (1H, d, J = 11.2 Hz), 7.71 (1H, d, J = 7.8 Hz), 10.03 (1H, s).

Example 282

5-{[(3R,4R)-1-(2,5-Dichloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1542] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 216.0-216.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.75 (1H, m), 1.92-1.98 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.80-3.09 (6H, m), 3.71 (1H, d, J = 8.8 Hz), 3.79-3.83 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.54 (1H, s), 4.93 (1H, d, J = 6.3 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.34 (1H, d, J = 7.3 Hz), 7.66 (1H, d, J = 9.1 Hz), 10.03 (1H, s).

Example 283

5-{[(3R,4R)-1-(4-Ethoxy-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-f luoro-3,4-dihydroquinolin-2(1H)-one

[1543] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.30 (3H, t, J = 7.0 Hz), 1.70-1.72 (1H, m), 1.91-1.97 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.77-3.05 (6H, m), 3.68 (1H, d, J = 8.8 Hz), 3.77-3.81 (1H, m), 3.97 (2H, q, J = 7.0 Hz), 4.02 (1H, d, J = 8.8 Hz), 4.47 (1H, s), 4.86 (1H, d, J = 6.5 Hz), 6.57 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.68 (1H, dd, J = 8.7 Hz, 2.4 Hz), 6.77 (1H, dd, J = 14.1 Hz, 2.8 Hz), 6.98-7.04 (2H, m), 10.02 (1H, s).

Example 284

5-{[(3R,4R)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-c hloro-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1544] Synthesized analogous to Example 260.
^{1}HNMR (DMSO-d6) δ ppm: 1.74 (1H, d, J = 13.6 Hz), 1.87-1.95 (1H, m), 2.46-2.50 (2H, m), 2.82-3.00 (4H, m), 3.10 (1H, d, J = 11.1 Hz), 3.17 (1H, dd, J = 11.1 Hz, 3.9 Hz), 3.75-3.78 (2H, m), 4.07 (1H, d, J = 9.0 Hz), 4.60 (1H, brs), 4.95 (1H, brs), 6.80 (1H, d, J = 11.4 Hz), 7.02 (1H, t, J = 9.1 Hz), 7.29 (1H, dd, J = 7.4 Hz, 1.2 Hz), 7.42 (1H, dd, J = 12.2 Hz, 2.3 Hz), 9.66 (1H, s).

Example 285

5-{[(3R*,4R*)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-c hloro-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1545] Synthesized analogous to Example 257.

(Ethyl acetate) m.p. 194 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74 (1H, d, J = 13.6 Hz), 1.87-1.95 (1H, m), 2.46-2.49 (2H, m), 2.82-3.00 (4H, m), 3.08-3.12 (1H, m), 3.17 (1H, dd, J = 11.1 Hz, 4.5 Hz), 3.74-3.78 (2H, m), 4.06 (1H, d, J = 9.1 Hz), 4.60 (1H, s), 4.95 (1H, d, J = 6.2 Hz), 6.80 (1H, d, J = 11.4 Hz), 7.02 (1H, t, J = 9.1 Hz), 7.29 (1H, dd, J = 8.6 Hz, 1.6 Hz), 7.42 (1H, dd, J = 12.3 Hz, 2.3 Hz), 9.66 (1H, s).

Example 286

5-{[(3R,4R)-1-(2-Chloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-7,8 -difluoro-3,4-dihydroquinolin-2(1H)-one

[1546] Synthesized analogous to Example 259.
(Acetic acid/water) m.p. 192.2-193.2 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.76 (1H, m), 1.89-1.95 (1H, m), 2.46-2.49 (2H, m), 2.78-3.05 (6H, m), 3.74-3.81 (2H, m), 4.02 (1H, d, J = 9.1 Hz), 4.53 (1H, s), 4.91 (1H, d, J = 6.4 Hz), 6.76 (1H, dd, J = 12.6 Hz, 6.2 Hz), 7.15-7.23 (2H, m), 7.40 (1H, dd, J = 8.6 Hz, 2.9 Hz), 10.03 (1H, s).

Example 287

5-{[(3R*,4R*)-1-(2-Chloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-7, 8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1547] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.76 (1H, m), 1.89-1.95 (1H, m), 2.46-2.49 (2H, m), 2.78-3.05 (6H, m), 3.74-3.81 (2H, m), 4.02 (1H, d, J = 9.1 Hz), 4.53 (1H, s), 4.91 (1H, d, J = 6.4 Hz), 6.76 (1H, dd, J = 12.6 Hz, 6.2 Hz), 7.15-7.23 (2H, m), 7.40 (1H, dd, J = 8.6 Hz, 2.9 Hz), 10.03 (1H, s).

Example 288

5-{[(3R,4R)-1-(3-Bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1548] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.89-1.96 (1H, m), 1.97-2.05 (1H, m), 2.63 (2H, t, J = 7.7 Hz), 2.93 (1H, brs), 2.94-3.06 (2H, m), 3.45-3.55 (2H, m), 3.68-3.75 (1H, m), 3.78-4.00 (2H, m), 4.04-4.10 (2H, m), 4.11-4.16 (1H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.8 Hz), 7.55 (1H, brs), 7.57 (1H, dd, J = 9.0 Hz, 2.4 Hz), 7.62 (1H, d, J = 2.3 Hz), 7.75 (1H, d, J = 9.0 Hz), 8.21 (1H, s).

Example 289

5-{[(3R,4R)-1-(6-Chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy1-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1549] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.83-1.91 (1H, m), 1.94-2.00 (1H, m), 2.50-2.60 (2H, m), 2.81 (1H, brs), 2.85-2.91 (2H, m), 3.07 (1H, brs), 3.34 (1H, dd, J = 13.0 Hz, 10.0 Hz), 3.39-3.47 (1H, m), 3.93-4.00 (3H, m), 4.21-4.28 (1H, m), 4.44-4.51 (1H, m), 6.46 (1H, dd, J = 9.2 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.3 Hz), 7.05 (1H, d, J = 9.2 Hz), 7.47 (1H, dd, J = 8.9 Hz, 2.6 Hz), 7.58 (1H, d, J = 2.4 Hz), 7.59-7.64 (2H, m), 7.82 (1H, d, J = 9.2 Hz).

Example 290

8-Chloro-5-{[(3R,4R)-1-(2,4-dichlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -3,4-dihydroquinolin-2(1H)-one

[1550] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 184.1-185.1 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.75-1.77 (1H, m), 1.92-1.98 (1H, m), 2.47-2.49 (2H, m), 2.80-3.12 (6H, m), 3.76 (1H, d, J = 8.9 Hz), 3.79-3.83 (1H, m), 4.06 (1H, d, J = 8.9 Hz), 4.55 (1H, s), 4.93 (1H, d, J = 6.4 Hz), 6.69 (1H, d, J = 9.0 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.25 (1H, d, J = 8.9 Hz), 7.36 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.53 (1H, d, J = 2.5 Hz), 9.35 (1H, s).

Example 291

8-Chloro-5-{[(3R,4R)-1-(2,5-dichloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy}-3,4-dihydroquinolin-2(1H)-one

[1551] Synthesized analogous to Example 259.
(Acetic acid/water) m.p. 237.7-238.6 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.91-1.97 (1H, m), 2.47-2.49 (2H, m), 2.80-3.09 (6H, m), 3.75 (1H, d, J = 8.9 Hz), 3.79-3.83 (1H, m), 4.06 (1H, d, J = 8.9 Hz), 4.55 (1H, s), 4.93 (1H, d, J = 6.4 Hz), 6.69 (1H, d, J = 9.0 Hz), 7.25 (1H, d, J = 8.9 Hz), 7.34 (1H, d, J = 7.4 Hz,), 7.66 (1H, d, J = 9.1 Hz), 9.36 (1H, s).

Example 292

8-Chloro-5-{[(3R,4R)-1-(2,4-dichloro-5-fluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy}-3,4-dihydroquinolin-2(1H)-one

[1552] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 180.2-180.6 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.91-1.97 (1H, m), 2.47-2.49 (2H, m), 2.80-3.18 (6H, m), 3.76 (1H, d, J = 8.9 Hz), 3.79-3.83 (1H, m), 4.06 (1H, d, J = 8.9 Hz), 4.57 (1H, s), 4.95 (1H, d, J = 6.4 Hz), 6.69 (1H, d, J = 9.0 Hz), 7.22-7.26 (2H, m), 7.71 (1H, d, J = 7.8 Hz), 9.35 (1H, s).

Example 293

5-{[(3R,4R)-1-(2-Chloro-4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-f luoro-3,4-dihydroquinolin-2(1H)-one

[1553] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.76 (1H, m), 1.93-1.99 (1H, m), 2.46-2.49 (2H, m), 2.79-3.06 (6H, m), 3.72 (1H, d, J = 8.9 Hz), 3.79-3.84 (1H, m), 4.03 (1H, d, J = 8.9 Hz), 4.49 (1H, s), 4.88 (1H, d, J = 6.4 Hz), 6.59 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.15-7.19 (1H, m), 7.22 (1H, dd, J = 9.0 Hz, 5.7 Hz), 7.39 (1H, dd, J = 8.6 Hz, 2.9 Hz), 10.01 (1H, s).

Example 294

8-Chloro-5-{[(3R,4R)-1-(4-chloro-2,5-difluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy}-3,4-dihydroquinolin-2(1H)-one

[1554] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.75 (1H, m), 1.90-1.96 (1H, m), 2.45-2.48 (2H, m), 2.82-3.25 (6H, m), 3.73 (1H, d, J = 8.8 Hz), 3.76-3.80 (1H, m), 4.05 (1H, d, J = 8.9 Hz), 4.62 (1H, s), 4.98 (1H, d, J = 6.3 Hz), 6.67 (1H, d, J = 9.0 Hz), 7.12 (1H, dd, J = 11.3 Hz, 7.9 Hz), 7.25 (1H, d, J = 8.9 Hz), 7.50 (1H, dd, J = 12.2 Hz, 7.1 Hz), 9.37 (1H, s).

Example 295

5-{[(3R,4R)-1-(4-Chloro-2,5-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1555] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.75 (1H, m), 1.87-1.93 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.77-3.25 (6H, m), 3.71-3.78 (2H, m), 4.02 (1H, d, J = 9.0 Hz), 4.62 (1H, s), 4.98 (1H, d, J = 6.3 Hz), 6.73 (1H, dd, J = 12.6 Hz, 6.1 Hz), 7.11 (1H, dd, J = 11.3 Hz, 7.9 Hz), 7.50 (1H, dd, J = 12.2 Hz, 7.1 Hz), 10.31 (1H, s).

Example 296

5-Chloro-2-[(3R,4R)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methy l}-3,4-dihydroxypiperidin-1-yl]benzonitrile

[1556] Synthesized analogous to Example 33.

^{1}HNMR ($CDCl_3$) δ ppm: 1.98-2.03 (1H, m), 2.04-2.12 (1H, m), 2.58-2.68 (2H, m), 2.73 (1H, brs), 2.79-2.83 (1H, m), 2.96-3.07 (3H, m), 3.15-3.23 (1H, m), 3.31-3.37 (1H, m), 3.46-3.52 (1H, m), 3.98-4.04 (2H, m), 4.09-4.15 (1H, m), 6.51 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.01 (1H, d, J = 8.9 Hz), 7.46 (1H, dd, J = 8.9 Hz, 2.6 Hz), 7.53 (1H, d, J = 2.3 Hz), 7.58 (1H, brs).

Example 297

5-[[(3R,4R)-1-(5-Chloro-3-fluoropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1557] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.94 (2H, m), 2.60-2.67 (2H, m), 2.73 (1H, brs), 2.77-2.80 (1H, m), 2.89-3.00 (2H, m), 3.19-3.27 (1H, m), 3.30-3.37 (1H, m), 3.79-3.85 (1H, m), 3.95-4.03 (4H, m), 6.50 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.29 (1H, dd, J = 12.0 Hz, 2.2 Hz), 7.57 (1H, brs), 7.97 (1H, dd, J = 2.2 Hz, 0.5 Hz).

Example 298

3,5-Difluoro-2-[(3R,4R)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]me thyl}-3,4-dihydroxypiperidin-1-yl]benzonitrile

[1558] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.97-2.03 (2H, m), 2.51-2.55 (1H, m), 2.61-2.68 (3H, m), 2.95-3.04 (3H, m), 3.11-3.18 (1H, m), 3.26-3.32 (1H, m), 3.42-3.48 (1H, m), 3.97-4.08 (3H, m), 6.52 (1H, dd, J = 9.2 Hz, 3.9 Hz), 6.84-6.88 (1H, m), 6.89-6.97 (2H, m), 7.53 (1H, brs).

Example 299

4-Chloro-5-fluoro-2-[(3R,4R)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)o xy]methyl}-3,4-dihydroxypiperidin-1-yl]benzonitrile

[1559] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.98-2.12 (2H, m), 2.62-2.67 (2H, m), 2.69-2.73 (2H, m), 2.94-3.06 (3H, m), 3.18 (1H, dt, J = 11.6 Hz, 3.1 Hz), 3.26-3.32 (1H, m), 3.41-3.47 (1H, m), 4.09-4.15 (3H, m), 6.51 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.12 (1H, d, J = 6.3 Hz), 7.36 (1H, d, J = 8.1 Hz), 7.55 (1H, brs).

Example 300

5-{[(3R,4R)-1-(4-Chlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1560] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.70 (1H, m), 1.87-1.93 (1H, m), 2.39-2.42 (2H, m), 2.70-2.99 (4H, m), 3.47-3.50 (2H, m), 3.66 (1H, d, J = 8.8 Hz), 3.70-3.75 (1H, m), 4.01 (1H, d, J = 8.8 Hz), 4.57 (1H, s), 4.89 (1H, d, J = 6.6 Hz), 6.55 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.93-6.97 (2H, m), 6.98-7.03 (1H, m), 7.20-7.23 (2H, m), 10.01 (1H, s).

Example 301

5-{[(3R*,4R*)-1-(4-Bromo-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1561] Synthesized analogous to Example 257.
(Ethyl acetate) m.p. 191-193 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (1H, d, J = 13.4 Hz), 1.87-1.94 (1H, m), 2.45-2.49 (2H, m), 2.84-2.99 (4H, m), 3.20 (1H, t, J = 10.7 Hz), 3.30-3.35 (1H, m), 3.68 (1H, d, J = 8.8 Hz), 3.71-3.76 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.53 (1H, s), 4.87 (1H, d, J = 6.5 Hz), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.35-7.40 (2H, m), 10.02 (1H, s).

Example 302

5-{[(3R,4R)-1-(4-Bromo-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1562] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 197-198 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (1H, d, J = 13.4 Hz), 1.87-1.94 (1H, m), 2.45-2.49 (2H, m), 2.82-2.99 (4H, m), 3.20 (1H, t, J = 10.9 Hz), 3.28-3.33 (1H, m), 3.68 (1H, d, J = 8.7 Hz), 3.70-3.76 (1H, m), 4.02 (1H, d, J = 8.7 Hz), 4.53 (1H, s), 4.87 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.35-7.40 (2H, m), 10.01 (1H, s).

Example 303

5-{[(3R*,4R*)-1-(2-Chloro-4,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1563] Synthesized analogous to Example 257.
(Ethyl acetate/hexane) m.p. 215-218 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.3 Hz), 1.91-1.99 (1H, m), 2.45-2.49 (2H, m), 2.75-2.95 (4H, m), 3.20-3.37 (2H, m), 3.69 (1H, d, J = 8.9 Hz), 3.74-3.79 (1H, m), 4.02 (1H, d, J = 8.9 Hz), 4.49 (1H, s), 4.82 (1H, d, J = 6.5 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.26-7.36 (2H, m), 10.02 (1H, s).

Example 304

5-{[(3R,4R)-1-(2-Chloro-4,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1564] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 188-189 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.3 Hz), 1.90-1.99 (1H, m), 2.45-2.49 (2H, m), 2.75-2.95 (4H, m), 3.21-3.37 (2H, m), 3.69 (1H, d, J = 8.8 Hz), 3.74-3.80 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.49 (1H, s), 4.82 (1H, d, J = 6.5 Hz), 6.59 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.26-7.35 (2H, m), 10.01 (1H, s).

Example 305

5-{[(3R*,4R*)-3,4-Dihydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1565] Synthesized analogous to Example 257.
(Acetic acid/water) m.p. 198-199 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.72 (1H, m), 1.86-1.96 (1H, m), 2.48 (2H, t, J = 7.7 Hz), 2.77-2.97 (4H, m), 3.21 (1H, t, J = 10.6 Hz), 3.28-3.38 (1H, m), 3.68 (1H, d, J = 8.8 Hz), 3.70-3.78 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.51 (1H, s), 4.84 (1H, d, J = 6.6 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.08-7.18 (2H, m), 10.03 (1H, s).

Example 306

5-{[(3R,4R)-3,4-Dihydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1566] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 191-192 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.72 (1H, m), 1.86-1.96 (1H, m), 2.48 (2H, t, J = 7.7 Hz), 2.77-2.97 (4H, m), 3.21 (1H, t, J = 10.6 Hz), 3.28-3.38 (1H, m), 3.68 (1H, d, J = 8.8 Hz), 3.70-3.78 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.51 (1H, s), 4.84 (1H, d, J = 6.6 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.08-7.18 (2H, m), 10.03 (1H, s).

Example 307

3,5-Dichloro-2-[(3R,4R)-4-{(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]m ethyl]-3,4-dihydroxypiperidin-1-yl]benzonitrile

[1567] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.94-2.01 (1H, m), 2.05-2.13 (1H, m), 2.56-2.60 (1H, m), 2.61-2.69 (3H, m), 2.95-3.13 (3H, m), 3.28-3.34 (1H, m), 3.47-3.54 (1H, m), 3.63-3.69 (1H, m), 3.99-4.05 (2H, m), 4.07-4.14 (1H, m), 6.51 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.3 Hz), 7.47 (1H, d, J = 2.5 Hz), 7.52 (1H, brs), 7.56 (1H, d, J = 2.5 Hz).

Example 308

8-Fluoro-5-({(3R,4R)-1-[2-fluoro-4-(trifluoromethoxy)phenyl]-3,4-dihydroxypiperid in-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

[1568] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 161.6-161.9 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.75 (1H, m), 1.92-1.98 (1H, m), 2.46 (2H, t, J = 7.7 Hz), 2.82-3.21 (6H, m), 3.69 (1H, d, J = 8.8 Hz), 3.78-3.81 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.57 (1H, s), 4.95 (1H, d, J = 5.9 Hz), 6.58 (1H, dd, J = 9.2 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.15-7.18 (2H, m), 7.31-7.33 (1H, m), 10.03 (1H, s).

Example 309

8-Fluoro-5-{[(3R,4R)-1-(2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4 -dihydroquinolin-2(1H)-one

[1569] Synthesized analogous to Example 259.
(Ethanol) m.p. 177.7-178.0 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.75 (1H, m), 1.93-1.99 (1H, m), 2.46 (2H, t, J = 7.8 Hz), 2.82-3.20 (6H, m), 3.69 (1H, d, J = 8.8 Hz), 3.79-3.83 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.52 (1H, s), 4.91 (1H, d, J = 6.4 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.93-7.14 (5H, m), 10.03 (1H, s).

Example 310

5-({(3R*,4R*)-1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-3,4-dihydroxypiperid in-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1570] Synthesized analogous to Example 257.
(Ethyl acetate-diisopropyl ether) m.p. 201-202 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.6 Hz), 1.86-1.94 (1H, m), 2.46-2.51 (2H, m), 2.76-2.95 (4H, m), 3.18-3.34 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.70-3.75 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.47 (1H, s), 4.73-4.81 (3H, m), 6.58 (1H, dd, J = 9.2 Hz, 3.8 Hz), 6.84-6.91 (2H, m), 7.02 (1H, t, J = 9.7 Hz), 10.01 (1H, s).

Example 311

5-({(3R,4R)-1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-3,4-dihydroxypiperidi n-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1571] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 187 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.6 Hz), 1.86-1.94 (1H, m), 2.46-2.50 (2H, m), 2.76-2.93 (4H, m), 3.18-3.32 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.70-3.75 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.47 (1H, s), 4.73-4.81 (3H, m), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.85-6.91 (2H, m), 7.02 (1H, t, J = 9.8 Hz), 10.01 (1H, s).

Example 312

5-{[(3R*,4R*)-1-(2,4-Dichloro-6-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1572] Synthesized analogous to Example 257.
^{1}HNMR (DMSO-d6) δppm: 1.68 (1H, d, J = 13.5 Hz), 1.91-1.98 (1H, m), 2.44-2.50 (2H, m), 2.86-2.95 (4H, m), 3.23-3.36 (2H, m), 3.69 (1H, d, J = 8.8 Hz), 3.75-3.80 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.53 (1H, s), 4.86 (1H, d, J = 6.4 Hz), 6.59 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.43-7.47 (2H, m), 10.03 (1H, s).

Example 313

5-{[(3R,4R)-1-(2,4-Dichloro-6-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1573] Synthesized analogous to Example 260.
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.3 Hz), 1.91-1.99 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.82-2.95 (4H, m), 3.20-3.36 (2H, m), 3.69 (1H, d, J = 8.8 Hz), 3.75-3.80 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.53 (1H, s), 4.87 (1H, d, J = 6.4 Hz), 6.59 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.43-7.47 (2H, m), 10.03 (1H, s).

Example 314

5-({(3R*,4R*)-1-[4-(Difluoromethoxy)-2,6-difluorophenyl]-3,4-dihydroxypiperidin-4 -yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1574] Synthesized analogous to Example 257.
(Ethyl acetate-diisopropyl ether) m.p. 167-169 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.3 Hz), 1.87-1.95 (1H, m), 2.46-2.50 (2H, m), 2.83-2.93 (4H, m), 3.18-3.35 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.71-3.76 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.51 (1H, s), 4.84 (1H, d, J = 6.5 Hz), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00-7.06 (3H, m), 7.24 (1H, t, J = 73.5 Hz), 10.02 (1H, s).

Example 315

5-({(3R,4R)-1-[4-(Difluoromethoxy)-2,6-difluorophenyl]-3,4-dihydroxypiperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1575] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 166 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (1H, d, J = 13.5 Hz), 1.87-1.95 (1H, m), 2.46-2.50 (2H, m), 2.83-2.93 (4H, m), 3.19-3.35 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.71-3.76 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.51 (1H, s), 4.85 (1H, d, J = 6.5 Hz), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00-7.06 (3H, m), 7.24 (1H, t, J = 73.5 Hz), 10.02 (1H, s).

Example 316

5-{[(3R*,4R*)-1-(4-Ethoxy-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1576] Synthesized analogous to Example 257.
(Ethyl acetate-diisopropyl ether) m.p. 199-202 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.29 (3H, t, J = 7.0 Hz), 1.67 (1H, d, J = 13.5 Hz), 1.86-1.93 (1H, m), 2.42-2.49 (2H, m), 2.72-2.93 (4H, m), 3.17-3.32 (2H, m), 3.68 (1H, d, J = 8.8 Hz), 3.69-3.75 (1H, m), 3.97-4.04 (3H, m), 4.45 (1H, s), 4.78 (1H, d, J = 6.5 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.64-6.68 (2H, m), 7.02 (1H, t, J = 9.7 Hz), 10.01 (1H, s).

Example 317

5-{[(3R,4R)-1-(4-Ethoxy-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1577] Synthesized analogous to Example 260.
(Acetic acid/water) m.p. 176-178 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.29 (3H, t, J = 7.0 Hz), 1.67 (1H, d, J = 13.4 Hz), 1.86-1.93 (1H, m), 2.46-2.50 (2H, m), 2.72-2.93 (4H, m), 3.17-3.32 (2H, m), 3.67 (1H, d, J = 8.8 Hz), 3.69-3.75 (1H, m), 3.97-4.02 (3H, m), 4.45 (1H, s), 4.78 (1H, d, J = 6.5 Hz), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.64-6.68 (2H, m), 7.02 (1H, t, J = 9.7 Hz), 10.01 (1H, s).

Example 318

5-{[(3R,4R)-1-(2-Chlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1578] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 161.3-161.4 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.76 (1H, m), 1.94-2.00 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.80-3.14 (6H, m), 3.72 (1H, d, J = 8.8 Hz), 3.80-3.85 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 4.50 (1H, s), 4.89 (1H, d, J = 6.4 Hz), 6.59 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01-7.05 (2H, m), 7.18 (1H, d, J = 7.3 Hz), 7.28-7.31 (1H, m), 7.40 (1H, dd, J = 7.9 Hz, 0.9 Hz), 10.03 (1H, s).

Example 319

5-{[(3R,4R)-1-(2,4-Difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1579] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 175.2-176.1 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.74 (1H, m), 1.92-1.97 (1H, m), 2.47 (2H, t, J = 7.8 Hz), 2.80-3.11 (6H, m), 3.69 (1H, d, J = 8.8 Hz), 3.78-3.82 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.53 (1H, s), 4.91 (1H, d, J = 6.4 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.97-7.21 (4H, m), 10.03 (1H, s).

Example 320

5-{[(3R,4R)-1-(2,6-Difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1580] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.70 (1H, m), 1.89-1.95 (1H, m), 2.45-2.49 (2H, m), 2.84-2.99 (4H, m), 3.21-3.25 (1H, m), 3.32-3.38 (1H, m), 3.68 (1H, d, J = 8.8 Hz), 3.72-3.77 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.51 (1H, s), 4.85 (1H, d, J = 6.5 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.99-7.08 (4H, m), 10.03 (1H, s).

Example 321

5-{[(3R,4R)-3,4-Dihydroxy-1-phenylpiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroq uinolin-2(1H)-one

[1581] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 202.8-203.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.71 (1H, m), 1.88-1.94 (1H, m), 2.39-2.42 (2H, m), 2.72-2.86 (3H, m), 2.92-2.98 (1H, m), 3.46-3.51 (2H, m), 3.67 (1H, d, J = 8.8 Hz), 3.72-3.77 (1H, m), 4.01 (1H, d, J = 8.8 Hz), 4.53 (1H, s), 4.86 (1H, d, J = 6.5 Hz), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.74 (1H, d, J = 8.0 Hz), 6.94 (2H, d, J = 8.0 Hz), 6.99-7.03 (1H, m), 7.20 (2H, dd, J = 7.3 Hz, 8.7 Hz), 10.01 (1H, s).

Example 322

5-({(3R,4R)-3,4-Dihydroxy-1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1582] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 196.0-197.1 °C

^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.71 (1H, m), 1.88-1.94 (1H, m), 2.38-2.41 (2H, m), 2.71-3.02 (4H, m), 3.50-3.53 (2H, m), 3.66 (1H, d, J = 8.8 Hz), 3.71-3.75 (1H, m), 4.01 (1H, d, J = 8.8 Hz), 4.58 (1H, s), 4.91 (1H, d, J = 6.6 Hz), 6.56 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.99-7.03 (3H, m), 7.18 (2H, d, J = 8.6 Hz), 10.02 (1H, s).

Example 323

5-({(3R,4R)-1-[4-(Difluoromethoxy)phenyl]-3,4-dihydroxypiperidin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1583] Synthesized analogous to Example 259.
(Ethanol/water) m.p. 163.1-164.6 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.71 (1H, m), 1.88-1.95 (1H, m), 2.40-2.43 (2H, m), 2.75-2.86 (3H, m), 2,92-2.97 (1H, m), 3.43-3.51 (2H, m), 3.66 (1H, d, J = 8.8 Hz), 3.72-3.77 (1H, m), 4.01 (1H, d, J = 8.8 Hz), 4.54 (1H, s), 4.87 (1H, d, J = 6.6 Hz), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.90-7.22 (6H, m), 10.01 (1H, s).

Example 324

5-{[(3R,4R)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-7,8 -difluoro-3,4-dihydroquinolin-2(1H)-one

[1584] Synthesized analogous to Example 259.
(Ethyl acetate) m.p. 192.6-193.4 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.77 (1H, m), 1.87-1.95 (1H, m), 2.45 (2H, t, J = 7.5 Hz), 2.77-2.90 (3H, m), 2.93-3.01 (1H, m), 3.06-3.13 (1H, m), 3.14-3.19 (1H, m), 3.71 (1H, d, J = 9.0 Hz)), 3.74-3.80 (1H, m), 4.01 (1H, d, J = 9.0 Hz), 4.59 (1H, s), 4.95 (1H, d, J = 6.0 Hz), 6.71 (1H, dd, J = 12.5 Hz, 6.0 Hz), 7.06 (1H, t, J = 9.0 Hz), 7.16 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.31 (1H, dd, J = 12.5 Hz, 2.5 Hz), 10.31 (1H, s).

Example 325

5-{[(3R,4R)-1-(4-Bromo-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1585] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 204.5-204.6 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.70 (1H, m), 1.84-1.90 (1H, m), 2.48 (2H, t, J = 7.5 Hz), 2.80-2.91 (3H, m), 2.95-2.98 (1H, m), 3.17-3.22 (1H, m), 3.30-3.38 (1H, m), 3.68-3.72 (1H, m), 3.71 (1H, d, J = 9.0 Hz), 4.01 (1H, d, J = 9.0 Hz), 4.56 (1H, brs), 4.89 (1H, d, J = 5.5 Hz), 6.73 (1H, dd, J = 12.5 Hz, 6.0 Hz), 7.35-7.40 (2H, m), 10.31 (1H, brs).

Example 326

5-{[(3R,4R)-1-(4-Bromo-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-chloro-3,4-dihydroquinolin-2(1H)-one

[1586] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 203.6-203.7 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.71 (1H, m), 1.86-1.92 (1H, m), 2.49 (2H, t, J = 7.5 Hz), 2.85-2.92 (3H, m), 2.94-2.98 (1H, m), 3.18-3.23 (1H, m), 3.30-3.38 (1H, m), 3.70-3.75 (1H, m), 3.72 (1H, d, J = 9.0 Hz), 4.05 (1H, d, J = 9.0 Hz), 4.57 (1H, brs), 4.89 (1H, d, J = 6.5 Hz), 6.68 (1H, d, J = 9.0 Hz), 7.25 (1H, d, J = 9.0 Hz), 7.35-7.41 (2H, m), 9.37 (1H, brs).

Example 327

8-Chloro-5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]met hoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1587] Synthesized analogous to Example 259.
^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.76 (1H, m), 1.88-1.94 (1H, m), 2.46-2.50 (2H, m), 2.79-3.18 (6H, m), 3.75-3.79 (2H, m), 4.06 (1H, d, J = 9.1 Hz), 4.61 (1H, s), 4.96 (1H, d, J = 6.3 Hz), 6.81 (1H, d, J = 11.5 Hz), 7.08 (1H, t, J = 9.2 Hz), 7.17 (1H, dd, J = 8.7 Hz, 2.2 Hz), 7.32 (1H, dd, J = 12.5 Hz, 2.5 Hz), 9.69 (1H, s).

Example 328

8-Chloro-5-[[(3,,4)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]met hoxy}-3,4-dihydroquinolin-2(1H)-one

[1588] Synthesized analogous to Example 259.
(Ethyl acetate/ethanol) m.p. 185.0-186.4 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.77 (1H, m), 1.90-1.98 (1H, m), 2.46 (2H, t, J = 7.5 Hz), 2.81-2.93 (3H, m), 2.93-3.02 (1H, m), 3.06-3.13 (1H, m), 3.14-3.19 (1H, m), 3.72 (1H, d, J = 9.0 Hz)), 3.74-3.83 (1H, m), 4.04 (1H, d, J = 9.0 Hz), 4.59 (1H, s), 4.94 (1H, d, J = 6.0 Hz), 6.67 (1H, d, J = 9.0 Hz), 7.06 (1H, t, J = 9.0 Hz), 7.17 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.24 (1H, d, J = 9.0 Hz), 7.31 (1H, dd, J = 12.5 Hz, 2.5 Hz), 9.37 (1H, s).

Example 329

5-{[(3R,4R)-1-(4-Bromo-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-chloro-7-fluoro-3,4-dihydroquinolin-2(1H)-one

[1589] Synthesized analogous to Example 42.
(Ethyl acetate/hexane) m.p. 199.0-199.6 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-2.00 (2H, m), 2.37 (1H, d, J = 7.5 Hz), 2.58 (1H, brs), 2.64 (2H, t, J = 7.5 Hz), 2.95-2.98 (2H, m), 3.03-3.06 (1H, m), 3.23-3.30 (2H, m), 3.34-3.39 (1H, m), 3.94-3.98 (1H, m), 4.00 (1H, d, J = 9.0 Hz), 4.03 (1H, d, J = 9.0 Hz), 6.50 (1H, d, J = 10.5 Hz), 7.02-7.07 (2H, m), 7.56 (1H, brs).

Example 330

5-{[(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-7, 8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1590] Synthesized analogous to Example 257.
(Ethyl acetate/methanol) m.p. 220.5-221.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.76 (1H, m), 1.86-1.96 (1H, m), 2.45 (2H, t, J = 7.5 Hz), 2.76-2.90 (3H, m), 2.93-3.00 (1H, m), 3.05-3.13 (1H, m), 3.14-3.19 (1H, m), 3.71 (1H, d, J = 8.9 Hz), 3.73-3.79 (1H, m), 3.98-4.05 (1H, m), 4.59 (1H, s), 4.95 (1H, d, J = 6.0 Hz), 6.71 (1H, dd, J = 12.6 Hz, 6.1 Hz), 7.06 (1H, t, J = 9.1 Hz), 7.16 (1H, dd, J = 8.1 Hz, 2.1 Hz), 7.31 (1H, dd, J = 12.5 Hz, 2.4 Hz), 10.31 (1H, s).

Example 331

5-{[(3R,4R)-1-(1,3-Benzoxazol-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1591] Synthesized analogous to Example 246.
(Ethanol/ethyl acetate) m.p. 190-191 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.76-1.82 (1H, m), 1.84-1.93 (1H, m), 2.36 (2H, t, J = 7.7 Hz), 2.71-2.86 (2H, m), 3.19-3.27 (1H, m), 3.30-3.41 (1H, m), 3.69-3.76 (2H, m), 3.93-4.02 (2H, m), 4.03 (1H, d, J = 8.9 Hz), 4.80 (1H, s), 5.17 (1H, d, J = 6.1 Hz), 6.56 (1H, dd, J = 9.2 Hz, 3.8 Hz), 6.97-7.04 (2H, m), 7.15 (1H, dt, J = 1.1 Hz, 7.7 Hz), 7.28 (1H, d, J = 7.3 Hz), 7.40 (1H, d, J = 7.8 Hz), 10.00 (1H, s).

Example 332

5-{[(3R,4R)-3,4-Dihydroxy-1-(1-methyl-1H-benzimidazol-2-yl)piperidin-4-yl]metho xy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1592] Synthesized analogous to Example 245.
(Ethanol) m.p. 138-147 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.75 (1H, m), 2.01-2.10 (1H, m), 2.41 (2H, t, J = 7.6 Hz), 2.79-2.91 (2H, m), 3.11 (1H, t, J = 11.3 Hz), 3.20-3.29 (1H, m), 3.36-3.44 (2H, m), 3.60 (3H, s), 3.70 (1H, d, J = 8.8 Hz), 3.92-4.01 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.62 (1H, s), 4.96 (1H, d, J = 6.4 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.05-7.11 (2H, m), 7.29-7.35 (1H, m), 7.37-7.42 (1H, m), 10.02 (1H, s).

Example 333

5-{[(3R,4R)-1-(6-Chloro-1,3-benzoxazol-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1593] Synthesized analogous to Example 246.
(Ethanol) m.p. 219-220 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.76-1.83 (1H, m), 1.83-1.93 (1H, m), 2.38 (2H, t, J = 7.7 Hz), 2.73-2.88 (2H, m), 3.24 (1H, t, J = 11.5 Hz), 3.35-3.43 (1H, m), 3.67-3.77 (2H, m), 3.91-4.00 (2H, m), 4.03 (1H, d, J = 8.9 Hz), 4.82 (1H, s), 5.19 (1H, d, J = 6.0 Hz), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.19 (1H, dd, J = 8.4 Hz, 2.0 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.58 (1H, d, J = 2.0 Hz), 10.01 (1H, s).

Example 334

8-Chloro-5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]me thoxy}-3,4-dihydroquinolin-2(1H)-one

[1594] Synthesized analogous to Example 257.
(Ethyl acetate) m.p. 195.5-195.6 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.95-2.02 (2H, m), 2.42 (2H, d, J = 7.0 Hz), 2.59 (1H, s), 2.62 (2H, t, J = 7.5 Hz), 2.91-3.02 (3H, m), 3.02-3.09 (1H, m), 3.15-3.21 (1H, m), 3.99-4.08 (3H, m), 6.57 (1H, d, J = 9.0 Hz), 6.90-6.94 (1H, m), 7.04-7.08 (2H, m), 7.19 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

Example 335

5-{[(3R,4R)-1-(1H-Benzimidazol-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1595] Synthesized analogous to Example 245.
(Ethanol/water) m.p. 279-281 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.77 (1H, m), 1.82-1.92 (1H, m), 2.31 (2H, t, J = 7.7 Hz), 2.66-2.80 (2H, m), 3.08 (1H, t, J = 11.5 Hz), 3.18-3.27 (1H, m), 3.69 (1H, d, J = 8.9 Hz), 3.69-3.76 (1H, m), 3.83-3.91 (1H, m), 3.97 (1H, dd, J = 12.3 Hz, 4.8 Hz), 4.02 (1H, d, J = 8.9 Hz), 4.68 (1H, s), 5.05 (1H, d, J = 6.7 Hz), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.88-6.95 (2H, m), 7.00 (1H, t, J = 9.7 Hz), 7.15-7.21 (2H, m), 9.99 (1H, s), 11.46 (1H, brs).

Example 336

8-Fluoro-5-{[(3R*,4R*)-1-(4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1596] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 182.4-182.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.71 (1H, m), 1.89-1.96 (1H, m), 2.42 (2H, t, J = 8.0 Hz), 2.75-2.84 (3H, m), 2.90-2.94 (1H, m), 3.37-3.41 (2H, m), 3.66 (1H, d, J = 8.5 Hz), 3.73-3.78 (1H, m), 4.01 (1H, d, J = 8.5 Hz), 4.53 (1H, brs), 4.86 (1H, d, J = 6.5 Hz), 6.56 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.95-7.06 (5H, m), 10.02 (1H, brs).

Example 337

8-Fluoro-5-{[(3R,4R)-1-(4-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4 -dihydroquinolin-2(1H)-one

[1597] Synthesized analogous to Example 42.
(Ethyl acetate) m.p. 185.2-185.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.71 (1H, m), 1.89-1.96 (1H, m), 2.42 (2H, t, J = 8.0 Hz), 2.75-2.84 (3H, m), 2.90-2.94 (1H, m), 3.37-3.41 (2H, m), 3.66 (1H, d, J = 9.0 Hz), 3.73-3.78 (1H, m), 4.01 (1H, d, J = 9.0 Hz), 4.53 (1H, brs), 4.86 (1H, d, J = 6.5 Hz), 6.56 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.95-7.06 (5H, m), 10.02 (1H, brs).

Example 338

8-Bromo-5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]met hoxy}-3,4-dihydroquinolin-2(1H)-one

[1598] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.78 (1H, m), 1.90-1.98 (1H, m), 2.48 (2H, t, J = 7.7 Hz), 2.81-2.94 (3H, m), 2.95-3.02 (1H, m), 3.07-3.13 (1H, m), 3.14-3.21 (1H, m), 3.73 (1H, d, J = 8.8 Hz), 3.76-3.83 (1H, m), 4.05 (1H, d, J = 8.8 Hz), 4.60 (1H, brs), 4.94-4.98 (1H, m), 6.65 (1H, d, J = 9.0 Hz), 7.08 (1H, t, J = 9.0 Hz), 7.17 (1H, dd, J = 8.7 Hz, 2.2 Hz), 7.32 (1H, dd, J = 12.5 Hz, 2.2 Hz), 7.40 (1H, d, J = 8.7 Hz), 8.95 (1H, brs).

Example 339

5-{[(3R*,4R*)-1-(4-Bromo-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-chloro-3,4-dihydroquinolin-2(1H)-one

[1599] Synthesized analogous to Example 257.
(Ethyl acetate) m.p. 195-198 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.70 (1H, d, J = 13.5 Hz), 1.86-1.93 (1H, m), 2.46-2.50 (2H, m), 2.85-2.99 (4H, m), 3.18-3.34 (2H, m), 3.70-3.75 (2H, m), 4.06 (1H, d, J = 8.7 Hz), 4.56 (1H, s), 4.88 (1H, d, J = 6.4 Hz), 6.68 (1H, d, J = 8.9 Hz), 7.25 (1H, d, J = 8.9 Hz), 7.34-7.41 (2H, m), 9.36 (1H, s).

Example 340

5-{[(3R*,4R*)-1-(2-Bromo-4-chloro-6-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]me thoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1600] To a solution of 5-{[(3R*,4R*)-1-(2-bromo-4-chloro-6-fluorophenyl)-3-{[tert-butyl(dimethyl)silyl]oxy}-4-hydroxypi peridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one (0.16 g) in tetrahydrofuran (THF) (3.2 mL) was added 1.0 M tetra-n-butylammonium fluoride (TBAF) tetrahydrofuran (THF) solution (0.304 mL), and the reaction mixture was stirred at room temperature for 30 min. To the reaction solution was added water, and the precipitate was collected on a filter. The obtained crystal was washed with acetone, the crystal was collected on a filter, and dried under reduced pressure (60 °C) to provide the title compound (0.11 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.68 (1H, d, J = 13.4 Hz), 1.73-1.80 (1H, m), 1.87-2.06 (1H, m), 2.47 (2H, t, J = 7.7 Hz), 2.73-2.85 (1H, m), 2.85-2.99 (2H, m), 3.16-3.28 (1H, m), 3.28-3.40 (1H, m), 3.68 (1H, d, J = 8.9 Hz), 3.75-3.86 (1H, m), 4.03 (1H, d, J = 8.9 Hz), 4.51 (1H, s), 4.84 (1H, d, J = 6.6 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 6.3 Hz), 7.49 (1H, dd, J = 11.5 Hz, 2.4 Hz), 7.59-7.65 (1H, m), 10.02 (1H, brs).

Example 341

8-Bromo-5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy}-3,4-dihydroquinolin-2(1H)-one

[1601] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.74 (1H, m), 1.85-1.94 (1H, m), 2.49 (2H, t, J = 7.7 Hz), 2.85-2.95 (4H, m), 3.08-3.15 (1H, m), 3.30-3.38 (1H, m), 3.69-3.76 (2H, m), 4.05 (1H, d, J = 8.9 Hz), 4.58 (1H, brs), 4.88-4.92 (1H, m), 6.65 (1H, d, J = 9.0 Hz), 7.24-7.31 (2H, m), 7.40 (1H, d, J = 9.0 Hz), 8.95 (1H, brs).

Example 342

5-{[(3R*,4R*)-1-(4-Chloro-2,5-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1602] Synthesized analogous to Example 257.
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.77 (1H, m), 1.86-1.98 (1H, m), 2.45 (2H, t, J = 7.7 Hz), 2.74-2.94 (3H, m), 2.96-3.07 (1H, m), 3.09-3.20 (1H, m), 3.20-3.26 (1H, m), 3.69 (1H, d, J = 8.8 Hz), 3.74-3.86 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 4.59 (1H, s), 4.96 (1H, d, J = 6.4 Hz), 6.57 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.11 (1H, dd, J = 11.3 Hz, 7.9 Hz), 7.50 (1H, dd, J = 10.6 Hz, 7.1 Hz), 10.02 (1H, brs).

Example 343

5-{[(3R,4R)-1-(5,6-Difluoro-1-methyl-1H-benzimidazol-2-yl)-3,4-dihydroxypiperidi n-4-yl]methoxy}-8-fluoro-3,4-dihydro-quinolin-2(1H)-one

[1603] Synthesized analogous to Example 245.
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.74 (1H, m), 1.98-2.08 (1H, m), 2.41 (2H, t, J = 7.6 Hz), 2.79-2.90 (2H, m), 3.11 (1H, t, J = 11.4 Hz), 3.19-3.28 (1H, m), 3.36-3.44 (2H, m), 3.59 (3H, s), 3.70 (1H, d, J = 8.9 Hz), 3.90-3.97 (1H, m), 4.03 (1H, d, J = 8.9 Hz), 4.63 (1H, s), 4.96 (1H, d, J = 6.4 Hz), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.43 (1H, dd, J = 11.3 Hz, 7.5 Hz), 7.51 (1H, dd, J = 10.8 Hz, 7.4 Hz), 10.01 (1H, s).

Example 344

5-({(3R,4R)-3,4-Dihydroxy-1-[1-(methoxymethyl)-1H-benzimidazol-2-yl]piperidin-4-yl}methoxy)-8-fluoro-3,4-dihydro-quinolin-2(1H)-one

[1604] Synthesized analogous to Example 245.
^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.75 (1H, m), 1.99-2.09 (1H, m), 2.40 (2H, t, J = 7.7 Hz), 2.79-2.91 (2H, m), 3.13 (1H, t, J = 11.4 Hz), 3.23-3.32 (1H, m), 3.36 (3H, s), 3.50-3.60 (2H, m), 3.70 (1H, d, J = 8.9 Hz), 3.89-3.97 (1H, m), 4.03 (1H, d, J = 8.9 Hz), 4.62 (1H, s), 4.96 (1H, d, J = 6.6 Hz), 5.33 (2H, s), 6.58 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.08-7.15 (2H, m), 7.38-7.42 (1H, m), 7.43-7.47 (1H, m), 10.01 (1H, s).

Example 345

8-Fluoro-5-{[(3R,4R)-1-(2-fluoro-4-hydroxyphenyl)-3,4-dihydroxypiperidin-4-yl]me thoxy}-3,4-dihydroquinolin-2(1H)-one

[1605] Under nitrogen atmosphere, a solution of 5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one (707 mg), tris(dibenzylideneacetone)dipalladium (0) (13.4 mg), di-tert-butyl[3,4,5,6-tetramethyl-2',4',6'-tri (propan-2-yl)biphenyl-2-yl]phosphane (14.07 mg) and potassium hydroxide (386 mg) in 1,4-dioxane-water (1:1) (1.5 mL) was stirred at 100 °C for 5 h. To the reaction solution was added 2 N hydrochloric acid, and the precipitate was collected on a filter. The obtained solid was washed with water and ethyl acetate, and vacuum-dried (100 °C) to provide the title compound (411 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.77-1.80 (1H, m), 2.13-2.18 (1H, m), 2.48 (2H, t, J = 7.5 Hz), 2.88-2.98 (2H, m), 3.10-3.30 (4H, m), 3.71 (1H, d, J = 9.0 Hz), 3.98-4.04 (1H, m), 4.05 (1H, d, J = 9.0 Hz), 6.59 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.63-6.64 (1H, m), 6.67-6.70 (1H, m), 7.03 (1H, t, J = 9.0 Hz), 7.27-7.35 (1H, m), 10.04 (1H, brs).

Example 346

5-{[(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -3,4-dihydroquinolin-2(1H)-one

[1606] A suspension of 5-hydroxy-3,4-dihydroquinolin-2(1H)-one (0.4g), (3R,4R)-6-(4-chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol (0.614 g) and potassium bicarbonate (0.021 mL) in N,N-dimethylformamide:2-propanol (1:4) (3 mL) was stirred at 70 °C for 21 h. To the reaction solution were added water and diisopropyl ether, the insoluble precipitate was collected on a filter, and the obtained solid was recrystallized form acetic acid/water. The precipitate was collected on a filter, and dried under reduced pressure (70 °C) to provide the title compound (0.73 g, 98 % ee).
m.p. 211-212 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.72 (1H, m), 1.86-1.98 (1H, m), 2.43 (2H, t, J = 7.8 Hz), 2.77-2.94 (3H, m), 2.94-3.00 (1H, m), 3.21 (1H, t, J = 10.7 Hz), 3.29-3.44 (1H, m, overlapping with H_2O signal), 3.68 (1H, d, J = 8.8 Hz), 3.71-3.79 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.54 (1H, s), 4.88 (1H, d, J = 6.5 Hz), 6.49 (1H, d, J = 8.1 Hz), 6.59 (1H, d, J = 8.1 Hz), 7.09 (1H, t, J = 8.1 Hz), 7.23-7.32 (2H, m), 10.04 (1H, s).

Example 347

5-{[(3R,4R)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4 -dihydroquinolin-2(1H)-one

[1607] Synthesized analogous to Example 346.
(Acetic acid/water) m.p. 226-227 °C

^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.78 (1H, m), 1.91-2.01 (1H, m), 2.42 (2H, t, J = 7.8 Hz), 2.75-2.90 (3H, m), 2.94-3.03 (1H, m), 3.06-3.14 (1H, m), 3.14-3.22 (1H, m), 3.69 (1H, d, J = 8.8 Hz), 3.78-3.85 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.57 (1H, s), 4.95 (1H, d, J = 6.4 Hz), 6.49 (1H, d, J = 8.1 Hz), 6.59 (1H, d, J = 8.1 Hz), 7.03 (1H, t, J = 9.1 Hz), 7.08 (1H, t, J = 8.1 Hz), 7.30 (1H, dd, J = 8.6 Hz, 1.8 Hz), 7.42 (1H, dd, J = 12.3 Hz, 2.3 Hz), 10.03 (1H, s).

Example 348

5-{[(3R,4R)-1-(2,6-Difluoro-4-hydroxyphenyl)-3,4-dihydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1608] Synthesized analogous to Example 345.
^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.67 (1H, m), 1.85-1.92 (1H, m), 2.46-2.50 (2H, m), 2.66-2.72 (1H, m), 2.75-2.79 (1H, m), 2.83-2.97 (2H, m), 3.16-3.21 (1H, m), 3.26-3.32 (1H, m), 3.67 (1H, d, J = 11.0 Hz), 3.68-3.74 (1H, m), 4.00 (1H, d, J = 11.0 Hz), 4.43 (1H, brs), 4.76 (1H, d, J = 8.0 Hz), 6.37-6.44 (2H, m), 6.56 (1H, dd, J = 11.5 Hz, 4.5 Hz), 7.02 (1H, t, J = 11.5 Hz), 10.00 (1H, brs), 10.02 (1H, brs).

Example 349

5-{[(3R*,4R*)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-3,4-dihydroquinolin-2(1H)-one

[1609] Synthesized analogous to Example 346.
(Acetic acid/water) m.p. 233 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.72 (1H, m), 1.86-1.98 (1H, m), 2.43 (2H, t, J = 7.8 Hz), 2.77-2.94 (3H, m), 2.94-3.00 (1H, m), 3.21 (1H, t, J = 10.7 Hz), 3.29-3.44 (1H, m, overlapping with H_2O signal), 3.68 (1H, d, J = 8.8 Hz), 3.71-3.79 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.54 (1H, s), 4.88 (1H, d, J = 6.5 Hz), 6.49 (1H, d, J = 8.1 Hz), 6.59 (1H, d, J = 8.1 Hz), 7.09 (1H, t, J = 8.1 Hz), 7.23-7.32 (2H, m), 10.04 (1H, s).

Example 350

5-{[(3R*,4R*)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3, 4-dihydroquinolin-2(1H)-one

[1610] Synthesized analogous to Example 346.
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.78 (1H, m), 1.91-2.01 (1H, m), 2.42 (2H, t, J = 7.8 Hz), 2.75-2.90 (3H, m), 2.94-3.03 (1H, m), 3.06-3.14 (1H, m), 3.14-3.22 (1H, m), 3.69 (1H, d, J = 8.8 Hz), 3.78-3.85 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.57 (1H, s), 4.95 (1H, d, J = 6.4 Hz), 6.49 (1H, d, J = 8.1 Hz), 6.59 (1H, d, J = 8.1 Hz), 7.03 (1H, t, J = 9.1 Hz), 7.08 (1H, t, J = 8.1 Hz), 7.30 (1H, dd, J = 8.6 Hz, 1.8 Hz), 7.42 (1H, dd, J = 12.3 Hz, 2.3 Hz), 10.03 (1H, s).

Example 351

5-{[(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -6,8-difluoro-3,4-dihydroquinolin-2(1H)-one

[1611] A solution of 6,8-difluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (23 mg), (3R,4R)-6-(4-chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol (31.8 mg) and potassium carbonate (3.19 mg) in 2-propanol-water (5: 1) (0.5 mL) was heated to reflux for 2 h. The reaction solution was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (38 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.88-1.95 (2H, m), 2.60 (1H, d, J = 6.5 Hz), 2.64 (2H, t, J = 7.5 Hz), 2.81 (1H, brs), 3.01-3.05 (1H, m), 3.08 (2H, t, J = 7.5 Hz), 3.26 (2H, d, J = 7.0 Hz), 3.33-3.39 (1H, m), 3.99 (1H, d, J = 9.0 Hz), 4.00-4.04 (1H, m), 4.12 (1H, d, J = 9.0 Hz), 6.85 (1H, t, J = 10.0 Hz), 6.86-6.92 (2H, m), 7.53 (1H, brs).

Example 352

5-{[(3R,4R)-1-(2,6-Difluoro-4-methoxyphenyl)-3,4-dihydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1612] To a suspension of 5-{[(3R,4R)-1-(2,6-difluoro-4-hydroxyphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one (244 mg) and potassium carbonate (230 mg) in N,N-dimethylformamide (2.4 mL) was added methyl iodide (0.313 mL), and the reaction mixture was stirred at 90-100 °C for 8 h. To the reaction solution

was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), and the product obtained from higher polarity fractions was recrystallized from ethyl acetate/hexane. The precipitate was collected on a filter and dried to provide the title compound (78 mg).
m.p. 167.1-167.3 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.68 (1H, m), 1.86-1.92 (1H, m), 2.47 (2H, t, J = 8.0 Hz), 2.72-2.74 (1H, m), 2.80-2.83 (1H, m), 2.84-2.95 (2H, m), 3.18-3.22 (1H, m), 3.28-3.35 (1H, m), 3.67 (1H, d, J = 9.0 Hz), 3.70-3.74 (1H, m), 3.73 (3H, s), 4.01 (1H, d, J = 9.0 Hz), 4.46 (1H, brs), 4.79 (1H, d, J = 6.5 Hz), 6.58 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.66-6.72 (2H, m), 7.02 (1H, t, J = 9.0 Hz), 10.03 (1H, brs).

Example 353

5-{[(3R,4R)-1-(2,6-Difluoro-4-methoxyphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-methyl-3,4-dihydroquinolin-2(1H)-one

[1613] The lower polarity fractions of Example 352 was vacuum-dried (100 °C) to provide the title compound (68 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-1.95 (2H, m), 2.56-2.60 (2H, m), 2.73 (1H, d, J = 8.0 Hz), 2.74 (1H, brs), 2.85-2.99 (3H, m), 3.18-3.24 (2H, m), 3.26-3.32 (1H, m), 3.42 (3H, d, J = 7.0 Hz), 3.75 (3H, s), 3.95-3.98 (1H, m), 4.00 (1H, d, J = 9.5 Hz), 4.07 (1H, d, J = 9.5 Hz), 6.40-6.46 (2H, m), 6.63 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.95 (1H, dd, J = 12.5 Hz, 9.0 Hz).

Example 354

5-{[(3R,4R)-1-(2,6-Difluoro-4-propoxyphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1614] Synthesized analogous to Example 148.
(Ethyl acetate/hexane) m.p. 194.8-195.0 °C
^{1}HNMR (DMSO-d6) δ ppm: 0.95 (3H, t, J = 7.0 Hz), 1.66-1.73 (3H, m), 1.86-1.92 (1H, m), 2.48 (2H, t, J = 7.5 Hz), 2.71-2.74 (1H, m), 2.79-2.83 (1H, m), 2.84-2.95 (2H, m), 3.18-3.22 (1H, m), 3.28-3.35 (1H, m), 3.67 (1H, d, J = 9.0 Hz), 3.70-3.74 (1H, m), 3.90 (2H, t, J = 6.5 Hz), 4.01 (1H, d, J = 9.0 Hz), 4.46 (1H, brs), 4.79 (1H, d, J = 6.5 Hz), 6.58 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.64-6.70 (2H, m), 7.02 (1H, t, J = 9.0 Hz), 10.03 (1H, brs).

Example 355

5-{[(3R,4R)-1-(4-Butoxy-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1615] Synthesized analogous to Example 148.
(Ethyl acetate/hexane) m.p. 185.8-186.2 °C
^{1}HNMR (DMSO-d6) δ ppm: 0.92 (3H, t, J = 7.0 Hz), 1.37-1.44 (2H, m), 1.63-1.69 (3H, m), 1.86-1.91 (1H, m), 2.48 (2H, t, J = 7.5 Hz), 2.71-2.74 (1H, m), 2.79-2.82 (1H, m), 2.85-2.96 (2H, m), 3.18-3.22 (1H, m), 3.28-3.35 (1H, m), 3.67 (1H, d, J = 8.5 Hz), 3.70-3.74 (1H, m), 3.93 (2H, t, J = 6.5 Hz), 4.01 (1H, d, J = 8.5 Hz), 4.46 (1H, brs), 4.79 (1H, d, J = 6.5 Hz), 6.58 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.64-6.70 (2H, m), 7.02 (1H, t, J = 9.0 Hz), 10.03 (1H, brs).

Example 356

5-{[(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1616] A solution of tert-butyl (1S*,6S*)-6-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-7-oxa-3-azabicyclo [4.1.0]heptane-3-carboxylate (392 mg) in trifluoroacetic acid (10 mL) was stirred at 60 °C for 3 h, and the reaction solution was concentrated. To the residue were added 2,3,5-trichloropyridine (219 mg), potassium carbonate (691 mg) and N-methyl-2-pyrrolidone (NMP) (5 mL), the mixture was stirred at 100 °C for 5 h, water was added thereto, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate), washed with diethyl ether and dried to provide the title compound (188 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.45-1.43 (1H, m), 2.03-2.11 (1H, m), 2.45 (2H, t, J = 7.6 Hz), 2.89-2.99 (2H, m), 3.16-3.27 (2H, m), 3.40-3.50 (2H, m), 3.60-3.70 (3H, m), 3.80 (1H, d, J = 9.4 Hz), 3.94 (1H, d, J = 9.4 Hz), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.99 (1H, t, J = 9.7 Hz), 7.94 (1H, d, J = 2.3 Hz), 8.20 (1H, d, J = 2.3 Hz), 9.99 (1H, brs).

Example 357

5-{[(3R*,4S*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1617] To a mixture of 5-{[(3R*,4S*)-3-{[tert-butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4 -yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (360 mg) and anisole (0.117 mL) was added trifluoroacetic acid (5 mL), the reaction mixture was stirred at 60 °C for 4 h, and the solvent was distilled off. The residue was dissolved into tetrahydrofuran (THF) (5 mL), and tetra-n-butylammonium fluoride (TBAF) (1 M tetrahydrofuran (THF) solution) (1.07 mL) was added thereto at 0 °C. The solution was stirred at room temperature for 5 h, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) and washed with diethyl ether to provide the title compound (65 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.52-1.59 (1H, m), 1.99-2.07 (1H, m), 2.45 (2H, t, J = 7.9 Hz), 2.94 (2H, t, J = 8.0 Hz), 3.01-3.08 (1H, m), 3.09-3.17 (2H, m), 3.20-3.26 (1H, m), 3.68 (1H, brs), 3.85 (1H, d, J = 9.4 Hz), 3.96 (1H, d, J = 9.4 Hz), 4.82 (2H, s), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.8 Hz), 7.06 (1H, t, J = 9.3 Hz), 7.14 (1H, dd, J = 8.7 Hz, 2.3 Hz), 7.29 (1H, dd, J = 12.6 Hz, 2.4 Hz), 10.01 (1H, brs).

Example 358

5-{[(3R*,4S*)-1-(2,4-Dichlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1618] Synthesized analogous to Example 357.
^{1}HNMR ($CDCl_3$) δ ppm: 1.73-1.79 (1H, m), 2.07-2.05 (1H, m), 2.44 (1H, brs), 2.65 (2H, t, J = 7.8 Hz), 2.95-3.05 (2H, m), 3.06-3.16 (2H, m), 3.22-3.27 (1H, m), 3.30 (1H, d, J = 9.9 Hz), 3.35-3.39 (1H, m), 3.78-3.83 (1H, m), 3.89 (1H, d, J = 8.9 Hz), 4.21 (1H, d, J = 8.9 Hz), 6.55 (1H, dd, J = 9.2 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.08 (1H, d, J = 8.6 Hz), 7.23 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.40 (1H, d, J = 2.5 Hz), 7.66 (1H, brs).

Example 359

5-{[(3R*,4S*)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1619] To a solution of 5-({(3R*,4S*)-1-(4-chloro-2,6-difluorophenyl)-4-hydroxy-3-[(4-methoxybenzyl)oxy]piperidin-4-yl} methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (68 mg) and anisole (0.026 mL) in dichloromethane (0.7 mL) was added trifluoroacetic acid (0.8 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 28.5 h. To the reaction solution was added water, neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), washed with hexane/ethyl acetate and dried to provide the title compound (19 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.49-1.52 (1H, m), 1.99-2.05 (1H, m), 2.45 (2H, t, J = 7.5 Hz), 2.94 (2H, t, J = 7.5 Hz), 2.95-3.00 (2H, m), 3.28-3.35 (1H, m), 3.52-3.54 (1H, m), 3.60-3.62 (1H, m), 3.83 (1H, d, J = 9.5 Hz), 3.95 (1H, d, J = 9.5 Hz), 4.70 (1H, d, J = 5.0 Hz), 4.82 (1H, brs), 6.57 (1H, dd, J = 9.0 Hz, 4.0 Hz), 7.00 (1H, t, J = 9.0 Hz), 7.22-7.28 (2H, m), 10.01 (1H, brs).

Example 360

5-{[(3R,4S)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1620] Synthesized analogous to Example 359.
^{1}HNMR (DMSO-d6) δ ppm: 1.49-1.52 (1H, m), 1.99-2.05 (1H, m), 2.45 (2H, t, J = 7.5 Hz), 2.94 (2H, t, J = 7.5 Hz), 2.95-3.00 (2H, m), 3.28-3.35 (1H, m), 3.52-3.54 (1H, m), 3.60-3.62 (1H, m), 3.83 (1H, d, J = 9.5 Hz), 3.95 (1H, d, J = 9.5 Hz), 4.69 (1H, d, J = 5.5 Hz), 4.82 (1H, brs), 6.57 (1H, dd, J = 9.0 Hz, 4.0 Hz), 7.00 (1H, t, J = 9.0 Hz), 7.22-7.28 (2H, m), 10.01 (1H, brs).

Example 361

5-{[(3S,4R)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1621] Synthesized analogous to Example 359.
(Acetic acid/water) m.p. 206.0-206.1 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.49-1.52 (1H, m), 1.99-2.05 (1H, m), 2.45 (2H, t, J = 7.5 Hz), 2.94 (2H, t, J = 7.5 Hz), 2.95-3.00 (2H, m), 3.28-3.35 (1H, m), 3.52-3.54 (1H, m), 3.60-3.62 (1H, m), 3.83 (1H, d, J = 9.5 Hz), 3.95 (1H, d, J = 9.5 Hz), 4.69 (1H, d, J = 5.5 Hz), 4.82 (1H, brs), 6.57 (1H, dd, J = 9.0 Hz, 4.0 Hz), 7.00 (1H, t, J = 9.0 Hz), 7.22-7.28 (2H, m), 9.99 (1H, brs).

Example 362

5-{[(3S,4R)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fl uoro- 3,4-dihydroquinolin-2(1H)-one

[1622] Synthesized analogous to Example 359.
(Acetic acid/water) m.p. 198.6-198.8 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.54-1.57 (1H, m), 2.00-2.06 (1H, m), 2.45 (2H, t, J = 7.5 Hz), 2.94 (2H, t, J = 7.5 Hz), 3.02-3.06 (1H, m), 3.10-3.15 (2H, m), 3.22-3.24 (1H, m), 3.67-3.70 (1H, m), 3.85 (1H, d, J = 9.5 Hz), 3.96 (1H, d, J = 9.5 Hz), 4.82 (1H, brs), 4.82 (1H, d, J = 4.5 Hz), 6.57 (1H, dd, J = 9.0 Hz, 4.0 Hz), 7.00 (1H, t, J = 9.0 Hz), 7.06 (1H, t, J = 9.0 Hz), 7.13-7.15 (1H, m), 7.28 (1H, dd, J = 12.5 Hz, 2.0 Hz), 10.01 (1H, brs).

Example 363

5-{[(3R,4S)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fl uoro-3,4-dihydroquinolin-2(1H)-one

[1623] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 194.7-194.8 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.54-1.56 (1H, m), 2.00-2.06 (1H, m), 2.45 (2H, t, J = 7.5 Hz), 2.94 (2H, t, J = 7.5 Hz), 3.03-3.07 (1H, m), 3.10-3.16 (2H, m), 3.22-3.24 (1H, m), 3.67-3.70 (1H, m), 3.84 (1H, d, J = 9.5 Hz), 3.96 (1H, d, J = 9.5 Hz), 4.82 (1H, brs), 4.83 (1H, d, J = 6.0 Hz), 6.57 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.98-7.03 (2H, m), 7.25-7.27 (1H, m), 7.38 (1H, dd, J = 12.5 Hz, 2.0 Hz), 10.01 (1H, brs).

Example 364

5-{[(3R,4S)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yllmethoxy}-8-c hloro-3,4-dihydroquinolin-2(1H)-one

[1624] Synthesized analogous to Example 42.
(Ethanol/water) m.p. 185.8-186.0 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.54-1.57 (1H, m), 2.01-2.06 (1H, m), 2.47 (2H, t, J = 7.5 Hz), 2.96 (2H, t, J = 7.5 Hz), 3.03-3.07 (1H, m), 3.11-3.17 (2H, m), 3.22-3.25 (1H, m), 3.68-3.70 (1H, m), 3.88 (1H, d, J = 9.5 Hz), 3.99 (1H, d, J = 9.5 Hz), 4.86 (1H, brs), 4.86 (1H, brs), 6.67 (1H, d, J = 9.0 Hz), 7.01 (1H, t, J = 9.5 Hz), 7.23 (1H, d, J = 9.0 Hz), 7.23-7.27 (1H, m), 7.38 (1H, dd, J = 12.5 Hz, 2.0 Hz), 9.35 (1H, brs).

Example 365

5-{[(3R*,4S*)-1-(4-Chloro-2,5-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1625] Synthesized analogous to Example 357.
(Ethanol/water) m.p. 184-185 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.49-1.59 (1H, m), 1.95-2.06 (1H, m), 2.45 (2H, t, J = 7.7 Hz), 2.94 (2H, t, J = 7.7 Hz), 3.03-3.15 (1H, m), 3.15-3.35 (3H, m), 3.62-3.70 (1H, m), 3.83 (1H, d, J = 9.3 Hz), 3.95 (1H, d, J = 9.3 Hz), 4.85 (1H, s), 4.89 (1H, d, J = 5.4 Hz), 6.56 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.09 (1H, dd, J = 11.3 Hz, 7.9 Hz), 7.45 (1H, dd, J = 12.3 Hz, 7.2 Hz), 10.01 (1H, s).

Example 366

5-{[(3S*,4R*)-1-(4-Bromo-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1626] Synthesized analogous to Example 359.
(Ethanol) m.p. 209-210 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.46-1.54 (1H, m), 1.97-2.06 (1H, m), 2.45 (2H, t, J = 7.7 Hz), 2.90-2.96 (2H, m), 2.96-3.03 (2H, m), 3.27-3.35 (1H, m), 3.49-3.56 (1H, m), 3.59-3.64 (1H, m), 3.82 (1H, d, J = 9.4 Hz), 3.95 (1H, d, J = 9.4 Hz), 4.69 (1H, d, J = 5.5 Hz), 4.81 (1H, s), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.7 Hz), 7.31-7.38 (2H, m), 10.01 (1H, s).

Example 367

5-{[(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy} -8-fluoroquinolin-2(1H)-one

[1627] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 247.4-247.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.79-1.82 (1H, m), 1.88-1.94 (1H, m), 2.92-2.94 (1H, m), 2.97-3.00 (1H, m), 3.22-3.30 (2H, m), 3.74-3.77 (1H, m), 3.88 (1H, d, J = 8.5 Hz), 4.12 (1H, d, J = 8.5 Hz), 4.66 (1H, brs), 4.91 (1H, brs), 6.57 (1H, d, J = 9.5 Hz), 6.67 (1H, dd, J = 9.0 Hz, 3.5 Hz), 7.25-7.31 (2H, m), 7.34 (1H, t, J = 9.0 Hz), 8.10 (1H, d, J = 9.5 Hz), 11.74 (1H, brs).

Example 368

8-Chloro-5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl] methoxy}quinolin-2(1H)-one

[1628] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 228.8-229.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.80-1.83 (1H, m), 1.87-1.93 (1H, m), 2.92-2.94 (1H, m), 2.97-3.00 (1H, m), 3.22-3.28 (2H, m), 3.74-3.75 (1H, m), 3.93 (1H, d, J = 9.0 Hz), 4.14 (1H, d, J = 9.0 Hz), 4.70 (1H, brs), 4.93 (1H, brs), 6.60 (1H, d, J = 10.0 Hz), 6.80 (1H, d, J = 9.0 Hz), 7.25-7.31 (2H, m), 7.59 (1H, d, J = 9.0 Hz), 8.15 (1H, d, J = 10.0 Hz), 10.92 (1H, brs).

Example 369

5-{[(3R*,4R*)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8 -fluoroquinolin-2(1H)-one

[1629] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.83-1.86 (1H, m), 1.93-1.99 (1H, m), 2.88 (1H, t, J = 11.0 Hz), 3.00 (1H, t, J = 11.0 Hz), 3.12-3.15 (1H, m), 3.18-3.21 (1H, m), 3.81-3.85 (1H, m), 3.88 (1H, d, J = 9.0 Hz), 4.12 (1H, d, J = 9.0 Hz), 4.73 (1H, brs), 5.02 (1H, d, J = 6.5 Hz), 6.55 (1H, d, J = 10.0 Hz), 6.68 (1H, dd, J = 9.0 Hz, 3.5 Hz), 7.34 (1H, t, J = 9.0 Hz), 7.30-7.37 (2H, m), 7.43 (1H, dd, J = 7.5 Hz, 2.0 Hz), 8.10 (1H, d, J = 10.0 Hz), 11.76 (1H, brs).

Example 370

5-{[(3R,4R)-1-(4-Bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-f luoroquinolin-2(1H)-one

[1630] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 224.5 °C (dec)
^{1}HNMR (DMSO-d6) δ ppm: 1.83-1.86 (1H, m), 1.93-1.99 (1H, m), 2.88 (1H, t, J = 11.0 Hz), 3.00 (1H, t, J = 11.0 Hz), 3.12-3.15 (1H, m), 3.18-3.21 (1H, m), 3.81-3.85 (1H, m), 3.88 (1H, d, J = 9.0 Hz), 4.12 (1H, d, J = 9.0 Hz), 4.73 (1H, brs), 5.02 (1H, d, J = 6.5 Hz), 6.55 (1H, d, J = 10.0 Hz), 6.68 (1H, dd, J = 9.0 Hz, 3.5 Hz), 7.34 (1H, t, J = 9.0 Hz), 7.30-7.37 (2H, m), 7.43 (1H, dd, J = 7.5 Hz, 2.0 Hz), 8.10 (1H, d, J = 10.0 Hz), 11.76 (1H, brs).

Example 371

5-{[(3R*,4R*)-1-(4-Chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy }-8-fluoroquinolin-2(1H)-one

[1631] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 232 °C

^{1}HNMR (DMSO-d6) δ ppm: 1.77-1.84 (1H, m), 1.86-1.95 (1H, m), 2.88-2.96 (1H, m), 2.96-3.02 (1H, m), 3.24 (1H, t, J = 10.7 Hz), 3.30-3.45 (1H, m, overlapping with H2O signal), 3.72-3.79 (1H, m), 3.88 (1H, d, J = 9.0 Hz), 4.11 (1H, d, J = 9.0 Hz), 4.69 (1H, s), 4.93 (1H, d, J = 6.5 Hz), 6.57 (1H, d, J = 9.8 Hz), 6.67 (1H, dd, J = 9.0 Hz, 3.4 Hz), 7.24-7.32 (2H, m), 7.35 (1H, dd, J = 10.8 Hz, 9.0 Hz), 8.10 (1H, dd, J = 9.8 Hz, 1.4 Hz), 11.76 (1H, s).

Example 372

5-({[1-(3,5-Dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1632] A solution of 5-amino-8-fluoro-3,4-dihydroquinolin-2(1H)-one (0.20 g), 6-(3,5-dichloropyridin-2-yl)-1-oxa-6-aza-spiro[2.5]octane (0.432 g) in acetic acid (4 mL) was stirred at 60 °C for 7 h. The reaction solution was concentrated, saturated aqueous sodium hydrogencarbonate and ethyl acetate were added to the residue, insoluble materials were filtered off, and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/ethyl acetate) to provide the title compound (55.2 mg).
(Ethanol) m.p. 193-194 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.71 (1H, s), 1.79-1.94 (4H, m), 2.68 (2H, t, J = 7.6 Hz), 2.82 (2H, t, J = 7.6 Hz), 3.16 (2H, d, J = 2.9 Hz), 3.21-3.30 (2H, m), 3.56-3.64 (2H, m), 3.72-3.81 (1H, m), 6.33 (1H, dd, J = 9.0 Hz, 4.2 Hz), 6.89 (1H, t, J = 9.4 Hz), 7.51 (1H, brs), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 373

5-({[1-(2,4-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1633] Synthesized analogous to Example 372.
(Ethyl acetate/ethanol) m.p. 226-227 °C^{1}HNMR ($CDCl_3$) δ ppm: 1.70 (1H, s), 1.81-1.88 (2H, m), 1.89-1.98 (2H, m), 2.68 (2H, t, J = 7.7 Hz), 2.82 (2H, t, J = 7.7 Hz), 2.98-3.07 (2H, m), 3.12-3.21 (4H, m), 3.72-3.79 (1H, m), 6.35 (1H, dd, J = 9.0 Hz, 4.3 Hz), 6.89 (1H, t, J = 9.4 Hz), 7.01 (1H, d, J = 8.7 Hz), 7.20 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.37 (1H, d, J = 2.5 Hz), 7.52 (1H, brs).

Example 374

5-({[1-(2,5-Dichloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1634] Synthesized analogous to Example 372.
^{1}HNMR ($CDCl_3$) δ ppm: 1.67 (1H, s), 1.81-1.88 (2H, m), 1.88-1.97 (2H, m), 2.68 (2H, t, J = 7.7 Hz), 2.83 (2H, t, J = 7.7 Hz), 2.97-3.05 (2H, m), 3.09-3.15 (2H, m), 3.17 (2H, brs), 3.75 (1H, brs), 6.35 (1H, dd, J = 9.0 Hz, 4.2 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.11 (1H, d, J = 7.2 Hz), 7.21 (1H, d, J = 8.6 Hz), 7.50 (1H, brs).

Example 375

5-({[1-(2-Chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1635] Synthesized analogous to Example 372.
(Acetic acid/ethyl acetate) m.p. 214-215 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.70 (1H, s), 1.81-1.87 (2H, m), 1.90-1.97 (2H, m), 2.69 (2H, t, J = 7.6 Hz), 2.83 (2H, t, J = 7.6 Hz), 2.97-3.05 (2H, m), 3.08-3.15 (2H, m), 3.17 (2H, brs), 3.77 (1H, brs), 6.35 (1H, dd, J = 9.0 Hz, 4.3 Hz), 6.90 (1H, t, J = 9.5 Hz), 6.92-6.98 (1H, m), 7.06 (1H, dd, J = 9.0 Hz, 5.5 Hz), 7.14 (1H, dd, J = 8.3 Hz, 3.0 Hz), 7.51 (1H, brs).

Example 376

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1636] Synthesized analogous to Example 372.
(Acetic acid/ethyl acetate) m.p. 225-226 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.70 (1H, s), 1.81-1.87 (2H, m), 1.87-1.97 (2H, m), 2.68 (2H, t, J = 7.6 Hz), 2.82 (2H, t, J = 7.6 Hz), 3.02-3.10 (2H, m), 3.15 (2H, s), 3.19-3.25 (2H, m), 3.78 (1H, brs), 6.34 (1H, dd, J = 9.0 Hz, 4.3 Hz), 6.86-6.95 (2H, m), 7.02-7.08 (2H, m), 7.53 (1H, brs).

Example 377

5-[{[1-(2,4-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methyl} (methyl)amino]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1637] Synthesized analogous to Example 6.
(Ethanol) m.p. 156-157 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.52-1.59 (2H, m), 1.68-1.76 (2H, m), 2.61 (1H, s), 2.62-2.67 (2H, m), 2.73 (3H, s), 2.92-3.00 (2H, m), 3.04-3.14 (6H, m), 6.90 (1H, dd, J = 8.9 Hz, 4.8 Hz), 6.95-7.00 (2H, m), 7.17 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.34 (1H, d, J = 2.5 Hz), 7.53 (1H, brs).

Example 378

5-({[1-(2,4-Dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1638] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.75 (4H, brs), 2.43-2.50 (2H, m), 2.75 (2H, t, J = 7.8 Hz), 2.90-3.10 (6H, m), 4.49-4.55 (1H, m), 4.70 (1H, s), 6.29 (1H, dd, J = 9.0 Hz, 4.2 Hz), 6.81-6.92 (1H, m), 7.24 (1H, d, J = 11.4 Hz), 7.70 (1H, d, J = 7.8 Hz), 9.82 (1H, s).

Example 379

5-({[1-(4-Chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1639] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.60-1.80 (4H, m), 2.40-2.60 (2H, m), 2.74 (2H, t, J = 7.8 Hz), 2.87-3.22 (6H, m), 4.40-4.60 (1H, m), 4.72 (1H, brs), 6.28 (1H, dd, J = 9.4 Hz, 3.9 Hz), 6.88 (1H, t, J = 9.4 Hz), 7.12 (1H, dd, J = 11.8 Hz, 7.4 Hz), 7.49 (1H, dd, J = 11.8 Hz, 7.4 Hz), 9.82 (1H, s).

Example 380

5-({[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1640] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.57-1.77 (4H, m), 2.40-2.57 (2H, m), 2.74 (2H, t, J = 7.8 Hz), 2.89-3.08 (4H, m), 3.20-3.45 (2H, m), 4.40-4.55 (1H, m), 4.68 (1H, brs), 6.29 (1H, dd, J = 9.5 Hz, 4.1 Hz), 6.88 (1H, t, J = 9.5 Hz), 7.19-7.35 (2H, m), 9.82 (1H, s).

Example 381

5-({[1-(2,4-Dichloro-6-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1641] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.62-1.74 (4H, m), 2.41-2.55 (2H, m), 2.69-2.79 (2H, m), 2.83-2.95 (2H, m), 3.03 (2H, d, J = 5.4 Hz), 3.25-3.45 (2H, m), 4.42-4.55 (1H, m), 4.71 (1H, brs), 6.30 (1H, dd, J = 9.2 Hz, 4.1 Hz), 6.89 (1H, t, J = 9.2 Hz), 7.38-7.50 (2H, m), 9.82 (1H, s).

Example 382

5-({[1-(2-Chloro-4,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1642] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.62-1.72 (3H, m), 2.25-2.30 (1H, m), 2.40-2.55 (2H, m), 2.69-2.78 (2H, m), 2.79-2.88 (2H, m), 2.97-3.08 (2H, m), 3.25-3.40 (2H, m), 4.41-4.52 (1H, m), 4.66 (1H, s), 6.30 (1H, dd, J = 9.2 Hz, 4.1 Hz), 6.82-6.95 (1H, m), 7.20-7.40 (2H, m), 9.82 (1H, s).

Example 383

8-Fluoro-5-({[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methyl}amino)-3,4-di hydroquinolin-2(1H)-one

[1643] Synthesized analogous to Example 6.
^{1}HNMR ($CDCl_3$) δ ppm: 1.57 (1H, brs), 1.76-1.82 (2H, m), 1.83-1.91 (2H, m), 2.68 (2H, t, J = 8.0 Hz), 2.82 (2H, t, J = 7.9 Hz), 3.00-3.06 (2H, m), 3.15 (2H, s), 3.33-3.41 (2H, m), 3.78 (1H, brs), 6.34 (1H, dd, J = 9.1 Hz, 4.3 Hz), 6.59-6.67 (2H, m), 6.89 (1H, t, J = 9.4 Hz), 7.51 (1H, brs).

Example 384

5-({[1-(2-Chloro-4-propylphenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1644] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 0.87 (3H, t, J = 7.4 Hz), 1.55 (2H, q, J = 7.4 Hz), 1.64-1.78 (4H, m), 2.41-2.57 (2H, m), 2.70-2.79 (2H, m), 2.90-3.09 (6H, m), 3.30-3.38 (2H, m), 4.42-4.52 (1H, m), 4.65 (1H, s), 6.30 (1H, dd, J = 9.2 Hz, 4.4 Hz), 6.81-6.97 (1H, m), 7.04-7.28 (3H, m), 9.82 (1H, s).

Example 385

5-({[1-(2-Chloro-4-ethylphenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1645] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.14 (3H, t, J = 7.5 Hz), 1.65-1.78 (4H, m), 2.40-2.60 (2H, m), 2.69-2.79 (2H, m), 2.90-3.09 (6H, m), 3.30-3.38 (2H, m), 4.42-4.55 (1H, m), 4.65 (1H, s), 6.30 (1H, dd, J = 9.0 Hz, 4.2 Hz), 6.59 (1H, t, J = 9.0 Hz), 7.05-7.28 (3H, m), 9.83 (1H, s).

Example 386

5-[({1-[2-Chloro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methyl)amin o]-8-fluoro- 3,4-dihydroquinolin-2(1H)-one

[1646] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.75 (4H, brs), 2.43-2.50 (2H, m), 2.75 (2H, t, J = 7.8 Hz), 2.90-3.10 (6H, m), 4.49-4.55 (1H, m), 4.70 (1H, s), 6.31 (1H, dd, J = 8.7 Hz, 4.2 Hz), 6.85-6.93 (1H, m), 7.26-7.35 (2H, m), 7.51 (1H, s), 9.82 (1H, s).

Example 387

8-Fluoro-5-[({1-[2-fluoro-4-(propan-2-yloxy)phenyl]-4-hydroxypiperidin-4-yl}meth yl)amino]-3,4-dihydroquinolin-2(1H)-one

[1647] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.21 (6H, d, J = 6 Hz), 1.65-1.75 (4H, brs), 2.43-2.50 (2H, m), 2.73 (2H, t, J = 7.8 Hz), 2.90-2.96 (4H, m), 3.01 (1H, d, J = 5.4 Hz), 4.46-4.53 (2H, m), 4.65 (1H, s), 4.69 (1H, s), 6.27 (1H, dd, J = 9.3 Hz, 4.2 Hz), 6.66 (1H, dd, J = 11.1 Hz, 2.7 Hz), 6.75 (1H, dd, J = 14.1 Hz, 2.7 Hz), 6.88 (1H, d, J = 9.0 Hz), 6.98 (1H, d, J = 9.0 Hz), 9.84 (1H, s).

Example 388

5-({[1-(4-Ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1648] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.28 (3H, t, J = 6.9 Hz), 1.65-1.75 (4H, brs), 2.43-2.50 (2H, m), 2.73 (2H, t, J = 7.8 Hz), 2.90-2.96 (4H, m), 3.11 (1H, d, J = 5.4 Hz), 3.95 (2H, t, J = 6.9 Hz), 4.47-4.50 (1H, m), 4.69 (1H, s), 6.27 (1H, dd, J = 9.3 Hz, 4.2 Hz), 6.66 (1H, dd, J = 8.7 Hz, 2.7 Hz), 6.75 (1H, dd, J = 14.1 Hz, 2.7 Hz), 6.88 (1H, d, J = 9.0 Hz), 7.00 (1H, d, J = 9.0 Hz), 9.84 (1H, s).

Example 389

8-Fluoro-5-[([1-[2-fluoro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}met hyl)amino]-3,4-dihydroquinolin-2(1H)-one

[1649] A solution of N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (100 mg), 6-[2-fluoro-4-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane (110 mg) and tripotassium phosphate (31.0 mg) in N,N-dimethylformamide (0.5 mL) was stirred at 100 °C for 16 h, 5 N aqueous sodium hydroxide (1.5 mL) was added thereto and the reaction solution was stirred at 90 °C for 3 h (reaction solution 1). Separately, a solution of N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (100 mg), 6-[2-fluoro-4-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane (110 mg) and tripotassium phosphate (31.0 mg) in N,N-dimethylformamide/2-propanol (1:1) (0.8 mL) was stirred at 100 °C for 18 h, 5 N aqueous sodium hydroxide (1 mL) was added thereto and the reaction mixture was stirred at 90 °C for 2 h (reaction solution 2). Reaction solutions 1 and 2 were combined, to which water was added, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved into ethanol (2 mL), a solution of sodium hydroxide (370 mg) in water (1.5 mL) was added to the solution, and the reaction mixture was heated to reflux for 2 h. To the reaction solution was added water, and the precipitate was collected on a filter and recrystallized from methanol to give 8-fluoro-5-[({1-[2-fluoro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methy l)amino]-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one. Anisole (70 mg) and trifluoroacetic acid (2 mL) were added to the product, the reaction mixture was heated to reflux for 2 h, and the solvent was distilled off. To the residue was added water, the solution was neutralized with diluted aqueous sodium hydroxide, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was washed with diethyl ether, the obtained solid was recrystallized from ethanol. The precipitate was collected on a filter and dried to provide the title compound (120 mg).

^{1}HNMR (DMSO-d6) δ ppm: 1.06 (3H, t, J = 7.1 Hz), 1.61-1.72 (4H, m), 2.41-2.56 (2H, m), 2.68-2.80 (2H, m), 2.90-3.16 (6H, m), 4.36 (2H, t, J = 5.1 Hz), 4.42-4.53 (1H, m), 4.68 (1H, s), 6.29 (1H, dd, J = 9.4, 4.1 Hz), 6.88 (1H, t, J = 9.4 Hz), 7.08-7.21 (2H, m), 7.23-7.34 (1H, m), 9.78 (1H, s).

Example 390

N-(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)-N-{[4-hydroxy-1-(2,4,6-trifluoro phenyl)piperidin-4-yl]methyl}acetamide

[1650] A solution of N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (2.0 g), 6-(2,4,6-trifluorophenyl)-1-oxa-6-azaspiro[2.5]octane (2.13 g) and tripotassium phosphate (0.62 g) in N,N-dimethylformamide/2-propanol (1:1) (20 mL) was stirred at 90 °C for 16 h. To the reaction solution was added sodium hydroxide (0.351 g), and the reaction mixture was stirred at 90 °C for 3 days. The solvent was distilled off, water was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]-N-{[4-hydroxyl-(2,4,6-trifluorophenyl)piperidin-4-yl]methyl}acetamide (0.22 g). Reactions analogous to Example 6 were done with the obtained compound, and the product was recrystallized from methanol. The precipitate was collected on a filter and dried to provide the title compound (131 mg).

^{1}HNMR (DMSO-d6) δ ppm: 1.46-1.88 (7H, m), 2.40-2.54 (3H, m), 2.64-2.78 (1H, m), 2.79-3.01 (2H, m), 3.15-3.42 (3H, m), 3.90 (1H, d, J = 14.1 Hz), 4.14 (1H, s), 6.80-7.15 (4H, m), 9.59 (1H, brs). DMSO at 90 deg.

Example 391

8-Chloro-5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-3,4-dihydroquinolin-2(1H)-one

[1651] Synthesized analogous to Example 6.

^{1}HNMR (DMSO-d6) δ ppm: 1.62-1.80 (4H, m), 2.44-2.54 (2H, m), 2.70-2.79 (2H, m), 2.95-3.15 (6H, m), 4.58 (1H, s), 4.70-4.74 (1H, m), 6.42 (1H, d, J = 9.0 Hz), 7.00-7.18 (3H, m), 7.25 (1H, dd, J = 12.5 Hz, 2.3 Hz), 8.81 (1H, brs).

Example 392

8-Chloro-5-({[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}ami no)-3,4-dihydroquinolin-2(1H)-one

[1652] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.77 (4H, m), 2.43-2.54 (2H, m), 2.70-2.80 (2H, m), 2.92-3.14 (6H, m), 4.60 (1H, brs), 4.71-4.74 (1H, m), 6.43 (1H, d, J = 8.9 Hz), 7.06 (1H, d, J = 8.9 Hz), 7.20 (1H, d, J = 11.4 Hz), 7.64 (1H, d, J = 7.8 Hz), 8.82 (1H, brs).

Example 393

8-Chloro-5-({[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}ami no)-3,4-dihydroquinolin-2(1H)-one

[1653] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.58-1.76 (4H, m), 2.44-2.55 (2H, m), 2.70-2.79 (2H, m), 2.89-3.00 (2H, m), 3.02-3.11 (2H, m), 3.23-3.39 (2H, m), 4.63 (1H, m), 4.73-4.78 (1H, m), 6.42 (1H, d, J = 8.9 Hz), 7.06 (1H, d, J = 8.9 Hz), 7.19-7.28 (2H, m), 8.95 (1H, s).

Example 394

8-Chloro-5-({[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methyl}amino)-3,4-dihydroquinolin-2(1H)-one

[1654] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.73 (4H, m), 2.44-2.55 (2H, m), 2.69-2.78 (2H, m), 2.81-2.93 (2H, m), 3.07 (2H, d, =5.7Hz), 3.22-3.48 (2H, m), 4.61 (1H, s), 4.74-4.77 (1H, m), 6.42 (1H, d, J=9.0Hz), 7.00-7.18 (3H, m), 8.95 (1H, brs).

Example 395

8-Chloro-5-({[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-3,4-dihydroquinolin-2(1H)-one

[1655] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.29 (3H, t, J = 6.9 Hz), 1.61-1.79 (4H, m), 2.45-2.53 (2H, m), 2.70-2.78 (2H, m), 2.89-2.99 (4H, m), 3.07 (2H, d, J = 5.4 Hz), 3.96 (2H, q, J = 6.9 Hz), 4.59 (1H, s), 4.73-4.77 (1H, m), 6.41 (1H, d, J = 9.0 Hz), 6.61-6.79 (2H, m), 6.95-7.10 (2H, m), 8.95 (1H, brs).

Example 396

8-Chloro-5-({[1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}ami no)-3,4-dihydroquinolin-2(1H)-one

[1656] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.78 (4H, m), 2.44-2.53 (2H, m), 2.69-2.78 (2H, m), 2.93-3.22 (6H, m), 4.70 (1H, s), 4.75-4.82 (1H, m), 6.41 (1H, d, J = 9.0 Hz), 7.05-7.13 (2H, m), 7.47 (1H, dd, J = 12.2 Hz, 7.1 Hz), 9.02 (1H, s).

Example 397

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-7,8-difluo ro-3,4-dihydroquinolin-2(1H)-one

[1657] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.62-1.76 (4H, m), 2.47 (2H, t, J = 7.6 Hz), 2.70 (2H, t, J = 7.6 Hz), 2.92 (6H, m), 4.54-4.86 (2H, m), 6.35 (1H, dd, J = 15.8 Hz, 6.5 Hz), 7.07 (1H, t, J = 9.1 Hz), 7.16 (1H, dd, J = 8.7 Hz, 2.2 Hz), 7.30 (1H, dd, J = 12.4 Hz, 2.5 Hz), 10.05 (1H, brs).

Example 398

5-({[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-7,8-difluo ro-3,4-dihydroquinolin-2(1H)-one

[1658] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.56-1.79 (4H, m), 2.47 (2H, t, J = 7.6 Hz), 2.70 (2H, t, J = 7.6 Hz), 2.92-3.15 (6H, m), 4.67

(1H, s), 4.77 (1H, t, J = 5.3 Hz), 6.35 (1H, dd, J = 13.9 Hz, 6.5 Hz), 7.02 (1H, t, J = 9.1 Hz), 7.28 (1H, dd, J = 8.5 Hz, 1.7 Hz), 7.40 (1H, dd, J = 12.2 Hz, 2.3 Hz), 10.04 (1H, s).

Example 399

5-{[1-(3,5-Dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinol in-2(1H)-one

[1659] Synthesized analogous to Example 33.
(Ethanol/ethyl acetate) m.p. 194-195 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.52-1.63 (2H, m), 1.89-1.96 (2H, m), 1.96-2.08 (1H, m), 2.60-2.67 (2H, m), 2.82-2.90 (2H, m), 3.01 (2H, t, J = 8.0 Hz), 3.82-3.88 (4H, m), 6.46 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.51 (1H, brs), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 400

8-Chloro-5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-3,4-dihydroquinol in-2(1H)-one

[1660] Synthesized analogous to Example 33.
(Ethyl acetate) m.p. 190-191 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.53-1.63 (2H, m), 1.89-1.96 (2H, m), 1.98-2.09 (1H, m), 2.58-2.65 (2H, m), 2.82-2.90 (2H, m), 3.01 (2H, t, J = 8.0 Hz), 3.82-3.90 (4H, m), 6.52 (1H, d, J = 8.9 Hz), 7.17 (1H, d, J = 8.9 Hz), 7.60 (1H, d, J = 2.3 Hz), 7.73 (1H, brs), 8.12 (1H, d, J = 2.3 Hz).

Example 401

1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ox y]-methyl}piperidine-4-carboxylic acid

[1661] Synthesized analogous to Example 6.
(Acetic acid) m.p. 276-277 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.79 (2H, m), 2.14-2.23 (2H, m), 2.44 (2H, t, J = 7.6 Hz), 2.80 (2H, t, J = 7.6 Hz), 2.97-3.08 (2H, m), 3.52-3.61 (2H, m), 4.03 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.5 Hz), 8.03 (1H, d, J = 2.3 Hz), 8.26 (1H, d, J = 2.3 Hz), 10.03 (1H, s), 12.72 (1H, brs).

Example 402

5-{[1-(3,5-Dichloropyridin-2-yl)-4-(dimethylamino) piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1662] To a solution of 5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydr oquinolin-2(1H)-one (0.3 g) in N-methyl-2-pyrrolidone (NMP) (3 mL) were added formalin aqueous solution (37 %) (0.5 mL) and sodium triacetoxyborohydride(0.342 g), and the reaction mixture was stirred at room temperature for 1.25 h. To the reaction solution was added 0.5 N aqueous sodium hydroxide, and the insoluble precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (basic silica gel: dichloromethane/ethyl acetate) and recrystallized from ethyl acetate. The precipitate was collected on a filter, and air-dried (60 °C) to provide the title compound (0.22 g).
m.p. 202-203 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.83-1.91 (2H, m), 2.01-2.09 (2H, m), 2.44 (6H, s), 2.62-2.68 (2H, m), 3.00 (2H, t, J = 7.7 Hz), 3.33-3.45 (4H, m), 3.95 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.51 (1H, brs), 7.58 (1H, d, J = 2.3 Hz), 8.11 (1H,d, J = 2.3 Hz).

Example 403

5-{[1-(3,5-Dichloropyridin-2-yl)-4-methoxypiperidin-4-yl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1663] Synthesized analogous to Example 6.
(Ethyl acetate) m.p. 181-182 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.90 (2H, m), 1.99-2.06 (2H, m), 2.61-2.67 (2H, m), 3.03 (2H, t, J = 7.7 Hz), 3.18-3.26 (2H, m), 3.35 (3H, s), 3.55-3.62 (2H, m), 3.92 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.51 (1H, brs), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 404

5-{[1-(3,5-Dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one

[1664] To a suspension of 5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihy droquinolin-2(1H)-one (0.4 g) in dichloromethane (8 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (0.335 mL) dropwise at -70 °C, and the reaction mixture was stirred at 0 °C for 3.5 h. To the reaction solution was added saturated aqueous sodium hydrogencarbonate, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate), then further purified by HPLC. The obtained product was recrystallized from ethyl acetate. The precipitate was collected on a filter, and air-dried (60 °C) to provide the title compound (0.10 g).
m.p. 186-187 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-2.15 (4H, m), 2.61-2.67 (2H, m), 3.03 (2H, t, J = 7.7 Hz), 3.19-3.29 (2H, m), 3.68-3.75 (2H, m), 4.00 (2H, d, J = 18.1 Hz), 6.46 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.50 (1H, brs), 7.61 (1H, d, J = 2.3 Hz), 8.13 (1H, d, J = 2.3 Hz).

Example 405

5-{[1-(3,5-Dichloropyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1665] Synthesized analogous to Example 6.
^{1}HNMR ($CDCl_3$) δ ppm: 1.72 (1H, t, J = 5.6 Hz), 1.78-1.84 (4H, m), 2.61-2.67 (2H, m), 2.99 (2H, t, J = 7.7 Hz), 3.30-3.36 (4H, m), 3.78 (2H, d, J = 5.7 Hz), 3.96 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.50 (1H, brs), 7.60 (1H, d, J = 2.4 Hz), 8.13 (1H, d, J = 2.4 Hz).

Example 406

Methyl [1-(3,5-dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxyl] methyl }piperidin-4-yl]carbamate

[1666] Synthesized analogous to Example 6.
(Ethyl acetate) m.p. 183 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.02 (2H, m), 2.23-2.32 (2H, m), 2.61-2.67 (2H, m), 2.99 (2H, t, J = 7.7 Hz), 3.09-3.18 (2H, m), 3.57-3.64 (2H, m), 3.64 (3H,s), 4.12 (2H, s), 4.69 (1H, s), 6.48 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.52 (1H, brs), 7.61 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 407

5-{[1-(3,5-Dichloropyridin-2-yl)-4-(methylamino) piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1667] To a solution of methyl [1-(3,5-dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy] methyl}piperidin-4-yl]methylcarbamate (0.2 g) in acetic acid (4 mL) was added conc. hydrochloric acid (3 mL), and the reaction mixture was stirred at 100 °C for 6 h. After the solvent was distilled off, to the residue was added water, the reaction mixture was made basic with 5 N aqueous sodium hydroxide, and the solution was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallized from ethyl acetate. The precipitate was collected on a filter, and air-dried (60 °C) to provide the title compound (29 mg).
m.p. 182-184 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.33-1.76 (1H, broad signal), 1.76-1.89 (4H, m), 2.37 (3H, s), 2.62-2.68 (2H, m), 3.01 (2H, t, J = 7.7 Hz), 3.32-3.41 (2H, m), 3.41-3.49 (2H, m), 3.86 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.52 (1H, brs), 7.59 (1H, d, J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

Example 408

N-[1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl) oxy]methyl}piperidin-4-yl]-N2,N2-dimethylglycinamide

[1668] To a solution of 5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydr oquinolin-2(1H)-one (300 mg) in N,N-dimethylformamide (8 mL) were added triethylamine (0.32 mL) and dimethylaminoacetyl chloride hydrochloride (190 mg) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. To the reaction solution was added sodium hydrogen carbonate aqueous solution, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/methanol), the obtained product was recrystallized from hexane/ethyl acetate, and the precipitate was collected on a filter and dried to provide the title compound (0.28 g).
m.p. 188.9-190.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.93-2.012 (2H, m), 2.31 (6H, s), 2.39-2.47 (2H, m), 2.58-2.64 (2H, m), 2.88 (2H, s), 2.95-3.00 (2H, m), 3.05-3.13 (2H, m), 3.63-3.70 (2H, m), 4.21 (2H, s), 6.47 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.87 (1H, t J = 9.5 Hz), 7.36 (1H, brs), 7.62 (1H, d, J = 2.0 Hz), 8.13 (1H, d, J = 1.5 Hz), 8.18 (1H, brs).

Example 409

N-[1-(2-Cyano-4-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl) oxy] methyl}piperidin-4-yl] acetamide

[1669] To a solution of 5-fluoro-2-(4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydrox ypiperidin-1-yl)benzonitrile (349 mg) in acetonitrile (40 mL)/dichloromethane (20 mL), conc. sulfuric acid (2 mL) was added dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 30 min, then at 50 °C for 4 h. To the reaction solution were added 3 N aqueous sodium hydroxide and sodium hydrogen carbonate aqueous solution under ice-cooling to make the reaction solution basic, the solution was extracted with dichloromethane, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/methanol), recrystallized from ethyl acetate, the precipitate was collected on a filter and dried to provide the title compound (88 mg).
m.p. 214.0-215.9 °C
^{1}HNMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.02-2.10 (2H, m), 2.40-2.46 (2H, m), 2.97 (2H, t, J = 7.8 Hz), 2.97 (2H, t, J = 7.8 Hz), 3.00-3.07 (2H, m), 3.30-3.36 (2H, m), 4.22 (2H, s), 5.16 (1H, s), 6.48 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.89 (1H, t, J = 9.5 Hz), 7.02 (1H, dd, J = 9.0 Hz, 5.0 Hz), 7.20-7.25 (1H, m), 7.28 (1H, dd, J = 8.0 Hz, 3.0 Hz), 7.49 (1H, brs).

Example 410

N-[1-(3-Cyano-5-fluoropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidin-4-yl]acetamide

[1670] Synthesized analogous to Example 409.
(Ethyl acetate) m.p. 237.8-238.2 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.93 (2H, m), 1.99 (3H, s), 2.38-2.47 (2H, m), 2.58 (2H, t, J = 7.5 Hz), 2.96 (2H, t, J = 7.5 Hz), 3.30-3.36 (2H, m), 3.95-4.03 (2H, m), 4.18 (2H, s), 6.46 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.81 (1H, s), 6.86 (1H, t, J = 9.8 Hz), 7.58 (1H, dd, J = 7.3 Hz, 3.0 Hz), 8.25 (1H, d, J = 3.0 Hz), 8.52 (1H, brs).

Example 411

5-{[4-(Aminooxy)-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1671] Synthesized analogous to Example 6.
White powder (Ethyl acetate) m.p. 147-149 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.88 (2H, m), 2.08-2.14 (2H, m), 2.64 (2H, t, J = 7.7 Hz), 3.03 (2H, t, J = 7.7 Hz), 3.12-3.20 (2H, m), 3.55-3.62 (2H, m), 3.99 (2H, s), 4.99 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.52 (1H, brs), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

Example 412

2-[4-(Aminooxy)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}pi peridin-1-yl]-5-fluorobenzonitrile

[1672] Synthesized analogous to Example 6.
(Ethyl acetate/ethanol) m.p. 207-208 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.87-1.96 (2H, m), 2.16-2.21 (2H, m), 2.65 (2H, t, J = 7.7 Hz), 3.00-3.11 (4H, m), 3.24-3.32 (2H, m), 4.00 (2H, s), 4.99 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.03 (1H, dd, J = 9.1 Hz, 4.6 Hz), 7.19-7.25 (1H, m), 7.28 (1H, dd, J = 7.8 Hz, 3.1 Hz), 7.53 (1H, brs).

Example 413

2-[4-(Aminooxy)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}pip eridin-1-yl]-5-fluoropyridine-3-carbonitrile

[1673] Synthesized analogous to Example 6.
^{1}HNMR ($CDCl_3$) δ ppm: 1.77-1.86 (2H, m), 2.11-2.18 (2H, m), 2.61-2.67 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.30-3.38 (2H, m), 3.94-4.01 (2H, m), 3.98 (2H, s), 5.01 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.5 Hz), 7.50-7.56 (2H, m), 8.24 (1H, d, J = 3.1 Hz).

Example 414

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluo ro-3,4-dihydroquinolin-2(1H)-one

[1674] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.72 (1H, m), 1.91-2.05 (2H, m), 2.63 (2H, t, J = 7.8 Hz), 2.65 (1H, d, J = 4.2 Hz), 2.80 (1H, dd, J = 11.8 Hz, 9.1 Hz), 2.93 (1H, dt, J = 11.8 Hz, 2.8 Hz), 2.94-3.05 (2H, m), 3.77-3.83 (1H, m), 3.88-3.98 (2H, m), 4.07-4.16 (2H, m), 6.52 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.3 Hz), 7.59 (1H, brs), 7.61 (1H, d, J = 2.4 Hz), 8.12 (1H, d, J = 2.4 Hz).

Example 415

5-Fluoro-2-[(3S*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]meth yl}-3-hydroxypiperidin-1-yl]pyridine-3-carbonitrile

[1675] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.73 (1H, m), 1.95-2.06 (2H, m), 2.61 (1H, d, J = 2.7 Hz), 2.63 (2H, t, J = 7.7 Hz), 2.91 (1H, dd, J = 12.7 Hz, 9.9 Hz), 2.93-3.03 (2H, m), 3.07 (1H, dt, J = 12.7 Hz, 2.7 Hz), 3.85-3.93 (1H, m), 4.07-4.16 (2H, m), 4.16-4.22 (1H, m), 4.28-4.34 (1H, m), 6.51 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.55 (1H, dd, J = 7.3 Hz, 3.0 Hz), 7.58 (1H, brs), 8.25 (1H, d, J = 3.1 Hz).

Example 416

5-{[(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3-hydroxypiperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1676] To a solution of (3R*,4S*)-1-(3,5-dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidin-3-yl 4-nitrobenzoate (1.0 g) in tetrahydrofuran (THF) (20 mL) was added 2 N lithium hydroxide aqueous solution (20 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and washed with diethyl ether to provide the title compound (0.35 g).
^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.70 (2H, m), 2.06-2.14 (1H, m), 2.63 (2H, t, J = 7.7 Hz), 2.94-3.04 (2H, m), 3.05-3.17 (2H, m), 3.82-3.89 (2H, m), 4.00 (1H, dt, J = 13.7 Hz, 2.5 Hz), 4.07-4.14 (2H, m), 4.37 (1H, d, J = 7.4 Hz), 6.51 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.56 (1H, brs), 7.65 (1H, d, J = 2.3 Hz), 8.10 (1H, d, J = 2.3 Hz).

Example 417

1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ox y]methyl}piperidine-4-carbonitrile

[1677] Synthesized analogous to Example 33.
(Ethyl acetate) m.p. 218 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.95 (2H, m), 2.16-2.24 (2H, m), 2.63-2.69 (2H, m), 3.07 (2H, t, J = 7.7 Hz), 3.19-3.30 (2H, m), 3.83-3.92 (2H, m), 4.01 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.54 (1H, brs), 7.63 (1H, d, J = 2.3 Hz), 8.15 (1H, d, J = 2.3 Hz).

Example 418

5-{[(3R*,4R*)-1-(2,4-Dichlorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1678] A solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (0.42 g), [(3R*,4R*)-1-(2,4-dichlorophenyl)-3-hydroxypiperidin-4-yl]methyl-4-methylbenzenesulfonate (1.0 g) and cesium carbonate (0.756 g) in N-methyl-2-pyrrolidone (NMP) (10 mL) was stirred at 100 °C for 3 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was washed with ethyl acetate, and recrystallized from 2-propanol. The precipitate was collected on a filter and dried to provide the title compound (0.34 g).
(2-Propanol) m.p. 222-224 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.57-1.76 (2H, m), 1.91-1.98 (1H, m), 2.38-2.52 (3H, m), 2.60-2.70 (1H, m), 2.87 (2H, d, J = 7.2 Hz), 3.19-3.27 (1H, m), 3.35-3.43 (1H, m), 3.55-3.65 (1H, m), 3.97-4.06 (1H, m), 4.13-4.19 (1H, m), 5.07 (1H, d, J = 5.5 Hz), 6.61 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.2 Hz), 7.16 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.54 (1H, d, J = 2.5 Hz), 10.01 (1H, brs).

Example 419

5-{[(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1679] To a solution of 5-{[(3R*,4R*)-3-{[tert-butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one (0.12 g) in tetrahydrofuran (THF) (4 mL) was added a solution of 1M tetra-n-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) (0.268 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution were added water and ethyl acetate, and the precipitate was collected on a filter. The obtained solid was recrystallized from 2-propanol, the precipitate was collected on a filter and dried to provide the title compound (83 mg).
m.p. 177.3-182.9 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.57-1.76 (2H, m), 1.88-1.97 (1H, m), 2.40-2.51 (3H, m), 2.61-2.70 (1H, m), 2.86 (2H, d, J = 7.2 Hz), 3.28-3.33 (1H, m), 3.41-3.48 (1H, m), 3.54-3.64 (1H, m), 3.97-4.05 (1H, m), 4.10-4.16 (1H, m), 5.07 (1H, d, J = 5.5 Hz), 6.60 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.3 Hz), 7.05 (1H, t, J = 9.3 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.32 (1H, dd, J = 12.3 Hz, 2.4 Hz), 10.00 (1H, brs).

Example 420

5-{[1-(2,4-Dichlorophenyl)-4-(hydroxymethyl)piperidin-4-yl]methoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1680] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.69 (4H, t, J = 5.4 Hz), 2.46 (2H, t, J = 7.6 Hz), 2.88 (2H, t, J = 7.6 Hz), 2.96 (4H, t, J = 5.4 Hz), 3.50 (2H, d, J = 5.3 Hz), 3.87 (2H, s), 4.68 (1H, t, J = 5.4 Hz), 6.64 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.52 (1H, d, J = 2.5 Hz), 10.00 (1H, s).

Example 421

5-{[(3R*,4R*)-1-(4-Chloro-2,5-difluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8 -fluoro-3,4-dihydroquinolin-2(1H)-one

[1681] Synthesized analogous to Example 6.
(2-Propanol) m.p. 168.9-172.7 °C

^{1}HNMR (DMSO-d6) δ ppm: 1.56-1.77 (2H, m), 1.88-1.97 (1H, m), 2.41-2.49 (3H, m), 2.64-2.73 (1H, m), 2.86 (2H, d, J = 7.3 Hz), 3.33-3.39 (1H, m), 3.47-3.63 (2H, m), 3.97-4.04 (1H, m), 4.09-4.15 (1H, m), 5.10 (1H, d, J = 5.5 Hz), 6.60 (1H, dd, J = 9.2 Hz, 4.0 Hz), 7.02 (1H, t, J = 9.6 Hz), 7.09 (1H, dd, J = 11.3 Hz, 7.8 Hz), 7.50 (1H, dd, J = 12.1 Hz, 7.1 Hz), 10.00 (1H, brs).

Example 422

5-{[(3R*,4R*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-(methylamino)piperidin-4-y 1]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1682] Synthesized analogous to Example 33.
^{1}HNMR (DMSO-d6) δ ppm: 1.52-1.62 (2H, m), 1.83-1.93 (1H, m), 2.29 (3H, s), 2.45 (2H, t, J = 7.6 Hz), 2.55-2.61 (1H, m), 2.86-3.03 (2H, m), 3.20-3.35 (2H, m), 3.52-3.54 (2H, m), 3.89 (1H, d, J = 9.4 Hz), 4.04 (1H, d, J = 9.4 Hz), 4.80 (1H, brs), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.99 (1H, t, J = 9.6 Hz), 8.03 (1H, d, J = 2.3 Hz), 8.27 (1H, d, J = 2.3 Hz), 9.99 (1H, brs).

Example 423

5-{[(3S*,4R*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-methoxypiperidin-4-yl]meth oxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1683] Synthesized analogous to Example 6.
(Ethanol) m.p. 186-187 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.70 (1H, m), 2.19-2.27 (1H, m), 2.39 (1H, s), 2.66 (2H, t, J = 7.7 Hz), 2.96-3.07 (2H, m), 3.31 (3H, s), 3.33-3.40 (2H, m), 3.46 (1H, dd, J = 13.7 Hz, 2.0 Hz), 3.62-3.68 (1H, m), 3.88 (1H, d, J = 9.1 Hz), 3.96 (1H, dd, J = 13.8 Hz, 3.0 Hz), 4.15 (1H, d, J = 9.1 Hz), 6.52 (1H, dd, J = 9.2 Hz, 4.0 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.56 (1H, brs), 7.58 (1H, d,J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

Example 424

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-methoxypiperidin-4-yl]meth oxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1684] Synthesized analogous to Example 6.
(2-Propanol) m.p. 162.8-164.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.88 (1H, m), 2.05-2.15 (1H, m), 2.45-2.49 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.92-3.07 (3H, m), 3.16-3.25 (1H, m), 3.43 (3H, s), 3.63-3.73 (2H, m), 3.78 (1H, d, J = 8.8 Hz), 3.93-4.00 (1H, m), 4.03 (1H, d, J = 8.8 Hz), 6.50 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.3 Hz), 7.53 (1H, brs), 7.62 (1H, d, J = 2.3 Hz), 8.13 (1H, d, J = 2.3 Hz).

Example 425

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-methylpiperidin-4-yl]metho xy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1685] Synthesized analogous to Example 33.
(ethanol/acetic acid) m.p. 222-223 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.13 (3H, d, J = 7.1 Hz), 1.69-1.77 (1H, m), 2.05-2.15 (2H, m), 2.22 (1H, brs), 2.66 (2H, t, J = 7.7 Hz), 3.02 (2H, t, J = 7.7 Hz), 3.32-3.42 (2H, m), 3.42-3.56 (2H, m), 3.88-3.98 (2H, m), 6.50 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.59 (1H, d, J = 2.4 Hz), 7.62 (1H, brs), 8.12 (1H, d, J = 2.4 Hz).

Example 426

5-{[(3R*,4R*)-3-Amino-1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]metho xy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1686] Synthesized analogous to Example 33.
^{1}HNMR ($CDCl_3$) δ ppm: 1.72-1.75 (1H, m), 2.04-2.10 (1H, m), 2.35 (1H, s), 2.65 (2H, t, J = 7.7 Hz), 3.02 (2H, t, J = 7.7 Hz), 3.09 (1H, brs), 3.28-3.33 (1H, m), 3.49-3.55 (3H, m), 3.97 (1H, d, J = 9.1 Hz), 4.23 (1H, d, J = 9.1 Hz), 6.55 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.56 (1H, brs), 7.62 (1H, d, J = 2.3 Hz), 8.14 (1H, d, J = 2.3 Hz).

Example 427

5-{[(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3-fluoro-4-hydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1687] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.61-1.69 (1H, m), 1.98-2.08 (1H, m), 2.46 (2H, t, J = 7.6 Hz), 2.85-3.03 (2H, m), 3.12-3.21 (1H, m), 3.35-3.52 (1H, m), 3.63-3.71 (1H, m), 3.82-3.87 (1H, m), 3.88-4.00 (2H, m), 4.69 (1H, d, J = 46.0 Hz), 5.37 (1H, brs), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.5 Hz), 8.02 (1H, d, J = 2.3 Hz), 8.26 (1H, d, J = 2.3 Hz), 10.01 (1H, brs).

Example 428

(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinoli n-5-yl)oxy]methyl}-4-hydroxypipend-ine-3-carbonitrile

[1688] Synthesized analogous to Example 6.
(Ethanol/water) m.p. 206-207 °C^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.88 (1H, m), 2.20-2.28 (1H, m), 2.61-2.64 (1H, m), 2.64-2.69 (2H, m), 2.97-3.08 (2H, m), 3.11-3.15 (1H, m), 3.26-3.34 (1H, m), 3.54 (1H, dd, J = 13.0 Hz, 2.8 Hz), 3.66-3.73 (1H, m), 3.92-3.99 (1H, m), 4.04 (1H, d, J = 9.4 Hz), 4.24 (1H, d, J = 9.4 Hz), 6.55 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.96 (1H, t, J = 9.4 Hz), 7.63-7.69 (2H, m), 8.15 (1H, d, J = 2.3 Hz).

Example 429

5-{[(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxy-3-methylpiperidin-4-yl]me thoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1689] To a solution of tert-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}meth yl)-1-methyl-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (493 mg) in anisole (0.05 mL) was added trifluoroacetic acid (5 mL), the reaction mixture was stirred at 65 °C for 3 h, and the solvent was distilled off. To the residue were added 2,3,5-trichloropyridine (1095 mg), potassium carbonate (553 mg) and N,N-dimethylformamide (5 mL), and the mixture was stirred at 100 °C for 9 h. To the reaction solution was added water, the solution was extracted with ethyl acetate, the organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (105 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.17 (3H, s), 1.69-1.78 (1H, m), 2.11-2.21 (1H, m), 2.42-2.49 (2H, m), 2.84-3.04 (2H, m), 3.14-3.23 (1H, m), 3.24-3.31 (1H, m), 3.35-3.43 (1H, m), 3.60-3.70 (1H, m), 3.96 (1H, d, J = 9.6 Hz), 4.06 (1H, d, J = 9.6 Hz), 4.48 (1H, brs), 4.82 (1H, brs), 6.57 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.5 Hz), 7.94 (1H, d, J = 2.3 Hz), 8.20 (1H, d, J = 2.3 Hz), 9.99 (1H, brs).

Example 430

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxy-3-methylpiperidin-4-yl]me thoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1690] Synthesized analogous to Example 6.
(2-Propanol) m.p. 182.6-187.5 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.25 (3H, s), 1.85-1.93 (1H, m), 1.98-2.07 (1H, m), 2.42-2.49 (2H, m), 2.79-2.91 (1H, m), 2.92-3.02 (1H, m), 3.14-3.33 (3H, m), 3.42-3.49 (1H, m), 3.88 (1H, d, J = 9.6 Hz), 4.04 (1H, d, J = 9.6 Hz), 4.52 (1H, brs), 4.58 (1H, brs), 6.62 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.5 Hz), 8.01 (1H, d, J = 2.3 Hz), 8.25 (1H, d, J = 2.3 Hz), 10.01 (1H, brs).

Example 431

5-{[(3S*,4S*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxy-3-methylpiperidin-4-yl]me thoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1691] Synthesized analogous to Example 6.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (3H, s), 1.91-2.08 (2H, m), 2.62-2.69 (2H, m), 2.91-3.09 (6H, m), 3.10-3.17 (2H, m), 3.94 (1H, d, J = 9.3 Hz), 4.22 (1H, d, J = 9.3 Hz), 6.54 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.85-7.00 (2H, m), 7.02-7.09 (2H, m), 7.56 (1H, brs).

Example 432

5-{[(3S*,4R*)-3-Amino-1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1692] To a solution of O-benzyl carbamate (337 mg) in 1-propanol (4 mL) were added 1 N aqueous sodium hydroxide (3.05 mL) and tert-butyl hypochlorite (0.480 mL), and the reaction mixture was stirred at room temperature for 5 min. To the mixture were added a solution of bis(dihydroquinidinyl)phthalazine ($(DHQD)_2PHAL$) (38.9 mg) in 1-propanol (3.5 mL), a solution of tert-butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl) -3,6-dihydropyridine-1(2H)-carboxylate (497 mg) in 1-propanol (6.5 mL) and potassium osmate(VI) dihydrate (14.74 mg), and the reaction mixture was stirred at room temperature for 3 days. Under ice-cooling, saturated sodium sulfite aqueous solution was added to the mixture, the solution was stirred for 10 min, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), and further purified by silica gel column chromatography (basic silica gel; dichloromethane/ethyl acetate) to give tert-butyl (3R,4S)-3-(benzyloxycarbonylamino)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3, 4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate. The obtained product was dissolved into ethanol (6 mL), 10 % palladium on carbon (containing water) (30 mg) was added to the solution, and the reaction mixture was stirred at room temperature for 1 h under hydrogen atmosphere. Insoluble materials were filtered off with Celite, and the solvent was distilled off. To the residue were added anisole (0.020 mL) and trifluoroacetic acid (4 mL), and the reaction mixture was stirred at 60 °C for 1 h. The reaction solution was concentrated, 2-bromo-3,5-dichloropyridine (48.8 mg), potassium carbonate (82 mg) and N-methyl-2-pyrrolidone (NMP) (4 mL) were added to the residue, and the mixture was stirred at 100 °C for 5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/methanol), washed with ethyl acetate-2-propanol, and the insoluble precipitate was collected on a filtered off to provide optically active compound 1 (27 mg, 19 % ee). On the other hand, the reactions identical to the above was repeated by using bis(dihydroquinidyl)phthalazine ($(DHQ)_2$ PHAL) in place of bis(dihydroquinidinyl)phthalazine ($(DHQD)_2PHAL$), another optically active compound 2 (38 mg, 34 % ee) was obtained. Optically active compound 1(11 mg) and optically active compound 2 (6 mg) were dissolved into a solvent mixture of ethyl acetate/ethanol/dichloromethane, the solvent was distilled off, and the residue was washed with ethyl acetate and 2-propanol. The insoluble precipitate was collected on a filter and dried under reduced pressure to provide the title compound (6 mg, < 1 % ee).
^{1}HNMR ($CDCl_3$) δ ppm: 1.13 (1H, d, J = 6.2 Hz), 1.87-1.90 (1H, m), 1.96-2.01 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.95-3.07 (3H, m), 3.23-3.28 (1H, m), 3.37 (1H, dd, J = 9.8 Hz, 4.4 Hz) 3.43-3.69 (3H, m), 3.92 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 3.4 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.54 (1H, brs), 7.61 (1H, s), 8.12 (1H, s).

Example 433

(3S*,4S*)-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinoli n-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate

[1693] To a solution of 5-{[(3S*,4S* 1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dih ydroquinolin-2(1H)-one (100 mg) in pyridine (1 mL) were added acetic anhydride (0.032 mL) and 4-(dimethylamino)pyridine (2.78 mg), and the reaction mixture was stirred at room temperature for 10 days. To the reaction solution was added water, and the solution was extracted with ethyl acetate, the organic layer was concentrated, the residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallized from ethyl acetate. The precipitate was collected on a filter and dried to provide the title compound (74 mg).
(Ethyl acetate) m.p. 182-185 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.82 (1H, d, J = 14.0 Hz), 1.98-2.05 (4H, m), 2.45 (2H, t, J = 7.9 Hz), 2.81-2.88 (2H, m), 3.01-3.27 (4H, m), 3.77 (1H, d, J = 9.2 Hz), 3.88 (1H, d, J = 9.2 Hz), 5.01 (1H, dd, J = 10.4 Hz, 4.6 Hz), 5.15 (1H, s), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.13-7.20 (2H, m), 7.34 (1H, dd, J = 12.4 Hz, 2.3 Hz), 10.03 (1H, s).

Example 434

(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquin olin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate

[1694] Synthesized analogous to Example 433.
(Ethyl acetate-diisopropyl ether) m.p. 163-165 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.79 (1H, d, J = 13.6 Hz), 1.95-2.02 (4H, m), 2.46 (2H, t, J = 7.4 Hz), 2.86-3.08 (4H, m), 3.30-3.40 (2H, m), 3.76 (1H, d, J = 9.2 Hz), 3.87 (1H, d, J = 9.2 Hz), 4.95 (1H, dd, J = 10.2 Hz, 4.8 Hz), 5.14 (1H, s), 6.56 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.27-7.33 (2H, m), 10.03 (1H, s).

Example 435

(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquin olin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl pyrazine-2-carboxylate

[1695] A solution of 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8 -fluoro-3,4-dihydroquinolin-2(1H)-one (100 mg), 2-pyrazinecarboxylic acid (97.8 mg), 4-(dimethylamino)pyridine (2.67 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (151.2 mg) in N,N-dimethylformamide (2 mL) was stirred at room temperature overnight. To the reaction solution was added water, the precipitate was collected on a filter and purified by silica gel column chromatography (hexane/ethyl acetate). The obtained product was washed with ethyl acetate/diisopropyl ether and dried to provide the title compound (53 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.88 (1H, d, J = 13.6 Hz), 2.02-2.09 (1H, m), 2.43 (2H, t, J = 7.6 Hz), 2.87 (2H, t, J = 7.6 Hz), 3.03 (1H, d, J = 11.5 Hz), 3.26-3.30 (1H, m), 3.41-3.54 (2H, m), 3.92 (1H, d, J = 9.5 Hz), 4.00 (1H, d, J = 9.5 Hz), 5.28 (1H, dd, J = 10.1 Hz, 4.8 Hz), 5.38 (1H, s), 6.55 (1H, dd, J = 9.2 Hz, 3.8 Hz), 6.93 (1H, t, J = 9.7 Hz), 7.28-7.35 (2H, m), 8.82 (1H, dd, J = 2.4 Hz, 1.4 Hz), 8.88 (1H, d, J = 2.4 Hz), 9.42 (1H, d, J = 1.4 Hz), 9.99 (1H, s).

Example 436

5-{[(4R)-1-(4-Chloro-2,6-difluorophenyl)-4-hydroxy-3-oxopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1696] To a solution of dimethyl sulfoxide (0.078 mL) in dichloromethane (3 mL) was added oxalyl chloride (0.057 mL) at -80 °C, and the mixture was stirred at the same temperature for 10 min. To the mixture was added a solution of 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8 -fluoro-3,4-dihydroquinolin-2(1H)-one (100 mg) in dichloromethane/dimethyl sulfoxide (1 mL/0.33 mL), the mixture was stirred at the same temperature for 20 min, then triethylamine (0.183 mL) was added thereto, and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added water, the solution was extracted with ethyl acetate, the solvent of the organic layer was distilled off, and then the residue was purified by silica gel column chromatography (hexane/ethyl acetate), and recrystallized from ethyl acetate/diisopropyl ether/hexane. The precipitate was collected on a filter and dried to provide the title compound (21 mg).
m.p. 127-130 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.96-2.06 (1H, m), 2.20-2.26 (1H, m), 2.43 (2H, t, J = 7.7 Hz), 2.76-2.85 (2H, m), 3.28-3.38 (2H, m), 3.51-3.55 (1H, m), 3.67 (1H, d, J = 14.7 Hz), 3.99 (1H, d, J = 14.7 Hz), 4.05 (1H, d, J = 9.6 Hz), 4.17 (1H, d, J = 9.6 Hz), 6.63 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.26-7.38 (2H, m), 10.03 (1H, s).

Example 437

(3R,4R)-1-(5-Chloro-3-fluoropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroqui nolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate

[1697] Synthesized analogous to Example 433.
White powder
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-1.96 (1H, m), 2.06-2.10 (1H, m), 2.08 (3H, s), 2.34-2.36 (1H, m), 2.61-2.65 (2H, m), 2.91-3.03 (2H, m), 3.28 (1H, dd, J = 12.3 Hz, 10.5 Hz), 3.35 (1H, dt, J = 12.5 Hz, 2.8 Hz), 3.80 (1H, d, J = 9.1 Hz), 3.83-3.89 (1H, m), 3.87 (1H, d, J = 9.1 Hz), 3.98-4.04 (1H, m), 5.22 (1H, dd, J = 10.4 Hz, 4.9 Hz), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.29 (1H, dd, J = 12.0 Hz, 2.1 Hz), 7.54 (1H, brs), 7.98 (1H, d, J = 2.1 Hz).

Example 438

5-{1-[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethoxy}-8-fluoro-3,4 -dihydroquinolin-2(1H)-one

[1698] A suspension of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (110 mg), 1-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl 4-methylbenzenesulfonate (284 mg) and potassium carbonate (126 mg) in acetonitrile (2 mL) was stirred at 70 °C for 1 h. To the reaction solution was added ethyl acetate, the precipitate was filtered off, and the filtrate was concentrated. To the residue were added tripotassium phosphate (25.8 mg) and N,N-dimethylformamide/2-propanol (1:1) (4 mL), and the mixture was stirred at 70 °C for 7 days. To the reaction solution was added water, the solution was extracted with ethyl acetate, and the solvent of the organic layer was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), and recrystallized form diisopropyl ether/hexane. The precipitate was collected on a filter and dried to provide the title compound (38 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.18 (3H, d, J = 6.0 Hz), 1.48 (1H, d, J = 13.6 Hz), 1.70-1.80 (3H, m), 2.44 (2H, t, J = 7.5 Hz), 2.79-2.99 (4H, m), 3.28-3.39 (2H, m), 4.14 (1H, q, J = 6.0 Hz), 4.52 (1H, s), 6.62 (1H, dd, J = 9.2 Hz, 3.9 Hz), 7.00 (1H, t, J = 9.7 Hz), 7.23-7.28 (2H, m), 9.99 (1H, s).

Example 439

5-{[(3S*,4R*)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]met hoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1699] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 223-224 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.59-1.66 (1H, m), 1.87-1.97 (1H, m), 2.46 (2H, t, J = 7.8 Hz), 2.85-3.04 (3H, m), 3.25-3.45 (2H, m), 3.50-3.65 (1H, m), 3.84 (1H, dd, J = 9.8 Hz, 2.8 Hz), 3.97 (1H, dd, J = 9.8 Hz, 1.9 Hz), 4.62 (1H, d, J = 46.6 Hz), 5.34 (1H, d, J = 1.0 Hz), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.25-7.32 (2H, m), 10.03 (1H, s).

Example 440

5-{[(3R*,4R*)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]met hoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1700] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 222-223 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.81 (1H, m), 1.89-1.98 (1H, m), 2.45-2.52 (2H, m), 2.84-2.97 (3H, m), 3.20-3.28 (1H, m), 3.28-3.38 (1H, m), 3.44-3.52 (1H, m), 3.81 (1H, d, J = 9.1 Hz), 4.04 (1H, d, J = 9.1 Hz), 4.73 (1H, ddd, J = 47.4 Hz, 10.1 Hz, 5.1 Hz), 5.30 (1H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.28-7.35 (2H, m), 10.04 (1H, s).

Example 441

5-{[(3S*,4R*)-1-(4-Chloro-2-fluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1701] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 190-191 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.71 (1H, m), 1.90-1.99 (1H, m), 2.46 (2H, t, J = 7.8 Hz), 2.86-3.03 (2H, m), 3.05-3.14 (1H, m), 3.16-3.23 (2H, m), 3.51 (1H, t, J = 13.1 Hz), 3.86 (1H, dd, J = 9.8 Hz, 2.8 Hz), 3.97 (1H, dd, J = 9.8 Hz, 1.8 Hz), 4.68 (1H, d, J = 46.1 Hz), 5.36 (1H, d, J = 1.3 Hz), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.10 (1H, t, J = 9.1 Hz), 7.17 (1H, dd, J = 8.8 Hz, 2.0 Hz), 7.32 (1H, dd, J = 12.5 Hz, 2.4 Hz), 10.03 (1H, s).

Example 442

5-{[(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1702] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 194-195 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.78-1.86 (1H, m), 1.92-2.02 (1H, m), 2.47 (2H, t, J = 7.9 Hz), 2.89 (2H, t, J = 7.4 Hz),

2.96-3.04 (1H, m), 3.09-3.21 (2H, m), 3.35-3.43 (1H, m), 3.82 (1H, d, J = 9.1 Hz), 4.04 (1H, d, J = 9.1 Hz), 4.81 (1H, ddd, J = 47.1 Hz, 10.3 Hz, 5.0 Hz), 5.31 (1H, s), 6.60 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.11-7.22 (2H, m), 7.35 (1H, dd, J = 12.4 Hz, 2.3 Hz), 10.04 (1H, s).

Example 443

5-{[(3S*,4R*)-1-(2-Chloro-4-fluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1703] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 204-205 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.71 (1H, m), 1.93-2.02 (1H, m), 2.46 (2H, t, J = 7.8 Hz), 2.86-3.09 (4H, m), 3.16-3.39 (2H, m), 3.88 (1H, dd, J = 9.8 Hz, 2.8 Hz), 3.99 (1H, dd, J = 9.8 Hz, 1.9 Hz), 4.68 (1H, d, J = 46.4 Hz), 5.32 (1H, d, J = 1.2 Hz), 6.62 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.15-7.21 (1H, m), 7.26 (1H, dd, J = 9.1 Hz, 5.6 Hz), 7.40 (1H, dd, J = 8.6 Hz, 3.0 Hz), 10.03 (1H, s).

Example 444

5-{[(3R*,4R*)-1-(2-Chloro-4-fluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methox y}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1704] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 218-220 °C
^{1}HNMR (DMSO-d6) δppm: 1.79-1.87 (1H, m), 1.93-2.02 (1H, m), 2.44-2.51 (2H, m), 2.85-2.96 (2H, m), 2.96-3.02 (2H, m), 3.11-3.19 (1H, m), 3.23-3.31 (1H, m), 3.84 (1H, d, J = 9.1 Hz), 4.06 (1H, d, J = 9.1 Hz), 4.81 (1H, ddd, J = 47.3 Hz, 10.2 Hz, 5.0 Hz), 5.29 (1H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.15-7.21 (1H, m), 7.30 (1H, dd, J = 9.0 Hz, 5.6 Hz), 7.42 (1H, dd, J = 8.6 Hz, 3.0 Hz), 10.05 (1H, s).

Example 445

5-{[(3R*,5R*)-1-(4-Chloro-2,6-difluorophenyl)-3,4,5-trihydroxypiperidin-4-yl]metho xy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1705] Synthesized analogous to Example 42.
(Ethyl acetate/methanol) m.p. 221.5-222.0 °C
^{1}HNMR ($CDCl_3$) δ ppm: 2.43 (1H, d, J = 9.0 Hz), 2.65 (2H, t, J = 7.5 Hz), 2.79 (1H, brs), 2.92-3.08 (4H, m), 3.18-3.21 (1H, m), 3.26-3.30 (1H, m), 3.73 (1H, d, J = 12.5 Hz), 3.92-3.94 (1H, m), 4.00-4.05 (1H, m), 4.32-4.36 (2H, m), 6.60 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.93-6.96 (3H, m), 7.53 (1H, brs).

Example 446

5-{[(3R,4S)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]meth oxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1706] Synthesized analogous to Example 42.
(Ethanol) m.p. 224-225 °C^{1}HNMR (DMSO-d6) δ ppm: 1.59-1.66 (1H, m), 1.87-1.97 (1H, m), 2.46 (2H, t, J = 7.8 Hz), 2.85-3.04 (3H, m), 3.25-3.45 (2H, m), 3.50-3.65 (1H, m), 3.84 (1H, dd, J = 9.8 Hz, 2.8 Hz), 3.97 (1H, dd, J = 9.8 Hz, 1.9 Hz), 4.62 (1H, d, J = 46.6 Hz), 5.34 (1H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.25-7.32 (2H, m), 10.03 (1H, s).

Example 447

5-{[(3S,4R)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]meth oxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1707] Synthesized analogous to Example 42.
(Ethanol) m.p. 224-225 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.59-1.66 (1H, m), 1.87-1.97 (1H, m), 2.46 (2H, t, J = 7.8 Hz), 2.85-3.04 (3H, m), 3.25-3.45

(2H, m), 3.50-3.65 (1H, m), 3.84 (1H, dd, J = 9.8 Hz, 2.8 Hz), 3.97 (1H, dd, J = 9.8 Hz, 1.9 Hz), 4.62 (1H, d, J = 46.6 Hz), 5.34 (1H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.25-7.32 (2H, m), 10.03 (1H, s).

Example 448

5-{[(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]meth oxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1708] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 207-209 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.81 (1H, m), 1.89-1.98 (1H, m), 2.45-2.52 (2H, m), 2.84-2.97 (3H, m), 3.20-3.28 (1H, m), 3.28-3.38 (1H, m), 3.44-3.52 (1H, m), 3.81 (1H, d, J = 9.1 Hz), 4.04 (1H, d, J = 9.1 Hz), 4.73 (1H, ddd, J = 47.4 Hz, 10.1 Hz, 5.1 Hz), 5.30 (1H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.28-7.35 (2H, m), 10.05 (1H, s).

Example 449

5-{[(3S,4S)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]meth oxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1709] Synthesized analogous to Example 42.
(Acetic acid/water) m.p. 209-210 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.81 (1H, m), 1.89-1.98 (1H, m), 2.45-2.52 (2H, m), 2.84-2.97 (3H, m), 3.20-3.28 (1H, m), 3.28-3.38 (1H, m), 3.44-3.52 (1H, m), 3.81 (1H, d, J = 9.1 Hz), 4.04 (1H, d, J = 9.1 Hz), 4.73 (1H, ddd, J = 47.4 Hz, 10.1 Hz, 5.1 Hz), 5.29 (1H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.28-7.35 (2H, m), 10.05 (1H, s).

Example 450

(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquin olin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate

[1710] To a suspension of 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8 -fluoro-3,4-dihydroquinolin-2(1H)-one (200 mg) in dichloromethane (4 mL) was added pyridine (0.053 mL), then ethyl chloroformate(0.063 mL) was added at 0 °C, and the mixture was stirred at room temperature for 1 h. To the reaction solution was added water and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (122 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.26 (3H, t, J = 7.2 Hz), 1.84-1.90 (1H, m), 2.05-2.13 (1H, m), 2.40 (1H, d, J = 2.0 Hz), 2.63-2.68 (2H, m), 3.00-3.06 (3H, m), 3.30-3.36 (1H, m), 3.43-3.53 (2H, m), 3.87-3.94 (2H, m), 4.07-4.21 (2H, m), 5.04 (1H, dd, J = 10.2 Hz, 5.2 Hz),6.46 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.86-6.95 (3H, m), 7.56 (1H, brs).

Example 451

4-{[(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydro quinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl]oxy}-4-oxobutanoic acid

[1711] A solution of 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8 -fluoro-3,4-dihydroquinolin-2(1H)-one (300 mg), 4-(dimethylamino)pyridine (16.1 mg) and succinic anhydride(99 mg) in N-methyl-2-pyrrolidone (NMP) (2 mL) was stirred at 100 °C for 2 h. To the reaction solution were added water and diethyl ether, and the precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (ethyl acetate/methanol), and washed with ethyl acetate/ diethyl ether to give the title compound (203 mg).
^{1}HNMR (DMSO-d6) δ ppm: 1.78-1.84 (1H, m), 1.93-2.01 (1H, m), 2.43-2.50 (5H, m), 2.82-2.95 (3H, m), 3.01-3.07 (1H, m), 3.30-3.42 (3H, m), 3.75-3.89 (2H, m), 4.93-4.98 (1H, m), 5.11 (1H, brs), 6.56 (1H, dd, J = 9.2 Hz, 3.6 Hz), 7.00 (1H, t, J = 9.6 Hz), 7.26-7.33 (2H, m), 10.03 (1H, brs), 12.30 (1H, brs).

Example 452

(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquin olin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethylcarbamate

[1712] A solution of 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8 -fluoro-3,4-dihydroquinolin-2(1H)-one (200 mg), dimethylaminopyridine (10.7 mg) and ethyl isocyanate (0.052 mL) in tetrahydrofuran (6 mL) was heated to reflux for 3 days. After 3 days, the reaction solution was concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate). The obtained product was recrystallized from ethyl acetate/diethyl ether, the precipitate was collected on a filter and dried to provide the title compound (177 mg).
m.p. 167-169 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.10 (3H, t, J = 7.3 Hz), 1.91-1.97 (1H, m), 2.02-2.10 (1H, m), 2.37 (1H, brs), 2.61-2.68 (2H, m), 2.96-3.09 (3H, m), 3.14-3.24 (2H, m), 3.26-3.32 (1H, m), 3.39-3.47 (2H, m), 3.84-3.96 (2H, m),4.72-4.78 (1H, m), 5.03-5.09 (1H, m), 6.46 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.85-6.94 (3H, m), 7.64 (1H, brs).

Example 453

(3R,4R)-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin -5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate

[1713] Synthesized analogous to Example 450.
(Ethyl acetate/diethyl ether) m.p. 171-172 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.26 (3H, t, J = 7.2 Hz), 1.89-1.95 (1H, m), 2.08-2.16 (1H, m), 2.54 (1H, d, J = 2.0 Hz), 2.59-2.69 (2H, m), 2.94-3.07 (2H, m), 3.10-3.18 (2H, m), 3.23-3.29 (1H, m), 3.47-3.53 (1H, m), 3.88-3.94 (2H, m), 4.09-4.22 (2H, m), 5.12 (1H, dd, J = 10.4 Hz, 5.0 Hz), 6.46 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.88-6.96 (2H, m), 7.03-7.09 (2H, m), 7.84 (1H, brs).

Example 454

(3R,4R)-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin -5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate

[1714] Synthesized analogous to Example 433.
^{1}HNMR ($CDCl_3$) δ ppm: 1.91-1.98 (1H, m), 2.09 (3H, s), 2.09-2.16 (1H, m), 2.32-2.34 (1H, m), 2.64 (2H, d, J = 7.6 Hz), 2.95-3.07 (2H, m), 3.09 (1H, t, J = 10.6 Hz), 3.15 (1H,dd, J = 12.1 Hz, 2.6 Hz), 3.24-3.30 (1H, m), 3.38-3.43 (1H, m), 3.82 (1H, d, J = 9.0 Hz), 3.89 (1H, d, J = 9.0 Hz), 5.28 (1H, dd, J = 10.3 Hz, 5.0 Hz), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.88-6.95 (2H, m), 7.03-7.08 (2H, m), 7.61 (1H, brs).

Example 455

(3R,4R)-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin -5-yl)oxy]methyl}piperidine-3,4-diyl diacetate

[1715] Synthesized analogous to Example 433.
^{1}HNMR ($CDCl_3$) δppm: 2.03 (3H, s), 2.14-2.22 (1H, m), 2,17 (3H, s), 2.61-2.68 (2H, m), 2.75-2.81 (1H, m), 2.86-2.93 (1H, m), 2.93-3.04 (2H, m), 3.16 (1H, t, J = 10.5 Hz), 3.29-3.36 (1H, m), 3.37-3.43 (1H, m), 4.15 (1H, d, J = 9.0 Hz), 4.68 (1H, d, J = 9.0 Hz), 5.43 (1H, dd, J = 10.1 Hz, 4.6 Hz), 6.45 (1H, dd, J = 9.2 Hz, 3.9 Hz), 6.87-6.95 (2H, m), 7.03-7.09 (2H, m), 7.63 (1H, brs).

Example 456

(3R,4R)-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin -5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethylcarbamate

[1716] Synthesized analogous to Example 452.
(Ethyl acetate/diethyl ether) m.p. 156-157 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.11 (3H, t, J = 7.3 Hz), 1.98-2.01 (1H, m), 2.04-2.13 (1H, m), 2.46 (1H, brs), 2.58-2.68 (2H, m), 2.94-3.06 (2H, m), 3.07-3.30 (5H, m), 3.41-3.47 (1H, m), 3.86 (1H, d, J = 9.0 Hz), 3.93 (1H, d, J = 9.0 Hz), 4.77-4.84 (1H, m), 5.11-5.17 (1H, m), 6.46 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.88-6.96 (2H, m), 7.03-7.09 (2H, m), 7.84 (1H, brs).

Example 457

(3R,4R)-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin -5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl hydrogen phosphonate

[1717] To a solution of diphenyl phosphite (1.309 mL) in pyridine (6 mL) was added, 5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one (1.0 g) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. To the reaction solution were added water and ethyl acetate for extraction. The aqueous layer was left to stand a day, the precipitated crystal was collected on a filter and dried to provide the title compound (0.85 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.76-1.83 (1H, m), 1.96-2.05 (1H, m), 2.46 (2H, t, J = 7.9 Hz), 2.89 (2H, t, J = 7.9 Hz), 3.00-3.07 (1H, m), 3.11-3.18 (2H, m), 3.34-3.40 (1H, m), 3.70-3.85 (2H, m), 3.96 (1H, d, J = 9.0 Hz), 4.48-4.56 (1H, m), 5.99 (0.5H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.5 Hz), 7.14 (1H, t, J = 9.1 Hz), 7.19 (1H, dd, J = 8.8 Hz, 2.3 Hz), 7.33 (0.5H, s), 7.35 (1H, dd, J = 12.3 Hz, 2.3 Hz), 10.04 (1H, brs).

Example 458

4-{[(3R,4R)-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquin olin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl]oxy}-4-oxobutanoic acid

[1718] Synthesized analogous to Example 451.
^{1}HNMR (DMSO-d6) δ ppm: 1.81-1.88 (1H, m), 1.95-2.04 (1H, m), 2.41-2.52 (6H, m), 2.80-2.92 (2H, m), 2,98-3.11 (2H, m), 3.14-3.20 (1H, m), 3.21-3.27 (1H, m), 3.79 (1H, d, J = 9.2 Hz), 3.87 (1H, d, J = 9.2 Hz), 5.02 (1H, dd, J = 10.4 Hz, 4.6 Hz), 5.14 (1H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.5 Hz), 7.00 (1H, t, J = 9.9 Hz), 7.12 (1H, t, J = 9.2 Hz), 7.18 (1H, dd, J = 8.7 Hz, 2.2 Hz), 7.34 (1H, dd, J = 12.3 Hz, 2.2 Hz), 10.02 (1H, brs), 12.20 (1H,brs).

Example 459

(3R,4R)-1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquin olin-5-yl)oxy]methyl}piperidine-3,4-diyl diacetate

[1719] Synthesized analogous to Example 433.
^{1}HNMR ($CDCl_3$) δ ppm: 2.02 (3H, s), 2.12-2.19 (1H, m), 2,18 (3H, s), 2.62-2.67 (2H, m), 2.70-2.76 (1H, m), 2.93-3.05 (2H, m), 3.06-3.12 (1H, m), 3.15-3.29 (2H, m), 3.44-3.51 (1H, m), 4.17 (1H, d, J = 9.0 Hz), 4.68 (1H, d, J = 9.0 Hz), 5.35 (1H, dd, J = 9.7 Hz, 4.6 Hz), 6.45 (1H, dd, J = 9.2 Hz, 3.9 Hz), 6.85-6.95 (3H, m), 7.63 (1H, brs).

Example 460

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1720] Synthesized analogous to Example 6.
(Acetic acid/water) m.p. 171-172 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.75-1.88 (4H, m), 2.04 (1H, s), 2.64-2.71 (2H, m), 2.99-3.08 (2H, m), 3.06 (2H, s), 3.14-3.23 (4H, m), 6.87-6.92 (1H, m), 6.97 (1H, t, J = 9.3 Hz), 7.01-7.07 (2H, m), 7.15 (1H, dd, J = 8.8 Hz, 5.1 Hz), 7.62 (1H, brs).

Example 461

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfinyl)-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1721] A suspension of 5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}-sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (0.22 g) and m-chloroperoxybenzoic acid (75 %) (0.144 g) in chloroform (10 mL) was stirred at room temperature for 7.5 h. The solvent was distilled off and to the residue were added saturated aqueous sodium hydrogencarbonate and ethyl acetate. The insoluble precipitate was collected on a filter, the obtained solid was purified by silica gel column chromatography (dichloromethane/methanol), and recrystallized from ethanol. The precipitate was collected on a filter and dried to provide the title compound (86 mg).
m.p. 241 °C
^{1}HNMR (DMSO-d6) δ ppm: 1.67-1.74 (1H, m), 1.77-1.85 (1H, m), 1.85-2.00 (2H, m), 2.47-2.61 (2H, m), 2.82-3.13 (8H, m), 5.15 (1H, s), 7.08 (1H, t, J = 9.1 Hz), 7.16 (1H, dd, J = 8.6 Hz, 1.9 Hz), 7.30 (1H, dd, J = 12.4 Hz, 2.5 Hz), 7.38 (1H,

t, J = 9.5 Hz), 7.45 (1H, dd, J = 8.8 Hz, 5.0 Hz), 10.34 (1H, s).

Example 462

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfonyl)-8-fluoro -3,4-dihydroquinolin-2(1H)-one

[1722] To a suspension of 5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxy-1-oxidopiperidin-4-yl]methyl}sulfonyl)-8 -fluoro-3,4-dihydroquinolin-2(1H)-one (0.1 g) in methanol (3 mL) was added carbon disulfide (3 mL), the mixture was heated to reflux for 3 h, and the solvent was distilled off. To the residue were added methanol/chloroform (1:1) (4 mL) and carbon disulfide (8 mL), and the reaction mixture was heated to reflux for 6 h. The solvent was distilled off, the residue was purified by silica gel column chromatography (dichloromethane/methanol), and recrystallized from ethyl acetate/ethanol. The precipitate was collected on a filter, and air-dried (60 °C) to provide the title compound (54 mg).
m.p. 236-238 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.93-2.02 (2H, m), 2.04-2.11 (2H, m), 2.69-2.76 (2H, m), 3.08-3.15 (2H, m), 3.15-3.21 (2H, m), 3.31 (2H, s), 3.48-3.54 (2H, m), 3.59 (1H, s), 6.90 (1H, t, J = 8.8 Hz), 7.02-7.07 (2H, m), 7.21 (1H, t, J = 9.1 Hz), 7.72 (1H, brs), 7.76 (1H, dd, J = 8.9 Hz, 5.3 Hz).

Example 463

5-{2-[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1723] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.53-1.62 (6H, m), 2.45-2.49 (2H, m), 2.60-2.64 (2H, m), 2.88-2.94 (4H, m), 3.29-3.34 (2H, m), 4.35 (1H, s), 6.80 (1H, dd, J = 8.6 Hz, 5.2 Hz), 6.96-7.00 (1H, m), 7.22-7.29 (2H, m), 9.96 (1H, s).

Example 464

5-({trans-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-[(4-methoxybenzyl)oxy]cyclohe xyl}methoxy)-8-fluoro-3,4-dihydro-quinolin-2(1H)-one

[1724] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.49 (2H, d, J = 12.4 Hz), 1.97-2.25 (6H, m), 2.31 (2H, t, J = 8.8 Hz), 2.75 (2H, t, J = 7.6 Hz), 3.70 (2H, s), 3.74 (3H, s), 4.02 (2H, s), 4.62 (1H, s), 6.55 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.87-6.93 (2H, m), 6.99 (1H, t, J = 9.7 Hz), 7.19-7.25 (2H, m), 7.33 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.42 (1H, dd, J = 11.9 Hz, 2.2 Hz), 7.50 (1H, t, J = 8.6 Hz), 10.00 (1H, brs).

Example 465

5-{[trans-4-(4-Chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1725] To a solution of 5-({trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-[(4-methoxybenzyl)oxy]cyclohexy l}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (0.30 g) in dichloromethane (6 mL) were added water (3 mL) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.146 g), and the mixture was stirred vigorously at room temperature for 30 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), washed with diisopropyl ether and dried under reduced pressure (40 °C) to provide the title compound (87 mg).
^{1}HNMR ($CDCl_3$) δ ppm: 1.71-1.83 (4H, m), 1.89-1.97 (2H, m), 1.97-2.09 (2H, m), 2.39-2.53 (2H, m), 2.60-2.70 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.85 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.5 Hz), 7.10 (1H, dd, J = 12.0 Hz, 2.1 Hz), 7.15 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.49 (1H, t, J = 8.7 Hz), 7.56 (1H, brs).

Example 466

5-({cis-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-[(4-methoxybenzyl)oxy]cyclohexy l}-methoxy)-8-fluoro-3,4-dihydroqui-nolin-2(1H)-one

[1726] Synthesized analogous to Example 42.
(Isopropylalcohol) m.p. 171.4-173.1 °C

^{1}HNMR ($CDCl_3$) δ ppm: 1.75-1.88 (2H, m), 1.98-2.19 (4H, m), 2.22-2.33 (3H, m), 2.58-2.68 (2H, m), 2.98 (2H, t, J = 7.7 Hz), 3.80 (3H, s), 3.95 (2H, s), 4.17 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.83-6.96 (3H, m), 7.06-7.17 (2H, m), 7.20-7.26 (2H, m), 7.39 (1H, t, J = 22 Hz), 7.56 (1H, brs).

Example 467

5-{[cis-4-(4-Chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3, 4-dihydroquinolin-2(1H)-one

[1727] Synthesized analogous to Example 465.
^{1}HNMR (DMSO-d6) δ ppm: 1.58-1.68 (2H, m), 1.69-1.78 (2H, m), 1.78-1.90 (2H, m), 1.96-2.09 (2H, m), 2.43 (2H, t, J = 7.7 Hz), 2.85 (2H, t, J = 7.6 Hz), 3.90 (2H, s), 4.67 (1H, s), 5.21 (1H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.23-7.33 (2H, m), 7.63 (1H, t, J = 8.7 Hz), 10.00 (1H, s).

Example 468

5-{[trans-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1728] Synthesized analogous to Example 42.
(Isopropylalcohol) m.p. 166.2-168.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.48-1.65 (2H, m), 1.68-1.81 (2H, m), 1.83-1.98 (2H, m), 2.09-2.21 (2H, m), 2.38 (1H, s), 2.61-2.70 (2H, m), 2.83-2.97 (1H, m), 3.02 (2H, t, J = 7.7 Hz), 4.04 (2H, s), 6.53 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.94 (1H, t, J = 9.4 Hz), 7.02-7.08 (2H, m), 7.08-7.17 (1H, m), 7.55 (1H, brs).

Example 469

5-{[cis-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-di hydroquinolin-2(1H)-one

[1729] Synthesized analogous to Example 42.
^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.70 (2H, m),1.70-1.81 (2H, m), 1.85-2.25 (5H, m), 2.56-2.73 (2H, m), 2.78-2.95 (1H, m), 3.02 (2H, t, J = 7.7 Hz), 3.81 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.05 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.10 (1H, dd, J = 8.3 Hz, 2.0 Hz), 7.24 (1H, t, J = 8,2 Hz), 7.59 (1H, brs).

Example 470

5-{[(1R*,2R*,4S*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1730] Synthesized analogous to Example 6.
^{1}HNMR ($CDCl_3$) δ ppm: 1.53-1.68 (1H, m), 1.80-1.94 (3H, m), 2.00-2.18 (2H, m), 2.57-2.72 (4H, m), 3.00 (2H, t, J = 7.7 Hz), 3.30-3.45 (1H, m), 4.05-4.15 (3H, m), 6.51 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.95 (1H, t, J = 9.4 Hz), 7.02-7.10 (2H, m), 7.13 (1H, t, J = 7.7 Hz), 7.54 (1H, brs).

Example 471

5-{[(1R*,2R*,4R*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1731] Synthesized analogous to Example 6.
^{1}HNMR (DMSO-d6) δ ppm: 1.44-1.56 (2H, m), 1.61-1.96 (4H, m), 2.47 (2H, t, J = 7.8 Hz), 2.77-3.00 (3H, m), 3.64 (1H, d, J = 8.6 Hz), 3.68-3.76 (1H, m), 4.02 (1H, d, J = 5.2 Hz), 4.40 (1H, s), 4.64 (1H, d, J = 6.5 Hz), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.26 (1H, dd, J = 8.4 Hz, 2.0 Hz), 7.32-7.42 (2H, m), 10.01 (1H, brs).

Example 472

(1R*,2R*,5S*)-5-(4-Chloro-2-fluorophenyl)-2-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroqui nolin-5-yl)oxy]methyl}-2,5-dihydroxycyclohexyl acetate

[1732] Synthesized analogous to Example 465.

^{1}HNMR (DMSO-d6) δ ppm: 1.37-1.51 (1H, m), 1.57-1.76 (2H, m), 1.93 (3H, s), 2.10-2.27 (1H, m), 2.29-2.44 (2H, m), 2.44-2.56 (2H, m), 2.90 (2H, t, J = 7.6 Hz), 3.69 (1H, d, J = 9.1 Hz), 3.83 (1H, d, J = 9.1 Hz), 4.91 (1H, s), 5.35 (1H, dd, J = 11.2 Hz, 4.8 Hz), 5.44 (1H, s), 6.54 (1H, dd, J = 9.2 Hz), 7.00 (1H, t, J = 9.7 Hz), 7.29 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.33 (1H, dd, J = 11.7 Hz, 2.1 Hz), 7.63 (1H, t, J = 8.7 Hz), 10.03 (1H, s).

Example 473

5-{[(1R*,2R*,4S*)-4-(4-Chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1733] To a solution of (1R*,2R*,5S*)-5-(4-chloro-2-fluorophenyl)-2-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-2,5-dihydroxycyclohexyl acetate (0.30 g) in N,N-dimethylformamide/methanol (5: 3) (8 mL) was added potassium carbonate (0.167 g), and the reaction mixture was stirred at room temperature for 30 min. The reaction solution was concentrated, to the residue was added water, the precipitate was collected on a filter, and dried to provide the title compound (0.25 g).
^{1}HNMR (DMSO-d6) δ ppm: 1.36-1.46 (1H, m), 1.47-1.61 (1H, m), 1.61-1.74 (1H, m), 2.06-2.20 (1H, m), 2.22-2.38 (2H, m), 2.38-2.58 (2H, m), 2.81-3.03 (2H, m), 3.63 (1H, d, J = 8.7 Hz), 3.97-4.11 (2H, m), 4.39 (2H, brs), 5.22 (1H, brs), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.28 (1H, dd, J = 8.4 Hz, 2.2 Hz), 7.31 (1H, dd, J = 11.6 Hz, 2.1 Hz), 7.63 (1H, t, J = 8.6 Hz), 10.03 (1H, brs).

Example 474

(1R*,2R*,5R*)-5-(4-Chloro-2-fluorophenyl)-2-{[(8-fluoro-2-oxo-l,2,3,4-tetrahydroqu inolin-5-yl)oxy]methyl}-2,5-dihydroxycyclohexyl acetate

[1734] Synthesized analogous to Example 465.
^{1}HNMR (DMSO-d6) δppm: 1.37-1.58 (1H, m), 1.63-1.76 (1H, m), 1.87-2.03 (4H, m), 2.07 (1H, t, J = 12.2 Hz), 2.21-2.37 (3H, m), 2.37-2.60 (3H, m), 3.61 (1H, d, J = 9.2 Hz), 3.77 (1H, d, J = 9.2 Hz), 4.77 (1H, dd, J = 11.6 Hz, 3.9 Hz), 5.02 (1H, s), 5.38 (1H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.95 (1H, t, J = 9.7 Hz), 7.32 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.40 (1H,dd, J = 12.2 Hz, 2.2 Hz), 7.68 (1H, t, J = 8.7 Hz), 9.98 (1H, s).

Example 475

5-{[(1R*,2R*,4R*)-4-(4-Chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy }-8-fluoro-3,4-dihydroquinolin-2(1H)-one

[1735] Synthesized analogous to Example 473.
^{1}HNMR (DMSO-d6) δ ppm: 1.45-1.60 (1H, m), 1.63-1.77 (1H, m), 1.79-1.90 (1H, m), 1.90-2.01 (1H, m), 2.16-2.27 (1H, m), 2.28-2.37 (2H, m), 2.37-2.57 (3H, m), 3.48-3.61 (2H, m), 3.93 (1H, d, J = 9.0 Hz), 4.49 (1H, brs), 4.84 (1H, brs), 5,42 (1H, brs), 6.67 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.97 (1H, t, J = 9.8 Hz), 7.30 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.37 (1H, dd, J = 12.2 Hz, 2.2 Hz), 7.54 (1H, t, J = 8.7 Hz), 9.99 (1H, brs).

Example 476

trans-1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile

[1736] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.69-1.87 (2H, m), 1.92-2.05 (2H, m), 2.05-2.17 (2H, m), 2.17-2.31 (2H, m), 2.37-2.48 (2H, m), 2.95 (2H, t, J = 7.6 Hz), 3.78 (2H, s), 4.86 (1H, s), 6.60 (1H, dd, J = 9.1 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.40 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.52-7.66 (2H, m), 10.03 (1H, brs).

Example 477

5-{[trans-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8 -fluoro-3,4-dihydroquinolin-2(1H)-one

[1737] Synthesized analogous to Example 42.

^{1}HNMR (DMSO-d6) δ ppm: 1.45-1.57 (2H, m), 1.77-1.90 (2H, m), 1.90-2.00 (2H, m), 2.06-2.20 (2H, m), 2.43-2.49 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 2.96 (3H, s), 3.72 (2H, s), 4.56 (1H, s), 6.58 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.7 Hz), 7.30 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.38 (1H, dd, J = 11.9 Hz, 2.1 Hz), 7.44 (1H, t, J = 8.6 Hz), 10.0 (1H, brs).

Example 478

5-{[trans-4-(4-Chloro-2,6-difluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-flu oro-3,4-dihydroquinolin-2(1H)-one

[1738] Synthesized analogous to Example 42.
(Methanol) m.p. 213.0-213.4 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.79 (2H, m), 1.93 (1H, s), 1.99-2.12 (4H, m), 2.45-2.58 (3H, m), 2.61-2.70 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.82 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.86-7.00 (3H, m), 7.54 (1H, brs).

Example 479

5-{[cis-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fl uoro-3,4-dihydroquinolin-2(1H)-one

[1739] Synthesized analogous to Example 42.
(2-Propanol) m.p. 155.4-158.8 °C
^{1}HNMR ($CDCl_3$) δ ppm: 1.73-1.87 (2H, m), 1.91-2.20 (6H, m), 2.30 (1H, s), 2.62-2.68 (2H, m), 2.98 (2H, t, J = 7.7 Hz), 3.11 (3H, s), 3.95 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.07 (1H, dd, J = 11.2 Hz, 2.1 Hz), 7.13 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.33 (1H, t, J = 8.5 Hz), 7.65 (1H, s).

Example 480

5-{[cis-4-(4-Chloro-2,6-difluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluor o-3,4-dihydroquinolin-2(1H)-one

[1740] Synthesized analogous to Example 42.
^{1}HNMR (DMSO-d6) δ ppm: 1.54-1.70 (2H, m), 1.71-1.82 (2H, m), 1.88-2.02 (2H, m), 2.10-2.25 (2H, m), 2.40 (2H, t, J = 7.6 Hz), 2.71 (2H, t, J = 7.6 Hz), 3.77 (2H, s), 4.63 (1H, s), 5.33 (1H, s), 6.55 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.98 (1H, t, J = 9.7 Hz), 7.20-7.32 (2H, m), 9.99 (1H, s).

Test Example 1

Antibacterial test (agar plate dilution method)

[1741] The minimum inhibitory concentration against Mycobacterium tuberculosis (M. tuberculosis H37Rv) of the fused heterocyclyl compound obtained from Example 259 was determined by using 7H11 medium (BBL). The bacterial strain was previously cultured on 7H9 medium (BBL), cryopreserved at -80 °C, and the viable bacterial count was calculated. The preserved bacterial solution was used to prepare the bacterial solution in which the final viable bacterial count was about 10^6 CFU/mL. About 5 μL of this bacterial solution was inoculated into the 7H11 agar medium containing the test compound. After incubated at 37 °C for 14 days, the minimum inhibitory concentration was determined.
[1742] The minimum inhibitory concentration against M. tuberculosis H37Rv was < 0.39 μg/mL.

Test Example 2

Antibacterial test (agar dilution method)

[1743] Regarding the test compounds shown in the following table, the respective minimum inhibitory concentrations against Mycobacterium tuberculosis (M. tuberculosis Kurono) were determined by using 7H11 medium (BBL). The bacterial strain was previously cultured on 7H9 medium (BBL), cryopreserved at -80 °C, and the viable bacterial count was calculated. The preserved bacterial suspension was used to prepare the bacterial suspension in which the final viable bacterial count was about 10^6 CFU/ mL. About 5 μL of this bacterial suspension was inoculated into the 7H11 agar medium containing the test compound, and incubated at 37 °C for 14 days, the minimum inhibitory concentration was determined.
[1744] The results are shown in the following Table.

[Table 1-1]

Test Compounds	Minimum inhibitory conc entration (MIC) kurono (μg/mL)
Compound of Example 1	< 0.39
Compound of Example 14	< 0.39
Compound of Example 17	< 0.39
Compound of Example 49	< 0.39
Compound of Example 52	< 0.39
Compound of Example 85	< 0.39
Compound of Example 102	< 0.39
Compound of Example 130	< 0.39
Compound of Example 138	< 0.39
Compound of Example 139	< 0.39
Compound of Example 152	< 0.39
Compound of Example 175	< 0.39
Compound of Example 194	< 0.39
Compound of Example 206	< 0.39
Compound of Example 214	< 0.39
Compound of Example 251	< 0.39
Compound of Example 252	< 0.39
Compound of Example 259	< 0.39
Compound of Example 260	< 0.39
Compound of Example 265	< 0.39
Compound of Example 288	< 0.39

[Table 1-2]

Compound of Example 347	< 0.39
Compound of Example 361	< 0.39
Compound of Example 364	< 0.39
Compound of Example 369	< 0.39
Compound of Example 372	< 0.39
Compound of Example 399	< 0.39
Compound of Example 404	< 0.39
Compound of Example 419	< 0.39
Compound of Example 446	< 0.39
Compound of Example 447	< 0.39
Compound of Example 448	< 0.39
Compound of Example 449	< 0.39
Compound of Example 450	< 0.39
Compound of Example 454	< 0.39

(continued)

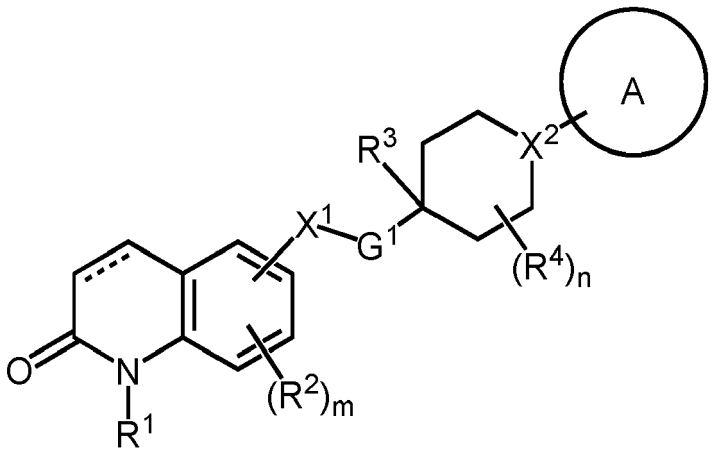
Compound of Example 460	< 0.39
Compound of Example 463	< 0.39
Compound of Example 465	< 0.39
Compound of Example 469	< 0.39
Compound of Example 471	< 0.39
Compound of Example 473	< 0.39
Compound of Example 476	< 0.39
Compound of Example 477	< 0.39

Industrial Applicability

[1745] The present invention can provide compounds with an excellent antibacterial activity against tuberculosis bacteria, multidrug-resistant tuberculosis bacteria and/or non-tuberculous mycobacteria.

Claims

1. A compound of the general formula (1) for use for diagnosing, preventing, and/or treating tuberculosis:



(1)

or a salt thereof, wherein the moiety:

represents single bond or double bond; and

wherein R^1 is

(1) hydrogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl or
(3) C_{1-6} alkyl;

R^2 is

(1) halogen,

(2) amino which may have one or two of the same or different C_{1-6} alkyl,
(3) C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) hydroxy;

m is an integer of 0 to 3;
provided that when m is 2 or 3, R^2 may be different from each other;
X^1 is $-CH_2-$, -O-, $-N(R^5)-$, -S-, -SO- or $-SO_2-$;
R^5 is

(1) hydrogen,
(2) C_{1-6} alkyl or
(3) C_{1-7} alkanoyl;

G^1 is C_{1-6} alkylene;
R^3 is

(1) hydrogen,
(2) carboxy,
(3) halogen,
(4) C_{1-6} alkyl, which may have one or more hydroxy,
(5) cyano,
(6) amino which may have one or two substituents independently selected from:

(a) C_{1-6} alkyl and
(b) $-C(=O)-R^6$ or

(7) $-O-R^7$;

R^6 is

(1) C_{1-6} alkoxy or
(2) C_{1-6} alkyl, wherein the C_{1-6} alkyl may have amino which may have one or two of the same or different C_{1-6} alkyl;

R^7 is

(1) hydrogen,
(2) amino,
(3) C_{1-7} alkanoyl or
(4) C_{1-6} alkyl;

R^4 is

(1) amino which may have one or two of the same or different C_{1-6} alkyl,
(2) halogen,
(3) cyano,
(4) C_{1-6} alkyl,
(5) oxo,
(6) $-O-R^8$ or
(7) $-O-C(=O)-R^9$;

R^8 is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -PH(=O)OH or
(4) benzyl which may have one or more of the same or different C_{1-6} alkoxy;

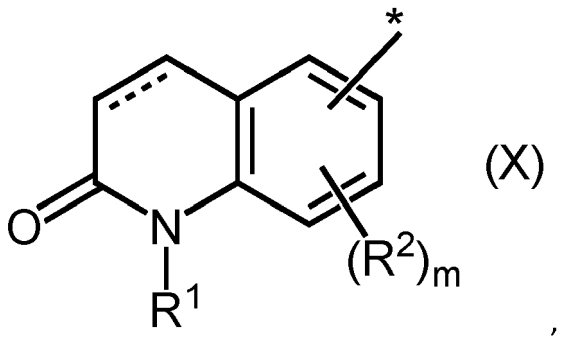
R^9 is

(1) C_{1-6} alkyl,
(2) -G^2-COOH,
(3) amino which may have one or two of the same or different C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) pyrazinyl;

G^2 is C_{1-6} alkylene;
n is an integer of 0 to 8;
provided that when n is 2 or more, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;
X^2 isN orCH;
provided that when X^2 is CH, H of the group may be replaced with R^4 which is defined as above, wherein multiple R^4s in formula (1) may be the same or different from each other; and
Ring A is

(1) aryl which may have one or more substituents, or
(2) heterocyclyl which may have one or more substituents.

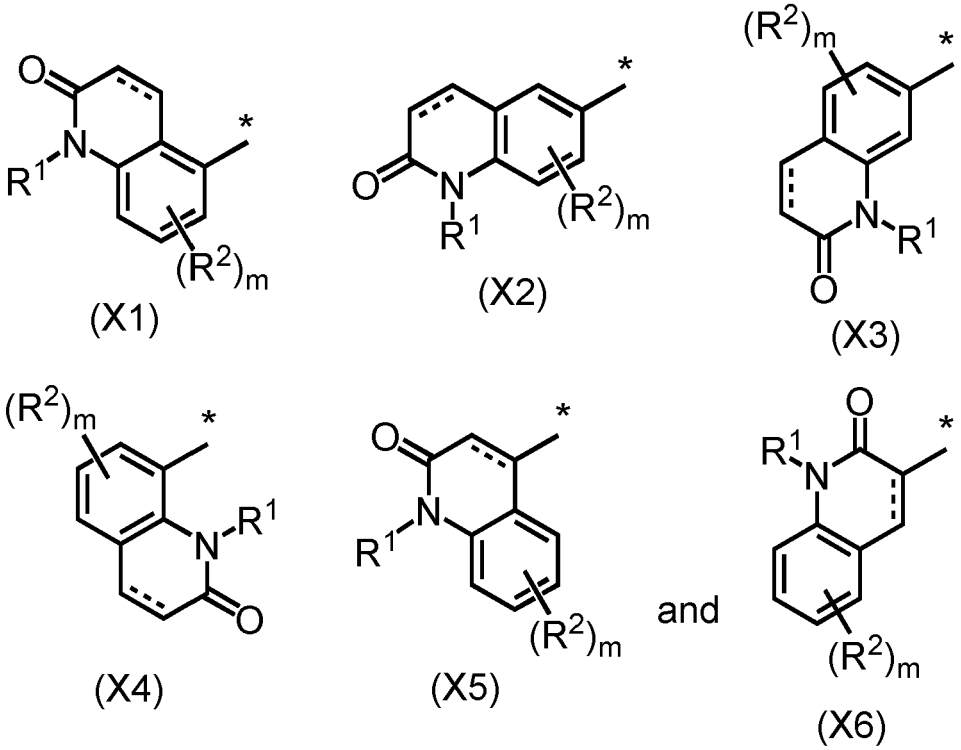
2. The compound for use according to claim 1, or a salt thereof, wherein a partial structure (X) of formula (1) is represented by the following partial structure:



(X)

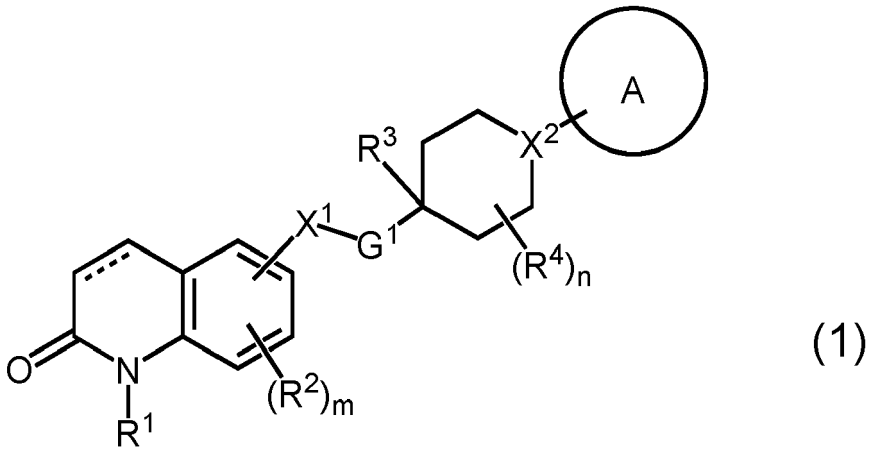
,

wherein * is binding point to X^1; and other symbols are as defined in claim 1, and
the partial structure (X) is any one of the structures selected from the group consisting of the following formulae (X1) to (X6):



wherein the symbols are as defined in the above and claim 1.

3. A compound of the general formula (1):



or a salt thereof,
wherein the moiety:

represents single bond or double bond; and

wherein R^1 is

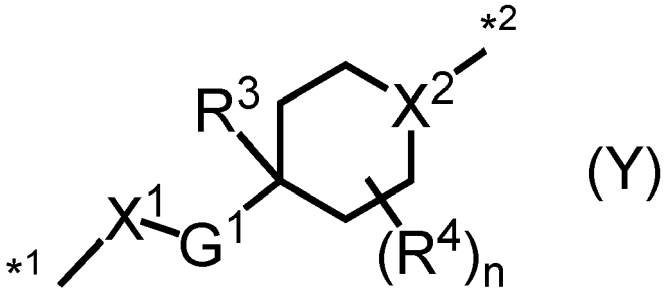
(1) hydrogen,
(2) amino which may have one or two of the same or different $C_{1\text{-}6}$ alkyl or

(3) C_{1-6} alkyl;

R^5 is

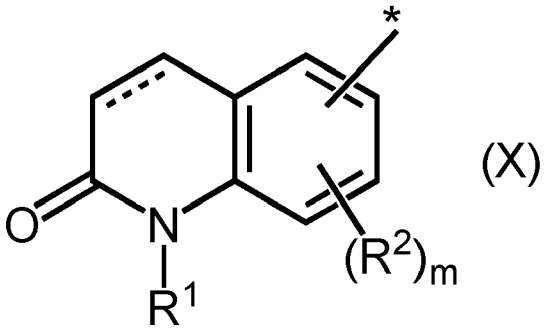
(1) halogen,
(2) amino which may have one or two of the same or different C_{1-6} alkyl,
(3) C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) hydroxy;

m is an integer of 0 to 3;
provided that when m is 2 or 3, R^2 may be different from each other;
a partial structure (Y) of formula (1) is represented by the following partial structure:



(Y)

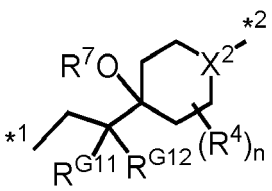
wherein *1 is a binding point to a partial structure (X) of formula (1) and *2 is a binding point to Ring A, and the partial structure (X) of formula (1) is represented by the following partial structure:



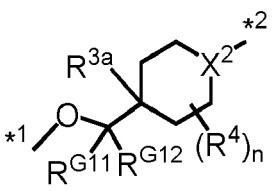
(X)

,

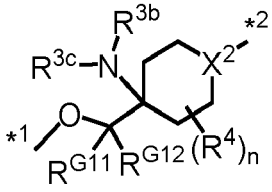
wherein * is a binding point to X^1,
the partial structure (Y) is any one of the structures selected from the group consisting of the following formulae (Y1) to (Y8):



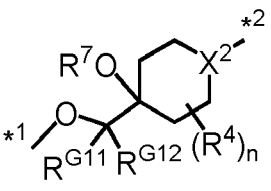
(Y1)



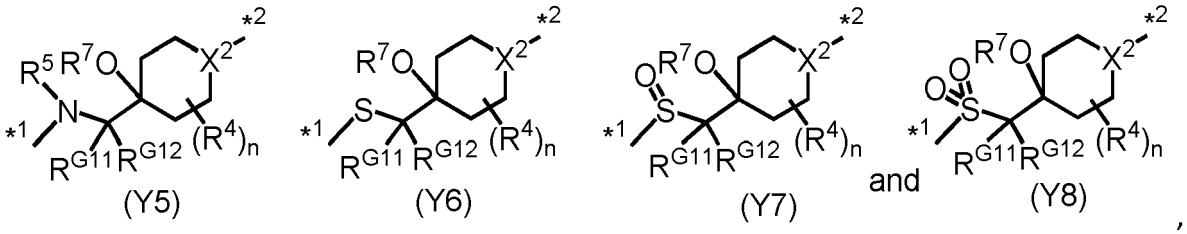
(Y2)



(Y3)



(Y4)



wherein R^{3a} is

(1) hydrogen,
(2) carboxy,
(3) halogen,
(4) C_{1-6} alkyl, which may have one or more hydroxy, or
(5) cyano;

R^{3b} and R^{3c} are each independently

(1) hydrogen,
(2) C_{1-6} alkyl, or
(3) -C(=O)-R^6;

R^{G11} and R^{G12} are each independently hydrogen or C_{1-6} alkyl;
the total number of carbon atoms in R^{G11} and R^{G12} is 0 to 5;
R^5 is

(1) hydrogen,
(2) C_{1-6} alkyl or
(3) C_{1-7} alkanoyl;

R^6 is

(1) C_{1-6} alkoxy or
(2) C_{1-6} alkyl, wherein the C_{1-6} alkyl may have amino which may have one or two of the same or different C_{1-6} alkyl;

R^7 is

(1) hydrogen,
(2) amino,
(3) C_{1-7} alkanoyl or
(4) C_{1-6} alkyl;

R^4 is

(1) amino which may have one or two of the same or different C_{1-6} alkyl,
(2) halogen,
(3) cyano,
(4) C_{1-6} alkyl,
(5) oxo,
(6) -O-R^8 or
(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,
(2) C_{1-6} alkyl,

(3) -PH(=O)OH or
(4) benzyl which may have one or more of the same or different C_{1-6} alkoxy;

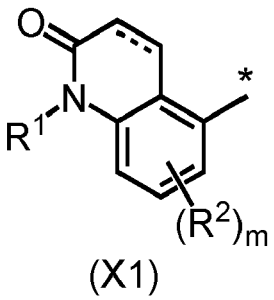
R^9 is

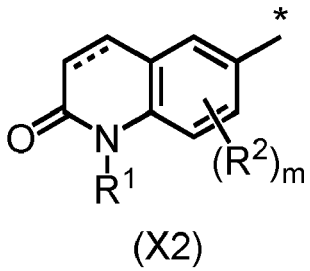
(1) C_{1-6} alkyl,
(2) -G^2-COOH,
(3) amino which may have one or two of the same or different C_{1-6} alkyl,
(4) C_{1-6} alkoxy or
(5) pyrazinyl;

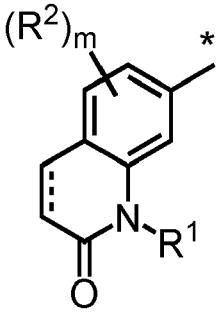
G^2 is C_{1-6} alkylene;
n is an integer of 0 to 8;
provided that when n is 2 or more, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;
X^2 is N orCH;
provided that when X^2 is CH, H of the group may be replaced with R^4 which is defined as above, wherein multiple R^4s in formula (1) may be the same or different from each other; and
Ring A is

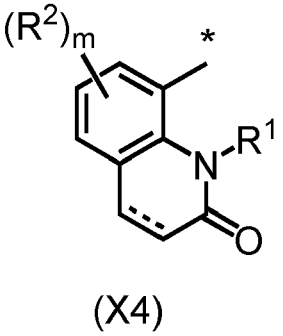
(1) aryl which may have one or more substituents, or
(2) heterocyclyl which may have one or more substituents.

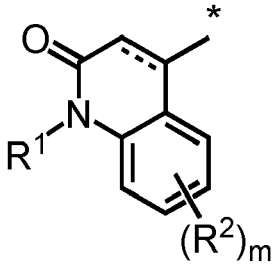
4. The compound of claim 3, or a salt thereof, wherein the partial structure (X) is any one of the structures selected from the group consisting of the following formulae (X1) to (X6):


(X1)

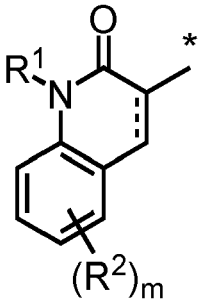

(X2)


(X3)


(X4)


(X5)

and


(X6)

wherein the symbols are as defined in the above and claim 3.

5. The compound of either claim 3 or 4, or a salt thereof, wherein Ring A is aryl or heterocyclyl which may have 1 to 5 substituents independently selected from:

(a) halogen;

(b) cyano;
(c) nitro;
(d) hydroxy;
(e) C_{1-6} alkyl which may have one or more substituents independently selected from:

(i) halogen,
(ii) hydroxy,
(iii) C_{1-6} alkoxy, and
(iv) aryloxy which may have one or more of the same or different halogen ;

(f) C_{1-6} alkoxy which may have one or more substituents independently selected from:

(i) halogen,
(ii) C_{1-6} alkoxy which may have one or more of the same or different C_{1-6} alkoxy,
(iii) aryloxy which may have one or more of the same or different halogen ,
(iv) heterocyclyl which may have one or more of the same or different C_{1-6} alkyl which may have one or more of the same or different halogen, and
(v) amino which may have one or two of the same or different C_{1-6} alkyl;

(g) C_{1-6} alkoxycarbonyl;
(h) C_{1-6} alkylsulfanyl;
(i) aryl which may have one or more of the same or different halogen;
(j) aryloxy; and
(k) aralkyloxy which may have one or more substituents independently selected from:

(i) halogen,
(ii) C_{1-6} alkyl which may have one or more of the same or different halogen, and
(iii) C_{1-6} alkoxy which may have one or more of the same or different halogen.

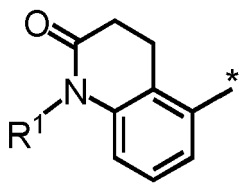
6. The compound of any one of claims 3 to 5, or a salt thereof, wherein R^1 is hydrogen.

7. The compound of any one of claims 3 to 6, or a salt thereof, wherein R^2 is halogen.

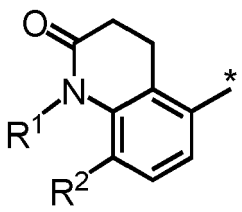
8. The compound of any one of claims 3 to 7, or a salt thereof, wherein m is 0, 1 or 2.

9. The compound of any one of claims 3 to 8, or a salt thereof, wherein n is 0, 1 or 2.

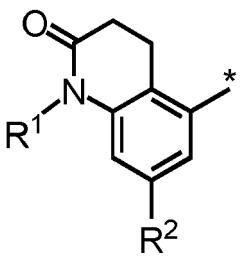
10. The compound of claim 3, or a salt thereof, wherein the partial structure (X) is a structure of a formula selected from the group consisting of the formulae (X1-1), (X1-2), (X1-3), (X1-4), (X1-6), and (X1-7):



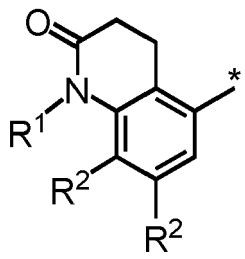
(X1-1)



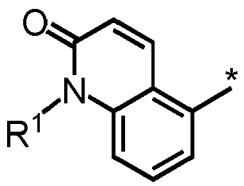
(X1-2)



(X1-3)

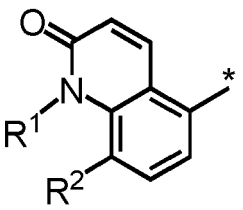


(X1-4)



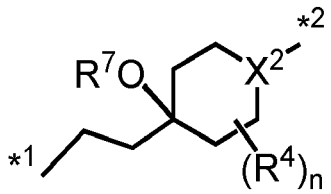
(X1-6)

and

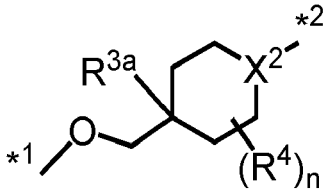


(X1-7)

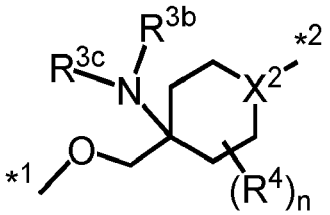
wherein * is binding point to X^1;
R^1 is hydrogen;
R^2 is substituent selected from (1) halogen or (2) C_{1-6} alkyl;
provided that when R^2 may be multiple, each of them may be different from each other;
the partial structure (Y) is a structure of a formula selected from the group consisting of the formulae (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y5-1), and (Y6-1):



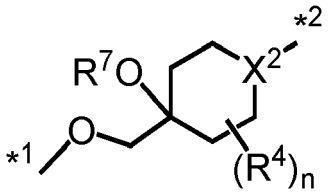
(Y1-1)



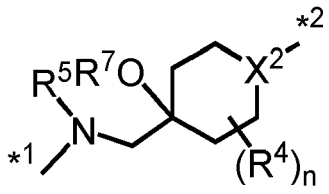
(Y2-1)



(Y3-1)

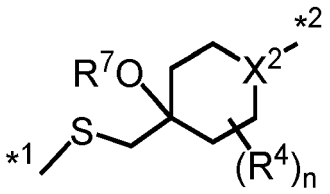


(Y4-1)



(Y5-1)

and



(Y6-1)

wherein *1 is binding point to the partial structure (X);
*2 is binding point to Ring A;
R^5 is hydrogen;
R^{3a} is (1) hydrogen or (2) halogen;
R^{3b} and R^{3c} are each hydrogen;
R^7 is hydrogen;
R^4 is substituent selected from (1) halogen, (2) -O-R^8, (3) -O-C(=O)-R^9, or (4) cyano;
R^8 is (1) hydrogen or (2) C C_{1-6} alkyl;
R^9 is (1) C_{1-6} alkyl or (2) C_{1-6} alkoxy;
n is an integer of 0 to 2;
provided that when n is 2, each of R^4, R^8, and R^9 may be different from each other and may be substituted on the same carbon atom;
X^2 is N orCH;
provided that when X^2 is CH, H of the group may be replaced with R^4 which is defined as above, wherein multiple R^4s in formula (1) may be the same or different from each other; and
Ring A is phenyl or pyridyl which may have 1 to 3 groups independently selected from:

(a) halogen;

(b) C_{1-6} alkoxy which may have (i) halogen and (ii) C_{1-6} alkoxy; or
(c) aralkyloxy which may have one or more of the same or different C_{1-6} alkoxy which may have one or more of the same or different halogen; or

quinolyl which may have 1 to 2 halogen.

11. The compound of claim 3, which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one;
5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one;
8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one;
8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one;
5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;

(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate;
(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate;
5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
trans-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile; and
5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

12. The compound of claim 3, which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one;
5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxylquinolin-2(1H)-one;
8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one;
8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one;

5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(3S,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate;
(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate;
5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;
trans-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile; and
5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one.

13. The compound of claim 3, which is 8-chloro-5-1[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

14. The compound of claim 3, which is 8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one.

15. The compound of claim 3, which is 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

16. The compound of claim 3, which is 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one.

17. The compound of claim 3, which is 5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

18. The compound of claim 3, which is 5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxyl-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one.

19. The compound of claim 3, which is 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

20. The compound of claim 3, which is 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one.

21. The compound of claim 3, which is (3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate, or a salt thereof.

22. The compound of claim 3, which is (3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate.

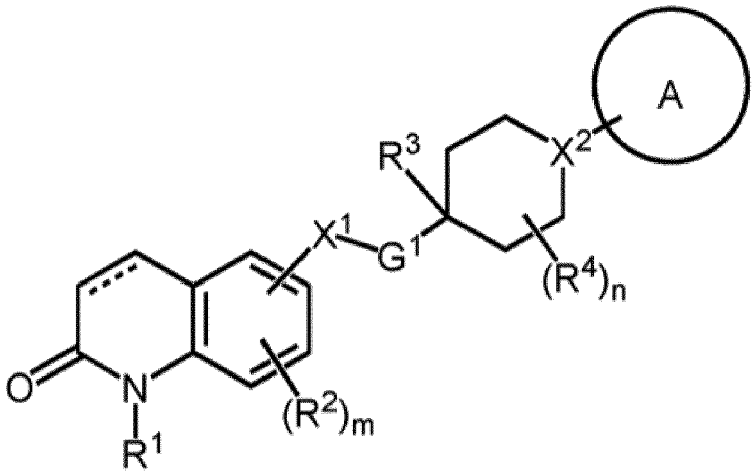
23. A pharmaceutical composition, comprising the compound of any one of claims 3 to 22, or a salt thereof and a pharmaceutically acceptable carrier.

24. An agent for diagnosing, preventing, and/or treating tuberculosis, comprising the compound of any one of claims 3 to 22, or a salt thereof and a pharmaceutically acceptable carrier.

25. The compound of any one of claims 3 to 22, or a salt thereof, for use of diagnosing, preventing, and/or treating tuberculosis.

Patentansprüche

1. Verbindung der allgemeinen Formel (1) zur Verwendung zur Diagnose, Vorbeugung und/oder Behandlung von Tuberkulose:



(1)

oder ein Salz davon, wobei die Gruppe:

eine Einzel- oder Doppelbindung darstellt; und

wobei R^1

(1) Wasserstoff,
(2) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann, oder
(3) C_{1-6}-Alkyl ist;

R^2

(1) Halogen,
(2) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann,
(3) C_{1-6}-Alkyl,
(4) C_{1-6}-Alkoxy oder
(5) Hydroxy ist;

m eine ganze Zahl von 0 bis 3 ist;

vorausgesetzt, dass, wenn m 2 oder 3 ist, R^2 voneinander verschieden sein können;
X^1 $-CH_2-$, -O-, $-N(R^5)-$, -S-, -SO- oder $-SO_2-$ist;
R^5

(1) Wasserstoff,
(2) C_{1-6}-Alkyl oder
(3) C_{1-7}-Alkanoyl ist;

G^1 C_{1-6}-Alkylen ist;
R^3

(1) Wasserstoff,
(2) Carboxy,
(3) Halogen,
(4) C_{1-6}-Alkyl, das ein oder mehrere Hydroxy aufweisen kann,
(5) Cyano,
(6) Amino, das einen oder zwei Substituenten aufweisen kann, die unabhängig ausgewählt sind aus:

(a) C_{1-6}-Alkyl und
(b) $-C(=O)-R^6$, oder

(7) $-O-R^7$ ist;

R^6

(1) C_{1-6}-Alkoxy oder
(2) C_{1-6}-Alkyl ist, wobei das C_{1-6}-Alkyl Amino aufweisen kann, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann,

R^7

(1) Wasserstoff,
(2) Amino,
(3) C_{1-7}-Alkanoyl oder
(4) C_{1-6}-Alkyl ist;

R^4

(1) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann,
(2) Halogen,
(3) Cyano,
(4) C_{1-6}-Alkyl,
(5) Oxo,
(6) $-O-R^8$ oder
(7) $-O-C(=O))R^9$ ist;

R^8

(1) Wasserstoff,
(2) C_{1-6}-Alkyl,
(3) -PH(=O)OH oder
(4) Benzyl ist, das ein oder mehrere gleiche oder verschiedene C_{1-6}-Alkoxy aufweisen kann;

R^9

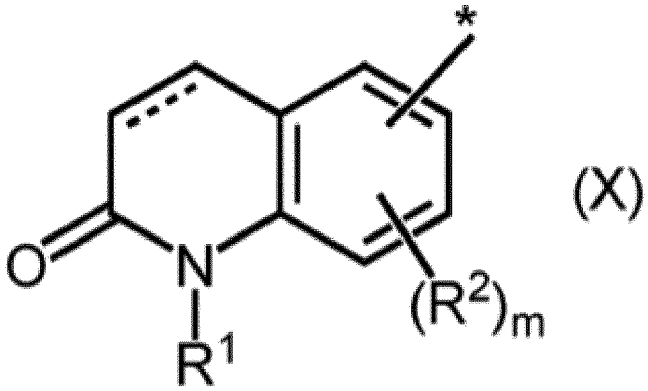
(1) C_{1-6}-Alkyl,
(2) $-G^2-COOH$,
(3) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann,

(4) C_{1-6}-Alkoxy oder
(5) Pyrazinyl ist;

G^2 C_{1-6}-Alkylen ist;
n eine ganze Zahl von 0 bis 8 ist; vorausgesetzt, dass, wenn n 2 oder mehr ist, jedes von R^4, R^8, R^9 und G^2 voneinander verschieden sein kann und an demselben Kohlenstoffatom substituiert sein kann;
X^2 N oder CH ist;
vorausgesetzt, dass, wenn X^2 CH ist, H der Gruppe mit R^4, das wie oben definiert ist, ersetzt sein kann, wobei mehrere R^4s in Formel (1) gleich oder voneinander verschieden sein können; und
Ring A

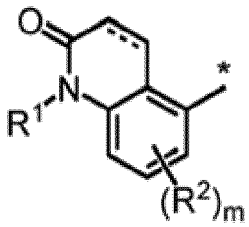
(1) Aryl ist, das einen oder mehrere Substituenten aufweisen kann, oder
(2) Heterocyclyl ist, das einen oder mehrere Substituenten aufweisen kann.

2. Verbindung zur Verwendung nach Anspruch 1, oder ein Salz davon, wobei eine Teilstruktur (X) der Formel (1) durch die folgende Teilstruktur dargestellt wird:

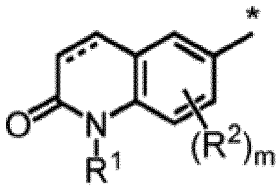


(X)

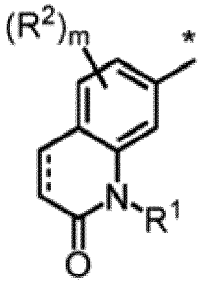
wobei * der Bindungspunkt an X^1 ist; und andere Symbole wie in Anspruch 1 definiert sind, und die Teilstruktur (X) eine der Strukturen ist, die aus der Gruppe ausgewählt sind, die aus den folgenden Formeln (X1) bis (X6) besteht:



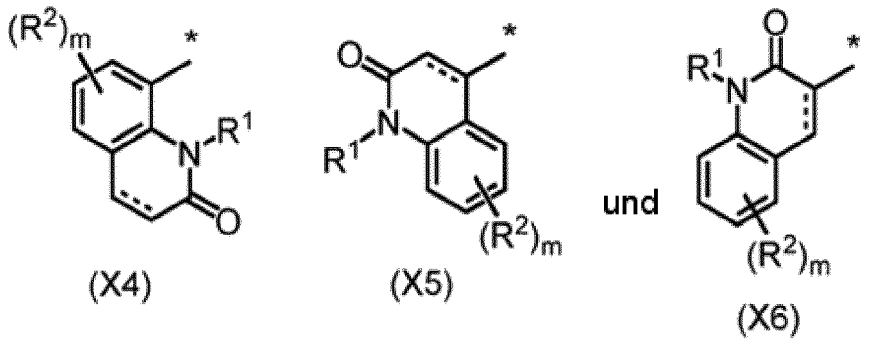
(X1)



(X2)



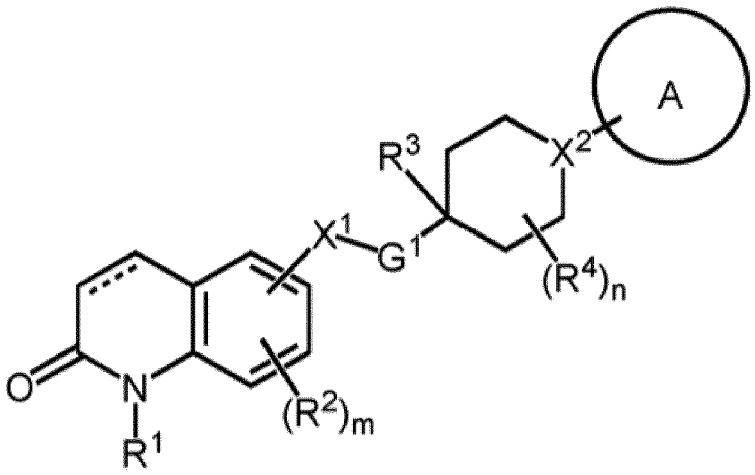
(X3)



,

wobei die Symbole wie oben und in Anspruch 1 definiert sind.

3. Verbindung der allgemeinen Formel (1):



(1)

oder ein Salz davon,
wobei die Gruppe:

eine Einzel- oder Doppelbindung darstellt; und

wobei R^1

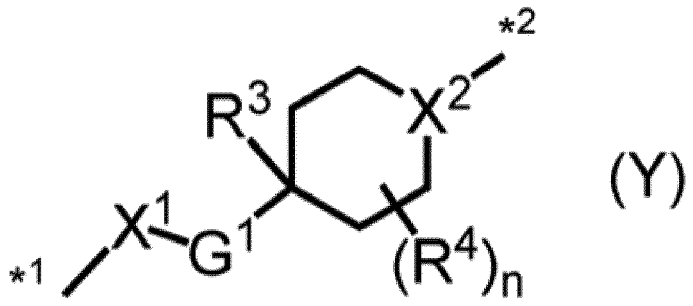
(1) Wasserstoff,
(2) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann, oder
(3) C_{1-6}-Alkyl ist;

R^2

(1) Halogen,
(2) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann,
(3) C_{1-6}-Alkyl,
(4) C_{1-6}-Alkoxy oder
(5) Hydroxy ist;

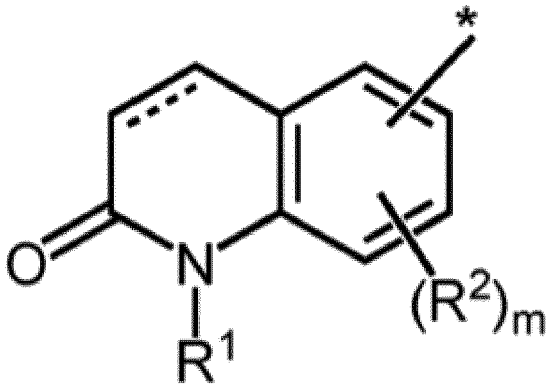
m eine ganze Zahl von 0 bis 3 ist;

vorausgesetzt, dass, wenn m 2 oder 3 ist, R^2 voneinander verschieden sein können;
eine Teilstruktur (Y) der Formel (1) durch die folgende Teilstruktur dargestellt wird:



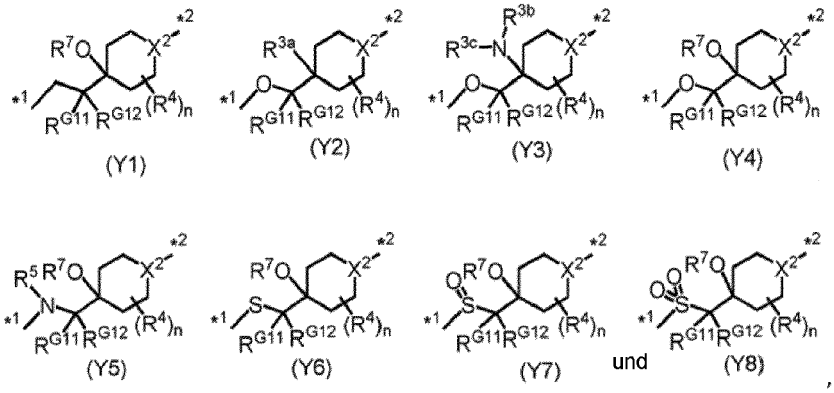
(Y)

wobei *1 ein Bindungspunkt an eine Teilstruktur (X) der Formel (1) ist und *2 ein Bindungspunkt an Ring A ist, und die Teilstruktur (X) der Formel (1) durch die folgende Teilstruktur dargestellt wird:



(X)

wobei * ein Bindungspunkt an X^1 ist,
die Teilstruktur (Y) eine der Strukturen ist, die aus der Gruppe ausgewählt sind, die aus den folgenden Formeln (Y1) bis (Y8) besteht;



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6) (Y7) und (Y8)

wobei R^{3a}

(1) Wasserstoff,
(2) Carboxy,
(3) Halogen,
(4) C_{1-6}-Alkyl, das ein oder mehrere Hydroxy aufweisen kann, oder
(5) Cyano ist;

R^{3b} und R^{3c} unabhängig voneinander

(1) Wasserstoff,
(2) C_{1-6}-Alkyl oder
(3) -C(=O)-R^6 sind;

R^{G11} und R^{G12} unabhängig voneinander Wasserstoff oder C_{1-6}-Alkyl sind;
die Gesamtanzahl der Kohlenstoffatome in R^{G11} und R^{G12} 0 bis 5 ist;
R^5

(1) Wasserstoff
(2) C_{1-6}-Alkyl oder
(3) C_{1-7}-Alkanoyl ist;

R^6

(1) C_{1-6}-Alkoxy oder
(2) C_{1-6}-Alkyl ist, wobei das C_{1-6}-Alkyl Amino aufweisen kann, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann;

R^7

(1) Wasserstoff,
(2) Amino,
(3) C_{1-7}-Alkanoyl oder
(4) C_{1-6}-Alkyl ist;

R^4

(1) Amino ist, das ein oder mehrere gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann,
(2) Halogen,
(3) Cyano,
(4) C_{1-6}-Alkyl,
(5) Oxo,
(6) -O-R^8 oder
(7) -O-C(=O)-R^9 ist;

R^8

(1) Wasserstoff,
(2) C_{1-6}-Alkyl,
(3) -PH(=O)OH oder
(4) Benzyl ist, das ein oder mehrere gleiche oder verschiedene C_{1-6}-Alkoxy aufweisen kann;

R^9

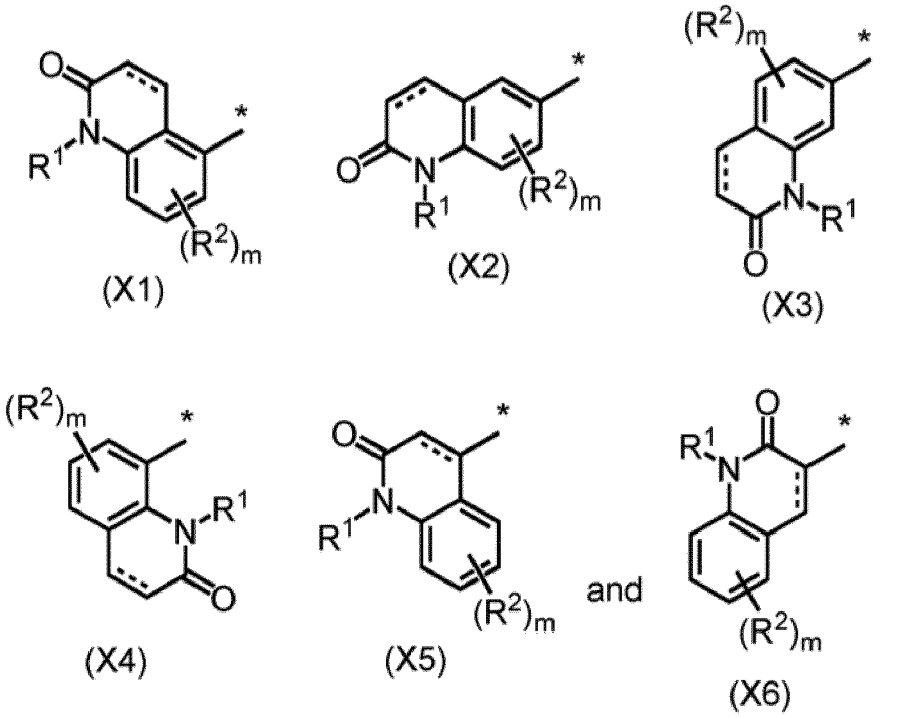
(1) C_{1-6}-Alkyl,
(2) -G^2-COOH,
(3) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann,
(4) C_{1-6}-Alkoxy oder
(5) Pyrazinyl ist;

G^2 C_{1-6}-Alkylen ist;
n eine ganze Zahl von 0 bis 8 ist;
vorausgesetzt, dass, wenn n 2 oder mehr ist, jedes von R^4, R^8, R^9 und G^2 voneinander verschieden sein kann und an demselben Kohlenstoffatom substituiert sein kann;
X^2 N oder CH ist;
vorausgesetzt, dass, wenn X^2 CH ist, H der Gruppe durch R^4, das wie oben definiert ist, ersetzt sein kann,

wobei mehrere R^4s in Formel (1) gleich oder voneinander verschieden sein können; und
Ring A

(1) Aryl ist, das einen oder mehrere Substituenten aufweisen kann, oder
(2) Heterocyclyl ist, das einen oder mehrere Substituenten aufweisen kann.

4. Verbindung nach Anspruch 3, oder ein Salz davon, wobei die Teilstruktur (X) eine der Strukturen ist, die aus der Gruppe ausgewählt sind, die aus den folgenden Formeln (X1) bis (X6) besteht:



wobei die Symbole wie oben und in Anspruch 3 definiert sind.

5. Verbindung nach Anspruch 3 oder 4, oder ein Salz davon, wobei Ring A Aryl oder Heterocyclyl ist, das 1 bis 5 Substituenten aufweisen kann, die unabhängig ausgewählt sind aus:

(a) Halogen;
(b) Cyano;
(c) Nitro;
(d) Hydroxy;
(e) C_{1-6}-Alkyl, das einen oder mehrere Substituenten aufweisen kann, die unabhängig ausgewählt sind aus:

(i) Halogen,
(ii) Hydroxy,
(iii) C_{1-6}-Alkoxy und
(iv) Aryloxy, das eines oder mehrere gleiche oder verschiedene Halogene aufweisen kann;

(f) C_{1-6}-Alkoxy, das einen oder mehrere Substituenten aufweisen kann, die unabhängig ausgewählt sind aus:

(i) Halogen,
(ii) C_{1-6}-Alkoxy, das ein oder mehrere gleiche oder verschiedene C_{1-6}-Alkoxy aufweisen kann,
(iii) Aryloxy, das eines oder mehrere gleiche oder verschiedene Halogene aufweisen kann,
(iv) Heterocyclyl, das ein oder mehrere gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann, das eines oder mehrere gleiche oder verschiedene Halogene aufweisen kann, und
(v) Amino, das ein oder zwei gleiche oder verschiedene C_{1-6}-Alkyl aufweisen kann;

(g) C_{1-6}-Alkoxycarbonyl;
(h) C_{1-6}-Alkylsulfanyl;
(i) Aryl, das eines oder mehrere gleiche oder verschiedene Halogene aufweisen kann;
(j) Aryloxy und
(k) Aralkyloxy, das einen oder mehrere Substituenten aufweisen kann, die unabhängig ausgewählt sind aus:

(i) Halogen,
(ii) C_{1-6}-Alkyl, das eines oder mehrere gleiche oder verschiedene Halogene aufweisen kann, und
(iii) C_{1-6}-Alkoxy, das eines oder mehrere gleiche oder verschiedene Halogene aufweisen kann.

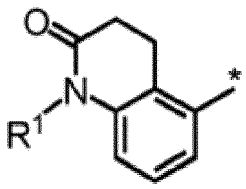
6. Verbindung nach einem der Ansprüche 3 bis 5, oder ein Salz davon, wobei R^1 Wasserstoff ist.

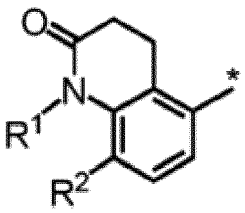
7. Verbindung nach einem der Ansprüche 3 bis 6, oder ein Salz davon, wobei R^2 Halogen ist.

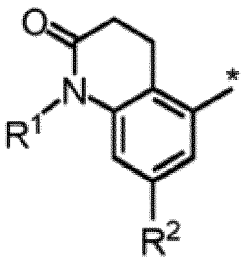
8. Verbindung nach einem der Ansprüche 3 bis 7, oder ein Salz davon, wobei m 0, 1 oder 2 ist.

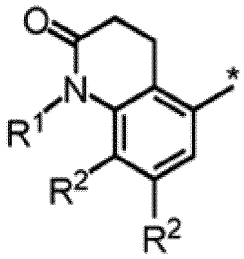
9. Verbindung nach einem der Ansprüche 3 bis 8, oder ein Salz davon, wobei n 0, 1 oder 2 ist.

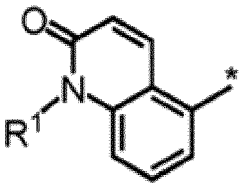
10. Verbindung nach Anspruch 3, oder ein Salz davon, wobei die Teilstruktur (X) eine Struktur einer Formel ist, die aus der Gruppe ausgewählt ist, die aus den Formeln (X1-1), (X1-2), (X1-3), (X1-4, (X1-6) und (X1-7) besteht:


(X1-1)

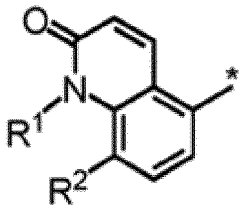

(X1-2)


(X1-3)


(X1-4)

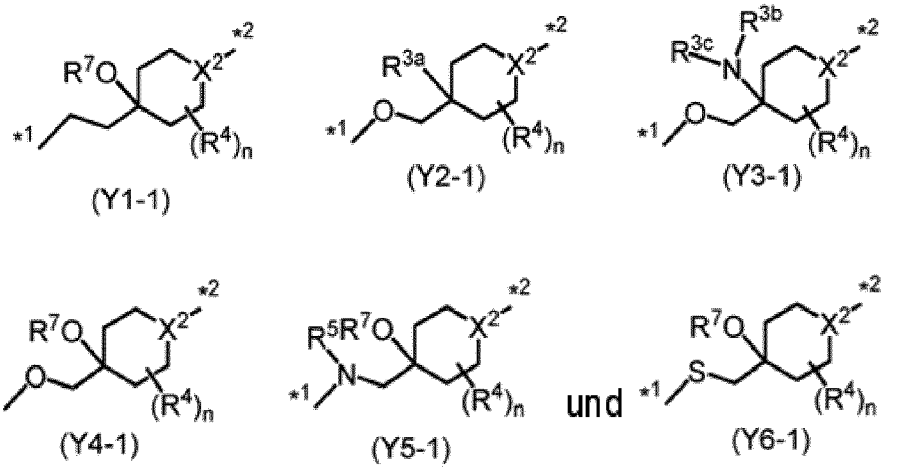

(X1-6)

und


(X1-7)

,

wobei * der Bindungspunkt an X^1 ist;
R^1 Wasserstoff ist;
R^2 ein Substituent ausgewählt aus (1) Halogen oder (2) C_{1-6}-Alkyl ist;
vorausgesetzt, dass, wenn R^2 mehrfach sein kann, jedes von ihnen voneinander verschieden sein kann; die Teilstruktur (Y) eine Struktur einer Formel ist, die aus der Gruppe ausgewählt ist, die aus den Formeln (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y5-1) und (Y6-1) ausgewählt ist:



wobei *1 der Bindungspunkt an die Teilstruktur (X) ist;
*2 der Bindungspunkt an Ring A ist;
R^5 Wasserstoff ist;
R^{3a} (1) Wasserstoff oder (2) Halogen ist;
R^{3b} und R^{3c} jeweils Wasserstoff sind;
R^7 Wasserstoff ist;
R^4 ein Substituent ausgewählt aus (1) Halogen, (2) -O-R^8, (3) -O-C(=O)-R^9 oder (4) Cyano ist;
R^8 (1) Wasserstoff oder (2) C_{1-6}-Alkyl ist;
R^9 (1) C_{1-6}-Alkyl oder (2) C_{1-6}-Alkoxy ist;
n eine ganze Zahl von 0 bis 2 ist;
vorausgesetzt, dass, wenn n 2 ist, R^4, R^8, und R^9 jeweils voneinander verschieden sein können und an demselben Kohlenstoffatom substituiert sein können;
X^2 N oder CH ist;
vorausgesetzt, dass, wenn X^2 CH ist, H der Gruppe durch R^4 ersetzt sein kann, das wie oben definiert ist, wobei mehrere R^4s in Formel (1) gleich oder voneinander verschieden sein können; und
Ring A Phenyl oder Pyridyl ist, das 1 bis 3 Gruppen aufweisen kann, die unabhängig ausgewählt sind aus:

(a) Halogen;
(b) C_{1-6}-Alkoxy, das (i) Halogen und (ii) C_{1-6}-Alkoxy aufweisen kann; oder
(c) Aralkyloxy, das ein oder mehrere gleiche oder verschiedene C_{1-6}-Alkoxy aufweisen kann, das eines oder mehrere gleiche oder verschiedene Halogene aufweisen kann; oder

Chinolyl, das 1 bis 2 Halogene aufweisen kann.

11. Verbindung nach Anspruch 3, die aus der Gruppe ausgewählt ist, die aus den folgenden Verbindungen besteht:

5-{[4-Amino-1-(3,5-dichlorpyridin-2-yl)piperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[4-Amino-1-(4-chlor-2-fluorphenyl)piperidin-4-yl]methoxy}-8-chlor-3,4-dihydrochinolin-2(1H)-on;
5-{[4-Amino-1-(4-chlor-2-fluorphenyl)piperidin-4-yl]methoxy}-8-chlorchinolin-2(1H)-on;
5-{[1-(4-Chlorpheny])-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Ethoxy-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
8-Chlor-5-{[1-(4-chlor-2,6-difluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Brom-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}chinolin-2(1H)-on;
8-Chlor-5-{[1-(3,5-dichlorpyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
8-Fluor-5-{[1-(2-fluor-4-{[4-(trifluormethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
8-Chlor-5-({1-[4-chlor-2-fluor-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluor-3,4-dihydrochinolin-2(1H)-on;

5-{[1-(2,4-Dichlor-5-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluor-8-methyl-3,4-dihydrochinolin-2(1H)-on;
8-Chlor-7-fluor-5-{[4-hydroxy-1-(2,4,6-trifluorphenyl)piperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(3,5-Dichlorpyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4S)-1-(3,5-Dichlorpyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Chlor-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4S)-1-(4-Chlor-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(3-Brom-6-chlorchinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Brom-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4R)-1-(4-Chlor-2,6-difluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4S)-1-(4-Brom-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chlor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R*,4R*)-1-(4-Brom-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluorchinolin-2(1H)-on;
5-({[1-(3,5-Dichlorpyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(3,5-Dichlorpyridin-2-yl)piperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(3,5-Dichlorpyridin-2-yl)-4-fluorpiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R*,4R*)-1-(4-Chlor-2-fluorphenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4S)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4R)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4S)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-ylethylcarbonat;
(3R,4R)-1-(4-Chlor-2-fluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-ylacetat;
5-({[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{2-[1-(4-Chlor-2,6-difluorphenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[trans-4-(4-Chlor-2-fluorphenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[cis-4-(4-Chlor-2-fluorphenyl)-1-hydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(1R*,2R*,4R*)-4-(4-Chlor-2-fluorphenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(1R,2R,4S)-4-(4-Chlor-2-fluorphenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
trans-1-(4-Chlor-2-fluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxycyclohexancarbonitril; und
5-{[trans-4-(4-Chlor-2-fluorphenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on, oder ein Salz davon.

12. Verbindung nach Anspruch 3, die aus der Gruppe ausgewählt ist, die aus den folgenden Verbindungen besteht:

5-{[4-Amino-1-(3,5-dichlorpyridin-2-yl)piperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[4-Amino-1-(4-chlor-2-fluorphenyl)piperidin-4-yl]methoxy}-8-chlor-3,4-dihydrochinolin-2(1H)-on;
5-{[4-Amino-1-(4-chlor-2-fluorphenyl)piperidin-4-yl]methoxy}-8-chlorchinolin-2(1H)-on;
5-{[1-(4-Chlorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;

5-{ [1-(4-Ethoxy-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
8-Chlor-5-{[1-(4-chlor-2,6-difluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
5-{ [1-(4-Brom-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}chinolin-2(1H)-on;
8-Chlor-5-{[1-(3,5-dichlorpyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
8-Fluor-5-{[1-(2-fluor-4-{[4-(trifluormethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
8-Chlor-5-({1-[4-chlor-2-fluor-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(2,4-Dichlor-5-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluor-8-methyl-3,4-dihydrochinolin-2(1H)-on;
8-Chlor-7-fluor-5-{[4-hydroxy-1-(2,4,6-trifluorphenyl)piperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(3,5-Dichlorpyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4S)-1-(3,5-Dichlorpyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Chlor-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4S)-1-(4-Chlor-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(3-Brom-6-chlorchinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Brom-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4R)-1-(4-Chlor-2,6-difluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4S)-1-(4-Brom-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chlor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R*,4R*)-1-(4-Brom-2-fluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluorchinolin-2(1H)-on;
5-({[1-(3,5-Dichlorpyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(3,5-Dichlorpyridin-2-yl)piperidin-4-yl] methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[1-(3,5-Dichlorpyridin-2-yl)-4-fluorpiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R*,4R*)-1-(4-Chlor-2-fluorphenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4S)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4R)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(3S,4S)-1-(4-Chlor-2,6-difluorphenyl)-3-fluor-4-hydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-ylethylcarbonat;
(3R,4R)-1-(4-Chlor-2-fluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-ylacetat;
5-({[1-(4-Chlor-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{2-[1-(4-Chlor-2,6-difluorphenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[trans-4-(4-Chlor-2-fluorphenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[cis-4-(4-Chlor-2-fluorpheny])-1-hydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(1R*,2R*,4R*)-4-(4-Chlor-2-fluorphenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
5-{[(1R,2R,4S)-4-(4-Chlor-2-fluorphenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on;
trans-1-(4-Chlor-2-fluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxycyclohexancarbonitril; und

5-{[trans-4-(4-Chlor-2-fluorphenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on.

13. Verbindung nach Anspruch 3, wobei es sich um 8-Chlor-5-{ [1-(4-chlor-2,6-difluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on oder ein Salz davon handelt.

14. Verbindung nach Anspruch 3, wobei es sich um 8-Chlor-5-{ [1-(4-chlor-2,6-difluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydrochinolin-2(1H)-on handelt.

15. Verbindung nach Anspruch 3, wobei es sich um 5-{[1-(4-Brom-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluor-3,4-dihydrochinolin-2(1H)-on oder ein Salz davon handelt.

16. Verbindung nach Anspruch 3, wobei es sich um 5-{[1-(4-Brom-2-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluor-3,4-dihydrochinolin-2(1H)-on handelt.

17. Verbindung nach Anspruch 3, wobei es sich um 5-{ [1-(2,4-Dichlor-5-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluor-8-methyl-3,4-dihydrochinolin-2(1H)-on oder ein Salz davon handelt.

18. Verbindung nach Anspruch 3, wobei es sich um 5-{ [1-(2,4-Dichlor-5-fluorphenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluor-8-methyl-3,4-dihydrochinolin-2(1H)-on handelt.

19. Verbindung nach Anspruch 3, wobei es sich um 5-{[(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on oder ein Salz davon handelt.

20. Verbindung nach Anspruch 3, wobei es sich um 5-{[(3R,4R)-1-(4-Chlor-2,6-difluorphenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluor-3,4-dihydrochinolin-2(1H)-on handelt.

21. Verbindung nach Anspruch 3, wobei es sich um (3R,4R)-1-(4-Chlor-2-fluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-ylacetat oder ein Salz davon handelt.

22. Verbindung nach Anspruch 3, wobei es sich um (3R,4R)-1-(4-Chlor-2-fluorphenyl)-4-{[(8-fluor-2-oxo-1,2,3,4-tetrahydrochinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-ylacetat handelt.

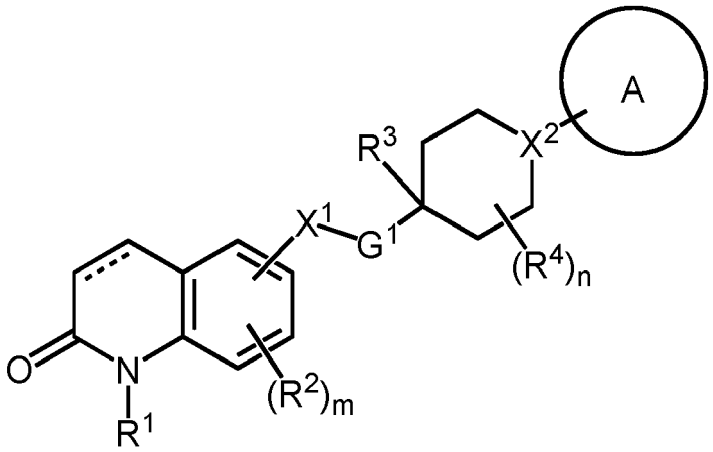
23. Pharmazeutische Zusammensetzung, umfassend die Verbindung nach einem der Ansprüche 3 bis 22 oder ein Salz davon und einen pharmazeutisch annehmbaren Träger.

24. Mittel zur Diagnose, Vorbeugung und/oder Behandlung von Tuberkulose, umfassend die Verbindung nach einem der Ansprüche 3 bis 22 oder ein Salz davon und einen pharmazeutisch annehmbaren Träger.

25. Verbindung nach einem der Ansprüche 3 bis 22 oder ein Salz davon zur Verwendung zur Diagnose, Vorbeugung und/oder Behandlung von Tuberkulose.

Revendications

1. Composé de formule générale (1) pour une utilisation pour le diagnostic, la prévention et/ou le traitement de la tuberculose :



(1)

ou un sel correspondant, le fragment :

représentant une simple liaison ou une double liaison ; et

R^1 représentant

(1) hydrogène,
(2) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents ou
(3) C_{1-6}-alkyle ;

R^2 représentant

(1) halogène,
(2) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents,
(3) C_{1-6}-alkyle,
(4) C_{1-6}-alcoxyle ou
(5) hydroxyle ;

m étant un entier de 0 jusqu'à 3 ;
étant entendu que lorsque m est 2 ou 3, les R^2 peuvent être différents les uns des autres ;
X^1 représentant $-CH_2-$, -O-, $-N(R^5)-$, -S-, -SO- ou $-SO_2-$;
R^5 représentant

(1) hydrogène,
(2) C_{1-6}-alkyle ou
(3) C_{1-7}-alcanoyle ;

G^1 représentant C_{1-6}-alkylène ;
R^3 représentant

(1) hydrogène,
(2) carboxyle,
(3) halogène,
(4) C_{1-6}-alkyle, pouvant comporter un ou plusieurs hydroxyle
(5) cyano,
(6) amino pouvant comporter un ou deux substituants indépendamment choisi(s) parmi :

(a) C_{1-6}-alkyle et

(b) -C(=O)-R^6 ou

(7) -O-R^7 ;

R^6 représentant

(1) C_{1-6}-alcoxyle ou
(2) C_{1-6}-alkyle, le C_{1-6}-alkyle pouvant comporter amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents ;

R^7 représentant

(1) hydrogène,
(2) amino,
(3) C_{1-7}-alcanoyle ou
(4) C_{1-6}-alkyle ;

R^4 représentant

(1) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents,
(2) halogène,
(3) cyano,
(4) C_{1-6}-alkyle
(5) oxo,
(6) -O-R^8 ou
(7) -O-C(=O)-R^9 ;

R^8 représentant

(1) hydrogène,
(2) C_{1-6}-alkyle,
(3) -PH(=O)OH ou
(4) benzyle pouvant comporter un ou plusieurs C_{1-6}-alcoxyle identiques ou différents ;

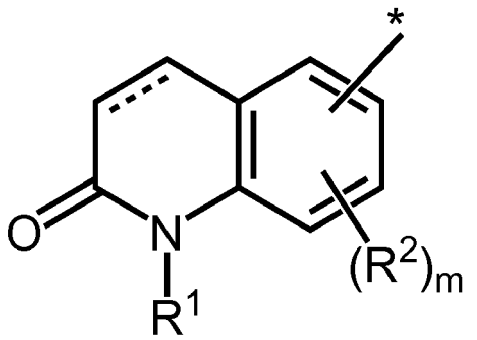
R^9 représentant

(1) C_{1-6}-alkyle,
(2) -G^2-COOH,
(3) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents,
(4) C_{1-6}-alcoxyle ou
(5) pyrazinyle ;

G^2 représentant C_{1-6}-alkylène ;
n étant un entier de 0 jusqu'à 8 ;
étant entendu que lorsque n est 2 ou plus, chacun parmi R^4, R^8, R^9 et G^2 peut être différent des autres et peut être substitué sur le même atome de carbone ;
X^2 représentant N ou CH ;
étant entendu que lorsque X^2 représente CH, H de ce groupe peut être remplacé par R^4 qui est tel que défini ci-dessus, plusieurs R^4 dans la formule (1) pouvant être identiques ou différents les uns des autres ; et
le cycle A représentant

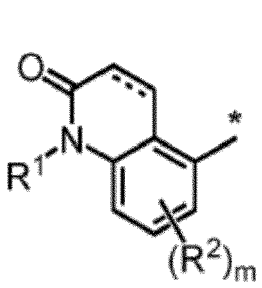
(1) aryle pouvant comporter un ou plusieurs substituant(s) ou
(2) hétérocyclyle pouvant comporter un ou plusieurs substituant(s).

2. Composé pour une utilisation selon la revendication 1 ou un sel correspondant, une structure partielle (X) de la formule (1) étant représentée par la structure partielle suivante :

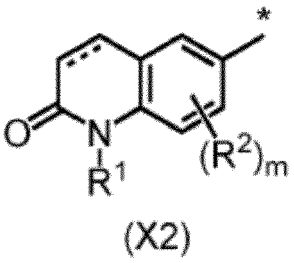


(X)

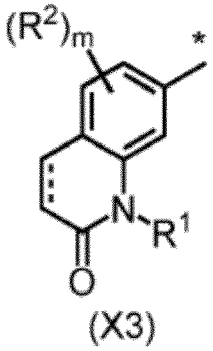
*représentant le point de liaison à X^1 ; et les autres symboles étant tels que définis selon la revendication 1 et la structure partielle (X) étant l'une quelconque des structures choisies dans le groupe constitué par les formules suivantes (X1) jusqu'à (X6) :



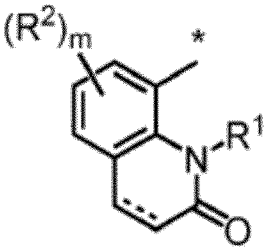
(X1)



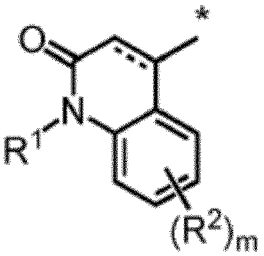
(X2)



(X3)

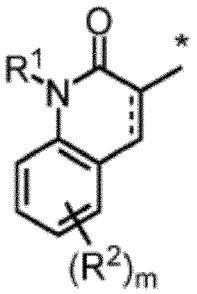


(X4)



(X5)

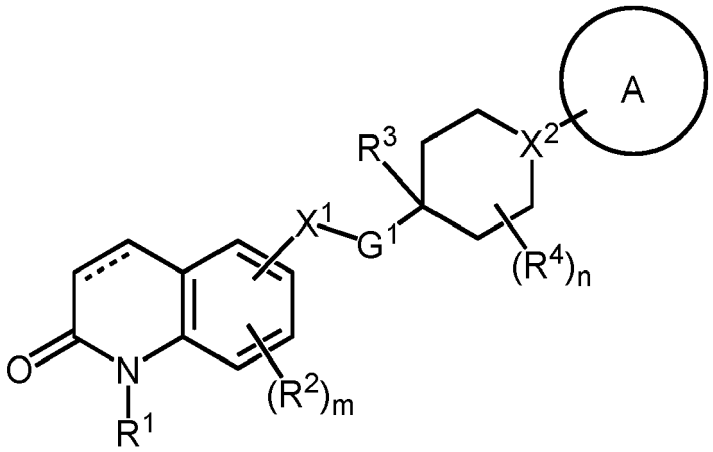
et



(X6)

les symboles étant tels que définis ci-dessus et selon la revendication 1.

3. Composé de formule générale (1) :



(1)

ou un sel correspondant,
le fragment :

représentant une simple liaison ou une double liaison ; et

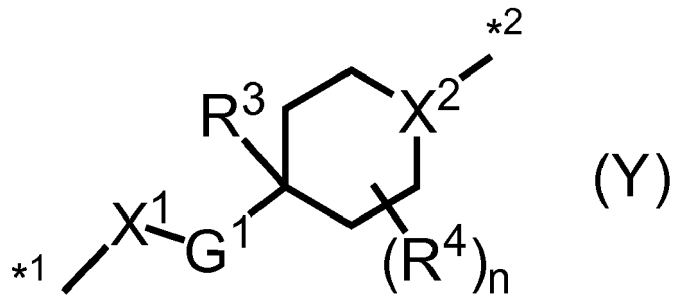
R^1 représentant

(1) hydrogène,
(2) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents ou
(3) C_{1-6}-alkyle ;

R^2 représentant

(1) halogène,
(2) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents,
(3) C_{1-6}-alkyle,
(4) C_{1-6}-alcoxyle ou
(5) hydroxyle ;

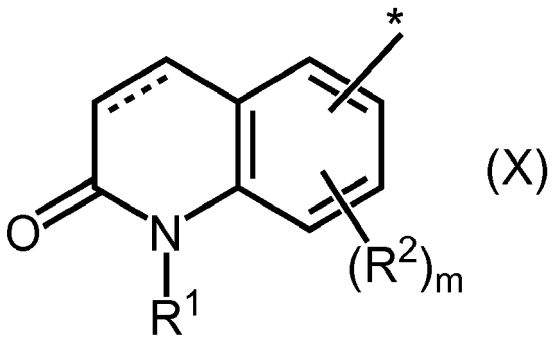
m étant un entier de 0 jusqu'à 3 ;
étant entendu que lorsque m est 2 ou 3, les R^2 peuvent être différents les uns des autres ;
une structure partielle (Y) de la formule (1) étant représentée par la structure partielle suivante :



(Y)

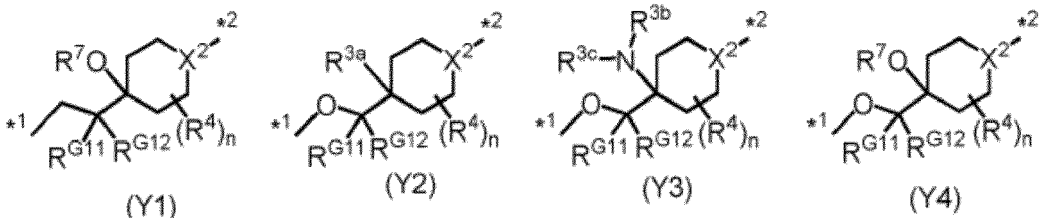
,

*1 représentant un point de liaison à une structure partielle (X) de la formule (1) et *2 étant un point de liaison au cycle A et la structure partielle (X) de la formule (1) étant représentée par la structure partielle suivante :

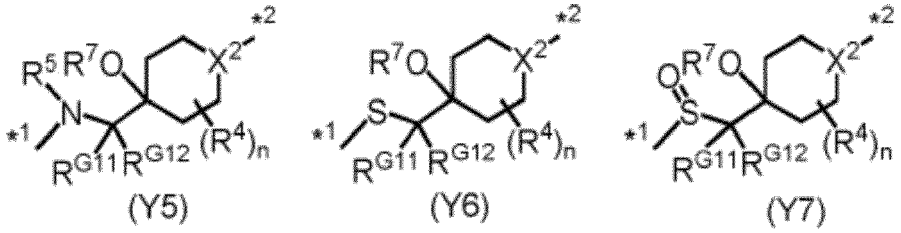


(X)

* représentant un point de liaison à X^1,
la structure partielle (Y) étant l'une quelconque des structures choisies dans le groupe constitué par les formules suivantes (Y1) jusqu'à (Y8) :

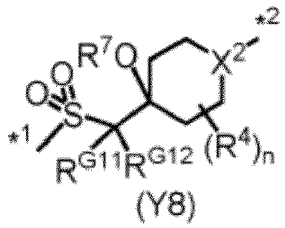


(Y1) (Y2) (Y3) (Y4)



(Y5) (Y6) (Y7)

et



(Y8)

,

R^{3a} représentant

(1) hydrogène,
(2) carboxyle,
(3) halogène,
(4) C_{1-6}-alkyle, pouvant comporter un ou plusieurs hydroxyle ou
(5) cyano ;

R^{3b} et R^{3c} représentant chacun indépendamment

(1) hydrogène,
(2) C_{1-6}-alkyle ou

(3) -C(=O)-R^6 ;

R^{G11} et R^{G12} représentant chacun indépendamment hydrogène ou C_{1-6}-alkyle ;
le nombre total d'atomes de carbone dans R^{G11} et R^{G12} étant de 0 jusqu'à 5;
R^5 représentant

(1) hydrogène,
(2) C_{1-6}-alkyle ou
(3) C_{1-7}-alcanoyle ;

R^6 représentant

(1) C_{1-6}-alcoxyle ou
(2) C_{1-6}-alkyle, le C_{1-6}-alkyle pouvant comporter amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents ;

R^7 représentant

(1) hydrogène,
(2) amino,
(3) C_{1-7}-alcanoyle ou
(4) C_{1-6}-alkyle ;

R^4 représentant

(1) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents,
(2) halogène,
(3) cyano,
(4) C_{1-6}-alkyle,
(5) oxo,
(6) -O-R^8 ou
(7) -O-C(=O)-R^9 ;

R^8 représentant

(1) hydrogène,
(2) C_{1-6}-alkyle,
(3) -PH(=O)OH ou
(4) benzyle pouvant comporter un ou plusieurs C_{1-6}-alcoxyle identiques ou différents ;

R^9 représentant

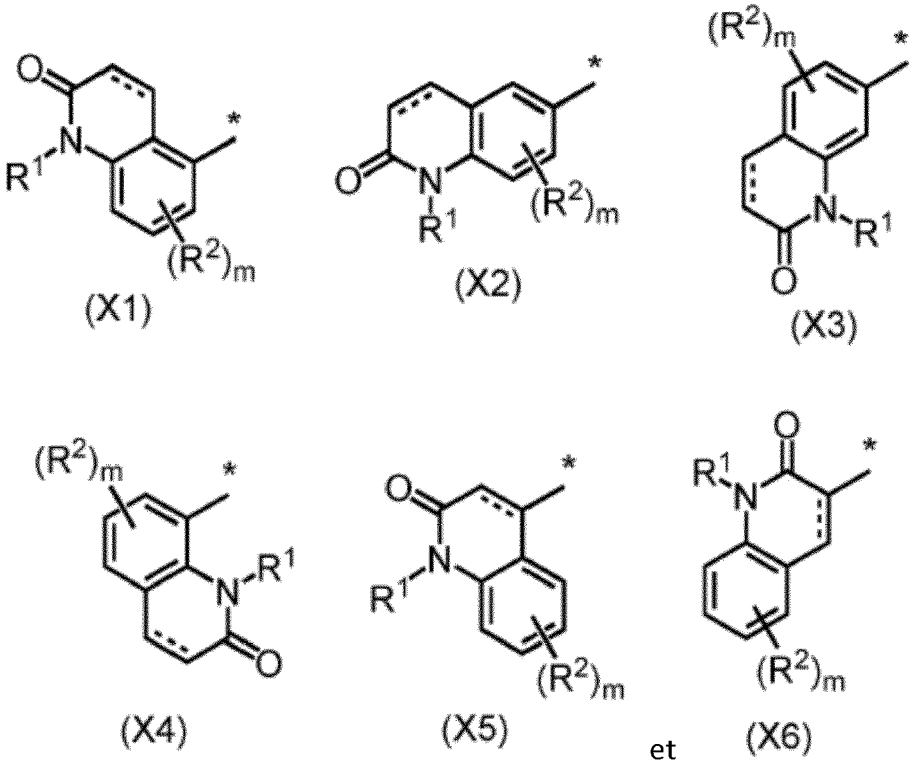
(1) C_{1-6}-alkyle,
(2) -G^2-COOH,
(3) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents,
(4) C_{1-6}-alcoxyle ou
(5) pyrazinyle ;

G^2 représentant C_{1-6}-alkylène ;
n étant un entier de 0 jusqu'à 8 ;
étant entendu que lorsque n est 2 ou plus, chacun parmi R^4, R^8, R^9 et G^2 peut être différent des autres et peut être substitué sur le même atome de carbone ;
X^2 représentant N ou CH ;
étant entendu que lorsque X^2 représente CH, H de ce groupe peut être remplacé par R^4 qui est tel que défini ci-dessus, plusieurs R^4 dans la formule (1) pouvant être identiques ou différents les uns des autres ; et
le cycle A représentant

(1) aryle pouvant comporter un ou plusieurs substituant(s) ou

(2) hétérocyclyle pouvant comporter un ou plusieurs substituant(s).

4. Composé selon la revendication 3 ou un sel correspondant, la structure partielle (X) étant l'une quelconque des structures choisies dans le groupe constitué par les formules suivantes (X1) jusqu'à (X6) :



les symboles étant tels que définis ci-dessus et selon la revendication 3.

5. Composé selon la revendication 3 ou 4 ou un sel correspondant, le cycle A représentant aryle ou hétérocyclyle pouvant comporter 1 jusqu'à 5 substituants indépendamment choisis parmi :

(a) halogène ;
(b) cyano ;
(c) nitro ;
(d) hydroxyle ;
(e) C_{1-6}-alkyle pouvant comporter un ou plusieurs substituant(s) indépendamment choisi(s) parmi :

(i) halogène,
(ii) hydroxyle,
(iii) C_{1-6}-alcoxyle et
(iv) aryloxyle pouvant comporter un ou plusieurs halogène(s) identiques ou différents ;

(f) C_{1-6}-alcoxyle pouvant comporter un ou plusieurs substituant(s) indépendamment choisi(s) parmi :

(i) halogène,
(ii) C_{1-6}-alcoxyle pouvant comporter un ou plusieurs C_{1-6}-alcoxyle identiques ou différents,
(iii) aryloxyle pouvant comporter un ou plusieurs halogène(s) identiques ou différents,
(iv) hétérocyclyle pouvant comporter un ou plusieurs C_{1-6}-alkyle identiques ou différents pouvant comporter un ou plusieurs halogène(s) identiques ou différents et
(v) amino pouvant comporter un ou deux C_{1-6}-alkyle identiques ou différents ;

(g) C_{1-6}-alcoxycarbonyle ;
(h) C_{1-6}-alkylsulfanyle ;

(i) aryle pouvant comporter un ou plusieurs halogène(s) identiques ou différents ;
(j) aryloxyle ; et
(k) aralkyloxyle pouvant comporter un ou plusieurs substituant(s) identiques ou différents indépendamment choisi(s) parmi :

(i) halogène,
(ii) C_{1-6}-alkyle pouvant comporter un ou plusieurs halogène(s) identiques ou différents et
(iii) C_{1-6}-alcoxyle pouvant comporter un ou plusieurs halogène(s) identiques ou différents.

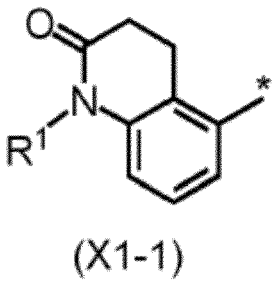
6. Composé selon l'une quelconque des revendications 3 à 5 ou un sel correspondant, R^1 représentant hydrogène.

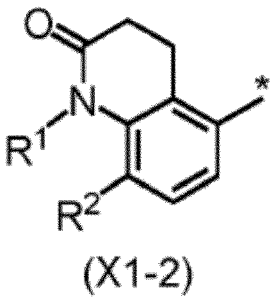
7. Composé selon l'une quelconque des revendications 3 à 6 ou un sel correspondant, R^2 représentant halogène.

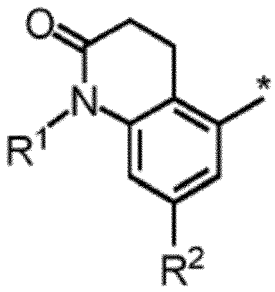
8. Composé selon l'une quelconque des revendications 3 à 7 ou un sel correspondant, m étant 0, 1 ou 2.

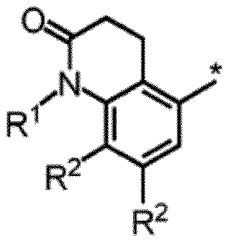
9. Composé selon l'une quelconque des revendications 3 à 8 ou un sel correspondant, n étant 0, 1 ou 2.

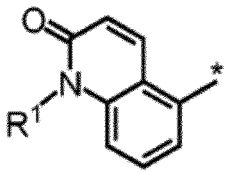
10. Composé selon la revendication 3 ou un sel correspondant, la structure partielle (X) étant une structure d'une formule choisie dans le groupe constitué par les formules (X1-1), (X1-2), (X1-3), (X1-4), (X1-6) et (X1-7) :

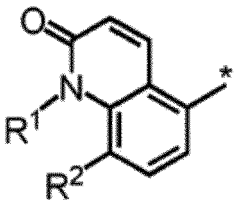

(X1-1)


(X1-2)


(X1-3)

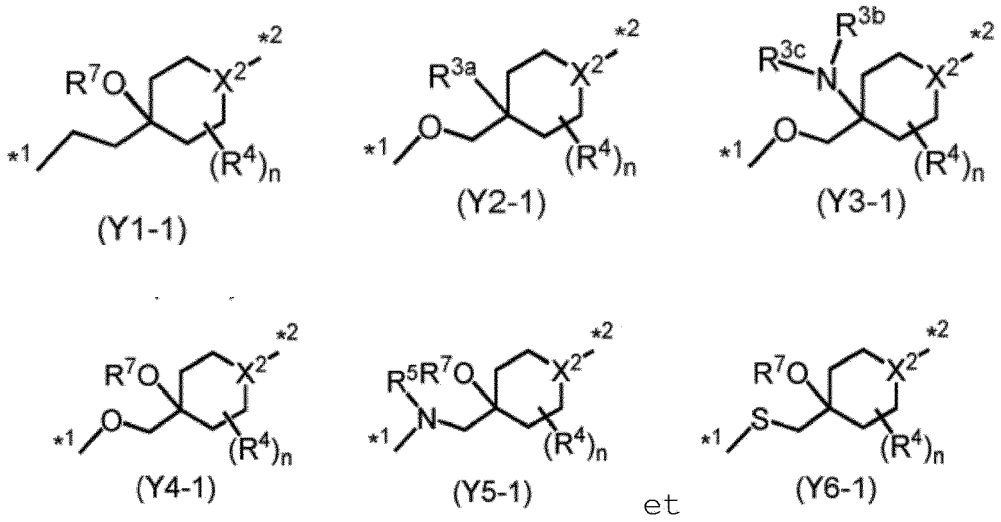

(X1-4)


(X1-6)


(X1-7)

et

* représentant le point de liaison à X^1 ;
R^1 représentant hydrogène ;
R^2 représentant un substituant choisi parmi (1) halogène ou (2) C_{1-6}-alkyle ;
étant entendu que lorsqu'on a plusieurs R^2, chacun peut être différent des autres ;
la structure partielle (Y) étant une structure d'une formule choisie dans le groupe constitué par les formules (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y5-1) et (Y6-1) :



et

*1 représentant le point de liaison à la structure partielle (X) ;
*2 représentant le point de liaison au cycle A ;
R^5 représentant hydrogène ;
R^{3a} représentant (1) hydrogène ou (2) halogène ;
R^{3b} et R^{3c} représentant chacun hydrogène ;
R^7 représentant hydrogène ;
R^4 représentant un substituant choisi parmi (1) halogène, (2) -O-R^8, (3) -O-C(=O)-R^9 ou (4) cyano ;
R^8 représentant (1) hydrogène ou (2) C_{1-6}-alkyle ;
R^9 représentant (1) C_{1-6}-alkyle ou (2) C_{1-6}-alcoxyle ;
n étant un entier de 0 jusqu'à 2 ;
étant entendu que lorsque n est 2, chacun parmi R^4, R^8 et R^9 peut être différent des autres et peut être substitué sur le même atome de carbone ;
X^2 représentant N ou CH ;
étant entendu que lorsque X^2 représente CH, H de ce groupe peut être remplacé par R^4 qui est tel que défini ci-dessus, plusieurs R^4 dans la formule (1) pouvant être identiques ou différents les uns des autres ; et
le cycle A représentant phényle ou pyridyle pouvant comporter 1 jusqu'à 3 groupes indépendamment choisis parmi :

(a) halogène ;
(b) C_{1-6}-alcoxyle pouvant comporter (i) halogène et (ii) C_{1-6}-alcoxyle ; ou
(c) aralkyloxyle pouvant comporter un ou plusieurs C_{1-6}-alcoxyle identiques ou différents pouvant comporter un ou plusieurs halogène(s) identiques ou différents ; ou

quinoléyle pouvant comporter 1 ou 2 halogène (s) .

11. Composé selon la revendication 3, qui est choisi dans le groupe constitué par les composés suivants :

5-{ [4-amino-1-(3,5-dichloropyridin-2-yl)pipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[4-amino-1-(4-chloro-2-fluorophényl)pipéridin-4-yl]méthoxy}-8-chloro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[4-amino-1-(4-chloro-2-fluorophényl)pipéridin-4-yl]méthoxy}-8-chloroquinoléin-2(1*H*)-one ;
5-{[1-(4-chlorophényl)-4-hydroxypipéridin-4-yl]méthoxyl-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-éthoxy-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
8-chloro-5-{[1-(4-chloro-2,6-difluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-bromo-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7,8-difluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}quinoléin-2(1*H*)-one ;
8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
8-fluoro-5-{[1-(2-fluoro-4-{ [4-(trifluorométhoxy)benzyl]oxy}phényl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihy-

droquinoléin-2(1*H*)-one ;
8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-méthoxyéthoxy)phényl]-4-hydroxypipéridin-4-yl}méthoxy)-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(2,4-dichloro-5-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7-fluoro-8-méthyl-3,4-dihydroquinoléin-2(1*H*)-one ;
8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophényl)pipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*S*)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(4-chloro-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*S*)-1-(4-chloro-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(3-bromo-6-chloroquinoléin-2-yl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(4-bromo-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*S*)-1-(4-bromo-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-chloro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R**,4*R**)-1-(4-bromo-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoroquinoléin-2(1*H*)-one ;
5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypipéridin-4-yl]méthyl}amino)-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(3,5-dichloropyridin-2-yl)pipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R**,4*R**)-1-(4-chloro-2-fluorophényl)-3-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*S*)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*S*)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
éthylcarbonate de (3*R*,4*R*)-1-(4-chloro-2,6-difluorophényl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxypipéridin-3-yle ;
acétate de (3*R*,4*R*)-1-(4-chloro-2-fluorophényl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxypipéridin-3-yle ;
5-({[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthyl}sulfanyl)-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{2-[1-(4-chloro-2,6-difluorophényl)-4-hydroxypipéridin-4-yl]éthyl}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[trans-4-(4-chloro-2-fluorophényl)-1,4-dihydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[*cis*-4-(4-chloro-2-fluorophényl)-1-hydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(1*R**,2*R**,4*R**)-4-(4-chloro-2-fluorophényl)-1,2-dihydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(1*R*,2*R*,4*S*)-4-(4-chloro-2-fluorophényl)-1,2,4-trihydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
trans-1-(4-chloro-2-fluorophényl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxycyclohexanecarbonitrile ; et
5-{[*trans*-4-(4-chloro-2-fluorophényl)-1-hydroxy-4-méthoxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-

2(1*H*)-one ou un sel correspondant.

12. Composé selon la revendication 3, qui est choisi dans le groupe constitué par les composés suivants :

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)pipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[4-amino-1-(4-chloro-2-fluorophényl)pipéridin-4-yl]méthoxy}-8-chloro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[4-amino-1-(4-chloro-2-fluorophényl)pipéridin-4-yl]méthoxy}-8-chloroquinoléin-2(1*H*)-one ;
5-{[1-(4-chlorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-éthoxy-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
8-chloro-5-{[1-(4-chloro-2,6-difluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-bromo-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7,8-difluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}quinoléin-2(1*H*)-one ;
8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluorométhoxy)benzyl]oxy}phényl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-méthoxyéthoxy)phényl]-4-hydroxypipéridin-4-yl}méthoxy)-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(2,4-dichloro-5-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7-fluoro-8-méthyl-3,4-dihydroquinoléin-2(1*H*)-one ;
8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophényl)pipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*S*)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(4-chloro-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*S*)-1-(4-chloro-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(3-bromo-6-chloroquinoléin-2-yl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*R*)-1-(4-bromo-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*S*)-1-(4-bromo-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-chloro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R**,4*R**)-1-(4-bromo-2-fluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoroquinoléin-2(1*H*)-one ;
5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypipéridin-4-yl]méthyl}amino)-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(3,5-dichloropyridin-2-yl)pipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R**,4*R**)-1-(4-chloro-2-fluorophényl)-3-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*R*,4*S*)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3*S*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3R,4R)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(3S,4S)-1-(4-chloro-2,6-difluorophényl)-3-fluoro-4-hydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;

éthylcarbonate de (3*R*,4*R*)-1-(4-chloro-2,6-difluorophényl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxypipéridin-3-yle ;
acétate de (3*R*,4*R*)-1-(4-chloro-2-fluorophényl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxypipéridin-3-yle ;
5-({[1-(4-chloro-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthyl}sulfanyl)-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{2-[1-(4-chloro-2,6-difluorophényl)-4-hydroxypipéridin-4-yl]éthyl}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[*trans*-4-(4-chloro-2-fluorophényl)-1,4-dihydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[*cis*-4-(4-chloro-2-fluorophényl)-1-hydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(1*R**,2*R**,4*R**)-4-(4-chloro-2-fluorophényl)-1,2-dihydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
5-{[(1*R*,2*R*,4*S*)-4-(4-chloro-2-fluorophényl)-1,2,4-trihydroxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ;
trans-1-(4-chloro-2-fluorophényl)-4-{ [(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxycyclohexanecarbonitrile ; et
5-{[trans-4-(4-chloro-2-fluorophényl)-1-hydroxy-4-méthoxycyclohexyl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one.

13. Composé selon la revendication 3, qui est la 8-chloro-5-{[1-(4-chloro-2,6-difluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one ou un sel correspondant.

14. Composé selon la revendication 3, qui est la 8-chloro-5-{[1-(4-chloro-2,6-difluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-3,4-dihydroquinoléin-2(1*H*)-one.

15. Composé selon la revendication 3, qui est la 5-{[1-(4-bromo-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7,8-difluoro-3,4-dihydroquinoléin-2(1*H*)-one ou un sel correspondant.

16. Composé selon la revendication 3, qui est la 5-{[1-(4-bromo-2-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7,8-difluoro-3,4-dihydroquinoléin-2(1*H*)-one.

17. Composé selon la revendication 3, qui est la 5-{[1-(2,4-dichloro-5-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7-fluoro-8-méthyl-3,4-dihydroquinoléin-2(1*H*)-one ou un sel correspondant.

18. Composé selon la revendication 3, qui est la 5-{[1-(2,4-dichloro-5-fluorophényl)-4-hydroxypipéridin-4-yl]méthoxy}-7-fluoro-8-méthyl-3,4-dihydroquinoléin-2(1*H*)-one.

19. Composé selon la revendication 3, qui est la 5-{[(3*R*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one ou un sel correspondant.

20. Composé selon la revendication 3, qui est la 5-{[(3*R*,4*R*)-1-(4-chloro-2,6-difluorophényl)-3,4-dihydroxypipéridin-4-yl]méthoxy}-8-fluoro-3,4-dihydroquinoléin-2(1*H*)-one.

21. Composé selon la revendication 3, qui est l'acétate de (3R,4R)-1-(4-chloro-2-fluorophényl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxypipéridin-3-yle ou un sel correspondant.

22. Composé selon la revendication 3, qui est l'acétate de (3*R*,4*R*)-1-(4-chloro-2-fluorophényl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tétrahydroquinoléin-5-yl)oxy]méthyl}-4-hydroxypipéridin-3-yle.

23. Composition pharmaceutique, comprenant le composé selon l'une quelconque des revendications 3 à 22 ou un sel correspondant et un véhicule pharmaceutiquement acceptable.

24. Agent pour le diagnostic, la prévention et/ou le traitement de la tuberculose, comprenant le composé selon l'une quelconque des revendications 3 à 22 ou un sel correspondant et un véhicule pharmaceutiquement acceptable.

25. Composé selon l'une quelconque des revendications 3 à 22 ou un sel correspondant, pour une utilisation de diagnostic, de prévention et/ou de traitement de la tuberculose.

REFERENCES CITED IN THE DESCRIPTION

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