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(56) References cited:

EP-A- 1 415 992 **EP-A1- 0 602 306**
EP-A1- 0 947 510 **WO-A-03/000657**
WO-A1-00/09480 **WO-A1-00/59913**
WO-A1-00/76942 **WO-A1-01/07440**
WO-A1-01/74774 **WO-A1-92/04017**
WO-A1-98/45262 **WO-A1-98/57952**
WO-A1-99/54308 **WO-A2-00/64902**
WO-A2-86/07257 **WO-A2-94/20062**
WO-A2-97/10853 **WO-A2-99/32225**

- **PANDEY B R ET AL: "Interrelationship between anticonvulsant and enzyme inhibitor properties of N-methyl-N-[2-(1-arylthiocarbamido) cyclopenty]nitrobenzamides" PHARMACOLOGICAL RESEARCH COMMUNICATIONS, ITALIAN PHARMACOLOGICAL SOCIETY, IT, vol. 13, no. 1, 1981, pages 65-74, XP002977669 ISSN: 0031-6989**
- **BIED, C. ET AL: "Chiral amino-urea derivatives of (1R,2R)-1,2-diaminocyclohexane as ligands in the ruthenium catalyzed asymmetric reduction of aromatic ketones by hydride transfer" TETRAHEDRON: ASYMMETRY , 12(2), 329-336 CODEN: TASYE3; ISSN: 0957-4166, 2001, XP004230915**
- **SMITH, PAUL J. ET AL: "Substrate-specific catalysis via ion pairs" ANGEWANDTE CHEMIE INT. ED. ENGL., 1993, 32(11), 1648-50, 1993, XP002384367**
- **GASPARRINI ET AL. J. CHROMATOGR., A vol. 724, no. 1-2, 1996, pages 79 - 90, XP002942487**
- **TORNEIRO MERCEDES ET AL. TETRAHEDRON vol. 53, no. 26, 1997, pages 8739 - 8750, XP004106087**

Description

TECHNICAL FIELD

[0001] The present invention relates to novel compounds which inhibit activated blood coagulation factor X (hereinafter abbreviated as "FXa") to exhibit a potent anticoagulant effect and can be orally administered, and anticoagulants or agents for preventing and/or treating thrombosis or embolism, which comprise such a novel compound as an active ingredient.

BACKGROUND ART

[0002] WO 00/09480 discloses sulfonyl derivatives having FXa-inhibitory effects.

[0003] In unstable angina, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep venous thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after angioplasty and thrombus formation during extracorporeal circulation, hypercoagulable state is a pivotal factor. Therefore, there is a demand for development of excellent anticoagulants which have good dose responsiveness, long duration, low risk of hemorrhage and little side effects and fast onset of sufficient effects even by oral administration (Thrombosis Research, vol. 68, pp. 507-512, 1992).

[0004] Based on the research of anticoagulants worked through various mechanism of action, it is suggested that FXa inhibitors are promising anticoagulants. A blood coagulation system comprises a series of reactions that a great amount of thrombin is produced through an amplification process by multi-stage enzyme reactions to form insoluble fibrin. In an endogenous system, activated factor IX activates into factor X on a phospholipid membrane in the presence of activated factor VIII and calcium ions after multi-stage reactions subsequent to activation of a contact factor. In an exogenous system, activated factor VII activates factor X in the presence of a tissue factor. More specifically, the activation of the factor X into FXa in the coagulation system is a crucial reaction in the formation of thrombin. The activated factor X (FXa) limitedly decomposes prothrombin to produce thrombin in the both systems. Since the produced thrombin activates coagulation factors in the upper stream, the formation of thrombin is more amplified. As described above, since the coagulation system in the upper stream of FXa is divided into the endogenous system and the exogenous system, production of FXa cannot be sufficiently inhibited by inhibiting enzymes in the coagulation system in the upper stream of FXa, leading to production of thrombin. Since the coagulation system comprises self-amplification reactions, inhibition of the coagulation system can be more efficiently achieved by inhibiting FXa in the upper stream of thrombin than the inhibition of thrombin (Thrombosis Research, Vol. 15, pp. 617-629, 1979).

[0005] An another excellent point of FXa inhibitors is a great difference between an effective dose in a thrombosis model and a dose elongating bleeding time in an experimental hemorrhagic model. From this experimental result, FXa inhibitors are considered to be anticoagulants having low risk of hemorrhage.

[0006] Various compounds have been reported as FXa inhibitors. It is known that antithrombin III and antithrombin III dependent pentasacchrides can generally not inhibit prothrombinase complexes which play a practical role in the thrombus formation in a living body (Thrombosis Research, Vol. 68, pp. 507-512, 1992; Journal of Clinical Investigation, Vol. 71, pp. 1383-1389, 1983; Mebio, Vol. 14, the August number, pp. 92-97). In addition, they do not exhibit effectiveness by oral administration. Tick anticoagulant peptide (TAP) (Science, Vol. 248, pp. 593-596, 1990) and antistasin (AST) (Journal of Biological Chemistry, Vol. 263, pp. 10162-10167, 1988) isolated from mites or leeches, which are bloodsuckers, also inhibit Fxa and exhibit anti-thrombotic effects against venous thrombosis and arterial thrombosis. However, these compounds are high-molecular weight peptides and unavailable in oral administration. As described above, development of antithrombin III independent low-molecular weight FXa inhibitors which directly inhibit coagulation factors has been conducted.

[0007] It is therefore an object of the present invention to provide a novel compound which has a potent FXa-inhibiting effect and exhibits an anti-thrombotic effect quickly, sufficiently and persistently by oral administration.

DISCLOSURE OF THE INVENTION

[0008] The present inventors have investigated synthesis and pharmacological effects of novel FXa inhibitors. As a result, diamine derivatives, salts thereof, and solvates and N-oxides thereof, which exhibit potent FXa-inhibiting effect and anticoagulant effect, have been found. It has also been found that these compounds promptly, persistently and potently inhibit FXa and exhibit potent anticoagulant effect and anti-thrombotic effect by oral administration, and are hence useful as prophylactics and remedies for various diseases based on thromboembolism, thus leading to completion of the present invention.

[0009] This invention provides a compound represented by the general formula (1):

Q^1-Q^2-T^0-$N(R^1)$-Q^3-$N(R^2)$-T^1-Q^4 (1)

which is further defined in claim 1;
a salt thereof, a solvate thereof, or an N-oxide thereof.

[0010] This invention also provides a medicine, an activated blood coagulation factor X inhibitor, an anticoagulant, an agent for preventing and/or treating thrombosis or embolism and an agent for preventing and/or treating cerebral infarction, cerebral embolism, myocardial infarction, angina pectoris, pulmonary infarction, pulmonary embolism, Buerger's disease, deep venous thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve or joint replacement, thrombus formation and reocclusion after angioplasty, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), thrombus formation during extracorporeal circulation, or blood clotting upon blood gathering, which each comprises the compound represented by the general formula (1), the salt thereof, the solvate thereof, or N-oxide thereof.

[0011] This invention further provides an intermediate useful for preparing the compound represented by the general formula (1).

[0012] This invention still further provides use of the compound represented by the general formula (1), the salt thereof, the solvate thereof, or N-oxide thereof for preparation of a medicine.

[0013] A method for treating thrombosis or embolism, which comprises administering an effective amount of the compound represented by the general formula (1), the salt thereof, the solvate thereof, or N-oxide thereof, is also disclosed.

BEST MODE FOR CARRYING OUT THE INVENTION

[0014] Substituents in the diamine derivatives according to the present invention represented by the general formula (1) will hereinafter be described.

<On group Q^4>

[0015] The group Q^4 means a phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl, 4-ethynylphenyl, 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl, 3-ethynylphenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chloro-2-fluorophenyl, 2-chloro-4-fluorophenyl, 4-bromo-2-fluorophenyl, 2-bromo-4-fluorophenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dibromophenyl, 4-chloro-3-methylphenyl, 4-fluoro-3-methylphenyl, 4-bromo-3-methylphenyl, 4-chloro-2-methylphenyl, 4-fluoro-2-methylphenyl, 4-bromo-2-methylphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dibromophenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-chloro-2-pyridyl, 4-fluoro-2-pyridyl, 4-bromo-2-pyridyl, 4-ethynyl-2-pyridyl, 4-chloro-3-pyridyl, 4-fluoro-3-pyridyl, 4-bromo-3-pyridyl, 4-ethynyl-3-pyridyl, 5-chloro-2-pyridyl, 5-fluoro-2-pyridyl, 5-bromo-2-pyridyl, 5-ethynyl-2-pyridyl, 4-chloro-5-fluoro-2-pyridyl, 5-chloro-4-fluoro-2-pyridyl, 5-chloro-3-pyridyl, 5-fluoro-3-pyridyl, 5-bromo-3-pyridyl, 5-ethynyl-3-pyridyl, 6-chloro-3-pyridazinyl, 6-fluoro-3-pyridazinyl, 6-bromo-3-pyridazinyl, 6-ethynyl-3-pyridazinyl, 4-chloro-2-thienyl, 4-fluoro-2-thienyl, 4-bromo-2-thienyl, 4-ethynyl-2-thienyl, 4-chloro-2-pyrrolyl, 4-fluoro-2-pyrrolyl, 4-bromo-2-pyrrolyl, 4-ethynyl-2-pyrrolyl, 4-chloro-2-furyl, 4-fluoro-2-furyl, 4-bromo-2-furyl, 4-ethynyl-2-furyl, 5-chloro-2-thienyl, 5-fluoro-2-thienyl, 5-bromo-2-thienyl, 5-ethynyl-2-thienyl , 5-chloro-2-thiazolyl, 5-fluoro-2-thiazolyl, 5-bromo-2-thiazolyl, 5-ethynyl-2-thiazolyl, 5-chloro-2-oxazolyl, 5-fluoro-2-oxazolyl, 5-bromo-2-oxazolyl or 5-ethynyl-2-oxazolyl.

<On group Q^1>

[0016] In the present invention, Q^1 means a saturated or unsaturated, bicyclic or tricyclic fused heterocyclic group which is selected from 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-cyclopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-carboxymethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-butyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-(4-pyridyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl, 5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-2-yl, 6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl, 5-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl, 5-methyl-4,6-dihydro-5H-pyrrolo[3,4-d]thiazol-2-yl, 5,7-dihydro-6-methyl-pyrrolo[3,4-d]pyrimidin-2-yl, 5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazin-2-yl, 5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[4,5-d]pyridazin-2-yl, 5-dimethylamino-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl, 5-(4-pyridyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl and 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl groups.

<On group Q^2>

[0017] The group Q^2 means a single bond.

[0018] The case where Q^2 is a single bond in the above-described combination means that the general formula (1):

Q^1-Q^2-T^0-N(R^1) -Q^3-N(R^2) -T^1-Q^4 (1)

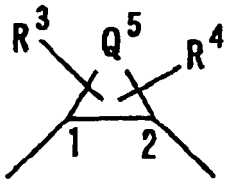
wherein R^1, R^2, Q^1 Q^2, Q^3, Q^4, T^0 and T^1 have the same meanings as defined above, comes to the following general formula (1') :

Q^1-T^0-N(R^1) -Q^3-N(R^2) -T^1-Q^4 (1')

wherein Q^1, R^1, R^2, Q^3, Q^4, T^0 and T^1 have the same meanings as defined above.

< On group Q^3>

[0019] The group Q^3 represents the following group:



in which Q^5 means an alkylene group having 4 carbon atoms, R^3 is a hydrogen atom, and R^4 is an N,N-dialkylcarbamoyl group having two linear, branched or cyclic C1-C6 alkyl groups.

[0020] This cyclic hydrocarbon group or heterocyclic group may have both cis and trans structures in the relation between position 1 and position 2. Both cis-form and trans-form are preferred in the 6- or 7-membered ring.

[0021] Examples of the N,N-dialkylcarbamoyl group means a carbamoyl group substituted with 2 linear, branched or cyclic C_1-C_6 alkyl groups , and examples thereof include N,N-dimethylcarbamoyl group, N,N-diethylcarbamoyl group, N-ethyl-N-methylcarbamoyl group, N-isopropyl-N-methylcarbamoyl group, and the like.

[0022] As specific preferable examples of R^4 may be mentioned N,N-dimethylcarbamoyl group, N,N-diethylcarbamoyl group, N-ethyl-N-methylcarbamoyl group, N-isopropyl-N-methylcarbamoyl group, N-methyl-N-propylcarbamoyl group.

<On group T^0>

[0023] The group T^0 represents a carbonyl group or thiocarbonyl group, with the carbonyl group being preferred.

<On group T^1>

[0024] The group T^1 represents a group -C(=O)-C(=O)-N(R')-, group -C(=S)-C(=O)-N(R')-, group -C(=O)-C(=S)-N(R')-, group -C(=S)-C(=S)-N(R')-, in which R' means a hydrogen atom, hydroxyl group, alkyl group or alkoxy group.

[0025] The alkyl group in R' means a linear, branched or cyclic alkyl group having 1 to 6 carbon atoms, and examples thereof include methyl, ethyl groups and the like. The alkoxy group means a linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms, and examples thereof include methoxy, ethoxy groups and the like.

<On group R^1 and group R^2>

[0026] R^1 and R^2 are, independently of each other, a hydrogen atom, hydroxyl group, alkyl group or alkoxy group, preferably a hydrogen atom or alkyl group, more preferably a hydrogen atom.

[0027] In R^1 and R^2, the alkyl group means a linear, branched or cyclic alkyl group having 1 to 6 carbon atoms, and examples thereof include methyl, ethyl groups and the like. The alkoxy group means a linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms, and examples thereof include methoxy, ethoxy groups and the like. R^1 and R^2 are preferably, independently of each other, a hydrogen atom or alkyl group, more preferably both hydrogen atoms.

[0028] Stereoisomers or optical isomers derived from an asymmetric carbon atom may be present in the compounds of the present invention represented by the general formula (1). However, these stereoisomers, optical isomers and mixtures thereof are all included in the present invention.

[0029] No particular limitation is imposed on salts of the compounds of the present invention represented by the general formula (1) so far as they are pharmaceutically acceptable salts. However, specific examples thereof include mineral acid salts such as hydrochlorides, hydrobromides, hydriodides, phosphates, nitrates and sulfates; benzoates; organic

sulfonates such as methanesulfonates, 2-hydroxyethanesulfonates and p-toluenesulfonates; and organic carboxylates such as acetates, propanoates, oxalates, malonates, succinates, glutarates, adipates, tartrates, maleates, malates and mandelates. In the case where the compounds represented by the general formula (1) have an acidic group, they may be salts of alkali metal ions or alkaline earth metal ions. No particular limitation is imposed on the solvates thereof so far as they are pharmaceutically acceptable solvates. As specific examples thereof, however, may be mentioned hydrates and solvates with ethanol. When a nitrogen atom is present in the general formula (1), such a compound may be converted to an N-oxide thereof.

[0030] As the compounds according to the present invention, are preferred the compounds described in the following Examples and salts thereof as well as the following compounds and salts thereof.

1) N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbothioyl]amino} - cyclohexyl)ethanediamide;

2) N^1-((1S,2R,4S)-4-(1-azetidinylcarbonyl)-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)-N^2-(5-chloropyridin-2-yl)ethanediamide;

3) N^1-(5-Chloropyridin-2-yl)-N^2-[(1S,2R,4S)-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-4-(1-pyrrolidinylcarbonyl)cyclohexyl]-ethanediamide;

4) N^1-(5-Chloropyridin-2-yl)-N^2-[(1S,2R,4S)-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-4-(1-piperidinylcarbonyl)cyclohexyl]-ethanediamide;

5) N^1-{(1R,2S,5S)-2-({2-[(6-Chloropyridazin-3-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)-carbonyl] cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide;

6) N-[(1R,2S,5S)-5-[(Dimethylamino)carbonyl]-2-({2-[(5-fluoro-2-thienyl)amino]-2-oxoethanethioyl}amino)-cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide;

7) N^1-(4-Chlorothiazol-2-yl)-N^2-(1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridin-2-yl)carbonyl] -amino}cyclohexyl)ethanediamide;

8) N^1-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)-N^2-(3-fluorophenyl)-ethanediamide;

9) N^1-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)-N^2-phenylethanediamide;

10) N^1-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl] amino}cyclohexyl)-N^2- (pyridin-2-yl)-ethanediamide;

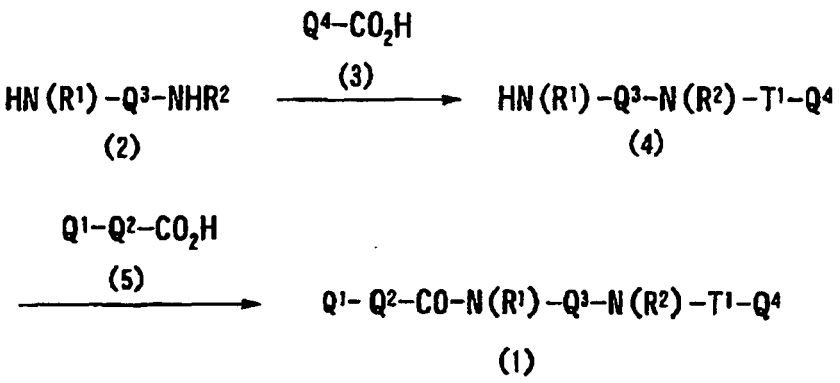
11) N^1-(5-Chloro-2-furyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-cyclohexyl)ethanediamide;

12) N^1-(5-Chloroxazol-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-cyclohexyl)ethanediamide;

[0031] The preparation process of the diamine derivatives (1) according to the present invention will hereinafter be described.

[Preparation Process 1] (Reference)

[0032] A compound represented by the general formula (1), a salt thereof, a solvate thereof, or an N-oxide thereof can be prepared in accordance with, for example, the following process:



wherein Q^1, Q^2, Q^3, Q^4, R^1 and R^2 have the same meanings as defined above, and T^1 represents a carbonyl group.

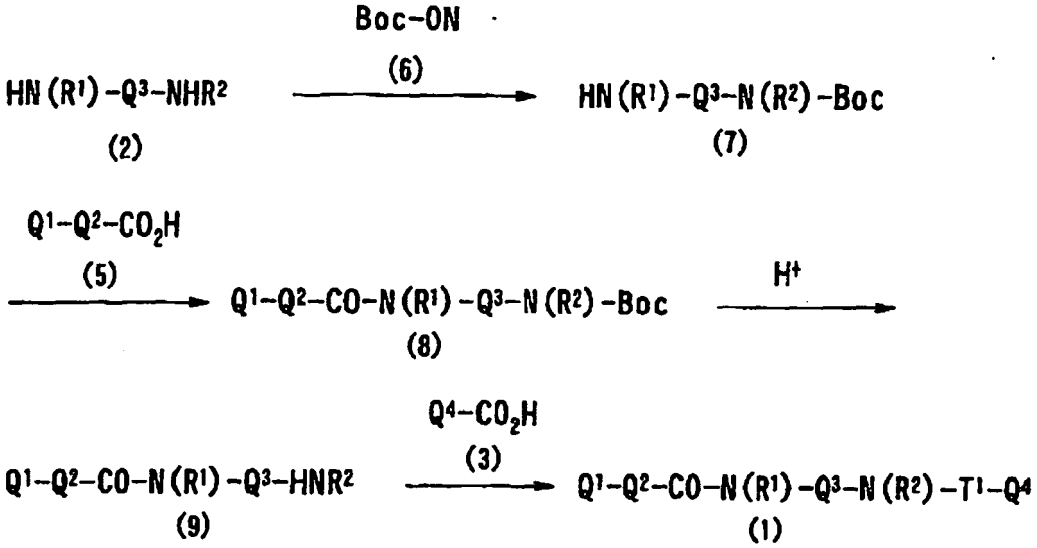
[0033] A mixed acid anhydride, acid halide, activated ester or the like, which is derived from carboxylic acid (3), may react with diamine (2), giving compound (4). The resultant compound (4) may react with carboxylic acid (5) under the same conditions, giving compound (1). In the above reaction steps, reagents and conditions, which are generally used in peptide synthesis, may be applied. The mixed acid anhydride can be prepared by, for example, reaction of a chloroformate such as ethyl chloroformate or isobutyl chloroformate with carboxylic acid (3) in the presence of a base. The acid halide can be prepared by treating carboxylic acid (3) with an acid halide such as thionyl chloride or oxalyl chloride. The activated ester includes various kinds of esters. Such an ester can be prepared by, for example, reaction of a phenol such as p-nitrophenol, N-hydroxybenzotriazol, or N-hydroxysccinimide with carboxylic acid (3) using a condensing agent such as N,N'-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The activated ester can also be prepared by reaction of carboxylic acid (3) with pentafluorophenyl trifluoroacetate or the like, reaction of carboxylic acid (3) with 1-benzotriazolyloxytripyrrolidinophosphonium hexafluorophosphite, reaction of carboxylic acid (3) with diethyl cyanophosphonate (Shioiri method), reaction of carboxylic acid (3) with triphenylphosphine and 2,2'-dipyridyl disulfide (Mukaiyama method) or the like. The thus-obtained mixed acid anhydride, acid halide or activated ester of carboxylic acid (3) may react with diamine (2) at -78°C to 150°C in the presence of a proper base in an inert solvent, giving compound (4). Thus-obtained compound (4) may react with a mixed acid anhydride, acid halide or activated ester of carboxylic acid (5) under the same conditions, giving compound (1) according to the present invention. The reagents and reaction conditions in the reaction of compound (4) with carboxylic acid (5) are the same as those in the reaction of diamine (2) with carboxylic acid (3).

[0034] As specific examples of the base used in each of the above mentioned step, may be carbonates of alkali metals or alkaline earth metals, such as sodium carbonate and potassium carbonate, alkali metal alkoxides such as sodium ethoxide and potassium butoxide, alkali metal hydroxides such as sodium hydroxide and potassium hydroxide, and hydrides of alkali metals or alkaline earth metals, such as sodium hydride and potassium hydride; organic metal bases exemplified by alkyllithium such as n-butyllithium, and dialkylaminolithium such as lithium diisopropylamide; organic metal bases exemplified by bis(silyl)amine, such as lithiumbis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0035] Examples of the inert solvent used in this reaction include alkyl halide type solvents such as dichloromethane, chloroform and carbon tetrachloride, etheric solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane, aromatic solvents such as benzene and toluene, and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. In addition to these solvent, a sulfoxide solvent such as dimethyl sulfoxide or sulfolane, a ketone solvent such as acetone or methyl ethyl ketone, or the like may be used in some cases.

[Preparation Process 2] (Reference)

[0036] Compound (1) can also be prepared in accordance with the following process:



wherein Q^1, Q^2, Q^3, Q^4, R^1 and R^2 have the same meanings as defined above, T^1 represents a carbonyl group, Boc represents a tert-butoxycarbonyl group, and Boc-ON represents a 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile.

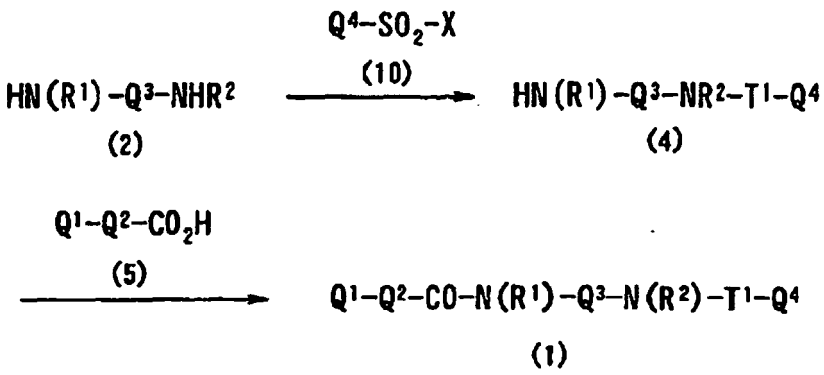
[0037] As described above, diamine (2) is treated with Boc-ON (6) to prepare compound (7) in which one of 2 amino

groups has been protected with tert-butoxycarbonyl group. The resultant compound (7) reacts with carboxylic acid (5) and affords compound (8). Compound (8) is successively treated with an acid to give compound (9). Compound (9) then reacts with the carboxylic acid (3), giving compound (1) according to the present invention. Compound (7) can be prepared by a reaction at -10°C to 40°C in the presence of triethylamine in a solvent such as dichloromethane. Reaction of compound (7) with the mixed acid anhydride, acid halide or activated ester of the carboxylic acid (5) is carried out using the same reagents and reaction conditions as those described in Preparation Process 1, whereby compound (8) can be prepared. The resultant compound (8) is treated with trifluoroacetic acid or the like at -20°C to 70°C, whereby amine (9) can be prepared. In the reaction of the resultant amine (9) with carboxylic acid (3), the same reagents and conditions as those described in Preparation Process 1 may be used.

[0038] By the way, the tert-butoxycarbonyl group of compound (7) may be replaced by other amino-protecting groups. In this case, reagent (6) is also changed to other reagents, and reaction conditions and the like according to the reagents must be used. As examples of other protecting groups for amino groups, may be mentioned alkanoyl groups such as an acetyl group, alkoxycarbonyl groups such as methoxycarbonyl and ethoxycarbonyl groups, arylmethoxycarbonyl groups such as benzyloxycarbonyl, p-methoxybenzyloxycarbonyl and p- or o-nitrobenzyloxy-carbonyl groups, arylmethyl groups such as benzyl and triphenylmethyl groups, aroyl groups such as a benzoyl group, and arylsulfonyl groups such as 2,4-dinitrobenzenesulfonyl and o-nitrobenzenesulfonyl groups. These protecting groups may be chosen for use according to the nature and the like of the compound of which amino group is to be protected. Upon leaving such a protecting group, reagents and conditions may be employed according to the protecting group.

[Preparation Process 3] (Reference)

[0039] Compound (1) can be prepared by reacting diamine (2) with sulfonyl halide (10) and then condensing the reaction product with carboxylic acid (5).

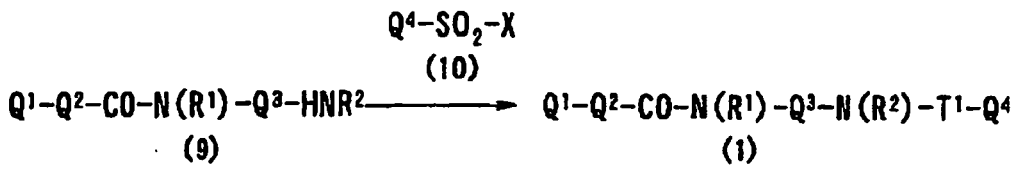


wherein Q^1, Q^2, Q^3, Q^4, R^1 and R^2 have the same meanings as defined above, T^1 represents a sulfonyl group, and X represents a halogen atom.

[0040] Diamine (2) reacts with sulfonyl halide (10) at -10°C to 30°C in the presence of a base such as triethylamine in an inert solvent, giving compound (4). The inert solvent and base may be suitably chosen for use from those described in Preparation Process 1. The resultant compound (4) is condensed with carboxylic acid (5) using the reagents and conditions described in Preparation Process 1, whereby compound (1) according to the present invention can be prepared. Sulfonyl halide (10) may be synthesized in a proper base in accordance with the publicly known process (WO96/10022, WO00/09480) or a process according to it.

[Preparation Process 4] (Reference)

[0041] Compound (1) Can also be prepared in accordance with the following process:

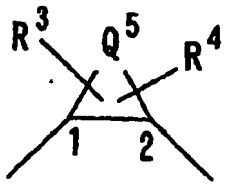


wherein Q^1, Q^2, Q^3, Q^4, R^1, R^2 and X have the same meanings as defined above, and T^1 represents a sulfonyl group.

[0042] More specifically, amine (9) may react with sulfonyl halide (10) at -10°C to 30°C in the presence of a base in an inert solvent, giving compound (1). The inert solvent and base may be suitably chosen for use from those described in Preparation Process 1.

[Preparation Process 5]

[0043] In the compounds (1) according to the present invention, geometrical isomers of trans-form and cis-form in the relation between position 1 and position 2 are present when Q^3 is the following group:

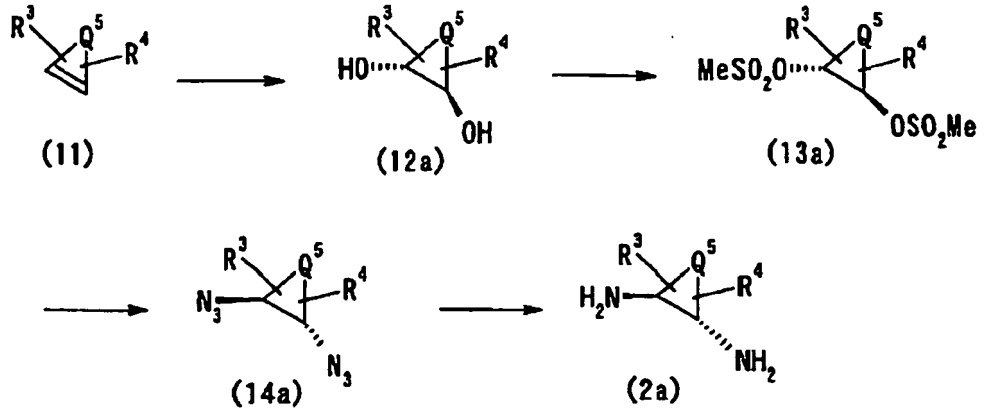


wherein R^3, R^4 and Q^5 have the same meanings as defined above, and numerals 1 and 2 indicate positions.

[0044] The preparation processes of such compounds (1) having the trans-form and the cis-form will hereinafter be described.

<Preparation process of trans-form>

[0045]



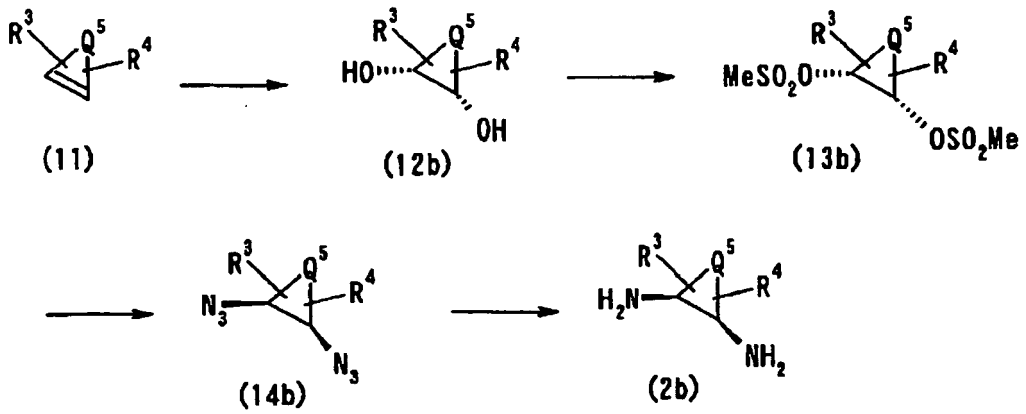
wherein Q^5, R^3 and R^4 have the same meanings as defined above.

[0046] As an example of preparation of trans-diol (12a) from cyclic alkene (11), conversion from, for example, cyclohexene to trans-cyclohexanediol (Organic Synthesis, 1995, Vol. III, p. 217) is known. As an example of preparation of trans-diamine (2a) from trans-diol (12a), conversion from trans-cyclopentanediol to trans-cyclopentanediamine (WO98/30574) is reported. Trans-diamine (2a) can be prepared from te cyclic alkene (11) according to these reports.

[0047] Trans-diamine (2a) prepared in accordance with the above-described process can be converted into trans-compound (1) by any of the above-described Preparation Processes 1 to 4.

<Preparation process of cis-form>

[0048]



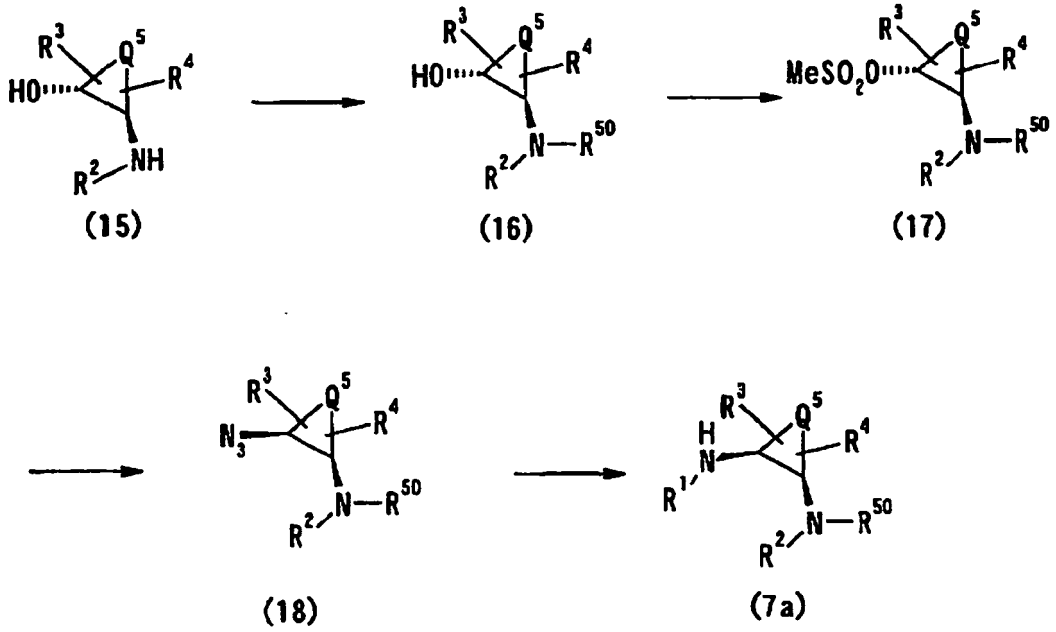
wherein Q^5, R^3 and R^4 have the same meanings as defined above, and numerals.

[0049] As an example of preparation of cis-diol (12b) from cyclic alkene (11), conversion from cyclohexene to cis-cyclohexanediol (J. Org. Chem., 1998, Vol. 63, p. 6094) and the like is known. As an example of preparation of cis-diamine (2b) from cis-diol (12a), conversion from cis-cyclopentanediol to cis-cyclopentanediamine (WO98/30574) and the like is reported. Cis-diamine (2b) can be prepared from cyclic alkene (11) according to these reports.

[0050] Cis-diamine (2b) prepared in accordance with the above-described process can be converted into the cis-compound (1) by any of the above-described Preparation Processes 1 to 4.

[Preparation Process 6]

[0051] As described above, either cis-form or trans-form generated in Q^3 may be present in the compounds (1) according to the present invention, and so geometrical isomers are present. Further, optical isomers may be present in the respective geometrical isomers. The preparation process of an optically active substance will hereinafter be described.



wherein Q^5, R^1, R^2, R^3 and R^4 have the same meanings as defined above, and R^{50} represents a protecting group for amino group.

[0052] With respect to the preparation process of optically active aminoalcohol derivative (15) of 1,2-trans-form, for example, the preparation process of optically active 1,2-trans-2-aminocyclopentanol from cyclopentene oxide or the preparation process of optically active 1,2-trans-2-aminocyclohexanol from cyclohexene oxide is known (Tetrahedron: Asymmetry, 1996, Vol. 7, p. 843; J. Org. Chem., 1985, Vol. 50, p. 4154; J. Med. Chem., 1998, Vol. 41, p. 38). When the amino group of optically active aminoalcohol derivative (15) prepared by such an already known process or by applying

such a process reacts with a proper protecting reagent, compound (16) can be produced. As a protecting group corresponding to R^{50} in compound (16), is preferred, among the ordinary acyl type protecting groups, an alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl group and the like, an arylmethoxycarbonyl group such as benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p- or o-nitrobenzyloxy-carbonyl group and the like, or an arylsulfonyl group such as 2,4-dinitrobenzenesulfonyl, o-nitrobenzenesulfonyl group and the like. When the amino group is protected with, for example, a tert-butoxycarbonyl group, aminoalcohol derivative (15) may react with di-tert-butyl dicarbonate at -78°C to 50°C in an inert solvent, giving compound (16). The inert solvent may be suitably chosen for use from those described in Preparation Process 1.

[0053] Compound (16) may react with methanesulfonyl chloride at -78°C to 50°C in the presence of a base in an inert solvent, giving compound (17). The inert solvent may be suitably chosen for use from those described in Preparation Process 1. As the base, is preferred an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) and the like.

[0054] Compound (17) may react with sodium azide at -10°C to 150°C in a proper solvent, giving compound (18). As the solvent, an amide solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidin-2-one, an alcoholic solvent such as methanol or ethanol, an etheric solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, benzenoid solvent such as toluene, a carbon halogenide such as dichloromethane, chloroform or carbon tetrachloride, acetone, dimethyl sulfoxide, or a mixed solvent of such a solvent with water is suitable.

[0055] As a process for converting azide derivative (18) into compound (7a), there are many processes such as a process of conducting hydrogenation with a palladium catalyst, Raney nickel catalyst or platinum catalyst, a reaction using a reducing agent such as lithium aluminum hydride, sodium borohydride or zinc borohydride, a reaction using zinc in the presence of nickel chloride or cobalt chloride, a reaction using triphenylphosphine and the like. Suitable reaction conditions may be selected according to the nature of the compound. For example, azide derivative (18) is hydrogenated at a temperature of -10°C to 70°C using 1 to 20% palladium carbon as a catalyst in a proper solvent, whereby compound (7a) can be prepared. The hydrogen pressure may be raised higher than atmospheric pressure. As the solvent, an alcoholic solvent such as methanol or ethanol, an etheric solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, an amide solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidin-2-one, an ester solvent such as ethyl acetate, acetic acid, hydrochloric acid, water, a mixed solvent thereof and the like is suitable.

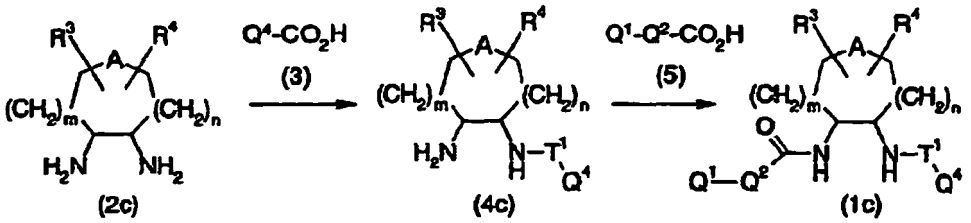
[0056] Optically active amine (7a) prepared in accordance with the above-described process can be converted to optically active compound (1) in accordance with the above-described Preparation Process 2. Antipode (1) of optically active substance (1) obtained from optically active amine (7a) may also be prepared in accordance with a similar process.

[0057] Optically active compound (1) may be prepared by separating racemic compound (1) through a column composed of an optically active carrier. It is also possible to separate intermediate (2), (4), (7), (8) or (9) for preparing racemic compound (1) through a column composed of an optically active carrier to isolate optically active intermediate (2), (4), (7), (8) or (9), and then prepare optically active compound (1) in accordance with any of Preparation Processes 1 to 4. As a process for isolating optically active compound (1), optically active intermediate (2), (4), (7), (8) or (9), a process of fractionally crystallizing a salt with an optically active carboxylic acid, or a process of fractionally crystallizing a salt with an optically active base on the contrary may be used.

[Preparation Process 7] (Reference)

[0058] Among the compounds (1) a preparation process of compound (1c) containing heteroatom(s) in the group Q^3 will hereinafter be described in detail.

[0059] A compound represented by the general formula (1c), a salt thereof, a solvate thereof, or an N-oxide thereof can be prepared in accordance with, for example, the following process:



wherein Q^1, Q^2, Q^3, Q^4, R^3, and R^4 have the same meanings as defined above, T^1 represents a carbonyl group m and n are independently of each other 0 or an integer of 1-3, and A means an oxygen atom, nitrogen atom, sulfur atom, -SO-, $-SO_2-$, -NH-, -O-NH-, -NH-NH-, -S-NH-, -SO-NH- or $-SO_2$-NH- .

[0060] A mixed acid anhydride, acid halide, activated ester or the like, which is derived from carboxylic acid (3), may

react with compound (2c), giving compound (4c). The resultant compound (4c) may react with carboxylic acid (5) under the same conditions, giving compound (1c) according to the present invention.

[0061] In the above reaction steps, reagents and conditions, which are generally used in peptide synthesis, may be applied. The mixed acid anhydride can be prepared by, for example, reaction of a chloroformate such as ethyl chloroformate or isobutyl chloroformate with carboxylic acid (3) in the presence of a base. The acid halide can be prepared by treating carboxylic acid (3) with an acid halide such as thionyl chloride or oxalyl chloride. The activated ester includes various kinds of esters. Such an ester can be prepared by, for example, reaction of a phenol such as p-nitrophenol, N-hydroxybenzotriazol, or N-hydroxysccinimide with carboxylic acid (3) using a condensing agent such as N,N'-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The activated ester can also be prepared by reaction of carboxylic acid (3) with pentafluorophenyl trifluoroacetate or the like, reaction of carboxylic acid (3) with 1-benzotriazolyloxytripyrrolidinophosphonium hexafluorophosphite, reaction of carboxylic acid (3) with diethyl cyanophosphonate (Shioiri method), reaction of carboxylic acid (3) with triphenylphosphine and 2,2'-dipyridyl disulfide (Mukaiyama method) or the like. The thus-obtained mixed acid anhydride, acid halide or activated ester of carboxylic acid (3) may react with compound (2c) at a temperature under cooling to a temperature under heating in the presence of a proper base in an inert solvent, giving compound (4c). Thus-obtained compound (4c) may react with a mixed acid anhydride, acid halide or activated ester of carboxylic acid (5) under the same conditions, giving compound (1c) according to the present invention. The reagents and reaction conditions in the reaction of compound (4C) with carboxylic acid (5) are the same as those in the reaction of diamine (2c) with carboxylic acid (3).

[0062] As specific examples of the base used in each of the above step, may be mentioned carbonates of alkali metals or alkaline earth metals, such as sodium carbonate and potassium carbonate, alkali metal alkoxides such as sodium ethoxide and potassium butoxide, alkali metal hydroxides such as sodium hydroxide and potassium hydroxide, and hydrides of alkali metals, such as sodium hydride and potassium hydride; organic metal bases exemplified by alkyllithium such as n-butyllithium, and organic metal bases exemplified by dialkylaminolithium such as lithium diisopropylamide; organic metal bases of bis(silyl)amine, such as lithium-bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo [5.4.0]undec-7-ene (DBU) or the like.

[0063] Examples of the inert solvent used in this reaction include alkyl halide type solvents such as methylene chloride and chloroform, etheric solvents such as tetrahydrofuran and 1,4-dioxane, aromatic solvents such as benzene and toluene, and amide solvents such as N,N-dimethylformamide. In addition to these solvent, a sulfoxide solvent such as dimethyl sulfoxide, a ketone solvent such as acetone, or the like may be used in some cases.

[0064] In the above-described preparation steps, processes such as attaching and leaving of a protecting group, and conversion of a functional group can be suitably applied, thereby preparing compound (1c).

[0065] As the protecting group for amino group, it is only necessary to use a protecting group, which is generally used as a protecting group for amino group in syntheses of organic compounds, particularly, peptide synthesis. As examples thereof, may be mentioned alkoxycarbonyl groups such as tert-butoxycarbonyl, methoxycarbonyl and ethoxycarbonyl groups, arylmethoxycarbonyl groups such as benzyloxycarbonyl, p-methoxybenzyloxycarbonyl and p- or o-nitrobenzyloxycarbonyl group, arylmethyl groups such as benzyl, 4-methoxybenzyl and triphenylmethyl groups, alkanoyl groups such as formyl and acetyl groups, aroyl groups such as a benzoyl group, and arylsulfonyl groups such as 2,4-dinitrobenzenesulfonyl and o-nitrobenzenesulfonyl groups.

[0066] As the protecting group for hydroxyl group, it is only necessary to use a protecting group for hydroxyl group, which is generally used in syntheses of organic compounds. As examples thereof, may be mentioned alkoxymethyl groups such as a methoxymethyl group, arylmethyl groups such as benzyl, 4-methoxybenzyl, triphenylmethyl groups, alkanoyl groups such as an acetyl group, aroyl groups such as a benzoyl group, and a tert-butyldiphenylsilyloxy group. A carboxyl group can be protected as an ester with an alkyl group such as a methyl group, ethyl group, tert-butyl group or an arylmethyl group such as a benzyl group. The attaching and leaving of the protecting group may be conducted in accordance with a method known *per se* in the art.

[0067] Compound (1c) according to the present invention can be converted into various derivatives by converting its functional group. For example, a compound in which A is a nitrogen atom having no substituent can be converted into an amide compound by acylation using a mixed acid anhydride, acid halide, activated ester or the like in accordance with ordinary organic chemical methods, a sulfonamide compound by reaction with a sulfonyl halide, an N-alkyl compound by reaction with an alkyl halide, an N-aryl compound by reaction with an aryl halide or a carbamate compound by reaction with an isocyanate. Incidentally, the compound in which A is a nitrogen atom having no substituent can be prepared by, for example, treating compound (1c) prepared from diamine (2c), in which A has been protected with tert-butoxycarbonyl group, in accordance with Preparation Process 7 with an acid.

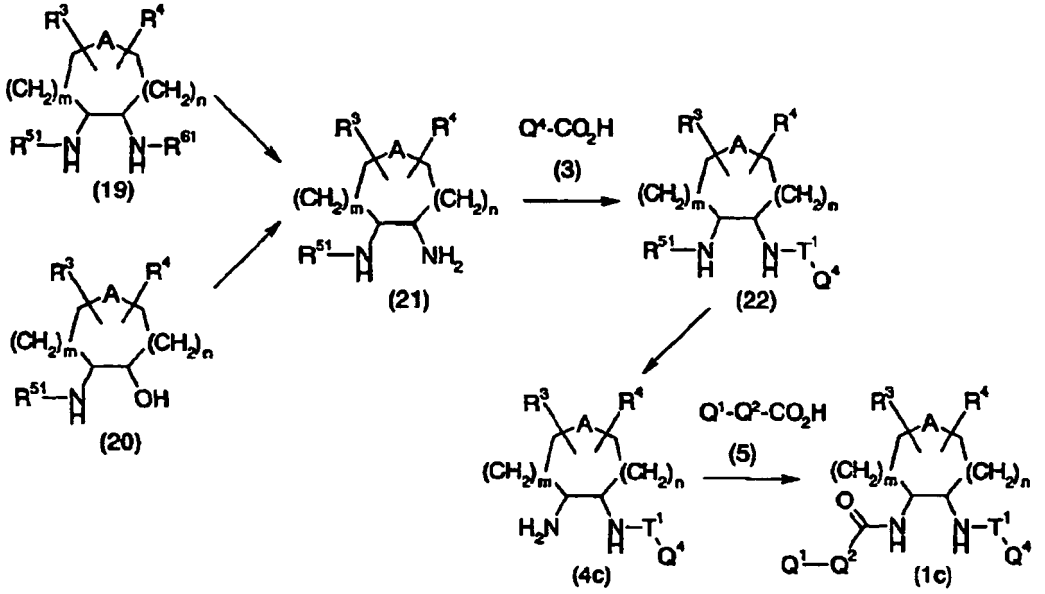
[0068] The compounds according to the present invention thus prepared can be isolated and purified by publicly known methods, for example, extraction, precipitation, fractional chromatography, fractional crystallization, recrystallization, etc. The compounds according to the present invention can be converted into desired salts in accordance with ordinary salt-forming reactions.

[0069] Optical isomers derived from an asymmetric carbon atom are present in the compounds of the present invention. Such an optically active isomer can be prepared by the process of preparing from optically active diamine (2c), and besides, a process of forming an optically active amine or acid and a salt from racemic compound (1c) and fractionally crystallizing it, a process of separating it by column chromatography using an optically active carrier.

[0070] Compound (1c), in which T^1 is a sulfonyl group, can be prepared by changing carboxylic acid (3) to sulfonyl halide (10) in the reaction of compound (2c) with carboxylic acid (3).

[Preparation Process 8] (Reference)

[0071] Compound (1c) can also be prepared in accordance with the following process:



wherein Q^1, Q^2, Q^4, R^3, R^4, A, m and n have the same meanings as defined above, T^1 represents a carbonyl group, and R^{51} and R^{61} represent protecting groups for amino group.

[0072] Compound (21) can be prepared by removing the protecting group R^{61} of compound (19) obtained by protecting the amino groups of compound (2c). No particular limitation is imposed on the protecting groups for amino acid illustrated as R^{51} and R^{61} so far as they are groups generally used in protection of the amino group. However, as typical examples thereof, may be mentioned the protecting groups for amino group described in Preparation Process 7. In this case, R^{51} and R^{61} are required to be protecting groups capable of leaving by different methods or conditions from each other. As typical examples thereof, may be mentioned a combination that R^{51} is a tert-butoxycarbonyl group, and R^{61} is a benzyloxycarbonyl group. These protecting groups may be chosen for use according to the nature and the like of the compound of which amino groups are to be protected. Upon leaving such a protecting group, reagents and conditions may be employed according to the protecting group.

[0073] Compound (21) can also be prepared by converting the hydroxyl group in aminoalcohol derivative (20) into an amino group. As an example of the preparation of aminoalcohol derivative (20), is known conversion of methionine into 3-hydroxy-4-aminothiopyrane-1,1-dioxide (Tetrahedron Lett., Vol. 37, p. 7457, 1996) or the like.

[0074] As a process for converting the hydroxyl group in aminoalcohol derivative (20) into an amino group, may be mentioned a process in which aminoalcohol derivative (20) may react with methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride or the like, the resultant product may then react with ammonia, a primary arylalkylamine such as benzylamine, p-methoxybenzylamine or 2,4-dimethoxybenzylamine, a secondary arylalkylamine such as dibenzylamine, or a hydroxylamine such as N-benzylhydroxylamine or N,O-dibenzylhydroxylamine, and benzyl group or the like is then removed as needed, thereby preparing diamine (21). Aminoalcohol derivative (20) can also be converted into diamine (21) by reacting it with phthalimide or succinimide in accordance with the reaction with triphenylphosphine and ethyl azodicarboxylate (Mukaiyama method) or the like, and then treating the reaction product with hydrazine, N-methylhydrazine or the like. When A in the formula is SO_2, and n is 0, diamine (21) can be prepared by adding ammonia, a primary arylalkylamine such as ammonia, benzylamine, p-methoxybenzylamine or 2,4-dimethoxybenzylamine, a secondary arylalkylamine such as dibenzylamine, or a hydroxylamine such as N-benzylhydroxylamine or N,O-dibenzylhydroxylamine to an α,β-unsaturated cyclic sulfone formed by reacting aminoalcohol derivative (20) with methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride or the like and then treating the

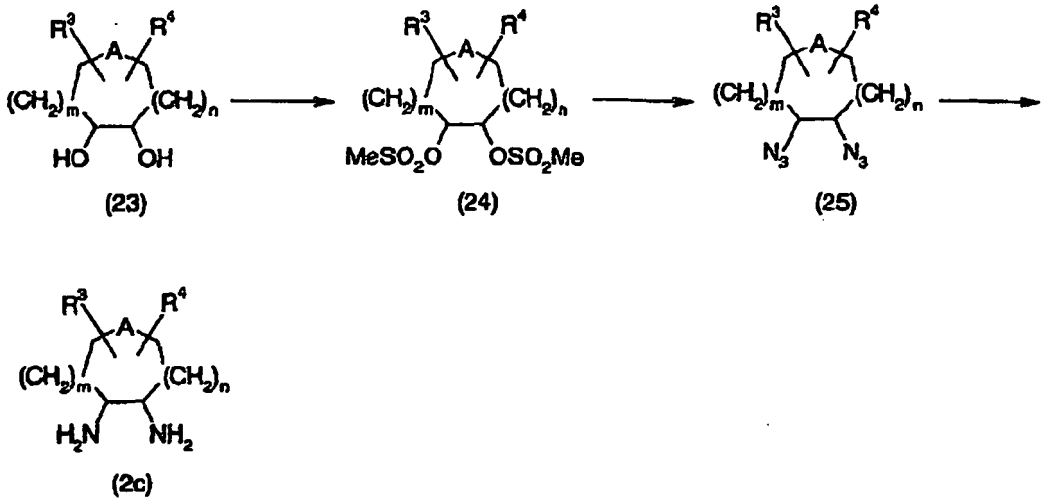
reaction product with a proper base or directly reacting aminoalcohol derivative (20) with triphenylphosphine and ethyl azodicarboxylate, and removing the benzyl group or the like as needed.

[0075] The resultant diamine (21) may react with carboxylic acid (3), giving compound (22). The protecting group R^{51} is successively removed, giving compound (4c). Compound (4c) may react with carboxylic acid (5), giving compound (1c) according to the present invention. The reagents and reaction conditions in the reaction of compound (21) with carboxylic acid (3) and the reaction of compound (4C) with carboxylic acid (5) may be the same as those described in Preparation Process 7.

[0076] Similarly, compound (1c) in which T^1 is a sulfonyl group can be prepared by changing carboxylic acid (3) to sulfonyl halide (10) in the reaction of compound (21) with carboxylic acid (3).

[Preparation Process 9] (Reference)

[0077] A typical preparation process of intermediate (2c) for preparation described in Preparation Process 7 will be described.



wherein R^3, R^4, A, m and n have the same meanings as defined above.

[0078] As preparation processes of diol derivative (23), are known, for example, conversion of 1,2,3,6-tetrahydropyridine into 1-benzyloxycarbonyl-3,4-cis-dihydroxypyrrolidine (Japanese Patent Application Laid-Open No. 138264/1995), conversion of L-tartaric acid into (R,R)-tetrahydrofurandiol or (R,R)-N-benzylpyrrolidinediol (Tetrahedron: Symmetry, Vol. 8, p. 1861, 1997) and the like. Diol derivative (23) can be prepared by using such an already known process or applying such a process and removing a protecting group or converting a functional group as needed.

[0079] Diol derivative (23) may react with methanesulfonyl chloride at a temperature under cooling to room temperature in the presence of a base in an inert solvent, giving compound (24). The inert solvent may be suitably chosen for use from those described in Preparation Process 7. However, particularly preferred are alkyl halide type solvents such as methylene chloride and chloroform, and etheric solvents such as tetrahydrofuran and 1,4-dioxane. As the base, is preferred an organic base such as pyridine, 2,6-lutidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo-[5.4.0] undec-7-ene (DBU).

[0080] Compound (24) may react with sodium azide at a temperature under cooling to a temperature under heating in a proper solvent, giving azide derivative (25). As the solvent, an amide solvent such as N,N-dimethylformamide, N-methylpyrrolidin-2-one, an alcoholic solvent such as methanol or ethanol, an etheric solvent such as tetrahydrofuran or 1,4-dioxane, aromatic solvent such as benzene or toluene, a carbon halogenide such as methylene chloride or chloroform, dimethyl sulfoxide, acetone, or the like is suitable. Such a solvent may be a mixed solvent with water.

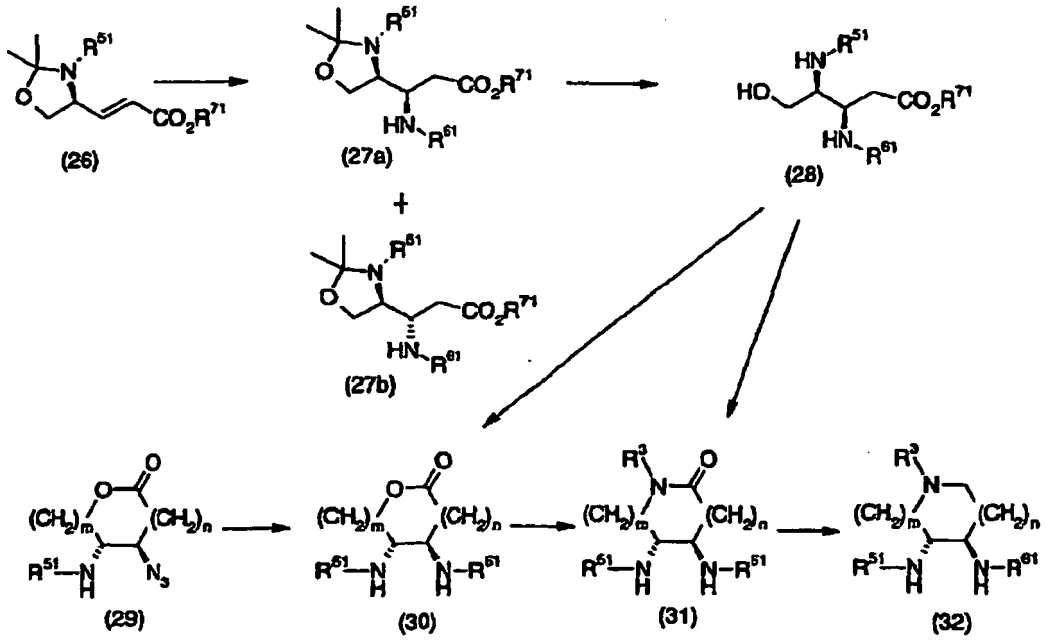
[0081] As a process for converting azide derivative (25) into compound (2c), there are many processes such as a process of conducting hydrogenation with a palladium catalyst, Raney nickel catalyst or platinum catalyst, a reaction using a reducing agent such as lithium aluminum hydride or sodium borohydride, a reaction using zinc in the presence of nickel chloride or cobalt chloride, and a reaction using triphenylphosphine ot the like. Suitable reagents and reaction conditions may be selected according to the nature of the compound. The hydrogen pressure may be raised higher than atmospheric pressure. As the solvent, an alcoholic solvent such as methanol or ethanol, an etheric solvent such as tetrahydrofuran or 1,4-dioxane, an amide solvent such as N,N-dimethylformamide or N-methylpyrrolidin-2-one, an ester solvent such as ethyl acetate, acetic acid, hydrochloric acid, water, a mixed solvent thereof or the like is suitable.

Compound (1c) according to the present invention can be derived from diamine derivative (2c) prepared in accordance with the above-described process in accordance with Preparation Process 7.

[0082] When diol derivative (23) is trans-3,4-dihydroxytetrahydrofuran or trans-1-substituted 3,4-dihydroxypyrrolidine and the like, optically active substances are present. These optically active diol derivatives (23) can be converted into optically active diamine derivatives (2c), and further into optically active compounds (1c) according to the present invention in accordance with Preparation Process 7.

[Preparation Process 10] (Reference)

[0083] A typical preparation process of optically active compounds (30), (31) and (32) included in compound (19) described in Preparation Process 8 will be described. Incidentally, the position of an asymmetric carbon atom shown in the following preparation scheme is indicated by way of example.



wherein m, n, R^3, R^{51} and R^{61} have the same meanings as defined above, and R^{71}, represents a protecting group for carboxyl group.

[0084] Optically active α,β-unsaturated ester derivative (26) can be prepared in accordance with the process described in literature (J. Org. Chem., Vol. 61, p. 581, 1996; J. Org. Chem., vol. 57, p. 6279, 1992, etc.) or by applying such a process. Optically active α,β-unsaturated ester derivative (26) may react with an amine at a temperature under cooling, or under heating in a proper solvent, giving diastereomers (27a) and (27b). The amine may be suitably chosen for use from those described in Preparation Process 8. The solvent is desirably an organic solvent unreactive to a substrate, product or reagent, particularly, an alcoholic solvent such as methanol or ethanol, or an etheric solvent such as tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane and the like. Diastereomers (27a) and (27b) can also be prepared by reaction of α,β-unsaturated ester derivative (26) with an organometallic base such as lithium N-benzyl-(trimethylsilyl)amide and the like by applying the process described in literature (J. Org. Chem., Vol. 63, p. 7263, 1998). The diastereomers may be separated to use, for example, diastereomer (27a) in the next reaction.

[0085] Compound (27a) is treated with an acid at a temperature under cooling, or under heating in a proper solvent, giving compound (28). Examples of the acid used include hydrochloric acid, sulfuric acid, Lewis acids such as boron trifluoride, trifluoroacetic acid, p-toluenesulfonic acid or the like. As the solvent, is used water or an alcoholic solvent such as methanol or ethanol. Such a solvent may be a mixed solvent with water. In this reaction, the protecting group R^{61} may be left in some cases. In such a case, such a compound is required to react with a proper protecting reagent for amino group as needed.

[0086] Compound (28) may be treated with an acid at a temperature under cooling, or under heating in a proper solvent, giving optically active compound (30). The acid used may be suitably chosen for use from the acids mentioned above, with a Lewis acid such as boron trifluoride, or p-toluenesulfonic acid or the like being particularly preferred. As the solvent used in the reaction, is used an etheric solvent such as 1,4-dioxane or tetrahydrofuran, or an aromatic solvents such as benzene or toluene. Compound (30) can also be prepared from azide derivative (29). As examples of

the preparation of optically active azide derivative (29), are known conversion of L-asparagic acid into (R,R)-(3S,4S)-3-amino-4-azide-5-oxotetrahydrofuran (Can. J. Chem., Vol. 71, p. 1047, 1993) and the like. Optically active azide derivative (29) can be prepared by using such an already known process or applying such a process and removing a protecting group or converting a functional group as needed. The azide in azide derivative (29) may be reduced into an amino group, and the resultant product may react with a proper protecting reagent for amino group, giving compound (30). The reagents and reaction conditions used in the reduction of azide (29) may be the same as those described in the process of converting azide derivative (25) into compound (2c).

[0087] The hydroxyl group portion of compound (28) may be converted into an amino group and then treated with a base, giving compound (31). The conversion of the hydroxyl group in compound (28) into the amino group can be performed in accordance with, for example, Preparation Process 8. Compound (31) can also be prepared by treating alcohol derivative (28) with an oxidizing agent and then reductively aminating the resultant aldehyde derivative. Specific preferable examples of the oxidizing agent used in the above reaction include pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), sulfur trioxide pyridine complexes or the like. Example of the amine include primary alkylamines such as ammonia, methylamine and ethylamine, and primary arylalkylamine such as benzylamine, p-methoxybenzylamine and 2,4-dimethoxybenzylamine. As the reducing process, there are a process of conducting hydrogenation with a palladium catalyst, Raney nickel catalyst or platinum catalyst, a reaction using a reducing agent such as sodium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride, and suitable reagents and reaction conditions may be selected according to the nature of the compound or the like. The base used in the above process may be suitably chosen for use from those described in Preparation Process 7. Compound (31) can also be prepared by using compound (30) and an amine in accordance with the process described in literature (Tetrahedron Lett., Vol. 41, p. 1141, 2000; Heterocycles, Vol. 53, p. 173, 2000) or by applying such a process. Examples of the amine used include primary alkylamines such as ammonia, methylamine and ethylamine, and primary arylalkylamine such as benzylamine and p-methoxybenzyl-amine.

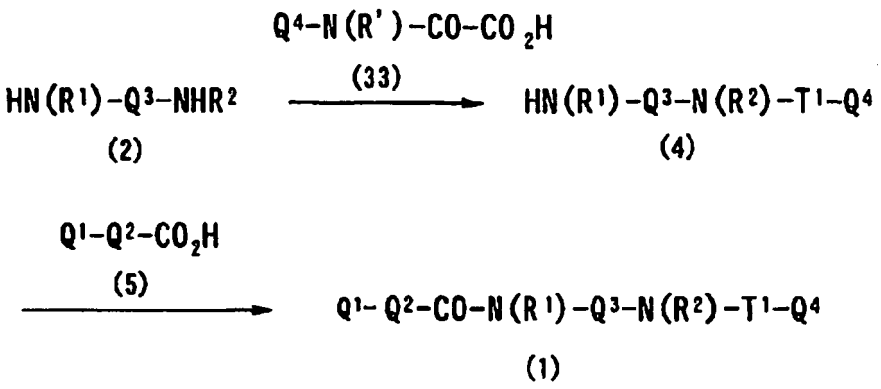
[0088] Compound (31) may be treated with a reducing agent at a temperature under cooling to a temperature under heating in a solvent, giving compound (32). Examples of the reducing agent include borane-tetrahydrofuran complexes, borane·methyl sulfide complexes, lithium aluminum hydride. However, suitable reagents and reaction conditions may be selected according to the nature of the compound or the like. The solvent is desirably an organic solvent unreactive to a substrate, product, reagentor the like, particularly, an etheric solvent such as tetrahydrofuran or 1,4-dioxane.

[0089] Optically active substances (1c) of the compounds according to the present invention can be derived from the compounds (30), (31) and (32) prepared by the processes described above.

[0090] In the above-described preparation scheme, one of optically active substances has been described by way of example. However, other optically active substances different in conformation from each other may also be prepared in accordance with similar preparation schemes by respectively using starting materials different in conformation from each other.

[Preparation Process 11]

[0091] Compound (1) in which T^1 is a group -CO-CO-N(R')-, in which R' has the same meaning as defined above, can be prepared in accordance with the following scheme:

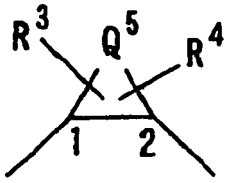


wherein Q^1, Q^2, Q^3, Q^4, R^1, R^2 and R' have the same meanings as defined above, and T^1 represents a group -CO-CO-N(R')-, in which R' has the same meaning as defined above.

[0092] An acid halide, activated ester or the like, which is derived from carboxylic acid (33), may react with diamine (2), giving compound (4). The resultant compound (4) may react with carboxylic acid (5) under the same conditions,

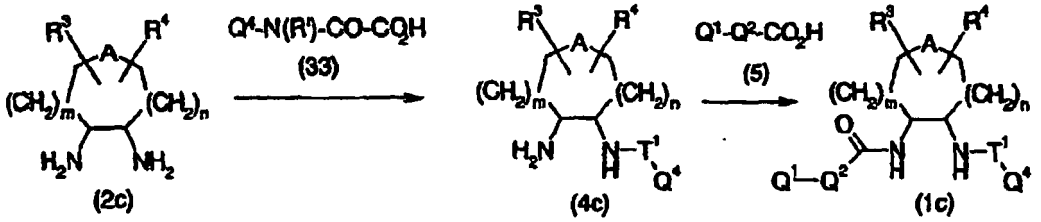
giving compound (1) according to the present invention. In the above reaction steps, reagents and conditions, which are generally used in peptide synthesis, may be applied. The acid halide can be prepared by treating carboxylic acid (33) with an acid halide such as thionyl chloride or oxalyl chloride. The activated ester includes various kinds of esters. Such an ester can be prepared by, for example, reaction of a phenol such as p-nitrophenol, N-hydroxybenzotriazol, or N-hydroxysccinimide with carboxylic acid (33) using a condensing agent such as N,N'-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The activated ester can also be prepared by reaction of carboxylic acid (33) with pentafluorophenyl trifluoroacetate or the like, reaction of carboxylic acid (33) with 1-benzotriazolyloxytripyrrolidinophosphonium hexafluorophosphite, reaction of carboxylic acid (33) with diethyl cyanophosphonate (Shioiri method), reaction of carboxylic acid (33) with triphenylphosphine and 2,2'-dipyridyl disulfide (Mukaiyama method) or the like. The thus-obtained mixed acid anhydride, acid halide or activated ester of carboxylic acid (33) may react with diamine (2) at -78°C to 150°C in the presence of a proper base in an inert solvent, giving compound (4). Thus-obtained compound (4) may react with a mixed acid anhydride, acid halide or activated ester of carboxylic acid (5) under the same conditions, giving compound (1) according to the present invention. The reagents and reaction conditions in the reaction of compound (4) with carboxylic acid (5) are the same as those in the reaction of diamine (2) with carboxylic acid (33). The bases and solvents used in the above respective steps may be suitably chosen from those described in Preparation Process 1.

[0093] When compound (1) in which Q^3 is the following group:



wherein R^3, R^4 and Q^5 have the same meanings as defined above, and numerals 1 and 2 indicate positions, and the relation between position 1 and position 2 is a trans-form or cis-form, is prepared, it is only necessary to use diamine (2a) or (2b) described in Preparation Process 5.

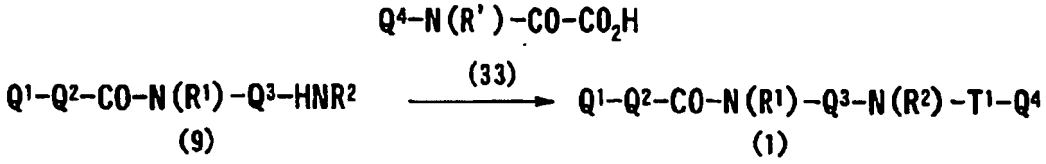
[0094] (Reference) When compound (1) in which a heteroatom such as a nitrogen atom, oxygen atom or sulfured atom is contained in Q^5 is prepared, it is only necessary to change carboxylic acid (3) to carboxylic acid (33) in the reaction of compound (2c) with carboxylic acid (3) as described in Preparation Process 7. Namely, compound (1) in which a heteroatom is contained in Q^5 in the following reaction scheme, i.e., compound (1c) can be prepared.



wherein Q^1, Q^2, Q^4, R^3, R^4, R', A, m and n have the same meanings as defined above, and T^1 represents a group -COCO-N (R')-, in which R' has the same meaning as defined above.

[Preparation Process 12]

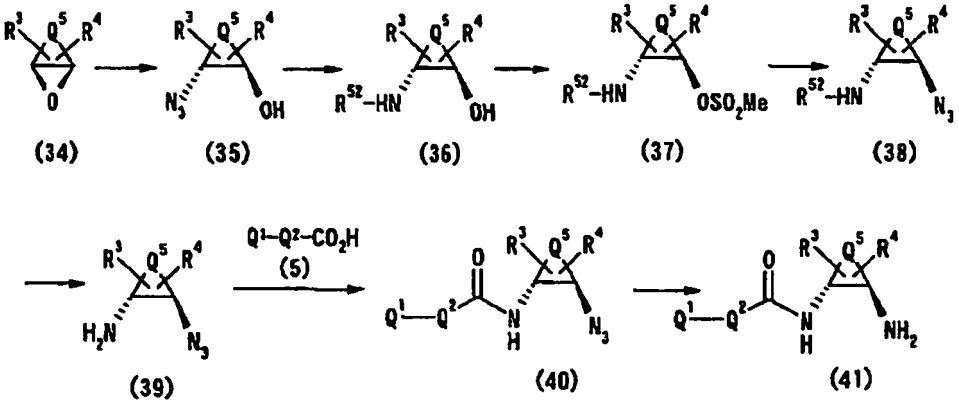
[0095] Compound (1) in which T^1 is a group -CO-CO-N(R')-, in which R' has the same meaning as defined above, can also be prepared in accordance with the following scheme:



wherein Q^1, Q^2, Q^3, Q^4 , R^1, R^2 and R' have the same meanings as defined above, and T^1 represents a group -CO-CO-N(R')-, in which R' has the same meaning as defined above.

[0096] In the reaction of amine (9) with carboxylic acid (33), the same reagents and conditions as those described in Preparation Process 1 may be used.

[0097] Amine (9) used herein can also be prepared in accordance with the following scheme shown as a preparation scheme of amine (41) in addition of the scheme described in Preparation Process 2.



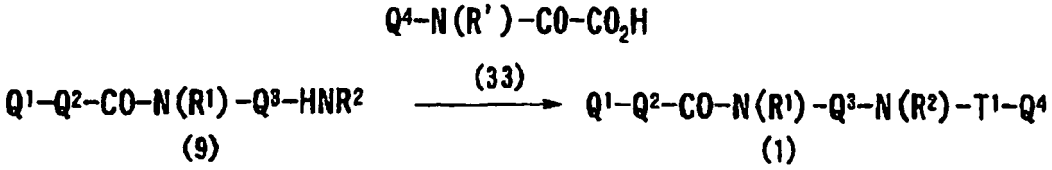
wherein R^3, R^4, Q^1, Q^2 and Q^5 have the same meanings as defined above, and R^{52} represents a protecting group for amino group.

[0098] Compound (34) in the above preparation scheme can be prepared by treating a cycloalkene with perbenzoic acid or a derivative thereof and the like in a solvent such as methylene chloride to epoxidate it. Ordinary conditions for epoxidation of an alkene may be applied to the conditions of this reaction. Compound (34) can also be prepared in accordance with the process described in J. Org. Chem., Vol. 61, pp. 8687-8691 (1996) or a process corresponding thereto.

[0099] Compound (34) may react with sodium azide or the like in accordance with a method known per se in the art, giving azide (35). Azide (35) may be catalytically reduced, and the amino group of the resultant compound may be protected, giving compound (36). As examples of the protecting group for amino group in this reaction, may be mentioned those described in Preparation Process 2. Compound (36) may be converted into azide (38) in a similar manner to the process described Preparation Process 5, and the protecting group for the amino group thereof may be left, giving compound (39). Compound (39) may react with carboxylic acid (5), giving compound (40). The compound (40) may then be catalytically reduced, giving compound (41).

[Preparation Process 13]

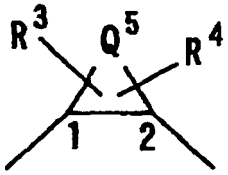
[0100] Compound (1) in which T^1 is a group -CO-CO-N(R')-, in which R' has the same meaning as defined above, can also be prepared by changing the reaction of compound (9) with carboxylic acid (3) in the scheme described in Preparation Process 2 to a reaction of compound (9) with compound (33).



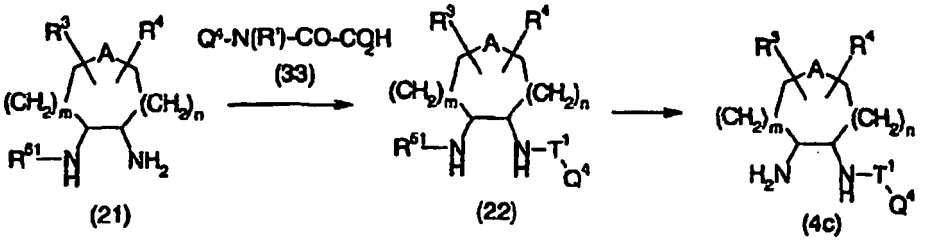
wherein Q^1, Q^2, Q^3, Q^4, R^1, R^2 and R' have the same meanings as defined above, and T^1 represents a group -CO-CO-N(R')-, in which R' has the same meaning as defined above.

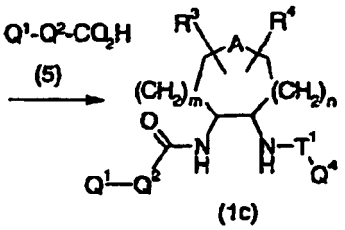
[0101] As the reaction conditions, may be applied those described in Preparation Process 2.

[0102] (Reference): when compound (1) in which Q^3 is the following group:



wherein R^3, R^4 and Q^5 have the same meanings as defined above, and numerals 1 and 2 indicate positions, and a heteroatom such as a nitrogen atom, oxygen atom or sulfured atom is contained in Q^5 is prepared, it is only necessary to change carboxylic acid (3) to carboxylic acid (33) in the reaction of compound (21) with carboxylic acid (3) as described in Preparation Process 8. Namely, compound (1) in which a heteroatom is contained in Q^5 in the following reaction scheme, i.e., compound (1c) can be prepared.

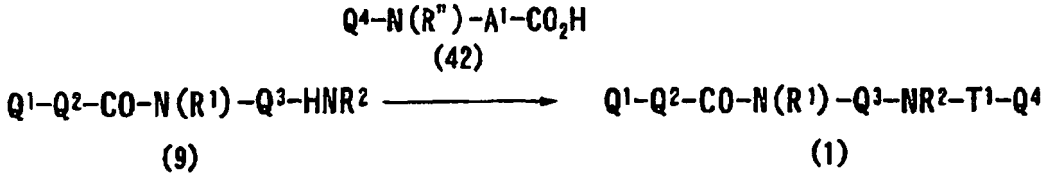




where in Q^1, Q^2, Q^4, R^3, R^4, R', A, m and n have the same meanings as defined above, and T^1 represents a group -COCO-N(R')-, in which R' has the same meaning as defined above, and R^{51} represents a protecting group for amino group.

[Preparation Process 14] (Referecnce)

[0103] Compound (1) in which T^1 is a group -CO-A^1-N(R")-, in which R" represents a hydrogen atom, hydroxyl group, alkyl group or alkoxy group, and A^1 represents an alkylene group having 1 to 5 carbon atoms, which may be substituted, can be prepared by reaction of compound (9) described in Preparation Process 2 with Q^4-N(R")-A^1-CO_2H (42) at -55°C to 50°C using a condensing agent in an inert solvent. As examples of the condensing agent, may be mentioned N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride or the like. As examples of the inert solvent, may be mentioned alkyl halide type solvents such as methylene chloride, chloroform and carbon tetrachloride, etheric solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane, aromatic solvents such as benzene and toluene, and amide solvents such as N,N-dimethylformamide.



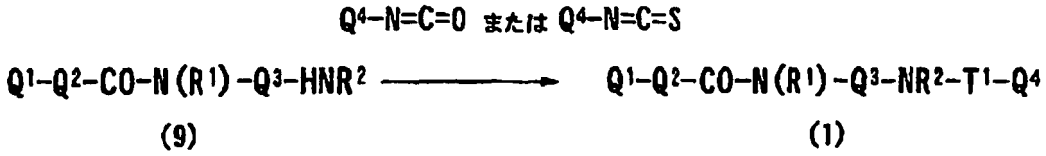
wherein Q^1, Q^2, Q^3, Q^4, R^1, R^2 and R" have the same meanings as defined above, and T^1 represents a group -CO-A^1-N(R")-, in which R" represents a hydrogen atom, hydroxyl group, alkyl group or alkoxy group, and A^1 represents an alkylene group having 1 to 5 carbon atoms, which may be substituted.

[0104] Compound (42) described in the preparation process described above can be prepared by, for example, reacting

an arylamine such as 4-chloroaniline with an ester of a bromoalkanoic acid at 40 to 120°C in the presence of a base such as potassium carbonate in a solvent such as acetonitrile or N,N-dimethylformamide and then hydrolyzing the ester with an alkali such as lithium hydroxide, potassium hydroxide or sodium hydroxide. Compound (42) may be used in reaction in the form of a salt such as a potassium salt as it is.

[Preparation Process 15] (Reference)

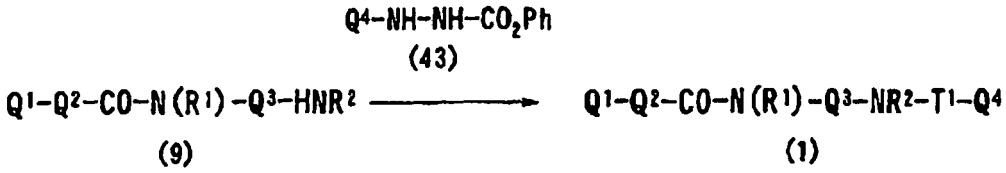
[0105] Compound (1) in which T' is a group -C(=O)-NH- or a group -C(=S)-NH-, can be prepared by reaction of compound (9) described in Preparation Process 2 with isocyanate (Q^4-N=C=O) or isothiocyanate (Q^4-N=C=S) at -20°C to 50°C in an inert solvent. A typical examples of the iner solvent is described in Preparation Process 14. When isocyanate or isothiocyanate is not commercialized, isocyanate or isothiocyanate can be synthesized using ordinary methods.



wherein Q^1, Q^2, Q^3, Q^4, R^1 and R^2 have the same meanings as defined above, and T^1 represents a group -C(=O)-NH- or group -C(=S)-NH-.

[Preparation Process 16] (Reference)

[0106] Compound (1) in which T^1 is a group -CO-NH-NH- can be prepared by reaction of compound (9) described in Preparation Process 2 with Q^4-NH-NH-CO_2Ph (43) at room temperature to 150°C in an inert solvent in the presence of a base if necessary. As typical examples of the inert solvent, may be mentioned acetonitrile and N,N-dimethylformamide, and besides those described in Preparation Process 14. As examples of the base, may be mentioned pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo [5.4.0]undec-7-ene (DBU).

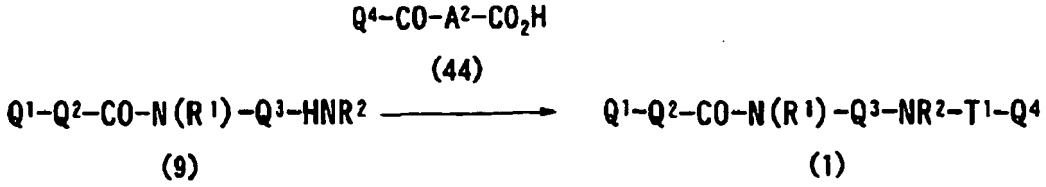


wherein Q^1, Q^2, Q^3, Q^4, R^1 and R^2 have the same meanings as defined above, T^1 represents a group -CO-NH-NH- and ph represents phenyl group.

[0107] Compound (43) described in the preparation process described above can be prepared by, for example, reacting an arylhydrazine such as 4-chlorophenylhydrazine with diphenyl carbonate at room temperature to 120°C in a solvent such as acetonitrile, N,N-dimethylformamide, methylene chloride, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, benzene or toluene.

[Preparation Process 17] (Reference)

[0108] Compound (1) in which T^1 is a group -CO-A^2-CO-, in which A^2 represents a single bond or alkylene group having 1 to 5 carbon atoms can be prepared by reaction of compound (9) described in Preparation Process 2 with Q^4-co-A^2-CO_2H (44) at -50°C to 50°C using a condensing agent in an inert solvent. As examples of the condensing agent, may be mentioned N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride or the like. As examples of the solvent, may be mentioned those described in Preparation Process 16 or the like.



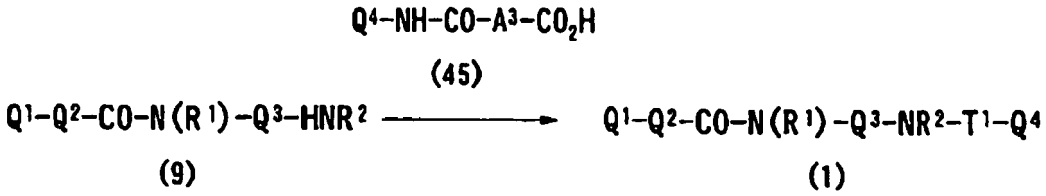
wherein Q^1, Q^2, Q^3, Q^9, R^1 and R^2 have the same meanings as defined above, and T^1 represents a group -CO-A^2-CO-, in which A^2 represents a single bond or alkylene group having 1 to 5 carbon atoms.

[0109] When A^2 is a single bond, compound (44) described in the preparation process described above can be prepared by, for example, hydrolyzing a compound (for example, Q^4-$COCO_2Et$) prepared by the Friedel-Crafts reaction of an aromatic hydrocarbon such as chlorobenzene or an aromatic heterocyclic compound such as thiophene with a chlorooxoacetate (for example, ClCO-CO_2Et) using an alkali such as lithium hydroxide, potassium hydroxide or sodium hydroxide.

[0110] When A^2 is a methylene group, compound (44) can be prepared by, for example, hydrolyzing a ketoester derivative (for example, Q^4-CO-CH_2-CO_2Et) obtained by reaction of an arylcarbonyl chloride such as 4-chlorobenzoyl chloride or a heteroarylcarbonyl chloride such as thiophenecarbonyl chloride with potassium malonic monoester monocarboxylate in the presence of magnesium chloride and triethylamine with an alkali such as lithium hydroxide, potassium hydroxide or sodium hydroxide. The ketoester derivative may be used in the above reaction with compound (9) in the form of a carboxylic acid obtained by hydrolysis after conversion of its carbonyl group into ethyleneketal. When A^2 is an alkylene group having at least 2 carbon atoms, compound (44) can be prepared by, for example, hydrolyzing a ketoester derivative (for example, Q^4-CO-A^2-CO_2Et) obtained by the Friedel-Crafts reaction of an aromatic hydrocarbon such as benzene or an aromatic heterocyclic compound such as thiophene with an alkylenedicarboxylic monoester monochloride using an alkali such as lithium hydroxide, potassium hydroxide or sodium hydroxide.

[Preparation Process 18] (Reference)

[0111] Compound (1) in which T^1 is a group -CO-A^3-CO-NH-, in which A^3 represents an alkylene group having 1 to 5 carbon atoms can be prepared by reaction of compound (9) described in Preparation Process 2 with Q^4-NH-CO-A^3-CO_2H (45) at -50 to 50°C using a condensing agent in an inert solvent. As examples of the condensing agent, may be mentioned N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and the like. Examples of the inert solvent include alkyl halide type solvents such as methylene chloride, chloroform, carbon tetrachloride, etheric solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane, aromatic solvents such as benzene and toluene, and amide solvents such as N,N-dimethylformamide.

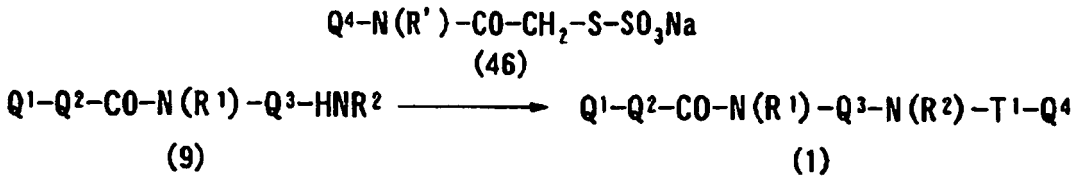


wherein Q^1, Q^2, Q^3, Q^4, R^1 and R^2 have the same meanings as defined above, and T^1 represents a group -CO-A^3-CO-, in which A^3 represents an alkylene group having 1 to 5 carbon atoms.

[0112] Compound (45) can be prepared by hydrolyzing a compound (for example, Q^4-NH-CO-A^3-CO_2Et) obtained by reaction of an arylamine such as 4-chloroaniline or a heteroarylamine such as aminopyridine corresponding to Q^4-NH_2 with potassium alkylenedicarboxylic monoester monocarboxylate at -50 to 50°C using a condensing agent in an inert solvent with an alkali such as lithium hydroxide, potassium hydroxide or sodium hydroxide.

[Preparation Process 19]

[0113] Compound (1) in which T^1 is a group -CS-CO-N(R')-, in which R' has the same meaning as defined above can be prepared in accordance with the following scheme:

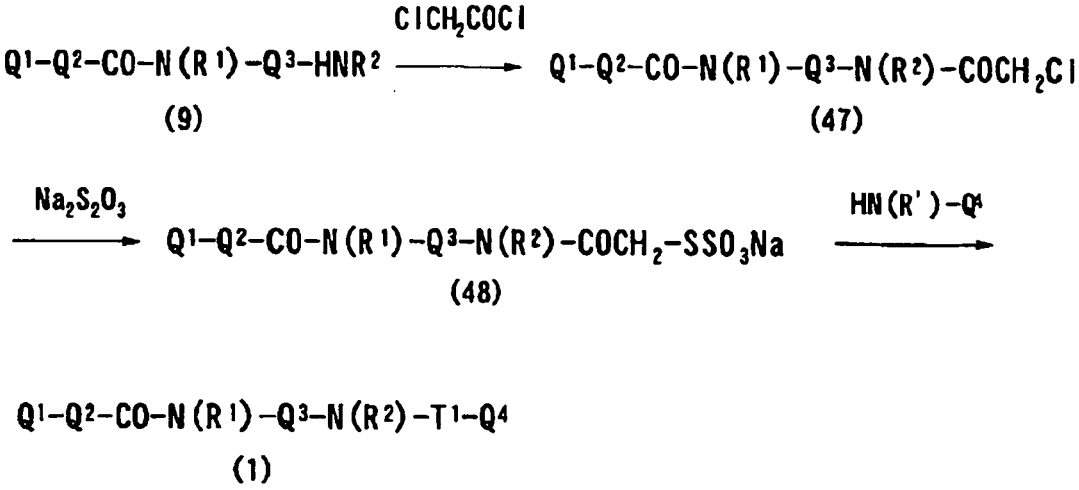


wherein Q^1, Q^2, Q^3, Q^4, R^1, R^2 and R' have the same meanings as defined above, and T^1 represents a group -CS-CO-N(R')-, in which R' has the same meaning as defined above.

[0114] More specifically, sodium thiosulfate (46) and compound (9) may be dissolved or dispersed in a solvent and heated, giving compound (1) according to the present invention. The reaction temperature is preferably 80 to 200°C, particularly preferably about 150°C. As the solvent used in this reaction, may be mentioned water, alcohols such as methanol and ethanol, basic solvents such as pyridine and N-methylmorpholine, alkyl halide type solvents such as methylene chloride, chloroform, etheric solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane, and amide solvents such as N,N-dimethylformamide. These solvents may be suitably mixed for use. As examples of mixed solvents, may be mentioned a mixed solvent of methanol and methylene chloride or the like. In this reaction, the solvent is not necessarily refluxed. For example, when the mixed solvent of methanol and methylene chloride is used, a reaction solution (or a reaction mixture) is heated at an external temperature of 150°C to distill off the solvent, and the residue is then heated at the same temperature.

[Preparation Process 20]

[0115] Compound (1) in which T^1 is a group -CO-CS-N(R')-, in which R' has the same meaning as defined above can be prepared in accordance with the following scheme:



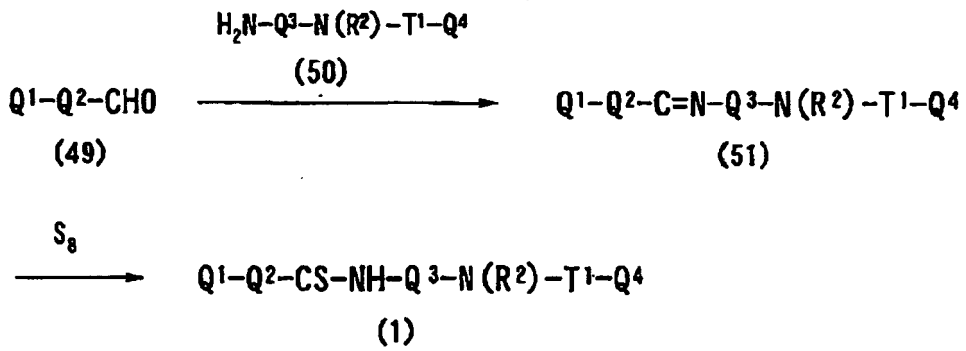
wherein Q^1, Q^2, Q^3, Q^4, R^1, R^2 and R' have the same meanings as defined above, and T^1 represents a group -CO-CS-N(R')-, in which R' has the same meaning as defined above.

[0116] More specifically, compound (9) may react with chloroacetyl chloride in the presence of a base, giving compound (47). Compound (47) may be heated together with sodium thiosulfate in a solvent, giving sodium thiosulfate derivative (48). The thus-obtained sodium thiosulfate derivative (48) may be heated with an amine, i.e., HN(R')-Q^4, giving compound (1) according to the present invention.

[0117] As conditions, solvent and the like for preparing compound (47) from compound (9), may be applied those commonly used in reaction of an amine with acid chloride. In order to prepare compound (48) from compound (47), it is only necessary to heat compound (47) together with sodium thiosulfate under reflux for about 1 hour in a solvent such as ethanol. When compound (47) is a salt with hydrochloric acid or the like, the reaction may be performed in the presence of a base such as sodium hydrogencarbonate. The preparation conditions of compound (48) are not limited to those described herein, and the temperature and the kinds of the solvent and base may be suitably changed. The conditions for the reaction of compound (48) with HN(R')-Q^4 are the same as those described in Preparation Process 19.

[Preparation Process 21]

[0118] Compound (1) in which T^0 is a thiocarbonyl group (-CS-) can be prepared in accordance with the following scheme:



wherein Q^1, Q^2, Q^3, Q^4 and R^2 have the same meanings as defined above, and T^1 represents a group $-SO_2-$, -CO-, -CO-NH-, -CS-NH-, -CO-NH-NH-, -CO-CO-N(R'), in which R' has the same meaning as defined above, -CO-CS-N(R'), in which R' has the same meaning as defined above, -CS-CO-N(R')-, in which R' has the same meaning as defined above, -CS-CS-N(R')-, in which R' has the same meaning as defined above,- CO-A^1-N(R")-, in which A^1 and R" have the same meanings as defined above, -CO-A^2-CO-, in which A^2 has the same meaning as defined above, -CO-A^3-CO-NH-, in which A^3 has the same meanings as defined above, or -CO-A^3-CO-, in which A^3 has the same meaning as defined above.

[0119] More specifically, compound (49) may be subjected to dehydration reaction with amine (50) in the presence of an acid catalyst such as p-toluenesulfonic acid, giving compound (51). Compound (51) may be heated together with sulfur powder in a solvent such as a mixed solvent of methanol/methylene chloride, giving compound (1) according to the present invention. As conditions for preparing compound (51) from compound (49) and amine (50), may be applied those commonly used in preparation of a Schiff base. Specifically, heating under reflux may be conducted in the presence of an acid catalyst in benzene or toluene under conditions that water is removed from the reaction system by, for example, using a Dean-Stark trap. Molecular sieve may also be used in removing water from the reaction system.

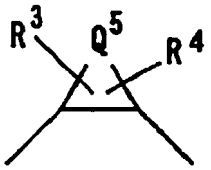
[0120] The important intermediates described in Preparation Process 1 to 21 of the compounds (1) according to the present invention will hereinafter be described.

1) The compounds described in Preparation Process 1, 3 and 11 and represented by the following general formula (4):

$$HN(R^1)\text{-}Q^3\text{-}N(R^2)\text{-}T^1\text{-}Q^4 \quad (4)$$

wherein R^1, R^2, Q^3 and Q^4 have the same meanings as defined above, and T^1 represents a carbonyl group, sulfonyl group or group -CO-CO-N(R'), in which R' has the same meaning as defined above, are important as intermediates for preparing compounds (1) according to the present invention.

Among the above-described intermediates, are preferred compounds in which T^1 is a group -C(=O)-C(=O)-N(R'), in which R' means a hydrogen atom, hydroxyl group, alkyl group or alkoxy group, and compounds in which T^1 in the above formula is a carbonyl group, and Q^3 is the following group:



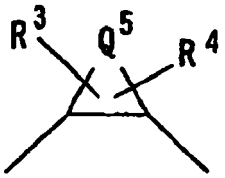
in which R^3 and R^4 have the same meanings as defined above, and Q^5 means a group $-(CH_2)_m\text{-}CH_2\text{-}A\text{-}CH_2\text{-}(CH_2)_n-$, in which m and n are independently of each other 0 or an integer of 1-3, and A means an oxygen atom, nitrogen atom, sulfur atom, -SO-, $-SO_2-$, -NH-, -O-NH-, -NH-NH-, -S-NH-, -SO-NH-or $-SO_2$-NH-.

2) The compounds described in Preparation Process 2, 4 and 12 and represented by the following general formula (9):

Q^1-Q^2-C(=O)-N(R^1)-Q^3-NHR^2 (9)

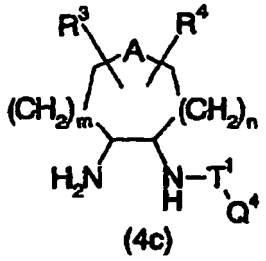
wherein R^1, R^2, Q^1, Q^2 and Q^3 have the same meanings as defined above, are important as intermediates for preparing compounds (1) according to the present invention.

Among the above-described intermediates, are preferred compounds in which Q^3 is the following group:



in which R^3 and R^4 have the same meanings as defined above, and Q^5 means a group - $(CH_2)_m$-CH_2-A-CH_2-$(CH_2)_n$-, in which m and n are independently of each other 0 or an integer of 1-3, and A means an oxygen atom, nitrogen atom, sulfur atom, -SO-, -SO_2-, -NH-, -O-NH-, -NH-NH-, -S-NH-, -SO-NH-or -SO_2-NH-.

3) (Reference) The following compounds (4C) described in Preparation Process 7, 11 and 13 are important as intermediates for preparing compounds (1) according to the present invention.

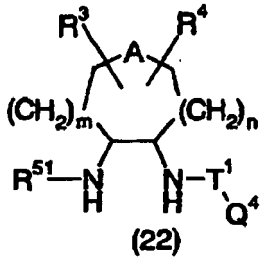


(4c)

wherein Q^4, R^3, R^4, A, m and n have the same meanings as defined above, and T^1 represents a carbonyl group, sulfonyl group or group -CO-CQ-N(R'), in which R' has the same meaning as defined above.

Among the above-described intermediates, are preferred compounds in which T^1 in the above formula is a group -CO-CO-N(R'), in which R' has the same meaning as defined above, and compounds in which T^1 is a carbonyl group, and A is an oxygen atom, nitrogen atom, sulfur atom, -SO-, -SO_2-, -NH-, -O-NH-, -NH-NH-, -S-NH-, -SO-NH- or -SO_2-NH-.

4) (Reference) The following compounds (22) described in Preparation Process 8 and 13 are important as intermediates for preparing compounds (1) according to the present invention.

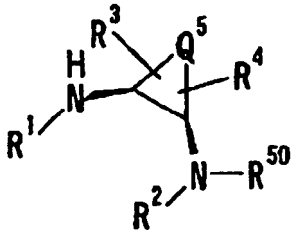


(22)

wherein Q^4, R^3, R^4, A, m and n have the same meanings as defined above, T^1 represents a carbonyl group, sulfonyl group or group -CO-CO-N(R'), in which R' has the same meaning as defined above, and R^{51} represents a protecting group for amino group.

Among the above-described intermediates, are preferred compounds in which T^1 in the above formula is a group -CO-CO-N(R'), in which R' has the same meaning as defined above, and compounds in which T^1 is a carbonyl group, and A is an oxygen atom, nitrogen atom, sulfur atom, -SO-, -SO_2-, -NH-, -O-NH-, -NH-NH-, -S-NH-, -SO-NH- or -SO_2-NH-.

5) The following optically active compounds (7a) described in Preparation Process 6 are important as intermediates for preparing compounds (1) according to the present invention.

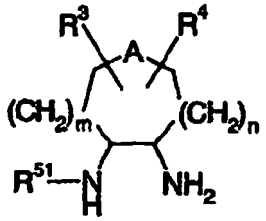


(7a)

wherein Q^5, R^1, R^2, R^3 and R^4 have the same meanings as defined above, and R^{50} represents a protecting group for amino group.

Among the above-described intermediates, are preferred compounds in which Q^5 in the above formula is a group $-(CH_2)_m-CH_2-A-CH_2-(CH_2)_n-$, in which m and n are independently of each other 0 or an integer of 1-3, and A means an oxygen atom, nitrogen atom, sulfur atom, -SO-, $-SO_2-$, NH-, -O-NH-, -NH-NH-, -S-NH-, -SO-NH- or $-SO_2-NH-$.

6) (Reference) The following compounds (21) described in Preparation Process 8 are important as intermediates for preparing compounds (1) according to the present invention.

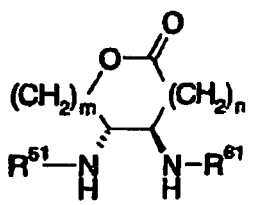


(21)

wherein R^3, R^4, A, m and n have the same meanings as defined above, and R^{51} represents a protecting group for amino group.

Among the above-described intermediates, are preferred compounds in which A in the above formula is an oxygen atom, nitrogen atom, sulfur atom, -SO-, $-SO_2-$, -NH-, -O-NH-, -NH-NH-, -S-NH-, -SO-NH- or $-SO_2-NH-$.

7) (Reference) The following compounds described in Preparation Process 10 are important as intermediates for preparing compounds (1) according to the present invention. More specifically, the following optically active trans-form compounds (30), (31) and (32):



(30)

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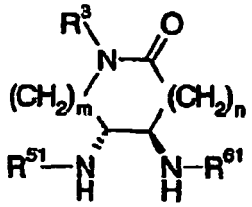

(31)

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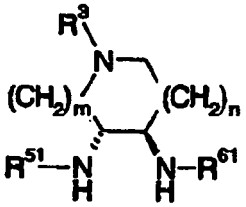
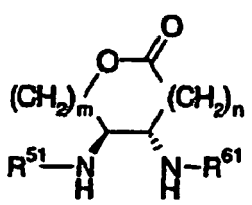
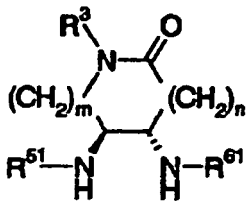


(32)

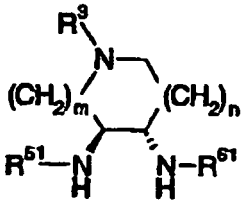
wherein R^3, m and n have the same meanings as defined above, and R^{51}, and R^{61} represent protecting groups for amino group, enantiomers (30a), (31a) and (32a) of the above compounds prepared in a similar manner:



(30a)

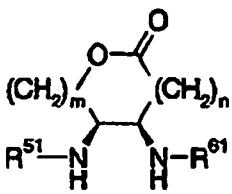


(31a)

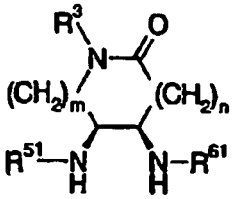


(32a)

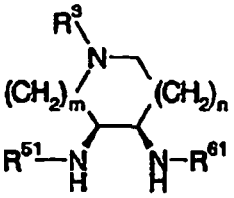
wherein R^3, m and n have the same meanings as defined above, and R^{51} and R^{61} represent protecting groups for amino group, cis-form compounds (30b), (31b) and (32b):



(30b)

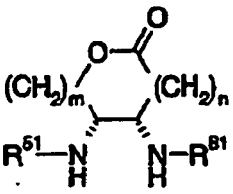


(31b)

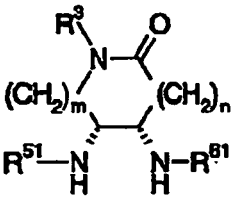


(32b)

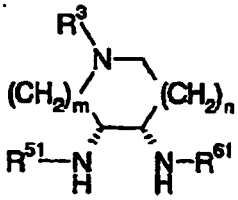
wherein R^3, m and n have the same meanings as defined above, and R^{51} and R^{61} represent protecting groups for amino group, and enantiomers (30c), (31c) and (32c) thereof:



(30c)



(31c)



(32c)

wherein R^3, m and n have the same meanings as defined above, and R^{51} and R^{61} represent protecting groups for amino group, are important as intermediates for preparing compounds (1) according to the present invention.

[0121] The diamine derivatives according to the present invention exhibit strong inhibitory effects on activated blood coagulation factor X and are thus useful for medicines for mammal including human, anticoagulants factor X, agents for preventing and/or treating thrombosis or embolism, agents for preventing and/or treating thrombtic diseases, and agents for preventing and/or treating cerebral infarction, cerebral embolism, myocardial infarction, angina pectoris, pulmonary infarction, pulmonary embolism, Buerger's disease, deep venous thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve or joint replacement, thrombus formation and reocclusion after angioplasty, systemic inflammatory reaction syndrome (SIRS), multiple organ disease syndrome (MODS), thrombus formation during extracorporeal circulation, or blood clotting upon blood gathering.

[0122] When a compound according to the present invention is used as a medicine for human body, the dose is within a range of 1 mg to 1 g, preferably 10 to 300 mg, per day for an adult. The dose for animal varies according to the object (treatment or prevention) of the administration, the kind and size of an animal to be treated, the kind of a contagium, and the condition of a disease attacked. However, it is generally within a range of 0.1 to 200 mg, preferably 0.5 to 100 mg, per kg of weight a day. Meanwhile, the administration may be once per day, or may be divided into 2 to 4 times per day. The dose per day may exceed the above range if necessary.

[0123] Medicinal compositions comprising the compound according to the present invention can be prepared by selecting a suitable preparation form according to an administration method in accordance with a preparation method for the preparation form used. As examples of the preparation forms of the medicinal compositions comprising the compound according to the present invention as a main component, may be mentioned tablets, tablets, powder, granules, capsules, solutions, syrups, elixirs, oil or aqueous suspensions or the like for oral preparations.

[0124] In the case of an injection, a stabilizer, a preservative and a dissolution aid may be used in a preparation. A solution which may contain these auxiliaries in some cases may also be provided as a solid form for preparing upon use by containing the solution into a container and then drying the solution by lyophilization or the like. A dose or doses of the injection may also be contained into a container.

[0125] As example of preparation forms for external application, may be mentions solutions, suspensions, emulsions, ointments, gel, creams, lotions, sprays, plasters or the like.

[0126] A solid preparation may contain pharmaceutically acceptable additives in addition to the compound according to the present invention. For example, fillers, extenders, binders, disintegrators, dissolution accelerators, wetting agents, etc. may be suitably selected and mixed, giving a preparation.

[0127] As example of preparation forms of a liquid preparation, may be mentioned solutions, suspensions, emulsions and the like. They may contain a suspending agent, emulsifier and/or the like in some cases.

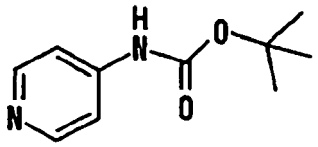
Examples

[0128] However, the present invention is not limited to these examples.

[Referential Example 1]

tert-Butyl pyridin-4-ylcarbamate:

[0129]



[0130] 4-Aminopyridine (10 g) was dissolved in tetrahydrofuran (500 ml), di-tert-butyl dicarbonate (25.5 g) was added to the solution, and the mixture was stirred at room temperature for 10 minutes. The resultant reaction mixture was concentrated under reduced pressure, and deposited solids were washed with hexane to obtain the title compound (16.9 g).

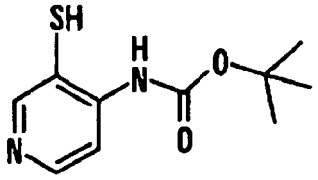
^{1}H-NMR ($CDCl_3$) δ: 1.53 (9H,s), 6.86 (1H,br.s), 7.30(2H,dd,J=1.5,4.9Hz), 8.44(2H,dd,J=1.5,4.9Hz).

MS (FAB) m/z: 195 $(M+H)^+$.

[Referential Example 2]

tert-Butyl 3-sulfanylpyridin-4-ylcarbamate:

[0131]



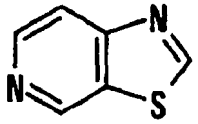
[0132] The compound (61.6 g) obtained in Referential Example 1 was dissolved in tetrahydrofuran (2,000 ml), and the solution was stirred at -78°C for 10 minutes. A hexane solution (1.59 mol/1, 500 ml) of n-butyllithium was added dropwise to the solution, and the mixture was stirred for 10 minutes and then for 2 hours with ice cooling. After the reaction mixture was cooled to -78°C, sulfur powder (12.2 g) was added, and the resultant mixture was warmed to room temperature and stirred for 1 hour. Water (1,000 ml) was added to the reaction mixture to separate a water layer. After 3N hydrochloric acid was added to the water layer to adjust the pH of the water layer to 3 to 4, methylene chloride was added to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 50:1) to obtain the title compound (33.2 g).

^{1}H-NMR (DMSO-d_6) δ: 1.52 (9H, s), 7.89(1H,d,J=6.4Hz), 7.99(1H,d,J=6.4Hz), 8.20 (1H, s), 9.91 (1H, br.s).

MS (FAB) m/z: 227 $(M+H)^+$.

[Referential Example 3] Thiazolo[5,4-c]pyridine:

[0133]

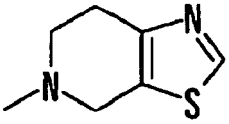


[0134] The compound (33.2 g) obtained in Referential Example 2 was dissolved in formic acid (250 ml), and the solution was heated under reflux for 3 days. The reaction mixture was concentrated under reduced pressure, and a 5N aqueous solution (100 ml) of potassium hydroxide and diethyl ether were added to the residue to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 25:1) to obtain the title compound (9.03 g).
^{1}H-NMR ($CDCl_3$) δ: 8.05(1H,d,J=5.4Hz), 8.70(1H,d,J=5.4Hz), 9.23 (1H,s), 9.34 (1H,s).
MS (FAB) m/z: 137 $(M+H)^+$.

[Referential Example 4]

5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine:

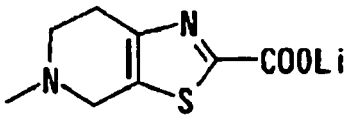
[0135]



[0136] The compound (1.61 g) obtained in Referential Example 3 was dissolved in N,N-dimethylformamide (50 ml), and to the solution methyl iodide (1.50 ml) was added, the resultant mixture was stirred at 80°C for 4 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methanol (100 ml), sodium borohydride (1.53 g) was added, and the resultant mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and a saturated aqueous solution of potassium carbonate and diethyl ether were added to the residue to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 25:1) to obtain the title compound (1.28 g).
^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 2.83(2H,t,J=5.9Hz), 2.98(2H,t,J=5.9Hz), 3.70 (2H, s), 8.63 (1H, s).
MS (FAB) m/z: 155 $(M+H)^+$.

[Referential Example 5]

Lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxylate:



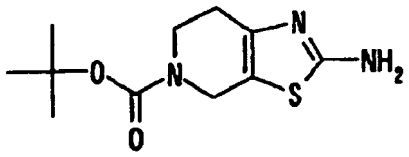
[0137] The compound (6.43 g) obtained in Referential Example 4 was dissolved in absolute tetrahydrofuran (200 ml), to the soltion n-butyllithium (1.47N hexane solution, 34.0 ml) was added dropwise at -78°C, and the resultant mixture was stirred for 40 minutes. After carbon dioxide gas was blown into the reaction mixture at -78°C for 1 hour, the reaction mixture was warmed to room temperature and then concentrated under reduced pressure to obtain the title compound (9.42 g).

^{1}H-NMR (DMSO-d_6) δ: 2.37 (3H, s), 2.64-2.77 (4H, m), 3.54 (2H, s).
MS (FAB) m/z : 199 $(M+H)^+$.

[Referential Example 6]

tert-Butyl 2-amino-6,7-dihydrothiazolo[5,4-c]pyridine-5[4H]-carboxylate :

[0138]

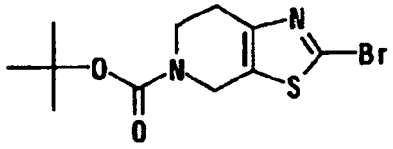


[0139] 1-tert-Butoxycarbonyl-4-piperidone (40.0 g) was dissolved in cyclohexane (80 ml), and to the solution p-toluenesulfonic acid monohydrate (191 mg) and pyrrolidine (17.6 ml) were added. The mixture was heated under reflux for 2 hours while removing water using a Dean-Stark trap. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in methanol (60 ml), and sulfur powder (6.42 g) was added. A methanol solution (10 ml) of cyanamide (8.44 g) was slowly added dropwise to the solution with ice cooling, and the mixture was stirred at room temperature for 5 hours. Precipitated solid materials were collected by filtration to obtain the title compound (31.0 g).
^{1}H-NMR (DMSO-d_6) δ: 1.41 (9H, s), 2.44(2H,t,J=5.6Hz), 3.57(2H,t,J=5.6Hz), 4.29(2H,s), 6.79(2H,s).
MS (EI) m/z: 255(M^+).

[Referential Example 7]

tert-Butyl 2-bromo-6,7-dihydrothiazolo[5,4-c]pyridine-5[4H]-carboxylate:

[0140]

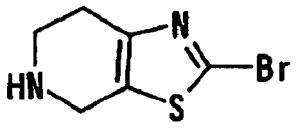


[0141] Copper(II) bromide (1.05 g) was suspended in N,N-dimethylformamide(20 ml), and tert-butyl nitrite (0.696 ml) and the compound (1.00 g) obtained in Referential Example 6 were added with ice cooling, the reaction mixture was heated and stirred at 40°C for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:5) to obtain the title compound (568 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 2.85 (2H, br.s), 3.72(2H,br.s), 4.56(2H,br.s).
MS (FAB) m/z: 319 $(M+H)^+$.

[Referential Example 8]

2-Bromo-4,5,6,7-tetrahydrothiazolo [5,4-c] pyridine trifluoroacetate:

[0142]

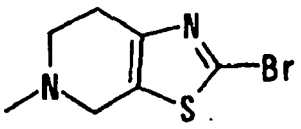


[0143] The compound (890 mg) obtained in Referential Example 7 was dissolved in methylene chloride (2 ml), and to the solution trifluoroacetic acid (15 ml) was added, and the mixture was stirred at room temperature for 30 seconds. The reaction mixture was concentrated under reduced pressure, and diethyl ether was added to the residue. Precipitated solid materials were collected by filtration to obtain the title compound (867 mg).
^{1}H-NMR (DMSO-d_6) δ: 2.98(2H,t,J=6.1Hz), 3.45(2H,t,J=6.1Hz), 4.35(2H,s), 9.53(2H,br.s).
MS (FAB) m/z: 219 $(M+H)^+$.

[Referential Example 9]

2-Bromo-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine:

[0144]

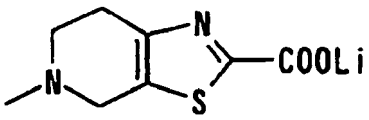


[0145] The compound (422 mg) obtained in Referential Example 8 was suspended in methylene chloride (10 ml), and triethylamine (0.356 ml) was added to make a solution. Acetic acid (0.216 ml), an aqueous solution (35% solution, 0.202 ml) of formaldehyde and sodium triacetoxyborohydride (428 mg) were successively added to the solution, and the resultant mixture was stirred at room temperature for 1 hour. A saturated aqueous solution (100 ml) of sodium hydrogencarbonate, methylene chloride (100 ml) and a 3N aqueous solution (3 ml) of sodium hydroxide were added to the reaction mixture to conduct liquid separation. After an organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 100:3) to obtain the title compound (286 mg).
^{1}H-NMR (CDC_3) δ: 2.49 (3H, s), 2.79(2H,t,J=5.7Hz), 2.85-2.93(2H,m), 3.58(2H,t,J=1.8Hz).
MS (FAB) m/z: 233 $(M+H)^+$.

[Referential Example 10]

Lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxylate:

[0146]

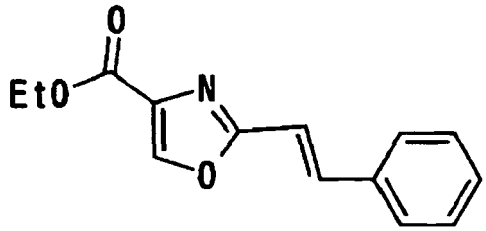


[0147] The compound (531 mg) obtained in Referential Example 9 was dissolved in absolute diethyl ether (20 ml), n-butyllithium (1.54N hexane solution, 1.63 ml) was added dropwise at -78°C, and the mixture was stirred for 30 minutes with ice cooling. After passing carbon dioxide into the reaction mixture at -78°C for 10 minutes, the mixture was warmed to room temperature. The reaction mixture was concentrated under reduced pressure to obtain the title compound (523 mg).
^{1}H-NMR (DMSO-d_6) δ: 2.37 (3H, s), 2.64-2.85(4H,m), 3.54(2H,s).

[Referential Example 11]

Ethyl 2-[(E)-2-phenylethenyl]oxazole-4-carboxylate:

[0148]

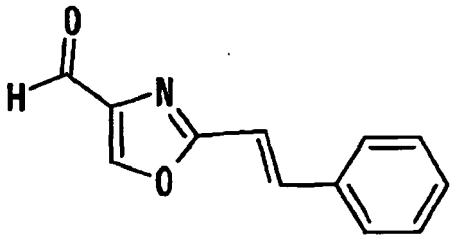


[0149] Synthesis was conducted in accordance with the report (J. Org. Chem., 1996, Vol. 61, p. 6496) by Panek et al. Sodium hydrogencarbonate (22.8 g) and ethyl bromopyruvate (10.5 ml) were added to a solution of cinnamamide (10.0 g) in tetrahydrofuran (250 ml) at room temperature, and the mixture was heated under reflux for 48 hours. The reaction mixture was allowed to cool to room temperature, filtered through Celite and then concentrated under reduced pressure to obtain residue. Trifluoroacetic anhydride (30 ml) was added to a solution of this residue in tetrahydrofuran (30 ml) at 0°C, and the mixture was gradually warmed to room temperature. After the mixture was stirred for 63 hours, a saturated aqueous solution (500 ml) of sodium hydrogencarbonate and ethyl acetate (150 ml) were added to the reaction mixture, and a water layer was separated. The water layer was extracted with ethyl acetate (150 ml). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (150 ml), dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 5:1 → 3:1) to obtain the title compound (10.9 g).
^{1}H-NMR ($CDCl_3$) δ: 1.41(3H,t,J=7.0Hz), 4.42(2H,q,J=7.0Hz), 6.96(1H,d,J=16.6Hz), 7.30-7.40(3H,m), 7.53(2H,d, J=6.8Hz), 7.63(1H,d,J=16.6Hz), 8.20 (1H, s).

[Referential Example 12]

2-[(E)-2-phenylethenyl]oxazole-4-carbaldehyde:

[0150]

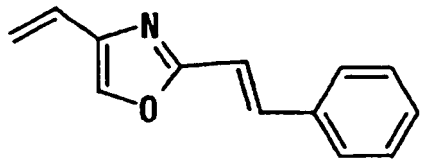


[0151] Diisobutylaluminum hydride (1.0N hexane solution, 66 ml) was added dropwise to a solution of the compound (8.57 g) obtained in Referential Example 11 in methylene chloride (80 ml) at -78°C. After 15 minutes, methanol (11 ml) was added dropwise, and the mixture was warmed to room temperature over 1 hour. The reaction mixture was filtered through Celite, and the resultant pasty substance was dissolved in ethyl acetate (200 ml) and a saturated aqueous solution (200 ml) of ammonium chloride was added, and a water layer was separated. The water layer was then extracted with methylene chloride (2 x 100 ml). The resultant organic layers were collected and washed with a saturated aqueous solution (100 ml) of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride (100 ml), combined with the filtrate obtained by the filtration through Celite and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:ethyl acetate = 5:1 → methylene chloride:methanol = 10:1) to obtain the title compound (5.86 g).
^{1}H-NMR ($CDCl_3$) δ: 6.96(1H,d,J=16.6Hz), 7.35-7.45(3H,m), 7.56(2H,d,J=6.4Hz), 7.67(1H,d,J=16.6Hz), 8.26 (1H,s), 9.98 (1H,s).
MS (FAB) m/z: 200$(M+H)^+$.

[Referential Example 13]

2-[(E)-2-Phenylethenyl]-4-vinyloxazole:

[0152]



[0153] n-Butyllithium (1.54N hexane solution, 14.2 ml) was added dropwise to a solution of methyltriphenylphosphonium bromide (8.16 g) in tetrahydrofuran (80 ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was cooled again to 0°C, a solution of the compound (3.64 g) obtained in Referential Example 12 in tetrahydrofuran (20 ml) was added, and the mixture was warmed to room temperature. After stirring for 2 hours, water (200 ml) and ethyl acetate (100 ml) were added and a water layer was separated. The water layer was extracted with ethyl acetate (50 ml). After the organic layers were combined, washed with saturated aqueous solution of sodium chloride (100 ml) and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1 → 3:1) to obtain the title compound (2.84 g).

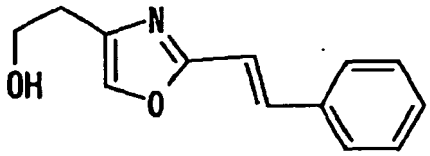
^{1}H-NMR ($CDCl_3$) δ: 5.33(1H,dd,J=1.5,10.7Hz), 5.98(1H,dd,J=1.5,17.6Hz), 6.56(1H,dd,J=10.7,17.6Hz), 6.95(1H,d, J=16.6Hz), 7.31-7.42(3H,m), 7.49-7.56(4H,m).

MS (FAB) m/z: 198$(M+H)^+$.

[Referential Example 14]

2-{2-[(E)-2-Phenylethenyl]oxazol-4-yl}-1-ethanol:

[0154]



[0155] 9-Borabicyclo[3.3.1]nonane (0.5N tetrahydrofuran solution, 158 ml) was added to a solution of the compound (13.0 g) obtained in Referential Example 13 in tetrahydrofuran (500 ml), and the mixture was stirred at room temperature for 15 hours. Water (10 ml), a 3N aqueous solution (80 ml) of sodium hydroxide and aqueous hydrogen peroxide (80 ml) were successively added dropwise to the reaction mixture at 0°C, and the mixture was stirred at room temperature for 6 hours. After water (600 ml) and ethyl acetate (200 ml) were added to the resultant reaction mixture to separate a water layer, the water layer was extracted with ethyl acetate (200 ml). After the organic layers were collected, washed with saturated aqueous solution of sodium chloride (200 ml) and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1 → ethyl acetate alone) to obtain the title compound (14.1 g)

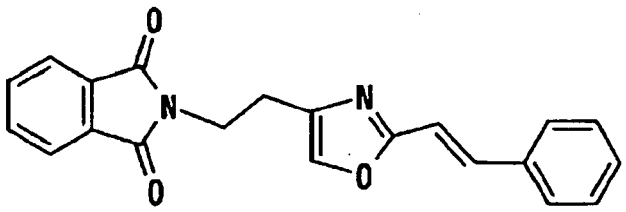
^{1}H-NMR ($CDCl_3$) δ: 2.69(1H,br.s), 2.80(2H,t,J=5.6Hz), 3.90-3.97(2H,m), 6.91(1H,d,J=16.6Hz), 7.30-7.42(4H,m), 7.43-7.56(3H,m).

MS (FAB) m/z: 216 $(M+H)^+$.

[Referential Example 15]

2-(2-{2-[(E)-2-Phenylethenyl]oxazol-4-yl}ethyl)-1H-isoindol-1,3(2H)-dione:

[0156]

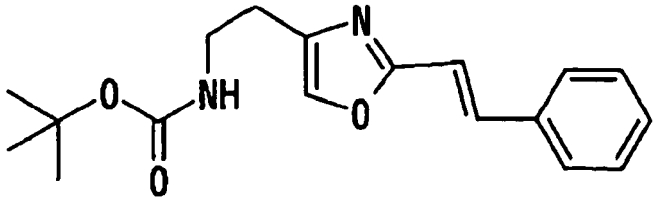


[0157] Phthalimide (200 mg), triphenylphosphine (357 mg) and diethyl azodicarboxylate (0.214 ml) were added to a solution of the compound (292 mg) obtained in Referential Example 14 in tetrahydrofuran (15 ml) at room temperature, and the mixture was stirred for 4 hours. The solvent of the reaction mixture was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (447 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.98(2H,t,J=7.2Hz), 4.03(2H,t,J=7.2Hz), 6.88(1H,d,J=16.6Hz), 7.28-7.45(5H, m), 7.48(2H,d, J=7.3Hz), 7.71(2H,dd,J=2.9,5.4Hz), 7.84(2H,dd,J=2.9,5.4Hz).
MS (FAB) m/z: 345 $(M+H)^+$.

[Referential Example 16]

tert-Buthyl 2-{2-[(E)-2-phenylethenylloxazol-4-yl}ethylcarbamate:

[0158]

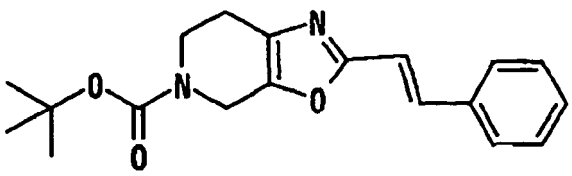


[0159] After hydrazine monohydrate (1.50 ml) was added to a solution of the compound (6.40 g) obtained in Referential Example 15 in ethanol (150 ml) at room temperature, and the mixture was stirred for 1 hour, hydrazine monohydrate (0.500 ml) was added again at room temperature, and the mixture was stirred for 2 hours. Methylene chloride (150 ml), a saturated aqueous solution (150 ml) of sodium hydrogencarbonate and di-tert-butyl dicarbonate (13.4 g) were added to the reaction mixture at room temperature. After stirring for 30 minutes, a water layer was separated and extracted with methylene chloride (50 ml). The resultant organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1 $\rightarrow$ 1:1) to obtain the title compound (5.06 g).
^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.75(2H,t,J=6.6Hz), 3.46(2H,dt,J=5.9,6.6Hz), 4.92(1H,br.s), 6.91(1H,d,J=16.6Hz), 7.29-7.45(4H,m), 7.48(1H,d,J=16.6Hz), 7.52(2H,d,J=7.3Hz).
MS (FAB) m/z: 315 $(M+H)^+$, 259 (M-isobutene+H)$^+$, 315 (M-Boc+H)$^+$.

[Referential Example 17]

tert-Buthyl 2-[(E)-2-phenylethenyl]-6,7-dihydrooxazolo-[5,4-c]pyridine-5(4H)-carboxylate:

[0160]



[0161] Paraformaldehyde (54.5 mg) and p-toluenesulfonic acid (7.2 mg) were added to a solution of the compound (190 mg) obtained in Referential Example 16 in toluene (15 ml) at room temperature. After heating under reflux for 1

hour, the reaction mixture was allowed to cool, and ethyl acetate (15 ml) and a saturated aqueous solution (15 ml) of sodium hydrogencarbonate were added to the reaction mixture to separate a water layer. After the water layer was extracted with ethyl acetate (10 ml), the resultant organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1 → 2:1) to obtain the title compound (153 mg).

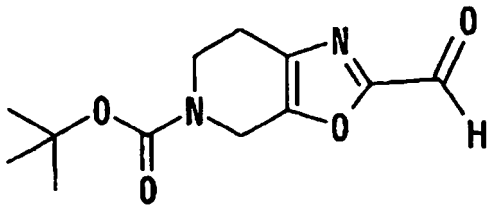
^{1}H-NMR ($CDCl_3$) δ: 1.50(9H,s), 2.67(2H,br.s), 3.73(2H,br.s), 4.55(2H,s), 6.90(1H,d,J=16.1Hz), 7.29-7.42(3H,m), 7.46 (1H,d,J=16.1Hz), 7.52(2H,d,J=7.3Hz).

MS (FAB) m/z: 327 $(M+H)^+$, 271 $(M\text{-isobutene}+H)^+$, 227 $(M\text{-Boc}+H)^+$.

[Referential Example 18]

tert-Butyl 2-formyl-6,7-dihydrooxazolo[5,4-c]pyridine-5(4H)-carboxylate:

[0162]



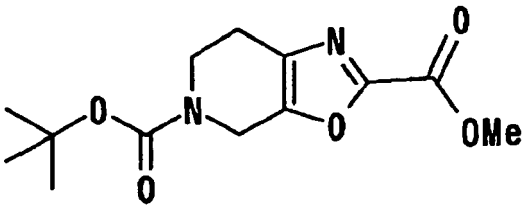
[0163] Acetone (8.0 ml), water (4.0 ml), N-methylmorpholine N-oxide (577 mg) and a 0.039 M aqueous solution (3.20 ml) of osmium tetroxide were added to a solution of the compound (803 mg) obtained in Referential Example 17 in tetrahydrofuran (16 ml) at room temperature, and the mixture was stirred overnight. Ethyl acetate (50 ml) and a 10% aqueous solution (50 ml) of sodium thiosulfate were added to the reaction mixture to separate a water layer. The water layer was then extracted with ethyl acetate (30 ml). After the resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. Methanol (8.0 ml), water (8.0 ml) and sodium metaperiodate (790 mg) were added to a solution of the residue in tetrahydrofuran (16 ml). After stirring for 3 hours, ethyl acetate (30 ml) and water (50 ml) were added to the reaction mixture to separate a water layer. The water layer was extracted with ethyl acetate (20 ml). After the resultant organic layers were combined, washed with a saturated solution (50 ml) of sodium hydrogencarbonate and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1 → 2:1) to obtain the title compound (234 mg). Since this aldehyde was unstable, it was immediately used in the next reaction.

^{1}H-NMR ($CDCl_3$) δ: 1.49(9H,s), 2.77(2H,br.s), 3.77(2H,br.s), 4.62 (2H,s), 9.70 (1H,s).

[Referential Example 19]

5-(tert-Butyl) 2-methyl 6,7-dihydrooxazolo[5,4-c]pyridine-2,5(4H)-dicarboxylate:

[0164]



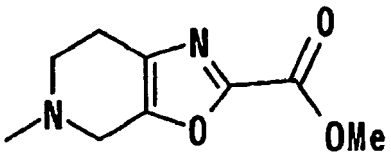
[0165] Sodium cyanide (220 mg) and manganese dioxide (780 mg) were added to a solution of the compound (225 mg) obtained in Referential Example 18 in methanol (9.0 ml) at room temperature. After stirring for 30 minutes, the reaction mixture was filtered through Celite with ethyl acetate. The filtrate was washed with water (50 ml) and saturated aqueous solution of sodium chloride (50 ml) and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:2 → 1:1) to obtain the title compound (120 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.49(9H,s), 2.73(2H,br.s), 3.74(2H,br.s), 4.01(3H,s), 4.59(2H,s).
MS (FAB) m/z: 283 $(M+H)^+$.

[Referential Example 20]

Methyl 5-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine-2-carboxylate:

[0166]

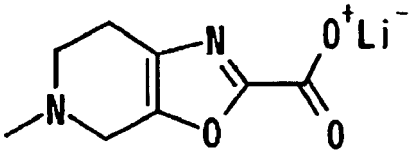


[0167] Trifluoroacetic acid (15 ml) was added to a solution of the compound (500 mg) obtained in Referential Example 19 in methylene chloride (15 ml) at room temperature, and the mixture was stirred for 10 minutes. The reaction mixture was concentrated under reduced pressure, and methylene chloride (20 ml), triethylamine (0.495 ml), acetic acid (205 ml), formalin (0.230 ml) and sodium triacetoxyborohydride (570 mg) were added to the resultant residue at room temperature. After stirring for 15 minutes, methylene chloride (20 ml) and a saturated aqueous solution (50 ml) of sodium hydrogencarbonate were added to separate an organic layer. The water layer was extracted with methylene chloride (3 x 20 ml). After the resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol = 20:1 $\rightarrow$ 10:1) to obtain the title compound (257 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.52(3H,s), 2.72-2.78(2H,m), 2.78-2.83 (2H,m), 3.61(2H,t,J=1.7Hz), 4.00 (3H, s).
MS (FAB) m/z: 197$(M+H)^+$, 165$(M-OCH_3)^+$.

[Referential Example 21]

Lithium 5-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]-pyridine-2-carboxylate:

[0168]

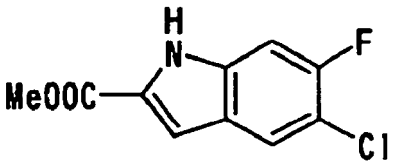


[0169] Water (6.0 ml) and lithium hydroxide (99.7 mg) were added to a solution of (800 mg) obtained in Referential Example 20 in tetrahydrofuran (24 ml) at room temperature, and the mixture was stirred for 10 minutes. The reaction mixture was concentrated under reduced pressure to obtain the title compound (825 mg).
^{1}H-NMR (DMSO-d_6) δ: 2.37(3H,s), 2.47(2H,t,J=5.6Hz), 2.64(2H,t,J=5.6Hz), 3.43(2H,s).

[Referential Example 22]

Methyl 5-chloro-6-fluoroindole-2-carboxylate:

[0170]



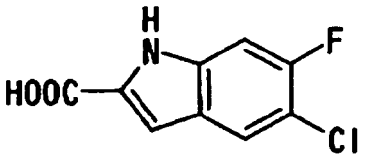
[0171] A mixture of methyl 3-chloro-4-fluoro-a-azidocinnamate (Japanese Patent Application Laid-Open No. 149723/1995) (1.85 g) and xylene (140 ml) was heated under reflux for 1 hour, and the solvent was then distilled off. The residue was purified by column chromatography on silica gel (methylene chloride) to obtain the title compound (491 mg).

^{1}H-NMR ($CDCl_3$) δ: 3.95(3H,s), 7.13-7.15(1H,m), 7.20(1H,dd,J=9.3,0.49Hz), 7.71(1H,d,J=7.3Hz), 8.93 (1H,br.s).
MS (FAB) m/z: 227 M^+.

[Referential Example 23]

5-Chloro-6-fluoroindole-2-carboxylic acid:

[0172]



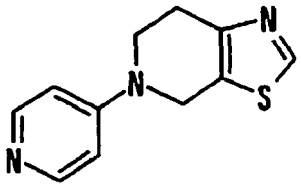
[0173] The compound (461 mg) obtained in Referential Example 22 was dissolved in a mixed solvent of tetrahydrofuran (15 ml), methanol (10 ml) and water (10 ml), lithium hydroxide (283 mg) was added at room temperature, and the mixture was stirred for 4 hours. The solvent was distilled off under reduced pressure, and 1N hydrochloric acid was added to the residue to weakly acidify it. The resultant powder was collected by filtration and dried to obtain the title compound (422 mg).

^{1}H-NMR ($CDCl_3$) δ: 7.08-7.10(1H,m), 7.34(1H,d,J=9.5Hz), 7.88(1H,d,J=7.6Hz), 12.04(1H,s), 13.16(1H,s).
MS (FAB) m/z: 213(M^+).

[Referential Example 24]

5-(Pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine:

[0174]



1) Diphosphorus pentasulfide (500 g) was suspended in formamide (3,000 ml) with ice cooling, and the suspension was stirred overnight. Water and diethyl ether were added to the reaction mixture, and an organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off to obtain an oil. After the oil was dissolved in n-butanol (350 ml), and ethyl 3-chloro-4-oxo-1-piperidinecarboxylate (150 g) synthesized according to the process described in literature (Tetrahedron, 1983, Vol. 39, p. 3767) was added to the solution, the resultant mixture was stirred at 100°C for 2.5 hours. The reaction mixture was filtered through Celite. The filtrate was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride→ethyl acetate:hexane = 1:2) to obtain ethyl 6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (79.0 g).

^{1}H-NMR ($CDCl_3$) δ: 1.30(3H,t,J=7.3Hz), 2.96(2H,br.s), 3.82(2H,br.s), 4.19(2H,q,J=7.3Hz), 4.73(2H,br.s), 8.68(1H,s).
MS (FAB) m/z: 213 $(M+H)^+$.

2) A 3.5N aqueous solution (250 ml) of sodium hydroxide was added to the reaction product (33.5 g) obtained above, and the mixture was heated under reflux overnight. After the reaction mixture was cooled to room temperature, di-tert-butyl dicarbonate (103 g) was added with ice cooling, and the mixture was stirred overnight at room temperature. After 3N hydrochloric acid was added to the reaction mixture to adjust the pH thereof to 1 to 2, methylene

chloride was added. After separation of an organic layer, the organic layer was washed successively with an aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. After the organic layer was concentrated under reduced pressure, the resultant residue was purified by column chromatography on silica gel (ethyl acetate: hexane = 1:2) to obtain tert-butyl 6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (21.1 g).

^{1}H-NMR ($CDCl_3$) δ: 1.49(9H,s), 2.94 (2H,br.s), 3.76 (2H,br.s), 4.68 (2H,s), 8.67 (1H,s).

MS (FAB) m/z: 241 $(M+H)^+$.

3) Trifluoroacetic acid (25 ml) was added to a solution of the compound (5.00 g) obtained in the step 2) in methylene chloride (25 ml) at room temperature. After stirring for 10 minutes, the reaction mixture was concentrated under reduced pressure, and 4-bromopyridine (5.20 g), N,N-dimethylformamide (30 ml) and triethylamine (15.5 ml) were added to the residue at room temperature, and the mixture was stirred at 150°C for 2 days and then allowed to cool to room temperature. Colorless precipitates were separated by filtration, and the filtrate was concentrated under reduced pressure. Thereafter, methylene chloride (50 ml) and a saturated aqueous solution (100 ml) of sodium hydrogencarbonate were added, and the resultant water layer was saturated with sodium chloride. After separation of an organic layer, the resultant water layer was extracted with methylene chloride (5 x 30 ml). After the resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1 $\rightarrow$ 8:1) to obtain the title compound (2.97 g).

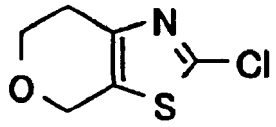
^{1}H-NMR ($CDCl_3$) δ: 3.07 (2H, t, J=5.9Hz), 3.81(2H, t, J=5.9Hz), 4.61(2H,s), 6.74(2H, t, J=6.5Hz), 8.30(2H, t, J=6.5Hz), 8.70(1H,s).

MS (ESI) m/z: 218$(M+H)^+$.

[Referential Example 25]

2-Chloro-6,7-dihydro-4H-pyrano[4,3-d]thiazole:

[0175]



1) Tetrahydro-4H-pyran-4-one (5.0 g) was dissolved in cyclohexane (20 ml), pyrrolidine (4.35 ml) and p-toluenesulfonic acid monohydrate (48 mg) were added, and the mixture was heated under reflux for 70 minutes while removing water by a Dean-Stark trap. The reaction mixture was cooled to room temperature, and a supernatant was taken out and concentrated under reduced pressure. The residue was dissolved in methanol (15 ml), and sulfur powder (1.60 g) was added with ice cooling. After 15 minutes, a methanol solution (10 ml) of cyanamide (2.10 g) was added dropwise over 20 minutes, and the mixture was stirred for 3 days. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1 $\rightarrow$ 10:1 $\rightarrow$ 4:1) to obtain 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamine (3.97 g).

^{1}H-NMR ($CDCl_3$) δ: 2.66-2.70(2H,m), 3.97(2H,t,J=5.6Hz), 4.63(2H,s), 4.94(2H,br.s).

MS (FAB) m/z: 157$(M+H)^+$.

2) Copper(II) chloride (4.10 g) was dissolved in acetonitrile (50 ml), and tert-butyl nitrite (3.93 g) was added in one portion with ice cooling. After 10 minutes, the compound obtained in the above-described reaction (3.97 g) was added over about 1 hour, and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was heated to 65°C and continuously stirred for 2 hours. After silica gel (20 g) was added to the reaction mixture, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (1.78 g).

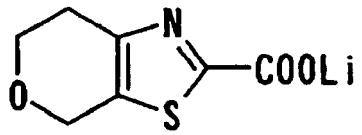
^{1}H-NMR ($CDCl_3$) δ: 2.85-2.89(2H,m), 4.02(2H, t, J=5.6H_2), 4.73(2H, s).

MS (FAB) m/z: 175$(M+H)^+$.

[Referential Example 26]

Lithium 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-carboxylate:

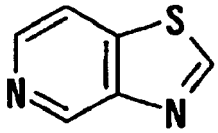
[0176]



1) The compound (1.78 g) obtained in Referential Example 25 was dissolved in methanol (30 ml), and to the solution 10% palladium on carbon (300 mg) and sodium acetate (830 mg) were added. The mixture was stirred for 5 days in a hydrogen stream of 5 atm. After the catalyst was separated by filtration, the solvent was concentrated, and the residue was subjected to column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain 6,7-dihydro-4H-pyrano[4,3-d]thiazole (1.14 g).
^{1}H-NMR ($CDCl_3$) δ: 2.97-3.01(2H,m), 4.04 (2H, t, J=5.6Hz), 4.87(2H, s), 8.69 (1H, s).
MS (FAB) m/z: 142 $(M+H)^+$.
2) After the product (1.14 g) obtained above was dissolved in diethyl ether (30 ml) and cooled to -78°C, 1.6 M butyllithium (6.6 ml) was added, and the mixture was stirred. After 20 minutes, bubbling was conducted with carbon dioxide for 15 minutes. The reaction mixture was warmed to room temperature and concentrated under reduced pressure to obtain the title compound (1.65 g).
^{1}H-NMR (DMSO-d_6) δ: 2.83(2H,t,J=5.6Hz), 3.92(2H,t,J=5.6Hz), 4.73(2H,s).

[Referential Example 27] Thiazolo[4,5-c]pyridine:

[0177]

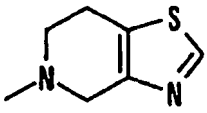


[0178] 3-(tert-Butoxycarbonylamino)-4-mercaptopyridine (Japanese Patent Application Laid-Open No. 321691/1992) (9.20 g) was dissolved in formic acid (60 ml) and heated under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure, and a 5N aqueous solution (100 ml) of potassium hydroxide and diethyl ether were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. Diethyl ether was added to the residue, and solids deposited were collected by filtration to obtain the title compound (3.97 g).
^{1}H-NMR ($CDCl_3$) δ: 7.93(1H,d,J=5.4Hz), 8.60(1H,d,J=5.4Hz), 9.07(1H,s), 9.46(1H,s).

[Referential Example 28]

5-Methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine:

[0179]

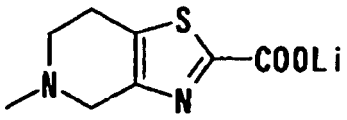


[0180] The title compound was obtained from the compound obtained in Referential Example 27 in a similar manner to Referential Example 4.
^{1}H-NMR ($CDCl_3$) δ: 2.52(3H,s), 2.77(2H,t,J=5.4Hz), 2.92-3.00(2H,m), 3.69(2H,t,J=2.0Hz), 8.61(1H,s).
MS (FAB) m/z: 155$(M+H)^+$.

[Referential Example 29]

Lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]-pyridine-2-carboxylate:

[0181]

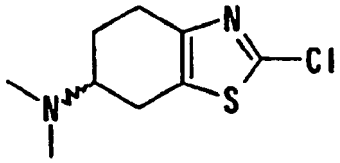


[0182] The title compound was obtained from the compound obtained in Referential Example 28 in a similar manner to Referential Example 5.
^{1}H-NMR (DMSO-d_6) δ: 2.38(3H,s), 2.64(2H,br.s), 2.80(2H,br.s), 3.44(2H,br.s).

[Referential Example 30]

2-Chloro-N,N-dimethyl-4,5,6,7-tetrahydrobenzothiazole-6-amine:

[0183]

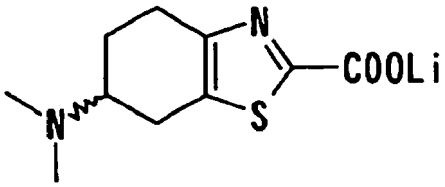


[0184] 2-Chloro-4,7-dihydro-1,3-benzothiazol-6(5H)-one (Helv. Cim. Acta., 1994, Vol. 77, p. 1256) (2.0 g) was dissolved in methanol (100 ml), and ammonium acetate (8.2 g) and sodium cyanoborohydride (4.0 g) were added to heat the mixture under reflux for 20 hours. Hydrochloric acid was added to the reaction mixture to decompose excessive sodium cyanoborohydride before the solvent was distilled off under reduced pressure. The residue was alkalified with a 1N solution of sodium hydroxide and then extracted with methylene chloride. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure to obtain a pale yellow oil. This oil was dissolved in methanol (50 ml), and an aqueous solution (4.29 g) of formaldehyde and sodium cyanoborohydride (3.49 g) were added to stir the mixture at room temperature for 12 hours. The solvent was distilled off under reduced pressure, and methylene chloride was added to the residue, the organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 10:1) to obtain the title compound (740 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.71-1.78(1H,m), 2.10-2.19(1H, m), 2.35(6H,s), 2.66-2.94(5H, m).
MS (FAB) m/z: 217$(M+H)^+$.

[Referential Example 31]

Lithium 6-(dimethylamino)-4,5,6,7-tetrahydrobenzothiazole-2-carboxylate:

[0185]

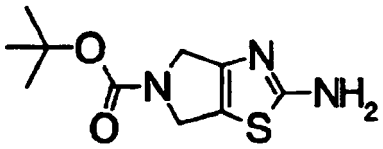


[0186] After the compound (750 mg) obtained in Referential Example 30 was dissolved in diethyl ether (15 ml), and the solution was cooled to -78°C, 1.5N t-butyllithium (3.5 ml) was added, the mixture was stirred for 20 minutes, and carbon dioxide was then bubbled for about 15 minutes. The reaction mixture was warmed to room temperature and concentrated under reduced pressure to obtain the title compound.
^{1}H-NMR (DMSO-d_6) δ: 1.75-1.78 (1H,m), 1.98-2.07 (1H,m), 2.50(6H,s), 2.64-2.88 (5H,m).

[Referential Example 32]

tert-Butyl 2-amino-4,6-dihydro-5H-pyrrolo[3,4-d]thiazole-5-carboxylate:

[0187]

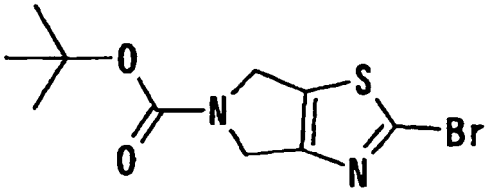


[0188] 1-tert-Butoxycarbonyl-3-pyrrolidone (1.58 g) was dissolved in cyclohexane (10 ml), p-toluenesulfonic acid monohydrate (8.12 mg) and pyrrolidine (607 mg) were added, and the mixture was heated under reflux for 1.5 hours while dewatering with a Dean-Stark trap. After a supernatant was taken out and concentrated under reduced pressure, the residue was dissolved in methanol (5 ml), and sulfur powder (274 mg) was added. The mixture was stirred for 15 minutes under ice cooling. A methanol solution (2 ml) of cyanamide (377 mg) was slowly added dropwise to the reaction mixture, and the mixture was stirred overnight at room temperature. The mixture was additionally heated under reflux for 2 hours, the reaction mixture was concentrated, and methylene chloride and a saturated aqueous solution of sodium hydrogen carbonate were added. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:39) to obtain the title compound (248 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.50(9H, s), 4.34-4.37(1H, m), 4.40-4.45(1H, m), 4.49-4.55(2H,m), 4.99(2H,m).

[Referential Example 33]

tert-Butyl 2-bromo-4,6-dihydro-5H-pyrrolo[3,4-d]thiazole-5-carboxylate:

[0189]

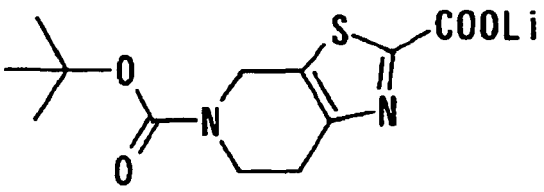


[0190] Copper(II) bromide (445 mg) was suspended in N,N-dimethylformamide, and tert-butyl nitrite (256 mg) was added dropwise at room temperature. After an N,N-dimethylformamide solution (1 ml) of the compound (400 mg) obtained in Referential Example 32 was added under ice cooling, the reaction mixture was heated and stirred at 60°C for 1.5 hours. Diethyl ether and saturated aqueous solution of sodium chloride were added to the reaction mixture, and the resultant organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (174 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.51(9H,s), 4.52-4.55(1H,m), 4.57-4.67(3H,m).
MS (FAB) m/z: 305$(M+H)^+$.

[Referential Example 34]

Lithium (5-tert-butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate:

[0191]

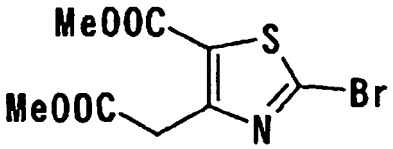


[0192] The title compound was obtained from the compound obtained in Referential Example 7 in a similar manner to Referential Example 10.
^{1}H-NMR (DMSO-d_6) δ: 1.42(9H,s), 2.69-2.77(2H,m), 3.60-3.68(2H,m), 4.51-4.58(2H,m).

[Referential Example 35]

Methyl 2-bromo-4-(2-methoxy-2-oxoethyl)thiazole-5-carboxylate:

[0193]

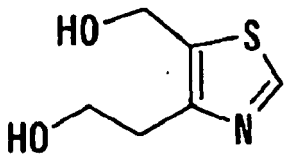


[0194] Copper(II) chloride (26.8 g) was added to a solution of tert-butyl nitrite (15.5 g) in acetonitrile (500 ml) at a time under ice cooling. A solution of methyl 2-amino-5-methoxycarbonylthiazole-4-acetate (Yakugaku Zasshi, 1966, Vol. 86, p. 300) (23.0 g) in acetonitrile (500 ml) was added dropwise to the reaction mixture over 45 minutes, and the resulting mixture was stirred for 1 hour under ice cooling and for 30 minutes at room temperature. The solvent was concentrated, and 10% hydrochloric acid and diethyl ether were added to the residue to separate an organic layer. The organic layer was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate: hexane = 1:4) to obtain the title compound (25.9 g).
^{1}H-NMR ($CDCl_3$) δ: 3.73(3H,s), 3.87(3H,s), 4.21(2H,s).

[Referential Example 36]

2-[5-(hydroxymethyl)thiazol-4-yl]-1-ethanol:

[0195]

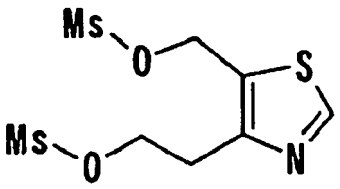


[0196] A solution of the compound (23.4 g) obtained in Referential Example 35 in tetrahydrofuran (500 ml) was added dropwise over 1 hour to a suspension of lithium aluminum hydride (9.03 g) in tetrahydrofuran (500 ml) under ice cooling. After stirring for additional 1 hour under ice cooling, water (9 ml), a 35% aqueous solution (9 ml) of sodium hydroxide and water (27 ml) were successively added, and the mixture was stirred at room temperature for 1 hour. After anhydrous magnesium sulfate was added to the reaction mixture, and the resultant mixture was stirred, insoluble matter was removed by filtration with Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (methanol:methylene chloride = 7:93) to obtain the title compound (8.64 g).
^{1}H-NMR ($CDCl_3$) δ: 3.01(2H,t,J=5.5Hz), 3.30(1H,br.s), 3.57(1H,br.s), 3.90(2H,br.s), 4.75(2H,br.s), 8.66(1H,s).
MS (ESI) m/z: 160$(M+H)^+$.

[Referential Example 37]

2-(5-{[(Methylsulfonyl)oxy]methyl}thiazol-4-yl)ethyl methanesulfonate:

[0197]



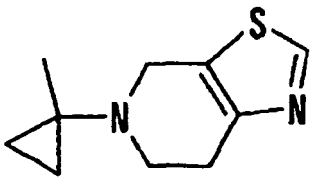
[0198] A methylene chloride solution of methanesulfonyl chloride (12.6 ml) was added dropwise to a solution of the compound (8.64 g) obtained in Referential Example 36 and triethylamine (45.4 ml) dissolved in methylene chloride (500 ml) over 20 minutes at -78°C. After stirring the reaction mixture for 15 minutes at -78°C and 1 hour at 0°C, water was added to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (13.4 g).

^{1}H-NMR ($CDCl_3$) δ: 2.93(3H,s), 3.03(3H,s), 3.28(2H,t,J=6.3Hz), 4.61(2H,t,J=6.3Hz), 5.44(2H,s), 8.84(1H,s).

[Referential Example 38]

5-(1-Methylcyclopropyl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine:

[0199]



[0200] 1-Methylcyclopropylamine hydrochloride (J. Org. Chem., 1989, Vol. 54, p. 1815) (1.89 g) was added to methylene chloride (20 ml) containing the compound obtained in Referential Example 37 (4.46 g) under ice cooling, and the mixture was stirred overnight at room temperature. 1-Methylcyclopropylamine hydrochloride (1.89 g) was additionally added, and the mixture was stirred for 20 hours at room temperature and 5 hours under refluxing.

[0201] Methylene chloride and water were added to the reaction mixture to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:49) to obtain the title compound (944 mg).

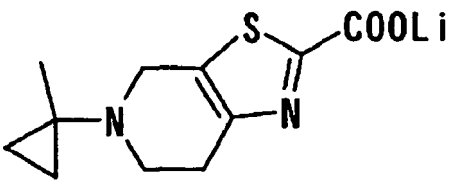
^{1}H-NMR ($CDCl_3$) δ: 0.40-0.50(2H,m), 0.68-0.73(2H,m), 1.16(3H,s), 2.88-2.94(2H,m), 3.03(2H,t,J=5.7Hz), 3.89(2H,br.s), 8.60(1H,s).

MS (ESI) m/z: 195$(M+H)^+$.

[Referential Example 39]

Lithium 5-(1-methylcyclopropyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate:

[0202]

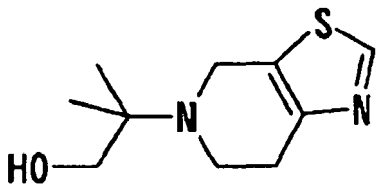


[0203] The title compound was obtained from the compound obtained in Referential Example 38 in a similar manner to Referential Example 5.
^{1}H-NMR (DMSO-d_6) δ: 0.39(2H,br.s), 0.56(2H,br.s), 1.10(3H,br.s), 2.66(2H,br.s), 2.89(2H,br.s), 3.75(2H,br.s).

[Referential Example 40]

2-[6,7-Dihydrothiazolo[5,4-c]pyridin-5(4H)-yl]-2-methyl-1-propanol:

[0204]

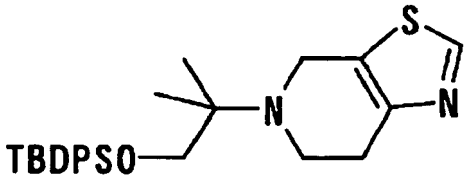


[0205] The title compound was obtained from the compound obtained in Referential Example 37 and 2-amino-2-methyl-1-propanol in a similar manner to Referential Example 38.
^{1}H-NMR ($CDCl_3$) δ: 1.15(6H,s), 2.91(4H,s), 3.45(2H,s), 3.87(2H,s), 8.63(1H,s).

[Referential Example 41]

5-(2-{[tert-Butyl(diphenyl)silyl]oxy}-1,1-dimethylethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine:

[0206]

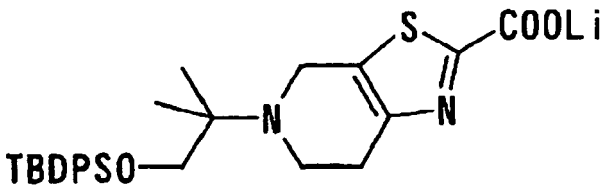


[0207] tert-Butylchlorodiphenylsilane (1.93 g) and imidazole (994 mg) were added to a solution of the compound obtained in Referential Example 40(1.24 g) in N,N-dimethylformamide (5 ml) at room temperature, and the mixture was stirred overnight. Water and diethyl ether were added to the reaction mixture to separate an organic layer. The organic layer was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 1:2) to obtain the title compound (2.46 g).
^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.15(6H,s), 2.83-2.90(2H,m), 2.93-3.00(2H,m), 3.63(2H,s), 3.97(2H,s), 7.35-7.48(6H,m), 7.63-7.70(4H,m), 8.58(1H,s).
MS (ESI) m/z: 451$(M+H)^+$.

[Referential Example 42]

Lithium 5-(2-{[tert-butyl(diphenyl)silyl]oxy}-1,1-dimethylethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate:

[0208]

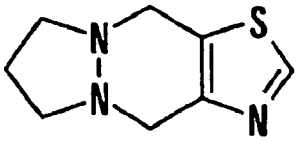


[0209] The title compound was obtained from the compound obtained in Referential Example 41 in a similar manner to Referential Example 5.
^{1}H-NMR (DMSO-d_6) δ: 1.01(9H,s), 1.11(6H,s), 2.55-2.65(2H,m), 2.80-2.90(2H,m), 3.57(2H,s), 3.80(2H,br.s), 7.40-7.52 (6H,m), 7.60-7.65(4H,m).

[Referential Example 43]

4,7,8,10-Tetrahydro-6H-pyrazolo[1,2-a]thiazolo[4,5-d]-pyridazine:

[0210]

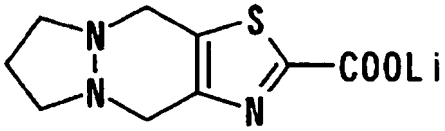


1) 4,5-Dimethylthiazole (5.00 g), N-bromosuccinimide (15.7 g) and α,α'-azobisisobutyronitrile (362 mg) were dissolved in ethylene dichloride (500 ml) at room temperature, and the solution was heated under reflux for 1 hour. The solvent was distilled off, and the residue was purified by column chromatography on silica gel (hexane:diethyl ether = 1:4) to obtain 4,5-bis-(bromomethyl)thiazole (5.24 g).
^{1}H-NMR ($CDCl_3$) δ: 4.64(2H,s), 4.74(2H,s), 8.75(1H,s).
2) 4,5-Bis(bromomethyl)thiazole (1.37 g) and 1,2-trimethylenehydrazine hydrochloride (WO9532965) (732 mg) were suspended in ethanol (15 ml) under ice cooling, and triethylamine (2.82 ml) was added dropwise over 5 minutes. After stirring the mixture at room temperature for 2 hours, the solvent was distilled off, and methylene chloride (50 ml) and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 3: 47) to obtain the title compound (358 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.10-2.25(2H,m), 3.01(4H,br.s), 3.95(2H,s), 3.99(2H,br.s), 8.64(1H,s).
MS (FAB) m/z: 182$(M+H)^+$.

[Referential Example 44]

Lithium 4,7,8,10-tetrahydro-6H-pyrazolo[1,2-a]thiazolo-[4,5-d]pyridazine-2-carboxylate :

[0211]

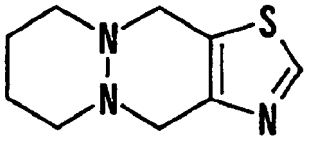


[0212] The title compound was obtained from the compound obtained in Referential Example 43 in a similar manner to Referential Example 5.
^{1}H-NMR (DMSO-d_6) δ: 1.90-2.10(2H,m), 2.60-3.10(4H,br.s), 3.65-4.00(4H,m).

[Referential Example 45]

4,6,7,8,9,11-Hexahydropyridazino[1,2-a]thiazolo[4,5-d]-pyridazine:

[0213]

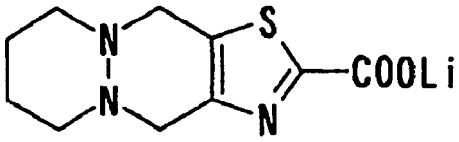


[0214] The title compound was obtained from 4,5-bis-(bromomethyl)thiazole (2.20 g) obtained in 1) of Referential Example 43 and 1,2-tetramethylenehydrazine hydrochloride (US 5,726,126) in a similar manner to Referential Example 43.
^{1}H-NMR ($CDCl_3$) δ: 1.77(4H,br.s), 2.20-3.50(4H,br), 3.92(4H,br.s), 8.65(1H,s).
MS (FAB) m/z: 196$(M+H)^+$.

[Referential Example 46]

Lithium 4,6,7,8,9,11-hexahydropyridazino[1,2-a]thiazolo-[4,5-d]pyridazine-2-carboxylate :

[0215]

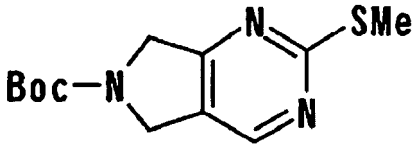


[0216] The title compound was obtained from the compound obtained in Referential Example 45 in a similar manner to Referential Example 5.

[Referential Example 47]

tert-Butyl 2-(methylsulfanyl)-5,7-dihydro-6H-pyrrolo-[3,4-d]pyrimidine-6-carboxylate:

[0217]

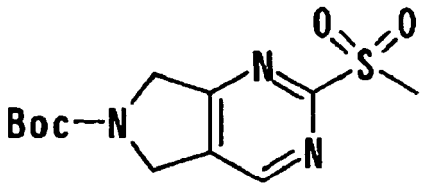


[0218] 1-tert-Butoxycarbonyl-3-pyrrolidone (4.57 g) was added to N,N-dimethylformamide dimethyl acetal (30 ml) at room temperature, and the mixture was heated for 1 hour at 140°C. After allowing the reaction mixture to cool to room temperature, it was concentrated under reduced pressure. Hexane was added to the residue, and yellow powder deposited was collected by filtration. This powder was dissolved in ethanol (100 ml), and methylisothiourea sulfate (9.24 g) and sodium ethoxide (4.52 g) were added to the resultant solution at room temperature, and the mixture was heated under reflux for 24 hours. Saturated aqueous solution of sodium chloride and diethyl ether were added to the reaction mixture to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol: methylene chloride = 1:99) to obtain the title compound (1.10 g).
^{1}H-NMR ($CDCl_3$) δ: 1.51(9H,s), 2.57(3H,m), 4.15-4.45(4H,m), 8.39(1/2H,s), 8.43(1/2H,s).
MS (FAB) m/z: 268$(M+H)^+$.

[Referential Example 48]

tert-Butyl 2-(methylsulfonyl)-5,7-dihydro-6H-pyrrolo-[3,4-d]pyrimidine-6-carboxylate:

[0219]

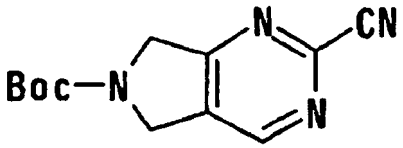


[0220] m-Chloroperbenzoic acid (1.99 g) was added to a methylene chloride solution (20 ml) of the compound (1.08 g) obtained in Referential Example 47 under ice cooling, and the mixture was stirred for 5 hours. A saturated aqueous solution of sodium sulfite, a saturated aqueous solution of sodium hydrogen carbonate and methylene chloride were added to separate an organic layer. The organic layer was then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, hexane was added to the residue, and powder deposited was collected by filtration to obtain the title compound (1.09 g).
^{1}H-NMR ($CDCl_3$) δ: 1.53(9H,s), 3.36(3H,m), 4.77-4.90(4H,m), 8.77(1/2H,s), 8.81(1/2H,s).
MS (FAB) m/z: 300$(M+H)^+$.

[Referential Example 49]

tert-Butyl 2-cyano-5,7-dihydro-6H-pyrrolo[3,4-d]-pyrimidine-6-carboxylate:

[0221]

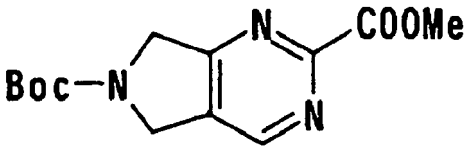


[0222] Tetrabutylammonium cyanide (1.04 g) was added to a solution of the compound (1.05 g) obtained in Referential Example 48 in methylene chloride (30 ml) at room temperature, and the mixture was stirred at room temperature for 1 hour. 1N sodium hydroxide was added to the reaction mixture to separate an organic layer, and the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:acetone = 20:1) to obtain the title compound (776 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.52(9H,s), 4.70-4.85(4H,m), 8.68-8.77(1H,m).
MS (FAB) m/z: 247$(M+H)^+$.

[Referential Example 50]

6-tert-Butyl 2-methyl 5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-2,6-dicarboxylate:

[0223]



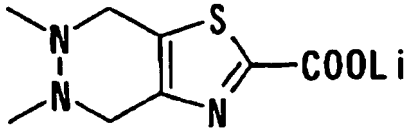
[0224] Concentrated hydrochloric acid (5 ml) was added to a solution of the compound (776 mg) obtained in Referential Example 49 in methanol (10 ml) at room temperature, and the mixture was stirred at 100°C for 1 hour. After allowing to cool, the reaction mixture was concentrated under reduced pressure, and the residue was dissolve in methanol (10 ml). Triethylamine (2.20 ml) and di-tert-butyl dicarbonate (1.37 g) were added to the solution at room temperature and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and methylene chloride and saturated aqueous solution of sodium chloride were added to the residue to separate an organic layer, and the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 3:97) to obtain the title compound (317 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.53(9H,s), 4.09(3H,s), 4.75-4.85(4H,m), 8.81(1/2H,s), 8.85(1/2H,s).

MS (FAB) m/z: 280$(M+H)^+$.

[Referential Example 51]

Lithium 5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]-pyridazine-2-carboxylate :

[0225]

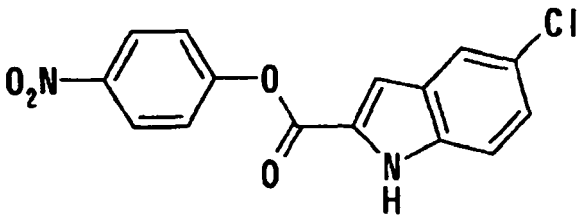


1) After 4,5-bis(bromomethyl)thiazole (600 mg) obtained in 1) of Referential Example 43 was dissolved in ethanol (20 ml), and 1,2-dimethylhydrazine hydrochloride (294 mg) was added under ice cooling, triethylamine (1.23 ml) was added at a time, and the mixture was stirred for 30 minutes at room temperature and 30 minutes at 50°C. The solvent was distilled off, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:19) to obtain 5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazine (90 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.43(3H,s), 2.56(3H,s), 3.92(2H,s), 4.06(2H,br.s), 8.68(1H,s).
MS (FAB) m/z: 170$(M+H)^+$.
2) The title compound was obtained from 5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazine in a similar manner to Referential Example 5.
^{1}H-NMR (DMSO-d_6) δ: 2.28(3H,s), 2.39(3H,s), 3.66(2H,br.s), 3.88(2H,br.s).

[Referential Example 52]

4-Nitrophenyl 5-chloroindole-2-carboxylate:

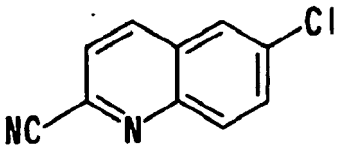
[0226]



[0227] After 5-chloroindole-2-carboxylic acid (20 g) was suspended in methylene chloride (1500 ml), and N,N-dimethylformamide (2 ml) was added, thionyl chloride (11 ml) was added dropwise at room temperature. The reaction mixture was heated overnight under reflux and then concentrated under reduced pressure. The residue was dissolved in methylene chloride (1000 ml), and triethylamine (84.7 ml) and p-nitrophenol (14.2 g) were added to the mixture under ice cooling. After stirring for 1 hour at room temperature, the reaction mixture was concentrated under reduced pressure, and ethyl acetate and 0.2N hydrochloric acid were added to the residue to separate an organic layer. The organic layer was successively washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (29.9 g).
^{1}H-NMR ($CDCl_3$) δ: 7.35(1H,dd,J=9.0,1.7Hz), 7.39-7.42(2H,m), 7.45(2H,dd,J=7.3,1.7Hz), 7.73(1H,d,J=1.0Hz), 8.35(2H,dd,J=7.3,1.7Hz), 9.09(1H,br.s).
MS (FD) m/z: 316(M^+).

[Referential Example 53] 6-Chloro-2-quinolinecarbonitrile:

[0228]

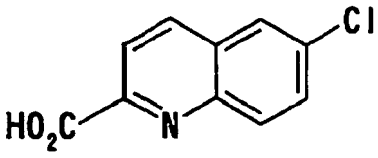


[0229] 6-Chloroquinoline (2.50 g) was dissolved in methylene chloride (25 ml), and m-chloroperbenzoic acid (3.71 g) was added under ice cooling to stir the mixture at room temperature for 1 hour. After the reaction mixture was diluted with methylene chloride, the diluted mixture was washed with an aqueous solution of sodium thiosulfate and an aqueous solution of sodium hydroxide and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was dissolved in methylene chloride (40 ml), and trimethylsilyl cyanide (2.0 ml) and N,N-dimethylcarbamoyl chloride (1.50 ml) were added to heat the resultant mixture for 9 hours under reflux. After trimethylsilyl cyanide (1.0 ml) and N,N-dimethylcarbamoyl chloride (0.80 ml) were additionally added, and the mixture was heated for 16 hours under reflux, the reaction mixture was diluted with methylene chloride, and a 10% aqueous solution (40 ml) of potassium carbonate was added to stir the mixture for 30 minutes. After an organic layer was separated and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. Methylene chloride was added to the residue, and crystals deposited were collected by filtration to obtain the title compound (1.77 g). Further, a mother liquor was purified by column chromatography on silica gel (methylene chloride) to obtain the title compound (0.80 g).
^{1}H-NMR (DMSO-d_6) δ: 7.94(1H,dd,J=9.0,2.2Hz), 8.09(1H,d,J=8.5Hz), 8.15(1H,d,J=9.0Hz), 8.29(1H,d,J=2.2Hz), 8.63 (1H,d,J=8.5Hz).
MS (FAB) m/z: 189$(M+H)^+$.

[Referential Example 54]

6-Chloro-2-quinolinecarboxylic acid:

[0230]

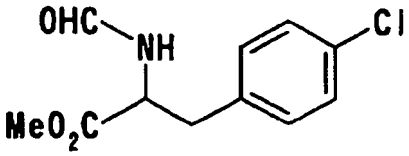


[0231] The compound (1.73 g) obtained in Referential Example 53 was dissolved in concentrated hydrochloric acid (40 ml), and the solution was heated for 19 hours under reflux. The reaction mixture was cooled to room temperature, and deposits were collected by filtration and then washed with water to obtain the title compound (1.81 g).
^{1}H-NMR (DMSO-d_6) δ: 7.87(1H,dd,J=9.0,2.4Hz), 8.10-8.20(2H,m), 8.24(1H,d,J=2.2Hz), 8.52(1H,d,J=8.5Hz).
MS(FAB)m/z:208 $(M + H)^+$.

[Referential Example 55]

Methyl 3-(4-chlorophenyl)-2-(formylamino) propionate:

[0232]



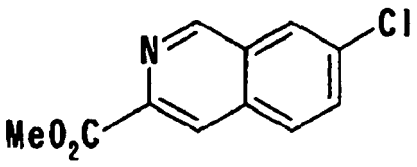
[0233] (±)-(4-Chlorophenyl)alanine methyl ester hydrochloride (2.00 g) was suspended in methylene chloride (20 ml), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.60 g), 1-hydroxybenzotriazole monohydrate (1.23 g), N-methylmorpholine (1.90 ml) and formic acid (0.30 ml) were added to stir the mixture for 15 minutes. After a process in which formic acid (0.30 ml) was additionally added to stir the mixture for 15 minutes was repeated 3 times, the reaction

mixture was diluted with methylene chloride. After an ogranic layer was washed with water and then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 40:1) to obtain the title compound (1.21 g).
^{1}H-NMR ($CDCl_3$) δ: 3.10(1H,dd,J=13.9, 5.6Hz), 3.18(1H,dd,J=13.9,5.9Hz), 3.75(3H,s), 4.95(1H,m), 6.07(1H,br), 7.05 (2H,d,J=8.3Hz), 7.27(2H,d,J=8.3Hz), 8.18(1H,s).
MS (FAB) m/z: 242 $(M+H)^+$.

[Referential Example 56]

Methyl 7-chloro-3-isoquinolinecarboxylate:

[0234]

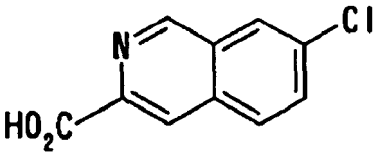


[0235] The compound (1.45 g) obtained in Referential Example 55 was dissolved in methylene chloride (40 ml), and oxalyl chloride (0.57 ml) was added dropwise. After the mixture was stirred at room temperature for 30 minutes, ferric chloride (1.17 g) was added at an ambient temperature of about -10°C to stir the mixture at room temperature for 4 days. 1N Hydrochloric acid was added, and the resultant mixture was diluted with methylene chloride to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was dissolved in methanol (38 ml), and concentrated sulfuric acid (2 ml) was added to heat the mixture for 20 hours under reflux. An aqueous solution of sodium hydrogencarbonate was added to the reaction mixture, the resultant mixture was extracted with methylene chloride, and the extract was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1 $\rightarrow$ ethyl acetate) to obtain the title compound (0.25 g).
^{1}H-NMR ($CDCl_3$) δ: 4.07(3H,s), 7.74(1H,dd,J=8.8,2.0Hz), 7.94(1H,d,J=8.8Hz), 8.06(1H,d,J=2.0Hz), 8.59(1H,s), 9.28 (1H,s).

[Referential Example 57]

7-Chloro-3-isoquinolinecarboxylic hydrochloride:

[0236]

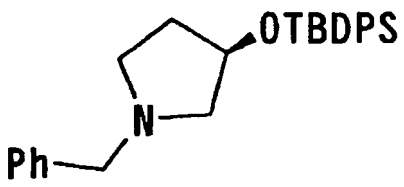


[0237] The compound (0.23 g) obtained in Referential Example 56 was dissolved in concentrated hydrochloric acid (10 ml) to heat the mixture for 18 hours under reflux. The temperature of the reaction mixture was dropped to room temperature, and deposits were collected by filtration and then washed with water to obtain the title compound (0.21 g).
^{1}H-NMR (DMSO-d_6) δ: 7.96(1H,m), 8.29(1H,d,J=8.5Hz), 8.44(1H,s), 8.72(1H,s), 9.45(1H,d,J=6.6Hz).
MS (FAB) m/z: 208 $(M+H)^+$.

[Referential Example 58]

(3R)-1-Benzyl-3-(tert-butyldiphenylsilyloxy)pyrrolidine:

[0238]

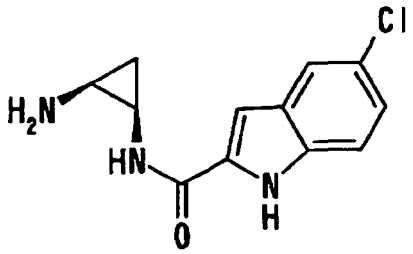


[0239] (3R)-1-Benzyl-3-hydroxypyrrolidine (500 μl) and imidazole (466 mg) were dissolved in N,N-dimethylformamide (15 ml), tert-butyldiphenylsilyl chloride (1.57 ml) was added under ice cooling, and the mixture was stirred at room temperature for 9 days. After the solvent was distilled off under reduced pressure, and methylene chloride and water were added to the residue to conduct liquid separation, the resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was subjected to flash column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (1.27 g).
^{1}H-NMR ($CDCl_3$) δ: 1.05(9H,s), 1.70-1.85(1H,m), 1.90-2.00(1H,m), 2.45-2.65(3H,m), 2.70-2.80(1H, m), 3.50-3.70(2H, m), 4.35-4.45(1H,m), 7.20-7.45(11H,m), 7.60-7.70(4H,m).
MS (ESI) m/z: 416 $(M+H)^+$.

[Referential Example 59]

N-[(1R*,2S*)-2-Aminocyclopropyl]-5-chloroindole-2-carboxamide:

[0240]

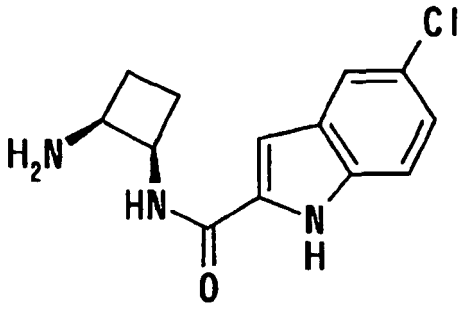


[0241] 1-Hydroxybenzotriazole monohydrate (377 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (642 mg) and diisopropylethylamine (1.95 ml) were added to a solution of cis-1,2-cyclopropanediamine hydrochloride (J. Med. Chem., 1998, Vol. 41, pp. 4723-4732) (405 mg) and 5-chloroindole-2-carboxylic acid (546 mg) in N,N-dimethylformamide (10 ml) at room temperature, and the mixture was stirred for 50 hours. After the reaction mixture was concentrated under reduced pressure, methylene chloride (50 ml) and a saturated solution (200 ml) of sodium hydrogencarbonate were added to separate colorless solid deposited by filtration. The filtrate was extracted with methylene chloride. After the resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain residue. The residue was purified by flash column chromatography on silica gel (methylene chloride:methanol = 100:7 → 10:1) to obtain the title compound (110 mg).
^{1}H-NMR (DMSO-d_6) δ: 0.44(1H,dd,J=10.7,4.4Hz), 1.11(1H,dd,J=14.0,7.4Hz), 2.63-2.70(1H,m), 3.07-3.16(1H,m), 6.77 (1H,s), 6.97(1H,br.s), 7.23(1H,dd,J=8.9,1.8Hz), 7.36(1H,d,J=8.9Hz), 7.60(1H,s), 9.32(1H,s).
MS (FAB) m/z: 250$(M+H)^+$.

[Referential Example 60]

N-[(1R*,2S*)-2-Aminocyclobutyl]-5-chloroindole-2-carboxamide:

[0242]

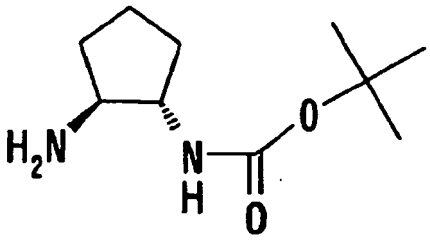


[0243] The title compound was obtained from cis-1,2-cyclobutanediamine hydrochloride (J. Am. Chem. Soc., 1942, Vol. 64, pp. 2696-2700) in a similar manner to Referential Example 59.
^{1}H-NMR (DMSO-d_6) δ: 1.55-2.20(4H,m), 3.52-3.62(1H,m), 4.35-4.50(1H,m), 7.16(1H,dd,J=8.7,2.1Hz), 7.19(1H,s), 7.42 (1H,d,J=8.7Hz), 7.70(1H,d,J=2.1Hz), 8.36(1H,d,J=7.8Hz), 11.77(1H,br.s).
MS (ESI) m/z: 264 $(M+H)^+$.

[Referential Example 61]

tert-Butyl (1R*,2R*)-2-aminocyclopentylcarbamate:

[0244]

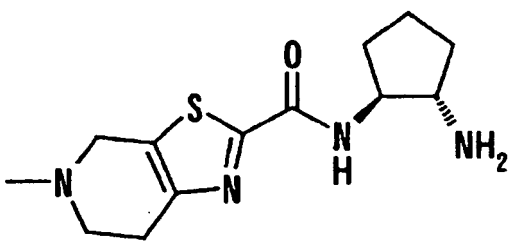


[0245] (±)-trans-1,2-Cyclopentanediamine (WO98/30574) (692 mg) was dissolved in methylene chloride (10 ml), to which triethylamine (1.1 ml) and 2-(tert-butoxycarbonyloxy-imino)-2-phenylacetonitrile (493 mg) were added, and the mixture was stirred at 0°C for 1 hour. Thereafter, 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (493 mg) were additionally added, and the mixture was stirred at room temperature for 7 hours. Water was added to the reaction mixture to separate an organic layer. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The residue was purified by flash column chromatography on silica gel (methylene chloride:methanol = 9:1) to obtain the title compound (395 mg).
^{1}H-NMR ($CDCl_3$) δ. 1.25-1.40(2H,m), 1.49(9H,s), 1.59-1.77(2H,m), 1.92-2.08(1H, m), 2.10-2.17(1H, m), 2.98(1H,q, J=7.2Hz), 3.48-3.53(1H,m), 4.49(1H,br.s).
MS (ESI) m/z: 201$(M+H)^+$.

[Referential Example 62]

N-[(1R*,2R*)-2-Aminocyclopentyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

[0246]

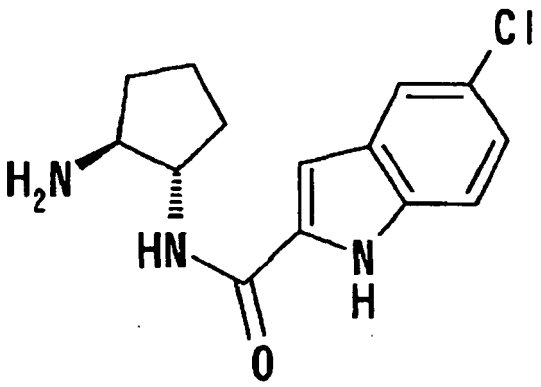


[0247] The compound (175 mg) obtained in Referential Example 61 was dissolved in N,N-dimethylformamide (3 ml), and to the solution lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (purity: 90%, 258 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (252 mg) and 1-hydroxybenzotriazole monohydrate (60 mg) were added. The mixture was stirred at room temperature for 2 days. The solvent was distilled off under reduced pressure using a pump, and methylene chloride and a saturated solution of sodium hydrogencarbonate were added to the residue to separate an organic layer. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by flash column chromatography on silica gel (methylene chloride:methanol = 47:3). The resultant pale yellow oil was dissolved in a ethanol solution (5 ml) of hydrochloric acid, and the solution was stirred at room temperature for 1 hour. Ethyl acetate was then added, and the solvent was distilled off under reduced pressure. Ethyl acetate was added to the residue to collect precipitate formed by filtration, thereby obtaining the title compound (120 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.63-1.73 (4H,m), 1.99-2.06(2H,m), 2.91(3H,s), 3.09-3.14(1H, m), 3.25-3.70(4H,m), 4.27-4.32 (1H, m), 4.42-4.46(1H, m), 4.68-4.71(1H, m), 8.20-8.23(3H, m), 9.09(1H,d,J=8.3Hz), 11.82-12.01(1H, m).
MS (ESI) m/z: 281$(M+H)^+$.

[Referential Example 63]

N-[(1R*,2R*)-2-Aminocyclopentyl]-5-chloro-1H-indol-2-carboxamide hydrochloride:

[0248]

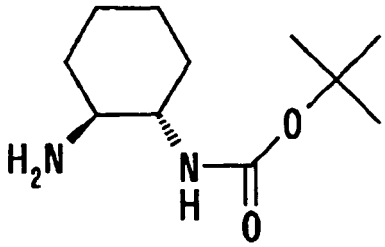


[0249] The compound (1.40 g) obtained in Referential Example 61 was dissolved in N,N-dimethylformamide (15 ml), and to the solution 5-chloroindole-2-carboxylic acid (1.64 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.68 g) and 1-hydroxybenzotriazole monohydrate (473 mg) were added. The mixture was stirred at room temperature for 23 hours. The solvent was distilled off under reduced pressure, and methylene chloride and a saturated solution of sodium hydrogencarbonate were added to the residue to collect precipitates by filtration. The precipitates were washed with ethyl acetate, methylene chloride and methanol. On the other hand, the filtrate was separated to give an organic layer, which was taken out and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by flash column chromatography on silica gel (methylene chloride:methanol = 19:1) to obtain a pale yellow solid. This pale yellow solid was combined with the precipitates obtained by the filtration and dissolved in methylene chloride (10 ml), and trifluoroacetic acid (10 ml) was added to stir the mixture at room temperature for 3 hours. The solvent was distilled off under reduced pressure, and methylen chloride and 1N aqueous solution of sodium hydroxide were added to the residue to collect precipitate by filtration. The organic layer of the filtrate was separated and dried over anhydrous sodium sulfate. The precipitates collected by the filtration were added to this solution, and a 4N dioxane solution (20 ml) of hydrochloric acid was further added. The solvent was distilled off under reduced pressure, and methylene chloride (10 ml) and a 4N dioxane solution (10 ml) of hydrochloric acid were added to the residue. The solvent was distilled off again under reduced pressure. Ethyl acetate was added to the residue to collect precipitates formed by filtration, thereby obtaining the title compound (1.83 g).
^{1}HNMR (DMSO-d_6) δ: 1.60-1.75(4H,m), 2.05-2.10(2H, m), 3.49(1H,q,J=7.6Hz), 4.27(4H,quintet,J=7.6Hz), 7.17(1H,d, J=8.6Hz), 7.19(1H,s), 7.42(1H,d,J=8.6Hz), 7.70(1H,s), 8.24(3H,br.s), 8.85(1H,d,J=7.3Hz), 11.91(1H,s).
MS (ESI) m/z: 278 $(M+H)^+$.

[Referential Example 64]

tert-Butyl (1R*,2R*)-2-aminocyclohexylcarbamate:

[0250]

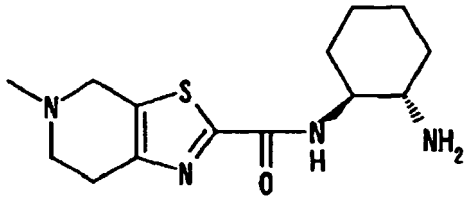


[0251] The title compound was obtained from (±)-trans-1,2-cyclohexanediamine in a similar manner to Referential Example 61. m.p.79-81.
^{1}H-NMR ($CDCl_3$) δ: 1.05-1.34(4H, m), 1.45(9H,s), 1.68-1.75(2H,m), 1.92-2.02(2H,m), 2.32(1H,dt,J=10.3,3.9Hz), 3.08-3.20(1H, m), 4.50(1H, br.s).
MS (FAB) m/z: 215$(M+H)^+$.

[Referential Example 65]

N-[(1R*,2R*)-2-Aminocyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide trifluoroacetate (hydrochloride):

[0252]

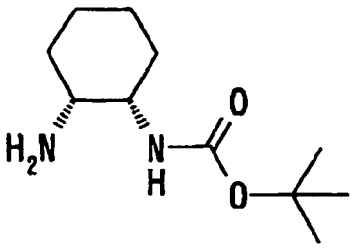


[0253] The title compound was obtained from the compound obtained in Referential Example 64 in a similar manner to Referential Example 62.
^{1}H-NMR (DMSO-d_6) δ: 1.10-1.80 (7H, m), 1.95-2.05 (1H, m), 2.97(3H,s), 3.00-3.20(3H,m), 3.63(2H,br.s), 3.72-3.88(1H, m), 4.61(2H,br.s), 7.98(3H,s), 8.89(1H,d,J=9.2Hz).
MS (FAB) m/z: 295$(M+H)^+$.
[0254] The hydrochloride was obtained in a similar manner.

[Referential Example 66]

tert-Butyl (1R*,2S*)-2-aminocyclohexylcarbamate:

[0255]

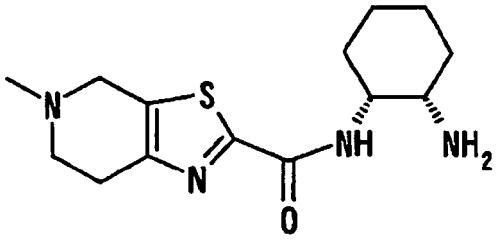


[0256] The title compound was obtained from cis-1,2-cyclohexanediamine in a similar manner to Referential Example 61.
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.70(17H,m), 2.98-3.05(1H, m), 3.60(1H, br.s), 4.98(1H, br.s).
MS (FAB) m/z: 215$(M+H)^+$.

[Referential Example 67]

N-[(1R*,2S*)-2-Aminocyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride (trifluoroacetate):

[0257]

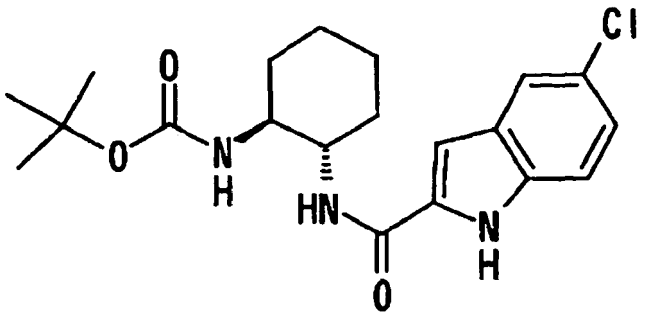


[0258] The title compound was obtained from the compound obtained in Referential Example 66 in a similar manner to Referential Example 62.
^{1}H-NMR (DMSO-d_6) δ: 1.30-1.90(8H, m), 2.92(3H,s), 3.05-3.79(5H, m), 4.23(1H, br.s), 4.34-4.79(2H,m), 8.01-8.34(3H, m), 8.30-8.49(1H, m), 11.90-12.30(1H, m).
MS (FAB) m/z: 295$(M+H)^+$.
[0259] The trifluoroacetate was obtained in a similar manner.

[Referential Example 68]

tert-Buthyl (1R*,2R*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexylcarbamate:

[0260]

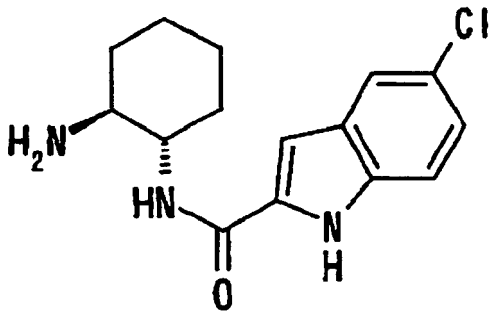


[0261] 5-Chloroindole-2-carboxylic acid (2.88 g), 1-hydroxybenzotriazole monohydrate (2.08 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.95 g) were added to a solution of the compound (3.00 g) obtained in Referential Example 64 in N,N-dimethylformamide (10 ml) at room temperature. After stirring for 3 days, the reaction mixture was concentrated under reduced pressure, and methylene chloride (30 ml), a saturated aqueous solution of sodium hydrogencarbonate (150 ml) and water (150 ml) were added to the residue. After collecting colorless precipitate formed by filtration and the precipitate was dried to obtain the title compound (5.21 g).
^{1}H-NMR (DMSO-d_6) δ: 1.10-1.45(4H,m), 1.21(9H,s), 1.68(2H,d,J=8.1Hz), 1.86(2H,t,J=16.2Hz), 3.22-3.42(1H, m), 3.69 (1H,br.s), 6.66(1H,d,J=8.5Hz), 7.02(1H, s), 7.15(1H,dd,J=8.5,2.0Hz), 7.41(1H,d,J=8.5Hz), 7.67(1H,d,J=2.0Hz), 8.15 (1H,d,J=8.1Hz), 11.73(1H,br.s).
MS (ESI) m/z: 392$(M+H)^+$.

[Referential Example 69]

N-[(1R*,2R*)-2-Aminocyclohexyl]-5-chloroindole-2-carboxamide hydrochloride:

[0262]

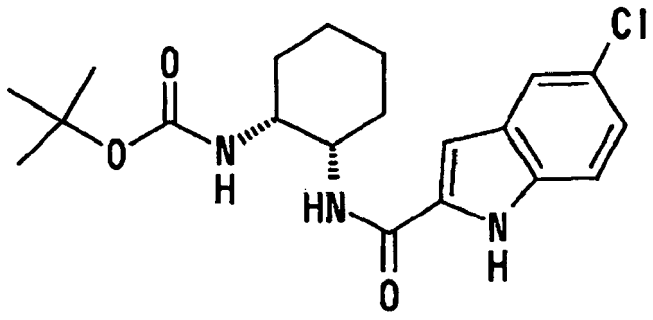


[0263] An ethanol solution (100 ml) of hydrochloric acid was added to a solution of the compound (5.18 g) obtained in Referential Example 68 in methylene chloride (100 ml) at room temperature. After stirring for 2 days, the reaction mixture was concentrated under reduced pressure, diethyl ether (300 ml) was added to the resultant residue, and colorless precipitate formed was collected by filtration and dried to obtain the title compound (4.30 g).
^{1}H-NMR (DMSO-d_6) δ: 1.20-1.36(2H,m), 1.36-1.50(2H,m), 1.60(2H,br.s), 1.90(1H,d,J=13.0Hz), 2.07(1H,d,J=13.7Hz), 3.06(1H,br.s), 3.83-3.96(1H,m), 7.15-7.24(2H,m), 7.45(1H,d,J=8.6Hz), 7.73(1H,s), 8.00(3H,br.s), 8.60(1H,d,J=8.3Hz), 11.86(1H, s).
MS (ESI) m/z: 292$(M+H)^+$.

[Referential Example 70]

tert-Buthyl (1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexylcarbamate:

[0264]

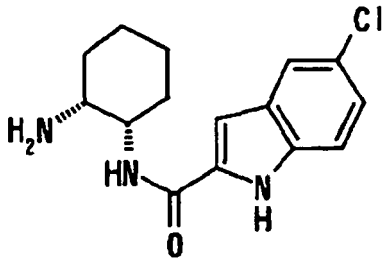


[0265] The title compound was obtained from the compound obtained in Referential Example 66 in a similar manner to Referential Example 68.
^{1}H-NMR (DMSO-d_6) δ: 1.20-1.45(11H, m), 1.45-1.70(4H,m), 1.70-1.85(2H, m), 3.76(1H, br.s), 4.08(1H, br.s), 6.64(1H, d,J=7.6Hz), 7.12(1H, s), 7.16(1H,dd,J=8.8,2.0Hz), 7.43(1H,d,J=8.8Hz), 7.69(1H,d,J=2.0Hz), 7.85(1H,d,J=6.9Hz), 11.80 (1H,br.s).
MS (ESI) m/z: 392 $(M+H)^+$.

[Referential Example 71]

N-[(1R*,2S*)-2-Aminocyclohexyl]-5-chloroindole-2-carboxamide hydrochloride:

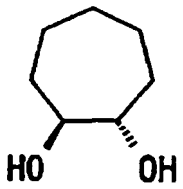
[0266]



[0267] The title compound was obtained from the compound obtained in Referential Example 70 in a similar manner to Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 1.30-1.50 (2H, m), 1.55-1.95 (6H, m), 3.41(1H, br.s), 4.32(1H, br.s), 7.19(1H,dd,J=8.7,2.0Hz), 7.33(1H, s), 7.45(1H,d,J=8.7Hz), 7.60-7.90(4H,m), 8.17(1H,d,J=7.1Hz), 11.91(1H, s).
MS (FAB) m/z: 292$(M+H)^+$.

[Referential Example 72] (1R*,2R*)-1,2-Cycloheptanediol:

[0268]

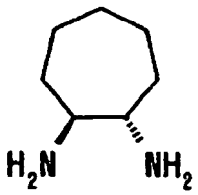


[0269] Cycloheptene (3.85 g) was added portionwise to 30% aqueous hydrogen peroxide (45 ml) and 88% formic acid (180 ml), and the mixture was stirred at 40 to 50°C for 1 hour and then at room temperature for a night. The solvent was distilled off under reduced pressure, and a 35% aqueous solution of sodium hydroxide was added to the residue to alkalify it. After this residue was stirred at 40 to 50°C for 10 minutes, ethyl acetate was added to conduct liquid separation. The resultant water layer was extracted 4 times with ethyl acetate. The resultant organic layers were collected and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound (4.56 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44-1.56(6H,m), 1.63-1.70 (2H, m), 1.83-1.91(2H,m), 2.91(2H,br.s), 3.40-3.44(2H,m).
MS (FAB) m/z: 131$(M+H)^+$.

[Referential Example 73]

(1R*,2R*)-1,2-Cycloheptanediamine hydrochloride:

[0270]



[0271] The compound (4.56 g) obtained in Referential Example 72 was dissolved in methylene chloride (35 ml), triethylamine (29 ml) was added, and the mixture was cooled to -78°C. Methanesulfonyl chloride (8.13 ml) was added dropwise thereto. Methylene chloride (10 ml) was slowly added, and the mixture was stirred for 20 minutes at the same temperature and then for 1.5 hours at 0°C. Water was added to the reaction mixture to conduct liquid separation, and the resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain an oil. This oil was dissolved

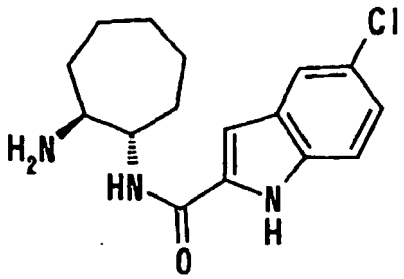
in N,N-dimethylformamide (90 ml), sodium azide (13.65 g) was added, and the mixture was stirred at 65°C for 18 hours. Ether and water was added to the reaction mixture to conduct liquid separation. The resultant ether layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain an oil.

[0272] This oil was dissolved in ethanol (70 ml), 10% palladium on carbon (containing 50% of water, 4 g) was added, and the mixture was stirred for 4 days in a hydrogen (3.5 atm) atmosphere. After separating the palladium on carbon by filtration, a 1N ethanol solution (70 ml) of hydrochloric acid was added to the filtrate, and the solvent was distilled off under reduced pressure. The residue was dissolved in methanol, ethyl acetate was added, and the solvent was distilled off under reduced pressure again. Precipitate formed was collected by filtration to obtain the title compound (3.57 g).
^{1}H-NMR (DMSO) δ: 1.44(4H,br.s), 1.73-1.81(6H,m), 3.43(2H,br.s), 8.63(6H,br.s).
MS (ESI) m/z: 129$(M+H)^+$.

[Referential Example 74]

N-[(1R*,2R*)-2-Aminocycloheptyl]-5-chloroindole-2-carboxamide:

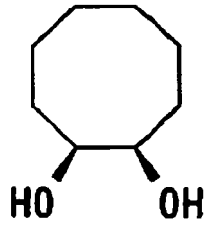
[0273]



[0274] The title compound was obtained from the compound obtained in Referential Example 73 in a similar manner to Referential Example 59.
^{1}H-NMR (DMSO-d_6) δ: 1.49-1.52(4H,m), 1.72-1.91(6H,m), 4.04-4.10(1H, m), 7.17-7.23(2H, m), 7.44(1H,d,J=8.8Hz), 7.72(1H,d,J=2.0Hz), 7.96(2H,br.s), 8.75(1H,d,J=8.5Hz), 11.89(1H, br.s).
MS (ESI) m/z: 306$(M+H)^+$.

[Referential Example 75] (1R*,2S*)-1,2-Cyclooctanediol:

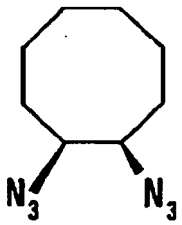
[0275]



[0276] Cyclooctene (4.41 g) was dissolved in acetonitrile (45 ml) and water (15 ml), and to the solution N-methylmorpholine N-oxide (5.15 g) and microcapsulated osmium tetroxide (1 g, containing 10% osmium tetroxide) were added, and the mixture was stirred at 40 to 50°C for 21 hours. Insoluble microcapsulated osmium tetroxide was removed by filtration, and washed with acetonitrile, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane:ethyl acetate = 1:1) to obtain the title compound (4.97 g).
^{1}H-NMR ($CDCl_3$) δ: 1.48-1.58 (6H, m), 1.64-1.75 (4H, m), 1.86-1.96(2H,m), 2.28(2H,d,J=2.9Hz), 3.90(2H,d,J=8.3Hz).
MS (FAB) m/z: 145$(M+H)^+$.

[Referential Example 76] (1R*,2S*)-1,2-diazidocyclooctane:

[0277]

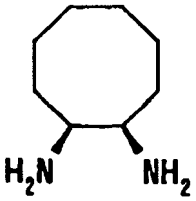


[0278] After cis-1,2-cyclooctanediol (4.82 g) was dissolved in methylene chloride (60 ml), and to the solution triethylamine (27.7 ml) was added, and the interior of a vessel was purged with argon, the mixture was cooled to - 78°C, and methanesulfonyl chloride (7.7 ml, 100 mmol) was added dropwise thereto. The mixture was stirred for 1 hour at the same temperature and then for 1 hour at 0°C. Water was then added to the reaction mixture to conduct liquid separation, and the resultant organic layer was washed with water, 0.5N hydrochloric acid, water and a saturated aqueous solution of sodium hydrogencarbonate and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was dissolved in N,N-dimethylformamide (80 ml), sodium azide (13.0 g) was added, and the mixture was stirred at 65°C for 19 hours. Ether and water was added to the reaction mixture to conduct liquid separation. The resultant ether layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane:ethyl acetate = 6:1) to obtain the title compound (4.85 g).
^{1}H-NMR ($CDCl_3$) δ: 1.49-1.64(6H,m), 1.67-1.78(2H,m), 1.81-1.97(4H,m), 3.74-3.76(2H,m).

[Referential Example 77]

(1R*,2S*)-1,2-Cyclooctanediamine hydrochloride:

[0279]

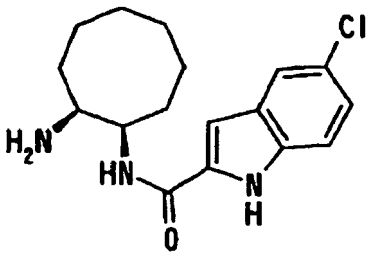


[0280] The compound (4.85 g) obtained in Referential Example 76 was dissolved in ethanol (55 ml), to the solution 10% palladium on carbon (containing 50% of water, 3.0 g) was added, and the mixture was stirred for 21 hours in a hydrogen (4.5 atm) atmosphere. After separating the catalyst by filtration, a 1N ethanol solution (50 ml) of hydrochloric acid was added to the filtrate, and the solvent was distilled off under reduced pressure. Ethyl acetate was added to the residue, and precipitate formed was collected by filtration to obtain the title compound (4.14 g).
^{1}H-NMR (DMSO) δ: 1.51(6H,br.s), 1.69(2H,br.s), 1.79-1.99(4H,m), 3.68-3.70(2H,m), 8.66(6H,br.s).
MS (ESI) m/z: 143$(M+H)^+$.

[Referential Example 78]

N-[(1R*,2S*)-2-aminocyclooctyl]-5-chloroindole-2-carboxamide:

[0281]

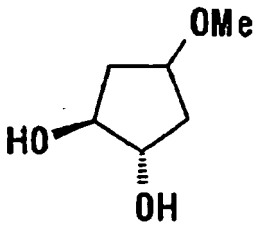


[0282] The title compound was obtained from the compound obtained in Referential Example 77 in a similar manner to Referential Example 59.
MS (ESI) m/z: 320$(M+H)^+$.

[Referential Example 79]

(1R*,2R*)-4-Methoxy-1,2-cyclopentanediol (mixture of 4-position stereoisomers):

[0283]



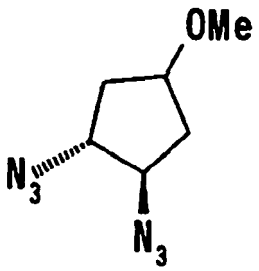
[0284] 60% Sodium hydride (800 mg) was added portionwise to a solution of 3-cyclopentene-1-ol (1.68 g) and methyl iodide (1.25 ml) dissolved in tetrahydrofuran (20 ml) under ice cooling, and the mixture was stirred overnight at room temperature. Water and diethyl ether was added to the reaction mixture to separate an organic layer, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure with ice cooling to obtain crude 4-methoxy-1-cyclopentene.

[0285] 88% Formic acid (90 ml) and 30% hydrogen peroxide (3.17 ml) were added to 4-methoxy-1-cyclopentene thus obtained, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and a 35% aqueous solution of sodium hydroxide was added to the residue to alkalify the reaction mixture, followed by stirring at 50°C for 10 minutes. The reaction mixture was cooled to room temperature and extracted with ethyl acetate to dry the organic layer over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:19) to obtain the title compound (1.21 g).
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.85(2H,m), 2.15-2.30(2H,m), 3.28(3H,s), 3.90-4.00(2H,m), 4.26(1H,br.s).

[Referential Example 80]

(1R*,2R*)-1,2-Diazido-4-methoxycyclopentane (mixture of 4-position stereoisomers):

[0286]

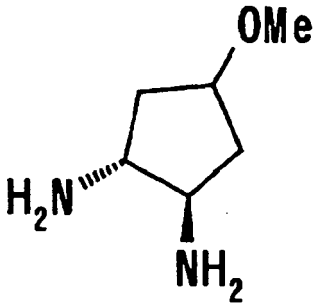


[0287] The compound (1.21 g) obtained in Referential Example 79 and triethylamine (7.66 ml) were dissolved in methylene chloride (20 ml), and methanesulfonyl chloride (2.13 ml) was added dropwise over 20 minutes at -78°C. After completion of drop addition, the mixture was warmed to 0°C and stirred for 80 minutes to obtain crude (1R*,2R*)-1,2-bis(methanesulfonyloxy)-4-methoxycyclopentane. This product was dissolved in N,N-dimethylformamide (20 ml), and sodium azide (3.57 g) was added to heat and stir the mixture at 65°C for 22 hours. Sodium azide (3.57 g) was additionally added to stir the mixture at 70°C for 2 days. The reaction mixture was allowed to cool, and water and diethyl ether was added to separate an organic layer. The organic layer was dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (584 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.80(2H,m), 2.05-2.18(1H,m), 2.25-2.40(1H,m), 3.21(3H,s), 3.55-3.65(1H,m), 3.75-3.90(2H,m).

[Referential Example 81]

(1R*,2R*)-4-Methoxy-1,2-cyclopentane diamine hydrochloride (mixture of 4-position stereoisomers):

[0288]

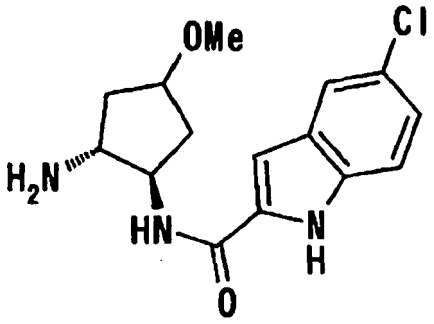


[0289] The compound (584 mg) obtained in Referential Example 80 was dissolved in ethanol, and 10% palladium on carbon (321 mg) was added to conduct hydrogenation at normal temperature and normal pressure for 2 days. After removing the catalyst by filtration, the reaction mixture was concentrated, and a 1N ethanol solution of hydrochloric acid and ethyl acetate were added to the residue. The mixture was concentrated to obtain the title compound (488 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.72-1.83(1H,m), 1.91-2.03(1H,m), 2.07-2.18(1H,m), 2.37-2.50(1H,m), 3.19(3H,s), 3.55-3.75(2H, br), 3.85-3.95(1H,m), 8.60-8.90(6H,br).
MS (ESI) m/z: 261$(2M+H)^+$.

[Referential Example 82]

N-[(1R*,2R*)-2-Amino-4-methoxycyclopentyl]-5-chloroindole-2-carboxamide (mixture of 4-position stereoisomers):

[0290]



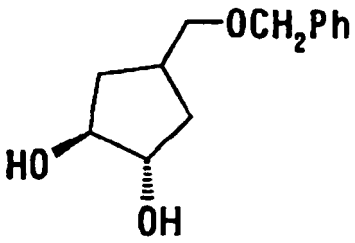
[0291] The compound (470 mg) obtained in Referential Example 81 was suspended in N,N-dimethylformamide (5 ml), and triethylamine (0.966 ml) and p-nitrophenyl 5-chloroindole-2-carboxylate (805 mg) was added. The mixture was stirred at room temperature for 4 days. After the solvent was distilled off under reduced pressure, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to conduct liquid separation, an organic

layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:9) to obtain the title compound (268 mg)..

[Referential Example 83]

(1R*,2R*)-4-[(Benzyloxy)methyl]-1,2-cyclopentanediol (mixture of 4-position stereoisomers):

[0292]

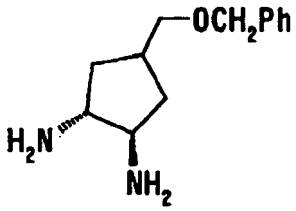


[0293] The title compound was obtained by benzylating 4-hydroxymethyl-1-cyclopentene (J. Heterocycl. Chem., 1989, Vol. 26, p. 451) with benzyl bromide and then reacting the product with formic acid-hydrogen peroxide in a similar manner to Referential Example 79.
^{1}H-NMR ($CDCl_3$) δ: 1.44-1.52(1H,m), 1.77-1.85(1H,m), 1.89-1.97(1H,m), 2.25-2.35(1H,m), 2.46-2.58(1H,m), 3.40-3.50 (2H,m), 3.89(1H,br.s), 4.08(1H,br.s), 4.54(2H,s), 7.27-7.39(5H,m).
MS (FAB) m/z: 223 $(M+H)^+$.

[Referential Example 84]

(1R*,2R*)-4-[(Benzyloxy)methyl]-1,2-cyclopentanediamine (mixture of 4-position stereoisomers):

[0294]

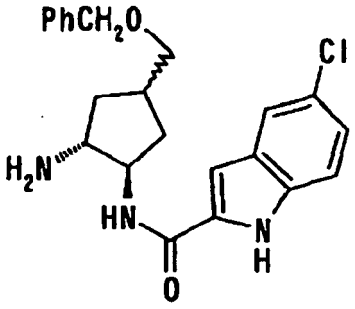


[0295] (1R*,2R*)-4-Benzyloxymethyl-1,2-diazidocyclopentane was obtained from the compound obtained in Referential Example 83 in a similar manner to Referential Example 80. The title compound was obtained in a similar manner to Referential Example 81 without purifying this product.

[Referential Example 85]

N-{(1R*,2R*)-2-Amino-4-[(benzyloxy)methyl]cyclopentyl}-5-chloroindole-2-carboxamide (mixture of 4-position stereoisomers):

[0296]

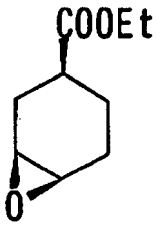


[0297] The title compound was obtained from the compound obtained in Referential Example 84 in a similar manner to Referential Example 59.
^{1}H-NMR (DMSO-d_6) δ: 1.07-1.15(0.5H,m), 1.26-1.35(0.5H,m), 1.47-1.55(0.5H,m), 1.61-1.79(1H,m), 1.83-1.92(0.5H,m), 1.99-2.10(0.5H,m), 2.12-2.20(0.5H,m), 2.27-2.40(1H,m), 3.10-3.20(1H,m), 3.33-3.39(2H,m), 3.81-3.92(1H,m), 4.48(2H, s), 7.13-7.20(2H,m), 7.22-7.39(5H,m), 7.43(1H,d,J=8.5Hz), 7.69(1H,d,J=2.2Hz), 8.34(1H,t,J=7.1Hz).
MS (FAB) m/z: 398$(M+H)^+$.

[Referential Example 86]

Ethyl (1R*,3R*,6S*)-7-oxabicyclo[4.1.0]heptane-3-carbooxylate:

[0298]

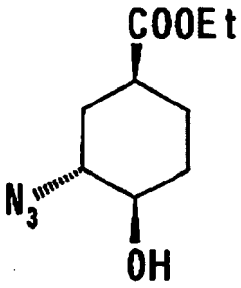


[0299] (1R*,4R*,5R*)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (J. Org. Chem., 1996, Vol. 61, p. 8687) (14.3 g) was dissolved in ethanol (130 ml), a 2N aqueous solution (34.5 ml) of sodium hydroxide was added under ice cooling, and the mixture was then stirred at room temperature for 7 hours. After the solvent was distilled off under reduced pressure, and water was added to the residue to conduct extraction with methylene chloride, the extract was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 83:17) to obtain the title compound (6.54 g).
^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.1Hz), 1.50-1.70(2H,m), 1.71-1.82(1H,m) , 2.08-2.28(4H,m), 3.16(2H,s), 4.12(2H,q, J=7.1Hz).

[Referential Example 87]

Ethyl (1R*,3S*,4S*)-3-azido-4-hydroxycyclohexane-carboxylate:

[0300]

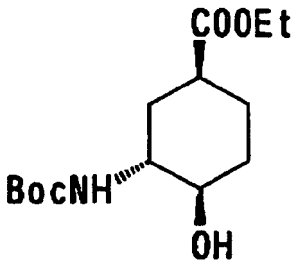


[0301] The compound (13.6 g) obtained in Referential Example 86 was dissolved in N,N-dimethylformamide (100 ml), ammonium chloride (6.45 g) and sodium azide (7.8 g) were successively added at room temperature, and the mixture was then stirred at 75°C for 12 hours. The solvent was concentrated to about 1/3, and the residue was diluted with water and ethyl acetate to conduct stirring for 3 minutes. The resultant organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (15.8 g).
^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.1Hz), 1.37-1.67(2H,m), 1.86-1.95(1H,m), 2.04-2.18(2H,m), 2.32-2.43(1H,m), 2.68-2.78(1H,m), 3.40-3.60(2H,m), 4.17(2H,q,J=7.1Hz).

[Referential Example 88]

Ethyl (1R*,3S*,4S*)-3-[(tert-butoxycarbonyl)amino]]-4-hydroxycyclohexanecarboxylate:

[0302]

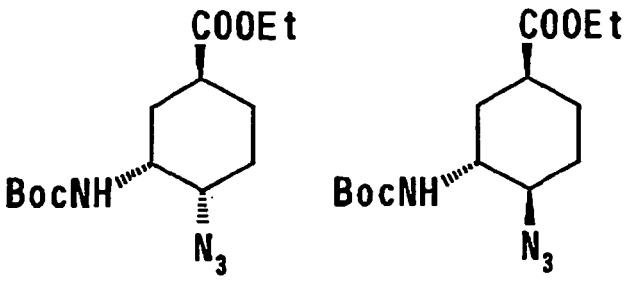


[0303] The compound (100 mg) obtained in Referential Example 87 and di-tert-butyl dicarbonate (133 mg) were dissolved in ethyl acetate (12 ml) and a catalytic amount of 10% palladium on carbon was added to stir the mixture at room temperature for 12 hours in a hydrogen atmosphere. After insoluble matter was removed by filtration, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (145 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.1Hz), 1.45 (9H,s), 1.38-1.57(2H,m), 1.86-1.95(1H,m), 2.05-2.17(1H,m), 2.29-2.39(2H,m), 2.61-2.68(1H,m), 3.25-3.66(3H,m), 4.17(2H,q,J=7.1Hz), 4.53(1H,br.s).

[Referential Example 89]

Ethyl (1R*,3S*,4R*)-4-azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate and ethyl (1R*,3S*,4S*)-4-azido-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate:

[0304]



[0305] After the compound (16 g) obtained in Referential Example 88 and triethylamine (38 ml) were dissolved in methylene chloride (150 ml), and the solution was cooled to -78°C, methanesulfonyl chloride (13 ml) was added dropwise at the same temperature. After stirring for 15 minutes at the same temperature, the mixture was heated to 0°C and stirred for 30 minutes and then 2 hours at room temperature. After 0.1N hydrochloric acid was added, and the mixture was diluted with methylene chloride, the resultant organic layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain crude ethyl (1R*,3S*,4S*)-3-[(tert-butoxycarbonyl)

amino]-4-[(methanesulfonyl)oxy]cyclohexane-carboxylate.

[0306] The product obtained above was dissolved in N,N-dimethylformamide (100 ml), and sodium azide (18 g) was added at room temperature. The mixture was heated to 75°C and stirred for 12 hours. The solvent was concentrated to about 1/3, and the residue was diluted with water and ethyl acetate to conduct stirring for 3 minutes. The resultant organic layer was separated, washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compounds [(1R*,3S*,4R*) -form (6.74 g) and (1R*,3S*,4S*)-form (1.32 g)].

(1R*,3S*,4R*)-form:

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.45(9H,s), 1.38-2.33(6H,m), 2.57-2.68(1H,m) , 3.77-4.20(4H,m), 4.63(1H,br.s).

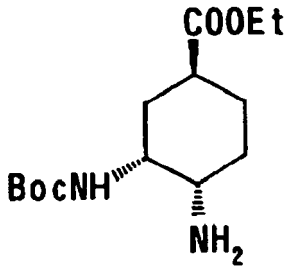
(1R*,3S*,4S*)-form:

^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t,J=7.1Hz), 1.46(9H,s), 1.53-2.30(6H,m), 2.50-2.65(1H,m), 3.42-3.72(2H,m), 4.15(2H, q.J=7.1Hz), 4.67(1H,br.s).

[Referential Example 90]

Ethyl (1R*,3S*,4R*)-4-amino-3-[(tert-butoxycarbonyl)-amino]cyclohexanecarboxylate:

[0307]

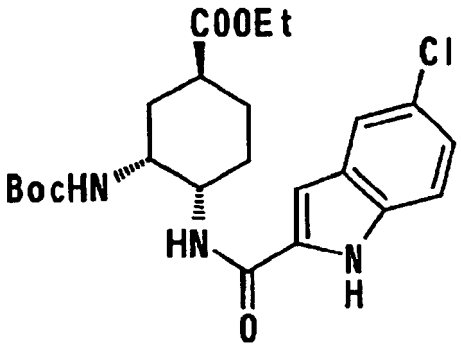


[0308] Ethyl (1R*,3S*,4R*)-4-azido-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate (5.4 g) obtained in Referential Example 89 was dissolved in a mixed solvent of ethanol (10 ml) and ethyl acetate (10 ml), and a catalytic amount of 10% palladium on carbon was added to stir the mixture at room temperature for 20 hours in a hydrogen atmosphere. After insoluble matter was removed by filtration, the solvent was distilled off under reduced pressure to obtain the title compound (4.7 g).

[Referential Example 91]

Ethyl (1R*,3S*,4R*)-3-[(tert-butoxycarbonyl)amino]-4-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexanecarboxylate:

[0309]



[0310] The compound (4.62 g) obtained in Referential Example 90 was dissolved in methylene chloride (50 ml), 5-chloroindole-2-carboxylic acid (3.63 g), 1-hydroxybenzotriazole monohydrate (2.43 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.45 g) were added at room temperature, and the mixture was stirred for 12 hours.

After 0.1N hydrochloric acid was added, and the mixture was extracted with methylene chloride, the resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 2:3) to obtain the title compound (5.3 g).
^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.43(9H,s), 1.35-2.46(7H,m), 3.91-4.02(1H,m), 4.10-4.22(2H,m), 4.79(1H,br.s), 6.79(1H,s), 7.18-7.40(2H,m), 7.59(1H,s), 8.00(1H,br.s), 9.13(1H,br.s).

[Referential Example 92]

Ethyl (1S,3S,6R)-7-oxabicyclo[4.1.0]heptane-3-carboxylate:

[0311] (1S,4S,5S)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (J. Org. Chem., 1996, Vol. 61, p. 8687) (89.3 g) was suspended in ethanol (810 ml), a 2N aqueous solution (213 ml) of sodium hydroxide was added, and the mixture was then stirred at room temperature for 3 hours. After the solvent was distilled off under reduced pressure, and water was added to the residue to conduct extraction with methylene chloride, the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 17:3) to obtain the title compound (41.3 g).
$[\alpha]_D^{25}$ = -58° (C=1.0, chloroform).

[Referential Example 93]

Ethyl (1S,3R,4R)-3-azido-4-hydroxycyclohexanecarboxylate:

[0312] The compound (41 g) obtained in Referential Example 92 was dissolved in N,N-dimethylformamide (300 ml), ammonium chloride (19.3 g) and sodium azide (23.5 g) were successively added at room temperature, and the mixture was then stirred at 76°C for 13 hours. The reaction mixture was filtered, the filtrate was concentrated, the product previously captured by the filter was put in the residue, and water was added to dissolve the collected product. The solution was extracted with ethyl acetate. The resultant organic layer was washed with water and saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (51.5 g).
$[\alpha]_D^{25}$ = +8° (C=1.0, chloroform).

[Referential Example 94]

Ethyl (1S,3R,4R)-3-[(tert-butoxycarbonyl)amino]-4-hydroxycyclohexanecarboxylate:

[0313] The compound (51.2 g) obtained in Referential Example 93 and di-tert-butyl dicarbonate (68.1 g) were dissolved in ethyl acetate (1000 ml), 5% palladium on carbon (5.0 g) was added, and the mixture was stirred overnight at room temperature under a hydrogen pressure of 7 kg/cm^2. After insoluble matter was removed by filtration, the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1 $\rightarrow$ 3:1), and hexane was added to solidify it to obtain the title compound (46.9 g).
$[\alpha]_D^{25}$ = +25° (C=1.0, chloroform).

[Referential Example 95]

Ethyl (1S,3R,4S)-4-azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate and ethyl (1S,3R,4R)-4-azido-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate:

[0314] The compound (53.5 g) obtained in Referential Example 94 and triethylamine (130 ml) were dissolved in methylene chloride (500 ml), and methanesulfonyl chloride (42 ml) was added dropwise over 20 minutes under cooling at -10°C to -15°C. After stirring for 20 minutes at the same temperature, the mixture was heated to room temperature over 2 hours. The reaction mixture was cooled to 0°C, 0.5N hydrochloric acid (800 ml) was added dropwise, and the mixture was extracted with methylene chloride. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain crude ethyl (1S,3R,4R)-3-[(tert-butoxycarbonyl)amino]-4-[(methylsulfonyl)oxy]cyclohexanecarboxylate.
[0315] The crude product obtained above was dissolved in N,N-dimethylformamide (335 ml), and sodium azide (60.5

g) was added to stir the mixture at 67°C to 75°C for 16 hours. The reaction mixture was filtered, the filtrate was concentrated to distill off 250 ml of the solvent, the product captured by the filter was put in the residue, and the collected product was dissolved in water and extracted with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compounds [(1S,3R,4S)-form (18.4 g) and (1S,3R,4R)-form (3.3 g)].
(1S,3R,4S)-form: $[\alpha]_D^{25}$ = +62° (C=1.0, chloroform).
(1S,3R,4R)-form: $[\alpha]_D^{25}$ = -19° (C=1.0, chloroform).

[Referential Example 96]

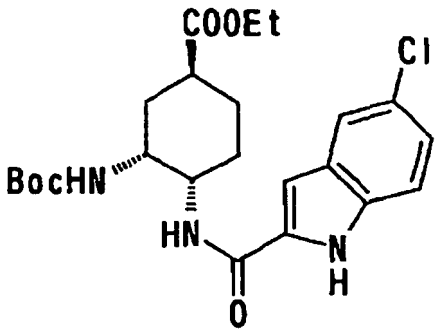
Ethyl (1S,3R,4S)-4-Amino-3-[(tert-butoxycarbonyl)amino] cyclohexanecarboxylate:

[0316] The compound (4.0 g) obtained in Referential Example 95 was dissolved in a mixed solvent of ethanol (150 ml) and ethyl acetate (150 ml), and 5% palladium on carbon (0.5 g) was added to stir the mixture at room temperature for 17 hours in a hydrogen atmosphere (5 kg/cm^2). After insoluble matter was removed by filtration, the solvent was distilled off under reduced pressure to obtain the title compound (4.2 g).

[Referential Example 97]

Ethyl (1S,3R,4S)-3-[(tert-butoxycarbonyl)amino]-4-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexanecarboxylate:

[0317]

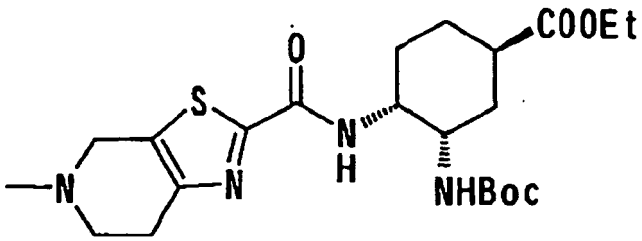


[0318] The compound (4.2 g) obtained in Referential Example 96 was dissolved in methylene chloride (50 ml), 5-chloroindole-2-carboxylic acid (3.33 g), 1-hydroxybenzotriazole monohydrate (2.52 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.15 g) were added at room temperature, and the mixture was stirred for 12 hours. After 0.1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with methylene chloride, the resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:1) to obtain the title compound (4.36 g).
$[\alpha]_D^{25}$ = -27° (C=1.0, chloroform).

[Referential Example 98]

Ethyl (1R*,3S*,4R*)-3-[(tert-butoxycarbonyl)amino]-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl] amino}cyclohexanecarboxylate:

[0319]

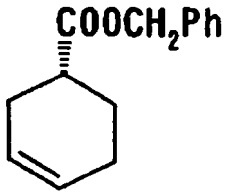


[0320] The title compound was obtained from the compound obtained in Referential Example 90 and the compound obtained in Referential Example 10 in a similar manner to Referential Example 91.

[Referential Example 99]

Benzyl 3-cyclohexene-1-carboxylate:

[0321]

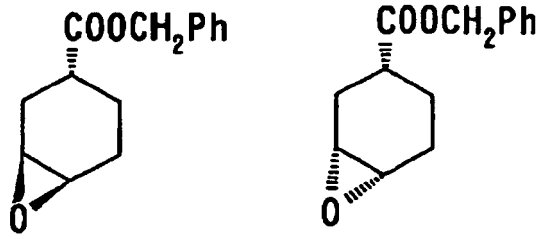


[0322] (+)-3-Cyclohexene-1-carboxylic acid (50 g) was dissolved in N,N-dimethylformamide (550 ml), and triethylamine (170 ml) and benzyl bromide (61 ml) were added under ice cooling to stir the mixture at room temperature for 12 hours. Water was added, extraction was conducted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (70.8 g).
^{1}H-NMR ($CDCl_3$) δ: 1.66-1.76(1H,m), 2.00-2.13(3H,m), 2.27-2.29(2H,m), 2.58-2.65(1H,m), 5.13(2H,s), 5.66(2H,br.s), 7.29-7.38(5H,m).

[Referential Example 100]

Benzyl (1R*,3S*,6S*)-7-oxabicyclo[4.1.0]heptane-3-carboxylate:

[0323]



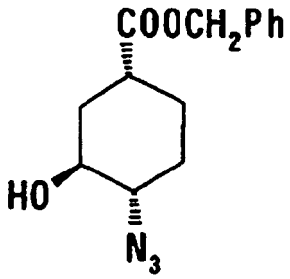
[0324] The compound (40 g) obtained in Referential Example 99 was dissolved in methylene chloride (500 ml), and m-chloroperbenzoic acid (86 g) was added under ice cooling to stir the mixture for 2 hours. After a 10% aqueous solution of sodium thiosulfate was added to conduct stirring for 20 minutes, an organic layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:9) to obtain the title compound (23.4 g) and benzyl (1R*,3R*,6S*)-7-oxabicyclo[4.1.0]heptane-3-carboxylate (12.1 g).
^{1}H-NMR ($CDCl_3$) δ: 1.39-1.49(1H,m), 1.75-1.82(1H,m), 1.90-2.04(3H,m), 2.30(1H,dd,J=14.9,4.9Hz), 2.54-2.61(1H,m) ,

3.12-3.14(1H,m), 3.22-3.24(1H,m), 5.12(2H,s), 7.30-7.39(5H,m).
MS (FAB) m/z: 233$(M+H)^+$.

[Referential Example 101]

Benzyl (1R*,3S*,4S*)-4-azido-3-hydroxycyclohexane-carboxylate:

[0325]

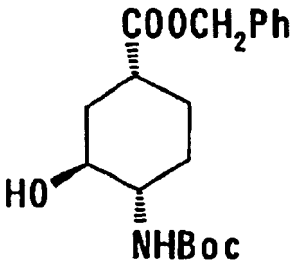


[0326] The compound (52.3 g) obtained in Referential Example 100 was dissolved in N,N-dimethylformamide (1000 ml), ammonium chloride (21.9 g) and sodium azide (18.1 g) were added, and the mixture was heated to 70°C and stirred for 24 hours. The solvent was distilled off under reduced pressure, and water was added to conduct extraction with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (61.8 g).
^{1}H-NMR ($CDCl_3$) 5: 1.51-1.66(2H,m), 1.91-1.98(1H,m), 2.07-2.10(1H,m), 2.27-2.32(1H,m), 2.51-2.52(1H,m), 2.81-2.86 (1H,m), 3.30-3.36(1H,m), 3.70-3.75(1H,m), 5.13(2H,s), 7.30-7.39(5H,m).

[Referential Example 102]

Benzyl (1R*,3S*,4S*)-4-[(tert-butoxycarbonyl)amino]-3-hydoxycyclohexanecarboxylate:

[0327]

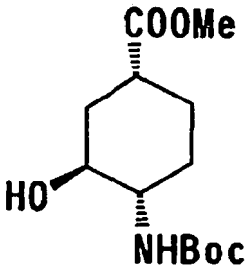


[0328] The compound (5.27 g) obtained in Referential Example 101 was dissolved in tetrahydrofuran (25 ml), and triphenylphosphine (5.53 g) and water (0.55 ml) were added to stir the mixture at room temperature for 20 hours. Di-tert-butyl dicarbonate (4.82 g) was added to the reaction mixture to continue stirring for additional 2 hours. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (6.22 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.59-1.66(2H,m), 1.88-2.00(2H,m), 2.29-2.32(1H,m), 2.80-2.85(1H,m), 3.02(1H,br.s), 3.42(1H,br.s), 3.59-3.65(1H,m), 4.56(1H,br.s), 5.12(2H,q,J=12.5Hz), 7.30-7.38(5H,m).
MS (FAB) m/z: 350$(M+H)^+$.

[Referential Example 103]

Methyl (1R*,3S*,4S*)-4-[(tert-butoxycarbonyl)amino]-3-hydroxycyclohexanecarboxylate:

[0329]

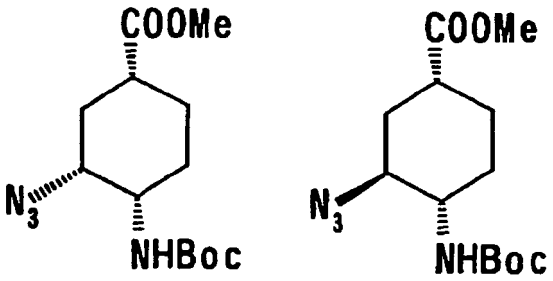


[0330] The compound (2.54 g) obtained in Referential Example 102 was dissolved in ethyl acetate (15 ml), and a catalytic amount of 10% palladium on charcoal was added to the solution. The mixture was stirred in a hydrogen stream at room temperature for 20 hours. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to give (1R*,3S*,4S*)-4-[(tert-butoxycarbonyl)amino]-3-hydroxycyclohexanecarboxylic acid as an colorless oil. The oil was dissolved in a mixture of methanol (8 ml) and toluene (15 ml), to which a 2N hexane solution (10 ml) of trimethylsilyldiazomethane was added under ice cooling, and the resulting mixture was stirred for 30 minutes at room temperature. After removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 1:1) to obtain the title compound (1.82 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.36-2.32(7H,m), 2.74-2.82(1H,m), 3.04(1H,br.s), 3.33-3.47(1H,m), 3.55-3.65(1H,m), 3.68(3H,s), 4.56(1H,br.s).
MS (FAB) m/z: 274$(M+H)^+$.

[Referential Example 104]

Methyl (1R*,3R*,4S*)-3-azido-4-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate and methyl (1R*,3S*,4S*)-3-azido-4-[(tert-butoxycarbonyl)-amino]cyclohexanecarboxylate:

[0331]



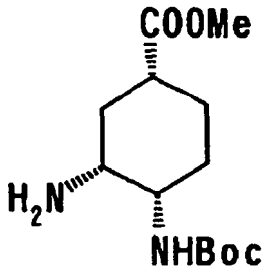
[0332] The compound (1.81 g) obtained in Referential Example 103 was dissolved in methylene chloride (36 ml), and triethylamine (4.6 ml) and methanesulfonyl chloride (1.63 ml) were added at -78°C. After 30 minutes, the mixture was heated to 0°C and stirred for 30 minutes. 1N Hydrochloric acid was added, extraction was conducted with methylene chloride, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain crude methyl (1R*,3S*,4S*)-4-[(tert-butoxycarbonyl)amino]-3-[(methylsulfonyl)oxy]-cyclohexanecarboxylate.

[0333] The crude product obtained above was dissolved in N,N-dimethylformamide (23 ml), sodium azide (1.29 g) was added, and the mixture was heated to 70°C and stirred for 12 hours. Water was added to the reaction mixture, extraction was conducted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatography on silica gel (ethyl acetate: hexane = 3:17) to obtain methyl (1R*,3S*,4S*)-3-azido-4-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate (85 mg) and methyl (1R*,3R*,4S*)-3-azido-4-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate (590 mg).
(1R*,3R*,4S*)-form: ^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.35-2.35(7H,m), 2.45-2.55(1H,m), 3.73(3H,s), 3.67-3.84(2H,m) , 4.70(1H,br.s).
MS (FAB) m/z: 299$(M+H)^+$.
(1R*,3S*,4S*)-form: ^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.56-2.25(7H,m), 2.68-2.80(1H,m), 3.70(3H,s), 3.48-3.68(2H,m), 4.56(1H,br.s).
MS (FAB) m/z: 299$(M+H)^+$.

[Referential Example 105]

Methyl (1R*,3R*,4S*)-3-amino-4-[(tert-butoxycarbonyl) - amino]cyclohexanecarboxylate:

[0334]

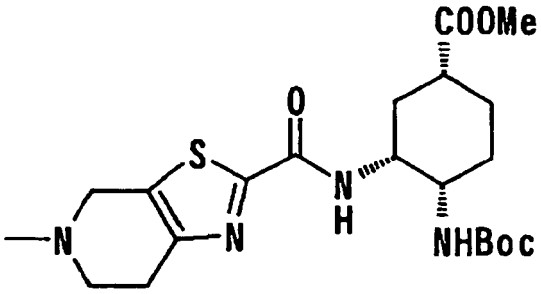


[0335] The (1R*,3R*,4S*)-compound (230 mg) obtained in Referential Example 104 was dissolved in ethyl acetate (8 ml), and a catalytic amount of 10% palladium on carbon was added to stir the mixture at room temperature for 20 hours in a hydrogen atmosphere. Insoluble matter was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain the title compound (220 mg).

[Referential Example 106]

Methyl (1R*,3R*,4S*)-4-[(tert-butoxycarbonyl)amino-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:

[0336]

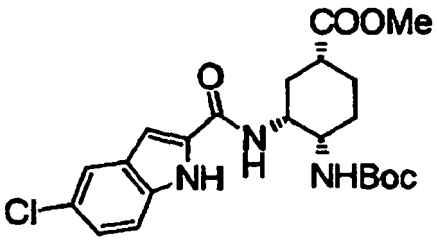


[0337] The title compound was obtained from the compound obtained in Referential Example 105 and the compound obtained in Referential Example 10 in a similar manner to Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.53-1.95(5H,m), 2.17-2.24(1H,m), 2.50(3H,s), 2.50-2.53(1H,m) , 2.80-2.96(4H,m), 3.67 (3H,s), 3.69-3.74(1H,m), 4.10(2H,br.s), 4.88(1H,br.s).
MS (FAB) m/z: 453$(M+H)^+$.

[Referential Example 107]

Methyl (1R*,3R*,4S*)-4-[(tert-butoxycarbonyl)amino-3-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexanecarboxylate:

[0338]



[0339] The title compound was obtained from the compound obtained in Referential Example 105 in a similar manner to Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.33(9H,s), 1.42-2.47(6H,m) 2.78-2.88(1H,m), 3.70(3H,s), 3.86-4.15(2H,m), 4.65-4.75(1H,m), 6.86 (1H,br.s), 7.18-7.38(2H,m), 7.57-7.61(1H,m), 8.32(1H,br.s).
MS (ESI) m/z: 450$(M+H)^+$.

[Referential Example 108]

Benzyl (1S,3R,6R)-7-oxabicyclo[4.1.0]heptane-3-carboxylate:

[0340]

1) Benzyl (1R)-3-cyclohexene-1-carboxylate was obtained from (1R)-3-cyclohexene-1-carboxylic acid (J. Am. Chem. Soc., 1978, Vol. 100, p. 5199) in a similar manner to Referential Example 99.
2) The title compound was obtained from the above-described product in a similar manner to Referential Example 100.

MS (FAB) m/z: 233$(M+H)^+$.

[Referential Example 109]

Benzyl (1R,3S,4S)-4-[(tert-butoxycarbonyl)amino]-3-hydroxycyclohexanecarboxylate:

[0341]

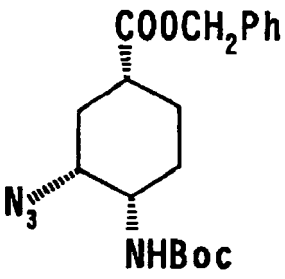
1) Benzyl (1R,3S,4S)-4-azido-3-hydroxycyclohexane-carboxylate was obtained from the compound obtained in Referential Example 108 in a similar manner to Referential Example 101.
2) The title compound was obtained from the above-described product in a similar manner to Referential Example 102.

MS (FAB) m/z: 350$(M+H)^+$.

[Referential Example 110]

Benzyl (1R,3R,4S)-3-azido-4-[(tert-butoxycarbonyl)-amino]cyclohexanecarboxylate:

[0342]



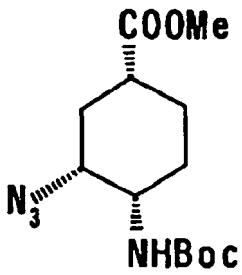
[0343] The title compound was obtained from the compound obtained in Referential Example 109 in a similar manner to Referential Example 104.
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.52-1.66(2H,m), 1.83-2.01(3H,m), 2.20-2.28(1H,m), 2.51-2.54(1H,m), 3.77(2H,br.s),

4.70(1H,br.s), 5.15(2H,ABq,J=12.2Hz), 7.33-7.38(5H,m).
MS (FAB) m/z: 375$(M+H)^+$.

[Referential Example 111]

Methyl (1R,3R,4S)-3-azido-4-[(tert-butoxycarbonyl)-amino]cyclohexanecarboxylate:

[0344]

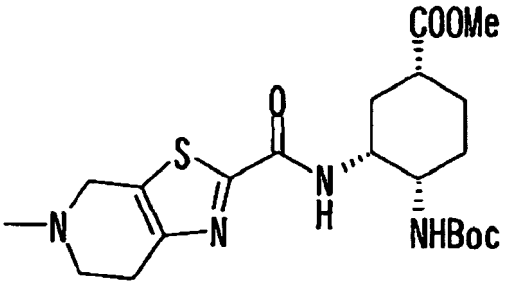


[0345] The compound (3.5 g) obtained in Referential Example 110 was dissolved in tetrahydrofuran (130 ml) and water (16 ml), and lithium hydroxide (291 mg) was added under ice cooling. After 10 minutes, the mixture was heated to room temperature to continue stirring. After 20 hours, the reaction was stopped, the solvent was distilled off under reduced pressure, and the resultant residue was subjected to column chromatography on silica gel (methanol:methylene chloride = 1:20) to obtain (1R,3R,4S)-3-azido-4-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid (3.34 g) as a pale yellow oil. This product was dissolved in methanol (18 ml) and toluene (64 ml), a 2N hexane solution (6.1 ml) of trimethylsilyldiazomethane was added under ice cooling. After 10 minutes, the mixture was heated to room temperature and stirred for 2 hours. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (ethyl acetate: hexane = 1:4) to obtain the title compound (3.35 g).
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.57-1.63(2H,m), 1.82-1.85(1H,m), 1.95-1.99(2H,m), 2.20-2.28(1H,m), 2.48-2.51(1H, m), 3.73(3H,s), 3.78(2H,br.s), 4.70-4.72(1H,m).
MS (FAB) m/z: 299$(M+H)^+$.

[Referential Example 112]

Methyl (1R,3R,4S)-4-[(tert-butoxycarbonyl)amino]-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl] amino}cyclohexanecarboxylate:

[0346]

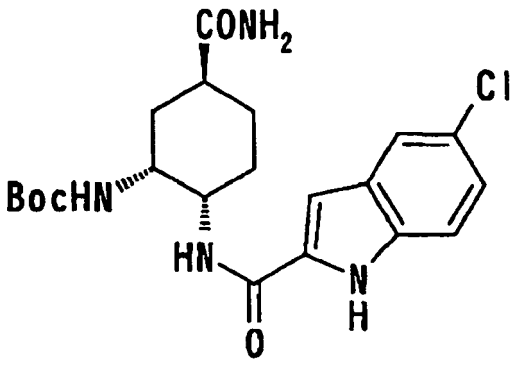


1) Methyl (1R,3R,4S)-3-amino-4-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate was obtained from the compound obtained in Referential Example 111 in a similar manner to Referential Example 105.
2) The title compound was obtained from the above-described product and the compound obtained in Referential Example 10 in a similar manner to Referential Example 106.
MS (FAB) m/z: 453$(M+H)^+$.

[Referential Example 113]

tert-Buthyl (1R*,2S*,5S*)-5-aminocarbonyl-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexylcarbamate:

[0347]

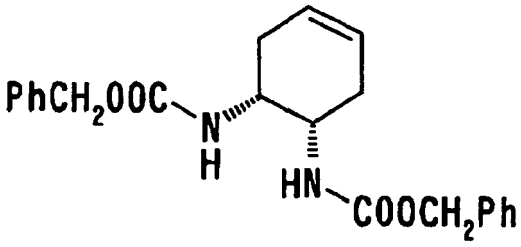


[0348] The compound (590 mg) obtained in Referential Example 91 was dissolved in a mixed solvent of ethanol (3 ml) and tetrahydrofuran (6 ml), a 1N aqueous solution (2.5 ml) of sodium hydroxide was added at room temperature, and the mixture was stirred for 12 hours. The solvent was distilled off to obtain sodium (1R*,3S*,4R*)-3-[(tert-butoxycarbonyl)amino]-4-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexanecarboxylate. This product was suspended in N,N-dimethylformamide (4 ml), di-tert-butyl dicarbonate (654 mg) and ammonium hydrogencarbonate (1 g) were added at room temperature, and the mixture was stirred for 18 hours. The solvent was distilled off under reduced pressure, and water was added to conduct extraction with chloroform. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 47:3) to obtain the title compound (82 mg).
MS (ESI) m/z: 435$(M+H)^+$.

[Referential Example 114]

Benzyl (1R,6S)-6-{[(benzyloxy)carbonyl]amino}-3-cyclohexen-1-ylcarbamate:

[0349]

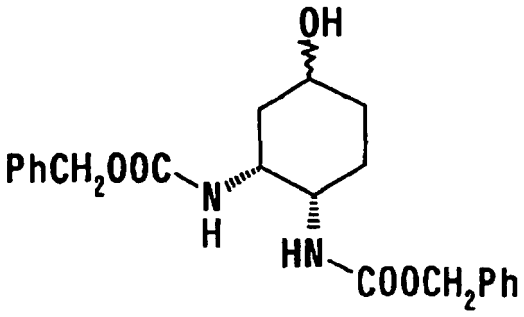


[0350] 4-Cyclohexene-1,2-diamine hydrochloride (4.0 g) was dissolved in a mixed solvent of water (20 ml) and acetonitrile (20 ml), and benzyl chloroformate (7.66 ml) and potassium carbonate (14.9 g) were added, and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured into water to conduct extraction with methylene chloride. The resultant organic layer was washed with saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride) to obtain the title compound (8.22 g).
^{1}H-NMR ($CDCl_3$) δ: 2.03(2H,m), 2.53(2H,d,J=17.1Hz), 3.77(2H,m), 5.03(2H,q,J=12.3Hz), 5.09(2H,q,J=12.3Hz), 5.59 (2H,s), 7.32(10H,m).
MS (ESI) m/z: 381$(M+H)^+$.

[Referential Example 115]

Benzyl (1R*,2S*)-2-{[(benzyloxy)carbonyl]amino}-5-hydroxy-cyclohexylcarbamate:

[0351]

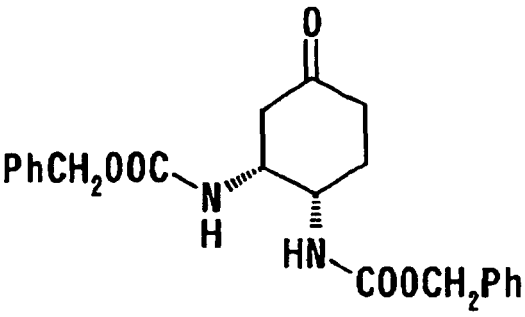


[0352] The compound (10 g) obtained in Referential Example 114 was dissolved in absolute tetrahydrofuran (70 ml), borane-dimethyl sulfide complex (7.4 ml) was added at 0°C, and the mixture was gradually heated to room temperature and stirred for 14 hours. Ice was added to the reaction mixture to decompose excessive borane, and a 1N aqueous solution (80 ml) of sodium hydroxide and 30% aqueous hydrogen peroxide (80 ml) were added to stir the mixture for 1 hour as it is. The reaction mixture was extracted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 2:1) to obtain the title compound (9.2 g).
^{1}H-NMR ($CDCl_3$) δ: 1.98(1H,m), 2.08(1H,m), 2.30(1H,m), 3.43(2H,m), 3.73(1H,m), 5.06(6H,m), 7.32(10H,s). MS (ESI) m/z: 399$(M+H)^+$.

[Referential Example 116]

Benzyl (1R*,2S*)-2-{[(benzyloxy)carbonyl]amino}-5-oxo-cyclohexylcarbamate:

[0353]

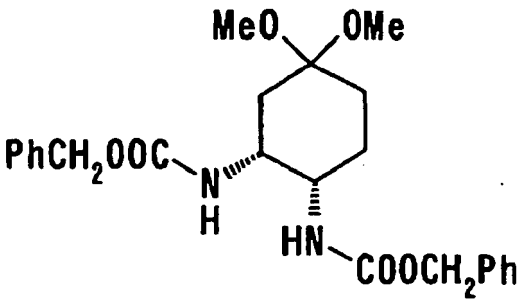


[0354] Dimethyl sulfoxide (8.2 ml) was added to a solution of oxalyl chloride (9.9 ml) in methylene chloride (90 ml) at -60°C, and a solution of the compound (9.2 g) obtained in Referential Example 115 in tetrahydrofuran (90 ml) was added to the mixture at a time. After 1 hour, the temperature of the mixture was raised to -40°C, and triethylamine (26 ml) was added at a time. The mixture was heated to room temperature as it is, and stirred for 3 hours. The reaction mixture was poured into water and extracted with methylene chloride. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate: hexane = 1:1) to obtain the title compound (8.0 g).
^{1}H-NMR ($CDCl_3$) δ: 2.27-2.43(4H,m), 2.78(1H,dd,J=14.4,3.9Hz), 3.86(2H,m), 5.08(4H,m), 5.22(2H,m), 7.32(10H,m). MS (ESI) m/z: 397$(M+H)^+$.

[Referential Example 117]

Benzyl (1R*,2S*)-2-{[(benzyloxy)carbonyl]amino}-5,5-dimethoxycyclohexylcarbamate:

[0355]

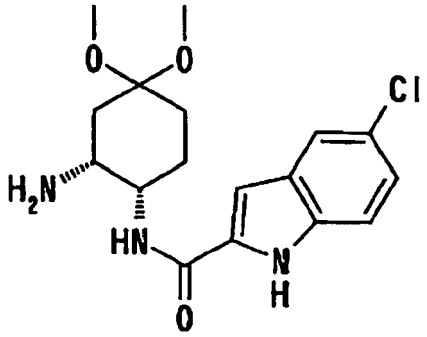


[0356] The compound (3.89 g) obtained in Referential Example 116 was dissolved in a mixed solvent of methanol (15 ml) and tetrahydrofuran (15 ml), 2,2-dimethoxypropane (10.7 ml) and p-toluenesulfonic acid (187 mg) were added, and the mixture was stirred at room temperature for 3 hours. The solvent was concentrated, and a saturated aqueous solution of sodium hydrogencarbonate was added to conduct extraction with ethyl acetate. After the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate: hexane = 1:2) to obtain the title compound (3.54 g).
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.41(4H,m), 1.93(1H,m), 2.38(1H,m), 3.19(6H,s), 3.46(1H,m), 3.59(1H,m), 5.03(2H,q, J=12.5Hz), 5.09(2H,q,J=12.5Hz), 7.32(10H,s).

[Referential Example 118]

N-[(1R*,2S*)-2-Amino-4,4-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide and N-[(1R*,2S*)-2-amino-5,5-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide:

[0357]



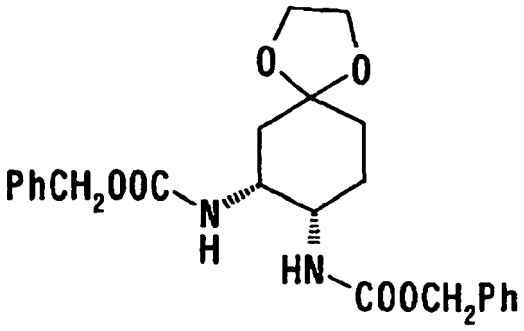
[0358] The compound (1.45 g) obtained in Referential Example 117 was dissolved in methanol (12 ml), and 10% palladium on carbon (290 mg) was added to stir the mixture at room temperature for 20 hours in a hydrogen atmosphere. 10% Palladium on carbon (290 mg) and methanol (10 ml) were additionally added to stir the mixture for 8 hours. The reaction mixture was filtered through Celite, and mother liquor was concentrated, and the residue was dissolved in N,N-dimethylformamide (10 ml). 5-Chloroindole-2-carboxylic acid (320 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (377 mg), 1-hydroxybenzotriazole monohydrate (301 mg) and N-methylmorpholine (360 ml) were added, and the mixture was stirred at room temperature for 14 hours. The reaction mixture was poured into an aqueous solution of sodium hydrogencarbonate and extracted with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was isolated and purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 93:7) to obtain N-[(1R*,2S*)-2-arnino-4,4-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide (or N-[(1R*,2S*)-2-amino-5,5-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide) (98 mg) and N-[(1R*,2S*)-

2-amino-5,5-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide (or N-[(1R*,2S*)-2-amino-4,4-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide)(105 mg).
N-[(1R*,2S*)-2-Amino-4,4-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide:
^{1}H-NMR ($CDCl_3$) δ: 1.45-1.50(2H,m), 2.06-2.10(2H,m), 2.34(1H,d,J=13.1Hz), 2.78(1H,dt,J=2.9,13.1Hz), 3.18(3H,s), 3.23(3H,s), 3.75-3.77(1H,m), 6.24(1H,d,J=8.3Hz), 6.79(1H,s), 7.23(1H,dd,J=8.8,2.0Hz), 7.35(1H,d,J=8.8Hz), 7.60(1H,d,J=8.8Hz), 9.53(1H,br.s).
MS (ESI) m/z: 352$(M+H)^+$.
N-[(1R*,2S*)-2-Amino-5,5-dimethoxycyclohexyl]-5-chloroindole-2-carboxamide:
^{1}H-NMR ($CDCl_3$) δ: 1.83-1.87(1H,m), 1.97-2.01(1H,m), 2.39(1H,br,J=13.2Hz), 2.86-2.90(1H,m), 3.22-3.28(10H,m), 4.00-4.02(1H,m), 6.77(1H,s), 7.23(1H,d,J=8.5Hz), 7.37(1H,d,J=8.5Hz), 7.61(1H,s), 9.49(1H,br.s).
MS (ESI) m/z: 352$(M+H)^+$.

[Referential Example 119]

Benzyl (7R*,8S*)-7-{[(benzyloxy)carbonyl]amino}-1,4-dioxaspiro[4.5]dec-8-ylcarbamate:

[0359]

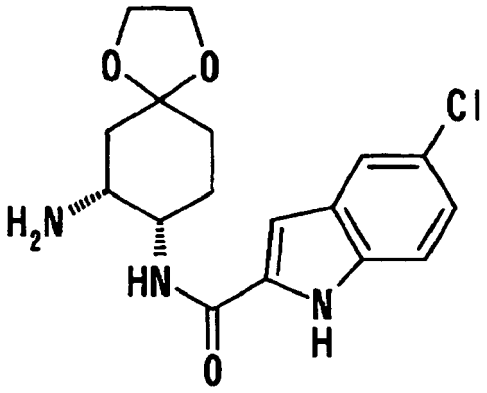


[0360] The compound (4.0 g) obtained in Referential Example 116 was dissolved in absolute tetrahydrofuran (30 ml), and ethylene glycol (5.6 ml) and p-toluenesulfonic acid (192 mg) were added to stir the mixture at room temperature for 17 hours. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate and extracted with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:1) to obtain the title compound (4.23 g).
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.71(4H,m), 2.00(1H,m), 2.11(1H,m), 3.49(1H,m), 3.73(1H,m), 3.93(4H,s), 5.03(2H,q,J=12.2Hz), 5.08(2H,q,J=12.2Hz), 7.32(10H,s).
MS (ESI) m/z: 441$(M+H)^+$.

[Referential Example 120]

N-[(7R*,8S*)-7-Amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide and N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide:

[0361]

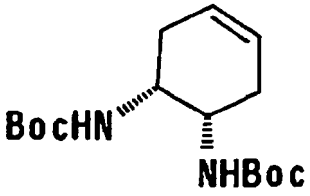


[0362] N-[(7R*,8S*)-7-Amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide) and N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-7-amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide) were obtained from the compound obtained in Referential Example 119 in a similar manner to Referential Example 118.
N-[(7R*,8S*)-7-Amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide:
^{1}H-NMR ($CDCl_3$) δ: 1.68-1.81(4H,m), 2.11(2H,m), 2.87(1H,td,J=3.9,11.2Hz), 3.77(1H,m), 3.97(4H,s), 6.27(1H,d,J=7.6Hz), 6.80(1H,s), 7.24(1H,d,J=9.0Hz), 7.35(1H,d,J=9.0Hz), 7.61(1H,s), 9.47(br.s,1H).
MS (ESI) m/z: 350$(M+H)^+$.
N-[(7R*,8S*)-8-Amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-7-amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide):
^{1}H-NMR ($CDCl_3$) δ: 1.65(2H,m), 1.88(1H,m), 1.96(1H,m), 2.31(1H,dd,J=12.9,3.2Hz), 2.96(1H,m), 3.98(1H,m), 4.02(4H,s), 4.12(1H,m), 6.77(1H,s), 7.06(1H,br.s), 7.23(1H,dd,J=8.8,2.0Hz), 7.37(1H,d,J=8.8Hz), 7.62(1H,d,J=2.0Hz), 9.49(1H,br.s).
MS (ESI) m/z: 350$(M+H)^+$.

[Referential Example 121]

tert-Butyl (1R,6S)-6-[(tert-butoxycarbonyl)amino]-3-cyclohexene-1-ylcarbamate:

[0363]

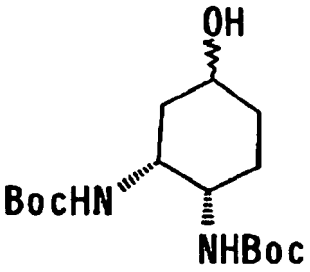


[0364] cis-4-Cyclohexene-1,2-diamine hydrochloride (4.0 g) was dissolved in a mixed solvent of water (40 ml) and acetonitrile (40 ml), and di-tert-butoxy carbonate (11.8 g) and triethylamine (12 ml) were added, and the mixture was stirred at room temperature for 4.5 hours. The reaction mixture was poured into water to conduct extraction with methylene chloride, and the resultant methylene chloride layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (6.12 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(18H,s), 1.98(2H,dd,J=9.3,15.9Hz), 2.48(2H,br.d,J=15.9Hz), 3.66(2H,br.s), 4.88(2H,br.s), 5.58(2H,d,J=2.7Hz).

[Referential Example 122]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-hydroxycyclohexylcarbamate (mixture of stereoisomers):

[0365]

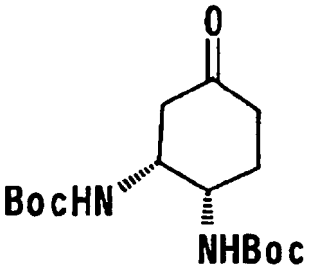


[0366] The compound (6.1 g) obtained in Referential Example 121 was dissolved in absolute tetrahydrofuran (40 ml), and borane-dimethyl sulfide complex (2.22 ml) was added under ice cooling. The mixture was stirred for 16 hours while gradually heating the mixture to room temperature as it is. Ice was added to the reaction mixture, and a 1N aqueous solution of sodium hydroxide and 30% aqueous hydrogen peroxide (50 ml) were added to stir the mixture at room temperature for 2 hours as it is. The reaction mixture was extracted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:2 $\rightarrow$ 2:1) to obtain the title compound (6.1 g).
^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 1.43(9H,s), 1.83-1.67(5H,m), 2.15(1H,m), 2.22(1H,s), 3.34(1H,m), 3.78(1H,m), 4.15(1H,s), 4.98(1H,q,J=9.0Hz), 5.02(1H,q,J=9.0Hz).
MS (ESI) m/z: 331$(M+H)^+$.

[Referential Example 123]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-oxocyclohexylcarbamate:

[0367]

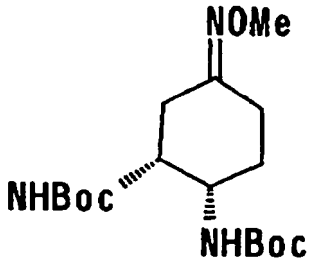


[0368] Oxalyl chloride (8.2 ml) and dimethyl sulfoxide (6.8 ml) were dissolved in methylene chloride (100 ml) at -60°C, and a solution of the compound (mixture of stereoisomers) (6.32 g) obtained in Referential Example 122 in tetrahydrofuran (80 ml) was added at a time, and the mixture was stirred for 1 hour. The temperature of the mixture was raised to -40°C, and triethylamine (21 ml) was added. The mixture was heated to room temperature. After 3 hours, the reaction mixture was poured into water and extracted with methylene chloride. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate: hexane = 1:1) to obtain the title compound (3.8 g).
^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 1.44(9H,s), 2.24-2.36(3H,m), 2.39-2.44(2H,m), 2.75(1H,dd,J=14.6,2.9Hz), 3.66-3.81(2H,m), 4.95-4.90(1H,m), 4.97-5.03(1H,m).
MS (ESI) m/z: 329$(M+H)^+$.

[Referential Example 124]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino)-5-(methoxyimino)cyclohexylcarbamate:

[0369]

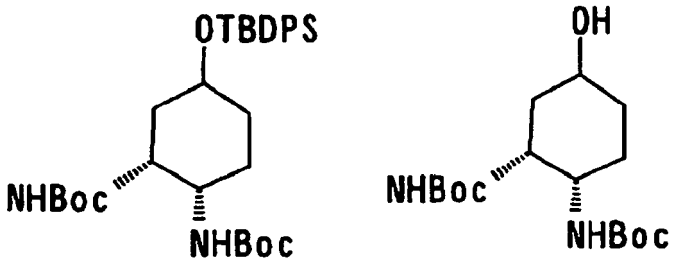


[0370] The compound (1.5 g) obtained in Referential Example 123 was dissolved in methanol (30 ml), and O-methylhydroxyamine hydrochloride (572 mg) and pyridine (737 ml) were added to stir the mixture at room temperature for 17 hours. After the reaction mixture was concentrated, water was added to conduct extraction with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (1.52 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(18H,s), 1.64(1H,m), 2.16(2H,m), 2.44(1H,m), 3.45-3.63(3H,m), 3.82(3H,s), 4.93(1H,m).
MS (ESI) m/z: 358$(M+H)^+$.

[Referential Example 125]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-{[tert-butyl(diphenyl)silyl]oxy}cyclohexylcarbamate (Stereoisomer A):

[0371]

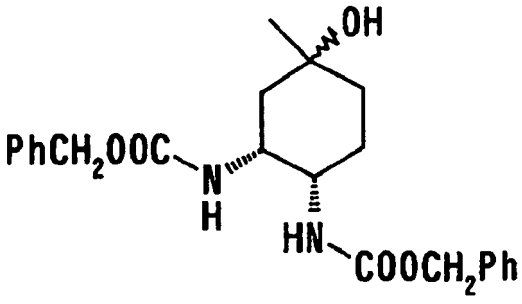


[0372] The title compound was obtained from the compound (mixture of stereoisomers) obtained in Referential Example 122 in a similar manner to Referential Example 58, and tert-butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino)-5-hydroxycyclohexylcarbamate (Stereoisomer B) was recovered.
^{1}H-NMR ($CDCl_3$) δ: 1.03(9H,s), 1.39(9H,s), 1.40(9H,s), 1.72(1H,m), 1.86(1H,m), 2.13(1H,m), 3.24(2H,m), 3.65(1H,m), 4.83(1H,m), 7.37(10H,m).

[Referential Example 126]

Benzyl (1R*,2S*)-2-{[(benzyloxy)carbonyl]amino}-5-hydroxy-5-methylcyclohexylcarbamate:

[0373]



[0374] Anhydrous cerium chloride (6.4 g) was suspended in tetrahydrofuran (50 ml), and the suspension was cooled to -78°C in an argon atmosphere. A methyllithium solution (1.14N diethyl ether solution, 22.5 ml) was added to the suspension, and the mixture was stirred at -78°C for 30 minutes. A tetrahydrofuran solution (50 ml) of the compound (3.0 g) obtained in Referential Example 116 was added dropwise at -78°C, and the mixture was stirred for 30 minutes. The reaction mixture was poured into a 3% aqueous solution (100 ml) of acetic acid, and diethyl ether (50 ml) was added to stir the mixture at room temperature for 10 minutes. The reaction mixture was extracted with ethyl acetate, and the resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified twice by column chromatography on silica gel (methanol:chloroform = 0:100 - 1:19) to obtain the title compound (Stereoisomer A) (780 mg) and the title compound (Stereoisomer B) (1.1 g).

Stereoisomer A:

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,s), 1.27-2.08(6H,m), 3.48(1H,br.s), 3.59(1H,br.s), 5.02-5.09(5H,m), 5.33(1H,br.s), 7.30-7.32(10H,s)
MS (FAB) m/z: 413$(M+H)^+$.

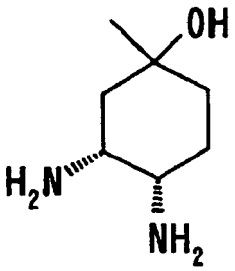
Stereoisomer B:

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,s), 1.29-2.07(6H,m), 3.39(1H,br.s), 3.82(1H,br.s), 5.02-5.23(6H,m), 7.30(10H,s)
MS(FAB) m/z: 413$(M+H)^+$.

[Referential Example 127]

(3R*,4S*)-3,4-Diamino-1-methylcyclohexanol (Stereoisomer A)

[0375]



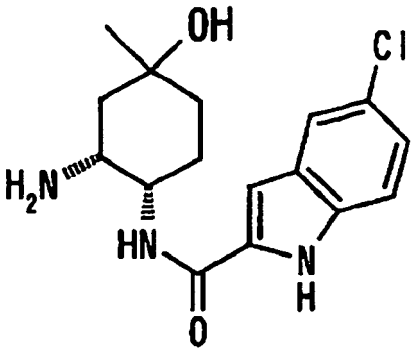
[0376] 10% Palladium on carbon (350 mg) was suspended in a methanol solution (100 ml) of the compound (Stereoisomer A) (780 mg) obtained in Referential Example 126, and the suspension was stirred for 5 hours in a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. After the residue was dissolved in methylene chloride (100 ml), and the solution was dried over anhydrous sodium sulfate, the solvent was distilled off to obtain the title compound (Stereoisomer A) (190 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.22(3H,s), 1.25-2.48(11H,m), 2.62(1H,br.s), 2.78(1H,br.s).

[Referential Example 128]

Mixture of N-[(1R*,2S*)-2-Amino-4-hydroxy-4-methylcyclohexyl]-5-chloroindole-2-carboxamide (Stereoisomer A) and N-[(1R*,2S*)-2-amino-5-hydroxy-5-methylcyclohexyl]-5-chloroindole-2-carboxamide

(Stereoisomer A):

[0377]

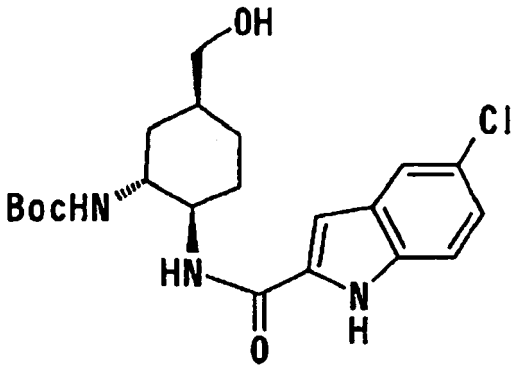


[0378] The title compound was obtained from the compound (Stereoisomer A) obtained in Referential Example 127 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 59.
^{1}H-NMR ($CDCl_3$) δ: 1.32(3H,s), 1.34-2.29(6H,m), 4.42-4.70(4H,br), 7.13(2H,s), 7.50(2H,s), 8.00(1H,s), 11.0(1H,br).

[Referential Example 129]

tert-Butyl (1R*,2R*,5S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(hydroxymethyl)cyclohexylcarbamate:

[0379]

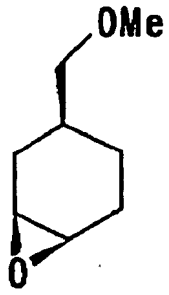


1) Ethyl (1R*3S*,4S*)-3-[(tert-butoxycarbonyl)-amino]-4-{[(5-chloroindol-2-yl)carbonyl]amino}-cyclohexanecarboxylate was obtained from the (1R*,3S*,4S*)-form obtained in Referential Example 89 in a similar manner to the process described in Referential Examples 90 and 91.
^{1}H-NMR ($CDCl_3$) δ: 1.22-1.72(6H,m), 2.15-2.28(2H,m), 2.41-2.49(1H,m), 2.85(1H,brs), 3.62-3.75(1H,m), 3.78-3.92 (1H,m), 4.12-4.28(2H,m), 4.56-4.63(1H,m), 6.88(1H,brs), 7.20(1H,dd,J=8.8 and 2.0Hz), 7.33(1H,d,J=8.8Hz), 7.52-7.57(1H,m), 7.59(1H,d,J=2.0Hz), 9.24(1H,s).
MS (ESI) m/z: 464(M+H)$^+$.
2) The product (735 mg) obtained above was dissolved in methylene chloride (10 ml), a 1N hexane solution (5 ml) of diisobutylalminium hydride was added at -78°C, and the mixture was stirred for 3 hours and then 30 minutes at 0°C. A saturated aqueous solution of ammonium chloride was added at -78°C, the mixture was extracted with methylene chloride, and the resultant organic layer was washed with a saturated aqueous solution of sodium bicarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 19:1) to obtain the title compound (480 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.20-2.30(7H,m), 3.60-3.86(4H,m), 4.64(1H,br.s), 6.87(1H,s), 7.20-7.48(3H,m), 9.15(1H,br.s).
MS(ESI) m/z: 422(M+H)$^+$.

[Referential Example 130]

(1R*,3R*,6S*)-3-(Methoxymethyl)oxabicyclo[4.1.0]heptane:

[0380]



1) (1R*,4R*,5R*)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (2.8 g) was dissolved in a mixed solvent of tetrahydrofuran (27 ml) and water (3 ml), concentrated hydrochloric acid (0.1 ml) was added, and the mixture was heated under reflux for 1 hour. The solvent was distilled off under reduced pressure to obtain (1R*,3R*,4R*)-3-hydroxy-4-iodocyclohexanecarboxylic acid (3.23 g) as a colorless solid.

2) The product (3.22 g) obtained by the reaction described above was dissolved in tetrahydrofuran (50 ml), borane-dimethyl sulfide complex (2 M tetrahydrofuran solution, 47 ml) was added under ice cooling, and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, the residue was dissolved in isopropanol (10 ml), a 1N aqueous solution (12 ml) of sodium hydroxide was added, and the mixture was stirred for 12 hours. After the solvent was concentrated to about 1/5, the reaction mixture was diluted with water and methylene chloride to stir it for 10 minutes. An organic layer was separated, successively washed with a saturated aqueous solution of ammonium chloride and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:2) to obtain (1R*,3R*,6S*)-7-oxabicyclo[4.1.0]hept-3-ylmethanol (1.25 g) as a colorless oil.

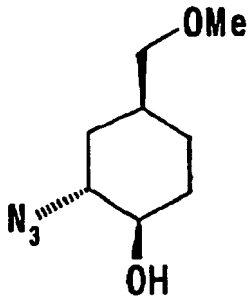
3) The product (4.63 g) obtained by the reaction in 2) was dissolved in tetrahydrofuran (50 ml), potassium bis(trimethylsilyl)amide (0.5N toluene solution, 80 ml) was added to the solution at -78°C. After stirring at same temperature for 10 minutes, methyl iodide (2.93 ml) was added. After heating the mixture to 0°C, it was stirred for 1 hour, quenched with a saturated aqueous solution of ammonium chloride and then diluted with diethyl ether. An organic layer was separated, washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (3.7 g).

^{1}H-NMR ($CDCl_3$) δ: 0.89-1.63(5H,m), 1.80-2.05(2H,m), 1.89-3.06(4H,m), 3.16(3H,s).

[Referential Example 131]

(1R*,2R*,4S*)-2-Azido-4-(methoxymethyl)cyclohexanol:

[0381]



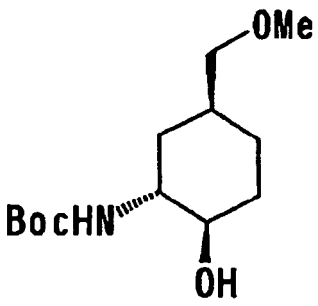
[0382] The title compound was obtained from the compound obtained in Referential Example 130 in a similar manner to Referential Example 87.

^{1}H-NMR ($CDCl_3$) δ: 1.45-1.70(5H,m), 1.77-1.95(2H;m), 1.98-2.08(1H,m), 3.30(2H,d,J=6.8Hz), 3.35(3H,s), 3.45-3.65(2H,m).

[Referential Example 132]

tert-Butyl (1R*,2R*,5S*)-2-hydroxy-5-(methoxymethyl)-cyclohexylcarbamate:

[0383]

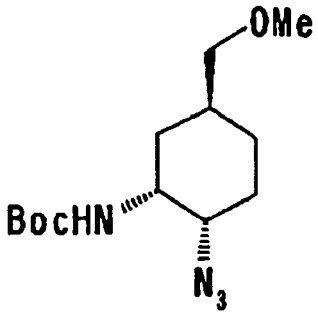


[0384] The title compound was obtained from the compound obtained in Referential Example 131 in a similar manner to Referential Example 88.
^{1}H-NMR ($CDCl_3$) δ: 1.35-2.01(16H,m), 3.05(1H,br.s), 3.32(2H,d,J=7.1Hz), 3.34(3H,s), 3.44-3.62(2H,m), 4.59(1H,br.s).

[Referential Example 133]

tert-Butyl (1R*,2S*,5S*)-2-azido-5-(methoxymethyl)-cyclohexylcarbamate:

[0385]

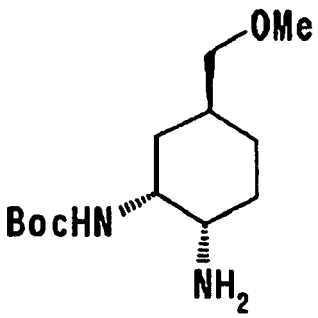


[0386] The title compound was obtained from the compound obtained in Referential Example 132 through the methansulfonate thereof in a similar manner to Referential Example 89.
^{1}H-NMR ($CDCl_3$) δ: 1.31-1.93(16H,m), 3.27(2H,d,J=6.4Hz), 3.32(3H,s), 3.57-3.70(1H,m), 3.67(1H,br.s), 3.95(1H,br.s).

[Referential Example 134]

tert-Butyl (1R*,2S*,5S*)-2-amino-5-(methoxymethyl)-cyclohexylcarbamate:

[0387]

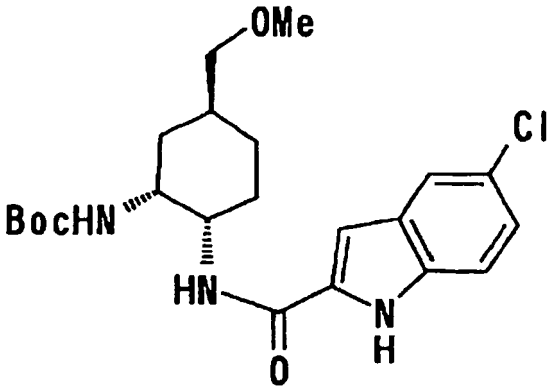


[0388] The title compound was obtained from the compound obtained in Referential Example 133 in a similar manner to Referential Example 90.

[Referential Example 135]

tert-Butyl (1R*,2S*,5S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(methoxymethyl)cyclohexylcarbamate:

[0389]

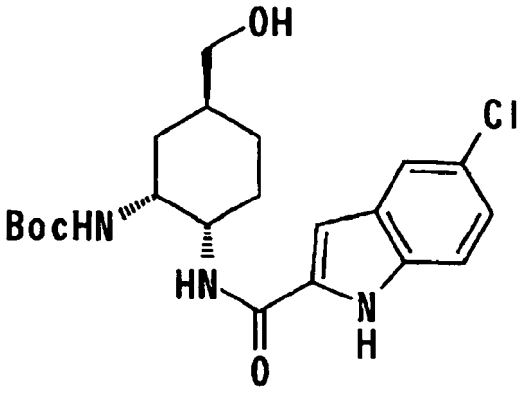


[0390] The title compound was obtained from the compound obtained in Referential Example 134 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.12-2.31(16H,m), 3.14-3.30(2H,m), 3.34(3H,s), 3.92 (1H, br.s), 4.13(1H,br.s), 4.88(1H,br.s), 6.82 (1H,s), 7.21(1H,br.d,J=8.8Hz), 7.33(1H,d,J=8.8Hz), 7.60(1H,s), 8.09(1H,br.s), 9.42(1H,br.s).
MS (ESI) m/z: 436$(M+H)^+$.

[Referential Example 136]

tert-Butyl (1R*,2S*,5S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(hydroxymethyl)cyclohexylcarbamate:

[0391]

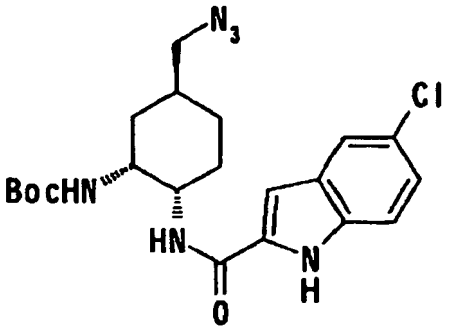


[0392] The title compound was obtained from the compound obtained in Referential Example 91 in a similar manner to Referential Example 129.
^{1}H-NMR ($CDCl_3$) δ: 0.78-2.30(16H,m), 3.41-3.59(3H,m), 3.86-3.95(1H,m), 4.12-4.20(1H,m), 4.82-4.91(1H,m), 6.81(1H,s), 7.17-7.40(2H,m), 7.60(1H,s), 8.03(1H,br.s), 9.18(1H,br.s).
MS (ESI) m/z: 422$(M+H)^+$.

[Referential Example 137]

tert-Butyl (1R*,2S*,5S*)-5-(azidomethyl)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexylcarbamate:

[0393]

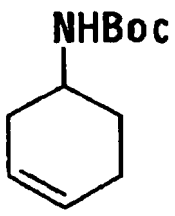


[0394] The title compound was obtained from the compound obtained in Referential Example 136 in a similar manner to Referential Example 80.

[Referential Example 138]

tert-Butyl 3-cyclohexen-1-ylcarbamate:

[0395]



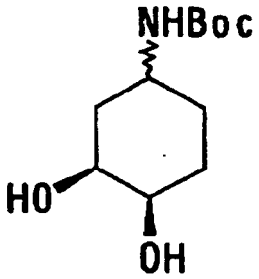
[0396] 3-Cyclohexene-1-carboxylic acid (25.3 g) was dissolved in tert-butanol (250 ml), triethylamine (28 ml) and diphenylphosphorylazide (43.0 ml) were added, and the mixture was stirred for 1 hour at room temperature and 2 days at 90°C. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography

on silica gel (methylene chloride) and then repurified by column chromatography on silica gel (hexane:ethyl acetate = 20:1) to obtain the title compound (24.9 g).
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.45-1.60(1H,m), 1.80-1.90(2H,m), 2.05-2.20(2H,m), 2.35-2.45(1H,m), 3.78(1H,br), 4.56 (1H,br), 5.55-5.65(1H,m), 5.65-5.75(1H,m).

[Referential Example 139]

tert-Butyl (3R*,4S*)-3,4-dihydroxycyclohexylcarbamate:

[0397]

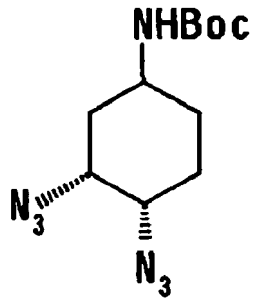


[0398] The compound (1.24 g) obtained in Referential Example 138 was dissolved in a mixed solvent of acetonitrile (15 ml) and water (5 ml), N-methylmorpholine N-oxide (0.90 g) and microcapsulated 10% osmium tetroxide(1 g) were added, and the mixture was stirred at about 80°C for a day. After insoluble matter was removed by filtration, the filtrate was concentrated under reduced pressure. The thus-obtained residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1) to obtain the title compound (1.28 g).
^{1}H-NMR ($CDCl_3$) δ: 1.15-1.30(1/2H,m), 1.35-2.00 (15H,m), 2.15-2.30(3/2H,m), 2.40-2.60(1H,m), 3.64(1H,br), 3.75-3.90 (3/2H,m), 4.00(1/2H,br).
MS (FAB) m/z: 232$(M+H)^+$.

[Referential Example 140]

tert-Butyl (3R*,4S*)-3,4-diazidocyclohexylcarbamate (Stereoisomer A and Stereoisomer B):

[0399]



[0400] The title compounds (Stereoisomer A and Stereoisomer B) were obtained from the compound obtained in Referential Example 139 in a similar manner to Referential Example 80.

Stereoisomer A:

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.40-1.55(1IH,m), 1.55-1.80(3H,m), 1.95-2.15(2H,m), 3.53(1H,m), 3.59(1H,br), 3.80(1H,m), 4.70(1H,br).

Stereoisomer B:

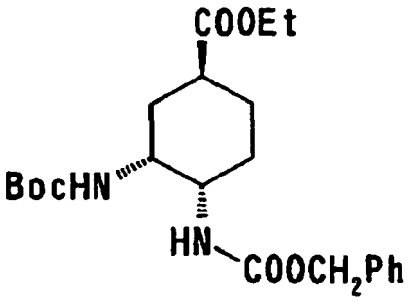
^{1}H-NMR ($CDCl_3$) δ: 1.27(1H,m), 1.44(9H,s), 1.40-1.55(1H,m), 1.80-2.00(2H,m), 2.00-2.15(1H,m), 2.21(1H,m),

3.48 (1H,m), 3.77(1H,br), 3.89(1H,br), 4.34(1H,br).

[Referential Example 141]

Ethyl (1S,3R,4S)-4-{[(benzyloxy)carbonyl]amino}-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate:

[0401]

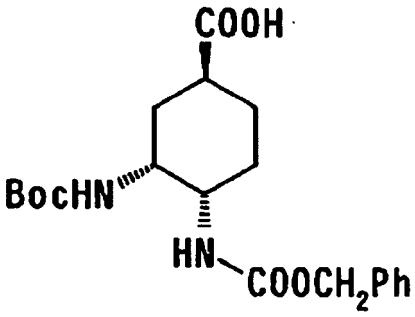


[0402] The compound (3.10 g) obtained in Referential Example 96 was dissolved in tetrahydrofuran (50 ml), and a saturated aqueous solution (50 ml) of sodium hydrogencarbonate was added. After benzyloxycarbonyl chloride (1.71 ml) was added dropwise to the reaction mixture under ice cooling, the mixture was stirred at room temperature for 4 days. Ethyl acetate (200 ml) and water (200 ml) were added to the reaction mixture to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. Solids deposited were collected by filtration to obtain the title compound (3.24 g).
^{1}H-NMR ($CDCl_3$) δ: 1.24(3H, t, J=7.1Hz), 1.29-1.44(1H,m), 1.44(9H,s), 1.51-1.64(1H,m), 1.72-2.10(4H,m), 2.27-2.43 (1H,m), 3.60-3.73(1H, m), 4.00-4.18(3H, m), 4.62(1H,br.s), 5.01-5.13(2H,m), 5.26(1H, br.s), 7.27-7.38(5H, m).

[Referential Example 142]

(1S,3R,4S)-4-{[(Benzyloxy)carbonyl]amino}-3-[(tert-butoxycarbonyl)amino] cyclohexanecarboxylic acid:

[0403]

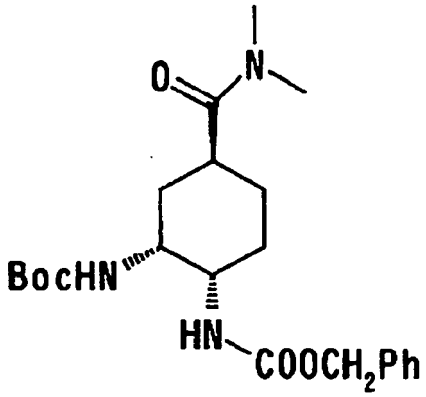


[0404] The compound (620 mg) obtained in Referential Example 141 was dissolved in tetrahydrofuran (20 ml), and an aqueous solution (10 ml) of lithium hydroxide monohydrate (93 mg) was added to stir the mixture at room temperature for 16 hours. After lithium hydroxide monohydrate (217 mg) was additionally added to the reaction mixture, and the mixture was stirred at room temperature for 2 hours, the reaction mixture was neutralized with 1N hydrochloric acid and extracted with methylene chloride. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (600 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.22-2.20(6H, m), 1.44(9H,s), 2.45(1H,br.s), 3.60-3.80(1H,br), 4.09(1H,br.s), 4.66 (1H,br.s), 5.00-5.20(2H,m), 5.26(1H,br.s), 7.20-7.40(5H,m).
MS (ESI) m/z: 393 $(M+H)^+$.

[Referential Example 143]

Benzyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)amino]-4-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0405]

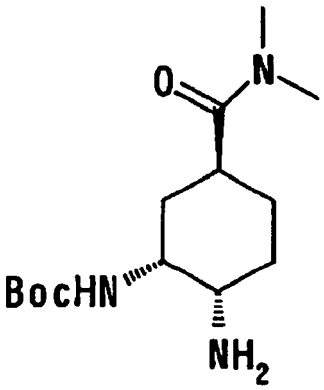


[0406] After the compound (600 mg) obtained in Referential Example 142 and dimethylamine hydrochloride (240 mg) were suspended in methylene chloride (50 ml), a proper amount of tetrahydrofuran was added to the suspension to prepare a solution. To this solution were added triethylamine (0.41 ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (422 mg) and 1-hydroxybenzotriazole monohydrate (338 mg), and the mixture was stirred at room temperature for 1 hour. Dimethylamine hydrochloride (480 mg) and triethylamine (0.82 ml) were additionally added to the reaction mixture to stir the mixture at room temperature for additional 18 hours. The reaction mixture was poured into water to separate an organic layer. After the organic layer was washed with 1N hydrochloric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 3:47 $\rightarrow$ 2:23) to obtain the title compound (620 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.20-1.50(2H,m), 1.44(9H,s), 1.50-2.10(4H,m), 2.60(1H,br.t,J=11.6Hz), 2.93(3H,s), 3.02(3H,s), 3.70(1H,br.s), 4.14(1H,br.s), 4.65(1H,br.s), 5.00-5.30(3H,m), 7.26-7.40(5H,m).
MS (ESI) m/z = 420$(M+H)^+$.

[Referential Example 144]

tert-Butyl (1R,2S,5S)-2-amino-5-[(dimethylamino)-carbonyl]cyclohexylcarbamate:

[0407]



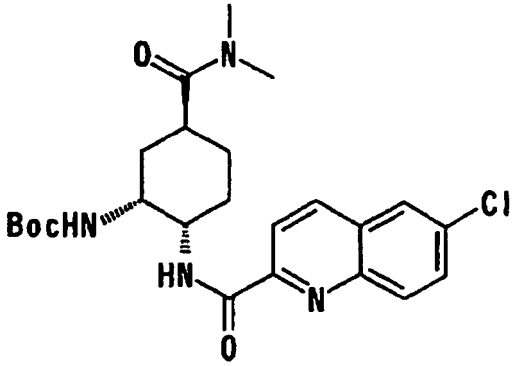
[0408] 10% Palladium on carbon (57 g) was added to a solution of the compound (190 g) obtained in Referential Example 143 in methanol (8000 ml), and the mixture was stirred for 3 hours under a hydrogen pressure (7 atm). After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure. After toluene was added to the residue, and the mixture was concentrated under reduced pressure, hexane (2500 ml) was added to solidify a

product. The product was collected by filtration and dried to obtain the title compound (121 g).
^{1}H-NMR ($CDCl_3$) δ: 1.20-1.77(6H,m), 1.45(9H,s), 2.20-2.35(1H,br), 2.63-2.74(1H,m), 2.92(3H,s), 3.02(3H,s), 3.02-3.11 (2H,m), 3.74-3.82(1H,m), 4.88-5.00(1H,br).
MS (ESI) m/z: 286$(M+H)^+$.

[Referential Example 145]

tert-Butyl (1R,2S,5S)-2-{[(6-chloroquinolin-2-yl)-carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0409]

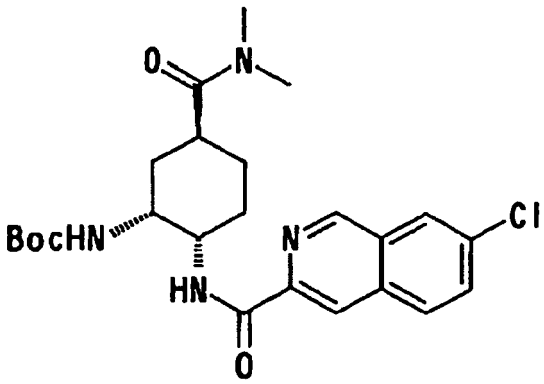


[0410] The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 54 in a similar manner to Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.41(9H,br), 1.50-1.70(1H,m), 1.75-1.95(2H,m), 1.95-2.25(3H,m), 2.65-2.80(1H,m), 2.96(3H,s), 3.07 (3H,s), 4.15-4.30(1H,m), 4.30-4.40(1H,m), 4.95(1H,br), 7.66(1H,d,J=8.8Hz), 7.84(1H,s), 8.00(1H,d,J=8.8Hz), 8.19(1H, d,J=8.6Hz), 8.30(1H,d,J=8.6Hz).
MS (FAB) m/z: 475$(M+H)^+$.

[Referential Example 146]

tert-Butyl (1R,2S,5S)-2-{[(7-chloroquinolin-3-yl)-carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0411]

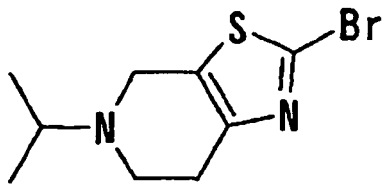


[0412] The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 57 in a similar manner to Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.65(10H,br), 1.75-1.90(2H,m), 1.90-2.25(3H,m), 2.65-2.90(1H,br), 2.96(3H,s), 3.08(3H,s), 4.20-4.30 (1H,m), 4.30-4.40(1H,m), 4.93(1H,br), 7.68(1H,m), 7.90(1H,br), 7.99(1H,s), 8.35-8.70(2H,m), 9.01(1H,br).
MS (FAB) m/z: 475$(M+H)^+$.

[Referential Example 147]

2-Bromo-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine:

[0413]

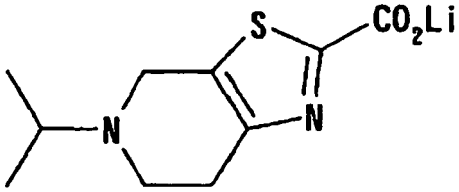


[0414] The title compound was obtained from the compound obtained in Referential Example 8 in a similar manner to Referential Example 9.
^{1}H-NMR ($CDCl_3$) δ: 1.13(6H,d,J=6.5Hz), 2.86(4H,s), 2.89-3.00(1H,m), 3.70(2H,s).

[Referential Example 148]

Lithium 5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxylate:

[0415]

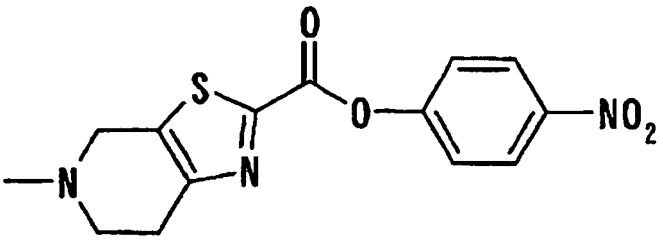


[0416] The title compound was obtained from the compound obtained in Referential Example 147 in a similar manner to Referential Example 10.
^{1}H-NMR (DMSO-d_6) δ: 1.05(6H,d,J=6.4Hz), 2.68-2.70(2H,m), 2.75-2.77(2H,m), 2.87-2.93(1H,m), 3.66(2H,s).

[Referential Example 149]

4-Nitrophenyl 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxylate:

[0417]

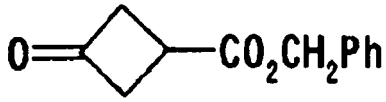


[0418] The title compound was obtained from the compound obtained in Referential Example 10 and p-nitrophenol in a similar manner to Referential Example 52.
^{1}H-NMR ($CDCl_3$) δ: 2.55(3H,s), 2.88(2H,t,J=5.7Hz), 3.06-3.12(2H,m), 3.80(2H,s), 7.46(2H,d,J=9.3Hz), 8.32(2H,d, J=9.3Hz).
MS (ESI) m/z: 320($M+H^+$).

[Referential Example 150]

Benzyl 3-oxocyclobutanecarboxylate:

[0419]

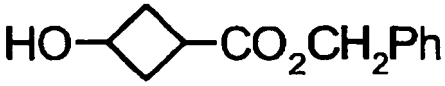


[0420] Triethylamine (2.0 ml) and benzyl bromide (1.2 ml) were added to a solution of 3-oxocyclobutanecarboxylic acid (J. Org. Chem., Vol. 53, pp. 3841-3843, 1981) (995 mg) in tetrahydrofuran (5.0 ml), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, and washed successively with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated saline and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:6) to obtain the title compound (886 mg).
^{1}H-NMR ($CDCl_3$) δ: 3.22-3.33(3H,m), 3.37-3.48(2H,m), 5.19(2H,s), 7.31-7.42(5H,m).
MS (FAB) m/z: 205 ($M+H^+$) .

[Referential Example 151]

Benzyl 3-hydroxycyclobutanecarboxylate:

[0421]

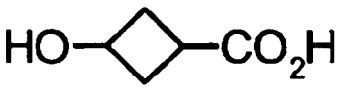


[0422] Sodium borohydride (76 mg) was added to a solution of the compound (781 mg) obtained in Referential Example 150 in a mixed solvent of tetrahydrofuran (10 ml) and methanol (0.5 ml) at 0°C, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride in that order and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:2) to obtain the title compound (770 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.13-2.27(3H,m), 2.55-2.71(3H,m), 4.14-4.23(1H,m), 5.12(2H,s), 7.28-7.39(5H,m).
MS (FAB) m/z: 207($M+H^+$).

[Referential Example 152]

3-Hydroxycyclobutanecarboxylic acid:

[0423]

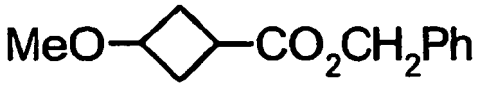


[0424] 10% Palladium on carbon (108 mg) was added to a solution of the compound (706 mg) obtained in Referential Example 151 in ethanol (10 ml), and the mixture was stirred at room temperature for 2 hours in a hydrogen atmosphere. After the catalyst was removed by filtration through Celite, the filtrate was concentrated under reduced pressure to obtain the title compound (399 mg).
^{1}H-NMR (CD_3OD) δ: 2.00-2.21(2H,m), 2.41-2.61(3H,m), 4.01-4.13(1H,m).

[Referential Example 153]

Benzyl 3-methoxycyclobutanecarboxylate:

[0425]



[0426] Methyl iodide (194 μl) and silver oxide (237 mg) were added to a solution of the compound (317 mg) obtained in Referential Example 151 in N,N-dimethylformamide (3.0 ml), and the mixture was stirred at 45°C for 1 hour. Methyl iodide (194 μl) and silver oxide (226 mg) were additionally added to the reaction mixture, and the mixture was stirred at 45°C for 16 hours. After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:10) to obtain the title compound (152 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.14-2.24(2H,m), 2.44-2.54(2H,m), 2.59-2.72(1H,m), 3.21(3H,s), 3.73-3.81(1H,m), 5.11(2H,s), 7.22-7.39(5H,m).
MS (ESI) m/z: 221($M+H^+$).

[Referential Example 154]

3-Methoxycyclobutanecarboxylic acid:

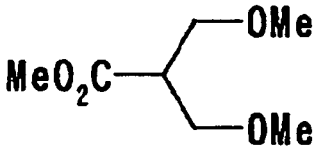
[0427]

[0428] The title compound was obtained from the compound obtained in Referential Example 153 in a similar manner to Referential Example 152.
^{1}H-NMR ($CDCl_3$) δ: 2.17-2.27(2H,m), 2.48-2.58(2H,m), 2.62-2.73(1H,m), 3.25(3H,s), 3.76-3.86(1H,m), 8.60-9.30(1H,br).

[Referential Example 155]

Methyl 3-methoxy-2-(methoxymethyl)propionate:

[0429]

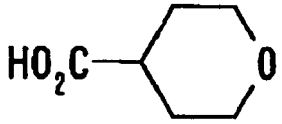


[0430] Sodium methoxide (1.21 g) was added to a solution of methyl 2-(bromomethyl)acrylate (1.0 ml) in methanol (10 ml), and the mixture was heated under reflux for 26 hours. After cooling, the reaction mixture was diluted with diethyl ether, and precipitate was collected by filtration and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (726 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.90-2.96(1H,m), 3.34(6H,s), 3.57(2H,dd,J=9.3,5.9Hz), 3.64(2H,dd,J=9.3,6.6Hz), 3.73(3H,s).
^{13}C-NMR ($CDCl_3$) δ: 172.71, 70.31, 59.91, 46.49.
MS (ESI) m/z: 163($M+H^+$).

[Referential Example 156]

Tetrahydro-2H-pyrane-4-carboxylic acid:

[0431]

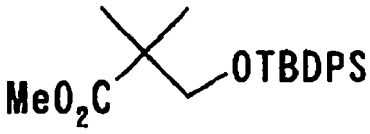


[0432] Dimethyl tetrahydro-4H-pyrane-4,4-dicarboxylate (4.04 g) was added to 20% hydrochloric acid (20 ml), and the mixture was heated under reflux for 19 hours. Water was added to the reaction mixture to conduct extraction with diethyl ether. After the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. After the resultant residue was solidified with hexane, the resultant solides were collected by filtration and washed to obtain the title compound (2.63 g).
^{1}H-NMR ($CDCl_3$) δ: 1.75-1.95(4H,m), 2.55-2.65(1H,m), 3.40-3.52(2H,m), 3.93-4.05(2H,m).

[Referential Example 157]

Methyl 3-{[tert-butyl(diphenyl)silyl]oxy}-2,2-dimethylpropionate:

[0433]

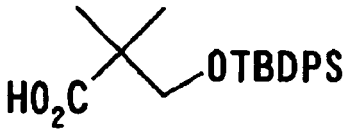


[0434] The title compound was obtained from methyl 2,2-dimethyl-3-hydroxypropionate in a similar manner to Referential Example 41.
^{1}H-NMR ($CDCl_3$) δ: 1.03(9H,s), 1.20(6H,s), 3.64-3.68(5H,m), 7.38-7.44(6H,m), 7.63-7.65(4H,m).

[Referential Example 158]

3-{[tert-Butyl(diphenyl)silyl]oxy}-2,2-dimethylpropionic acid:

[0435]

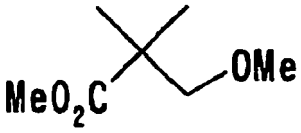


[0436] Water (0.24 ml) was added to a suspension composed of potassium tert-butoxide (5.32 g) and diethyl ether (100 ml) under ice cooling, and the mixture was stirred for 5 minutes. The compound (2.22 g) obtained in Referential Example 157 was added thereto, and the resultant mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was acidified with 1N hydrochloric acid and extracted 3 times with diethyl ether. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:6) to obtain the title compound (735 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.04(9H,d,J=0.7Hz), 1.22(6H,s), 3.65(2H,s), 7.36-7.45(6H,m), 7.64-7.66(4H,m).

[Referential Example 159]

Methyl 3-methoxy-2,2-dimethylpropionate:

[0437]

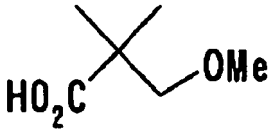


[0438] A solution of methyl 3-hydroxy-2,2-dimethylpropionate (25.0 g) in tetrahydrofuran (300 ml) was added dropwise to a suspension composed of a 60% oil suspension of sodium hydride (8.32 g) and tetrahydrofuran (100 ml) under ice cooling, and the mixture was stirred at 60°C for 1 hour. Methyl iodide (53.7 g) was added to the reaction mixture, and the resultant mixture was stirred at room temperature for 2 hours. Water was carefully added to conduct extraction twice with methylene chloride. After the resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant oil was distilled to obtain the title compound (12.8 g).
Boiling point: 140-142°C (ordinary pressure).
^{1}H-NMR ($CDCl_3$) δ : 1.19(6H,d,J=1.0Hz), 3.33(3H,d,J=1.0Hz), 3.38(2H,d,J=1.0Hz), 3.69(3H,d,J=1.0Hz).

[Referential Example 160]

3-Methoxy-2,2-dimethylpropionic acid:

[0439]



[0440] The title compound was obtained from the compound obtained in Referential Example 159 in a similar manner to Referential Example 158.
^{1}H-NMR ($CDCl_3$) δ: 1.22(6H,d,J=0.7Hz), 3.38(3H,d,J=0.7Hz), 3.40(2H,d,J=0.7Hz).

[Referential Example 161]

1-(Methoxycarbonyl)cyclopropanecarboxylic acid:

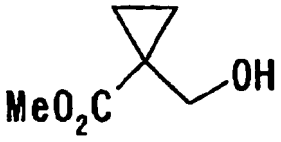
[0441]

[0442] Dimethyl 1,1-cyclopropanecarboxylate (25 g) was dissloved in methanol (250 ml), and the solution was cooled with ice. A 1N aqueous solution of sodium hydroxide (158 ml) was then added dropwise, and the resultant mixture was warmed to room temperature and stirred overnight. After methanol was distilled off, the residue was washed with chloroform, and a water layer was cooled with ice, adjusted to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound (16.8 g).
^{1}H-NMR ($CDCl_3$) δ: 1.76-1.80(2H,m), 1.82-1.88(2H,m), 3.79(3H,s), 12.73 (1H,br).

[Referential Example 162]

Methyl 1-(hydroxymethyl)cyclopropanecarboxylate:

[0443]

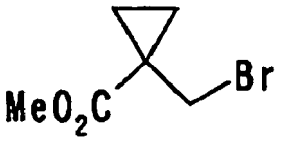


[0444] The compound (9.0 g) obtained in Referential Example 161 and triethylamine (9.7 ml) were dissolved in tetrahydrofuran (180 ml), and the solution was cooled to -10°C, to which isobutyl chloroformate (9.1 ml) was added dropwise, and the resultant mixture was stirred for 1 hour. On the other hand, sodium borohydride (7.1 g) was dissolved in tetrahydrofuran (100 ml)-water (25 ml) and cooled with ice. While removing insoluble matter by filtration, the solution prepared previously was added dropwise, and the resultant mixture was stirred at the same temperature for 1 hour. The reaction mixture was poured into a cooled 10% aqueous solution of citric acid to conduct extraction with ethyl acetate. After the extract was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:9 - 2:1) to obtain the title compound (4.25 g).
^{1}H-NMR ($CDCl_3$) δ: 0.87-0.93(2H,m), 1.28-1.30(2H,m), 3.63(2H,s), 3.70(3H,s).

[Referential Example 163]

Methyl 1-(bromomethyl)cyclopropanecarboxylate:

[0445]

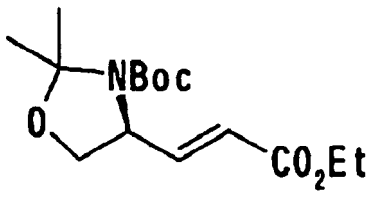


[0446] Triphenylphosphine (10 g) and carbon tetrabromide (16 g) were added to a solution of the compound (4.20 g) obtained in Referential Example 162 in methylene chloride (168 ml) at room temperature under a nitrogen atmosphere. After 2 minutes, a saturated aqueous solution of sodium hydrogencarbonate was added thereto. After the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:19) to obtain the title compound (2.15 g).
^{1}H-NMR ($CDCl_3$) δ: 1.00-1.05(2H,m), 1.52-1.59(2H,m), 3.61(2H,s), 3.73(3H,s).

[Referential Example 164]

tert-Butyl (4S)-4-[(E)-3-ethoxy-3-oxo-1-propenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

[0447]



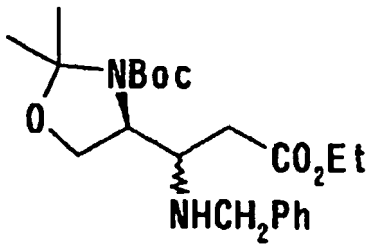
[0448] A mixture solution composed of tert-Butyl (4R)-4-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (11.7 g),

(carboethoxymethylene)triphenylphosphorane (20.7 g) and toluene (100 ml) was heated and stirred at 100°C for 18 hours. The reaction mixture was concentrated, and the resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 8:1) to obtain the title compound (17 g).
^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t,J=6.6Hz), 1.43-1.56(15H,m), 3.80 (1H,dd,J=9.0,2.4Hz), 4.09 (1H,dd,J=9.0,6.6Hz), 4.11-4.23(2H,m), 4.30-4.61(1H,m), 5.83-6.02(1H,m), 6.74-6.89(1H,m).

[Referential Example 165]

tert-Butyl (4S)-4-[1-(benzylamino)-3-ethoxy-3-oxopropyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

[0449]

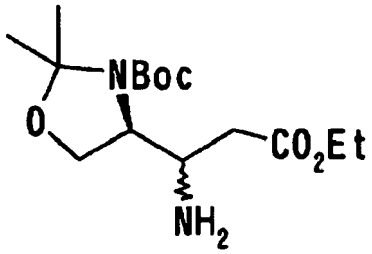


[0450] A mixture solution composed of the compound (22.2 g) obtained in Referential Example 164, benzylamine (16 g) and ethanol (100 ml) was heated under reflux for 2 days. The reaction mixture was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 8:1) to obtain the title compound (26 g).
^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=6.6Hz), 1.42-1.63(15H,m), 2.24-2.33(0.5H,m), 2.40-2.50(1H,m), 2.63-2.74(0.5H,m), 3.41-3.52(1H,m), 3.67-3.80(1H,m), 3.83(2H,s), 3.89-4.00(1H,m), 4.03-4.22(4H,m), 7.23-7.45(5H,m).

[Referential Example 166]

tert-Butyl (4S)-4-(1-amino-3-ethoxy-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

[0451]

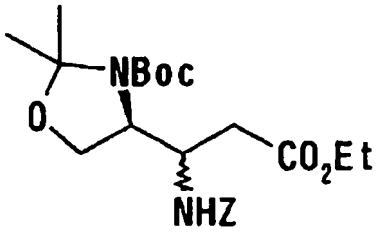


[0452] 10% Palladium on carbon (10 g) was added to a solution of the compound (13.6 g) obtained in Referential Example 165 in ethanol (200 ml), and the mixture was stirred for 2 days under a hydrogen atmosphere. Insoluble matter was removed through Celite pad, and the filtrate was concentrated under reduced pressure to obtain the title compound (10.5 g).
^{1}H-NMR (DMSO-d_6) δ: 1.19(1.5H,t,J=6.6Hz), 1.20(1.5H,t,J=6.6Hz), 1.32-1.50(15H,m), 2.63-2.81(2H,m), 3.22-3.34(2H,m), 3.93(1H,dd,J=10.0,6.8Hz), 4.08(2H,q,J=6.6Hz), 4.20-4.30(1H,m).

[Referential Example 167]

tert-Butyl (4S)-4-(1-{[(benzyloxy)carbonyl]amino}-3-ethoxy-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

[0453]

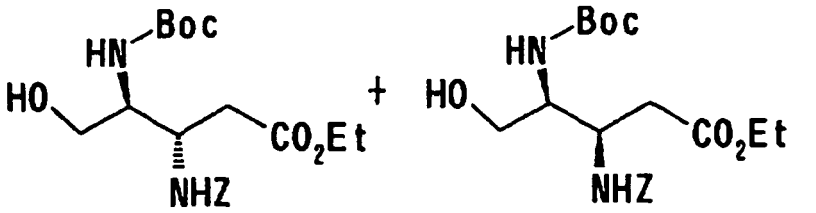


[0454] The compound (3.0 g) obtained in Referential Example 166 was suspended in a 9% aqueous solution (56 ml) of sodium hydrogencarbonate, and a solution of N-(benzyloxycarbonyloxy)succinimide (2.3 g) in dioxane (12 ml) was added dropwise to the suspension under ice cooling. The resultant mixture was stirred for 3 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water, a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform) to obtain the title compound (3.8 g).
^{1}H-NMR ($CDCl_3$) δ: 1.23(3H,t,J=6.6Hz), 1.48(9H,s), 1.56(6H,s),2.40-2.51 (2H,m), 2.63-2.70(2H,m), 3.92-4.04(1H,m), 4.06-4.10(2H,m), 4.14-4.22(1H,m), 5.09(2H,s), 7.30-7.43(5H,m).

[Referential Example 168]

Ethyl (3S,4S)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]-5-hydroxyvalerate (low-polar compound) and ethyl (3R,4S)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]-5-hydroxyvalerate (high-polar compound):

[0455]



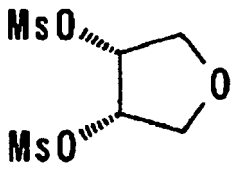
Low-polar compound High-polar compound

[0456] Trifluoroacetic acid (100 ml) was added dropwise to a solution of the compound (30 g) obtained in Referential Example 167 in methylene chloride (100 ml) under ice cooling, and the mixture was stirred for 3 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in methylene chloride (100 ml). Triethylamine (20 ml) and a solution of di-tert-butyl dicarbonate (19 g) in methylene chloride (100 ml) were successively added dropwise to this solution under ice cooling, and the mixture was stirred for 4 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was concentrated under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1) to obtain the title low-polar compound (7.6 g) and the title high-polar compound (10 g).
Low-polar compound:
^{1}H-NMR ($CDCl_3$) δ: 1.24(3H,t,J=6.6Hz), 1.42(9H,s), 2.63(2H,d,J=4.4Hz), 3.30-3.41(1H,m), 3.50(1H,t,J=9.7Hz), 3.65(1H,t,J=9.7Hz), 3.75(1H,d,J=11.7Hz), 3.90-4.00(1H,m), 4.03-4.23(2H,m), 5.12(2H,s), 5.13-5.25(1H,m), 5.79-6.02(1H,m), 7.32-7.41(5H,m).
High-polar compound:
^{1}H-NMR ($CDCl_3$) δ: 1.22(3H,t,J=6.6Hz), 1.41(9H,s), 2.50-2.70(2H,m), 3.20-3.31(1H,m), 3.43-3.51(1H,m), 3.56-3.70(1H,m), 3.74-3.78(1H,m), 4.00-4.19(2H,m), 4.23-4.30(1H,m), 4.78-4.89(1H,m), 5.10(2H,s), 5.56-5.67(1H,m), 7.31-7.40(5H,m).

[Referential Example 169]

(3R,4S)-4-[(Methylsulfonyl)oxy]tetrahydro-3-furanyl methanesulfonate:

[0457]

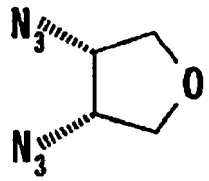


[0458] Triethylamine (12.0 ml) and methanesulfonyl chloride (3.6 ml) were successively added dropwise to a solution of 1,4-anhydroerythritol (5.0 g) in methylene chloride (50 ml) under ice cooling, and the mixture was stirred for 10 minutes under ice cooling. The reaction mixture was diluted with methylene chloride and washed with 10% hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound (9.2 g).
^{1}H-NMR ($CDCl_3$) δ: 3.15(6H,s), 3.99(2H,dd,J=11.2,2.5Hz), 4.16(2H,dd,J=11.2,4.6Hz), 5.10-5.20(2H,m).

[Referential Example 170]

(3R,4S)-3,4-Diazidotetrahydrofuran:

[0459]

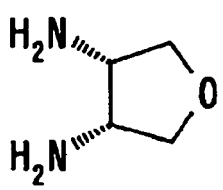


[0460] The compound (9.2 g) obtained in Referential Example 169 was dissolved in N,N-dimethylformamide (50 ml), sodium azide (18 g) was added, and the resultant mixture was heated and stirred at 100°C for 18 hours. The reaction mixture was diluted with ethyl acetate and washed with water and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound (3.8 g).
^{1}H-NMR ($CDCl_3$) δ: 3.83(2H,dd,J=8.6,2.0Hz), 3.96-4.12(4H,m).

[Referential Example 171]

(3R,4S)-Tetrahydro-3,4-furandiamine dihydrochloride:

[0461]



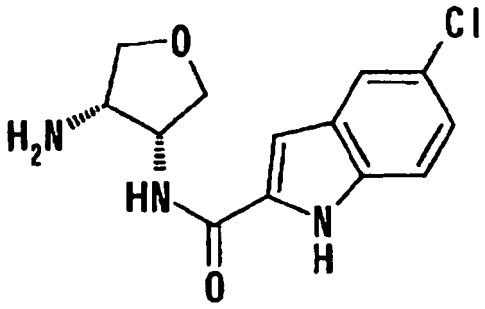
[0462] The compound (3.8 g) obtained in Referential Example 170 was dissolved in ethanol (50 ml), 10% palladium on carbon (1.0 g) was added to the solution, and the mixture was stirred for 18 hours under a hydrogen atmosphere. Insoluble matter was removed through Celite pad, and the filtrate was concentrated under reduced pressure. A 1N ethanol solution of hydrochloric acid was added to the resultant residue, giving the hydrochloride salt. The hydrochloride

was recrystallized from a mixed solvent of ethanol and diethyl ether to obtain the title compound (2.0 g).
^{1}H-NMR ($CDCl_3$) δ: 3.90(2H,dd,J=9.0,3.7Hz), 4.01-4.13(4H,m), 8.84(6H,s).

[Referential Example 172]

N-[(3R*,4S*)-4-Aminotetrahydro-3-furanyl]-5-chloroindole-2-carboxamide:

[0463]

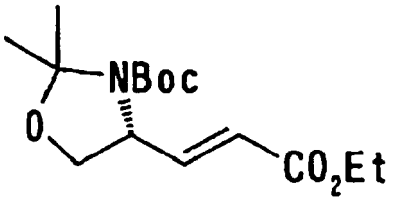


[0464] 5-Chloroindole-2-carboxylic acid (0.29 g), 1-hydroxybenzotriazole monohydrate (0.2 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 g) were successively added to a solution of the compound (0.5 g) obtained in Referential Example 171 in N,N-dimethylformamide (10 ml), and the mixture was heated and stirred at 50°C for a day. The reaction mixture was concentrated, and the resultant residue was diluted with a mixed solvent composed of chloroform and methanol (9:1) and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 95:5) to obtain the title compound (0.2 g).
^{1}H-NMR ($CDCl_3$) δ: 1.80-1.92(1H,m), 3.62(1H,dd,J=9.3,4.2Hz), 3.68-3.80(2H,m), 4.06(1H,dd,J=9.3,5.6Hz), 4.21(1H,dd, J=9.3,6.8Hz), 4.36-4.52(2H,m), 6.87(1H,s), 7.24(1H,dd,J=8.8,2.0Hz), 7.36(1H,d,J=8.8Hz), 7.44-7.56(1H,m), 7.62(1H, d,J=2.0Hz), 9.41(1H,s).

[Referential Example 173]

tert-Buthyl (4R)-4-[(E)-3-ethoxy-3-oxo-1-propenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

[0465]

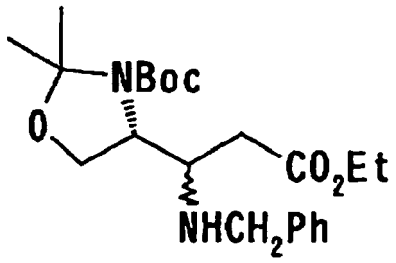


[0466] The title compound was obtained from tert-Butyl (4S)-4-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate in a similar manner to Referential Example 164.
^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t,J=6.6Hz), 1.40-1.60(15H,m), 3.80(1H,dd,J=9.0,2.4Hz), 4.09(1H,dd,J=9.0,6.6Hz), 4.11-4.21(2H,m), 4.32-4.64(1H,m), 5.78-6.01(1H,m), 6.67-6.89(1H,m).

[Referential Example 174]

tert-Butyl (4R)-4-[1-(benzylamino)-3-ethoxy-3-oxopropyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

[0467]

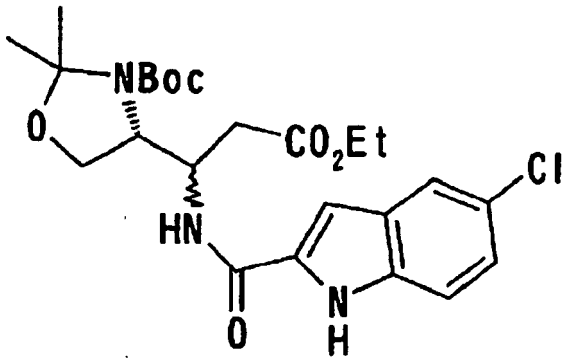


[0468] The title compound was obtained from the compound obtained in Referential Example 173 in a similar manner to Referential Example 165.
^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=6.6Hz), 1.40-1.61(15H,m), 2.21-2.32(0.5H,m), 2.40-2.51(1H,m), 2.61-2.72(0.5H,m), 3.43-3.50(1H,m), 3.67-3.80(1H,m), 3.83(2H,s), 3.90-4.03(1H,m), 4.04-4.22(4H,m), 7.20-7.40(5H,m).

[Referential Example 175]

tert-Butyl (4R)-4-(1-{[(5-chloroindol-2-yl)carbonyl]amino}-3-ethoxy-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

[0469]

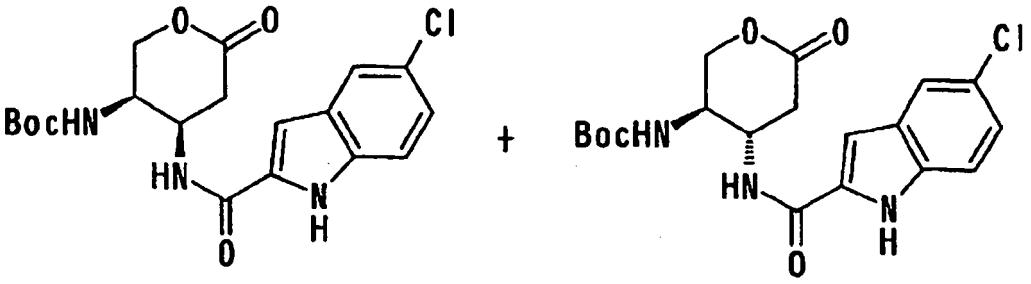


[0470] The title compound was obtained by reducing the compound obtained in Referential Example 174 in a similar manner to Referential Example 166 to remove a benzyl group and then condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 172.
^{1}H-NMR ($CDCl_3$) δ:1.23(1.5H,t,J=6.6Hz), 1.25(1.5H,t,J=6.6Hz), 1.50(4.5H,s), 1.54(4.5H,s), 1.62(6H,s), 2.50-2.70(1.5H, m), 2.86(0.5H,dd,J=16.4,5.5Hz), 3.80-3.90(0.5H,m), 4.00-4.31(5H,m), 4.41-4.67(0.5H,m), 6.85(0.5H,s), 6.87(0.5H,s), 7.10-7.20(1H,m), 7.34(0.5H,d,J=8.8Hz), 7.38(0.5H,d,J=8.8Hz), 7.57(0.5H,s), 7.63(0.5H,s), 7.88(0.5H,d,J=7.6Hz), 8.54 (0.5H,d,J=7.6Hz), 9.40(0.5H,s), 9.54(0.5H,s).

[Referential Example 176]

tert-Butyl (3R,4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-6-oxotetrahydro-2H-pyran-3-ylcarbamate (low-polar compound) and tert-butyl and (3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-6-oxotetrahydro-2H-pyran-3-ylcarbamate (high-polar compound):

[0471]



Low-polar compound High-polar compound

[0472] A 1N aqueous solution (4.0 ml) of sodium hydroxide was added to a solution of the compound (1.0 g) obtained in Referential Example 175 in ethanol (20 ml), and the mixture was stirred for 4 hours. Citric acid was added to the reaction mixture to adjust the pH of the reaction mixture to 4.0. The reaction mixture was extracted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The resultant residue was dissolved in methanol (50 ml), and toluenesulfonic acid monohydrate (0.1 g) was added to the solution to stir the resultant mixture for 18 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 99:1) to obtain the title low-polar compound (0.3 g) and the title high-polar compound (0.3 g).

Low-polar compound:

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 2.70(1H,dd,J=16.5,4.9Hz), 2.85(1H,dd,J=16.5,4.6Hz), 3.50-3.61(1H,m), 3.71-3.81(2H,m), 4.30-4.40(1H,m), 5.30(1H,d,J=9.5Hz), 6.89(1H,s), 7.23(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=8.8Hz), 7.62(1H,d,J=2.0Hz), 7.93(1H,d,J=9.5Hz), 9.30(1H,s).

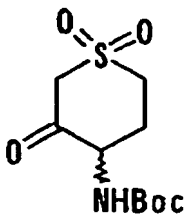
High-polar compound:

^{1}H-NMR ($CDCl_3$) δ: 1.39(9H,s), 2.75(1H,dd,J=16.5,4.9Hz), 2.82(1H,dd,J=16.5,4.6Hz), 3.41-3.52(2H,m), 3.71-3.82(1H,m), 3.85-3.94(1H,m), 5.03(1H,d,J=9.3Hz), 6.99(1H,s), 7.22-7.31(1H,m), 7.34(1H,d,J=8.8Hz), 7.61(1H,d,J=2.0Hz), 7.83(1H,d,J=9.3Hz), 9.28(1H,s).

[Referential Example 177]

tert-Butyl 1,1,3-trioxohexahydro-1-thiopyran-4-ylcarbamate:

[0473]



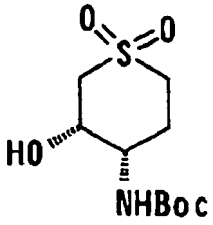
[0474] A solution of N-tert-butoxycarbonyl-L-methionine sulfone methyl ester (60.2 g) in tetrahydrofuran (900 ml) was cooled to -78°C, to which 0.5 M potassium bis-(trimethylsilyl)amide (toluene solution, 900 ml) was added dropwise, and the mixture was stirred for 2 hours at -78°C and for 4.5 hours at room temperature. A 1 M aqueous solution of ammonium chloride was added, and the mixture was stirred. The reaction mixture was subjected to liquid separation, and the resultant organic layer was then washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and solids formed were collected by filtration to obtain the title compound (12.4 g). The water layer separated previously was extracted twice with ethyl acetate, and the resultant organic layers were combined, washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The water layers used in the washing were further combined, and extracted again with ethyl acetate, and the extract was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The ethyl acetate extracts were combined, dried and then concentrated

under reduced pressure to obtain the title compound (27.7 g) (total amount of the title compound: 40.1 g).
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.85-1.96(1H,m), 2.76-2.78(1H,m), 3.34-3.46(2H,m), 4.05(1H,dd,J=13.5,3.7Hz), 4.14 (1H,d,J=13.5Hz), 4.38-4.44(1H,m), 5.46(1H,br).
MS (ESI) m/z: 262(M-H)$^-$.

[Referential Example 178]

tert-Butyl (3R*,4R*)-3-hydroxy-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:

[0475]

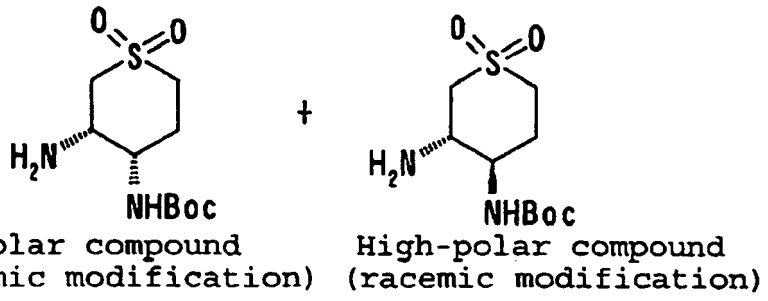


[0476] Sodium borohydride (2.17 g) was added to a suspension of the compound (10.1 g) obtained in Referential Example 177 in methanol (200 ml), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. After ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation, the resultant water layer was extracted twice with ethyl acetate. The resultant organic layers were combined, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain the title compound (9.96 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 2.21-2.36(2H,m), 3.03-3.17(2H,m), 3.26-3.28(2H,m), 3.77-3.80(2H,m), 4.26-4.28(1H, m), 5.05-5.07(1H,m).
MS (ESI) m/z: 264(M-H)$^-$.

[Referential Example 179]

tert-Butyl (3R*,4R*)-3-amino-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate (low-polar compound) and tert-Butyl (3R*, 4S*)-3-amino-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate (high-polar compound):

[0477]



Low-polar compound (racemic modification)

High-polar compound (racemic modification)

[0478] Diethyl azodicarboxylate (6.96 g) was added to a solution of the compound (9.66 g) obtained in Referential Example 178 and triphenylphosphine (10.5 g) in tetrahydrofuran (150 ml), and the mixture was stirred at room temperature for 4.5 hours. After the reaction mixture was concentrated under reduced pressure, diethyl ether was added to the residue, and solids formed were collected by filtration. The thus-collected solids were purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 7:3) to obtain a mixture (7.25 g) containing tert-butyl 1,1-dioxo-1,2,3,4-tetrahydropyran-4-ylcarbamate as a colorless solid. The mother liquor was concentrated under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 7:3) to obtain a mixture (9.18 g) containing tert-butyl 1,1-dioxo-1,2,3,4-tetrahydropyran-4-ylcarbamate as a colorless solid (total amount: 16.4 g). The thus-obtained mixtures were dissolved in dioxane (60 ml), and 28% aqueous ammonia (60 ml) was added. The resultant

mixture was stirred at 60°C for 4.5 hours in a sealed tube. After allowing to cool, the reaction mixture was concentrated under reduced pressure. After dioxane was distilled off, the residue was extracted 5 times with methylene chloride. The resultant organic layers were combined and concentrated under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 96:4) to obtain the title low-polar compound (2.31 g) and the title high-polar compound (4.31 g).

Low-polar compound:

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 2.14-2.28(2H,m), 3.01-3.08(3H,m), 3.23(1H,dd,J=13.8,3.9Hz), 3.47-3.49(1H,m), 3.71-3.76(1H,m), 5.32(1H,d,J=7.3Hz).

MS (ESI) m/z: 265($M+H^+$).

High-polar compound:

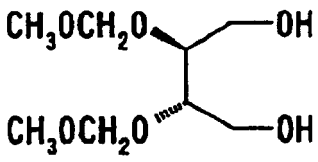
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.94-2.01(1H,m), 2.37-2.44(1H,m), 2.91(1H,dd,J=11.2,14.1Hz), 3.04-3.07(2H,m), 3.12-3.19(1H,m), 3.26-3.30(1H,m), 3.39-3.42(1H,m), 4.62(1H,br).

MS (ESI) m/z: 265($M+H^+$).

[Referential Example 180]

(2S,3S)-2,3-Bis(methoxymethoxy)-1,4-butanediol:

[0479]



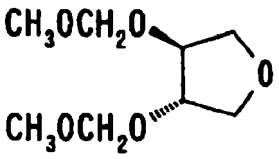
[0480] Chloromethyl methyl ether (4.8 ml) was added dropwise to a mixture solution composed of diethyl L-tartrate (8.6 g), diisopropylethylamine (40 ml) and methylene chloride (40 ml) under ice cooling, and the mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was concentrated, and the resultant residue was diluted with ethyl acetate and washed with 10% hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was dissolved in tetrahydrofuran. The solution was added dropwise to a tetrahydrofuran suspension of lithium aluminum hydride (2.2 g) under ice cooling, and the mixture was stirred for 2 hours under ice cooling. After a 10% aqueous solution of sodium hydrogensulfate was carefully added under ice cooling, and the mixture was stirred for 1 hour, the reaction mixture was diluted with saturated aqueous solution of sodium chloride and extracted with ethyl acetate. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound (3.0 g).

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.64(2H,m), 3.44(6H,s), 3.70-3.81(6H,m), 4.70(2H,d,J=6.9Hz), 4.76(2H,d,J=6.9Hz).

[Referential Example 181]

(3S,4S)-3,4-Bis(methoxymethoxy)tetrahydrofuran:

[0481]



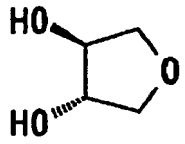
[0482] Diethyl azodicarboxylate (2.46 ml) was added dropwise to a mixture solution composed of the compound (3.0 g) obtained in Referential Example 180, triphenylphosphine (4.5 g), tetrahydrofuran (10 ml) and toluene (40 ml), and the mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure, a mixed solvent (160 ml) of hexane and diethyl ether (1:1) was added to the resultant residue, and the mixture was

stirred for 3 hours. Insoluble matter deposited was then collected by filtration. The filtrate was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (1.95 g).
^{1}H-NMR ($CDCl_3$) δ: 3.38(6H,s), 3.80(2H,dd,J=9.2,1.7Hz), 4.00(2H,dd,J=9.2,4.4Hz), 4.23(2H,dd,J=4.4,1.7Hz), 4.67(2H,d,J=6.9Hz), 4.71(2H,d,J=6.9Hz).

[Referential Example 182]

(3S,4S)-Tetrahydro-3,4-furandiol:

[0483]

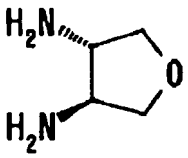


[0484] Concentrated hydrochloric acid (2.1 ml) was added to a solution of the compound (1.95 g) obtained in Referential Example 181 in methanol (6.0 ml), and the mixture was stirred for 18 hours. After the reaction mixture was concentrated, and the resultant residue was diluted with chloroform and dried over potassium carbonate, the solvent was distilled off under reduced pressure to obtain the title compound (0.52 g).
^{1}H-NMR ($CDCl_3$) δ: 1.77(2H,d,J=4.7Hz), 3.73(2H,d,J=10.2Hz), 4.08(2H,dd,J=10.2,3.7Hz), 4.18-4.34(2H,m).

[Referential Example 183]

(3S,4S)-Tetrahydro-3,4-furandiamine:

[0485]

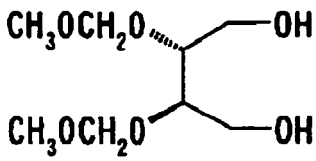


[0486] The title compound was obtained from the compound obtained in Referential Example 182 in a siminar manner to the processes described in Referential Examples 169 to 171.
^{1}H-NMR ($CDCl_3$) δ: 1.35-1.46(4H,m), 3.19(2H,dd,J=5.6,4.1Hz), 3.50(2H,dd,J=9.0,4.1Hz), 4.09(2H,dd,J=9.0,5.6Hz).

[Referential Example 184]

(2R,3R)-2,3-Bis(methoxymethoxy)-1,4-butanediol:

[0487]

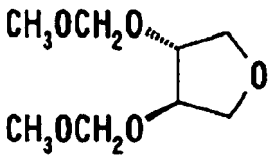


[0488] The title compound was obtained from diethyl D-tartrate in a similar manner to Referential Example 180.
^{1}H-NMR : The same as that of the enantiomer in Referential Example 180.

[Referential Example 185]

(3R,4R)-3,4-Bis(methoxymethoxy)tetrahydrofuran:

[0489]

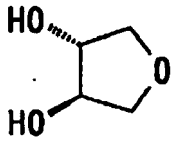


[0490] The title compound was obtained from the compound obtained in Referential Example 184 in a similar manner to Referential Example 181.
^{1}H-NMR : The same as that of the enantiomer in Referential Example 181.

[Referential Example 186]

(3R,4R)-Tetrahydro-3,4-furandiol:

[0491]

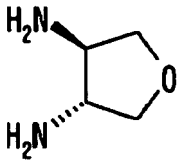


[0492] The title compound was obtained from the compound obtained in Referential Example 185 in a similar manner to Referential Example 182.
^{1}H-NMR : The same as that of the enantiomer in Referential Example 182.

[Referential Example 187]

(3R,4R)-Tetrahydro-3,4-furandiamine:

[0493]

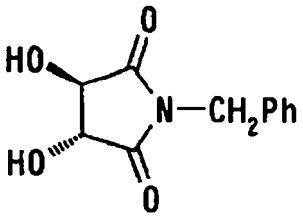


[0494] The title compound was obtained from the compound obtained in Referential Example 186 in a similar manner to Referential Example 183.
^{1}H-NMR ($CDCl_3$) δ: The same as that of the enantiomer in Referential Example 183.

[Referential Example 188]

(3R,4R)-1-Benzyl-3,4-dihydroxy-2,5-pyrrolidinedione:

[0495]

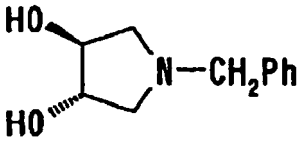


[0496] L-Tartaric acid (30 g) and benzylamine (22 ml) were added to xylene (150 ml), and the mixture was heated under reflux at 150°C for 3 hours using a Dean-Stark trap. After the reaction mixture was allowed to cool overnight, crystals were collected by filtration and washed with acetone. The resultant crude product was recrystallized from ethanol to obtain the title compound (23.2 g).
^{1}H-NMR (DMSO-d_6) δ: 4.36-4.40(2H,m), 4.55(each 1H, AB type d,J=15Hz), 6.26-6.30(2H,m), 7.25-7.35(5H,m).

[Referential Example 189]

(3S,4S)-1-Benzyl-3,4-pyrrolidinediol:

[0497]

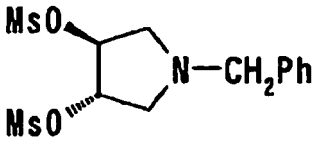


[0498] The compound (11 g) obtained in Referential Example 188 was dissolved in tetrahydrofuran (110 ml), and lithium aluminum hydride (5.69 g) was added portionwise to the solution under ice cooling. The mixture was heated to room temperature for 1 hour and heated under reflux and for additional a night. After allowing the reaction mixture to cool, water (5.7 ml), a 15% aqueous solution (5.7 ml) of sodium hydroxide and water (17.1 ml) were added under ice cooling in that order, and the mixture was heated to room temperature and stirred for 1 hour. After deposits were filtered through Celite, and the mother liquor was concentrated under reduced pressure, the resultant residue was recrystallized from ethyl acetate to obtain title compound (6.35 g).
^{1}H-NMR ($CDCl_3$) δ: 2.40-2.44(2H,m), 2.88-2.92(2H,m), 3.58(each 1H,AB type d,J=7.8Hz), 4.04(2H,t,J=4.2Hz), 7.25-7.34 (5H,m).

[Referential Example 190]

(3S,4S)-1-Benzyl-4-[(methylsulfonyl)oxy]pyrrolidinyl methanesulfonate:

[0499]

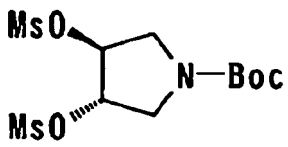


[0500] The title compound was obtained from the compound obtained in Referential Example 189 in a similar manner to Referential Example 169.
^{1}H-NMR ($CDCl_3$) δ: 2.76(2H,dd,J=11,4.6Hz), 3.08(6H,s), 3.64(2H,d,J=2.5Hz), 3.68-3.75(2H,m), 5.12-5.15(2H,m), 7.27-7.35(5H,m).

[Referential Example 191]

tert-Butyl (3S,4S)-3,4-bis[(methylsulfonyl)oxy]-1-pyrrolidinecarboxylate:

[0501]

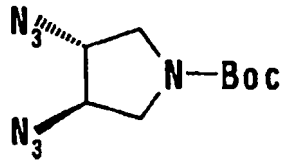


[0502] The compound (1.57 g) obtained in Referential Example 190 was dissolved in 1,2-dichloroethane (16 ml), 1-chloroethyl chloroformate (0.73 ml) was added at room temperature, and the resultant mixture was heated under reflux for 4 hours. After the solvent was distilled off under reduced pressure, methanol (16 ml) was added to the resultant residue, and the resultant mixture was heated under reflux for 1 hour, allowed to cool and concentrated. Crystals obtained by recrystallization from ethyl acetate were collected by filtration to obtain (3S,4S)-3,4-bis-[(methylsulfonyl)oxylpyrrolidine hydrochloride (1.30 g) as colorless crystals. Di-tert-butyl dicarbonate (1.15 ml) was added to a solution of the hydrochloride thus obtained and triethylamine (1.40 ml) in methylene chloride (26 ml), and the mixture was stirred overnight at room temperature. After the reaction mixture was concentrated, the residue was diluted with ethyl acetate, washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (ethyl acetate: hexane = 1:9 - 1:1) to obtain the title compound (1.40 g).
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 3.12(6H,s), 3.70-3.73(2H,m), 3.79(1H,d,J=4.5Hz), 3.82(1H,d,J=4.5Hz), 5.19(2H,br).

[Referential Example 192]

tert-Butyl (3R,4R)-3,4-diazido-1-pyrrolidinecarboxylate:

[0503]

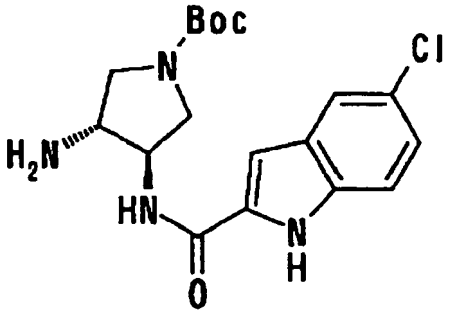


[0504] The title compound was obtained from the compound obtained in Referential Example 191 in a similar manner to Referential Example 170.
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 3.37-3.46(2H,m), 3.64-3.71(2H,m), 3.96(2H,t,J=3.2Hz).

[Referential Example 193]

tert-Butyl (3R,4R)-3-amino-4-{[(5-chloroindol-2-yl)carbonyl]amino}pyrrolidine-1-carboxylate:

[0505]



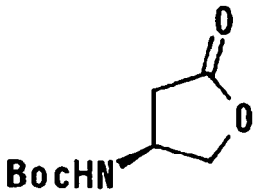
[0506] The title compound was obtained from the compound obtained in Referential Example 192 in a similar manner to Referential Examples 171 and 172.
^{1}H-NMR (DMSO-d_6) δ: 1.39(9H,s), 2.95-3.00(1H,m), 3.09-3.13(1H,m), 3.52(1H,dd,J=10,6.5Hz), 3.68(1H,dd, J=10,7.8Hz), 4.04-4.09(2H,m), 7.16(1H,s), 7.18(1H,s), 7.42(1H,d,J=8.5Hz), 7.69(1H,d,J=1.5Hz), 8.50(1H,d,J=6.5Hz),

11.77(1H,br).

[Referential Example 194]

tert-Butyl (3S)-5-oxotetrahydro-3-furanylcarbamate:

[0507]

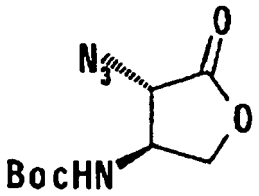


[0508] di-tert-Butyl dicarbonate (4.1 g) and 10% palladium on carbon (0.4 g) were added to a solution of benzyl (3S)-(-)-tetrahydro-5-oxo-3-furanylcarbamate (3.3 g) in tetrahydrofuran (20 ml), and the mixture was stirred for a day in a hydrogen atmosphere. After insoluble matter was filtered through Celite pad, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (1.5 g).
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 2.45(1H,dd,J=17.8,2.7Hz), 2.86(1H,dd,J=17.8,7.3Hz), 4.12-4.23(1H,m), 4.54-4.62(2H,m), 4.85-4.95(1H,m).

[Referential Example 195]

tert-Butyl (3S,4S)-4-azido-5-oxotetrahydro-3-furanylcarbamate:

[0509]

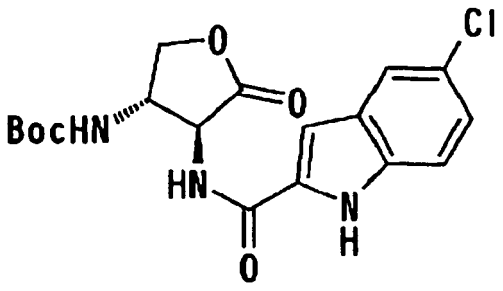


[0510] 1 M Lithium bis(trimethylsilyl)amide (tetrahydrofuran solution, 8.65 ml) was added dropwise to a solution of the compound (0.87 g) obtained in Referential Example 194 in tetrahydrofuran (20 ml) at -78°C, and the mixture was stirred for 30 minutes. After a solution of p-toluenesulfonylazide (1.02 g) in tetrahydrofuran (10 ml) was then added, and the mixture was stirred for 5 minutes, trimethylchlorosilane (1.7 ml) was added, and the mixture was stirred for 2 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with diethyl ether, washed with 10% hydrochloric acid, a 5% saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (0.62 g).
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 4.09(1H,dt,J=15.3,7.6Hz), 4.12-4.23(1H,m), 4.37-4.50(1H,m), 4.54(1H,dd,J=9.0,7.6Hz), 4.81-4.90(1H,m).

[Referential Example 196]

tert-Butyl (3S,4S)-4-{[(5-chloroindol-2-yl)carbonyl]-aminol-5-oxotetrahydro-3-furanylcarbamate:

[0511]

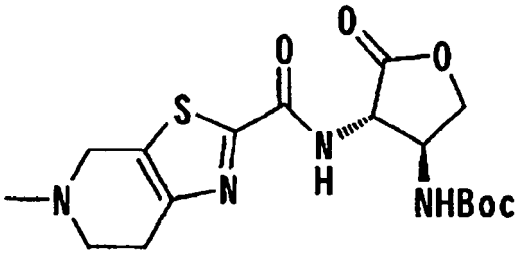


[0512] The title compound was obtained from the compound obtained in Referential Example 195 in a similar manner to Referential Examples 90 and 91.
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 4.01-4.13(1H,m), 4.20-4.36(1H,m), 4.78-4.93(2H,m), 6.15(1H,s), 6.93(1H,s), 7.03-7.11 (1H,m), 7.20-7.28(1H,m), 7.30(1H,d,J=8.BHz), 7.61(1H,s), 9.27(1H,s).

[Referential Example 197]

tert-Butyl (3S,4S)-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-5-oxotetrahydro-3-furanylcarbamate:

[0513]

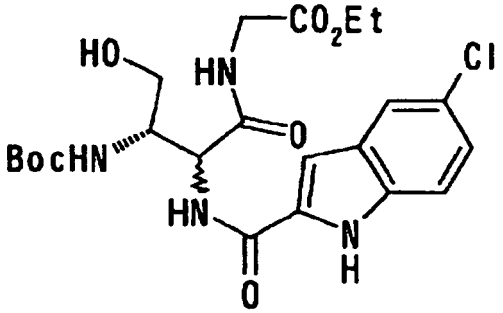


[0514] The title compound was obtained by getting tert-butyl (3S,4S)-4-amino-5-oxotetrahydro-3-furanylcarboxylate from the compound obtained in Referential Example 195 in a similar manner to Referential Example 90 and then reacting with the compound obtained in Referential Example 10 in accordance with the reaction conditions of Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 2.52(3H,s), 2.83(2H,t,J=5.9Hz), 2.79-3.02(2H,m), 3.74(2H,s), 4.03-4.12(1H,m), 4.21-4.36(1H,m), 4.80-4.95(2H,m), 6.14-6.24(1H,m), 7.76-7.85(1H,m).

[Referential Example 198]

Ethyl 2-[((3S)-3-[(tert-butoxycarbonyl)amino]-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-hydroxybutanoyl)amino]-acetate:

[0515]

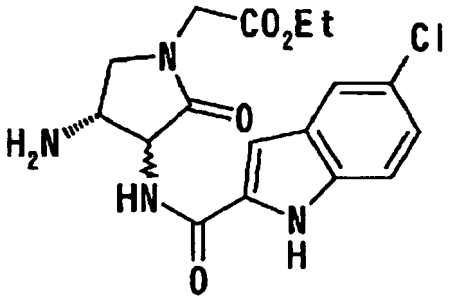


[0516] The compound (0.4 g) obtained in Referential Example 196, glycine ethyl ester hydrochloride (1.0 g) and triethylamine (1.0 ml) were added to ethanol (20 ml), and the mixture was heated and stirred at 60°C for 18 hours. The reaction mixture was diluted with chloroform and washed with a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 98:2) to obtain title compound (0.31 g).
^{1}H-NMR (DMSO-d_6) δ: 1.17(3H,t,J=7.0Hz), 1.34(6H,s), 1.36(3H,s), 3.51-3.63(0.6H,m), 3.72-3.80(2H,m), 4.06(2H,q, J=7.0Hz), 4.11-4.23(1.4H,m), 4.67-4.82(1H,m), 4.85-4.91(1H,m), 6.48(0.4H,d,J=9.5Hz), 6.80(0.6H,d,J=9.5Hz), 7.10-7.22(2H,m), 7.42(1H,d,J=8.8Hz), 7.72(0.4H,d,J=2.0Hz), 7.73(0.6H,d,J=2.0Hz), 8.23-8.31(0.6H,m), 8.34-8.41 (0.4H,m), 8.43-8.50(1H,m), 11.83(1H,s).

[Referential Example 199]

Ethyl 2-((4R)-4-amino-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-2-oxopyrrolidin-l-yl)acetate hydrochloride:

[0517]

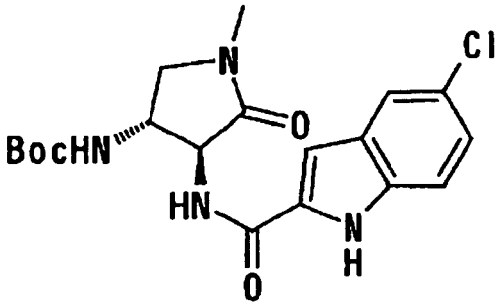


[0518] The title compound was obtained by converting the compound obtained in Referential Example 198 into a pyrrolidone derivative using the reaction conditions described in Referential Example 181 and then removing a tert-butoxycarbonyl group in a similar manner to Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 1.17(2H,t,J=7.0Hz), 1.23(1H,t,J=7.0Hz), 3.31-3.40(0.6H,m), 3.57(0.4H,d,J=11.2Hz), 3.90-4.23 (4H,m), 4.42 (0.6H,dd,J=12.0,6.1Hz), 4.50-4.60(0.4H,m), 4.62(0.6H,dd,J=12.0,3.9Hz), 5.12-5.23(0.4H,m), 7.17(0.4H, s), 7.20(0.4H, dd,J=8.8,2.0Hz), 7.28(0.6H,dd,J=8.8,2.0Hz), 7.30(0.6H,s), 7.44(0.4H,d,J=8.8Hz), 7.50(0.6H,d,J=8.8Hz), 7.75(1H,d,J=2.0Hz), 8.20-8.33(1H,m), 8.71-8.94(3.6H,m), 9.22-9.35(0.4H,m), 11.97(0.4H,s), 12.44(0.6H,s).

[Referential Example 200]

tert-Butyl (3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-1-methyl-5-oxopyrrolidin-3-ylcarbamate:

[0519]

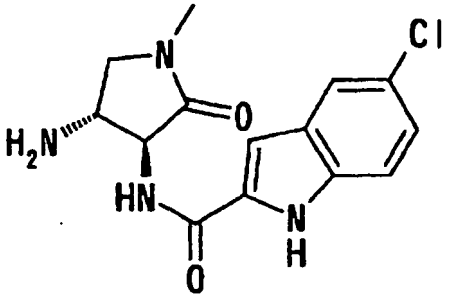


[0520] The title compound was obtained by treating a compound obtained by reaction of the compound obtained in Referential Example 196 with methylamine (40% methanol solution) in a similar manner to Referential Example 198 under the same conditions as those in Referential Example 181.
^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 2.90(3H,s), 4.26(1H,br.s), 4.36(2H,m), 4.51-4.52(1H,m), 5.35(1H,br.s), 6.95-6.99(2H, m), 7.22-7.32(3H,m), 7.63(1H,s), 8.95(1H,br.s).

[Referential Example 201]

N-[(3S,4R)-4-Amino-1-methyl-2-oxopyrrolidin-3-yl]-5-chloroindole-2-carboxamide:

[0521]

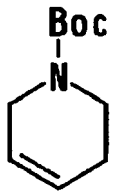


[0522] The title compound was obtained by treating the compound obtained in Referential Example 200 in a similar manner to Referential Example 69.
^{1}H-NMR ($CDCl_3$) δ: 2.95 (3H, d, J=5.1Hz), 3.91-3.93 (1H, m), 4.19 (1H, d, J=3.7Hz), 4.36 (1H, dd, J=11, 1.7Hz), 4.48 (1H, dd, J=11, 2.0Hz), 6.90-6.97(2H,m), 7.21-7.33(2H,m), 7.62 (1H, d, J=2.0Hz), 8.90 (1H, s).

[Referential Example 202]

tert-Butyl 3,6-dihydro-1(2H)-pyridinecarboxylate:

[0523]

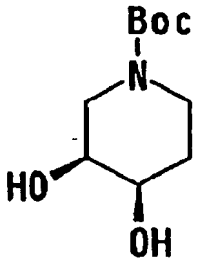


[0524] tert-Butyl dicarbonate (6.55 g) was added to a mixture of 1,2,3,6-tetrahydropyridine (2.50 g) and a 10% aqueous solution (3.0 ml) of sodium carbonate, and the mixture was stirred at room temperature for 20 hours. Water was added to the reaction mixture to conduct extraction with ethyl acetate. The resultant organic layer was washed with 0.5N hydrochloric acid, water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride in that order and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure to obtain the title compound (5.08 g).
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 2.12(2H,br.s), 3.48(2H,t,J=5.6Hz), 3.88(2H,br.s), 5.60(1H,br.s), 5.78-5.90(1H,m).

[Referential Example 203]

tert-Butyl (3R*,4S*)-3,4-dihydroxy-1-piperidinecarboxylate:

[0525]

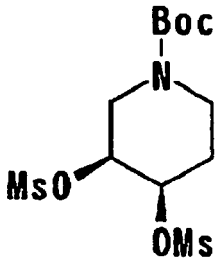


[0526] The compound (18.45 g) obtained in Referential Example 202 was dissolved in acetonitrile (200 ml), and water (38 ml), a 0.039 M aqueous solution (82 ml) of osmium tetroxide and N-methylmorpholine N-oxide (23.13 g) were added. The mixture was stirred at room temperature for 17 hours. An excessive oxidizing agent was treated with a saturated aqueous solution of sodium sulfite to conduct extraction with ethyl acetate. The resultant organic layer was washed with water, 0.5N hydrochloric acid, water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride in that order, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 1:3) to obtain the title compound (15.0 g).
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.60-1.73(1H,m), 1.77-1.90(1H,m), 2.68(1H,br.s), 2.80-3.20(1H,br), 3.22-3.32 (1H, m), 3.42 (1H, dd, J=14.3, 3.4Hz), 3.50-3.62(2H,m), 3.77(1H,brs), 3.81-3.92(1H,m).

[Referential Example 204]

tert-Butyl (3R*,4S*)-3,4-bis[(methylsulfonyl)oxy]-1-piperidinecarboxylate:

[0527]

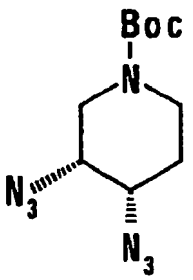


[0528] The title compound was obtained from the compound obtained in Referential Example 203 in a similar manner to Referential Example 169.
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.85-1.97(1H,m), 2.08-2.20(1H,m), 3.00-4.20(4H,m), 3.12(6H,s), 4.85(1H,br.s), 4.94 (1H,br.s).

[Referential Example 205]

tert-Butyl (3R*,4S*)-3,4-diazido-1-piperidinecarboxylate:

[0529]

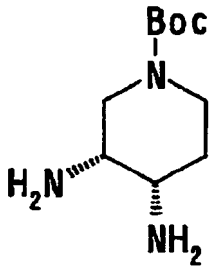


[0530] The title compound was obtained from the compound obtained in Referential Example 204 in a similar manner to Referential Example 170.
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.70-1.60 (1H, m), 1.90-2.00 (1H, m), 3.05-4.00(6H,m).

[Referential Example 206]

tert-Butyl (3R*,4S*)-3,4-diamino-1-piperidinecarboxylate:

[0531]

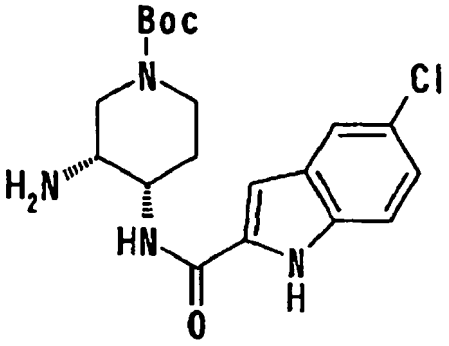


[0532] The title compound was obtained from the compound obtained in Referential Example 205 in a similar manner to Referential Example 171.
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.48-1.60(2H,m), 1.80-2.10(4H,br), 2.85-2.91(2H, m), 2.97(1H,br.s), 3.09(1H,dd, J=13.6,2.7Hz), 3.74(1H,dd,J=13.6,4.2Hz), 3.81 (1H, s).

[Referential Example 207]

tert-Butyl (3R*,4S*)-3-amino-4-{[(5-chloroindol-2-yl)-carbonyl]amino}-1-piperidinecarboxylate:

[0533]

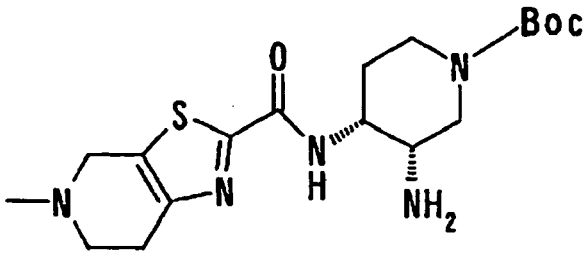


[0534] The compound (3.23 g) obtained in Referential Example 206 was dissolved in N,N-dimethylformamide (100 ml), and triethylamine (2.08 ml) and the compound (3.80 g) obtained in Referential Example 52 were added to the solution. The mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and water was added to the residue to conduct extraction with methylene chloride. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 20:1 - 10:1) to obtain the title compound (2.70 g).
^{1}H-NMR (DMSO-d_6) δ: 1.40-1.58(3H,m), 1.41(9H,s), 1.75-1.90(1H,m), 2.95 (1H, br.s), 2.98-3.05 (1H, m), 3.19-3.28 (1H, m), 3.74 (1H, dd, J=19.5, 15.4Hz), 3.79 (1H, br.s), 4.04-4.12 (1H, m), 7.17 (1H, dd, J=8.7, 1.9Hz), 7.21 (1H, s), 7.42 (1H, d, J=8.7Hz), 7.68 (1H, d, J=1.9Hz), 8.00 (1H, br. d, J=7.6Hz), 11.80 (1H, s).

[Referential Example 208]

tert-Butyl (3R*,4S*)-3-amino-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-1-piperidine-carboxylate:

[0535]

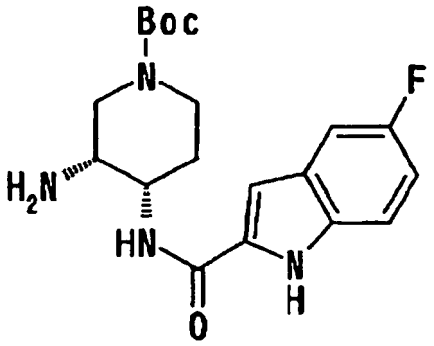


[0536] The compound (3.23 g) obtained in Referential Example 206 was dissolved in N,N-dimethylformamide (100 ml), and triethylamine (2.08 ml) was added. The compound (3.83 g) obtained in Referential Example 149 was then added, and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and water was added to the residue to conduct extraction with methylene chloride. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 10:1 - 5:1) to obtain the title compound (2.27 g).
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.62 (3H, m), 1.47(9H,s), 1.78-1.88 (1H, m), 2.51(3H,s), 2.81 (2H, t, J=5.9Hz), 2.85-2.98(3H, m), 3.00-3.15 (2H, m), 3.71(2H,s), 3.80-4.15 (3H, m), 7.79 (1H, br.s).

[Referential Example 209]

tert-Butyl (3R*,4S*)-3-amino-4-{[(5-fluoroindol-2-yl)-carbonyl]amino}-1-piperidinecarboxylate:

[0537]

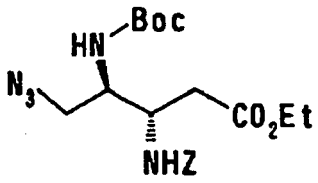


[0538] The title compound was obtained from the compound obtained in Referential Example 206 and 5-fluoroindole-2-carboxylic acid in a similar manner to Referential Example 172.
^{1}H-NMR ($CDCl_3$) δ: 1.40-1.70 (3H, m), 1.48(9H,s), 2.79-2.92 (1H, m), 2.99-3.14 (1H, m), 4.00-4.23(3H,m), 6.85 (1H, s), 7.04 (1H, td, J=9.0, 2.4Hz), 7.07-7.20 (1H, br), 7.27 (1H, dd, J=9.0, 2.4Hz), 7.35 (1H, d, J=9.0, 4.4Hz), 9.25-9.50 (1H, br).
MS (ESI)m/z: 377 $(M+H)^+$.

[Referential Example 210]

Ethyl (3S,4R)-5-azido-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]valerate:

[0539]

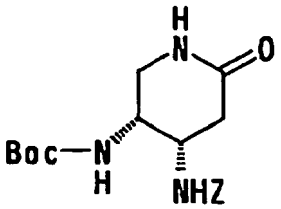


[0540] Triethylamine (4.80 ml) and methanesulfonyl chloride (1.55 ml) were successively added dropwise to a solution of the (3S,4S)-compound obtained in Referential Example 168 (low-polar compound) (7.1 g) in methylene chloride (100 ml) under ice cooling, and the mixture was stirred for 30 minutes under ice cooling. The reaction mixture was diluted with chloroform and washed with a 10% aqueous solution of citric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain a methanesulfonyl derivative (9.20 g). A mixture solution composed of the thus-obtained methanesulfonyl derivative, sodium azide (5.64 g) and N,N-dimethylformamide (100 ml) was stirred at 80°C for 20 hours. The reaction mixture was diluted with ethyl acetate and washed with water and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform) to obtain the title compound (5.42 g).
^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.1Hz), 1.43 (9H, s), 2.56-2.68(2H,m), 3.48-3.60(2H,m), 3.88-3.97 (1H, m), 4.04-4.20 (3H, m), 4.88-4.97 (1H, br), 5.10 (2H, s), 5.60-5.75 (1H, br), 7.30-7.40 (5H, m).
MS (ESI) m/z: 436 $(M+H)^+$.

[Referential Example 211]

Benzyl (4S,5R)-5-[(tert-butoxycarbonyl)amino]-2-oxo-piperidin-4-ylcarbamate:

[0541]

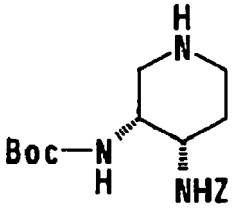


[0542] A Lindlar catalyst (2.71 g) was added to a solution of the compound (5.42 g) obtained in Referential Example 210 in a mixed solvent of ethanol (150 ml) and tetrahydrofuran (10.0 ml), and the mixture was stirred for 3 hours under a hydrogen atmosphere and then for 14 hours under nitrogen conditions. After insoluble matter was removed through Celite pad, and the filtrate was concentrated under reduced pressure, the resultant residue was dissolved in tetrahydrofuran (30 ml), and triethylamine (3.0 ml) was added thereto. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with a 10% aqueous solution of citric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 25:1) to obtain the title compound (2.50 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H, s), 2.30-2.50 (1H, br), 2.65-2.90 (1H, br), 3.15-3.30 (1H, br), 3.35-3.65 (1H, br), 4.00-4.25 (2H, br), 5.11(2H,s), 5.55-5.60 (1H, br), 5.65-5.90 (1H, br), 6.25-6.55 (1H, br), 7.28-7.40 (5H, m).
MS (ESI) m/z: 364 $(M+H)^+$.

[Referential Example 212]

Benzyl (3R,4S)-3-[(tert-butoxycarbonyl)amino]piperidin-4-ylcarbamate:

[0543]

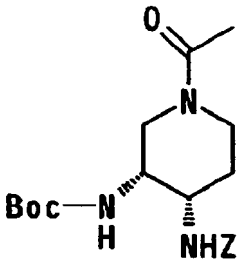


[0544] 1 M Borane-tetrahydrofuran complex (tetrahydrofuran solution, 34.0 ml) was added dropwise to a tetrahydrofuran solution (70 μl) of the compound (2.49 g) obtained in Referential Example 211 under ice cooling, and the mixture was stirred for 20 hours while the temperature of the system was gradually raised to room temperature. Methanol (100 ml) was added to the reaction mixture, and the solvent was distilled off under reduced pressure. Ethanol (45 ml), water (5 ml) and triethylamine (10 ml) were aded to the residue, and the mixture was heated under reflux for 24 hours. The reaction mixture was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol: water = 7:3:1, lower layer) to obtain the title compound (1.61 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.65-1.72 (2H, m), 2.67 (1H, t, J=12.0Hz), 2.82 (12H, d, J=12.0Hz), 2.90-3.10 (1H, br), 3.60-3.80(2H,m), 3.90-4.00 (1H, m), 5.00-5.20(2H,m), 5.40-5.60(2H,br), 7.25-7.74 (5H, m).
MS (FAB) m/z: 350 $(M+H)^+$.

[Referential Example 213]

tert-Buthyl (3R,4S)-1-acetyl-4-{[(benzyloxy)carbonyl]amino}-piperidin-3-ylcarbamate:

[0545]

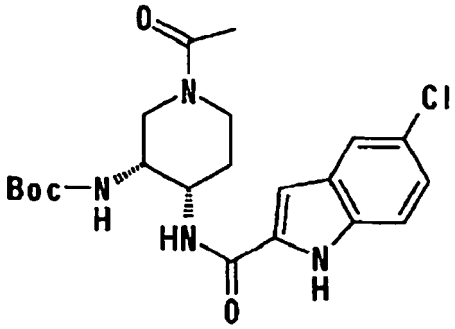


[0546] The title compound was obtained by reaction of the compound obtained in Referential Example 212 with acetyl chloride and triethylamine in methylene chloride.
^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.85-2.15 (2H, m), 2.07 (1.5H, s), 2.14(1.5H,s), 2.75-2.90 (1H, m), 3.10-3.20(0.5H,m), 3.25-3.35 (0.5H, br. d, J=14.2Hz), 3.65-4.05(3H,m), 4.38-4.47 (0.5H, br. d, J=13.0Hz), 4.5,4-4.63(0.5H,m), 4.69-4.83 (1H, br), 4.98-5.20 (2.5H, m), 5.90-6.05 (0.5H, br), 7.30-7.40 (5H, m).
MS (ESI) m/z: 392 $(M+H)^+$.

[Referential Example 214]

tert-Butyl (3R,4S)-1-acetyl-4-{[(5-chloroindol-2-yl)-carbonyl]amino}piperidin-3-ylcarbamate:

[0547]

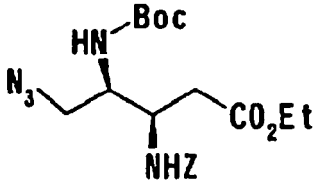


[0548] 10% Palladium on carbon (532 mg) was added to a solution of the compound (745 mg) obtained in Referential Example 213 in ethanol (50 ml), and the mixture was stirred at room temperature for 16 hours under a hydrogen atmosphere. Insoluble matter was removed by filtration through Celite, and the filtrate was then concentrated under reduced pressure. The resultant residue was treated with 5-chloroindole-2-carboxylic acid (467 mg) in a similar manner to Referential Example 68 to obtain the title compound (650 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s), 1.60-1.80 (2H, m), 2.12 (1H, s), 2.16(2H,s), 2.30-2.45(0.5H,m), 2.67-2.82(0.3H,m), 2.89 (0.7H, d, J=13.7Hz), 3.23 (0.7H, t, J=12.9Hz), 3.37(0.3H,d,J=13.7Hz), 3.81-3.95 (1H, m), 4.05-4.33(2H,m), 4.62-4.72 (0.3H, br), 4.77(0.7H,d,J=13.7Hz), 5.10-5.27 (1H, m), 6.81(0.3H,br.s), 6.85 (0.7H, s), 7.21 (1H, br. d, J=8.8Hz), 7.34 (1H, d, J=8.8Hz), 7.57 (0.3H, br. s), 7.61 (0.7H, s), 8.55-8.65(0.5H,br), 9.43-9.53(0.7H,br), 9.60-9.70 (0.3H, br).
MS (ESI) m/z: 435 $(M+H)^+$.

[Referential Example 215]

Ethyl (3R,4R)-5-azido-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]valerate:

[0549]

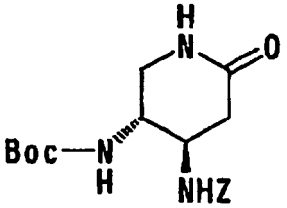


[0550] The title compound was obtained from the (3R,4S)-compound (high-polar compound) obtained in Referential Example 168 in a similar manner to Referential Example 210.
^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=6.6Hz), 1.42(9H,s), 2.51-2.63(2H,m), 3.43-3.50(2H,m), 3.84-3.92 (1H, m), 4.03-4.23 (3H,m), 5.10(2H,s), 5.11-5.24 (1H, m), 5.54-5.60 (1H, m), 7.32-7.44 (5H, m).

[Referential Example 216]

Benzyl (4R,5R)-5-[(tert-butoxycarbonyl)amino]-2-oxo-piperidin-4-ylcarbamate:

[0551]



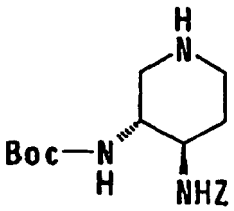
[0552] The title compound was obtained by treating the compound obtained in Referential Example 215 in a similar manner to Referential Example 211.

^{1}H-NMR (DMSO-d_6) δ: 1.35(9H,s), 2.19 (1H, dd, J=17.4, 9.1Hz), 2.41-2.51 (1H, m), 2.97 (1H, t, J=9.1Hz), 3.00-3.11 (1H, m), 3.51-3.64 (1H, m), 3.67-3.73 (1H, m), 5.00(2H,s), 6.71-6.80 (1H, m), 7.20-7.30 (5H, m), 7.44-7.52 (1H, m), 8.30 (1H, s).

[Referential Example 217]

Benzyl (3R,4R)-3-[(tert-butoxycarbonyl)amino]piperidin-4-ylcarbamate:

[0553]

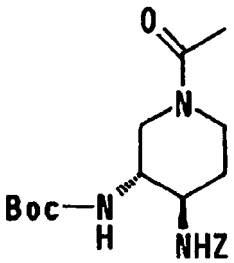


[0554] The title compound was obtained by treating the compound obtained in Referential Example 216 in a similar manner to Referential Example 212.
^{1}H-NMR ($CDCl_3$) δ: 1.39(9H,s), 2.05 (2H, d, J=12.9Hz), 2.40 (1H, t, J=11.0Hz), 2.63 (1H, t, J=12.0Hz), 3.09 (1H, d, J=12.0Hz), 3.37 (1H, d, J=11.0Hz), 3.42-3.53(2H,m), 4.80-4.91 (1H, m), 5.09(2H,s), 5.23-5.32 (1H, m), 7.34-7.41 (5H, m).

[Referential Example 218]

tert-Butyl (3R,4R)-1-acetyl-4-{[(benzyloxy)carbonyl]amino}-piperidin-3-ylcarbamate:

[0555]

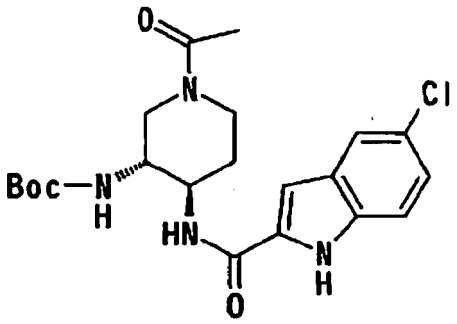


[0556] The title compound was obtained by treating the compound obtained in Referential Example 217 in a similar manner to Referential Example 213.
^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s), 1.53-1.67 (1H, m), 1.89-2.00 (1H, m), 2.09(1.5H,s), 2.15 (1.5H, s), 2.57 (1H, t, J=12.0Hz), 2.78 (1H, t, J=12.0Hz), 3.20-3.30 (1H, m), 3.40-3.56 (2H, m), 4.23-4.31 (1H, m), 4.45-4.56 (1H, m), 5.01-5.08 (1H, m), 5.10(2H,s), 7.32-7.44 (5H, m).

[Referential Example 219]

tert-Butyl (3R,4R)-1-acetyl-4-{[(5-chloroindol-2-yl)-carbonyl]amino}piperidin-3-ylcarbamate:

[0557]

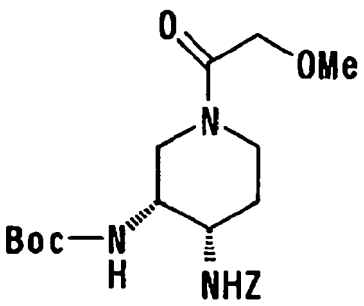


[0558] The title compound was obtained by treating the compound obtained in Referential Example 218 in a similar manner to Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.35 (9H, s), 1.42-1.56 (2H, m), 2.00-2.10 (1H, m), 2.12 (1.5H, s), 2.17(1.5H,s), 2.31-2.43 (1H, m), 2.67-3.00 (1H, m), 3.55-3.63 (1H, m), 3.78-4.00 (1H, m), 4.03-4.21 (1H, m), 4.78-5.24(2H,m), 6.91 (0.5H, s), 6.92 (0.5H, s), 7.22-7.32 (1H, m), 7.33 (1H, d, J=8.8Hz), 7.58 (1H, s), 9.45 (0.5H, s), 9.51 (0.5H, s).

[Referential Example 220]

Benzyl (3R,4S)-3-[(tert-butoxycarbonyl)amino]-1-(2-methoxyacetyl)piperidin-4-ylcarbamate:

[0559]

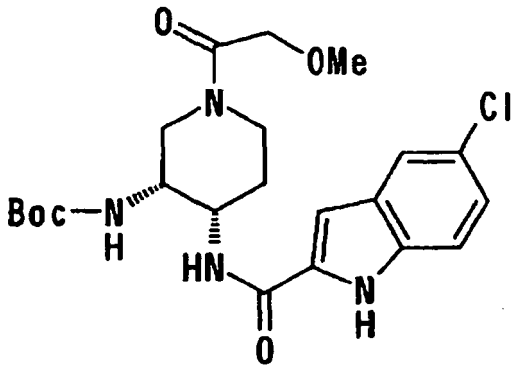


[0560] The title compound was obtained from the compound obtained in Referential Example 212 and methoxyacetyl chloride in a similar manner to Referential Example 213.
^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.70-2.15 (2H, m), 2.70-2.85 (1H, m), 2.90-3.30 (1H, m), 3.35-3.70 (1H, m), 3.43 (3H, s), 3.75-3.90(2H,m), 3.90-4.25(3H,m), 4.40-4.80 (1H, m), 5.05-5.09 (1H, m), 5.10(2H,br.s), 7.30-7.40 (5H, m). MS (ESI) m/z: 322 ($M+H^+$).

[Referential Example 221]

tert-Butyl (3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-ylcarbamate:

[0561]

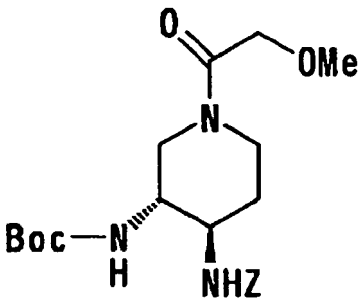


[0562] The title compound was obtained from the compound obtained in Referential Example 220 in a similar manner to Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s), 1.60-1.80 (1H, m), 2.20-2.40 (1H, m), 2.70-2.80(0.6H,m), 2.90-3.00(0.4H,m), 3.15-3-30 (0.4H, m), 3.32-3.40(0.6H,m), 3.46,3.49(total 3H,each s), 3.85-4.30 (5H, m), 4.55-4.80 (1H, m), 5.11 (0.4H, br.s), 6.05 (0.6H, br. s), 6.86 (1H, s), 7.20 (1H, dd, J=8.7, 2.0Hz), 7.33 (1H, d, J=8.7Hz), 7.61 (1H,s), 8.40-8.60 (1H, m), 9.41 (1H, br.s). MS (FAB) m/z: 465 $(M+H)^+$.

[Referential Example 222]

Benzyl (3R,4R)-3-[(tert-butoxycarbonyl)amino]-1-(2-methoxyacetyl)piperidin-4-ylcarbamate:

[0563]

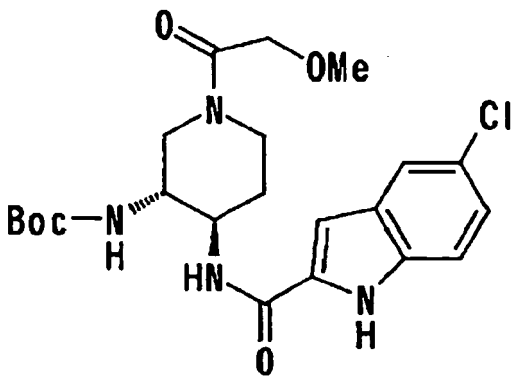


[0564] The title compound was obtained from the compound obtained in Referential Example 217 and methoxyacetyl chloride in a similar manner to Referential Example 213.
^{1}H-NMR ($CDCl_3$) δ: 1.41(9H,s), 1.45-1.67 (1H, m), 2.01-2.14 (1H, m), 2.63 (1H, t, J=12.0Hz), 2.75 (1H, t, J=12.0Hz), 3.20-3.30 (1H, m), 3.32-3.41 (5H, m), 3.44-3.56(2H,m), 4.21-4.32 (1H, m), 4.50-4.63 (1H, m), 5.03-5.08 (1H, m), 5.09 (2H,s), 7.32-7.40 (5H, m).

[Referential Example 223]

tert-Butyl (3R,4R)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-1-(2-methoxyacetyl)piperidin-3-ylcarbamate:

[0565]

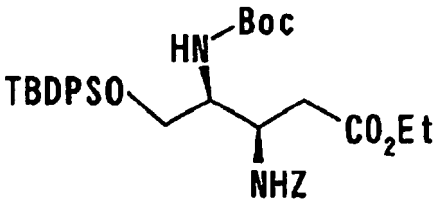


[0566] The title compound was obtained from the compound obtained in Referential Example 222 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.35(9H,s), 1.41-1.56(2H,m), 2.11-2.23 (0.5H, m), 2.34-2.50 (0.5H, m), 2.78-2.89(0.5H,m), 3.01-3.12 (0.5H,m), 3.42 (5H, s), 3.45-3.56 (1H, m), 3.78-3.89 (1H, m), 4.00-4.21 (2H, m), 4.78-5.21(2H,m), 6.91 (0.5H, s), 6.93 (0.5H,s), 7.23 (1H, dd, J=8.8, 2.0Hz), 7.33 (1H, d, J=8.8Hz), 7.59 (1H, s), 9.37 (0.5H, s), 9.54 (0.5H, s).

[Referential Example 224]

Ethyl (3R,4S)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]-5-{[tert-butyl(diphenyl)silyl]oxy}-valerate:

[0567]

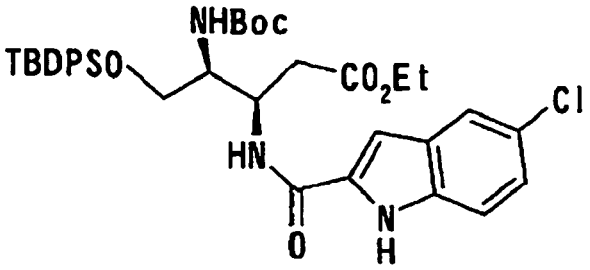


[0568] Triethylamine (0.47 ml), imidazole (0.19 g) and tert-butylchlorodiphenylsilane (0.7 ml) were successively added to a solution of the (3R,4S)-compound (high-polar compound) (0.74 g) obtained in Referential Example 168 in N,N-dimethylformamide (30 ml) under ice cooling, and the mixture was stirred for 4 days while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with ethyl acetate and washed with a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 8:1) to obtain the title compound (0.85 g).
^{1}H-NMR ($CDCl_3$) δ: 1.07 (9H, s), 1.19 (3H, t, J=7.4Hz), 1.40(9H,s), 2.40-2.50 (1H, m), 2.60 (1H, dd, J=15.9, 4.5Hz), 3.56-3.67 (1H, m), 3.74 (1H, dd, J=11.2, 4.5Hz), 3.78-3.89 (1H, m), 4.08(2H,q,J=7.4Hz), 4.21-4.30 (1H, m), 4.99-5.13 (3H,m), 5.41-5.52 (1H, m), 7.40-7.53 (6H, m), 7.60-7.72(4H,m).

[Referential Example 225]

Ethyl (3R,4S)-4-[(tert-butoxycarbonyl)amino]-5-{[tert-butyl(diphenyl)silyl]oxy}-3-{[(5-chloroindol-2-yl)-carbonyl]amino} valerate:

[0569]

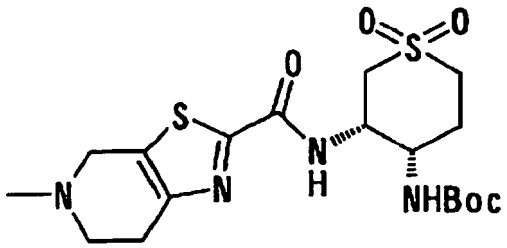


[0570] The title compound was obtained by removing the benzyloxycarbonyl group of the compound obtained in Referential Example 224 and condensing with 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.10 (9H, s), 1.20 (3H, t, J=7.4Hz), 1.32(9H,s), 2.40-2.52 (1H, m), 2.71 (1H, dd, J=15.9, 4.5Hz), 3.67-3.81(2H,m), 4.00-4.20(2H,m), 4.56-4.74 (1H, m), 5.00-5.11 (1H, m), 6.81 (1H, s), 7.21 (1H, dd, J=8.8, 2.0Hz), 7.32 (1H, d, J=8.8Hz), 7.40-7.50(6H,m), 7.58 (1H, d, J=8.5Hz), 7.63-7.74 (5H, m), 9.01-9.14 (1H, m).

[Referential Example 226]

tert-Butyl (3R*,4R*)-3-{[(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-1,1-dioxo-hexahydro-1-thiopyran-4-ylcarbamate:

[0571]

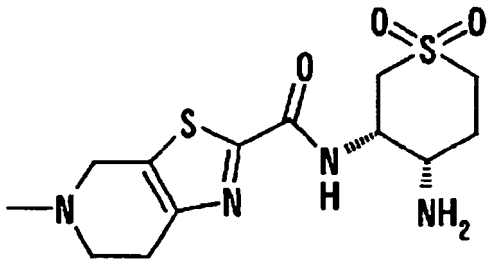


[0572] The title compound was obtained from the (3R*,4R*)-compound (low-polar compound) obtained in Referential Example 179 and the compound obtained in Referential Example 10 in a similar manner to Referential Example 68.
^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 2.30-2.37(2H,m), 2.51(3H,s), 2.82-2.85(2H,m), 2.92-2.95(2H,m), 3.17-3.20(4H,m), 3.40-3.43 (1H, m), 3.69-3.77(2H,m), 3.97-3.98 (1H, m), 4.98 (1H, br), 5.25 (1H, br).

[Referential Example 227]

N-(3R*,4R*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

[0573]



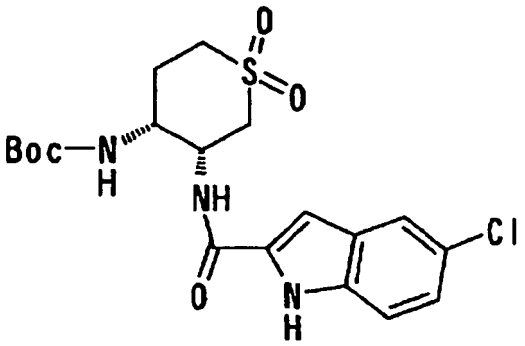
[0574] The title compound was obtained by treating the compound obtained in Referential Example 226 in a similar manner to Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 2.29-2.33(2H,m), 2.93(3H,s), 3.16(2H,br), 3.40(2H,br), 3.52(2H,br), 3.69-3.76(3H,m), 4.48 (1H,

br), 4.71-4.82(2H,m), 8.34(2H,br), 8.82 (1H, br).
MS (ESI) m/z: 345 $(M+H)^+$.

[Referential Example 228]

tert-Butyl (3R*,4R*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:

[0575]

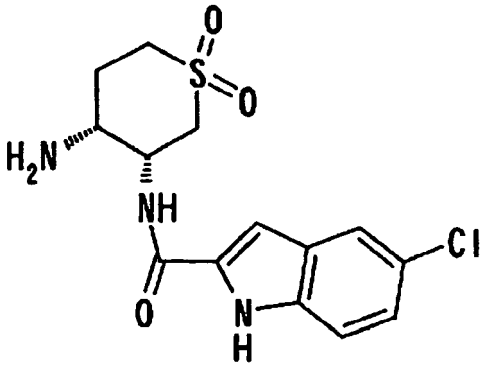


[0576] The title compound was obtained from the (3R*,4R*)-compound (low-polar compound) obtained in Referential Example 179 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 68.
^{1}H-NMR (DMSO-d_6) δ: 1.34 (9H, s), 2.09 (2H, br), 3.07 (1H, d, J=12.6Hz), 3.24-3.28 (1H, m), 3.48(2H,br), 4.12 (1H, br), 4.53 (1H, br), 7.04 (1H, s), 7.16-7.18(2H,m), 7.44 (1H, d, J=8.7Hz), 7.67 (1H, s), 8.37 (1H, br), 11.81 (1H, s).
MS (ESI) m/z: 442 $(M+H)^+$.

[Referential Example 229]

N-[(3R*,4R*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-chloroindole-2-carboxamide hydrochloride:

[0577]

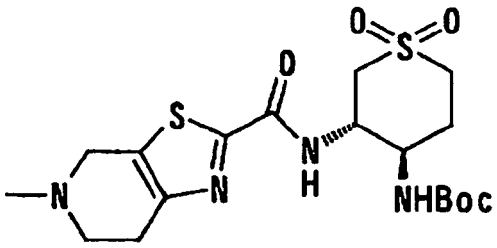


[0578] The title compound was obtained by treating the compound obtained in Referential Example 228 in a similar manner to Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 2.24-2.33(2H,m), 3.43-3.55(3H,m), 3.60-3.66 (1H,m), 3.77 (1H, br), 4.75-4.79 (1H, m), 7.18-7.21 (2H,m), 7.46 (1H, d, J=8.8Hz), 7.72 (1H, d, J=1.7Hz), 8.39(2H,br), 8.58 (1H, d, J=6.8Hz), 11.93 (1H, s).
MS (ESI) m/z: 342 $(M+H)^+$.

[Referential Example 230]

tert-Butyl (3R*,4S*)-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:

[0579]

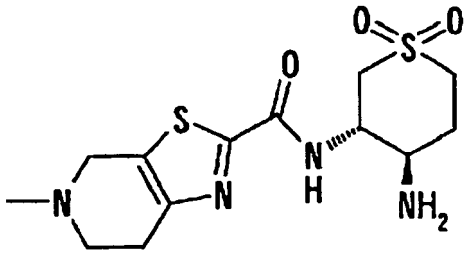


[0580] The title compound was obtained from the (3R*,4S*)-compound (high-polar compound) obtained in Referential Example 179 and the compound obtained in Referential Example 10 in a similar manner to Referential Example 98.
^{1}H-NMR ($CDCl_3$) δ: 1.32(9H,s), 2.14-2.24 (1H, m), 2.33-2.38 (1H, m), 2.50(3H,s), 2.78-2.83(2H,m), 2.86-2.95 (2H, m), 3.08-3.14 (3H, m), 3.55 (1H, d, J=13.4Hz), 3.68 (1H, d, J=15.5Hz), 3.72 (1H, d, J=15.5Hz), 3.86-3.88 (1H, m), 4.45-4.53 (1H, m), 4.75 (1H, d, J=8.5Hz), 7.76 (1H, d, J=8.3Hz).
MS (ESI) m/z: 445 $(M+H)^+$.

[Referential Example 231]

N-[(3R*,4S*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

[0581]

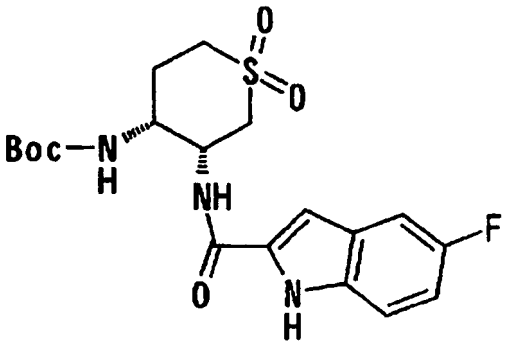


[0582] The title compound was obtained by treating the compound obtained in Referential Example 230 in a similar manner to Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 2.03-2.12 (1H, m), 2.51 (1H, br), 2.93(3H,s), 3.14(2H,d,J=12.2Hz), 3.28(2H,br), 3.33(2H,br), 3.48 (3H, br), 3.72 (2H, br), 4.49 (2H, br), 4.71-4.74 (1H, m), 8.38(2H,br), 9.21-9.24 (1H, m).
MS (ESI) m/z: 345 $(M+H)^+$.

[Referential Example 232]

tert-Butyl (3R*,4R*)-3-{[(5-fluoroindol-2-yl)carbonyl]-amino}-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:

[0583]

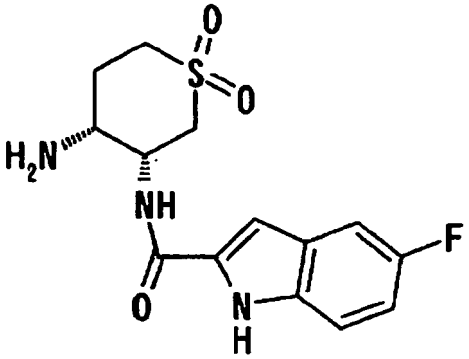


[0584] The title compound was obtained from the (3R*,4R*)-compound (low-polar compound) obtained in Referential Example 179 and 5-fluoroindole-2-carboxylic acid in a similar manner to Referential Example 68.
^{1}H-NMR (DMSO-d_6) δ: 1.37(9H,s), 2.10-2.13 (2H, m), 3.06 (1H, br), 3.37-3.49(3H,m), 4.13 (1H, br), 4.57 (1H, br), 6.95-7.01(2H,m), 7.14 (1H, br), 7.30 (1H, d, J=8.5Hz), 7.41 (1H, dd, J=8.8, 4.5Hz), 8.28 (1H, br), 11.68 (1H, s).
MS (ESI) m/z: 426 $(M+H)^+$.

[Referential Example 233]

N-[(3R*, 4R*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-fluoroindole-2-carboxamide hydrochloride:

[0585]

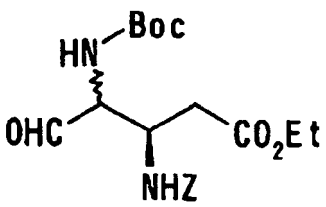


[0586] The title compound was obtained by treating the compound obtained in Referential Example 232 in a similar manner to Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 2.25-2.31 (1H, m), 2.47 (1H, br), 3.30 (1H, br), 3.49-3.53(2H,m), 3.60-3.66 (1H, m), 3.78 (1H, br), 4.79 (1H, br), 7.01-7.05 (1H, m), 7.21 (1H, s), 7.38 (1H, d, J=9.0Hz), 7.44 (1H, dd, J=8.8, 4.4Hz), 8.40(2H,br), 8.56 (1H, br), 11.81 (1H, s).
MS (ESI) m/z: 326 $(M+H)^+$.

[Referential Example 234]

Ethyl (3R)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]-5-oxovalerate:

[0587]

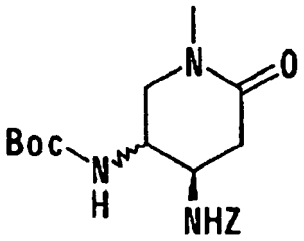


[0588] Sulfur trioxide-pyridine comples (1.5 g) was gradually added to a mixed solvent composed of the (3R,4S)-compound (high-polar compound) (0.5 g) obtained in Referential Example 168, dimethyl sulfoxide (6.8 ml) and triethylamine (2.6 ml), and the mixture was stirred for 20 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The resultant organic layer was washed with a saturated aqueous solution of ammonium chloride, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (0.51 g).
^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.4Hz), 1.44 (9H, s), 2.51-2.70(2H,m), 4.01-4.23(2H,m), 4.45-4.67 (1H, m), 5.00-5.23 (2H,s), 5.24-5.42 (1H, m), 7.23-7.43 (5H, m), 9.63(0.5H,s), 9.67 (0.5H, s).

[Referential Example 235]

Benzyl (4R)-5-[(tert-butoxycarbonyl)amino]-1-methyl-2-oxopiperidin-4-ylcarbamate:

[0589]

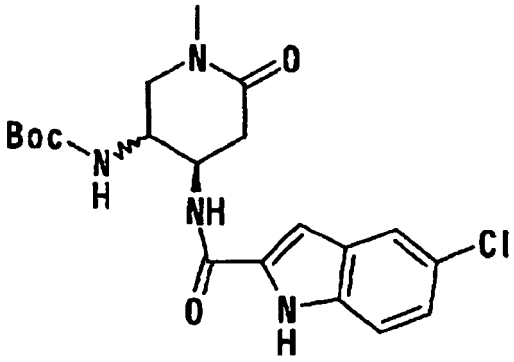


[0590] Acetic acid (0.27 ml) and 2 M methylamine (tetrahydrofuran solution, 1.0 ml) were successively added to a solution of the compound (0.51 g) obtained in Referential Example 234 in ethanol (10 ml) under ice cooling, and the mixture was stirred for 1 hour while the temperature of the system was gradually raised to room temperature. Sodium cyanoborohydride (0.15 g) was added to stir the mixture for 18 hours. The reaction mixture was diluted with chloroform and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was dissolved in toluene (20 ml). Triethylamine (2 ml) was added to this solution, and the mixture was heated under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 98:2) to obtain the title compound (0.28 g) .
^{1}H-NMR (DMSO-d_6) δ: 1.36 (3.6H, s), 1.38 (5.4H, s), 2.22-2.43 (1H, m), 2.44-2.61 (1H, m), 2.72 (1.2H.s), 2.80(1.8H.s), 3.10 (0.5H, dd, J=12.5, 8.3Hz), 3.21-3.30 (0.5H, m), 3.33-3.45 (1H, m), 3.56-3.82 (1H, m), 3.89-4.00 (1H, m), 4.94 (1H, d, J=8.1Hz), 5.00 (1.2H.s), 5.01 (0.8H, s), 6.89-7.02(0.5H,m), 7.23-7.44 (5.5H, m).

[Referential Example 236]

tert-Butyl (4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-methyl-6-oxopiperidin-3-ylcarbamate:

[0591]

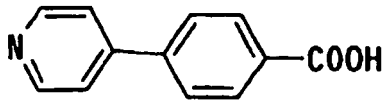


[0592] The title compound was obtained from the compound obtained in Referential Example 235 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 214.
^{1}H-NMR (DMSO-d_6) δ: 1.24 (5.4H, s), 1.35 (3.6H, s), 2.43-2.56(2H,m), 2.80 (3H, s), 3.10-3.20 (1H, m), 3.30-3.52 (1H, m), 3.83-3.91(0.4H,m), 4.02-4.10(0.6H,m), 4.20-4.31(0.6H,m), 4.43-4.54 (0.4H, m), 6.94 (0.6H, d, J=8.1Hz), 7.08 (1H, s), 7.16 (1H, dd, J=8.8, 2.0Hz), 7.42 (1H, d, J=8.8Hz), 7.69 (1H, d, J=2.0Hz), 8.30 (0.4H, s), 8.36(0.4H,d,J=7.3Hz), 8.43 (0.6H,d,J=8.3Hz), 11.75(0.6H,s), 11.78(0.4H,s).

[Referential Example 237]

4-(Pyridin-4-yl)benzoic acid hydrochloride:

[0593]

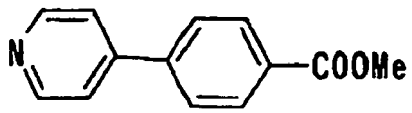


[0594] 4-Bromopyridine hydrochloride (11.7 g) and 4-carboxyphenylboric acid (10.0 g) were dissolved in a mixed solvent of toluene (250 ml) and water (250 ml), tetrakis(triphenylphosphine)palladium(0) (5.0 g) and anhydrous sodium carbonate (25.4 g) were successively added, and the mixture was heated under reflux at 120°C for 19 hours. After the reaction mixture was cooled to room temperature, ethyl acetate was added to the reaction mixture to extract it with water. Concentrated hydrochloric acid was added to the water layer to acidify it. The water layer was washed with ethyl acetate and then concentrated, and solids deposited were collected to obtain the title compound (8.37 g).
^{1}H-NMR (DMSO-d_6) δ: 8.11 (2H, d, J=8.8Hz), 8.14 (2H, dJ=8.8Hz), 8.35(2H,d,J=6.6Hz), 8.97(2H,d,J=6.6Hz).
MS (FAB) m/z: 200 $(M+H)^+$.

[Referential Example 238]

Methyl 4-(Pyridin-4-yl)benzoate:

[0595]

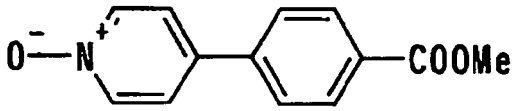


[0596] The compound (12.4 g) obtained in Referential Example 237 was dissolved in methanol (200 ml), concentrated sulfuric acid (5 ml) was added at room temperature, and the mixture was heated under reflux for 3 hours. After completion of the reaction, the solvent was distilled off, and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue to extract it with ethyl acetate. The extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and hexane was added to the residue to solidify it, thereby obtaining the title compound (9.86 g).
^{1}H-NMR ($CDCl_3$) δ: 3.96(3H,s), 7.54 (2H, d, J=5.9Hz), 7.71 (2H, dJ=8.3Hz), 8.16 (2H, d, J=8.3Hz), 8.71 (2H, d, J=5.9Hz).

[Referential Example 239]

4-[4-(Methoxycarbonyl)phenyl]pyridine N-oxide:

[0597]



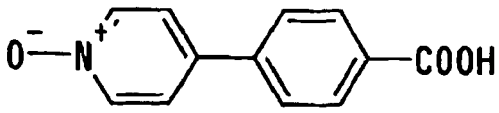
[0598] The compound (1.49 g) obtained in Referential Example 238 was dissolved in methylene chloride (30 ml), 70% m-chloroperbenzoic acid (3.46 g) was added, and the mixture was stirred at room temperature for 1 hour. An aqueous

solution of sodium sulfite was added to conduct liquid separation. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and then dried over anhydrous sodium sulfate. The solvent was distilled off to obtain the title compound (1.33 g).
^{1}H-NMR (DMSO) δ: 3.88(3H,s), 7.86(2H,d,J=7.2Hz), 7.94 (2H, d, J=8.3Hz), 8.05 (2H, d, J=8.3Hz), 8.30 (2H, d, J=7.2Hz).
MS (FAB) m/z: 230 $(M+H)^+$.

[Referential Example 240]

4-(4-Carboxyphenyl)pyridine N-oxide:

[0599]

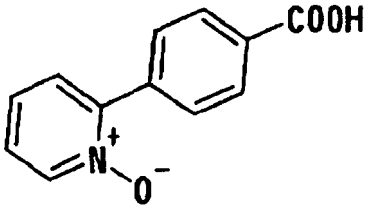


[0600] The compound (802 mg) obtained in Referential Example 239 was dissolved in dioxane (20 ml), a 1N aqueous solution (5 ml) of sodium hydroxide was added, and the mixture was refluxed for 1 hour and then stirred at room temperature for 2 hours. 1N Hydrochloric acid (5 ml) was added to neutralize it. Further, water (5 ml) was added, and precipitate formed was collected by filtration to obtain the title compound (627 mg).
^{1}H-NMR (DMSO) δ: 7.85(2H,d,J=7.2Hz), 7.91 (2H, d, J=8.3Hz), 8.03(2H,d,J=8.3Hz), 8.30(2H,d,J=7.2Hz).

[Referential Example 241]

2-(4-Carboxyphenyl)-1-pyridine N-oxide:

[0601]

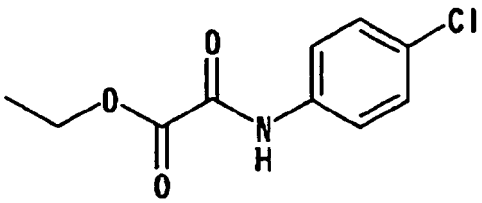


[0602] The title compound was obtained from 2-bromopyridine in similar manners to Referential Examples 237, 238, 239 and 240.
^{1}H-NMR (DMSO-d_6) δ: 7.41-7.45(2H,m), 7.65-7.69 (1H, m), 7.94 (2H, d, J=8.3Hz), 8.02 (2H, d, J=8.3Hz), 8.34-8.38 (1H, m), 13.09 (1H, s).
MS (FAB) m/z: 216 $(M+H)^+$.

[Referential Example 242]

Ethyl 2-(4-chloroanilino)-2-oxoacetate:

[0603]



[0604] Triethylamine (1.52 ml) and ethyl chlorooxoacetate (1.11 ml) were successively added to a solution of 4-chlo-

roaniline (1.16 g) in methylene chloride (26 ml), and the mixture was stirred at room temperature for 14 hours. After a saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct liquid separation, the resultant organic layer was successively washed with a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, hexane was added to the residue to deposit crystals, and the crystals were collected by filtration and dried to obtain the title compound (1.89 g).

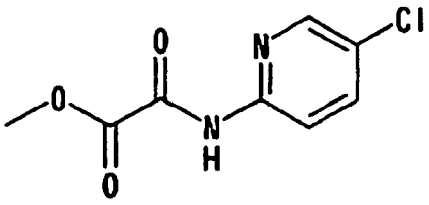
^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.1Hz), 4.42 (2H, q, J=7.1Hz), 7.34 (2H, d, J=8.8Hz), 7.60 (2H, d, J=8.8Hz), 8.86 (1H, br.s).

MS (ESI) m/z: 228 $(M+H)^+$.

[Referential Example 243]

Methyl 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate:

[0605]



[0606] 2-Amino-5-chloropyridine (1.16 g) and triethylamine (1.51 ml) were dissolved in methylene chloride (26 ml), ethyl chlorooxoacetate (1.10 ml) was added to the solution under ice cooling, and the mixture was stirred at room temperature for 14 hours. After a saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct liquid separation, the resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 3:1). The thus-obtained pale yellow solids were dissolved in methanol (20 ml), and the solution was stirred at 50°C for 11 hours. The reaction mixture was concentrated under reduced pressure, and crystals deposited were collected by filtration and dried to obtain the title compound (0.43 g).

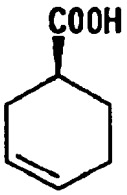
^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.73 (1H, dd, J=8.8, 2.2Hz), 8.24 (1H, d, J=8.8Hz), 8.31 (1H, d, J=2.2Hz), 9.39 (1H, br.s).

MS (ESI) m/z: 215 $(M+H)^+$.

[Referential Example 244]

(1S)-3-Cyclohexene-1-carboxylic acid:

[0607]



[0608] The (R)-(+)-α-methylbenzylamine salt (J. Am. Chem. Soc., Vol. 100, pp. 5199-5203, 1978) (95.0 g) of (1S)-3-cyclohexene-1-carboxylic acid was dissolved in a mixture of ethyl acetate (1.6 1) and 2N hydrochloric acid (1.6 1). After an organic layer was taken out, a water layer was extracted with ethyl acetate (500 ml x 2 times). The resultant organic layers were combined and washed with saturated aqueous solution of sodium chloride (300 ml x 2 times) to take out an organic layer. After a water layer was extracted with ethyl acetate (200 ml), the resultant organic layer was washed with saturated aqueous solution of sodium chloride (100 ml). All organic layers were combined and dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain the title compound (48.3 g).

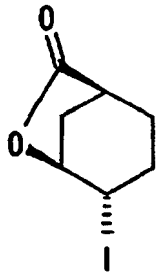
$[\alpha]^{25}_D$ = -104° (c = 1, chloroform).

^{1}H-NMR ($CDCl_3$) δ: 1.66-1.77 (1H, m), 2.00-2.20(3H,m), 2.20-2.38(2H,m), 2.57-2.65 (1H, m), 5.65-5.75(2H,m).

[Referential Example 245]

(1S,4S,5S)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one:

[0609]

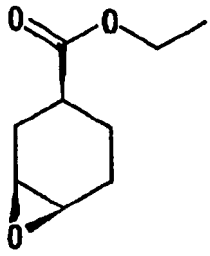


[0610] Iodine (125.4 g) was added to a mixture of the compound (48.0 g) obtained in Referential Example 244, methylene chloride (580 ml), potassium iodide (82. 1 g), sodium hydrogencarbonate (42.0 g) and water (530 ml) at an internal temperature of 5°C, and the resultant mixture was stirred at room temperature for 3 hours. After a 1N aqueous solution (800 ml) of sodium thiosulfate was added to the reaction mixture, the resultant mixture was extracted with methylene chloride (1 L, 500 ml). The resultant organic layer was washed with an aqueous solution (300 ml) of sodium hydrogencarbonate, water (500 ml) and saturated aqueous solution of sodium chloride (300 ml), dried over anhydrous magnesium sulfate and then concentrated. Crystals deposited were collected by filtration, washed with hexane and then dried to obtain the title compound (89.5 g).
Mp. 130-131°C
$[\alpha]^{25}_{D}$ = -41° (c = 1, chloroform).
^{1}H-NMR ($CDCl_3$) δ: 1.78-1.96 (2H, m),
2.12 (1H, dd, J=16.5Hz, 5.2Hz), 2.35-2.50(2H,m), 2.65-2.70 (1H, m), 2.80 (1H, d, J=12.2Hz), 4.45-4.55 (1H, m), 4.77-4.87 (1H, m).

[Referential Example 246]

Ethyl (1S,3S,6R)-7-oxabicyclo[4.1.0]heptane-3-carboxylate:

[0611]

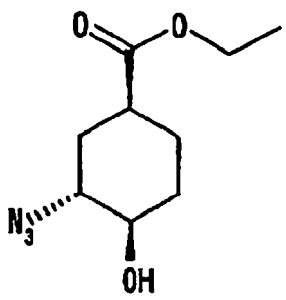


[0612] A 2N aqueous solution (213 ml) of sodium hydroxide was added to an ethanol (810 ml) suspension of the compound (89.3 g) obtained in Referential Example 245, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure on a hot bath of 35°C, and water (500 ml) was added to the resultant oil to conduct extraction with methylene chloride (500 ml and 300 ml). The extract was washed with water (300 ml) and dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resultant oil was purified by column chromatography on silica gel (hexane:ethyl acetate = 85:15) to obtain the title compound (41.3 g).
$[\alpha]^{25}_{D}$ = -58° (c = 1, chloroform).
^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.2Hz), 1.50-1.70 (2H, m), 1.71-1.82 (1H, m), 2.08-2.28(4H,m), 3.16(2H,s), 4.12 (2H, q, J=7.2Hz).

[Referential Example 247]

Ethyl (1S,3R,4R)-3-azido-4-hydroxycyclohexanecarboxylate:

[0613]

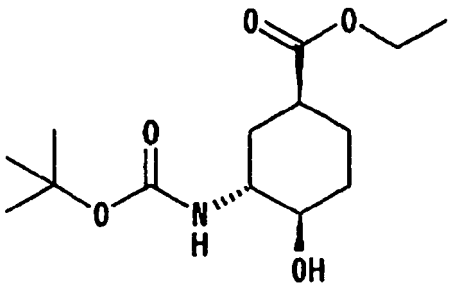


[0614] A mixture of the compound (41.0 g) obtained in Referential Example 246, N,N-dimethylformamide (300 ml), ammonium chloride (19.3 g) and sodium azide (23.5 g) was stirred at 76°C for 13 hours. After insoluble matter was taken out by filtration, the filtrate was concentrated under reduced pressure without solidifying, and the product previously taken out by filtration was added to the residue, and the mixture was dissolved in water (500 ml). The solution was extracted with ethyl acetate (500 ml and 300 ml), and the extract was washed with water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then concentrated to obtain the title compound (51.5 g).
$[\alpha]^{25}_{D}$ = +8° (c = 1, chloroform).
^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.1Hz), 1.37-1.64(3H,m), 1.86-1.95 (1H, m), 2.04-2.16 (1H, m), 2.32-2.41 (1H, m), 2.44 (1H, br.s), 2.68-2.78 (1H, m), 3.45-3.60(2H,m), 4.17 (2H, q, J=7.1Hz).

[Referential Example 248]

Ethyl (1S,3R,4R)-3-[(tert-butoxycarbonyl)amino]-4-hydroxycyclohexanecarboxylate:

[0615]

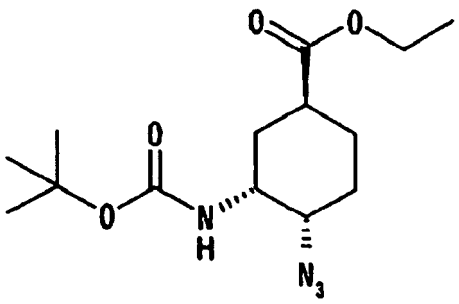


[0616] A mixture of the compound (51.2 g) obtained in Referential Example 247, di-tert-butyl dicarbonate (68.1 g), 5% palladium on carbon (5.0 g) and ethyl acetate (1000 ml) was stirred overnight at room temperature under a hydrogen pressure (7 kg/cm^2). An oil obtained by filtering the reaction mixture and concentrating the filtrate was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1 → 3:1). The purified product was crystallized from hexane to obtain the title compound (46.9 g). The mother liquor was additionally purified by column chromatography on silica gel (chloroform:methanol = 100:1) to obtain the title compound (6.74 g).
$[\alpha]^{25}_{D}$ = +25° (c = 1, chloroform).
^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.1Hz), 1.38-1.57 (3H, m), 1.45(9H,s), 1.86-1.95 (1H, m), 2.05-2.17 (1H, m), 2.29-2.39 (1H, m), 2.61-2.68 (1H, m), 3.34 (1H, br.s), 3.39-3.48 (1H, m), 3.53-3.64 (1H, m), 4.10-4.24(2H,m), 4.54 (1H, br.s).

[Referential Example 249]

Ethyl (1S,3R,4S)-4-azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate:

[0617]

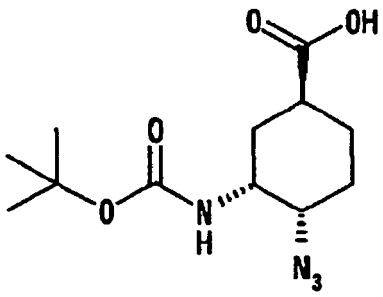


[0618] Methanesulfonyl chloride (42 ml) was added dropwise to a solution containing the compound (53.5 g) obtained in Referential Example 248, methylene chloride (500 ml) and triethylamine (130 ml) over 20 minutes at -10°C to -15°C. The mixture was heated to room temperature over 2 hours and stirred for 2 hours. 0.5N Hydrochloric acid (800 ml) was added dropwise to the reaction mixture at 0°C to acidify it, and extraction was conducted with methylene chloride (500 ml and 300 ml). The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The crystals thus obtained were dissolved in N,N-dimethylformamide (335 ml), sodium azide (60.5 g) was added, and the mixture was stirred at 67°C to 75°C for 16 hours. After the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to distill off 250 ml of the solvent. The residue was combined with the product previously taken out by filtration, and the mixture was dissolved in water (500 ml). The solution was extracted with ethyl acetate (1 L and 300 ml), and the extract was washed with saturated aqueous solution of sodium chloride (400 ml and 200 ml), dried over anhydrous magnesium sulfate and then concentrated. The crystals thus obtained were purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compounds (18.4 g).
$[\alpha]^{25}_{D}$ = +62° (c = 1, chloroform).
^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1Hz), 1.35-2.00 (15H, s), 2.60-2.68 (1H, m), 3.80-3.96(2H,m), 4.15 (2H, q, J=7.1Hz), 4.61 (1H, br.s).

[Referential Example 250]

(1S,3R,4S)-4-Azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylic acid:

[0619]

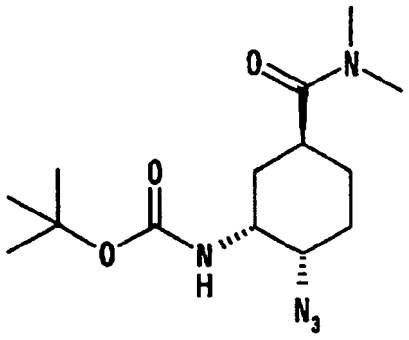


[0620] Lithium hydroxide (102 mg) and water (5 ml) were added to a solution of the compound (1.0 g) obtained in Referential Example 249 in tetrahydrofuran (25 ml). After stirring for 17 hours, lithium hydroxide (50 mg) was additionally added to stir the mixture for 4 hours. 1N Hydrochloric acid (6.3 ml) was added to the reaction mixture to conduct extraction with ethyl acetate. After the resultant organic layer was dried, the solvent was distilled off under reduced pressure to obtain the title compound (980 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.30-2.20(6H,m), 1.45(9H,s), 2.70-2.80 (1H, m), 3.94(2H,br.s), 4.73 (1H, br.s).

[Referential Example 251]

tert-Butyl (1R,2S,5S)-2-azido-5-[(dimethylamino)carbonyl] cyclohexylcarbamate:

[0621]

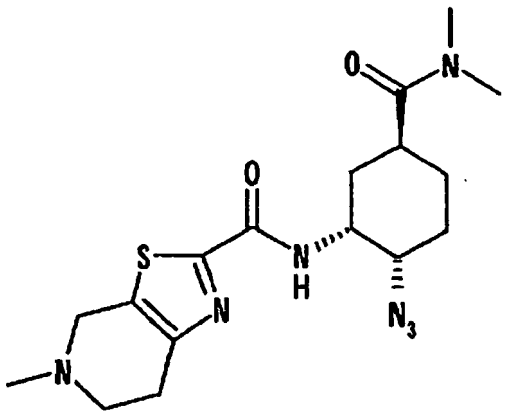


[0622] The compound (4.77 g) obtained in Referential Example 250 was dissolved in methylene chloride (150 ml), to which dimethylamine hydrochloride (3.26 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.60 g), 1-hydroxybenzotriazole monohydrate (3.24 g) and N-methylmorpholine (8.09 g) were added, and the mixture was stirred at room temperature for 18 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct liquid separation. The resultant organic layer was then dried, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methanol:methylene chloride = 1:50) to obtain the title compound (4.90 g).
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.90(4H,m), 1.45(9H,s), 1.97-2.18(2H,m), 2.75-2.85(1H,m), 2.92(3H,s), 3.02(3H,s), 3.68-3.80 (1H,m), 4.05-4.20(1H,m), 4.55-4.75(1H,m).

[Referential Example 252]

N-{(1R,2S,5S)-2-Azido-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

[0623]



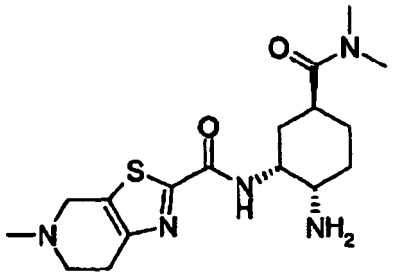
[0624] The compound (9.13 g) obtained in Referential Example 251 was dissolved in methylene chloride (100 ml), and an ethanol solution (100 ml) of hydrochloric acid was added to stir the mixture at room temperature for 1 minute. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in N,N-dimethylformamide (200 ml). To the solution were added the compound (7.75 g) obtained in Referential Example 10, 1-hydroxybenzotriazole monohydrate (4.47 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.2 g) and triethylamine (2.02 ml), and the mixture was stirred overnight at room temperature. The compound (2.38 g) obtained in Referential Example 10 and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.60 g) were additionally added to stir the mixture for 3 days. The reaction mixture was concentrated under reduced pressure, and methylene

chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was then purified by column chromatagraphy on silica gel (methylene chloride: methanol = 47:3) to obtain the title compound (7.38 g).
^{1}H-NMR ($CDCl_3$) δ: 1.72-1.97(4H,m), 2.10-2.27(2H,m), 2.51(3H,s), 2.77-3.05(11H,m), 3.68(1H,d,J=15.4Hz), 3.74(1H, d,J=15.4Hz), 3.86-3.93(1H,m), 4.54-4.60(1H,m), 7.25(1H,d,J=7.6Hz).

[Referential Example 253]

N-{(1R,2S,5S)-2-Amino-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

[0625]

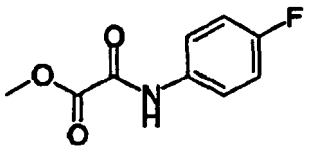


[0626] 10% Palladium on carbon (6.0 g) was added to a solution of the compound (9.0 g) obtained in Referential Example 252 in methanol (300 ml), and the mixture was vigorously stirred at room temperature for 11 hours under a hydrogen pressure of 4 atm. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain the title compound (7.67 g).
^{1}H-NMR ($CDCl_3$) δ: 1.42-1.54(1H,m), 1.66-1.89(5H,m), 2.30-2.40(1H,m), 2.51(3H,s), 2.68-3.05(6H,m), 2.92(3H,s), 3.00 (3H,s), 3.10-3.18(1H,m), 3.65-3.77(2H,m), 4.21-4.28(1H,m), 7.52(1H,d,J=6.1Hz).

[Referential Example 254]

Methyl 2-(4-fluoroanilino)-2-oxoacetate:

[0627]

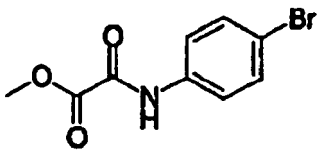


[0628] The title compound was obtained from 4-fluoroaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 7.00-7.14(2H,m), 7.55-7.68(2H,m), 8.85(1H,br.s).
MS (ESI) m/z: 198$(M+H)^+$.

[Referential Example 255]

Methyl 2-(4-bromoanilino)-2-oxoacetate:

[0629]

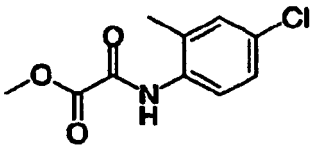


[0630] The title compound was obtained from 4-bromoaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 7.49 (2H, d, J=9.0Hz), 7.55 (2H, d, J=9.0Hz), 8.85 (1H, br.s).
MS (FAB)m/z: 258 M^+.

[Referential Example 256]

Methyl 2-(4-chloro-2-methylanilino)-2-oxoacetate:

[0631]

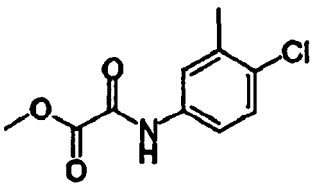


[0632] The title compound was obtained from 4-chloro-2-methylaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 2.31(3H,s), 3.99(3H,s), 7.15-7.30(2H,m), 7.98 (1H, d, J=8.8Hz), 8.77(1H,br).
MS (FAB) m/z: 228$(M+H)^+$.

[Referential Example 257]

Methyl 2-[(4-chloro-3-methylanilino)-2-oxoacetate:

[0633]

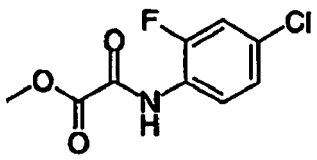


[0634] The title compound was obtained from 4-chloro-3-methylaniline and methyl chlorooxoacetate in a similar manner to Reference Example 242.
^{1}H-NMR($CDCl_3$)δ:2.39(3H,s), 3.98(3H,s), 7.33(1H,d,J=12.5Hz), 7.44(1H,dd,J=12.5,2.5Hz), 7.53(1H,d,J=2.5Hz), 8.81 (1H,br.s).
MS(ESI)m/z:228$(M+H)^+$.

[Referential Example 258]

Methyl 2-(4-chloro-2-fluoroanilino)-2-oxoacetate:

[0635]

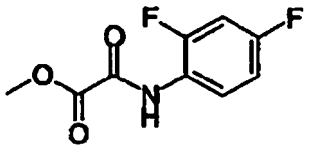


[0636] The title compound was obtained from 4-chloro-2-fluoroaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.15-7.24(2H,m), 8.33(1H,t,J=8.4Hz), 9.05(1H,br.s).
MS (ESI) m/z: 232$(M+H)^+$.

[Referential Example 259]

Methyl 2-(2,4-difluoroanilino)-2-oxoacetate:

[0637]

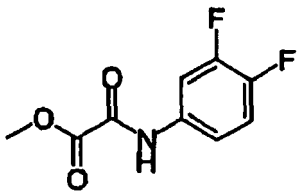


[0638] The title compound was obtained from 2,4-difluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 6.87-7.00(2H,m), 8.29-8.38(1H,m), 8.99(1H,br.s).
MS (ESI) m/z: 215 M^+.

[Referential Example 260]

Methyl 2-(3,4-difluoroanilino)-2-oxoacetate:

[0639]

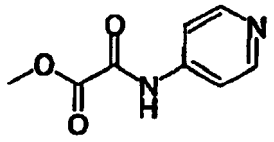


[0640] The title compound was obtained from 3,4-difluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 7.10-7.28(2H,m), 7.67-7.78(1H,m), 8.83(1H,br.s).
MS (ESI) m/z: 215 M^+.

[Referential Example 261]

Methyl 2-oxo-2-(pyridin-4-ylamino)acetate:

[0641]

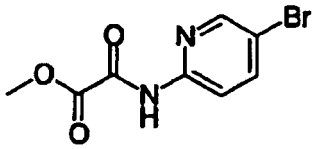


[0642] The title compound was obtained from 4-aminopyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.58(2H,dd,J=4.8, 1.6Hz), 8.60(2H,dd,J=4.8, 1.6Hz), 9.04(1H,br.s).
MS (ESI) m/z: 181$(M+H)^+$.

[Referential Example 262]

Methyl 2-[(5-bromopyridin-2-yl)amino]-2-oxoacetate:

[0643]

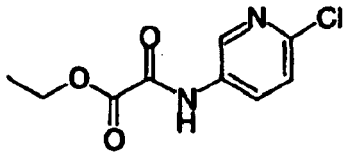


[0644] The title compound was obtained from 2-amino-5-bromopyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.87(1H,dd,J=8.8, 2.4Hz), 8.19(1H,d,J=8.8Hz), 8.41(1H,d,J=2.4Hz), 9.38(1H,br.s).
MS (FAB) m/z: 259 M^+.

[Referential Example 263]

Ethyl 2-[(6-chloropyridin-3-yl)amino]-2-oxoacetate:

[0645]

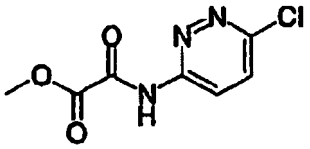


[0646] 5-Amino-2-chloropyridine (386 mg) was dissolved in N,N-dimethylformamide (8 ml), and potassium 2-ethoxy-2-oxoacetate (469 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (863 mg) and 1-hydroxybenzotriazole monohydrate (203 mg) were added to stir the mixture at room temperature for 2 days. After the solvent was distilled off under reduced pressure, methylene chloride and saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation, the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, the residue was purified by flash column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1) to obtain residue (200 mg) containing the title compound.
^{1}H-NMR ($CDCl_3$) δ: 1.43(3H,t,J=7.2Hz), 4.44(2H,q,J=7.2Hz), 7.36(1H,d,J=8.7Hz), 8.24(1H,dd,J=8.7, 2.7Hz), 8.55(1H, d,J=2.7Hz), 9.03(1H,br.s).

[Referential Example 264]

Methyl 2-[(6-chloropyridazin-3-yl)amino]-2-oxoacetate:

[0647]

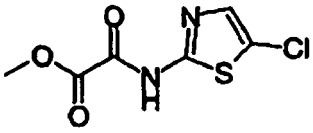


[0648] 3-Amino-6-chloropyridazine (516 mg) was dissolved in pyridine (26 ml), and triethylamine (665 μl) and methyl chlorooxoacetate (441 μl) were successively added under ice cooling to stir the mixture at room temperature for 14 hours. After water was added to the reaction mixture to conduct liquid separation, the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (748 mg).
^{1}H-NMR ($CDCl_3$) δ: 4.03(3H,s), 7.59(1H,d,J=9.3Hz), 8.52(1H,d,J=9.3Hz), 9.88(1H,br.s).
MS (FAB) m/z: 215M^+.

[Referential Example 265]

Methyl 2-[(5-chlorothiazol-2-yl)amino]-2-oxoacetate:

[0649]

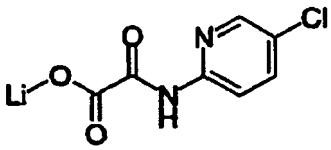


[0650] The title compound was obtained from 2-amino-5-chlorothiazole and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 4.02(3H,s), 7.48(1H,s), 11.03(1H,br.s).
MS (ESI) m/z: 221$(M+H)^+$.

[Referential Example 266]

Lithium 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate:

[0651]

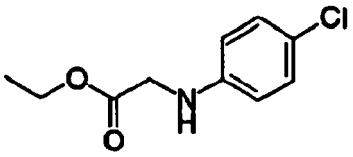


[0652] Water (5.0 ml) and lithium hydroxide (128 mg) were added to a solution of the compound (1.12 g) obtained in Referential Example 243 in tetrahydrofuran (20 ml) at room temperature, and the mixture was stirred for 5 hours. The solvent was distilled off under reduced pressure, hexane (30 ml) was added to the resultant white solids, and the mixture was stirred for 30 minutes. The solides were collected by filtration and then dried to obtain the title compound (1.02 g).
^{1}H-NMR (DMSO-d_6) δ: 7.90(1H,dd,J=8.9, 2.6Hz), 8.12(1H,d,J=8.9Hz), 8.34(1H,d,J=2.6Hz), 10.18(1H,s).

[Referential Example 267]

Ethyl 2-(4-chloroanilino)acetate:

[0653]

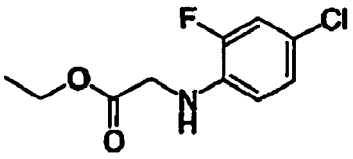


[0654] 4-Chloroaniline (2.0 g) was dissolved in acetonitrile (20 ml), and ethyl bromoacetate (2.1 g) and potassium carbonate (2.2 g) were added to stir the mixture at 60°C for 2 days. The reaction mixture was filtered through Celite pad, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (hexane:chloroform = 2:1) to obtain the title compound (2.3 g).
^{1}H-NMR ($CDCl_3$) δ: 1.30(3H,t,J=7.3Hz), 3.86(2H,s), 4.24(2H,q,J=7.3Hz), 4.26-4.35(1H,m), 6.53(2H,dd,J=6.6,2.2Hz), 7.14(2H,dd,J=6.6,2.2Hz).

[Referential Example 268]

Ethyl 2-(4-chloro-2-fluoroanilino)acetate:

[0655]

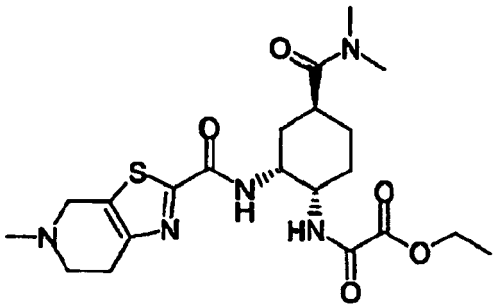


[0656] The title compound was obtained from 4-chloro-2-fluoroaniline and ethyl bromoacetate in a similar manner to the process described in Referential Example 267.
^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H,t,J=7.3Hz), 3.91(2H,s), 4.22(2H,q,J=7.3Hz), 4.42-4.51(1H,m), 6.49(1H,t,J=8.8Hz), 6.98 (1H,dt,J=8.8,2.5Hz), 7.01(1H,dd,J=11.3,2.5Hz).

[Referential Example 269]

Ethyl 2-[((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl] amino}cyclohexyl)amino]-2-oxoacetate:

[0657]



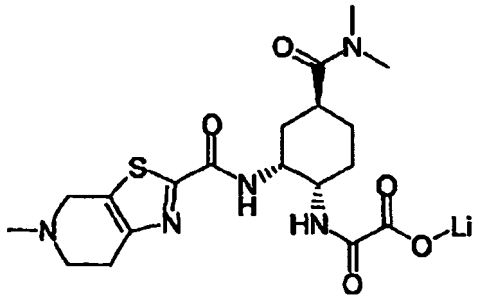
[0658] The compound (1.5 g) obtained in Referential Example 253 was dissolved in N,N-dimethylformamide (15 ml), and potassium 2-ethoxy-2-oxoacetate (962 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.18 g) and 1-hydroxybenzotriazole monohydrate (227 mg) were added to stir the mixture at room temperature for 14 hours. After the solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by flash column chromatagraphy on silica gel (methylene chloride:methanol = 47:3) to obtain the title compound (1.13 g).
^{1}H-NMR ($CDCl_3$) δ: 1.37(3H,t,J=7.1Hz), 1.55-2.15(6H,m), 2.52(3H,s), 2.77-2.89(3H,m), 2.94(5H,br.s), 3.06(3H,s), 3.71

(1H,d,J=15.5Hz), 3.73(1H,d,J=15.5Hz), 4.06-4.13(1H,m), 4.32(2H,q,J=7.1Hz), 4.60-4.63(1H,m), 7.39(1H,d,J=8.3Hz), 7.83(1H,d,J=7.6Hz).
MS (ESI) m/z: 466$(M+H)^+$.

[Referential Example 270]

Lithium 2-[((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino}cyclohexyl)amino]-2-oxoacetate:

[0659]

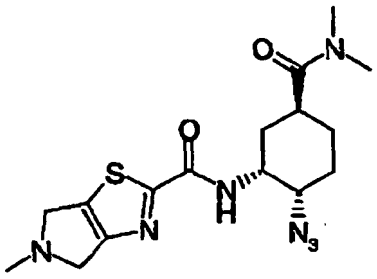


[0660] The compound (1.13 g) obtained in Referential Example 269 was dissolved in tetrahydrofuran (20 ml), methanol (10 ml) and water (10 ml), and lithium hydroxide (58 mg) was added to stir the mixture at room temperature for 30 minutes. The solvent was distilled off under reduced pressure to obtain the title compound (1.10 g).
^{1}H-NMR (DMSO-d_6) δ: 1.41-1.73(4H,m), 2.00-2.07(2H,m), 2.39(3H,s), 2.74-2.99(11H,m), 3.67(2H,s), 3.82-3.88(1H,m), 4.28-4.30(1H,m), 8.66-8.70(2H,m).

[Referential Example 271]

N-{(1R,2S,5S)-2-Azido-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazole-2-carboxamide:

[0661]

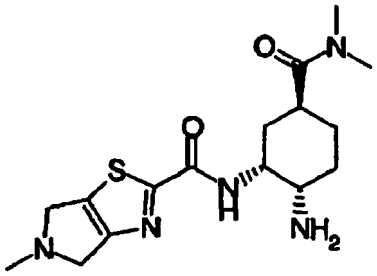


[0662] The title compound was obtained from the compound obtained in Referential Example 293 and the compound obtained in Referential Example 251 in a similar manner to the process described in Referential Example 252.
^{1}H-NMR ($CDCl_3$) δ: 1.73-1.87(4H,m), 2.11-2.20(2H,m), 2.67(3H,s), 2.85-2.90(1H,m), 2.93(3H,s), 3.00(3H,s), 3.90-4.10(5H,m), 4.57-4.62(1H,m), 7.20-7.22(1H,m).
MS (FAB) m/z: 378$(M+H)^+$.

[Referential Example 272]

N-{(1R,2S,5S)-2-Amino-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazole-2-carboxamide:

[0663]

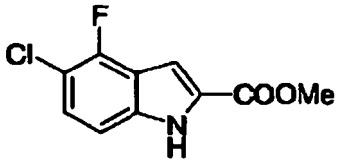


[0664] The title compound was obtained from the compound obtained in Referential Example 271 in a similar manner to the process described in Referential Example 253.
^{1}H-NMR ($CDCl_3$) δ: 1.67-1.97(6H,m), 2.36-2.40(1H,m), 2.67(3H,s), 2.92(3H,s), 3.00(3H,s), 3.07-3.18(1H,m), 3.92-3.95 (2H,m), 4.02-4.06(2H,m), 4.23-4.26(1H,m), 7.50-7.52(1H,m).

[Referential Example 273]

Methyl 5-chloro-4-fluoroindole-2-carboxylate:

[0665]

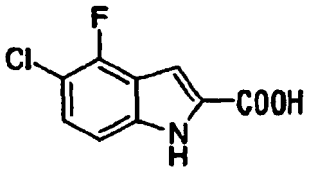


[0666] Ethanol (100 ml) was added to sodium hydride (content: 60%, 4.7 g) at 0°C under an argon atmosphere, and the mixture was stirred for 10 minutes. After 2-nitropropane (11 ml) was added to the reaction mixture to stir the mixture for 10 minutes, 1-(bromomethyl)-3-chloro-2-fluorobenzene (10 g) was added to stir the resultant mixture at room temperature for 3.5 hours. Precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was partitioned in diethyl ether and water, and an organic layer was successively washed with a 1N aqueous solution of sodium hydroxide, water and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 3:7) to obtain crude 3-chloro-2-fluorobenzaldehyde (5.5 g) as a pale yellow oil. Methanol (20 ml) was added to sodium hydride (content: 60%, 1.6 g) at 0°C under an argon atmosphere, and the mixture was stirred for 10 minutes. The reaction mixture was cooled to -20°C, and the crude 3-chloro-2-fluorobenzaldehyde (5.5 g) and a solution of methyl 2-azidoacetate (5.0 g) in methanol (10 ml) were added within 20 minutes. The temperature of the reaction mixture was raised to 0°C , and after the mixture was stirred for 2.5 hours, water (40 ml) was added thereto. The reaction mixture was concentrated under reduced pressure, the residue was extracted with a mixed solvent of methylene chloride and ethyl acetate. The extract was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatagraphy on silica gel (toluene:hexane = 3:17) to obtain crude methyl 2-azido-3-[(3-chloro-2-fluoro)phenyl]acrylate (2.6 g). This product was dissolved in xylene (50 ml), and the solution was stirred at 130°C to 140°C for 3 hours. The reaction mixture was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (methylene chloride) and then crystallized from diethyl ether-hexane to obtain the title compound (440 mg).
^{1}H-NMR (DMSO-d_6) δ: 4.08(3H,s), 7.20(1H,s), 7.31-7.38(2H,m).
MS (FAB) m/z: 228$(M+H)^+$.

[Referential Example 274]

5-Chloro-4-fluoroindole-2-carboxylic acid:

[0667]

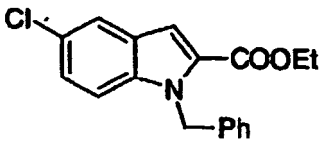


[0668] The compound (440 mg) obtained in Referential Example 273 was dissolved in tetrahydrofuran (10 ml), an aqueous solution (5 ml) of lithium hydroxide (160 mg) was added, and the mixture was stirred at room temperature for 3 hours. After an aqueous solution (5 ml) of lithium hydroxide (240 mg) was additionally added to the reaction mixture, and the mixture was stirred for additional 1 hour, the reaction mixture was concentrated under reduced pressure. The residue was neutralized with 1N hydrochloric acid and extracted 3 times with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (390 mg).
^{1}H-NMR (DMSO-d_6) δ: 6.79(1H,s), 7.16-7.26(2H,m).
MS (FAB) m/z: 214$(M+H)^+$.

[Referential Example 275]

Ethyl 1-benzyl-5-chloroindole-2-carboxylate:

[0669]

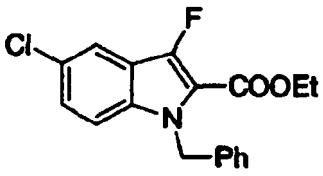


[0670] Ethyl 5-chloroindole-2-carboxylate (1.4 g) was dissolved in N,N-dimethylformamide (30 ml), and potassium carbonate (2.9 g) and benzyl chloride (2.4 ml) were added. The mixture was heated and stirred for 1.5 hours on a hot bath controlled to 100°C. The reaction mixture was concentrated under reduced pressure, and the residue was poured into ice water and extracted with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 1:19) and crystallized from diethyl ether-hexane to obtain the title compound (1.6 g).
^{1}H-NMR ($CDCl_3$) δ: 1.36(3H,t,J=7.1Hz), 4.33(2H,q,J=7.1Hz), 5.83(2H,s), 7.00-7.02(2H,d), 7.20-7.38(6H,m), 7.67(1H,d, J=1.7Hz).

[Referential Example 276]

Ethyl 1-benzyl-5-chloro-3-fluoroindole-2-carboxylate:

[0671]



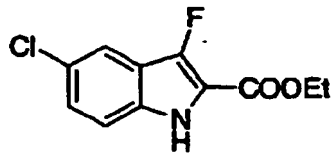
[0672] 1-Fluoro-2,6-dichloropyridinium triflate (4.4 g) was added to a methylene chloride solution (30 ml) of the compound (2.2 g) obtained in Referential Example 275, and the mixtrue was heated under reflux for 3 days. The reaction mixture was partitioned in ethyl acetate and water, and a water layer was extracted with ethyl acetate. The resultant organic layers were combined, successively washed with 1N hydrochloric acid, water and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 1:24) to obtain the crude title compound (2.8

g). A part of this product was purified by preparative thin-layer chromatography on silica gel to obtain the title compound. ^{1}H-NMR (DMSO-d_6) δ: 1.25(3H,t,J=7.1Hz), 4.29(2H,q,J=7.1Hz), 5.77(2H,s), 6.97-6.99(2H,m), 7.18-7.28(3H,m), 7.39 (1H,dd,J=9.0,2.1Hz), 7.69(1H,dd,J=9.0,2.1Hz), 7.78(1H,d,J=2.1Hz).

[Referential Example 277]

Ethyl 5-chloro-3-fluoroindole-2-carboxylate:

[0673]

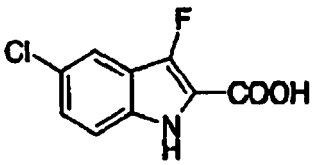


[0674] The crude compound (1.4 g) obtained in Referential Example 276 was dissolved in anisole (30 ml), and aluminum chloride (2.9 g) was added portionwise to the solution under ice cooling. The reaction mixture was stirred at room temperature for 30 minutes, and aluminum chloride (2.9 g) was additionally added to stir the mixture for 18 hours. Aluminum chloride (8.0 g) was added to the reaction mixture, and the mixture was stirred for 5 hours, to which water was added. The reaction mixture was extracted with ethyl acetate, the resultant organic layers were combined, successively washed with saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride) to obtain the title compound (470 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.43(3H,t,J=7.2Hz), 4.45(2H,q,J=7.2Hz), 7.25-7.31(2H,m), 7.66(1H,d,J=0.73Hz), 8.53(1H,br.s). MS (FAB) m/z: 242$(M+H)^+$.

[Referential Example 278]

5-Chloro-3-fluoroindole-2-carboxylic acid:

[0675]

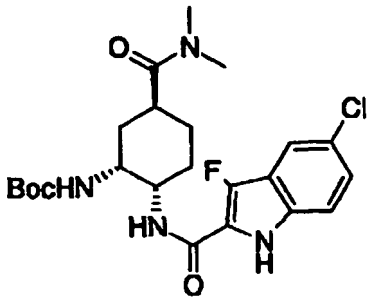


[0676] The title compound was obtained from the compound obtained in Referential Example 277 in a similar manner to Referential Example 274.
^{1}H-NMR (DMSO-d_6) δ: 7.31(1H,dd,J=8.8,1.9Hz), 7.42(1H,dd,J=8.8,1.9Hz), 7.70(1H,d,J=1.9Hz), 11.78(1H,s)
MS (FAB) m/z: 214$(M+H)^+$.

[Referential Example 279]

tert-Butyl (1R,2S,5S)-{[(5-chloro-3-fluoroindol-2-yl)-carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0677]

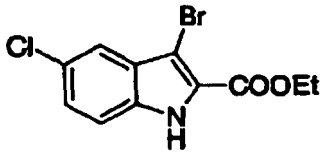


[0678] The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 278 in a similar manner to Referential Example 97.
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.73-2.11(6H,m), 2.65(1H,br.s), 2.96(3H,s), 3.07(3H,s), 4.20(1H,br.s), 4.28(1H,br.s), 4.78(1H,br),7.23-7.30(3H,m), 7.58(1H,s), 9.03(1H.s).
MS (FAB) m/z: 481$(M+H)^+$.

[Referential Example 280]

Ethyl 3-bromo-5-chloroindole-2-carboxylate:

[0679]

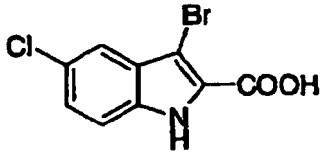


[0680] N-Bromosuccinimide (440 mg) was added to a solution of ethyl 5-chloroindole-2-carboxylate (500 mg) in N,N-dimethylformamide (10 ml). The reaction mixture was stirred at room temperature for 18 hours, and the solvent was distilled off under reduced pressure. The residue was partitioned in ethyl acetate and water, and a water layer was extracted with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off, the residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 1:9), and white powder thus obtained was washed with hexane to obtain the title compound (680 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.42-1.48(3H,m), 4.43-4.49(2H,m), 7.30-7.32(2H,m), 7.65(1H,d,J=0.74Hz), 9.11(1H,s)
MS (FAB) m/z: 303 $(M+H)^+$.

[Referential Example 281]

3-Bromo-5-chloroindole-2-carboxylic acid:

[0681]

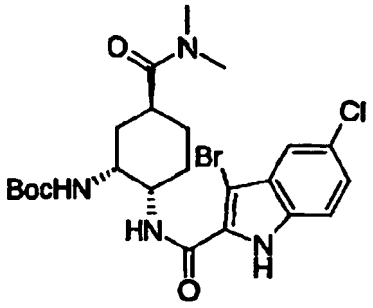


[0682] The title compound was obtained from the compound obtained in Referential Example 280 in a similar manner to Referential Example 274.
^{1}H-NMR (DMSO-d_6) δ: 7.35(1H,dd,J=8.8,2.0Hz), 7.48-7.53(2H,m), 12.33(1H,s)
MS (FAB) m/z: 275$(M+H)^+$.

[Referential Example 282]

tert-Butyl (1R,2S,5S)-2-{[(3-bromo-5-chloroindol-2-yl)-carbonyl]amino}-5-(dimethylamino)carbonyl]cyclohexylcarbamate:

[0683]

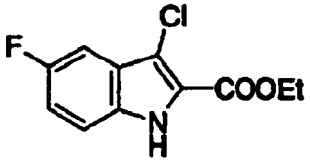


[0684] The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 281 in a similar manner to Referential Example 97.
^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 1.58-2.17(6H,m), 2.70(1H,br.s), 2.96(3H,s), 3.07(3H,s), 4.23-4.28(2H,m). 4.83(1H,br), 7.34-7.41(3H,m), 7.52(1H,s), 9.76(1H,s).
MS (FAB) m/z: 542$(M+H)^+$.

[Referential Example 283]

Ethyl 3-chloro-5-fluoroindole-2-carboxylate:

[0685]

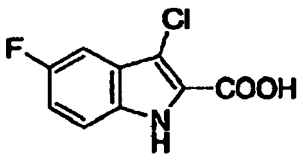


[0686] Ethyl 5-fluoroindole-2-carboxylate (2.0 g) was dissolved in N,N-dimethylformamide (20 ml), and a solution of N-chlorosuccinimide (1.4 g) in N,N-dimethylformamide (10 ml) was added dropwise to the solution under ice cooling. The mixture was stirred at room temperature for 18 hours, and the reaction mixture was diluted with ethyl acetate and successively washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The resultant organic layer was then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 5:1) to obtain the title compound (1.9 g).
^{1}H-NMR ($CDCl_3$) δ: 1.45(3H,t,J=7.4Hz), 4.46(2H,q,J=7.4Hz), 7.14(1H,dt,J=8.0,2.7Hz), 7.32-7.36(2H,m), 8.91(1H,br),

[Referential Example 284]

3-Chloro-5-fluoroindole-2-carboxylic acid:

[0687]

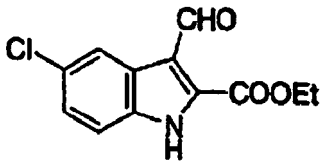


[0688] The title compound was obtained from the compound obtained in Referential Example 283 in a similar manner to Referential Example 274.
^{1}H-NMR (DMSO-d_6) δ: 7.20(1H,dt,J=8.8,2.4Hz), 7.31(1H,dd,J=8.8,2.4Hz), 7.46(1H,dd,J=8.8,4.4Hz), 12.12(1H,br).

[Referential Example 285]

Ethyl 5-chloro-3-formylindole-2-carboxylate:

[0689]

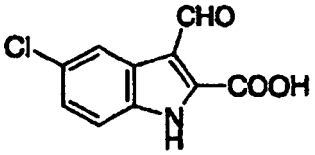


[0690] After phosphorus oxychloride (2.0 ml) was added to N-methylformanilide (2.9 g), and the mixture was stirred for 15 minutes, 1,2-dichloroethane (50 ml) and ethyl 5-chloroindole-2-carboxylate (4.0 g) were added, and the resultant mixture was heated under reflux for 1 hour. The reaction mixture was poured into an aqueous solution (28 ml) of sodium acetate (14 g) under ice cooling. After stirring for 18 hours, insoluble matter was collected by filtration. This product was successively washed with water and diethyl ether to obtain the title compound (3.56 g).
^{1}H-NMR (DMSO-d_6) δ: 1.38(3H,t,J=7.1Hz), 4.44(2H,q,J=7.1Hz), 7.38(1H,dd,J=8.0,1.4Hz), 7.56(1H,d,J=8.0Hz), 8.19 (1H,d,J=1.4Hz), 10.53(1H,s).

[Referential Example 286]

5-Chloro-3-formylindole-2-carboxylic acid:

[0691]

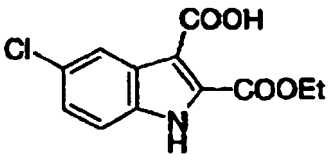


[0692] The compound (1.0 g) obtained in Referential Example 285 was dissolved in ethanol (10 ml), and a 1N aqueous solution (10 ml) of sodium hydroxide was added dropwise to stir the mixture at 50°C for 2 hours. 1N Hydrochloric acid (11 ml) was added to the reaction mixture, the resultant mixture was stirred, and insoluble matter was collected by filtration to obtain the title compound (0.86 g).
^{1}H-NMR (DMSO-d_6) δ: 7.39(1H,d,J=8.0Hz), 7.55(1H,d,J=8.0Hz), 8.20(1H,s), 10.58(1H,s), 12.90(1H,br).

[Referential Example 287]

5-Chloro-2-ethoxycarbonylindole-3-carboxylic acid:

[0693]



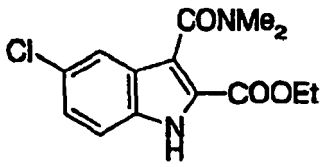
[0694] The compound (1.5 g) obtained in Referential Example 286 and sulfamic acid (1.7 g) were dissolved in tert-bu-

tanol (30 ml)-water (30 ml), and sodium chlorite (1.6 g) was added to stir the mixture for 8 hours. The reaction mixture was diluted with water and extracted with ethyl acetate, and the extract was successively washed with 1N hydrochloric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was recrystallized from a mixed solvent of isopropyl ether and hexane to obtain the title compound (0.7 g).
^{1}H-NMR (DMSO-d_6) δ: 1.34(3H,t,J=7.1Hz), 4.38(2H,q,J=7.1Hz), 7.33(1H,dd,J=8.0,1.4Hz), 7.52(1H,d,J=8.0Hz), 7.97 (1H,d,J=1.4Hz), 12.75(1H,br).

[Referential Example 288]

Ethyl 5-chloro-3-[(dimethylamino)carbonyl]indole-2-carboxylate:

[0695]

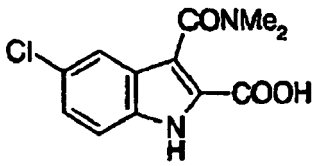


[0696] The compound (0.7 g) obtained in Referential Example 287 was dissolved in N,N-dimethylformamide (10 ml), and dimethylamine hydrochloride (0.26 g), 1-hydroxybenzotriazole monohydrate (0.43 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.0 g) were added to stir the mixture at room temperature for 2 days. After the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride in that order, the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure , and the residue was recrystallized from a mixed solvent of isopropyl ether and hexane to obtain the title compound (0.6 g).
^{1}H-NMR (DMSO-d_6) δ: 1.29(3H,t,J=7.1Hz), 2.78(3H,s), 3.04(3H,s), 4.30(2H,q,J=7.1Hz), 7.31(1H,dd,J=8.0,1.4Hz), 7.45 (1H,d,J=1.4Hz), 7.48(1H,d,J=8.0Hz), 12.29(1H,s).

[Referential Example 289]

5-Chloro-3-[(dimethylamino)carbonyl]indole-2-carboxylic acid:

[0697]

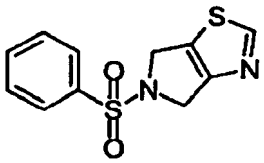


[0698] The title compound was obtained from the compound obtained in Referential Example 288 in a similar manner to Referential Example 286.
^{1}H-NMR (DMSO-d_6) δ: 2.91(6H,s), 7.29(1H,d,J=8.0Hz), 7.44(1H,d,J=8.0Hz), 7.47(1H,s), 12.16(1H,s).

[Referential Example 290]

5-(Phenylsulfonyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole:

[0699]

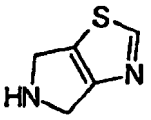


[0700] Benzenesulfonamide (638 mg) and 4,5-bis(bromomethyl)thiazole (M. Al. Hariri, O. Galley, F. Pautet, H. Fillion, Eur. J. Org. Chem., 1998, 593-594.) (1.10 g) were dissolved in N,N-dimethylformamide (10 ml), sodium hydride (60% in oil, 357 mg) was added at a time, and the mixture was stirred at room temperature for 3 hours. Water and methylene chloride were added to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was purified by column chromatography on silica gel (methylene chloride:ethyl acetate = 9:1) to obtain the title compound (137 mg).
^{1}H-NMR ($CDCl_3$) δ: 4.60-4.63(2H,m), 4.70-4.73(2H,m), 7.52-7.64(3H,m), 7.88-7.92(2H,m), 8.71(1H,s).
MS (FAB) m/z: 267$(M+H)^+$.

[Referential Example 291]

5,6-Dihydro-4H-pyrrolo[3,4-d]thiazole dihydrobromide:

[0701]

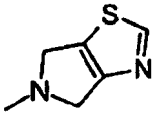


[0702] A mixture of the compound (800 mg) obtained in Referential Example 290, phenol (800 μl) and 47% hydrobromic acid (5.00 ml) was heated under reflux for 2 hours. After the reaction mixture was cooled to room temperature, ethyl acetate and water were added to conduct liquid separation. The resultant water layer was concentrated under reduced pressure. Ethyl acetate was added to the residue, precipitate was collected by filtration to obtain the title compound (521 mg).
^{1}H-NMR (DMSO-d_6) δ: 4.42(2H,br.s), 4.56(2H,br.s), 9.14(1H,s).
MS (FAB) m/z: 127$(M+H)^+$.

[Referential Example 292]

5-Methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole:

[0703]

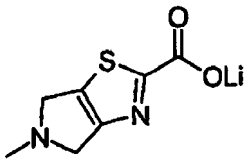


[0704] The title compound was obtained from the compound obtained in Referential Example 291 in a similar manner to Referential Example 9.
^{1}H-NMR ($CDCl_3$) δ: 2.67(3H,s), 3.95-3.99(2H,m), 4.01-4.05(2H,m), 8.69(1H,s).
MS (ESI) m/z: 141$(M+H)^+$.

[Referential Example 293]

Lithium 5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole-2-carboxylate:

[0705]

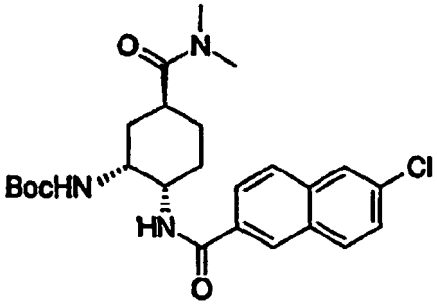


[0706] The title compound was obtained from the compound obtained in Referential Example 292 in a similar manner to Referential Example 5.
^{1}H-NMR (DMSO-d_6) δ: 2.52(3H,s), 3.73(2H,t,J=3.2Hz), 3.87(2H,t,J=3.2Hz).

[Referential Example 294]

tert-Butyl (1R,2S,5S)-2-[(6-chloro-2-naphthoyl)amino]-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0707]

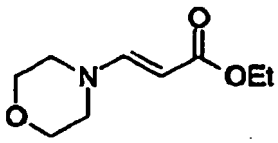


[0708] The title compound was obtained from the compound obtained in Referential Example 144 and 6-chloronaphthalene-2-carboxylic acid (Eur. J. Chem-Chim. Ther., 1984, Vol. 19, pp. 205-214) in a similar manner to Referential Example 97.
^{1}H-NMR ($CDCl_3$) δ: 1.30-2.00(15H,m), 2.60-2.80(1H,m), 2.96(3H,s), 3.09(3H,s), 4.00-4.20(1H,m), 4.20-4.30(1H,m), 4.75-4.95(1H,m), 7.44(1H,d,J=9.0Hz), 7.70-7.95(5H,m), 8.31(1H,s).
MS (FAB) m/z: 474$(M+H)^+$.

[Referential Example 295]

Ethyl (E)-3-(morpholin-4-yl)-2-acrylate:

[0709]

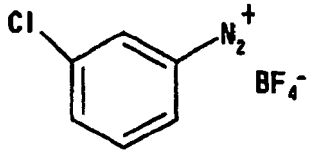


[0710] Ethyl propionate (2.0 ml) was dissolved in methylene chloride (20 ml), and morpholine (1.70 ml) was added dropwise under ice cooling. After stirring at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 20:1) to obtain the title compound (3.72 g).
^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 3.21(4H,t,J=5.1Hz), 3.71(4H,t,J=5.1Hz), 4.14(2H,q,J=7.1Hz), 4.70(1H,d, J=13.4Hz), 7.36(1H,d,J=13.4Hz).
MS (FAB) m/z: 186$(M+H)^+$.

[Referential Example 296]

3-Chlorobenzenediazonium tetrafluoroborate:

[0711]

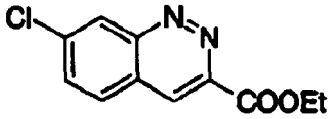


[0712] 3-Chloroaniline (2.0 g) was dissolved in a mixed solvent of water (30 ml) and concentrated hydrochloric acid (3.5 ml), and sodium nitrite (1.30 g) was added under ice cooling to stir the mixture for 10 minutes. After concentrated hydrochloric acid (5.3 ml) and sodium tetrafluoroborate (6.90 g) were added to the reaction mixture to stir the mixture for 30 minutes under ice cooling, precipitate was collected by filtration and washed with water, methanol and diethyl ether to obtain the title compound (2.63 g). This compound was used in the next reaction as it was.

[Referential Example 297]

Ethyl 7-chlorocinnoline-3-carboxylate:

[0713]

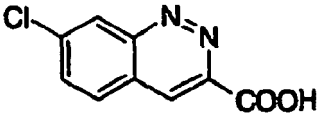


[0714] The compound (1.45 g) obtained in Referential Example 295 was dissolved in acetonitrile (100 ml), and the compound (1.73 g) obtained in Referential Example 296 was added. After stirred at room temperature for 1 hour, the mixture was heated under reflux for 7 days. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride → methylene chloride:ethyl acetate = 10:1, then, hexane:ethyl acetate = 4:1 → 1:1) to obtain the title compound (0.25 g).
^{1}H-NMR ($CDCl_3$) δ: 1.53(3H,t,J=7.1Hz), 4.62(2H,q,J=7.1Hz), 7.80(1H,dd,J=8.8,2.0Hz), 7.95(1H,d,J=8.8Hz), 8.64(1H, s), 8.68(1H,d,J=2.0Hz).

[Referential Example 298]

7-Chlorocinnoline-3-carboxylic acid:

[0715]

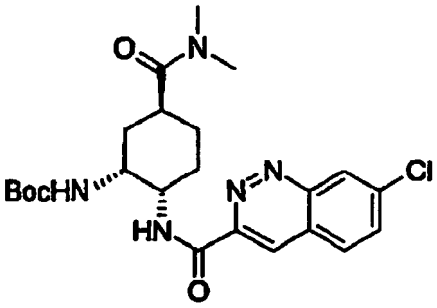


[0716] The title compound was obtained from the compound obtained in Referential Example 297 in a similar manner to Referential Example 286.
^{1}H-NMR (DMSO-d_6) δ: 8.02(1H,dd,J=8.8,2.0Hz), 8.34(1H,d,J=8.8Hz), 8.70(1H,s), 8.90(1H,s).
MS (FAB) m/z: 209$(M+H)^+$.

[Referential Example 299]

tert-Butyl (1R,2S,5S)-2-{[(7-chlorocinnolin-3-yl)carbonyl]-amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0717]

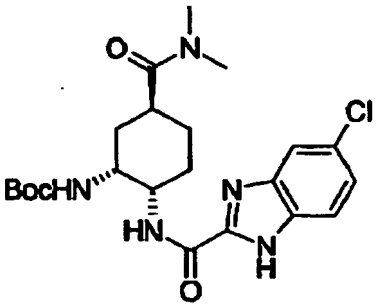


[0718] The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 298 in a similar manner to Referential Example 97.
^{1}H-NMR ($CDCl_3$) δ: 1.36(9H,s), 1.80-2.20(5H,m), 2.72(1H,m), 2.96(3H,s), 3.07(3H,s), 3.49(1H,d,J=3.7Hz), 4.30-4.45 (2H,m), 4.87(1H,br), 7.77(1H,dd,J=8.8,2.0Hz), 7.96(1H,d,J=8.8Hz), 8.59(2H,br), 8.72(1H,s).
MS (FAB) m/z: 476$(M+H)^+$.

[Referential Example 300]

tert-Butyl (1R,2S,5S)-2-{[(5-chloro-1H-benzimidazol-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0719]

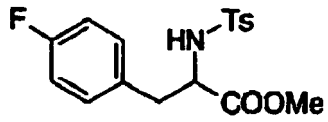


[0720] 10% Palladium on carbon (50 mg) was added to a solution of the compound (235 mg) obtained in Referential Example 143 in tetrahydrofuran (5.0 ml), and the mixture was stirred overnight at room temperature under a hydrogen atmosphere. To a solution of the product obtained by filtering the reaction mixture and concentrating the filtrate and 5-chlorobenzimidazole-2-carboxylic acid (Bull. Chem. Soc. Jpn., Vol. 62, p. 2668, 1989) (165 mg) in N,N-dimethylformamide (5.0 ml) were added 1-hydroxybenzotriazole monohydrate (100 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (171 mg) at room temperature, and the mixture was stirred for 4 days. After concentrating the reaction mixture, methylene chloride, a saturated aqueous solution of sodium hydrogencarbonate and water were added to conduct liquid separation, and the resultant water layer was extracted with methylene chloride. After the resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by flash column chromatagraphy on silica gel (methylene chloride:methanol = 10:1) to obtain the title compound (250 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.01-2.00(6H,m), 1.34(9H,s), 2.79(3H,s), 2.80-2.95(1H,m), 2.98(3H,s), 3.89-4.06(2H,m), 7.08 (1H,d,J=6.6Hz), 7.31(1H,d,J=8.5Hz), 7.62(2H,br.s), 8.47(1H,d,J=8.5Hz), 13.46(1H,br.s).
MS (ESI) m/z: 466$(M+H)^+$.

[Referential Example 301]

Methyl 3-(4-fluorophenyl)-2-{[(4-methylphenyl)sulfonyl]-amino}propionate:

[0721]

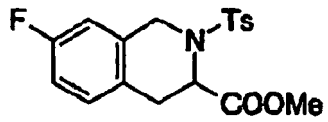


[0722] Methyl 2-amino-3-(4-fluorophenyl)propionate (2.01 g), p-toluenesulfonyl chloride (2.25 g) and 4-dimethylaminopyridine (309 mg) were dissolved in chloroform (30 ml), and pyridine (3.0 ml) was added to heat the mixture under reflux for 4.5 hours. P-Toluenesulfonyl chloride (2.20 g) was additionally added, and the mixture was heated under reflux for 3.5 hours. The reaction mixture was poured into ice and 1N hydrochloric acid (17 ml) to conduct liquid separation. The resultant organic layer was successively washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 9:1 $\rightarrow$ 2:1) to obtain the title compound (2.89 g).
^{1}H-NMR ($CDCl_3$) δ: 2.41(3H,s), 2.90-3.10(2H,m), 3.51(3H,s), 4.10-4.20(1H,m), 5.04(1H,d,J=9.0Hz), 6.85-6.95(2H,m), 7.00-7.10(2H,m), 7.20-7.30(2H,m), 7.60-7.70(2H,m).
MS (ESI) m/z: 352$(M+H)^+$.

[Referential Example 302]

Methyl 7-fluoro-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate:

[0723]

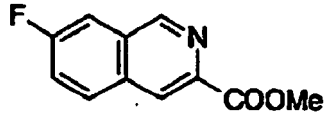


[0724] The compound (1.50 g) obtained in Referential Example 301 and paraformaldehyde (207 mg) were dissolved in chloroform (40 ml), and the system was purged with argon. Trifluoroborane-diethyl ether complex (1.20 ml) was then added, and the mixture was stirred at room temperature for 7.5 hours. The reaction mixture was poured into ice and a saturated aqueous solution of sodium hydrogencarbonate to conduct liquid separation. The resultant organic layer was then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (1.45 g).
^{1}H-NMR ($CDCl_3$) δ: 2.42(3H,s), 3.15(2H,d,J=3.9Hz), 3.46(3H,s), 4.45(1H,d,J=15.9Hz), 4.69(1H,d,J=15.9Hz), 5.01(1H,t,J=4.4Hz), 6.70-6.80(1H,m), 6.80-6.90(1H,m), 7.00-7.10(1H,m), 7.29(2H,d,J=8.1Hz), 7.72(2H,d,J=8.3Hz).
MS (ESI) m/z: 364$(M+H)^+$.

[Referential Example 303]

Methyl 7-fluoroisoquinoline-3-carboxylate:

[0725]



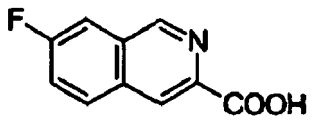
[0726] The compound (1.45 g) obtained in Referential Example 302 was dissolved in N,N-dimethylformamide (40 ml). Oxygen was introduced into this solution, and the solution was stirred at 100°C for 3.5 hours. After the reaction mixture was concentrated under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate and meth-

ylene chloride were added to the residue to conduct liquid separation, the resultant organic layer was succesively washed with a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 1:1) to obtain the title compound (0.59 g).
^{1}H-NMR ($CDCl_3$) δ: 4.07(3H,s), 7.55-7.65(1H,m), 7.65-7.75(1H,m), 8.00-8.05(1H,m), 8.61(1H,s), 9.30(1H,s).
MS (ESI) m/z: 206$(M+H)^+$.

[Referential Example 304]

7-Fluoroisoquinoline-3-carboxylic hydrochloride:

[0727]

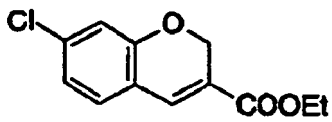


[0728] The compound (1.45 g) obtained in Referential Example 303 was dissolved in concentrated hydrochloric acid (18 ml), and the solution was heat under reflux for 2.5 hours. The reaction mixture was cooled, and crystals were collected by filtration, washed with water and then dried to obtain the title compound (0.46 g).
^{1}H-NMR (DMSO-d_6) δ: 7.90-8.00(1H,m), 8.15-8.25(1H,m), 8.40-8.50(1H,m), 8.82(1H,s), 9.55(1H,s).
MS (FAB) m/z: 192$(M+H)^+$.

[Referential Example 305]

Ethyl 7-chloro-2H-chromene-3-carboxylate:

[0729]

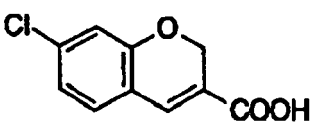


[0730] 4--Chloro-2-hydroxybenzaldehyde (Acta. Chem. Scand., Vol. 53, p. 258, 1999) (510 mg) was dissolved in tetrahydrofuran (40 ml), sodium hydride (60% in oil, 157 mg) was added, and the mixture was stirred at room temperature for 2 hours. A tetrahydrofuran solution (10 ml) of ethyl 2-diethylphosphonoacrylate (J. Org. Chem., Vol. 43, P. 1256, 1978) (769 mg) was added to the reaction mixture, and the resultant mixture was stirred at room temperature for 2 hours and then heated overnight under reflux. After the reaction mixture was cooled to room temperature, water and diethyl ether were added to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to obtain the title compound (247 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.33(3H,t,J=7.1Hz), 4.27(2H,q,J=7.1Hz), 4.99(2H,d,J=1.2Hz), 6.85(1H,d,J=1.2Hz), 6.89(1H,dd, J=8.1,2.0HZ), 7.04(1H,d,J=8.1Hz), 7.38(1H,d,J=1.0Hz).
MS (EI) m/z: 238(M^+).

[Referential Example 306]

7-Chloro-2H-chromene-3-carboxylic acid:

[0731]

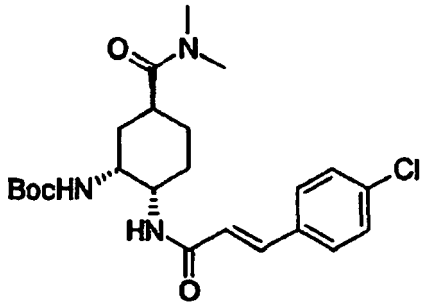


[0732] The title compound was obtained from the compound obtained in Referential Example 305 in a similar manner to Referential Example 274.
^{1}H-NMR (DMSO-d_6) δ: 4.92(1H,d,J=2.0Hz), 6.95(1H,d,J=2.0Hz), 7.01(1H,dd,J=8.1,2.2Hz), 7.35(1H,d,J=8.1Hz), 7.44 (1H,s).
MS (EI) m/z: 210 M^+.

[Referential Example 307]

tert-Butyl (1R,2S,5S)-2-{[(E)-3-(4-chlorophenyl)-2-propenoyl]amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0733]

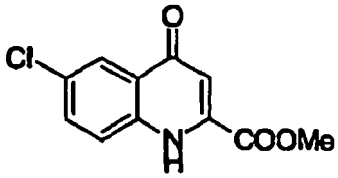


[0734] The title compound was obtained from the compound obtained in Referential Example 144 and 4-chlorocinnamic acid in a similar manner to Referential Example 97.
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.55(3H,m), 1.48(9H,s), 1.60-2.30(4H,m), 2.57-2.70(1H,m), 2.95(3H,s), 3.06(3H,s), 4.01(1H, br s), 4.10-4.20(1H,m), 4.78(1H,br.s), 6.30(1H,d,J=15.6 Hz), 7.02(1H,s), 7.31(2H,d,J=8.5 Hz), 7.40(2H,d,J=8.5 Hz), 7.52 (1H,d,J=15.6 Hz).
MS (ESI)m/z: 450$(M+H)^+$.

[Referential Example 308]

Methyl 6-chloro-4-oxo-1,4-dihydroquinoline-2-carboxylate:

[0735]

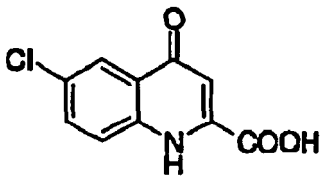


[0736] Dimethyl acetylenedicarboxylate (13.5 ml) was added to a solution of 4-chloroaniline (12.76 g) in methanol (150 ml), and the mixture was heated under reflux for 8 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in diphenyl ether (70 ml), and the solution was heated under reflux at 240°C for 4 hours. After cooling the reaction mixture, a mixed solvent of hexane and diethyl ether was added, and crystals deposited were collected by filtration and washed to obtain the title compound (11.09 g).
^{1}H-NMR (DMSO-d_6) δ: 3.97(3H,s), 7.76(1H,dd,J=9.0,2.5Hz), 7.90-8.05(2H,m), 12.28(1H,br.s).
MS (ESI) m/z: 238$(M+H)^+$.

[Referential Example 309]

6-Chloro-4-oxo-1,4-dihydroquinoline-2-carboxylic acid:

[0737]

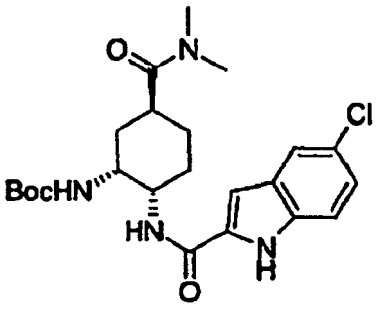


[0738] The title compound was obtained from the compound obtained in Referential Example 308 in a similar manner to Referential Example 286.
^{1}H-NMR (DMSO-d_6) δ: 6.90-7.05(1H,m), 7.90-8.05(2H,m) , 10.10-10.30(1H,m), 12.13(1H,br.s).
MS (ESI) m/z: 224$(M+H)^+$.

[Referential Example 310]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0739]

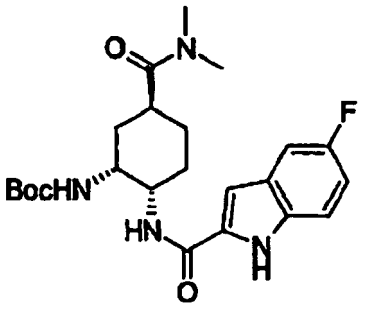


[0740] Water (10 ml) and lithium hydroxide (263 mg) were added to a solution of the compound (5.00 g) obtained in Referential Example 97 in tetrahydrofuran (40 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was filtered, the filtrate was concentrated, and 1-hydroxybenzotriazole monohydrate (1.75 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.32 g) and diisopropylethylamine (11.3 ml) were added to a solution of the resultant residue and dimethylamine hydrochloride (1.85 g) in N,N-dimethylformamide (100 ml) at room temperature. The resultant mixture was stirred for 2 days. After concentrating the reaction mixture, methylene chloride, a saturated aqueous solution of sodium hydrogencarbonate and water were added to conduct liquid separation. The resultant water layer was extracted with methylene chloride. The organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by column chromatagraphy on silica gel (methylene chloride:acetone = 2:1 $\rightarrow$ 1:1) to obtain the title compound (4.59 g).
^{1}H-NMR ($CDCl_3$) δ: 1.60-1.76(2H,m), 1.73(9H,s), 1.76-1.87(1H,m), 1.93(1H,br.s), 2.14(1H,br.s), 2.28(1H,br.s), 2.65(1H, br.s), 2.95(3H,s), 3.05(3H,s), 4.01(1H,br.s), 4.21(1H,br.s),4.84(1H,br.s), 6.81(1H,br.s), 7.20(1H,dd,J=8.8,1.9Hz), 7.36 (1H,d,J=8.8Hz), 7.59(1H,br.s), 8.02(1H,br.s), 10.06(1H,br.s).
MS (FAB) m/z: 465$(M+H)^+$.

[Referential Example 311]

tert-Butyl (1R,2S,5S)-2-{[(5-fluoroindol-2-yl)carbonyl]-amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0741]



1) Ethyl (1S,3R,4S)-3-[(tert-butoxycarbonyl)amino]-4-{[(5-fluoroindol-2-yl)carbonyl]amino}-cyclohexanecarboxylate was obtained from the compound obtained in Referential Example 96 and 5-fluoroindole-2-carboxylic acid in a similar manner to Referential Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.52(9H,s), 1.67-2.41(7H,m), 3.97(1H,br.s), 4.15(2H,q,J=7.1Hz), 4.08-4.22 (1H,m), 6.83(1H,s), 7.00-7.05(1H,m), 7.32-7.36(1H,m), 8.02(1H,s), 9.51(1H,s).

MS (FAB) m/z: 448$(M+H)^+$.

2) The title compound was obtained from the compound obtained above in a similar manner to Referential Example 310.

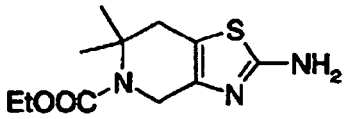
^{1}H-NMR ($CDCl_3$) δ: 1.52(9H,s), 1.57-1.79(2H,m), 1.79-2.00(2H,m), 2.14(1H,br.s), 2.31(1H,br.s), 2.65(1H,br.s), 2.95 (3H,s), 3.07(3H,s), 4.02(1H,br.s), 4.17-4.25(1H,m), 4.80(1H,br.s), 6.82(1H,br.s), 7.02(1H,dt,J=2.3,9.0Hz), 7.24(1H, br.s), 7.35(1H,dd,J=9.0,4.3Hz), 7.91(1H,br.s), 9.49(1H,br.s).

MS (FAB) m/z: 447$(M+H)^+$.

[Referential Example 312]

Ethyl 2-amino-6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]pyridine-5(4H)-carboxylate:

[0742]



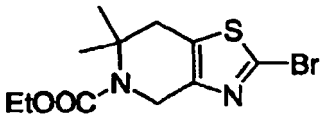
[0743] After copper(I) cyanide (918 mg) was suspended in tetrahydrofuran (50 ml) under an argon atmosphere, and the suspension was cooled to -20°C, n-butyllithium (1.56 N hexane solution, 6.41 ml) was added dropwise over 5 minutes, and the mixture was stirred at -20°C for 30 minutes. After the reaction mixture was cooled to -50°C, diisobutylaluminum hydride (1.00 M hexane solution) was added dropwise over 20 minutes, and the mixture was stirred at -50°C for 1 hour. A solution of ethyl 2,2-dimethyl-5-oxo-5,6-dihydro-2H-pyridine-1-carboxylate (Helv. Chim. Acta, Vol. 81, p. 303, 1998) (986 mg) in tetrahydrofuran (5 ml) was added dropwise to the reaction mixture over 5 minutes, and the mixture was stirred at -50°C for 2 hours. After raising the temperature of the reaction mixture to -20°, bromine (4.90 ml) was added at a time, and the mixture was stirred at -20°C for 30 minutes. Water and ethyl acetate were added to the reaction mixture to conduct liquid separation. The resultant organic layer was washed with a saturated aqueous solution of sodium sulfite and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was dissolved in N,N-dimethylformamide (10 ml), thiourea (760 mg) was added, and the mixture was stirred overnight at 50°C. After the solvent was distilled off, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 4:1) to obtain the title compound (412 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.1Hz), 1.54(6H,s), 2.65-2.67(2H,m), 4.09(2H,q,J=7.1Hz), 4.44-4.46(2H,m), 4.78(2H, br.s).

[Referential Example 313]

Ethyl 2-bromo-6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]-pyridine-5(4H)-carboxylate:

[0744]

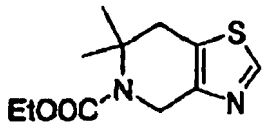


[0745] Copper(II) bromide (431 mg) was suspended in acetonitrile (8 ml), and tert-butyl nitrite (249 mg) was added dropwise at room temperature. After an acetonitrile solution (8 ml) of the compound (412 mg) obtained in Referential Example 312 was added to the reaction mixture under ice cooling, the mixture was heated to 50°C and stirred for 15 minutes. The solvent was distilled off under reduced pressure, and diethyl ether and 10% hydrochloric acid were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 6:1) to obtain the title compound (151 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.55(6H,s), 2.79-2.81(2H,m), 4.10(2H,q,J=7.1Hz), 4.65-4.67(2H,m).
MS (ESI) m/z: 319$(M+H)^+$.

[Referential Example 314]

Ethyl 6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]-pyridine-5(4H)-carboxylate:

[0746]

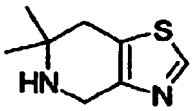


[0747] n-Butyllithium (1.56N hexane solution, 1.04 ml) was added to a solution with the compound (432 mg) obtained in Referential Example 313 in diethyl ether (5 ml) at -78°C, and the mixture was stirred at -78°C for 30 minutes. Water and diethyl ether were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off to obtain the title compound (307 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.1Hz), 1.55(6H,s), 2.90(2H,s), 4.12(2H,q,J=7.1Hz), 4.75(2H,m), 8.63(1H,s).

[Referential Example 315]

6,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine:

[0748]

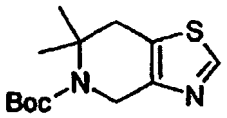


[0749] The compound (307 mg) obtained in Referential Example 314 was dissolved in a mixed solvent of water (5 ml), ethanol (5 ml) and dioxane (5 ml), and lithium hydroxide (598 mg) was added to this reaction mixture to heat the mixture under reflux for 7 days. After allowing the reaction mixture to cool to room temperature, water and methylene chloride were added to conduct liquid separation. The resultant water layer was extracted 6 times with methylene chloride. The resultant organic layers were dried over anhydrous sodium sulfate, and the solvent was distilled off to obtain the title compound (207 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.23(6H,s), 2.71-2.73(2H,m), 4.09-4.11(2H,m), 8.61(1H,s).
MS (ESI) m/z: 168(M^+).

[Referential Example 316]

tert-Butyl 6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]pyridine-5(4H)-carboxylate:

[0750]

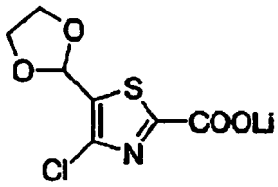


[0751] The compound (207 mg) obtained in Referential Example 315 was dissolved in methylene chloride (5 ml), and di-tert-butyl dicarbonate (404 mg) and 4-(N,N-dimethylamino)-pyridine (151 mg) were added to stir the mixture at room temperature for 2 hours. Di-tert-butyl dicarbonate (404 mg) was additionally added, and the mixture was stirred overnight at room temperature. Further, di-tert-butyl dicarbonate (1.00 g) was added, and the mixture was stirred for 1 hour. Methylene chloride and 10% hydrochloric acid were added to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (95.4 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.52(6H,s), 2.87(2H,s), 4.69(2H,s), 8.62(1H,s).
MS (ESI) m/z: 269$(M+H)^+$.

[Referential Example 317]

Lithium 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate:

[0752]

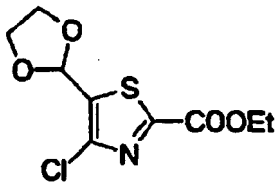


[0753] 2,4-Dichlorothiazole-5-carbaldehyde ethyleneacetal (J. Chem. Soc. Perkin Trans. 1, 1992, p. 973) (2.26 g) was dissolved in tetrahydrofuran (15 ml), and n-butyllithium (1.5N hexane solution, 6.8 ml) was added under cooling with dry ice-acetone to stir the mixture for 20 minutes. At the same temperature, carbon dioxide was then introduced. The reaction mixture was gradually heated to room temperature over 1.5 hours and then concentrated. Hexane was added to the reaction mixture to powder the product. The product was collected by filtration and suspended in ethyl acetate, and formed powder was collected again by filtration to obtain the title compound (1.65 g).

[Referential Example 318]

Ethyl 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate:

[0754]



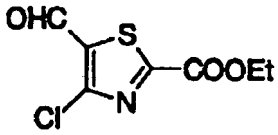
[0755] The compound (242 mg) obtained in Referential Example 317 and ethanol (0.2 ml) were dissolved in N,N-dimethylformamide (2 ml), and 1-hydroxybenzotriazole monohydrate (136 mg) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (250 mg) were added to stir the mixture at room temperature for a night. The solvent was distilled off under reduced pressure, and diethyl ether and diluted hydrochloric acid were added to separate an organic layer. The organic layer was washed with water and a saturated aqueous solution of sodium hydrogencarbonate and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (170 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.43(3H,t,J=7.3Hz), 4.00-4.10(2H,m), 4.10-4.20(2H,m), 4.48(2H,q,J=7.3Hz), 6.15(1H,s).

MS (ESI) m/z: 264$(M+H)^+$.

[Referential Example 319]

Ethyl 4-chloro-5-formylthiazole-2-carboxylate:

[0756]

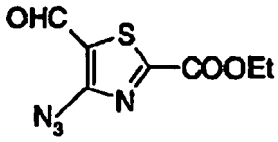


[0757] The compound (132 mg) obtained in Referential Example 318 was dissolved in diethyl ether (5 ml), and 20% hydrochloric acid (0.3 ml) was added to stir the mixture at room temperature for 7 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with diethyl ether. The extract was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound (110 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.46(3H,t,J=7.1Hz), 4.52(2H,q,J=7.1Hz), 10.12(1H,s).

[Referential Example 320]

Ethyl 4-azido-5-formylthiazole-2-carboxylate:

[0758]

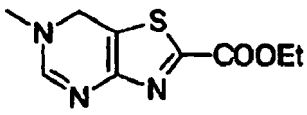


[0759] The compound (5.15 g) obtained in Referential Example 319 was dissolved in dimethyl sulfoxide (30 ml), and sodium azide (1.52 g) was added to stir the mixture at room temperature for 2.5 hours. Ice water was added to the reaction mixture to conduct extraction with diethyl ether. The extract was washed twice with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (1.78 g)
^{1}H-NMR ($CDCl_3$) δ: 1.45(3H,t,J=7.1Hz), 4.50(2H,q,J=7.1Hz), 9.95(1H,s).

[Referential Example 321]

Ethyl 6-methyl-6,7-dihydrothiazolo[4,5-d]pyrimidine-2-carboxylate:

[0760]



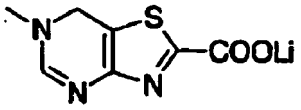
[0761] The compound (1.56 g) obtained in Referential Example 320 was dissolved in methylene chloride (20 ml), and acetic acid (2 ml), methylamine (2N tetrahydrofuran solution, 21 ml) and sodium triacetoxyborohydride (2.98 g) were added to stir the mixture. After 1 hour, sodium triacetoxyborohydride (2.98 g) was additionally added, and the stirring was continued for additional 4.5 hours. A 0.5N aqueous solution (100 ml) of sodium hydroxide was added to the reaction mixture to alkalify it. After the reaction mixture was extracted with methylene chloride, the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain a brown oil (1.43 g). This oil was dissolved in ethanol (50 ml), 10% palladium on carbon (2.0 g) was added to conduct hydrogenation at normal temperature

and pressure. After 2.5 hours, the catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in methylene chloride (30 ml), and trimethyl orthoformate (0.7 ml) and boron trifluoride-diethyl ether complex (0.3 ml) were added to stir the mixture at room temperature for 15 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with methylene chloride. The extract was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 97:3) to obtain the title compound (100 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.41(3H,t,J=7.1Hz), 2.95(3H,s), 4.44(2H,q,J=7.1Hz), 4.87(2H,s), 7.06(1H,s).
MS (ESI) m/z: 226$(M+H)^+$.

[Referential Example 322]

Lithium 6-methyl-6,7-dihydrothiazolo[4,5-d]pyrimidine-2-carboxylate:

[0762]

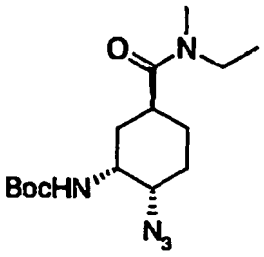


[0763] The compound (463 mg) was dissolved in tetrahydrofuran (20 ml), and lithium hydroxide (54.1 mg) and water (4 ml) were added to stir the mixture at room temperature for 4.5 hours. The solvent was distilled off under reduced pressure, and the residue was dried by means of a vacuum pump to obtain the title compound (460 mg).
^{1}H-NMR -(DMSO-d_6) δ: 2.86(3H,s), 4.71(2H,s), 7.03(1H,s).

[Referential Example 323]

tert-Butyl (1R,2S,5S)-2-azido-5-{[ethyl(methyl)amino]-carbonyl}cyclohexylcarbamate:

[0764]

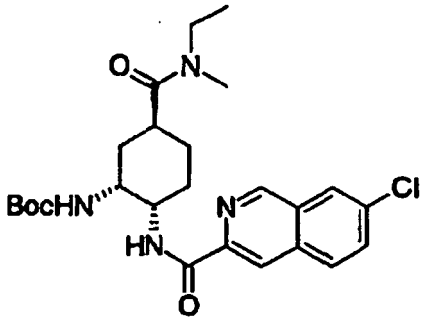


[0765] The title compound was obtained by condensing the compound obtained in Referential Example 250 with ethylmethylamine.
^{1}H-NMR ($CDCl_3$) δ: 1.08,1.18(total 3H,each t,J=7.1Hz), 1.46(9H,s), 1.52-1.80(4H,m), 2.04-2.08(2H,m), 2.71-2.77(1H,m), 2.89,2.98(total 3H,each s), 3.32,3.39(total 2H,each q,J=7.1Hz), 3.74-3.76(1H,m), 4.09-4.11(1H,m), 4.60(1H,br.s).
MS (EI) m/z: 326$(M+H)^+$.

[Referential Example 324]

tert-Butyl (1R,2S,5S)-2-{[(7-chloroisoquinolin-3-yl)-carbonyl]amino}-5-{[ethyl(methyl)amino]carbonyl}-cyclohexylcarbamate:

[0766]



[0767] The compound (1.44 g) obtained in Referential Example 323 was dissolved in methanol (20 ml), 10% palladium on carbon (150 mg) was added, and the mixture was stirred under a hydrogen atmosphere. After 24 hours, the catalyst was removed by filtration, and the solvent was then concentrated under reduced pressure to obtain a colorless oil. This oil was used in the next reaction as it is.

[0768] The above-obtained oil was dissolved in methylene chloride (30 ml), and the compound (850 mg) obtained in Referential Example 57, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.27 g), 1-hydroxybenzotriazole monohydrate (900 mg) and N-methylmorpholine (1.34 g) were added to stir the mixture at room temperature. After 17 hours, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation, and the resultant organic layer was dried over anhydrous magnesium sulfate. The solvent was disilled off under reduced pressure, and the residue was subjected to column chromatagraphy on silica gel (methanol:methylene chloride = 1:50) to obtain the title compound (1.61 g).

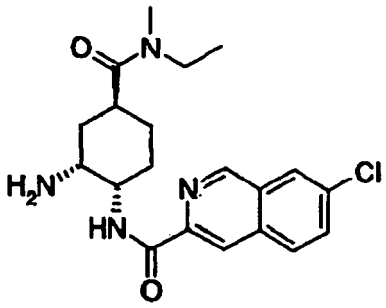
^{1}H-NMR ($CDCl_3$) δ: 1.10,1.22(total 3H,each t,J=7.1Hz), 1.43(9H,s), 1.84-2.17(6H,m), 2.66(1H,br.s), 2.92, 3.03(total 3H, each s), 3.35-3.44(2H,m), 4.20-4.30(2H,m), 5.30(1H,br.s), 7.70(1H,d,J=8.6Hz), 7.92(1H,d,J=8.6Hz), 8.00(1H,s), 8.40 (1H,br.s), 8.56(1H,s), 9.03(1H,s).

MS (FAB) m/z: 489$(M+H)^+$.

[Referential Example 325]

N-((1S,2R,4S)-2-Amino-4-[(7-chloroisoquinolin-3-yl)-carbonyl]-4-{[ethyl(methyl)amino]carbonyl}cyclohexyl)-7-chloroisoquinoline-3-carboxamide:

[0769]



[0770] The compound (1.60 g) obtained in Referential Example 324 was dissolved in an ethanol solution (25 ml) of hydrochloric acid, and the solution was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure, and methylene chloride and a 1N aqueous solution of sodium hydroxide were added to the residue to conduct liquid separation. The resultant water layer was extracted with methylene chloride, and organic layers were combined and dried over potassium carbonate. The solvent was distilled off under reduced pressure, hexane was added to the residue, and precipitate was collected by filtration to obtain the title compound (1.22 g).

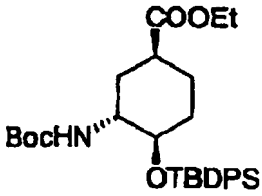
^{1}H-NMR (DMSO-d_6) δ: 1.10,1.23(total 3H,each t,J=7.1Hz), 1.26(2H,br.s), 1.69-2.11(6H,m), 2.89(1H,br.s), 2.93,3.05 (total 3H,each s), 3.38-3.45(2H,m), 3.52(1H,s), 4.18(1H,br.s), 7.70(1H,dd,J=8.8,2.0Hz), 7.94(1H,d,J=8.8Hz), 8.02(1H, d,J=2.0Hz), 8.50(1H,br.s), 8.59(1H,s), 9.11(1H,s).

MS (FAB) m/z: 389$(M+H)^+$.

[Referential Example 326]

Ethyl (1R*,3S*,4S*)-3-[(tert-butoxycarbonyl)amino]-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexanecarboxylate:

[0771]

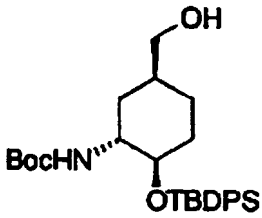


[0772] The compound (28.0 g) obtained in Referential Example 88 was dissolved in N,N-dimethylformamide (500 ml), and tert-butyldiphenylsilyl chloride (63.5 ml) and imidazole (19.9 g) were added. After the mixture was stirred at room temperature for 10 hours, ethyl acetate and water were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted with ethyl acetate, and organic layers were combined, washed twice with water and dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 1:0 → 47:3) to obtain the title compound (52.5 g) containing 0.4 molecules of N,N-dimethylformamide.
^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.27(3H,t,J=7.1Hz), 1.38(9H,s), 1.43-1.59(3H,m), 1.63-1.67(1H,m), 1.92-1.98(1H,m), 2.25-2.32(1H,m), 2.37-2.42(1H,m), 3.66(1H,br.s), 3.80(1H,br.s), 4.16(2H,q,J=7.1Hz), 4.32(1H,d,J=8.1Hz), 7.34-7.46 (6H,m), 7.65-7.73(4H,m).

[Referential Example 327]

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-oxy}-5-(hydroxymethyl)cyclohexanecarbmate:

[0773]

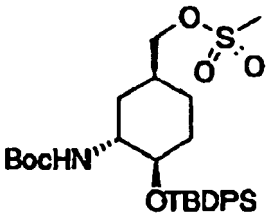


[0774] Lithium aluminum hydride (7.11 g) was suspended in absolute diethyl ether (100 ml) at 0°C while purging with argon, and a diethyl ether solution (500 ml) of the compound (52.5 g) obtained in Referential Example 326 was added dropwise over 30 minutes. After stirring at 0°C for 30 minutes, methanol (100 ml) was added dropwise to the reaction mixture. The resultant slurry was removed by filtration through Celite, and the filtrate was concentrated. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (29.6 g).
^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.32-1.74(16H,m), 1.87(1H,t,J=10.4Hz), 3.35-3.55(2H,m), 3.71(1H,br.s), 3:79(1H,br.s), 4.36(1H,br.s), 7.34-7.44(6H,m), 7.65-7.72(4H,m).

[Referential Example 328]

((1R*,3S*,4S*)-3-[(tert-Butoxycarbonyl)amino]-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)methyl methanesulfonate:

[0775]

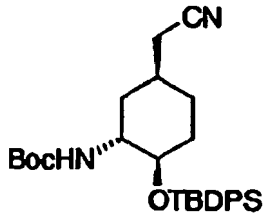


[0776] The compound (29.5 g) obtained in Referential Example 327 was dissolved in methylene chloride (200 ml) and pyridine (20 ml), and methanesulfonyl chloride (9.5 ml) was added to stir the mixture at room temperature for 6 hours. The solvent was distilled off under reduced pressure, and ethyl acetate and water were added to the residue to conduct liquid separation. The resultant water layer was extracted with ethyl acetate, and organic layers were combined, washed twice with water and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (29.8 g).
^{1}H-NMR ($CDCl_3$) δ: 1.08(9H,s), 1.38(9H,s), 1.43-1.61(5H,m), 1.86-1.89(2H,m), 3.02(3H,s), 3.77(1H,br.s), 3.81(1H,br.s), 4.10(2H,d,J=5.4Hz), 4.32(1H,br.s), 7.35-7.45(6H,m), 7.64-7.68(4H,m).
MS (ESI) m/z: 562$(M+H)^+$.

[Referential Example 329]

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-oxy}-5-(cyanomethyl)cyclohexanecarbamate:

[0777]

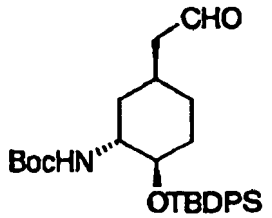


[0778] The compound (29.8 g) obtained in Referential Example 328 was dissolved in N,N-dimethylformamide (400 ml), and sodium cyanide (3.64 g) was added to stir the mixture at 80°C for 11 hours. Ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted twice with ethyl acetate, and organic layers were combined, washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 5:1) to obtain the title compound (20.6 g).
^{1}H-NMR ($CDCl_3$) δ: 1.08(9H,s), 1.38(9H,s), 1.43-1.68(5H,m), 1.79-1.85(1H,m), 1.88-1.95(1H,m), 2.32(2H,d,J=7.1Hz), 3.77(1H,br.s), 3.82(1H,br.s), 4.32(1H,br.d,J=6.8Hz), 7.35-7.45(6H,m), 7.65-7.71(4H,m).

[Referential Example 330]

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-oxy}-5-(2-oxoethyl)cyclohexanecarbamate:

[0779]



[0780] The compound (2.00 g) obtained in Referential Example 329 was dissolved in absolute methylene chloride (20

ml), and the system was purged with argon and then cooled to -78°C. To the solution, was added dropwise diisobutylaluminum hydride (0.95 M hexane solution, 8.55 ml). The temperature of the mixture was then allowed to raise to room temperature and stirred for 3 hours. The reaction mixture was cooled to 0°C, and methanol (10 ml) was added dropwise. The resultant slurry was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 1:0 → 49:1) to obtain the title compound (1.45 g).

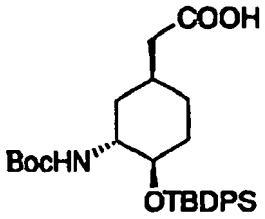
^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.38(9H,s), 1.43-1.54(5H,m), 1.82-1.88(1H,m), 2.06(1H,br.s), 2.42-2.43(2H,m), 3.72 (1H,br.s), 3.77(1H,br.s), 4.38(1H,br.s), 7.34-7.44(6H,m), 7.65-7.68(4H,m), 9.77(1H,t,J=1.7Hz).

MS (FAB) m/z: 496$(M+H)^+$.

[Referential Example 331]

2-((1R*,3S*,4S*)-3-[(tert-Butoxycarbonyl)amino]-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)acetic acid:

[0781]



[0782] The compound (8.40 g) obtained in Referential Example 330 was dissolved in a mixed solvent of water (33 ml) and tert-butanol (120 ml), and 2-methyl-2-butene (8.08 ml), sodium dihydrogenphosphate dihydrate (2.64 g) and sodium chlorite (3.45 g) were added to stir the mixture at room temperature for 1.5 hours. Methylene chloride and water were added to the reaction mixture to dilute it. The resultant water layer was adjusted to pH of about 4 with 1N hydrochloric acid. Liquid separation was conducted, and the resultant water layer was extracted twice with methylene chloride. Organic layers were combined and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1 → 1:1) to obtain the title compound (7.62 g).

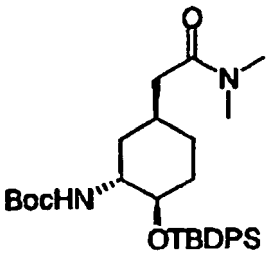
^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.22-1.63(15H,m), 1.82(1H,br.s), 2.17(1H,br.s), 2.27-2.33(1H,m), 3.69(1H,br.s), 3.84 (1H,br.s), 7.00(1H,br.s), 7.33-7.42(6H,m), 7.63-7.65(4H,m).

MS (ESI) m/z: 512$(M+H)^+$.

[Referential Example 332].

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-oxy}-5-[2-(dimethylamino)-2-oxoethyl]cyclohexanecarbamate:

[0783]



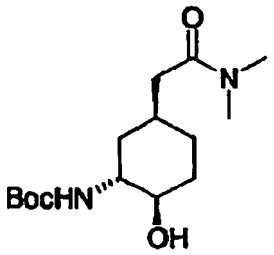
[0784] The compound (7.62 g) obtained in Referential Example 331 was dissolved in N,N-dimethylformamide (150 ml), and dimethylamine hydrochloride (6.07 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.56 g), 1-hydroxybenzotriazole monohydrate (1.01 g) and triethylamine (10.3 ml) were added to stir the mixture at room temperature for 4 days. The solvent was distilled off under reduced pressure, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was extracted with methylene chloride, and organic layers were combined and dried over anhydrous

sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 1:1). The solvent was distilled off, hexane was added to the residue, and formed white precipitate was collected by filtration to obtain the title compound (6.42 g).
^{1}H-NMR ($CDCl_3$) δ: 1.08(9H,s), 1.38(9H,br.s), 1.43-1.55(5H,m), 1.79-1.86(1H,m), 2.03(1H,br.s), 2.21-2.32(2H,s), 2.94 (3H,s), 3.03(3H,s), 3.74(1H,br.s), 3.80(1H,br.s), 4.49(lH,br.s), 7.33-7.44(6H,m), 7.64-7.69(4H,m).
MS (ESI) m/z: 539$(M+H)^+$.

[Referential Example 333]

tert-Butyl (1R*,2R*,5S*)-5-[2-(dimethylamino)-2-oxoethyl]-2-hydroxycyclohexanecarbamate:

[0785]

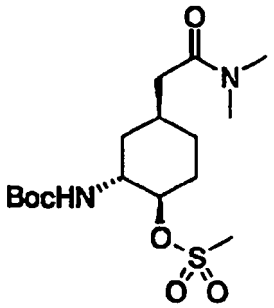


[0786] The compound (6.36 g) obtained in Referential Example 332 was dissolved in tetrahydrofuran (50 ml), and tetrabutylammonium fluoride (1N tetrahydrofuran solution, 17.85 ml) was added to stir the mixture at room temperature for 13 hours. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatagraphy on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (3.49 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.46-1.60(4H,m), 1.79-1.84(2H,m), 2.28-2.35(3H,s), 2.82(1H,br.s), 2.95(3H,s), 3.01(3H, s),3.56(2H,br.s), 4.67(1H,br.s).
MS (ESI) m/z: 301$(M+H)^+$.

[Referential Example 334]

((1R*,2R*,4S*)-2-[(tert-Butoxycarbonyl)amino]-4-[2-(dimethylamino)-2-oxoethyl]cyclohexyl methanesulfonate:

[0787]

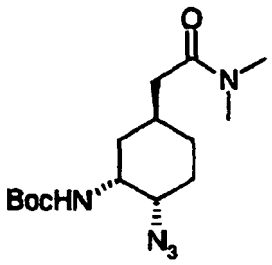


[0788] The compound (8.05 mg) obtained in Referential Example 333 was dissolved in methylene chloride (50 ml), and the solution was cooled to -78°C under an argon atmosphere to add dropwise methanesulfonyl chloride (2.70 ml). After the temperature of the mixture was allowed to raise to 0°C and stirred for 30 minutes, it was stirred at room temperature for 2 hours. Water was added to the reaction mixture to conduct liquid separation, and the resultant water layer was extracted with methylene chloride. Organic layers were combined, washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatagraphy on silica gel (hexane:ethyl acetate = 1:1 → 0:1) to obtain the title compound (3.63 g).
^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 1.59-1.74(4H,m), 1.85-2.30(5H,m), 2.95(3H,s), 3.00(3H,s), 3.10(3H,s), 3.79-3.83(1H, m), 4.72(1H,br.s), 4.91(1H,br.s).
MS (ESI) m/z: 379$(M+H)^+$.

[Referential Example 335]

tert-Butyl (1R*,2S*,5S*)-2-azido-5-[2-(dimethylamino)-2-oxoethyl]cyclohexanecarbamate:

[0789]

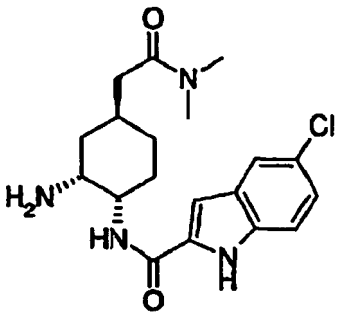


[0790] The compound (3.62 g) obtained in Referential Example 334 was dissolved in N,N-dimethylformamide (20 ml), and sodium azide (3.11 g) was added to stir the mixture at 75°C for 17 hours. The reaction mixture was poured into a mixed solvent of water and ethyl acetate to conduct liquid separation. The resultant water layer was extracted twice with ethyl acetate, and organic layers were combined, washed with water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatagraphy on silica gel (ethyl acetate) to obtain the title compound (1.30 g).
^{1}H-NMR ($CDCl_3$) δ: 1.14-1.21(1H,m), 1.33-1.40(1H,m), 1.45(9H,s), 1.61-1.71(1H,m), 1.78-1.91(3H,m), 2.22-2.27(3H,m), 2.94(3H,s), 3.00(3H,s), 3.60-3.62(1H,m), 3.97(lH,br.s), 4.76(1H,br.s).
MS (ESI) m/z: 326$(M+H)^+$.

[Referential Example 336]

N-{(1R*,2S*,4R*)-2-Amino-4-[2-(dimethylamino)-2-oxoethyl]-cyclohexyl}-5-chloroindole-2-carboxamide hydrochloride:

[0791]

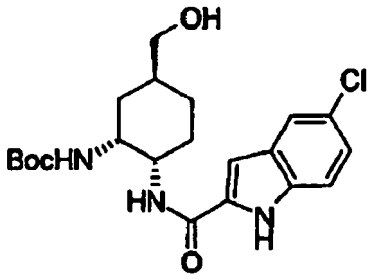


[0792] The title compound was obtained by treating, in a similar manner to Referential Example 69, a product obtained by catalytically reducing the compound obtained in Referential Example 335 in a similar manner to Referential Example 324 and then condensing it with 5-chloroindole-2-carboxylic acid.
^{1}H-NMR (DMSO-d_6) δ: 1.16-1.19(1H,m), 1.51-1.56(1H,m), 1.70-1.73(1H,m), 1.81-1.91(2H,m), 1.99-2.03(1H,m), 2.19-2.30(3H,m), 2.83(3H,s), 2.99(3H,s), 3.63(1H,br.s), 4.08(1H,br.s), 7.19(1H,dd,J=8.7,1.7Hz), 7.35(1H,s), 7.44(1H,d,J=8.7Hz), 7.69(1H,d,J=1.7Hz), 8.22(3H,br.s), 8.62(1H,d,J=7.1Hz), 11.91(1H,s).
MS (ESI) m/z: 377$(M+H)^+$.

[Referential Example 337]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(hydroxymethyl)cyclohexanecarbamate:

[0793]

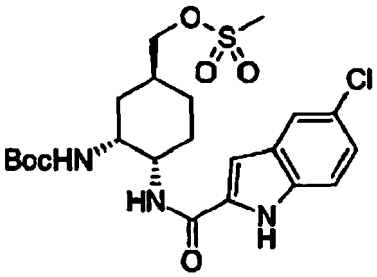


[0794] The title compound was obtained from the compound obtained in Referential Example 97 in a similar manner to step 2) of Referential Example 129.

[Referential Example 338]

((1S,3R,4S)-3-[(tert-butoxycarbonyl)amino]-4-{[(S-chloroindol-2-yl)carbonyl]amino}cyclohexyl)methyl methanesulfonate:

[0795]

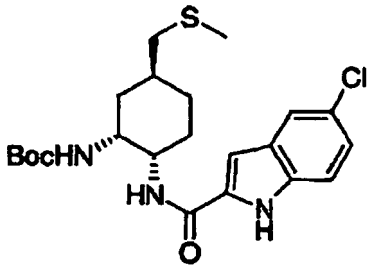


[0796] The compound (500 mg) obtained in Referential Example 337 and triethylamine (329 ml) were suspended in tetrahydrofuran (8ml)-methylene chloride (8 ml), and the suspension was cooled to -78°C. After methanesulfonyl chloride (138 ml) was added dropwise to the suspension, the temperature of the suspension was gradually raised to -5°C, and the suspension was stirred for 15 hours at the same temperature. After the reaction mixture was concentrated, water was added to the residue to conduct extraction 3 times with methylene chloride. The resultant organic layers were washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure to obtain the title compound (654 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.57(9H,s), 1.84-2.01(4H,m), 2.28-2.31(1H,m), 3.04(3H,s), 3.68(1H,s), 3.74-3.75(1H, m), 3.91-3.93 (1H,m), 4.02-4.12(2H,m), 4.18-4.20(1H,m), 4.85(1H,br.s), 6.81(1H,s), 7.21(1H,dd,J=2.0,8.8Hz), 7.34(1H,d,J=8.8Hz), 7.60(1H,s), 8.02(1H,br.s), 9.27(1H,br.s).
MS (ESI) m/z: 500$(M+H)^+$.

[Referential Example 339]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-[(methylsulfanyl)methyl]cyclohexanecarbamate:

[0797]

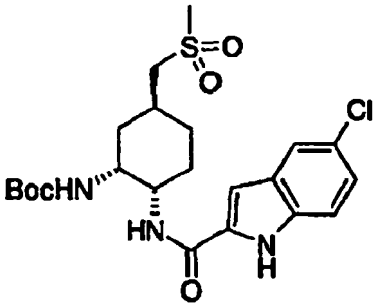


[0798] The compound (654 mg) obtained in Referential Example 338 was dissolved in N,N-dimethylformamide (8 ml), and a 15% aqueous solution (1.8 ml) of sodium thiomethoxide was added to stir the mixture at room temperature for 4 hours. The reaction mixture was poured into water and extracted 3 times with ethyl acetate. The resultant organic layers were washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (492 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.52(9H,s), 1.87-3.04(13H,m), 3.91-3.94(1H,m), 4.12-4.15(1H,m), 4.95(1H,br.s), 6.81(1H,s), 7.19 (1H,dd,J=8.8,1.2Hz), 7.35(1H,d,J=8.8Hz), 7.57(1H,s), 9.82(lH,br.s) .
MS (ESI) m/z: 452$(M+H)^+$.

[Referential Example 340]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-[(methylsulfonyl)methyl]cyclohexanecarbamate:

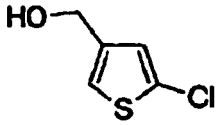
[0799]



[0800] The compound (300 mg) obtained in Referential Example 339 was dissolved in methylene chloride (10 ml), and m-chloroperbenzoic acid (70%, 400 mg) was added at 0°C under stirring. After stirring was continued for 1 hour as it is, the reaction mixture was poured into water and extracted 3 times with ethyl acetate. The resultant organic layers were washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated. After the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 24:1), liquid separation was conducted with a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate, and the resultant organic layer was concentrated to obtain the title compound (254 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.44-2.19(13H,m), 2.22-2.30(2H,m), 2.89-3.25(7H,m), 3.93-4.15(2H,m), 4.98(1H,br.s), 6.82(1H,s), 7.21(1H,dd,J=8.8,2.0Hz), 7.34(1H,d,J=8.8Hz), 7.60(1H,br.s), 9.54(1H,br.s).

[Referential Example 341] (5-Chlorothien-3-yl)methanol:

[0801]

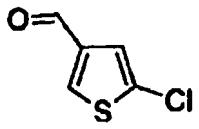


[0802] 5-Chlorothiophene-3-carboxylic acid (Monatsh. Chem., Vol. 120, p. 53, 1989) (6.93 g) was dissolved in tetrahydrofuran (750 ml), and triethylamine (27.3 ml) and ethyl chloroformate (18.7 ml) were added to stir the mixture at room temperature for 2.5 hours. An aqueous solution (41 ml) of sodium borohydride (19.3 g) was added dropwise over 10 minutes, and the mixture was stirred at room temperature for 18.5 hours. After acetic acid was added to the reaction mixture to acidify it, the solvent was distilled off under reduced pressure. Water and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was washed with water and a saturated aqueous solution of sodium hydrogencarbonate. After drying the organic layer, the solvent was distilled off under reduced pressure. The residue was purified by flash column chromatagraphy on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (5.17 g).
^{1}H-NMR ($CDCl_3$) δ: 1.63(1H,t,J=5.8Hz), 4.59(2H,d,J=5.3Hz), 6.91(lH,d,J=1.7Hz), 6.98-6.99(1H,m).

[Referential Example 342]

5-Chlorothiophene-3-carbaldehyde:

[0803]

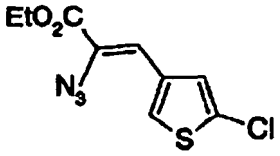


[0804] The compound (5.17 g) obtained in Referential Example 341 was dissolved in methylene chloride (400 ml), and manganese dioxide (51.3 g) was added to stir the mixture at room temperature for 15 hours. After the reaction mixture was filtered, the solvent was distilled off under reduced pressure to obtain the title compound (2.84 g).
^{1}H-NMR ($CDCl_3$) δ: 7.35(1H,d,J=1.7Hz), 7.88(1H,d,J=1.7Hz), 9.75(1H,s).

[Referential Example 343]

Ethyl 2-azido-3-(5-chlorothien-3-yl)acrylate:

[0805]

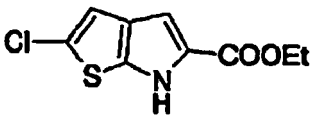


[0806] After ethanol (15 ml) was added to a 20% ethanol solution (10.7 ml) of sodium ethoxide, and the mixture was cooled to 0°C, a mixture of the compound (1.01 g) obtained in Referential Example 342 and ethyl azidoacetate (3.55 g) was added dropwise over 30 minutes, and the resultant mixture was stirred at 0°C for 3 hours. A cooled aqueous solution of ammonium chloride was added to the reaction mixture to conduct extraction 3 times with diethyl ether. Organic layers were combined, and the solvent was distilled off under reduced pressure. The residue was purified by flach column chromatagraphy on silica gel (ethyl acetate:hexane = 1:49) to obtain the title compound (1.04 g).
^{1}H-NMR ($CDCl_3$) δ: 1.38(3H,t,J=7.1Hz), 4.34(2H,q,J=7.1Hz), 6.75(1H,s), 7.39(1H,d,J=1.7Hz), 7.54(1H,d,J=1.7Hz).

[Referential Example 344]

Ethyl 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylate:

[0807]

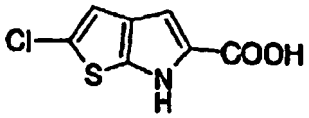


[0808] The compound (0.97 g) obtained in Referential Example 343 was dissolved in xylene (20 ml), and the solution was heated under reflux for 30 minutes. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure. Hexane was added to the residue, solids formed were collected by filtration to obtain the title compound (0.608 g).
^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.0Hz), 4.35(2H,q,J=7.0Hz), 6.90(1H,s), 7.00(1H,d,J=1.9Hz), 9.32(1H,br).

[Referential Example 345]

2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid:

[0809]

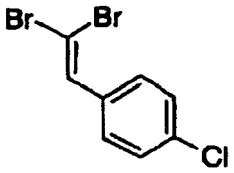


[0810] The title compound was obtained from the compound obtained in Referential Example 344 in a similar manner to Referential Example 274.
^{1}H-NMR ($CD_3$0D) δ: 3.35(1H, s), 6.94(1H,s), 6.96(1H,s).
MS (ESI) m/z: 200(M-H)-.

[Referential Example 346]

1-Chloro-4-(2,2-dibromovinyl)benzene:

[0811]

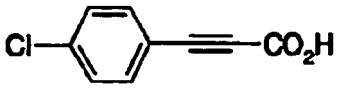


[0812] 4-Chlorobenzaldehyde (2.81 g) was dissolved in methylene chloride (300 ml), and carbon tetrabromide (13.3 g) and triphenylphosphine (21.0 g) were added to stir the mixture at room temperature for 90 minutes. After insoluble matter deposited was removed by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 20:1) to obtain the title compound (5.54 g).
^{1}H-NMR ($CDCl_3$) δ: 7.33(2H,d,J=8.5Hz), 7.43(1H,s), 7.47(2H,d,J=8.5Hz).
MS (EI) m/z: 296 (M^+)

[Referential Example 347]

3-(4-Chlorophenyl)-2-propiolic acid:

[0813]

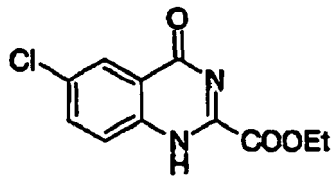


[0814] The compound (1.0 g) obtained in Referential Example 346 was dissolved in tetrahydrofuran (30 ml), and n-butyllithium (1.59 N hexane solution, 4.46 ml) was added dropwise at -78°C under an argon atmosphere. The temperature of the reaction mixture was allowed to raise to room temperature and stirred for 1 hour. The reaction mixture was cooled again to -78°C, stirred for 2 minutes under a carbon dioxide atmosphere and then warmed to room temperature. After the reaction mixture was concentrated under reduced pressure, saturated aqueous solution of sodium chloride and ethyl acetate were added to the residue to conduct liquid separation. 3N Hydrochloric acid was added to the resultant water layer to acidify it, and extraction was conducted with ethyl acetate. The resultant organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the title compound (453 mg).
^{1}H-NMR (DMSO-d_6) δ: 7.55(2H,d,J=8.5Hz), 7.66(2H,d,J=8.5Hz), 13.90(1H,br.s).
MS (EI) m/z: 180 (M^+).

[Referential Example 348]

Ethyl 6-chloro-4-oxo-1,4-dihydroquinazoline-2-carboxylate:

[0815]

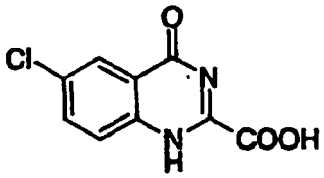


[0816] Ethyl chlorooxoacetate (2.0 ml) was added to a solution of 2-amino-5-chlorobenzamide (2.50 g) in pyridine (15 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in acetic acid (50 ml). Acetic anhydride (5.0 ml) was added to the solution, and the mixture was heated under reflux for 16 hours. The solvent was distilled off under reduced pressure, and ethanol was added to the residue. Crystals deposited were collected by filtration and washed to obtain the title compound (2.71 g).
^{1}H-NMR (DMSO-d_6) δ: 1.35(3H,t,J=7.1Hz), 4.38(2H,q,J=7.1Hz), 7.85(1H,d,J=8.6Hz), 7.91(1H,dd,J=8.6,2.3Hz), 8.10 (1H,d,J=2.3Hz), 12.85(1H,br.s).
MS (ESI) m/z: 253(M+H)'.

[Referential Example 349]

6-Chloro-4-oxo-1,4-dihydroquinazoline-2-carboxylic acid:

[0817]

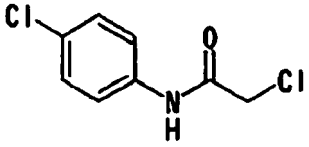


[0818] Lithium hydroxide (263 mg) was added to a solution of the compound (1.26 g) obtained in Referential Example 348 in a mixed solvent of water (5 ml) and tetrahydrofuran (15 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was neutralized with 1N hydrochloric acid (11 ml) under ice cooling and stirred for 1 hour. Crystals deposited were collected by filtration and washed with water to obtain the title compound (0.96 g).
^{1}H-NMR (DMSO-d_6) δ: 7.50-8.20(3H,m), 12.44(1H,br.s).
MS (ESI) m/z: 265$(M+H+CH_3CN)^+$.

[Referential Example 350]

2-Chloro-N-(4-chlorophenyl)acetamide:

[0819]



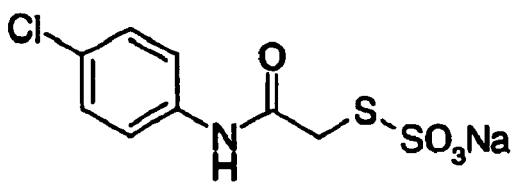
[0820] p-Chloroaniline (3.82 g) was dissolved in ethyl acetate (30 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 3.5 hours, crystals deposited were collected by filtration to obtain the title compound (4.78 g). The filtrate was concentrated to about

1/4, and crystals deposited were collected by filtration to obtain the title compound (1.01 g).
^{1}H-NMR ($CDCl_3$) δ: 4.19(2H,s), 7.33(2H,d,J=9.0Hz), 7.51(2H,d,J=9.0Hz), 8.22(1H,br.s).

[Referential Example 351]

Sodium S-[2-(4-chloroanilino)-2-oxoethyl]thiosulfate:

[0821]

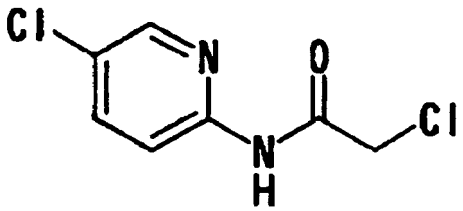


[0822] The compound (5.79 g) obtained in Referential Example 350 was dissolved in ethanol (140 ml), and an aqueous solution (140 ml) of sodium thiosulfate pentahydrate (7.04 g) was added at a time at 70°C to heat the mixture under reflux for 1.5 hours. The reaction mixture was concentrated to about 1/10, and crystals deposited were collected by filtration to obtain the title compound (8.20 g).
^{1}H-NMR (DMSO-d_6) δ: 3.73(2H,s), 7.35(2H,d,J=8.8Hz), 7.57(2H,d,J=8.8Hz), 10.30(1H,s).

[Referential Example 352]

2-Chloro-N-(5-chloropyridin-2-yl)acetamide hydrochloride:

[0823]

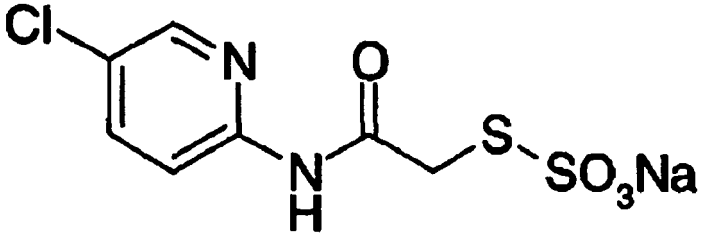


[0824] 2-Amino-5-chloropyridine (3.85 g) was dissolved in ethyl acetate (60 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 30 minutes, chloroacetyl chloride (0.5 ml) was additionally added, and the mixture was stirred at 60°C for additional 1 hour. Powder deposited was collected by filtration to obtain the title compound (6.18 g).
^{1}H-NMR (DMSO-d_6) δ: 4.36(2H,s), 7.94(1H,dd,J=8.8,2.7Hz), 8.09(1H,d,J=8.8Hz), 8.40(1H,d,J=2.7Hz), 11.03(1H,s).

[Referential Example 353]

Sodium S-{2-[(5-chloropyridin-2-yl)amino]-2-oxoethyl}thiosulfate:

[0825]



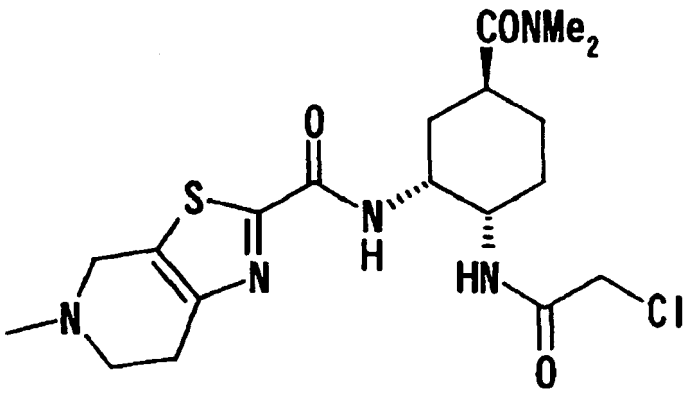
[0826] An aqueous solution (130 ml) with sodium thiosulfate pentahydrate (6.35 g) and sodium hydrogencarbonate

(2.15 g) dissolved therein was added to a solution with the compound (6.18 g) obtained in Referential Example 352 dissolved in ethanol (130 ml) at a time at 80°C under stirring, and the mixture was heated under reflux at 110°C for 2 hours. The reaction mixture was concentrated to solids under reduced pressure, and ethanol (500 ml) was added to the residue. The resultant mixture was heated and extracted twice. The extract was concentrated to about 1/20, and diethyl ether was added. Insoluble matter deposited was collected by filtration to obtain the title compound (6.65 g).
^{1}H-NMR (DMSO-d_6) δ: 3.77(2H,s), 7.89(1H,dd,J=9.0,2.7Hz), 8.09(1H,d,J=9.0Hz), 8.34(1H,d,J=2.7Hz), 10.57(1H,s).

[Referential Example 354]

N-{(1R,2S,5S)-2-[(2-chloroacetyl)amino]-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrathiazolo[5,4-c] pyridine-2-carboxamide hydrochloride:

[0827]

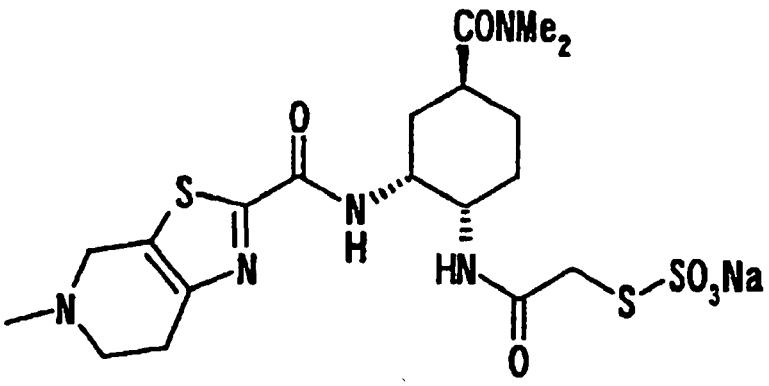


[0828] The compound (100 mg) obtained in Referential Example 253 was disslved in ethyl acetate (10 ml), and chloroacetyl chloride (21.6 μl) was added to heat and stir the mixture at 60°C for 30 minutes. After allowing the reaction mixture to cool, insoluble matter was collected by filtration and dissolved in methylene chloride-methanol, and the solvent was distilled off under reduced pressure to obtain the crude title compound (112 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(1H,m), 1.55-2.00(5H,m), 2.78(3H,s), 2.98(3H,s), 3.00-3.25(5H,m), 3.17(3H,s), 3.80-3.90(1H, m), 3.96(1H,d,J=12.9Hz), 4.00-4.15(1H,m), 4.02(1H,d,J=12.9Hz), 4.45-4,70(2H,m), 7.85-8.00(1H,br), 8.12(lH,d,J=7.3Hz), 8.35(1H,d,J=8.3Hz).
MS (ESI) m/z: 442 $(M+H)^+$.

[Referential Example 355]

Sodium S-{2-[((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrathiazolo[5,4-c]pyridine-2-yl)-carbonyl]amino}cyclohexyl)amino]-2-oxoethyl}thiosulfate:

[0829]

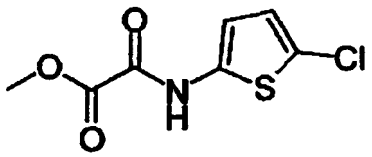


[0830] The compound (106 mg) obtained in Referential Example 354 was dissolved in ethanol (1.5 ml), and an aqueous solution (1.5 ml) of sodium thiosulfate pentahydrate (55 mg) and sodium hydrogencarbonate (18.6 mg) dissolved therein was added at a time at 90°C under stirring. The resultant mixture was heated under reflux for 1 hour. The reaction mixture was concentrated to solids under reduced pressure, and ethanol (10 ml) was added to the residue. The resultant mixture was heated and extracted. The extract was concentrated to about 1/2, and isopropyl ether (10 ml) was added. Insoluble matter deposited was collected by filtration to obtain the title compound (72 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(1H,m), 1.55-1.90(5H,m), 2.40(3H, s), 2.78(3H,s), 2.80-3.10(5H,m), 2.96(3H,s), 3.44 (1H,d,J=14.2Hz), 3.50(1H,d,J=14.2Hz), 3.68(2H,s), 3.75-3.90(1H,m), 4.45-4.50(1H,m), 8.01(1H,d,J=7.4Hz), 8.15(1H, d,J=8.3Hz) .

[Referential Example 356]

Methyl 2-[(5-chlorothien-2-yl)amino]-2-oxoacetate:

[0831]



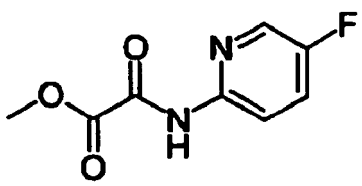
[0832] Triethylamine (1.25 ml) and diphenylphosphoryl azide (1.55 ml) were added to a suspension of 5-chlorothiophene-2-carboxylic acid (0.99 g) in toluene (20 ml), and the mixture was stirred at 80°C for 1 hour. After the reaction mixture was cooled to room temperature, tert-butanol (2 ml) was added, and the mixture was heated under reflux for 19 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (200 ml) was added to the resultant residue. The resultant mixture was successively washed with distilled water, a 10% aqueous solution of citric acid, distilled water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain tert-butyl 5-chloro-2-thienylcarbamate (1.05 g).
^{1}H-NMR ($CDCl_3$) δ: 1.51(9H,s), 6.21(1H,d,J=3.1Hz), 6.60(1H,d,J=3.1Hz), 6.91(1H,br.s).
MS (ESI) m/z: 234$(M+H)^+$.

[0833] After the product (1.87 g) obtained above was added to a 4N dioxane solution (40 ml) of hydrochloric acid, and the mixture was stirred at room temperature for 4 hours, the solvent was distilled off under reduced pressure. The residue was suspended in tetrahydrofuran (50 ml), and sodium hydrogencarbonate (2.02 g) and methyl chlorooxoacetate (0.883 ml) were added under ice cooling to stir the mixture at room temperature for 18 hours. After the solvent was distilled off under reduced pressure, and water and methylene chloride were added to the residue to conduct liquid separation, the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1), and the solvent was distilled off to obtain the title compound (1.44 g).
^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 6.61(1H,d,J=4.2HZ), 6.75(1H,d,J=4.2Hz), 9.42(1H,br.s).
MS (FAB) m/z: 220$(M+H)^+$.

[Referential Example 357]

Methyl 2-[(5-fluoropyridin-2-yl)amino]-2-oxoacetate:

[0834]

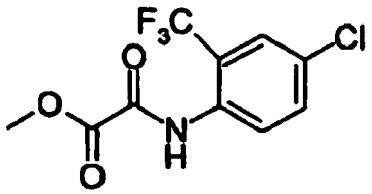


[0835] The title compound was obtained from 2-amino-5-fluoropyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.48-7.53(1H,m), 8.21(1H,d,J=2.9Hz), 8.27-8.31(1H,m), 9.41(1H,br.s).
MS (FAB) m/z: 198$(M+H)^+$.

[Referential Example 358]

Methyl 2-[4-chloro-2-(trifluoromethyl)anilino]-2-oxoacetate:

[0836]

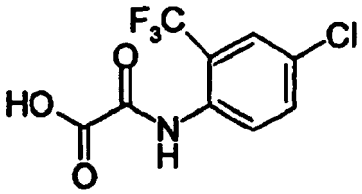


[0837] The title compound was obtained from 4-chloro-2-trifluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 4.01(3H,s); 7.58(1H,dd, J=8.8,2.2Hz), 7.65(1H,d,J=2.2Hz), 8.34(1H,d,J=8.8Hz), 9.30(1H,br.s).
MS (EI) m/z: 281$(M+H)^+$.

[Referential Example 359]

2-[4-Chloro-2-(trifluoromethyl)anilino]-2-oxoacetic acid:

[0838]

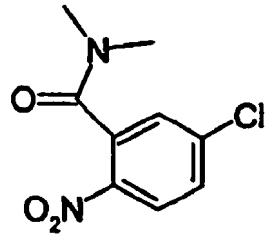


[0839] Lithium hydroxide (28 mg) was added to a solution of the compound (297 mg) obtained in Referential Example 358 in a mixed solvent of tetrahydrofuran (7ml) and water (3 ml), and the mixture was stirred at room temperature for 2 hours. 1N Hydrochloric acid (8 ml) and methylene chloride (20 ml) were added to the reaction mixture to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was dried to obtain the title compound (291 mg).
^{1}H-NMR ($CDCl_3$) δ: 7.61(1H,dd,J=8.8,2.5Hz), 7.68(1H,d,J=2.5Hz), 8.26(1H,d,J=8.8Hz), 9.36(1H,br.s).
MS (ESI, anion) m/z: 267$(M-H)^-$.

[Referential Example 360]

5-Chloro-N,N-dimethyl-2-nitrobenzamide:

[0840]

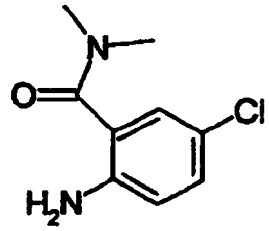


[0841] The title compound was obtained by condensing 5-chloro-2-nitrobenzoic acid with dimethylamine in a similar manner to the process described in Referential Example 143.
^{1}H-NMR ($CDCl_3$) δ: 2.86(3H,s), 3.16(3H,s), 7.38(1H,d,J=2.2Hz), 7.51(1H,dd,J=8.8,2.2Hz), 8.15(1H,d,J=8.8Hz).

[Referential Example 361]

2-Amino-5-chloro-N,N-dimethylbenzamide:

[0842]

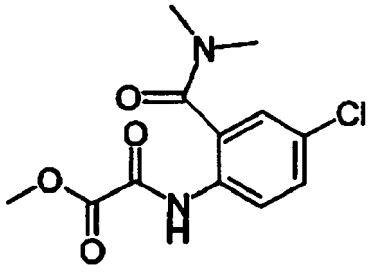


[0843] Iron(III) chloride hexahydrate (9.93 g) and zinc powder (8.01 g) were added to a solution of the compound (2.8 g) obtained in Referential Example 360 in a mixed solvent of N,N-dimethylformamide (80 ml) and water (40 ml), and the mixture was heated under reflux for 20 minutes. The reaction mixture was filtered through Celite 545, and ethyl acetate (200 ml) was added to the filtrate to conduct liquid separation. The resultant water layer was washed with ethyl acetate (100 ml x 2), and organic layers were combined, washed with distilled water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was subjected to column chromatography on silica gel (methylene chloride:hexane = 1:1 $\rightarrow$ 1:0 $\rightarrow$ methanol:methylene chloride = 1:100) to obtain the title compound (2.41 g).
^{1}H-NMR ($CDCl_3$) δ: 3.13(6H,s), 4.33(2H,br), 6.65(1H,d,J=8.5Hz), 7.07(1H,d,J=2.2Hz), 7.11(1H,dd,J=8.5,2.2Hz).
MS (ESI) m/z: 240(M+MeCN)$^+$.

[Referential Example 362]

Methyl 2-{4-chloro-2-[(dimethylamino)carbonyl]anilino}-2-oxoacetate:

[0844]

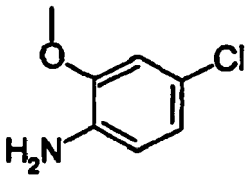


[0845] The title compound was obtained from the compound obtained in Referential Example 361 and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.09(6H,br), 3.96(3H,s), 7.30(1H,d,J=2.4Hz), 7.41(1H,d,J=8.8,2.4Hz), 8.34(1H,d,J=8.8Hz), 10.46

(1H,br).
MS (ESI) m/z: 285$(M+H)^+$.

[Referential Example 363] 4-Chloro-2-methoxyaniline:

[0846]

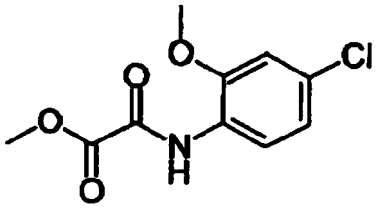


[0847] The title compound was obtained from 5-chloro-2-nitroanisole in a similar manner to the process described in Referential Example 361.
^{1}H-NMR ($CDCl_3$) δ: 3.65-3.95(2H,br), 3.87(3H,s), 6.61(1H,d,J=8.8Hz), 6.74-6.78(2H,m).
MS (ESI) m/z: 199$(M+MeCN+H)^+$.

[Referential Example 364]

Methyl 2-(4-chloro-2-methoxyanilino)-2-oxoacetate:

[0848]

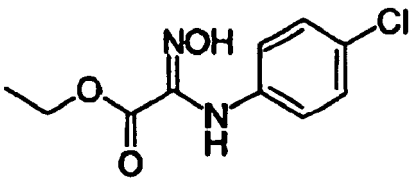


[0849] The title compound was obtained from the compound obtained in Referential Example 363 and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.92(3H,s), 3.97(3H,s), 6.90(1H,d,J=2.2Hz), 6.98(1H,dd,J=8.8,2.2Hz), 8.35(1H,d,J=8.8Hz), 9.33-9.44(1H,br).
MS (ESI) m/z: 244$(M+H)^+$.

[Referential Example 365]

Ethyl 2-(4-chloroanilino)-2-(hydroxyimino)-acetate:

[0850]

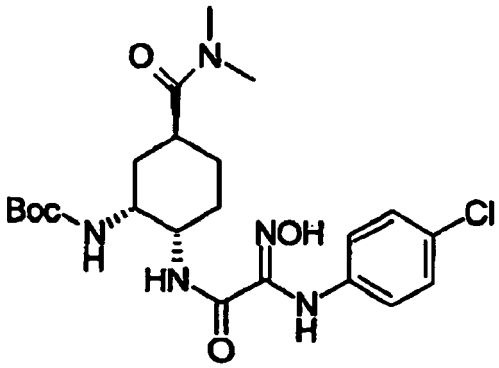


[0851] The title compound was obtained from 4-chloroaniline (3.03 g) and ethyl 2-chloro-2-hydroxyiminoacetate in a similar manner to the process described in literature (Gilchrist, T. L.; Peek, M. E.; Rees, C. W.; J. Chem. Soc. Chem. Commun., 1975, 913).
^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.60-1.80(1H,br), 4.28(2H,q,J=7.1Hz), 6.85(2H,d,J=8.6Hz), 7.24(2H,d,J=8.6Hz), 8.15-8.45(1H,br).
MS (ESI) m/z: 243$(M+H)^+$.

[Referential Example 366]

tert-Butyl (1R,2S,5S)-2-{[2-(4-chloroanilino)-2-(hydroxyimino)acetyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:

[0852]

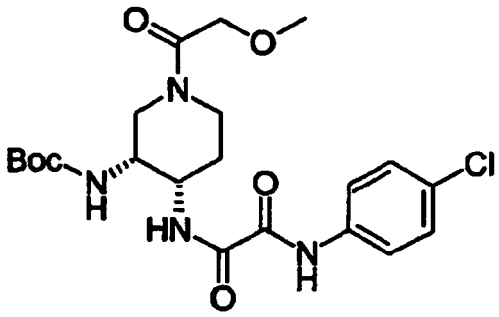


[0853] The compound (597 mg) obtained in Referential Example 144 was added to a solution of the compound (350 mg) obtained in Referential Example 365 in ethanol (5.0 ml), and the mixture was stirred at 70°C for 3 days. After the reaction mixture was concentrated under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1) to obtain the title compound (180 mg).
^{1}H-NMR (CD_3OD) δ: 1.46(9H,s), 1.47-1.84(6H,m), 1.88-1.95(1H,m), 2.90(3H,s), 3.08(3H,s), 3.90-3.97(1H,m), 4.11-4.17(1H,m), 6.84(2H,d,J=8.8Hz), 7.18(2H,d,J=8.8Hz).
MS (ESI) m/z: 504$(M+Na)^+$.

[Referential Example 367]

tert-Butyl (3R,4S)-4-{[2-(4-chloroanilino)-2-oxoacetyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

[0854]

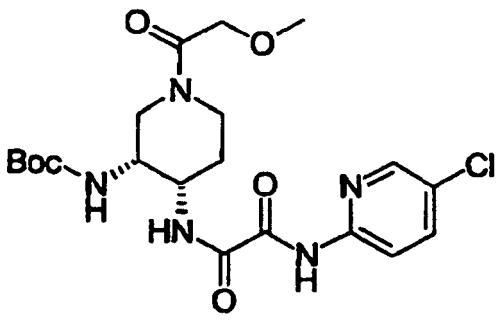


[0855] The title compound was obtained from the compound obtained in Referential Example 374 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.94-2.07(1H,br), 2.70-3.00(1H,m), 3.10-3.37(1H,m), 3.44(3H,s), 3.88-4.22(4H,m), 4.55-4.69(1H,br), 4.80-4.90(0.5H,br), 5.36-5.48(0.5H,br), 7.20-7.30(1H,br), 7.32(2H,d,J=8.8Hz), 7.62(2H,d,J=8.8Hz), 8.20-8.40(1H,br), 9.15-9.25(1H,br).
MS (ESI) m/z: 469$(M+H)^+$.

[Referential Example 368]

tert-Butyl (3R,4S)-4-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

[0856]

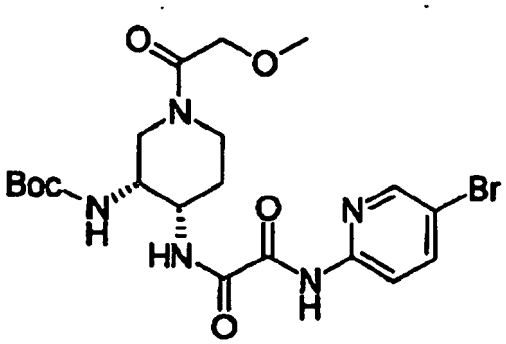


[0857] The title compound was obtained from the compound obtained in Referential Example 266 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.65-2.30(2H,br), 2.68-3.02(1H,m), 3.10-3.35(1H,m), 3.44(3H,s), 3.80-4.25(4H,m), 4.45-4.70(1H,m), 5.05-5.20(0.5H,m), 5.80-5.93(0.5H,m), 7.30-7.40(1H,br), 7.71(1H,br d,J=8.7Hz), 7.95-8.05(0.3H,br), 8.19(1H,br d,J=8.8 Hz), 8.31(1H,br.s), 8.38-8.53(0.7H,br), 9.74-9.84(1H,br).
MS (ESI) m/z: 470$(M+H)^+$.

[Referential Example 369]

tert-Butyl (3R,4S)-4-({2-[(5-bromopyridin-2-yl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

[0858]

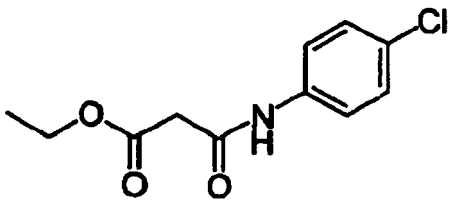


[0859] The title compound was obtained from the compound obtained in Referential Example 375 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.50-1.75(1H,m), 1.95-2.13(1H,br), 2.70-2.98(1H,m), 3.05-3.36(1H,m), 3.45(3H,s), 3.80-4.24(4H,m), 4.57-4.73(1H,br), 4.85-4.95(0.25H,br), 5.10-5.15(0.25H,br), 5.45-5.58(0.5H,br), 7.30-7.38(1H,m), 7.84 (1H,dd,J=8.8,2.2Hz), 8.16(1H,d,J=8.8Hz), 8.30-8.55(1H,br), 8.40(1H,d,J=2.2Hz), 9.68(1H,br.s).

[Referential Example 370]

Ethyl 3-(4-chloroanilino)-3-oxopropionate:

[0860]

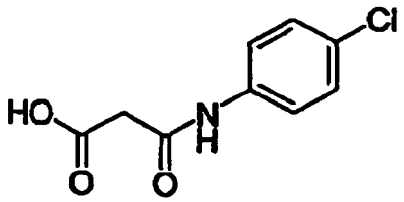


[0861] Potassium ethyl malonate (3.2 g), 1-hydroxybenzotriazole (2.1 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide-hydrochloride (4.5 g) were successively added to a solution of 4-chloroaniline (2.0 g) in N,N-dimethylformamide (20 ml) at room temperature, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium hydrogencarbonate, a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound (4.0 g).
^{1}H-NMR ($CDCl_3$) δ: 1.33(3H,t,J=7.3Hz), 3.47(2H,s), 4.26(2H,q,J=7.3Hz), 7.29(2H,d,J=8.8Hz), 7.51(2H,d,J=8.8Hz), 9.32 (1H,br.s).

[Referential Example 371]

3-(4-Chloroanilino)-3-oxopropionic acid:

[0862]

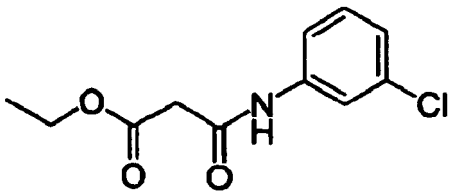


[0863] A 1N aqueous solution (10 ml) of sodium hydroxide was added dropwise to a solution of the compound (1.0 g) obtained in Referential Example 370 in ethanol (10 ml) at room temperature, and the mixture was stirred for 2 hours. 1N Hydrochloric acid (10 ml) was added to the reaction mixture, the mixture was stirred, and insoluble matter deposited was then collected by filtration to obtain the title compound (0.5 g).
^{1}H-NMR (DMSO-d_6) δ: 3.34(2H,s), 7.35(2H,d,J=8.8Hz), 7.59(2H,d,J=8.8Hz), 10.26(1H,s), 12.66(1H,br.s).

[Referential Example 372]

Ethyl 3-(3-chloroanilino)-3-oxopropionate:

[0864]

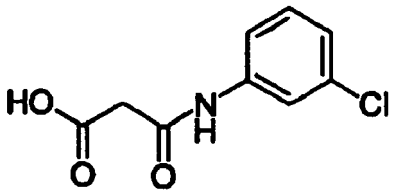


[0865] The title compound was obtained by condensing 3-chloroaniline with potassium ethyl malonate in a similar manner to the process described in Referential Example 370.
^{1}H-NMR ($CDCl_3$) δ: 1.33(3H,t,J=7.3Hz), 3.47(2H,s), 4.26(2H,q,J=7.3Hz), 7.09(1H,d,J=8.8Hz), 7.22-7.26(1H,m), 7.39 (1H,d,J=8.8Hz), 7.69(1H,s), 9.35(1H,br.s).

[Referential Example 373]

3-(3-Chloroanilino)-3-oxopropionic acid:

[0866]

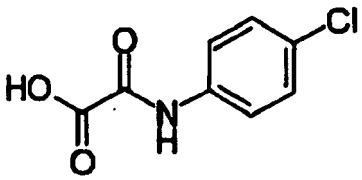


[0867] The title compound was obtained from the compound obtained in Referential Example 372 in a similar manner to the process described in Referential Example 371.
^{1}H-NMR (DMSO-d_6) δ: 3.35(2H,s), 7.11(1H,d,J=8.8Hz), 7.33(1H,t,J=8.8Hz), 7.39(1H,d,J=8.8Hz), 7.78(1H,s), 10.31(1H,s), 12.67(1H,br.s).

[Referential Example 374]

2-(4-Chloroanilino)-2-oxoacetic acid:

[0868]

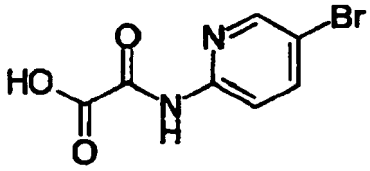


[0869] The title compound was obtained from the compound obtained in Referential Example 242 in a similar manner to the process described in Referential Example 359.
^{1}H-NMR (DMSO-d_6) δ: 7.37(2H,d,J=8.8Hz), 7.79(2H,d,J=8.8Hz), 10.66(1H,s).

[Referential Example 375]

2-[(5-Bromopyridin-2-yl)amino]-2-oxoacetic acid:

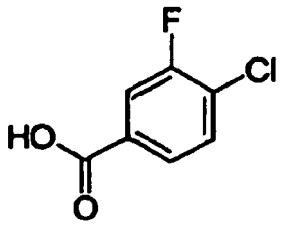
[0870]



[0871] The title compound was obtained from the compound obtained in Referential Example 262 in a similar manner to the process described in Referential Example 359.
^{1}H-NMR (DMSO-d_6) δ: 7.95-8.00(1H,m), 8.08(1H,dd,J=8.8,2.0Hz), 8.50(1H,d,J=2.0Hz), 10.74(1H,s).

[Referential Example 376] 4-Chloro-3-fluorobenzoic acid:

[0872]

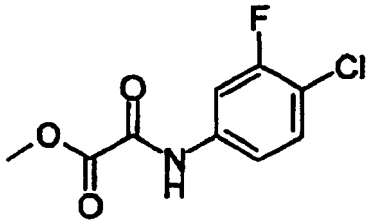


[0873] Sodium chlorite (17 g) was added portionwise to a mixture solution composed of 4-chloro-3-fluorobenzaldehyde (10 g), amidosulfuric acid (18 g), tert-butyl alcohol (50 ml) and water (50 ml) under ice cooling, and the mixture was stirred for 4 days while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water, 1N hydrochloric acid and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure, the resultant residue was recrystallized from a mixed solvent of diisopropyl ether and hexane to obtain the title compound (11.2 g).
^{1}H-NMR (DMSO-d_6) δ: 7.72(1H,dt,J=8.3,1.5Hz), 7.77(1H,dt,J=8.3,1.6Hz), 7.82(1H,dt,J=9.7,1.5Hz), 13.45(1H,s).

[Referential Example 377]

Methyl 2-(4-chloro-3-fluoroanilino)-2-oxoacetate:

[0874]

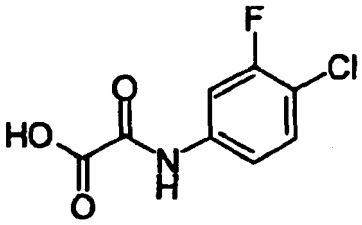


[0875] The title compound was obtained by subjecting the compound obtained in Referential Example 376 to Curtius rearrangement reaction and then condensing this product with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 356.
^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.25-7.27(1H,m), 7.39(1H,t,J=8.5Hz), 7.72(1H,dd,J=10.4,2.4Hz), 8.90(1H,br.s).

[Referential Example 378]

2-(4-Chloro-3-fluoroanilino)-2-oxoacetic acid:

[0876]

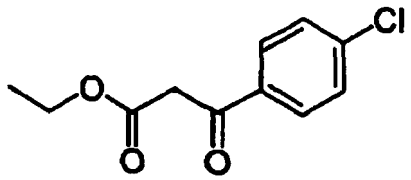


[0877] The title compound was obtained from the compound obtained in Referential Example 377 in a similar manner to the process described in Referential Example 359.
^{1}H-NMR (DMSO-d_6) δ: 7.52(1H,t,J=8.8Hz), 7.63(1H,dd,J=8.8,2.2Hz), 7.88(1H,dd,J=12.0,2.2Hz), 10.83(1H,br.s).

[Referential Example 379]

Ethyl 3-(4-chlorophenyl)-3-oxopropionate:

[0878]

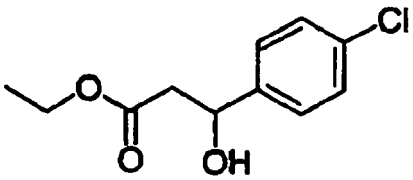


[0879] Triethylamine (17 ml) and magnesium chloride (5.5 g) were added to a suspension of potassium ethyl malonate (8.2 g) in ethyl acetate (100 ml) under ice cooling, and the mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. On the other hand, a suspension composed of 4-chlorobenzoic acid (5.0 g), thionyl chloride (12 ml), N,N-dimethylformamide (one drop) and toluene (100 ml) was heated under reflux for 1 hour, and the reaction mixture was then concentrated. The resultant residue was dissolved in ethyl acetate, and the solution was added dropwise to the reaction mixture previously prepared under ice cooling. The resultant mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. A 10% aqueous solution of citric acid was added to the reaction mixture, and the mixture was stirred for 30 minutes to separate the resultant organic layer. The organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was isolated and purified by column chromatography on silica gel (chloroform) to obtain the title compound (6.4 g).
^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.3Hz), 3.96(2H,s), 4.21(2H,q,J=7.3H_z), 7.46(2H,d,J=8.8Hz), 7.89(2H,d,J=8.8Hz).

[Referential Example 380]

Ethyl 3-(4-chlorophenyl)-3-hydroxypropionate:

[0880]

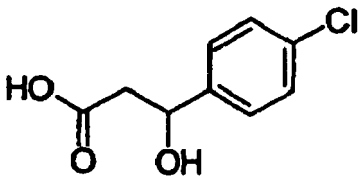


[0881] Sodium borohydride (0.2 g) was added portionwise under ice cooling to a solution of the compound (1.0 g) obtained in Referential Example 379 in tetrahydrofuran (10 ml), and the mixture was stirred for 2 hours while the temperature of the system was gradually raised to room temperature. A 10% aqueous solution of citric acid was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was isolated and purified by column chromatography on silica gel (chloroform) to obtain the title compound (0.56 g).
^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t,J=7.3Hz), 2.70(1H,d.J=7.8Hz), 2.71(1H,d,J=3.4Hz), 3.37(1H,d,J=3.4Hz), 4.18(2H,q, J=7.3Hz), 5.09-5.13(1H,m), 7.30-7.35(5H,m).

[Referential Example 381]

3-(4-Chlorophenyl)-3-hydroxypropionic acid:

[0882]

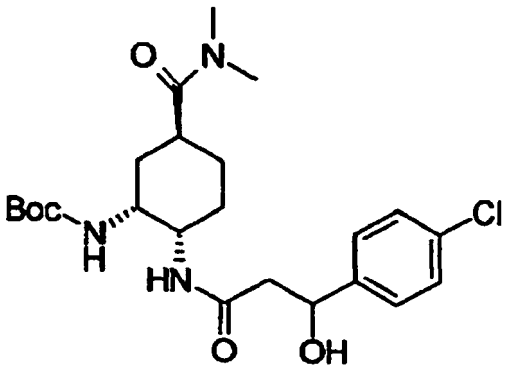


[0883] The title compound was obtained from the compound obtained in Referential Example 380 in a similar manner to the process described in Referential Example 359.
^{1}H-NMR (DMSO-d_6) δ: 3.25-3.32(1H,m), 4.89-4.95(1H,m), 5.45-5.53(1H,m), 7.35-7.36(5H,m), 12.11-12.18(1H,m).
MS (ESI,anion) m/z: 198(M-H)$^-$.

[Referential Example 382]

tert-Butyl (1R,2S,5S)-2-{[3-(4-chlorophenyl)-3-hydroxypropanoyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:

[0884]

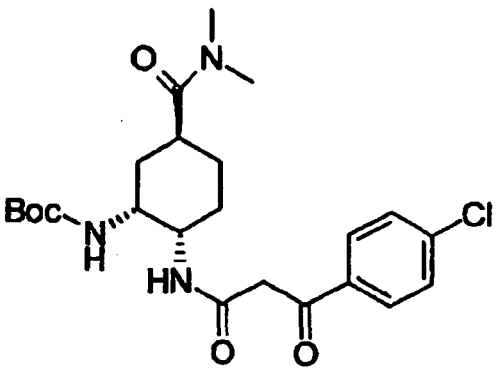


[0885] The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 381 in a similar manner to the process described in Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.21-1.44(2H,m), 1.46(9H,s), 1.76-1.92(2H,m), 1.95-2.10(2H,m), 2.40-2.55(2H,m), 2.55-2.68(1H,m), 2.94(3H,s), 3.05(3H,s), 3.82-3.96(1H,m), 4.02-4.17(1H,m), 4.65-4.80(2H,m), 5.03-5.13(1H,m), 7.28-7.33(5H,m).
MS (ESI) m/z: 468(M+H)$^+$.

[Referential Example 383]

tert-Butyl (1R,2S,5S)-2-{[3-(4-chlorophenyl)-3-oxopropanoyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:

[0886]

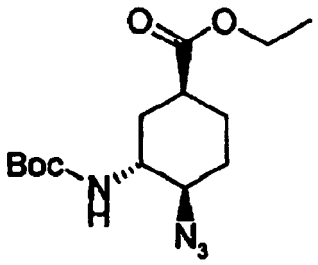


[0887] Manganese dioxide (0.47 g) was added to a solution of the compound (0.5 g) obtained in Referential Example 382 in 1,4-dioxane (20 ml) at room temperature, and the mixture was stirred for 4 days. Insoluble matter was removed by filtration through Celite pad, and the resultant filtrate was concentrated under reduced pressure to obtain the title compound (0.46 g).
^{1}H-NMR (DM50-d_6) δ: 1.28-1.39(1H,m), 1.40(9H,s), 1.41-1.63(3H,m), 2.25-2.42(2H,m), 2.76(3H,s), 2.90-2.97(1H,m), 2.98(3H,s), 3.56(2H,s), 3.89-3.97(1H,m), 4.88-4.98(1H,m), 6.65-6.70(1H,m), 7.30-7.35(4H,m), 7.33(1H,dd, J=2.9,1.7Hz).
MS (ESI,anion) m/z: 464$(M-H)^-$.

[Referential Example 384]

Ethyl (1S,3R,4R)-4-azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate:

[0888]

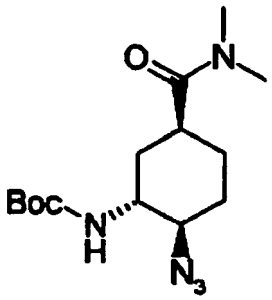


[0889] The title compound was obtained from the compound obtained in Referential Example 248 in a similar manner to the process described in Referential Example 249.
$[\alpha]_D^{25}$ +62° (c=1, chloroform)
^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t,J=7.1Hz), 1.46(9H,s), 1.61(1H,s), 1.61-1.71(2H,m), 1.81-1.90(1H,m), 1.97-2.03(1H,m), 2.22-2.28(1H,m), 2.56-2.60(1H,m), 3.54(1H,br.s), 3.63-3.68(1H,m), 4.16(2H,q,J=7.1Hz), 4.58(1H,br.s).

[Referential Example 385]

tert-Butyl (1R,2R,5S)-2-azido-5-[(dimethylamino)carbonyl] cyclohexylcarbamate:

[0890]

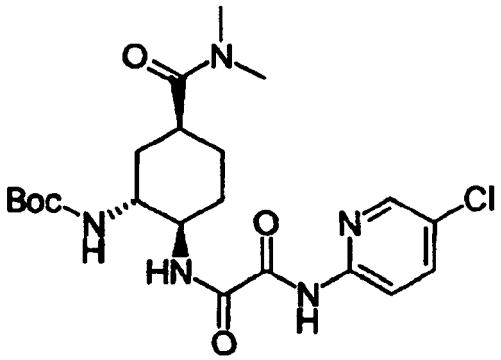


[0891] The title compound was obtained from the compound obtained in Referential Example 384 in similar manners to Referential Examples 250 and 251.
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.40-2.20(6H,m), 2.70-2.80(1H,m), 2.93(3H,s), 3.03(3H,s), 3.60-3.78(1H,m), 3.83-3.95 (1H,m), 4.65(1H,d,J=7.2Hz).

[Referential Example 386]

tert-Butyl (1R,2R,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:

[0892]

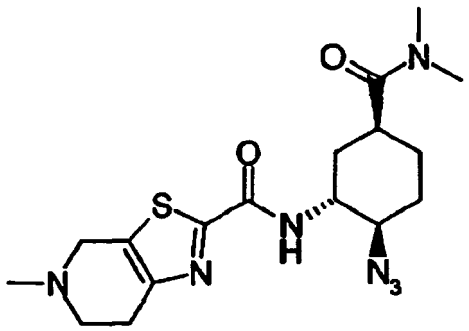


[0893] The title compound was obtained by converting the azide group of the compound obtained in Referential Example 385 into an amino group in a similar manner to the process described in Referential Example 90 and then condensing this product with the compound obtained in Referential Example 266 in a similar manner to the process described in Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.13-2.25(16H,m), 2.94(3H,s), 3.03(3H,s), 3.60-3.78(1H,m), 4.13-4.31(1H,m), 4.45-4.65(1H,m), 7.80 (1H,dd,J=8.8,2.4Hz), 8.03(1H,br.s), 8.21(1H,d,J=8.8Hz), 8.29(1H,d,J=2.4Hz), 9.71(1H,s).
MS (ESI) m/z: 468$(M+H)^+$.

[Referential Example 387]

N-{(1R,2R,5S)-2-Azido-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

[0894]

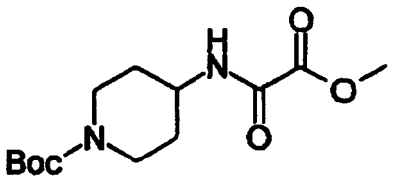


[0895] The title compound was obtained from the compound obtained in Referential Example 385 and the compound obtained in Referential Example 10 in a similar manner to the process described in Referential Example 252.
^{1}H-NMR ($CDCl_3$) δ: 1.75-2.08(6H,m), 2.20-2.32(1H,m), 2.51(3H,s), 2.75-2.97(4H,m), 2.95(3H,s), 3.04(3H,s), 3.65-3.80 (3H,m), 4.27-4.39(1H,m), 7.17-7.28(1H,m).
MS (ESI) m/z: 392$(M+H)^+$.

[Referential Example 388]

tert-Butyl 4-[(2-methoxy-2-oxoacetyl)amino]piperidine-1-carboxylate:

[0896]

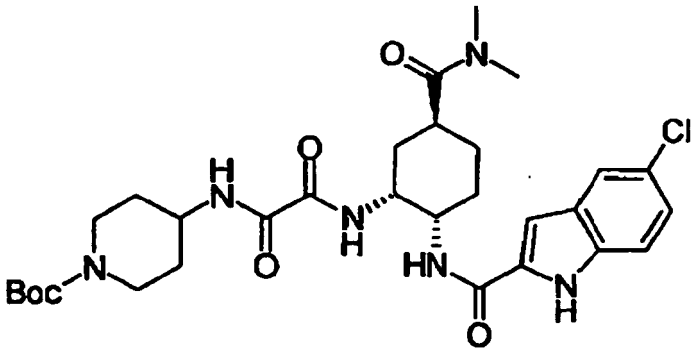


[0897] The title compound was obtained from (4-amino-N-tert-butoxycarbonyl)piperidine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR (DMSO-d_6) δ: 1.46(9H,s), 1.34-1.51(2H,m), 1.89-1.98(2H,m), 2.82-2.96(2H,m), 3.91(3H,s), 3.88-4.14(3H,m), 6.96-7.07(1H,m).
MS (FAB) m/z: 287$(M+H)^+$.

[Referential Example 389]

tert-Butyl 4-{[2-({(1R,2S,SS)-2-{[(S-chloroindol-2-yl)-carbonyl]amino}-5-[(dimethylamino)carboyl]cyclohexyl}-amino)-2-oxoacetyl]amino}piperidine-1-carboxylate:

[0898]

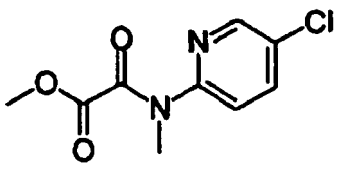


[0899] The title compound was obtained from the compound obtained in Referential Example 310 and the compound obtained in Referential Example 388 in a similar manner to the process described in Referential Example 191.
^{1}H-NMR (DMSO-d_6) δ: 1.46(9H,s), 1.35-2.28(11H,m), 2.70-3.18(9H,m), 3.80-4.57(4H,m), 6.78(1H,s), 7.15-8.12(6H,m), 9.45(1H,s).
MS (FAB) m/z: 617$(M+H)^+$.

[Referential Example 390]

Methyl 2-[(5-chloropyridin-2-yl)(methyl)amino]-2-oxoacetate:

[0900]

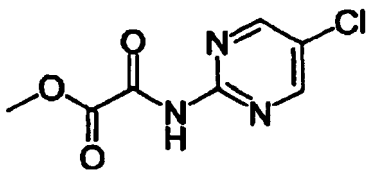


[0901] The title compound was obtained from 5-chloro-N-methyl-2-pyridineamine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.43(3H,s), 3.81(3H,s), 7.08(1H,br.s), 7.68-7.78(1H,m), 8.27(1H,br.s).
MS (ESI) m/z: 229$(M+H)^+$.

[Referential Example 391]

Methyl 2-[(5-chloropyrimidin-2-yl)amino]-2-oxoacetate:

[0902]

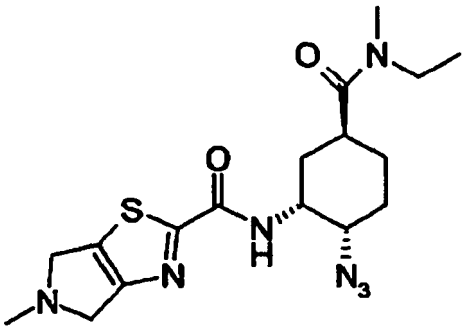


[0903] The title compound was obtained from 2-amino-5-chloropyrimidine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 4.00(3H,s), 8.63(2H,s), 9.58(1H,br.s).
MS (ESI) m/z: 215$(M+H)^+$.

[Referential Example 392]

N-((1R,2S,5S)-2-Azido-5-{[ethyl(methyl)amino]carbonyl}-cyclohexyl)-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazole-2-carboxamide:

[0904]

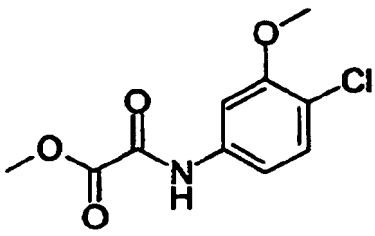


[0905] The title compound was obtained from the compound obtained in Referential Example 323 and the compound obtained in Referential Example 293 in a similar manner to the process described in Referential Example 252.
^{1}H-NMR ($CDCl_3$) δ: 1.08,1.15(3H,each t,J=7.1Hz), 1.74-1.88(4H,m), 2.12-2.22(2H,m), 2.67(3H,s), 2.81-2.86(1H,m), 2.89,2.96(3H,each s), 3.28-3.43(2H,m), 3.91-4.10(5H,m), 4.60-4.62(1H,m), 7.21(1H,d,J=7.6Hz).
MS (ESI) m/z: 392$(M+H)^+$.

[Referential Example 393]

Methyl 2-(4-chloro-3-methoxyanilino)-2-oxoacetate:

[0906]

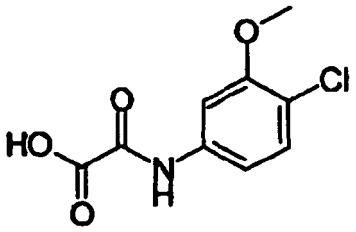


[0907] The title compound was obtained by reducing 2-chloro-5-nitroanisole in a similar manner to the process described in Referential Example 361 into an amino derivative and then condensing the amino derivative with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.93(3H,s), 3.98(3H,s), 7.00(1H,dd,J=8.5,2.4Hz), 7.33(1H,d,J=8.5Hz), 7.57(1H,d,J=2.4Hz), 8.89 (1H,br.s).

[Referential Example 394]

2-(4-Chloro-3-methoxyanilino)-2-oxoacetic acid:

[0908]

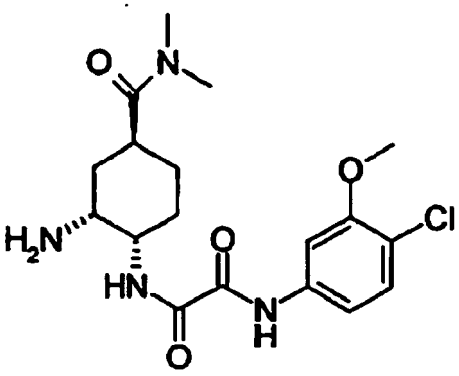


[0909] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 393 in a similar manner to the process described in Referential Example 359.
^{1}H-NMR (DMSO-d_6) δ: 3.81(3H,s), 7.36(1H,d,J=8.7Hz), 7.43(1H,d,J=8.7Hz), 7.65(1H,d,J=2.2Hz), 10.79(1H,s).
MS (ESI, anion) m/z: 228$(M-H)^-$.

[Referential Example 395]

N^1-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(4-chloro-3-methoxyphenyl)ethanediamide:

[0910]

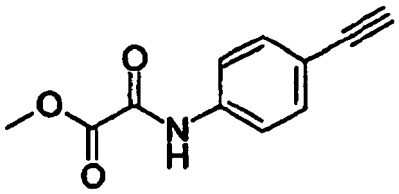


[0911] The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 394 in a similar manner to the process described in Referential Example 97, treating this product with hydrochloric acid in a similar manner to the process described in Referential Example 69 and then neutralizing it with a 1N aqueous solution of sodium hydroxide.
^{1}H-NMR ($CDCl_3$) δ: 1.48-2.00(8H,m), 2.84-2.93(lH,m), 2.95(3H,s), 3.08(3H,s), 3.33-3.35(1H,m), 3.89-3.94(4H,m), 7.06 (1H, dd,J=8.5,2.2Hz), 7.32(1H,d,J=8.5Hz), 7.56(1H,d,J=2.2Hz), 8.05(1H,d,J=8.5Hz), 9.43(1H,br.s).
MS (ESI) m/z: 397(M^+).

[Referential Example 396]

Methyl 2-(4-ethynylanilino)-2-oxoacetate:

[0912]

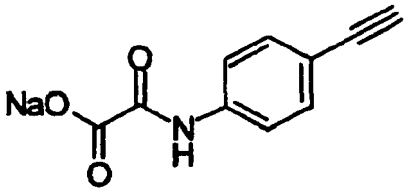


[0913] The title compound was obtained from 4-ethynylaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 3.09(1H,s), 3.98(3H,s), 7.50(2H,d,J=8.4Hz), 7.62(2H,d,J=8.4Hz), 8.89(1H,br.s).

[Referential Example 397]

Sodium 2-(4-ethynylanilino)-2-oxoacetate:

[0914]

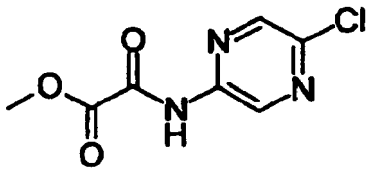


[0915] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 396 with sodium hydroxide in a similar manner to the process described in Referential Example 266.
^{1}H-NMR (DMSO-d_6) δ: 4.06(1H,s), 7.39(2H,d,J=8.4Hz), 7.80(2H,d,J=8.4Hz), 10.33(1H,br.s).

[Referential Example 398]

Methyl 2-[(5-chloropyrazin-2-yl)amino]-2-oxoacetate:

[0916]

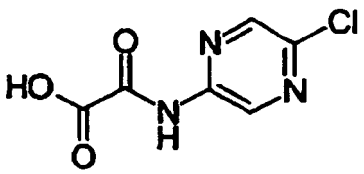


[0917] The title compound was obtained from 2-amino-5-chloropyrazine synthesized in accordance with literature (Sato, Nobuhiro et al., J. Heterocycl. Chem., 1982, 19(3), 673-4) and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.
^{1}H-NMR ($CDCl_3$) δ: 4.02(3H,s), 8.35(1H,d,J=1.5Hz), 9.37(IH,d,J=1.5Hz), 9.41(1H,br.s).
MS (FAB) m/z: 216$(M+H)^+$.

[Referential Example 399]

2-[(5-Chloropyrazin-2-yl)amino]-2-oxoacetic acid:

[0918]

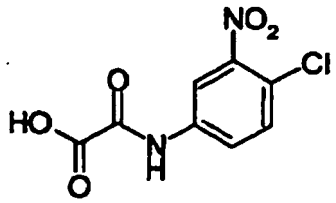


[0919] The title compound was obtained from the compound obtained in Referential Example 398 in a similar manner to the process described in Referential Example 359.
^{1}H-NMR (DMSO-d_6) δ: 8.62(1H,s), 9.02(1H,br.s), 11.30(1H,s). MS (EI) m/z: 201 M^+.

[Referential Example 400]

2-(4-Chloro-3-nitroanilino)-2-oxoacetic acid:

[0920]

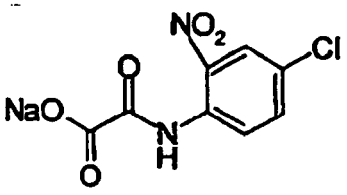


[0921] The title compound was obtained by condensing 4-chloro-3-nitroaniline with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242 and then hydrolyzing this product in a similar manner to the process described in Referential Example 359.
^{1}H-NMR (DMSO-d_6) δ: 7.76(1H.dd,J=8.8Hz),
8.04(1H,dd,J=8.8,2.4Hz), 8.55(1H,d,J=2.4Hz), 11.24(1H,s). No proton attributable to the carboxylic acid was observed.
MS (EI) m/z: 244 M^+.

[Referential Example 401]

Sodium 2-(4-chloro-2-nitroanilino)-2-oxoacetate:

[0922]

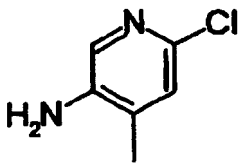


[0923] The title compound was obtained by condensing 4-chloro-2-nitroaniline with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242, hydrolyzing this product in a similar manner to the process described in Referential Example 266, dissolvig the resultant residue in methanol, adding a 1N aqueous solution of sodium hydroxide and collecting precipitate formed by filtration.
^{1}H-NMR (DMSO-d_6) δ: 7.84(1H,dd,J=9.0,2.5Hz), 8.20(1H,d,J=2.5Hz), 8.67(1H,d,J=9.0Hz), 11.89(1H,s).

[Referential Example 402]

6-Chloro-4-methyl-3-pyridineamine:

[0924]

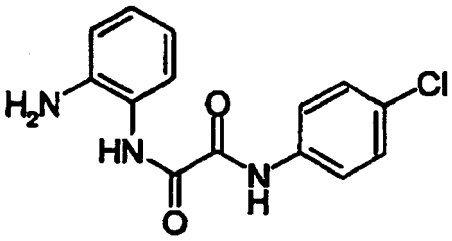


[0925] 2-Chloro-4-methyl-5-nitropyridine (173 mg) was dissolved in ethanol (5 ml), and a catalytic amount of Raney nickel catalyst was added to stir the mixture at room temperature for 9 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:2) to obtain the title compound (113 mg).
^{1}H-NMR ($CDCl_3$) δ: 2.13(3H,s), 3.85(2H,br.s), 6.96(1H,s), 7.74(1H,s).
MS (EI) m/z: 142 M^+.

[Referential Example 403]

N^1- (2-Aminophenyl) -N^2- (4-chlorophenyl)ethanamide:

[0926]

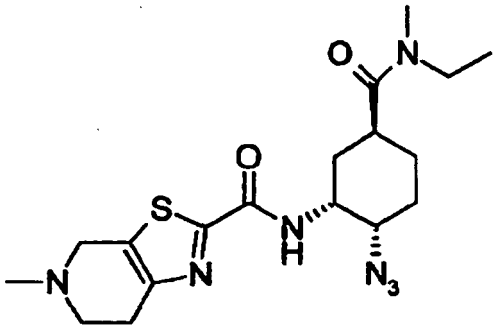


[0927] The title compound was obtained by condensing 1,2-benzenediamine with the compound obtained in Referential Example 374 in a similar manner to the process described in Referential Example 59.
^{1}H-NMR (DMSO-d_6) δ: 5.00(2H,s), 6.59-6.63(1H,m), 6.78(1H,dd,J=8.1,1.2Hz), 6.96-7.01(1H,m), 7.25(1H,dd,J-7.8,1.2Hz), 7.44(2H,d,J=8.8Hz), 7.91(2H,d,J=8.8Hz), 10.04(lH,s),10.91(1H,s).
MS (FAB) : 290$(M+H)^+$.

[Referential Example 404]

N-((1R,2S,5S)-2-Azido-5-{[ethyl(methyl)amino]carbonyl}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

[0928]

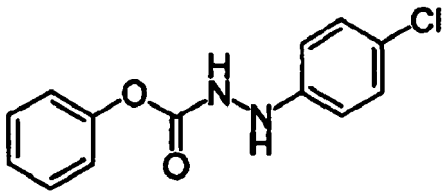


[0929] The title compound was obtained by treating the compound obtained in Referential Example 323 with hydrochloric acid, performing deprotection and then condensing this product with the compound obtained in Referential Example 10 in a similar manner to the process described in Referential Example 252.
^{1}H-NMR ($CDCl_3$) δ: 1.08(1/2 of 3H,t,J=7.2Hz), 1.14(1/2 of 3H,t,J=7.2Hz), 1.70-1.90(4H,m), 2.10-2.25(2H,m), 2.52(3H,s), 2.78-3.00(BH,m), 3.25-3.45(2H,m), 3.69(1H,d,J=13.4Hz), 3.73(1H,d,J=13.4Hz), 3.87-3.95(1H,m), 4.55-4.62(1H,m), 7.26(1H,d,J=7.6Hz).

[Referential Example 405]

Phenyl 2-(4-chlorophenyl)-1-hydrazinecarboxylate:

[0930]

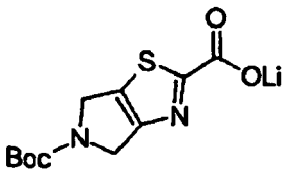


[0931] (4-Chlorophenyl)hydrazine hydrochloride (3.00 g) was dissolved in tetrahydrofuran (50 ml), diethyl ether (50 ml) and a saturated aqueous solution of sodium hydrogencarbonate. An organic layer was separated, dried over anhydrous sodium sulfate and then concentrated, giving (4-chlorophenyl)hydrazine as a brown solid. This product was dissolved in benzene (15 ml), and the solution was heated under reflux, to which a solution of diphenyl carbonate (5.22 g) in benzene (8.0 ml) was added dropwise over at least 30 minutes. After refluxing for 19 hours, the reaction mixture was allowed to cool and concentrated. Benzene (15 ml) was then added to the residue. The mixture was subjected to ultrasonic treatment, giving a suspension. After hexane (50 ml) was added to the suspension, and the mixture was stirred for 30 minutes, insoluble matter was collected by filtration and dried to obtain the title compound (1.05 g).
^{1}H-NMR ($CDCl_3$) δ: 5.86(1H,br.s), 6.83-6.92(3H,m), 7.17(1H,br.s), 7.20-7.32(4H,m), 7.37(2H,t,J=7.7Hz).
MS (ESI) m/z: 263$(M+H)^+$.

[Referential Example 406]

Lithium 5-tert-butoxycarbonyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole-2-carboxylate:

[0932]



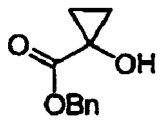
[0933] The title compound was obtained from the compound obtained in Referential Example 33 in a similar manner

to the process described in Referential Example 10.
^{1}H-NMR (DMSO-d_6) δ: 1.46(9H,s), 4.30-4.70(4H,m).

[Referential Example 407]

Benzyl 1-hydroxycyclopropanecarboxylate:

[0934]

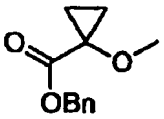


[0935] Triethylamine (1.0 ml) and benzyl bromide (650 μl) were added to a solution of 1-hydroxycyclopropane-carboxylic acid (409 mg) in tetrahydrofuran (3.0 ml), and the mixture was stirred at room temperature for 23 hours. Methylene chloride and 1N hydrochloric acid were added to the reaction mixture to separate the mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. A crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (607 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.16(2H,dd,J=7.9,4.9Hz), 1.32(2H,dd,J=7.9,4.9Hz), 3.09(0.5H,s), 3.11(0.5H,s), 5.17(2H,s), 7.30-7.39(5H,m).
MS (FAB) m/z: 192 $(M+H)^+$.

[Referential Example 408]

Benzyl 1-methoxycyclopropanecarboxylate:

[0936]

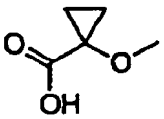


[0937] 60% Sodium hydride in oil (345 mg) and methyl iodide (900 μl) were added to a solution of the compound (600 mg) obtained in Referential Example 407 in tetrahydrofuran (5.0 ml), and the mixture was heated under reflux for 28 hours. Ethyl acetate and a saturated aqueous solution of ammonium chloride were added to the reaction mixture to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. A crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to obtain the title compound (340 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.16(2H,dd,J=7.9,4.8Hz), 1.31(2H,dd,J=7.9,4.8Hz), 3.42(3H,s), 5.18(2H,s), 7.30-7.39(5H,m).
MS (FAB) m/z: 207 $(M+H)^+$.

[Referential Example 409]

1-Methoxycyclopropanecarboxylic acid:

[0938]

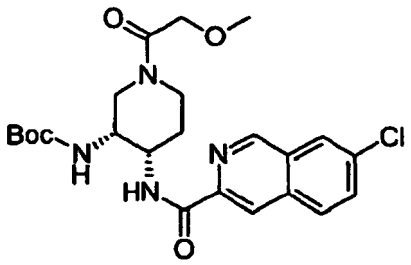


[0939] The title compound was obtained from the compound obtained in Referential Example 408 in a similar manner to the process described in Referential Example 152.
^{1}H-NMR ($CDCl_3$) δ: 1.23(2H,dd,J=8.0,4.9Hz), 1.38(2H,dd,J=8.0,4.9Hz), 3.45(3H,s), 8.80-9.00(1H,br).

[Referential Example 410]

tert-Butyl (3R,4S)-4-({7-chloroisoquinolin-3-yl}carbonyl)-amino}-1-(2-methoxyacetyl)piperidin-3-ylcarbamate:

[0940]

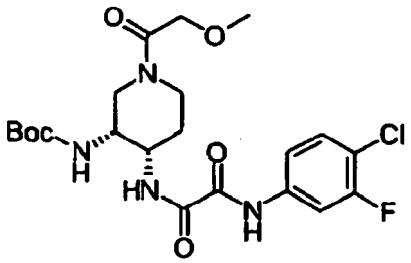


[0941] The title compound was obtained from the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,br s), 1.62-1.80(1H,m), 2.04-2.22(1H,m), 2.95-3.32(1H,m), 3.38-3.53(1H,m), 3.46(3H,s), 3.84-3.95(1H,m), 4.02-4.27(3H,m), 4.30-4.65 (2H,m), 4.87-4.98(0.5H,br), 5.32-5.43(0.5H,br), 7.71(1H,dd,J=8.8,2.0Hz), 7.94(1H,d,J=8.8Hz), 8.02(1H,s), 8.55-8.66(0.7H,br), 8.58(1H,s), 8.73-8.85(0.3H,br), 9.14(1H,br s).
MS (ESI) m/z: 477$(M+H)^+$.

[Referential Example 411]

tert-Butyl (3R,4S)-4-{[2-(4-chloro-3-fluoroanilino)-2-oxoacetyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

[0942]

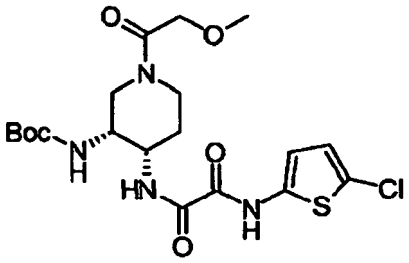


[0943] The title compound was obtained by condensing the compound obtained in Referential Example 220 with the compound obtained in Referential Example 337 in a similar manner to the process described in Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.60-1.75(1H,m), 1.92-2.08(1H,m), 2.68-2.80(0.5H,m), 2.88-3.03(0.5H,m), 3.06-3.24 (0.5H,m), 3.27-3.36(0.5H,m), 3.45(3H,s), 3.90-4.22(5H,m), 4.56-4.71(1H,m), 4.80-4.92(0.3H,br), 5.44-5.54(0.7H,br), 7.24(1H,d,J=12.9Hz), 7.35(1H,t,J=8.3Hz), 7.72(1H,dd,J=8.3,2.3Hz), 8.20-8.42(1H,br), 9.18-9.28(1H,br).
MS (ESI) m/z: 487 $(M+H)^+$.

[Referential Example 412]

tert-Butyl (3R,4S)-4-({2-[(5-chloro-2-thienyl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

[0944]

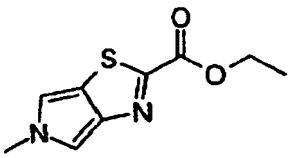


[0945] The title compound was obtained from the compound obtained in Referential Example 220 and the lithium salt of a carboxylic acid obtained by hydrolyzing the compound obtained in Referential Example 356 in a similar manner to the process described in Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.90-2.10(1H,br), 2.68-2.80(0.7H,m), 2.90-3.03(0.3H,br), 3.07-3.22 (0.3H,br), 3.25-3.35(0.7H,br), 3.45(3H,s), 3.83-4.22(5H,m), 4.55-4.70(1H,br), 4.80-4.90(0.2H,br), 5.07-5.14(0.2H,br), 5.44-5.55(0.6H,br), 6.58-6.64(1H,br), 6.73(1H,d,J=3.9Hz), 8.05-8.27(1H,br), 9.65-9.88(1H,br).
MS (FAB) m/z: 475$(M+H)^+$.

[Referential Example 413]

Ethyl 5-methyl-5H-pyrrolo[3,4-d]thiazolo-2-carboxylate:

[0946]

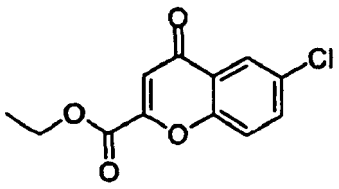


1) Ethyl 2-thioxoacetate (26.75 g) was added to a solution of 3-bromo-2-butanone (26.36 g) in ethanol (250 ml), and the mixture was heated under reflux for 14 hours. After cooling the reaction mixture, it was concentrated, and ethyl acetate and saturated aqueous solution of sodium chloride were added to separate the mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 6:1) to obtain ethyl 4,5-dimethylthiazole-2-carboxylate (19.53 g).
^{1}H-NMR ($CDCl_3$) δ: 1.42(3H,t,J=7.1Hz), 2.42(3H,s), 2.44(3H,s), 4.45(2H,q,J=7.1Hz).
2) N-Bromosuccinimide (62.42 g) and 2,2'-azobisisobutyronitrile (227 mg) were added to a solution of the above-described product (19.53 g) in 1,2-dichloroethane (500 ml), and the mixture was refluxed for 42 hours. After cooling the reaction mixture, water and methylene chloride were added to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then concentrated under reduced pressure to obtain a crude product (40.54 g) as a dark brown oil. Triethylamine (8.0 ml) and a 2 M tetrahydrofuran solution (11.0 ml) of methylamine were added to the crude product (8.41 g), and the mixture was stirred at room temperature for 3 days. After the reaction mixture was concentrated under reduced pressure, methylene chloride and saturated aqueous solution of sodium chloride were added to the residue to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (270 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.45(3H,t,J=7.1Hz), 3.91(3H, s), 4.48(2H,q,J=7.1Hz), 6.73(1H,d,J=1.7Hz), 7.30(1H,d,J=1.7Hz).
MS (ESI) m/z: 211$(M+H)^+$.

[Referential Example 414]

Ethyl 6-chloro-4-oxo-4H-chromene-2-carboxylate:

[0947]

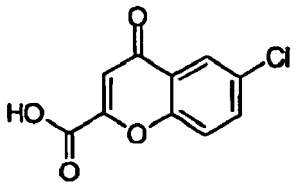


[0948] About 60% sodium hydride in oil (1.68 g) was added to ethanol (10 ml) under purging with argon, and the mixture was stirred at room temperature for 10 minutes. After diethyl oxalate (3.36 ml) was added, an ethanol solution (20 ml) of 5'-chloro-2'-hydroxyacetophenone (2.82 g) was added dropwise. Ethanol (40 ml) was additionally added, and the mixture was refluxed for 1.5 hours and stirred at 50°C for 14 hours. Concentrated sulfuric acid (1.5 ml) and ethanol (10 ml) were added to the reaction mixture, and the resultant mixture was refluxed for 4 hours. After cooling, the solvent was decreased to a half by concentration under reduced pressure. Toluene and a 1N aqueous solution (15 ml) of sodium hydroxide were added to the concentrated the reaction mixture. Extraction was conducted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 7:1), the resultant solids were washed with hexane to obtain the title compound (1.20 g).
^{1}H-NMR ($CDCl_3$) δ: 1.44(3H,t,J=7.1Hz), 4.47(2H,q,J=7.1Hz), 7.12(1H,s), 7.58(1H,d,J=9.0Hz), 7.69(1H,dd,J=9.0,2.7Hz), 8.16(1H,d,J=2.7Hz).
MS (ESI) m/z: 293$(M+MeCN+H)^+$.

[Referential Example 415]

6-Chloro-4-oxo-4H-chromene-2-carboxylic acid:

[0949]

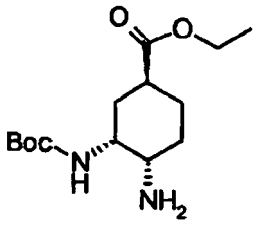


[0950] The title compound was obtained from the compound obtained in Referential Example 414 in a similar manner to the process described in Referential Example 359.
^{1}H-NMR ($CDCl_3$) δ: 7.12(1H,s), 7.60(1H,d,J=8.8Hz), 7.69(1H,dd,J=8.8,2.7Hz), 8.15(1H,d,J=2.7Hz).
MS (FAB) m/z: 225 $(M+H)^+$.

[Referential Example 416]

Ethyl (1S,3R,4S)-4-amino-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate:

[0951]



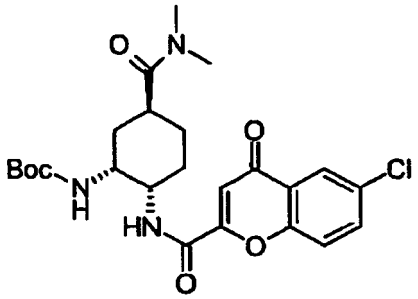
[0952] The title compound was obtained from the compound obtained in Referential Example 249 in a similar manner

to the process described in Referential Example 90.
^{1}H-NMR ($CDCl_3$) δ: 1.20-1.80(4H,m), 1.25(3H,t,J=7.3Hz), 1.46(9H,s), 1.85-2.00(1H,m), 2.10-2.20(1H,m), 2.30-2.45(1H,m), 2.90-3.00(1H,m), 3.84(1H,br s), 4.12(2H,q,J=7.3Hz), 4.75(1H,br s).

[Referential Example 417]

tert-Butyl (1R,2S,5S)-2-{[(6-chloro-4-oxo-4H-chromen-2-yl)carbonyl]amino)-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0953]

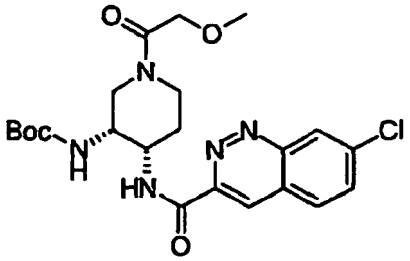


[0954] N,N-Dimethylformamide (0.02 ml) was added to a solution of the compound (213 mg) obtained in Referential Example 415 in thionyl chloride (2.0 ml), and the mixture was refluxed for 15 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (4.0 ml). To the solution were added triethylamine (500 μl) and the compound (294 mg) obtained in Referential Example 144, and the mixture was stirred at room temperature for 15 minutes. Ethyl acetate and a 10% aqueous solution of citric acid to separate the reaction mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1) to obtain the title compound (230 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.33-1.77(3H,m), 1.50(9H,s), 1.81-2.34(3H,m), 2.63-2.80(1H,m), 2.95(3H,s), 3.10(3H,s), 3.90-4.04(1H,br), 4.18-4.31(1H,br), 4.93-5.12(1H,br), 7.13(1H,s), 7.55(1H,d,J=8.8Hz), 7.66(1H,dd,J=8.8,2.4Hz), 8.14(1H,d,J=2.4Hz), 8.77-8.92(1H,br).
MS (ESI) m/z: 492 $(M+H)^+$.

[Referential Example 418]

tert-Butyl (3R,4S)-4-{[(7-chlorocinnolin-3-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

[0955]



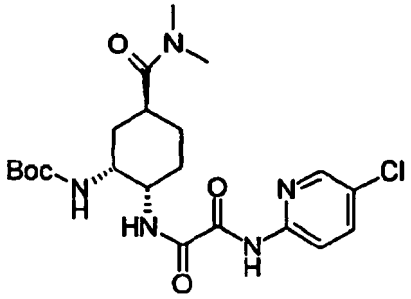
[0956] The title compound was obtained from the compound obtained in Referential Example 220 and the lithium salt of a carboxylic acid obtained by hydrolyzing the ester described in Referential Example 297 in a similar manner to the process described in Referential Example 214.
^{1}H-NMR ($CDCl_3$) δ: 1.38(9H,s), 1.65-1.90(1H,m), 1.90-2.15(1H,m), 2.80-3.00(0.6H,m), 3.00-3.15(0.4H,m), 3.20-3.50(1H,m), 3.46(3H,s), 3.80-4.70(6H,m), 4.87(0.4H,br s), 5.30(0.6H,br s), 7.78(1H,d,J=8.8Hz), 7.97(1H,d,J=8.8Hz), 8.61(1H,s), 8.62-8.90(1H,br), 8.73(1H,s).

MS (ESI) m/z: 478(M+H)$^+$.

[Referential Example 419]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:

[0957]

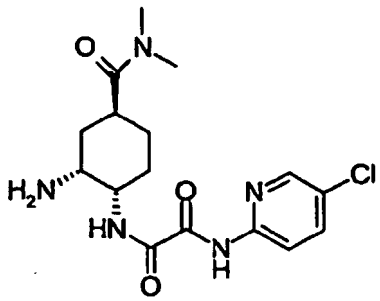


[0958] The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 266 in a similar manner to the process described in Referential Example 68.
^{1}H-NMR ($CDCl_3$) δ: 1.35-1.65(1H,m), 1.45(9H,s), 1.65-1.89(2H,m), 1.90-2.10(3H,m), 2.56-2.74(1H,br), 2.95(3H,s), 3.06(3H,s), 3.94-4.01(1H,m), 4.18-4.27(1H,m), 4.70-4.90(0.7H,br), 5.80-6.20(0.3H,br), 7.68(1H,dd,J=8.9,2.6Hz), 7.83(1H,br s), 8.14(1H,br d,J=7.8Hz), 8.30(1H,s), 9.72(1H,s).
MS (ESI) m/z: 468 (M+H)$^+$.

[Referential Example 420]

N^1-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(5-chloropyridin-2-yl)ethanediamide hydrochloride:

[0959]

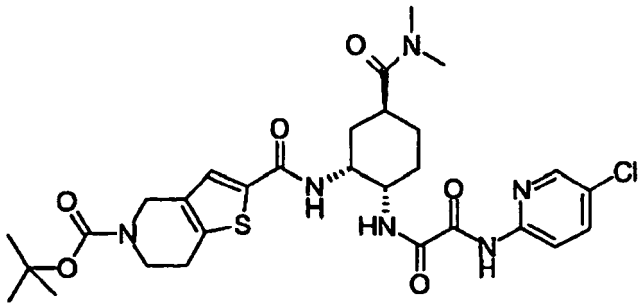


[0960] The title compound was obtained from the compound obtained in Referential Example 419 in a similar manner to the process described in Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 1.38-1.51(1H,m), 1.65-1.85(3H, m), 1.96-2.10(2H, m), 2.81(3H,s), 3.07(3H,s), 3.23-3.33(1H,m), 3.74(1H,br s), 3.84-3.92(1H,m), 8.02(1H,dd,J=9.0,2.5Hz), 8.07(1H,d,J=9.0Hz), 8.34(3H, br s), 8.46(1H,d,J=2.5Hz), 8.96(1H,d,J=6.6Hz), 10.34(1H,s).
MS (ESI) m/z: 368 (M+H)$^+$.

[Referential Example 421]

tert-Butyl 2-[({1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexyl}amino)carbonyl]-6,7-dihydrothieno[3,2-c]-pyridine-5(4H)-carboxylate:

[0961]

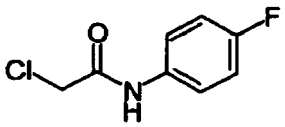


[0962] The title compound was obtained by condensing the compound obtained in Referential Example 420 with 5-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599).
^{1}H-NMR ($CDCl_3$) δ: 1.50(9H,s), 1.73-1.95(3H,m), 1.95-2.06(1H,m), 2.08-2.20(2H,m), 2.82(3H,br s), 2.94(3H,s), 3.03 (3H,s), 3.60-3.80(2H,m), 3.96-4.08(1H,m), 4.44(2H,br s), 4.66(1H,br s), 6.74(1H,br s), 7.20-7.32(1H,m), 7.66(1H,dd, J=9.0,2.4Hz), 8.13(1H,d,J=9.0Hz), 8.13-8.25(1H,m), 8.28(1H,d,J=2.4Hz), 9.75(1H,s).
MS (ESI) m/z: 633 $(M+H)^+$.

[Referential Example 422]

2-Chloro-N-(4-fluorophenyl)acetamide:

[0963]

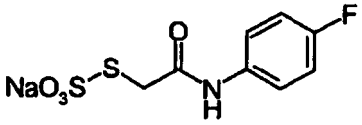


[0964] The title compound was obtained from p-fluoroaniline in a similar manner to the process described in Referential Example 350.
^{1}H-NMR ($CDCl_3$) δ: 4.19(2H,s), 7.05(2H,t,J=8.6Hz), 7.51(2H,dd,J=9.1,4.7Hz), 8.19(1H,br s).

[Referential Example 423]

Sodium S-[2-(4-fluoroanilino)-2-oxoethyl]thiosulfate:

[0965]

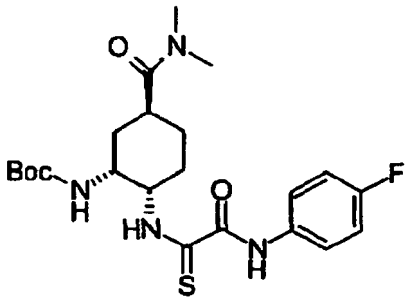


[0966] The title compound was obtained from the compound obtained in Referential Example 422 in a similar manner to the process described in Referential Example 351.
^{1}H-NMR (DMSO-d_6) δ: 3.72(2H,s), 7.14(2H,t,J=9.0Hz), 7.56(2H,dd,J=9.0,5.1Hz), 10.21(1H,s).

[Referential Example 424]

tert-Butyl (1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-{[2-(4-fluoroanilino)-2-oxoethanethioyl]amino}cyclohexylcarbamate:

[0967]

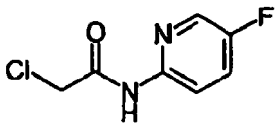


[0968] The compound (1.1 g) obtained in Referential Example 144 and the compound (1.2 g) obtained in Referential Example 423 were dissolved in N-methylmorpholine (20 ml), and the temperature of a bath was raised from room temperature to 140°C over 15 minutes to heat and stir the mixture for 15 minutes at the same temperature. After allowing to cool, ice water was added to the reaction mixture to collect insoluble matter by filtration. This product was purified by column chromatography on silica gel (methylene chloride:methanol = 200:1 → 197:3) to obtain the title compound (1.43 g).
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.70-2.10(5H,m), 2.10-2.30(1H,m), 2.60-2.80(1H,m), 2.96(3H,s), 3.07(3H,s), 4.30-4.50 (2H,m), 4.65-4.85(1H,m), 7.06(2H,t,J=8.5Hz), 7.50-7.70(2H,m), 9.75-9.95(1H,m), 10.13(1H,s).
MS (ESI) m/z: 467 $(M+H)^+$.

[Referential Example 425]

2-Chloro-N-(5-fluoropyridin-2-yl)acetamide hydrochloride:

[0969]

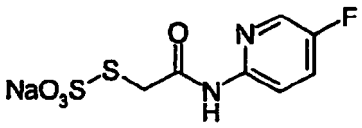


[0970] The title compound was obtained from 2-amino-5-fluoropyridine in a similar manner to the process described in Referential Example 352.
^{1}H-NMR (DMSO-d_6) δ: 4.35(2H,s), 7.74-7.82(1H,m), 8.10(1H,dd,J=9.0,4.2Hz), 8.36(1H,d,J=2.9Hz), (1H,br s).
MS (ESI) m/z: 188 $(M+H)^+$.

[Referential Example 426]

Sodium S-{2-[(5-fluoropyridin-2-yl)amino]-2-oxoethyl}thiosulfate:

[0971]

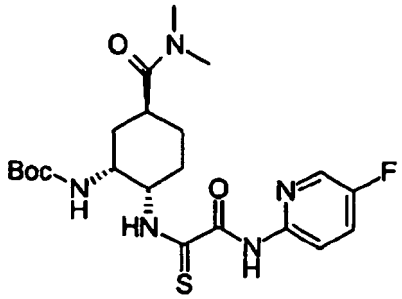


[0972] The title compound was obtained from the compound obtained in Referential Example 425 in a similar manner to the process described in Referential Example 353.
^{1}H-NMR (DMSO-d_6) δ: 3.75(2H,s), 7.67-7.77(1H,m), 8.07(1H,dd,J=9.2,4.2Hz), 8.28(1H,d,J=2.9Hz), 10.48(1H,s).

[Referential Example 427]

tert-Butyl (1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-({2-[{5-fluoropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-cyclohexylcarbamate:

[0973]

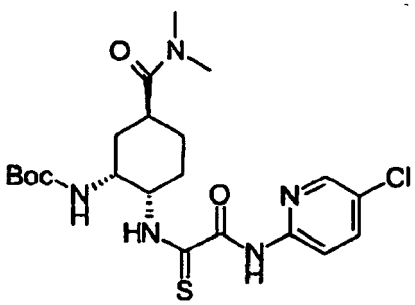


[0974] A solution of the compound (1.20 g) obtained in Referential Example 144 in pyridine (70 ml) was heated to 120°C, and the compound (2.42 g) obtained in Referential Example 426 was added. After stirring the mixture for 30 minutes, the reaction mixture was allowed to cool to room temperature, and the solvent was distilled off under reduced pressure. Methylene chloride (100 ml), a saturated aqueous solution (100 ml) of sodium hydrogencarbonate and water (50 ml) were added to the resultant residue to conduct liquid separation. A water layer was then extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:tetrahydrofuran = 1:1). After the resultant solids were slurried for 1 hour in isopropyl ether (40 ml), they were collected by filtration and dried to obtain the title compound (920 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.70-2.10(5H,m), 2.27(1H,br s), 2.70(1H,br s), 2.96(3H,s), 3.08(3H,s), 4.34-4.44(2H,m), 4.77(1H,br s), 7.44-7.51(1H,m), 8.18-8.27(2H,m), 9.90(1H,br s), 10.57(1H,s).
MS (ESI) m/z: 468 $(M+H)^+$.

[Referential Example 428]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:

[0975]

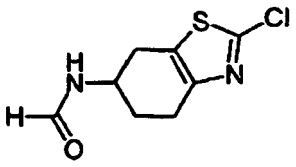


[0976] The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 353 in a similar manner to the process described in Referential Example 427.
^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 1.65-2.35(6H,m), 2.70(1H,br s), 2.95(3H,s), 3.09(3H,s), 4.30-4.60(2H,m), 4.87(1/2H,br s), 6.92 (1/2H,br s), 7.69(1H,dd,J=8.9,2.6Hz), 7.95-8.20(1H,br), 8.29(1H,s), 9.67(1/2H,br s), 9.93(1/2H,br s), 10.54(1H, br s).

[Referential Example 429]

2-Chloro-4,5,6,7-tetrahydrobenzothiazol-6-ylformamide:

[0977]

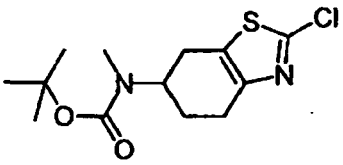


[0978] Ammonium acetate (18.58 g) and sodium cyanoborohydride (10.68 g) were added to a solution of 2-chloro-5-oxo-4,5,6,7-tetrahydrobenzo[d]thiazole (Helv. Cim. Acta., 1994, Vol. 77, p. 1256) (4.53 g) in methanol (200 ml), and the mixture was heated under reflux. After 19 hours, hydrochloric acid was added to decompose excessive reagents before the reaction mixture was concentrated under reduced pressure. After the residue was alkalified with a 1N aqueous solution of sodium hydroxide, methylene chloride was added to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was subjected to column chromatography on silica gel (methylene chloride:methanol = 20:1), and the solvent was distilled off to obtain a pale yellow oil (2.42 g). This oil was dissolved in methylene chloride (100 ml), and formic acid (530 μl), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.68 g), 1-hydroxybenzotriazole (2.60 g) and N-methylmorpholine (3.88 g) were added to stir the mixture at room temperature. After 20 hours, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, the solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1) to obtain the title compound (2.21 g).
^{1}H-NMR ($CDCl_3$) δ: 1.93-2.11(2H,m), 2.63-2.69(1H,m), 2.83-2.89(2H,m), 3.13(1H,dd,J=16.2,4,4Hz), 4.46-4.48(1H,m), 5.76(1H,br s), 8.17(1H,s).

[Referential Example 430]

tert-Butyl N-(2-chloro-4,5,6,7-tetrahydrobenzothiazol-6-yl)-N-methylcarbamate:

[0979]

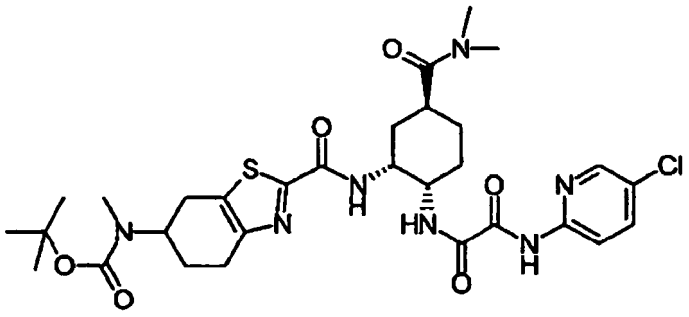


[0980] A 1 M tetrahydrofuran solution (14.6 ml) of borane-tetrahydrofuran complex was added to a solution of the compound (2.11 g) obtained in Referential Example 429 in tetrahydrofuran (50 ml), and the mixture was heated under reflux. After 15 hours, a 1 M tetrahydrofuran solution (6.0 ml) of borane-tetrahydrofuran complex was additionally added to heat the mixture under reflux. After 4 hours, ethanol (10 ml) and 1N hydrochloric acid (15 ml) were added to heat the mixture under reflux. After 3 hours, the reaction mixture was concentrated under reduced pressure. A 1N aqueous solution of sodium hydroxide and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was dissolved in methylene chloride (50 ml), and triethylamine (1.28 g) and di-tert-butyl dicarbonate (2.21 g) were added to stir the mixture at room temperature. After 30 minutes, methylene chloride and 1N hydrochloric acid were added to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (2.26 g).
^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.96-1.98(2H,m), 2.80-2.96(7H,m), 4.40-4.50(1H,m).
MS (FAB) m/z: 303 $(M+H)^+$.

[Referential Example 431]

tert-Butyl N-(2-[({(1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexyl}amino)carbonyl]-4,5,6,7-tetrahydrobenzothiazol-6-yl)-N-methylcarbamate:

[0981]



[0982] After a solution of the compound (1.0 g) obtained in Referential Example 430 in diethyl ether (10 ml)-tetrahydrofuran (5 ml) was cooled -78°C, a 1.6N pentane solution (3.1 ml) of tert-butyllithium was added, and the mixture was stirred for 20 minutes. Carbon dioxide was then introduced for 20 minutes. The reaction mixture was warmed to room temperature and concentrated under reduced pressure, giving lithium 6-[(tert-butoxycarbonyl)(methyl)-amino]-4,5,6,7-tetrahydrobenzothiazole-2-carboxylate.

[0983] The lithium salt (350.2 mg) of the carboxylic acid obtained by the above-described reaction, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (287.6 mg), 1-hydroxybenzotriazole (202.7 mg) and N-methylmorpholine (0.319 ml) were added to a solution of the compound (490.5 mg) obtained in Referential Example 420 in N,N-dimethylformamide (20 ml), and the mixture was stirred at room temperature for 4 days. The solvent was distilled off under reduced pressure, and water and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was then successively washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (methylene chloride:methanol = 40:1 → 20:1) to obtain the title compound (323.9 mg).

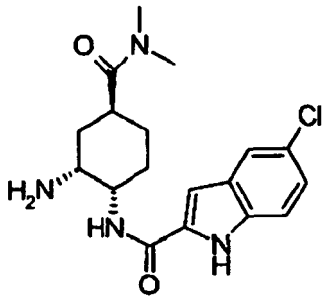
^{1}H-NMR ($CDCl_3$) δ: 1.48,1.49(total 9H,each s), 1.60-1.92(4H,m), 1.95-2.20(6H,m), 2.78-3.10(3H,m), 2.83(3H,s), 2.95(3H,s), 3.06, 3.07(total 3H,each s), 4.05-4.15(1H,m), 4.20-4.60(1H,m), 4.63-4.73(1H,m), 7.39(1H,d,J=8.6Hz), 7.68(1H,dt,J=8.8,2.6Hz), 7.95-8.10(1H,m), 8.13-8.22(1H,m), 8.30-8.35(1H,m), 9.72(1H,brs).

MS (ESI) m/z: 662 $(M+H)^+$.

[Referential Example 432]

N-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-5-chloroindole-2-carboxamide hydrochloride:

[0984]



[0985] The title compound was obtained by deprotecting the compound obtained in Referential Example 310 in a similar manner to the process described in Referential Example 69.

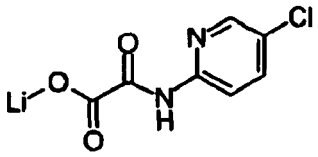
^{1}H-NMR (DMSO-d_6) δ: 1.43-1.56 (0.5H,m), 1.72-1.97(4.5H,m), 2.82(3H,s), 3.06(3H,s), 3.11-3.26(1H,m), 3.75-3.84(1H,

m), 4.07-4.14(1H,m), 4.22-4.41(1H,m), 7.19(1H,dd,J=2.0,8.8Hz), 7.29(1H,d,J=2.0Hz), 7.45(1H,d,J=8.8Hz), 7.72 (1H, 9), 8.07(3H,br), 8.47(1H,m), 11.85(1H,br).

[Referential Example 433]

Lithium 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate:

[0986]

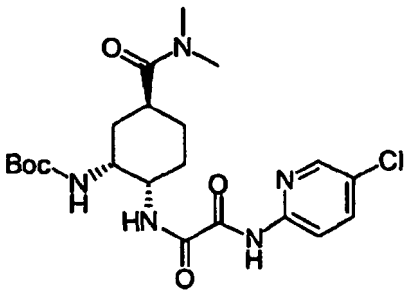


[0987] Methyl chlorooxoacetate (78.7 ml) was added dropwise to a suspension of 2-amino-5-chloropyridine (100 g) and sodium hydrogencarbonate (78.4 g) in tetrahydrofuran (2000 ml) at 0°C, and the mixture was stirred at room temperature for 2 hours. After the reaction mixture was added to a mixture of diethyl ether (2000 ml), ammonium chloride (62.4 g) and water (1000 ml), liquid separation was performed. The resultant water layer was extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain methyl 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate (162 g). Water (450 ml) and lithium hydroxide (18.2 g) were added to a solution of this ester (160 g) in tetrahydrofuran (1800 ml). After the mixture was stirred at room temperature for 2 hours, the solvent was distilled off under reduced pressure, and hexane (3000 ml) was added to the resultant residue to stir the mixture for 3 hours. Solids were collected by filtration and dried. Acetonitrile (1000 ml) was added to the solids (190 g), and the mixture was stirred for 1 hour. Solids formed were collected by filtration, washed with diethyl ether (500 ml) and then dried to obtain the title compound (158 g).
^{1}H-NMR (DMSO-d_6) δ: 7.92(1H,dd,J=9.1,2.7Hz), 8.13(1H,dd,J=9.1,0.5Hz), 8.36(1H,dd,J=2.7,0.5Hz), 10.19(1H,s).

[Referential Example 434]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:

[0988]

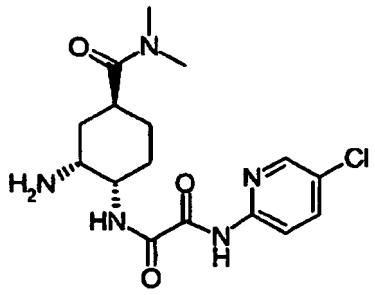


[0989] The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 433 in a similar manner to Referential Example 91.
^{1}H-NMR ($CDCl_3$) δ: 1.25-1.55(1H,m), 1.45(9H,s), 1.60-2.15(5H,m), 2.56-2.74(1H,br), 2.95(3H,s), 3.06(3H,s), 3.90-4.01 (1H,m), 4.18-4.27(1H,m), 4.70-4.85(0.7H,br), 5.70-6.00(0.3H,br), 7.70(1H,dd,J=8.8,2.4Hz), 7.75-8.00(1H,br), 8.16(1H, br d,J=8.8Hz), 8.30(1H,d,J=2.4Hz), 9.73(1H,s).
MS (ESI) m/z: 468 $(M+H)^+$.

[Referential Example 435]

N^1-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(5-chloropyridin-2-yl)ethanediamide hydrochloride:

[0990]

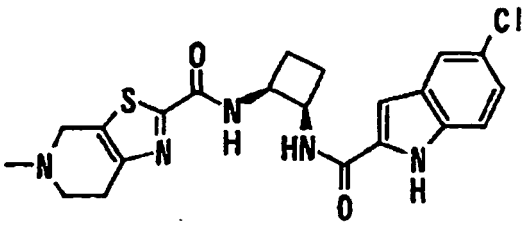


[0991] The title compound was obtained from the compound obtained in Referential Example 434 in a similar manner to Referential Example 69.
^{1}H-NMR (DMSO-d_6) δ: 1.38-1.51(1H,m), 1.65-1.85(3H,m), 1.92-2.09(2H,m), 2.80 (3H, s), 3.06(3H,s), 3.20-3.32(1H,m), 3.55-4.40(2H,br), 8.02(1H,dd,J=9.1,2.5Hz), 8.07(1H,d,J=9.1Hz), 8.15-8.40 (3H, br), 8.45(1H,d,J=2.5Hz), 8.96(1H,d, J=6.6Hz), 10.33(1H,s).

[Example A] (Reference)

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclobutyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:

[0992]

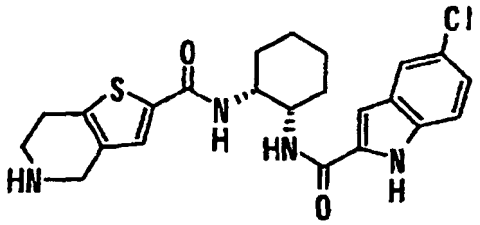


[0993] The compound (136 mg) obtained in Referential Example 10, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (255 mg) and 1-hydroxybenzotriazole monohydrate (90 mg) were added to a solution with the compound (117 mg) obtained in Referential Example 60 dissolved in N,N-dimethylformamide (5 ml), and the mixture was stirred overnight at room temperature. The solvent was then distilled off under reduced pressure using a vacuum pump, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 7:93). After ethyl acetate and a 1N ethanol solution of hydrochloric acid were added to the thus-obtained compound to acidify it, and the solvent was distilled off under reduced pressure. Ethyl acetate was added again, and precipitate formed was collected by filtration and dried to obtain the title compound (56 mg).
^{1}H-NMR (DMSO-d_6) δ: 2.00-2.35(4H,m), 2.88(3H,m), 3.10(2H,br.s), 3.20-3.75(3H,m), 4.20-4.85(3H,m), 7.09(1H,s), 7.16 (1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.71(1H,s), 8.63(1H,d,J=8.3Hz), 8.85(1H,d,J=8.6Hz), 10.85-11.20(1H,br), 11.81 (1H,s),
MS (FAB) m/z: 444 $(M+H)^+$.

[Example B] (Reference)

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide hydrochloride:

[0994]



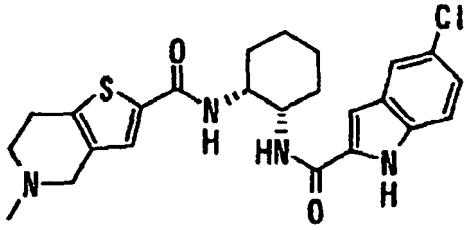
[0995] The title compound was obtained by condensing the compound obtained in Referential Example 71 with 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine-2-carboxylic acid (WO94/21599) and treating the formed product with hydrochloric acid to deprotect in a similar manner to Example A.

^{1}H-NMR (DMSO-d_6) δ: 1.42(2H,br.s), 1.56-1.76(4H,m), 1.98-2.11(2H,m), 3.04(2H,br.s), 3.32-3.45(2H,m), 4.15(3H,br.s), 4.26(1H,br.s), 7.14(1H,dd,J=8.8,2.0Hz), 7.23(1H,s), 7.41(1H,d,J=8.8Hz), 7.62(1H,s), 7.77(1H,s), 8.18-8.30(2H,m), 9.42(2H,br.s), 11.92(1H,s).
MS (FAB) m/z: 457 $(M+H)^+$.

[Example C] (Reference)

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine-2-carboxamide hydrochloride:

[0996]



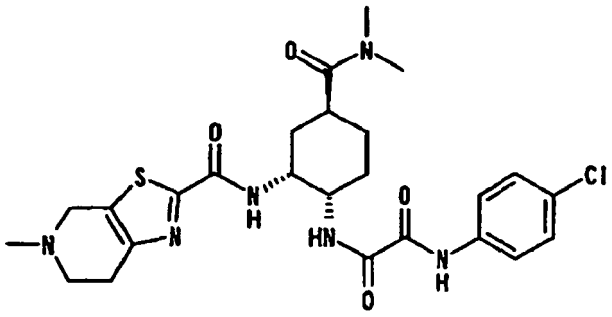
[0997] The compound (171 mg) obtained in Example B was suspended in methylene chloride (10 ml), and triethylamine (0.104 ml) was added to stir the mixture at room temperature for 10 minutes. After acetic acid (0.059 ml) was added to the reaction mixture, a 35% aqueous formaldehyde solution (0.070 ml) and sodium triacetoxyborohydride (118 mg) were added, and the mixture was stirred at room temperature for 30 minutes. After a 1N aqueous solution (3 ml) of sodium hydroxide was added to the reaction mixture, water was added to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was then distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 50:3) to obtain a colorless foamy substance. This substance was suspended in 1N hydrochloric acid, and the suspension was concentrated under reduced pressure to obtain the title compound (85 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.40(2H,br.s), 1.50-1.71(4H,m), 1.97-2.05(2H,m), 2.87(3H,s), 2.98-3.20(1H,m), 3.30-3.38(2H,m), 3.54-3.70(1H,m), 4.05-4.42(4H,m), 7.14(1H,d,J=8.6Hz), 7.23(1H,s), 7.40(1H,d,J=8.6Hz), 7.63(1H,s), 7.77(1H,s), 8.17-8.27(2H,m), 10.83(1H,br.s), 11.92(1H,s).
MS (FAB) m/z: 471 $(M+H)^+$.

[EXAMPLE 1]

N^1-(4-Chlorophenyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:

[0998]

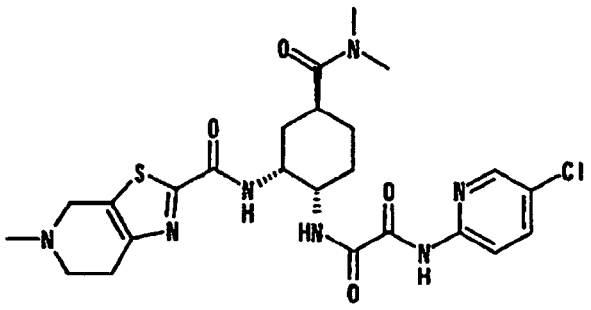


[0999] The compound (288 mg) obtained in Referential Example 242 was dissolved in tetrahydrofuran (8.0 ml), lithium hydroxide (46 mg) and water (1.0 ml) were successively added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain a crude product (292 mg) of lithium 2-(4-chloroanilino)-2-oxoacetate as a colorless solid. This crude product and the compound obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole monohydrate (164 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (251 mg) were added to stir the mixture at room temperature for 64.5 hours. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 47:3). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (0.52 ml) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (245 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.55(1H,m), 1.60-1.80(3H,m), 1.95-2.10(2H,m), 2.79(3H,s), 2.80-3.00(1H,m), 2.92(3H,s), 2.94(3H,s), 3.10-3.40(2H,m), 3.40-3.80(2H,m), 3.95-4.05(1H,m), 4.40-4.80(3H,m), 7.40(2H,d,J=8.8Hz), 7.83(2H,d, J=8.8Hz), 8.75(1H,d,J=7.1Hz), 9.00-9.10(1H,br), 10.81(1H,s), 11.45-11.75(1H,m).
MS (FAB) m/z: 547 $(M+H)^+$.

[Example 2]

N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S) -4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1000]



[1001] The compound (240 mg) obtained in Referential Example 243 was dissolved in tetrahydrofuran (8.0 ml), lithium hydroxide (41 mg) and water (1.0 ml) were successively added to the solution, and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure to obtain lithium 2-[(5-chlo-

ropyridin-2-yl)amino]-2-oxoacetate (249 mg).

[1002] On the other hand, 10% palladium on carbon (200 mg) was added to a solution of the compound (293 mg) obtained in Referential Example 252 in methanol (10 ml), and the mixture was stirred at room temperature for 18 hours under a hydrogen atmosphere. After removing palladium on carbon by filtration, the filtrate was concentrated under reduced pressure to obtain a crude product (259 mg) of N-{(1R,2S,5S)-2-amino-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide.

[1003] This crude product (259 mg) and the lithium salt (249 mg) prepared above were added to N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole monohydrate (166 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (235 mg) were added to stir the mixture at room temperature for 63.5 hours. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 93:7). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (0.855 ml) of hydrochloric acid was added to the solution, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (209 mg).

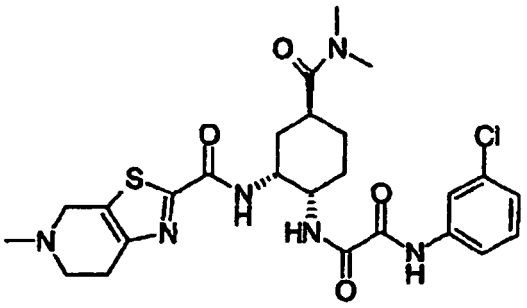
^{1}H-NMR (DMSO-d_6) δ: 1.40-1.57(1H,m) , 1.60-1.80(3H,m), 1.95-2.13(2H,m), 2.79(3H,s). 2.80-3.00(1H,m), 2.92(3H,s), 2.94(3H,s), 3.10-3.40(2H,m), 3.40-3.80(2H,m), 3.95-4.05(1H,m), 4.37-4.80(3H,m), 7.90-8.10(2H,m). 8.45(1H,d, J=2.2Hz), 8.71(1H,d,J=7.6Hz), 9.10-9.30(1H,br), 10.26(1H,s), 11.30-11.60(1H,br).

MS (FAB) m/z: 548(M+H)$^+$.

[Example 3]

N^1-(3-Chlorophenyl)-N^2- (1S,2R,4S)-4- [(dimethylamino) - carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:

[1004]



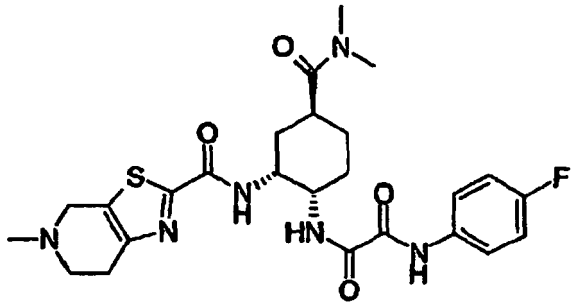
[1005] The compound (222 mg) obtained in Referential Example 270 and 3-chloroaniline (63 μl) were dissolved in N,N-dimethylformamide (10 ml), and 1-hydroxybenzotriazole monohydrate (68 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144 mg) were added to stir the mixture at room temperature for 40 hours. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol -30:1). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (0.50 ml) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Diethyl ether was added to the residue, and precipitate formed was collected by filtration to obtain the title compound (174 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.45-1.62(1H,m), 1.65-1.90(3H,m), 1.98-2.20(2H,m), 2.79(3H,s), 2.88-3.10(1H,m), 2.93(3H,s), 2.94(3H,s), 3.15-3.40(2H,m), 3.40-3.90(2H,m), 3.95-4.10(1H,m), 4.40-4.80(3H,m), 7.19(1H,dd,J=9.3,2.0Hz), 7.37(1H, d,J=8.2Hz), 7.77(1H,d,J=8.3Hz), 7.92-8.05(1H,m), 8.75(1H,d,J=7.3Hz), 8.95-9.20(1H,br), 10.87(1H,s), 11.25-11.45(1H, br).

[Example 4]

N^1-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)-N^2-(4-fluorophenyl)-ethanediamide hydrochloride:

[1006]

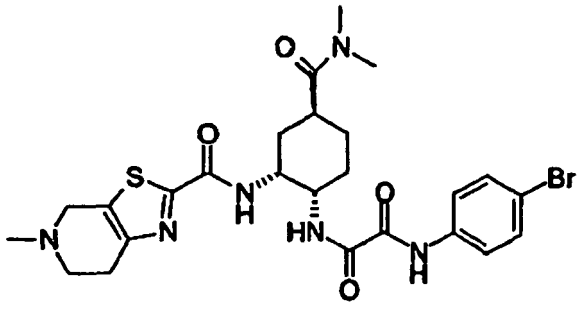


[1007] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 254, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.40-2.13(6H,m), 2.77(3H,s), 2.93(3H,s), 2.97(3H,s), 3.12-3.82(7H,m), 3.93-4.04(1H,m), 4.38-4.46(1H,m), 4.35-4.75(1H,m), 7.11-7.21(2H,m), 7.72-7.84(2H,m), 8.73(1H,d,J=7.6Hz), 8.93-9.02(1H,m), 10.70(1H,s).
MS (FAB) m/z: 531 $(M+H)^+$.

[Example 5]

N^1-(4-Bromophenyl)-N^2-((1S,2A,4S)-4-[(dimethylamino)-carbonyl]-2-([(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino]cyclohexyl)ethanediamide hydrochloride:

[1008]



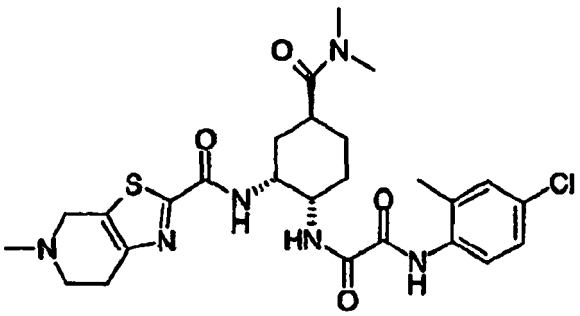
[1009] The compound (152 mg) obtained in Referential Example 255 was dissolved in tetrahydrofuran (5.0 ml), a 1N aqueous solution (1.20 ml) of sodium hydroxide and methanol (5.0 ml) were successively added, and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (10 ml) and 1N hydrochloric acid (2.0 ml) were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain a crude product (280 mg) of 2-(4-bromoanilino)-2-oxoacetic acid as a colorless solid. This crude product and the compound (280 mg) obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (30 ml), and 1-hydroxybenzotriazole monohydrate (90 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (226 mg) were added to stir the mixture at room temperature for a night. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 97:3). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (191 μl) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether

were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (103 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.43-1.57(1H,m), 1.59-1.80(3H,m), 1.97-2.10(2H,m), 2.79(3H,s). 2.84-2.98(7H,m),3.18(2H,br.s), 3.39-3.72(2H,m), 3.95-4.05(1H,m), 4.20-4.80(3R,m), 7.53(2H,d,J=8.8Hz), 7.77(2H,d,J=8.8Hz), 8.75(1H,d,J=7.3Hz), 8.97-9.09(1H,m), 10.82(1H,s), 11.11(1H,br.s).
MS (FAB) m/z: 591 $(M+H)^+$.

[Example 6]

N^1-(4-Chloro-2-methylphenyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1010]

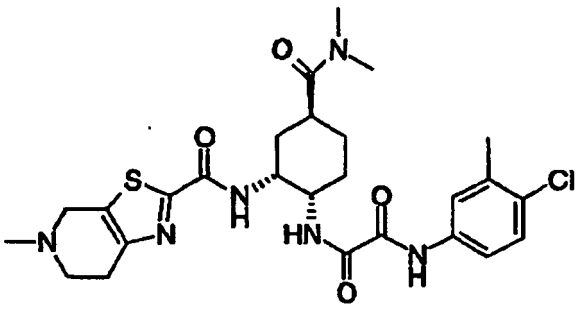


[1011] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 256, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
1H-NMR (DMSO-d6) δ: 1.45-1.55(1H,m), 1.60-1.80(3H,m), 2.00-2.10(2H,m), 2.19(3H,s), 2.79(3H,s), 2.80-3.00(7H,m), 3.31(2H,br.s), 3.40-3.70(2H,br), 3.95-4.05(1H,m), 4.35-4.70(3H,m), 7.20-7.30(1H,m), 7.35(1H,d,J=2.5Hz), 7.43(1H,d, J=8.6Hz), 8.76(1H,d,J=6.6Hz), 9.00-9.15(1H,br), 10.19(1H,s).
MS (FAB) m/z: 561$(M+H)^+$.

[Example 7]

N^1-(4-Chloro-3-methylphenyl) -N^2- ((1S,2R, 4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1012]

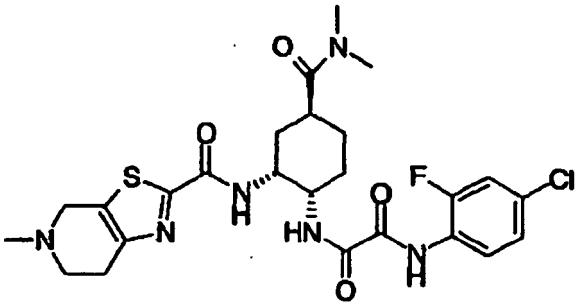


[1013] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 257, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.47-1.53(1H,m), 1.68-1.80(3H,m), 1.98-2.09 (2H,m), 2.29 (3H, s), 2.79 (3H, s), 2.80-3.00(1H, m), 2.95(6H,s), 3.17-3.19(3H,m), 3.40-3.80(1H,m), 3.93-4.02(1H,m), 4.44-4.56(3H,m), 7.38(1H,d,J=8.8Hz), 7.65(1H,d, J=8.8Hz), 7.74(1H,s), 8.75(1H,d,J=7.8Hz), 8.96 (1H,d,J=8.0Hz), 10.69(1H,s).
MS (FAB) m/z: 561$(M+H)^+$.

[Example 8)

N^1-(4-Chloro-2-fluorophenyl) -N^2- ((1S,2R,4S) -4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1014]

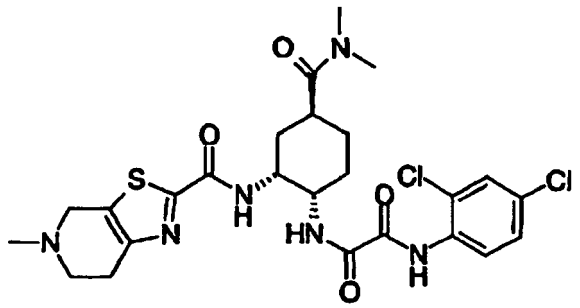


[1015] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 258, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.40-1.55(1H,m), 1.58-1.80(3H,m), 1.95-2.12(2H,m), 2.77(3H,s), 2.80-3.00(1H,m), 2.91(3H,s), 2.92(3H,s), 3.10-3.40(2H,m), 3.40-3.80(2H,m), 3.95-4.05(1H,m), 4.30-4.80(3H,m), 7.29(1H,d,J=8.5Hz), 7.52(1H,dd, J=10.3,2.0Hz), 7.61(1H,t,J=8.4Hz), 8.72(1H,d,J=6.8Hz), 9.00-9.20(1H,br), 10.38(1H,s), 11.20-11.45 (1H,br).
MS (FAB) m/z : 565 $(M+H)^+$.

[Example 9]

N^1-(2,4-Dichlorophenyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:

[1016]



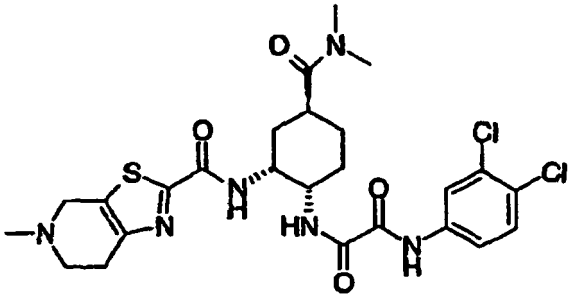
[1017] The compound (300 mg) obtained in Referential Example 270 was dissolved in N,N-dimethylformamide (5 ml), and 2,4-dichloroaniline (165 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (260 mg) and 1-hydroxybenzotriazole monohydrate (91 mg) were added to stir the mixture at room temperature for 2 days. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 47:3) to obtain a free base of the title compound. This product was dissolved in methylene chloride, a 1N ethanol solution (108 μl) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. A small amount of methanol was added to the residue, and diethyl ether was added dropwise while irradiating with ultrasonic waves to collect precipitate formed by filtration. This product was washed with diethyl ether to obtain the title compound (60 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.77(4H,m), 2.03-2.12(2H,m), 2.79(3H,s), 2.92-2.96(7H,m), 3.25(2H,br.s), 3.49(1H,br.s), 3.69(1H,br.s), 3.98-4.04(1H,m), 4.40-4.43(1H,m), 4.45(1H,br.s), 4.69(1H,br.s), 7.48(1H,dd,=8.5,2.4Hz), 7.75(1H,d, J=2.4Hz), 7.89(1H,d,J=8.5Hz), 8.75(1H,d,J=6.8Hz), 9.21(1H,br,s), 10.25(1H,s), 11.55(1H,br.s).

MS (FAB) m/z: 581(M+H)$^+$.

[Example 10]

N^1-(3,4-Dichlorophenyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide:

[1018]

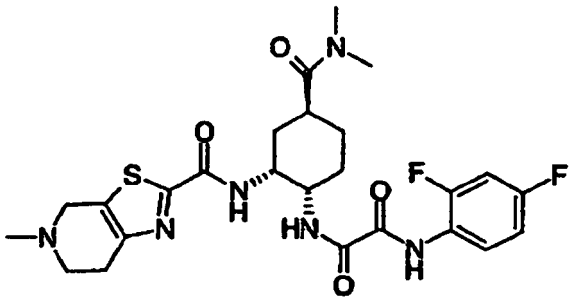


[1019] 3,4-Dichloroaniline (1.62 g) was dissolved in methylene chloride (20 ml), and triethylamine (1.67 ml) and methyl chlorooxoacetate (1.01 ml) were successively added under ice cooling, and the mixture was stirred at room temperature for 21 hours. Water and methylene chloride were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted with methylene chloride. Organic layers were combined and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was dissolved in ethanol (50 ml), and water (25 ml) and lithium hydroxide monohydrate (629 mg) were successively added to stir the mixture at room temperature for 12.5 hours. Lithium hydroxide monohydrate (629 mg) was additionally added to stir the mixture at room temperature for 5.5 hours. The reaction mixture was concentrated under reduced pressure to solidity. Water and diethyl ether were added to the residue to conduct liquid separation. Hydrochloric acid was added to the resultant water layer to acidify it. Solid formed were collected by filtration to obtain a crude product (1.62 g) of 2-(3,4-dichloroanilino)-2-oxoacetic acid as a colorless solid. This crude product (191 mg) and the compound obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (10 ml), and 1-hydroxybenzotriazole monohydrate (110 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (157 mg) were added to stir the mixture at room temperature for 67 hours. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogen-carbonate and ethyl acetate were added to the residue to conduct liquid separation, and the resultant water layer was extracted 3 times with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 95:5) to obtain the title compound (154 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.77-1.88(1H,m), 1.91-1.95(1H,m), 2.05-2.10(3H,m), 2.51(3H,s), 2.77-2.99(6H,m), 2.95(3H,s), 3.05 (3H,s), 3.68(1H,d,J=15.5Hz), 3.74(1H,d,J=15.5Hz), 4.08-4.13(1H,m), 4.69-4.72(1H,m), 7.40(2H,s), 7.41(1H,d,J-7.7Hz), 7.90(1H,s), 8.01(1H,d,J-7.7Hz), 9.27(1H,s).
MS (ESI) m/z: 581 (M+H)$^+$.

[Example 11]

N^1-(2,4-Difluorophenyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]amino]cyclohexyl)ethanediamide:

[1020]



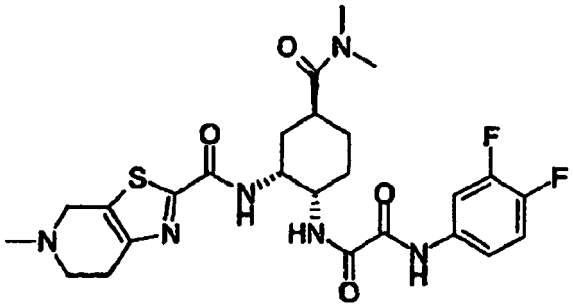
[1021] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 259 and condensing the hydrolyzate with the compound obtained in Referential Example 253 in a similar manner to the process described in Example 1.

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.62(1H,m), 1.67-1.98(2H,m), 2.01-2.18(4H,m), 2.52(3H,s), 2.77-3.00(4H,m), 2.95(3H,s),2.99 (3H,s), 3.65-3.78(2H,m), 4.06-4.15(1H,m), 4.66-4.73(1H,m), 6.85-6.94(2H,m), 7.38(1H,d,J=8.5Hz), 7.96(1H,d,J=7.3Hz), 8.22-8.29(1H,m), 9.36(1H,br).

[Example 12]

N^1-(3,4-Difluorophenyl)-N^2- ((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]amino]cyclohexyl)ethanediamide:

[1022]



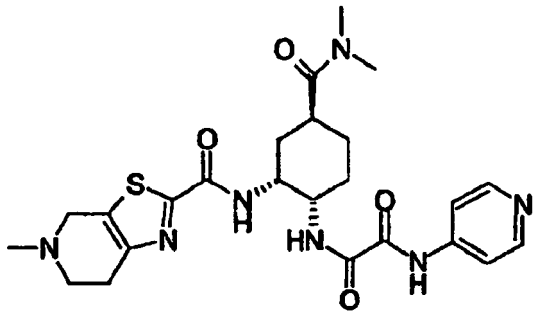
[1023] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 260 and condensing the hydrolyzate with the compound obtained in Referential Example 253 in a similar manner to the process described in Example 1.

^{1}H-NMR ($CDCl_3$) δ: 1.56-1-73(1H,m), 1.77-1.99(2H,m), 2.00-2.18(4H,m), 2.52(3H,s), 2.75-3.00(4H,m), 2.95(3H,s), 3.06 (3H,s), 3.64-3.79(2H,m), 4.05-4.14(1H,m), 4.68-4.75(1H,m), 7.09-7.21(2H,m), 7.38(1H,d,J=8.8Hz), 7.72(1H,ddd, J=12.0, 7.1,2.6Hz), 7.95(1H,d,J=7.8Hz), 9.22(1H,br).

[Example 13]

N^1-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)-N^2-(pyridin-4-yl)ethanediamide hydrochloride:

[1024]

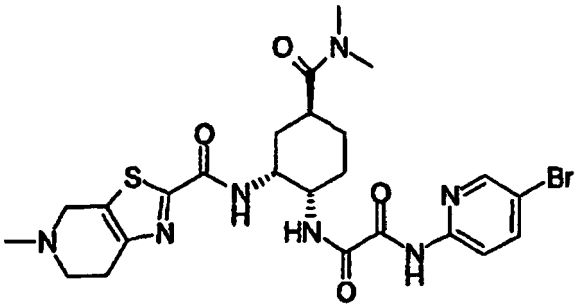


[1025] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 261, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.40-2.10(6H,m), 2.77(3H,s), 2.927(3H,s), 2.933(3H,s), 3.05-4.20 (8H,m) , 4.40-4.55(1H,m), 8.27 (2H,d,J=6.8Hz), 8.67(1H,d,J=8.0Hz), 8.71(2H,d,J=6.8Hz), 9.10-9.30(1H, br), 11.81(1H,s).
MS (FAB) m/z: 514$(M+H)^+$.

[Example 14]

N^1-(5-Bromopyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:

[1026]

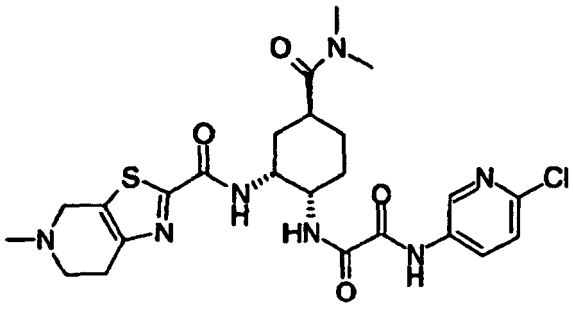


[1027] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 262, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 5.
^{1}H-NMR (DMSO-d_6) δ: 1.43-1.57 (1H,m) , 1.61-1.81(3H,m), 1.98-2.15(2H,m), 2.79(38,s), 2.86(3H,s), 2.89-3.01(4H,m), 3.18(2H,br.s), 3.50(2H,br.s), 3.95-4.05(1H,m), 4.35-4.62(3H,m), 7.97(1H,d,J=9.0Hz). 8.12(1H,dd,J=9.0,2.4Hz), 8.52 (1H,d,J=2.4Hz), 8.70(1H,d,J=7.5Hz), 9.18(1H,d,J=7.5Hz), 10.25(1H, br.s).
MS (FAB) m/z: 592$(M+H)^+$.

[Example 15]

N^1-(6-Chloropyridin-3-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyzidin-2-yl)carbonyl]amino}-cyclohexyl)ethanediamide hydrochloride:

[1028]

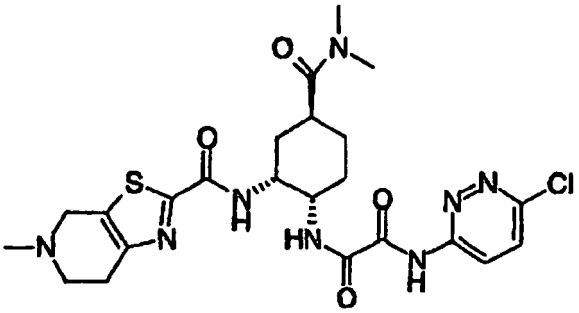


[1029] The compound (200 mg) obtained in Referential Example 263, which was a crude product, was dissolved in methanol (10 ml) to heat the solution to 50°C, and a 1N aqueous solution (3 ml) of sodium hydroxide to stir the mixture for 5 minutes. To this mixture was added 1N hydrochloric acid to adjust the pH to a weak acidity. The solvent was distilled off under reduced pressure to obtain residue containing 2-[(2-chloropyridin-5-yl)amino]-2-oxoacetic acid. This residue and the compound (250 mg) obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (5 ml), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (328 mg) and 1-hydroxybenzotriazole monohydrate (46 mg) were added to stir the mixture at room temperature for 3 days. The solvent was distilled off under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 47:3) to obtain a free base of the title compound as a pale yellow solid. This product was dissolved in methylene chloride, a 1N ethanol solution (862 μl) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. A small amount of methanol was added to the residue, and ethyl acetate and diethyl ether were added dropwise while irradiating with ultrasonic waves to collect precipitate formed by filtration. This product was washed with diethyl ether to obtain the title compound (229 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.46-1.75(4H,m), 1.99-2.09(2H,m), 2.79(3H,s), 2.92-2.95(7H,m), 3.12-3.53(3H,m), 3.70(1H,br.s), 3.99-4.06(1H,m), 4.44(2H,br.s), 4.69.4.73(1H, each s), 7.53(1H,d,J=8.5Hz), 8.23-8.25(1H,m), 8.72-8.77(1H,m), 8.85 (1H,s), 9.07,9.16(1H, each d.J=8.1Hz), 11.09(1H,d,J=8.1Hz), 11.78(1H,br.s).
MS (FAB) m/z: 548(M+H)$^+$.

[Example 16]

N^1-(6-Chloropyridazin-3-yl)-N^3-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1030]

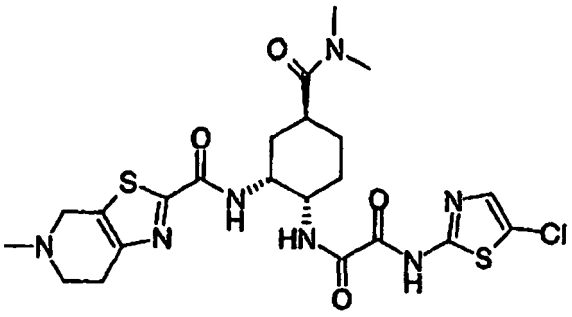


[1031] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 264, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.94-1.57(1H,m), 1.62-1.80(3H,m), 2.00-2.10(2H,m), 2.79(3H,s), 2.86(3H,br.s), 2.94(3H,s), 2.95-3.01(1H,m), 3.14-3.23(2H,m), 3.45-3.63(2H,m), 3.96-4.08(1H,m), 4.40-4.60(3H,m), 7.97(1H,d,J=9.3Hz), 8.26(1H, d,J=9.3Hz), 8.69(1H,d,J=7.6Hz), 9.20(1H,d,J=7.6Hz), 11.06(1H,s).
MS (FAB) m/z: 549(M+H)$^+$.

[Example 17]

N^1-(5-Chlorothiazol-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino]cyclohexyl}ethanediamide hydrochloride:

[1032]

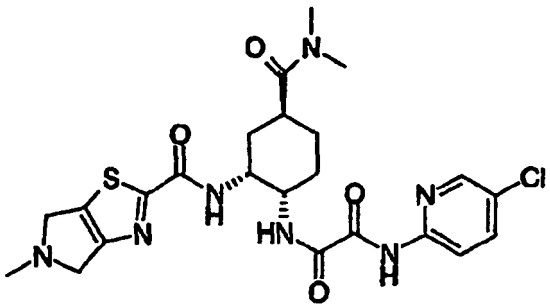


[1033] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 265, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.35-2.10(6H,m), 2.77(3H,s), 2.92(3H,s), 2.93(3H,s), 3.05-4.23(8H,m), 4.32-4.80(2H,m), 7.59(1H,s), 8.63(1H,d,J=7.6Hz), 9.14(1H,d,J=7.6Hz).
MS (FAB) m/z: 554$(M+H)^+$.

[Example 18]

N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:

[1034]

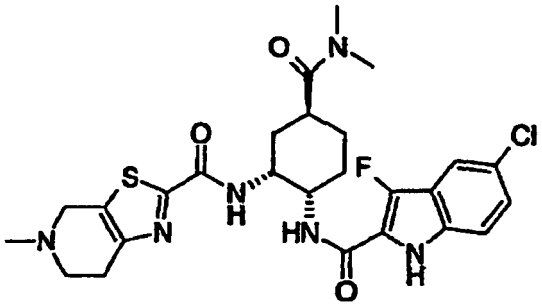


[1035] The compound (210 mg) obtained in Referential Example 266 and the compound (350 mg) obtained in Referential Example 272 were dissolved in N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole monohydrate (205 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg) were added to stir the mixture at room temperature for 20 hours. The solvent was distilled off under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (0.46 ml) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (248 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.47-1.50(1H,m), 1.69-1.76(3H,m), 1.98-2.06(2H,m), 2.79(3H,s), 2.95(3H,s), 2.98-3.05(1H,m), 3.10(3H,s), 3.49-4.62(6H,m), 7.98-8.03(2H,m), 8.45(1H,s), 8.73(1H,d,J=7.6Hz), 9.10(1H,d,J-8.0Hz), 10.30(1H,s).
MS (FAB) m/z: 534$(M+H)^+$.

[Example D] (Reference)

N-{(1R,2S,5S)-2-{[(5-Chloro-3-fluoroindol-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

[1036]

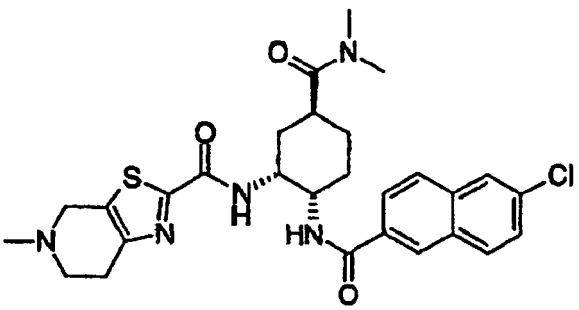


[1037] The compound (250 mg) obtained in Referential Example 279 was dissolved in methylene chloride (60 ml), and a 4N dioxane solution (1.3 ml) of hydrochloric acid was added. After the reaction mixture was stirred at room temperature for 5.5 hours, a 4N dioxane solution (0.65 ml) of hydrochloric acid was additionally added, and the mixture was stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure, methylene chloride (10 ml) was added to the residue, and the mixture was concentrated. This process was repeated 3 times. The residue was dried under reduced pressure, and the thus-obtained crude product was dissolved in N,N-dimethylformamide (50 ml), and the compound (160 mg) obtained in Referential Example 10, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (150 mg) and 1-hydroxybenzotriazole monohydrate (120 mg) were added to stir the mixture at room temperature for 18 hours. The solvent was distilled off under reduced pressure, and the residue was partitioned in a mixed solvent of water-ethyl acetate, and a water layer was extracted with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified twice by column chromatography on silica gel (methanol:methylene chloride = 2:23 → 1:9) to obtain a free base (260 mg) of the title compound. This product was dissolved in methylene chloride, and a 1N ethanol solution (0.69 ml) of hydrochloric acid was added to stir the mixture at room temperature for 30 minutes. The solvent was distilled off. The residue was dissolved in methanol, and diethyl ether and hexane were added. The thus-obtained crystals were collected by filtration to obtain the title compound (230 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.50-1.56(1H,m), 1.73-1.78(3H,m), 1.94-2.02(2H,m), 2.33-3.55(6H,m), 2.80(3H,s), 2.92(3H,s), 2.98(3H,s), 4.17(1H,br.s), 4.30-4.80(1H,br), 4.62(1H,br.s), 7.25(1H,d,J=8.8,1.7Hz), 7.40(1H,d,J=8.8,1.7Hz), 7.65(1H,d, J=1.7Hz), 7.72(1H,d,J=5.9Hz), 8.74(1H,d,J=8.0Hz), 10.85-11.35(1H,br), 11.71(1H,s).
MS (FAB) m/z: 561$(M+H)^+$.

[Example E] (Reference)

N-{(1R,2S,5S)-2-[(6-Chloro-2-naphthoyl)amino]-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

[1038]

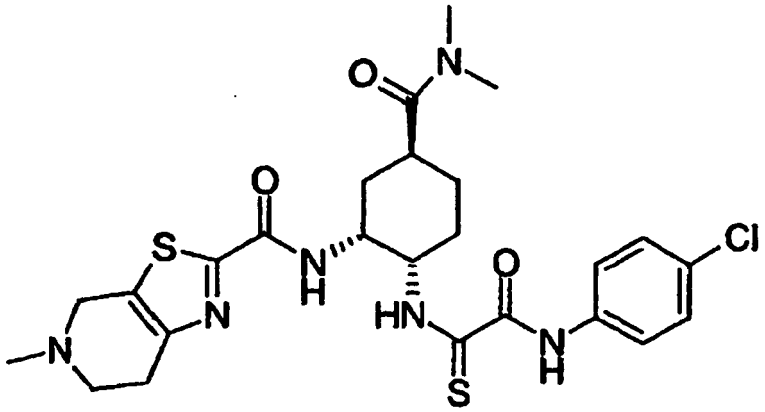


[1039] The compound (270 mg) obtained in Referential Example 294 was dissolved in methylene chloride (10 ml), and a 1N ethanol solution (10 ml) of hydrochloric acid was added to stir the mixture for 90 minutes. The solvent was distilled off under reduced pressure, and the resultant residue was dissolved in N,N-dimethylformamide (7 ml). The compound (110 mg) obtained in Referential Example 10, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg) and 1-hydroxybenzotriazole monohydrate (70 mg) were added to stir the mixture at room temperature for 23 hours. The reaction mixture was concentrated under reduced pressure, and water was added to conduct extraction with ethyl acetate. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified twice by column chromatography on silica gel (methylene chloride: methanol = 20:1 → 10:1). The thus-obtained free base was dissolved in methanol, and a 1N ethanol solution (0.30 ml) of hydrochloric acid was added. The residue was washed with ethyl acetate to obtain the title compound (130 mg).
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.60(1H,m), 1.70-1.90 (3H,m), 1.90-2.10(2H,m), 2.81(3H,s), 2.91(3H,s), 3.00(3H,s), 3.00-3.22(3H,m), 3.53(2H,br), 4.10-4.20(1H,m), 4.30-4.70(3H,m), 7.59(1H,dd,J=8.8,2.2Hz), 7.87(1H,d,J=8.5Hz), 7.96 (1H,d,J=8.5Hz), 8.02(1H,d,J=8.8Hz), 8.10(1H,d,J=2.2Hz), 8.33(1H,s), 8.43(1H,d,J=8.1Hz), 8.52(1H,d,J=7.3Hz).
MS(FAB)m/z:554$(M+H)^+$.

[Example 19]

N-{(1R,2S,5S)-2-{[2-(4-Chloroanilino)-2-oxoethane-thioyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

[1040]

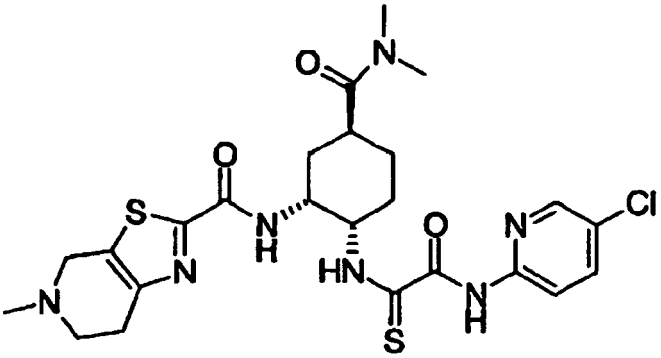


[1041] The compound (184 mg) obtained in Referential Example 253 and the compound (150 mg) obtained in Referential Example 351 were dissolved in a mixed solvent of methanol (1 ml)-methylene chloride (4 ml), the solution was heated and stirred at 150°C, and the heating was continued for 5 minutes after distilling off the solvent. After the reaction mixture was allowed to cool, the formed product was purified by column chromatography on silica gel (methylene chloride: methanol = 24:1) to obtain the title compound (59 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.90(2H,m), 1.90-2.00(1H,m), 2.00-2.15(2H,m),2.20-2.30(1H,m),2.52(3H,s),2.75-2.95(5H,m), 2.96(3H,s),3.07(3H,s),3.68(1H,d,J=15.2Hz), 3.75(1H,d,J=15.7Hz), 4.45-4,60(1H,m),4.80-4.85(1H,m), 7.31(2H,d, J=8.8Hz),7.44(1H,d,J=8.6Hz),7.60(2H,d,J=8.8Hz), 9.99(1H,d,J=7.6Hz),10.15(1H,s).
MS (ESI) m/z: 563$(M+H)^+$.

[Example 20]

N-{(1R,2S,5S)-2-({2-[(5-Chloropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

[1042]

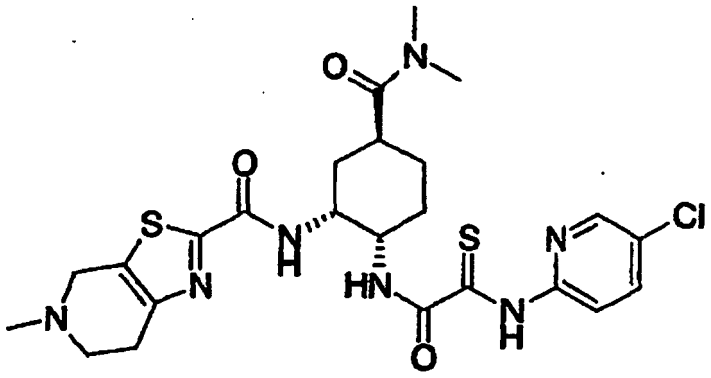


[1043] The compound (184 mg) obtained in Referential Example 253 and the compound (150 mg) obtained in Referential Example 353 were dissolved in a mixed solvent of methanol (0.3 ml)-methylene chloride (0.3 ml), the solution was heated and stirred at 150°C, and the heating was continued for 5 minutes after distilling off the solvent. reaction mixture was allowed to cool, the formed product was purifiec by column chromatography on silica gel (methylene chloride: methanol = 24:1) to obtain the title compound (52 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.60-2.00(3H,m),2.00-2.20(2H,m), 2.25-2.40(1H,m),2.53(3H,s),2.80-2.95(5H,m),2.96(3H,s), 3.08 (3H,s),3.70(1H,d,J=15.4Hz),3.75(1H,d,J=15.4Hz), 4.45-4,60(1H,m),4.75-4.85(1H,m),7.45(1H,d,J=8.3Hz), 7.67(1H,dd, J=8.8,2.5Hz),8.18(1H,d,J=8.8Hz), 8.31(1H,d,J=2.0Hz),10.06(1H,d,J=6.3Hz),10.56(1H,s).
MS (ESI) m/z: 564$(M+H)^+$.

[Example 21]

N-{(1R,2S,5S)-2-({2-[(5-Chloropyridin-2-yl)amino]-2-thioxoacetyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

[1044]

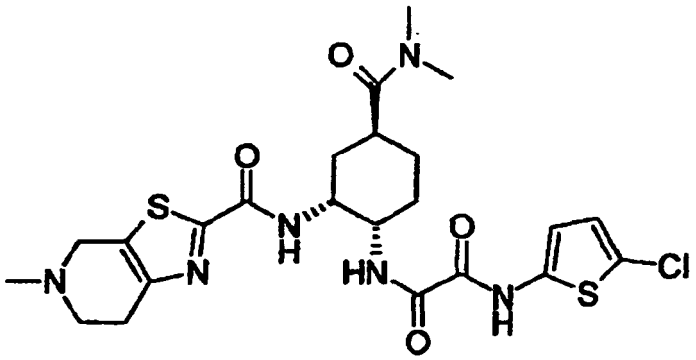


[1045] The compound (72 mg) obtained in Referential Example 355 and 2-amino-5-chloropyridine (100 mg) were dissolved in a mixed solvent of methanol (0.2 ml)-methylene chloride (0.2 ml), the solution was heated and stirred at 150°C, and the heating was continued for 8 minutes after distilling off the solvent. After the reaction mixture was allowed to cool, the formed product was purified by preparative thin-layer chromatography on silica gel (methylene chloride: methanol = 23:2) to obtain the title compound (4 mg).
^{1}H-NMR ($CDCl_3$) δ: 1.60-2.00(3H,m),2.00-2.20(3H,m), 2.53(3H,s),2.75-3.00(5H,m),2.95(3H,s).3.05(3H,s), 3.65-3.80 (2H,m),4.05-4.15(1H,m),4.70-4.80(1H,m),7.28(1H,d), 7.43(1H,d,J=9.3Hz),7.75(1H,dd,J=8.8,2.7Hz), 8.41(1H,d,J=2.7 Hz),9.05(1H,d,J=8.8Hz),11.56(1H,s).
MS (ESI) m/z: 564$(M+H)^+$.

[Example 21a]

N^1-(5-chloro-2-thienyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1046]

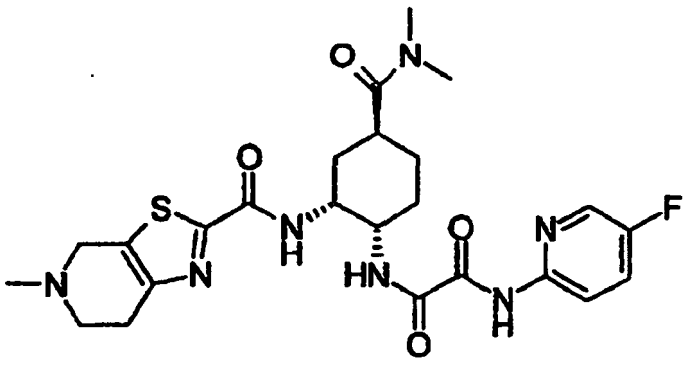


[1047] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 356, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ:1.40-1.55(1H,m),1.60-1.85(3H,m), 1.90-2.15(2H,m),2.79(3H,s),2.90-3.15(1H,m),2.92(3H,s), 2.94(3H,s),3.15-3.30(2H,m),3.50-3.80(2H,m),3.95-4.05(1H,m), 4.35-4.90(3H,m),6.90(1H,d,J=4.2Hz),6.94(1H,d,J-4.2 Hz), 8.72(1H,d,J=7.3Hz),9.13(1H,br.s),11.21(1H,br.s). 12.32(1H,br.s).
MS (ESI) m/z: 553$(M+H)^+$.

[Example 22]

N^1-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]-amino}cyclohexyl)-N^2-(5-fluoropyridin-2-yl)ethanediamide hydrochloride:

[1048]

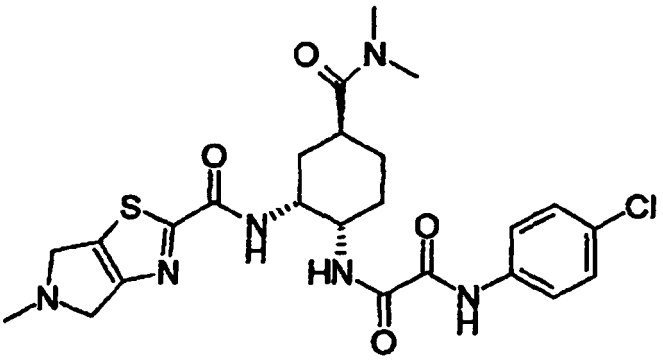


[1049] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 357, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.47-1.53(1H,m),1.68-1.75(3H,m), 1.99-2.10(2H,m),2.80(3H,s),2.80-3.00(1H,m),2.95(6H,s), 3.18-3.21(2H,m),3.40-3.80(2H,m),3.87-4.82(4H,m), 7.82-7.85(1H,m), 8.01-8.05(1H,m),8.40(1H,d,J=2.9Hz), 8.71(1H,d, J=7.7Hz) 9.13(1H,d,J=7.3Hz) 10.27(1H,s).
MS (FAB) m/z: 532$(M+H)^+$.

[Example 23]

N^1-(4-Chlorophenyl)-N^2-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazol-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:

[1050]

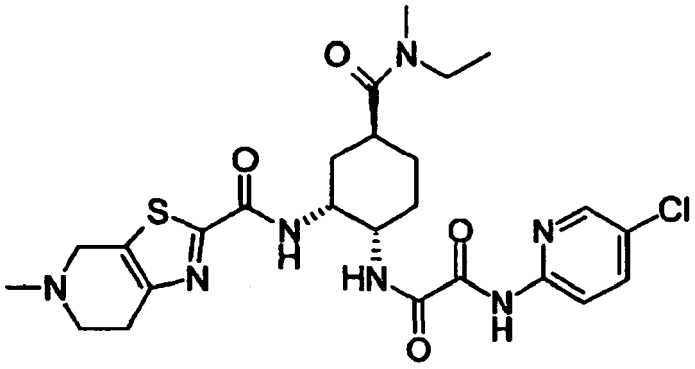


[1051] The title compound was obtained from the compound obtained in Referential Example 242 and the compound obtained in Referential Example 272 in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.47-1.51(1H,m),1.69-1-75(3H,m), 1.98-2.05(2H,m),2.80(3H,s),2.95(3H,s),2.98-3.04(1H,m), 3.10(3H,s),3.40-4.61(6H,m),7.41(2H,d,J=8.8Hz), 7.81(2H,d,J=8.8Hz),8.76(1H,d,J=7.6Hz),B.95(1H,d,J=8.3Hz), 10.79 (1H,8).
MS (FAB) m/z: 533$(M+H)^+$.

[Example 24]

N^1- (5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-{[ethyl(methyl)amino]carbonyl}-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1052]



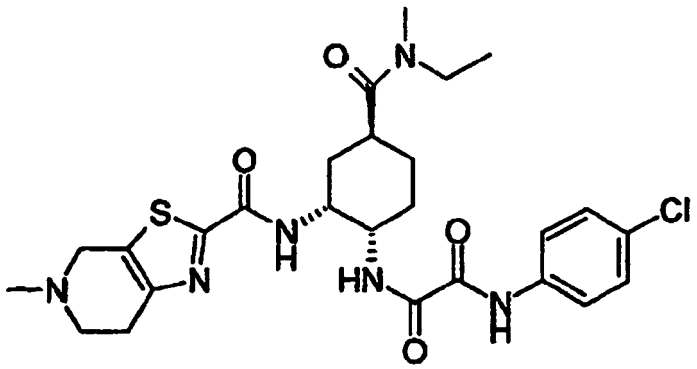
[1053] 10% Palladium on carbon (0.3 g) was added to a solution of the compound (0.33 g) obtained in Referential Example 404 in ethanol (20 ml), and the mixture was stirred at room temperature for 24 hours under a hydrogen atmosphere. After removing insoluble matter by filtration through Celite pad, the filtrate was concentrated under reduced pressure. The resultant residue (0.37 g) was dissolved in N,N-dimethylformamide (20 ml), and the compound (0.3 g) obtained in Referential Example 266, 1-hydroxybenzotriazole monohydrate (0.2 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.37 g) were successively added to stir the mixture at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, and the resultant residue was diluted with a mixed solvent of chloroform-methanol (9:1) and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure, the resultant residue was purified by column chromatography on silica gel (chloroform:methanol = 95:5) to concentrate the intended fraction. A 1N ethanol solution of hydrochloric

acid was added to form a hydrochloride. This salt was recrystallized from a mixed solvent of methanol and diethyl ether to obtain the title compound (0.28 g).
^{1}H-NMR (DMSO-d_6) δ: 0.95(1.5H,t,J=6.9Hz), 1.42(1.5H,t,J=6.9Hz), 1.40-1.52(1H,m),1.60-1.78(3H,m), 1.92-2.11(2H,m),2.74(3H,s),2.90(3H,s),3.10-3.38(5H,m), 3.40-3.52(1H,m),3.68-3.70(1H,m),3.96-4.05(1H,m),4.41(2H,s), 4.70(1H,d,J=15.9Hz),8.00-8.01(2H,m),8.44(1H,s), 8.71(1H,dd,J=10.1,2.2Hz),9.14(0.5H,d,J=7.8Hz), 9.22(0.5H,d,J=8.3Hz),10.24(0.5H,s),10.28(0.5H,s), 11.48(1H,br.s),11.61(1H,br.s).
MS (FAB) m/z: 562$(M+H)^+$.

[Example 25]

N^1-(4-Chlorophenyl)-N^2-((1S,2R,4S)-4-{[ethyl(methyl)amino]-carbonyl}-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2 -yl) carbonyl] amino}cyclohexyl) ethanediamide hydrochloride:

[1054]

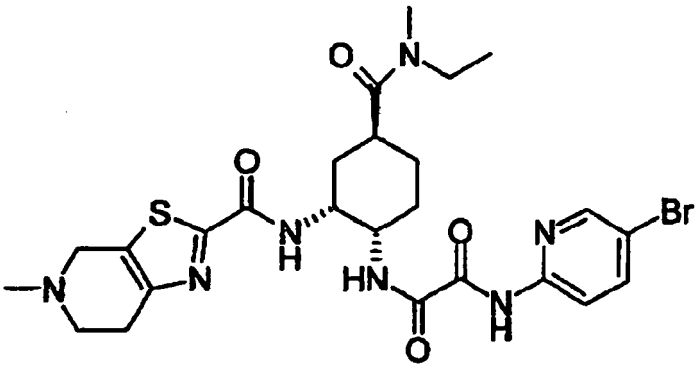


[1055] The title compound was obtained by converting the compound obtained in Referential Example 404 into an amine, condensing the amine with the compound obtained in Referential Example 374 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 24.
^{1}H-NMR (DMSO-d_6) δ: 0.97(1.5H,t,J=6.9Hz), 1.04(1.5H,t,J=6.9Hz),1.40-1.60(1H,m),1.60-1.80(3H,m), 1.92-2.11(2H,m), 2.74(3H,s),2.89(3H,s),3.10-3.32(5H,m), 3.40-3.52(1H,m),3.65-3.80(1H,m),3.90-4.05(1H,m), 4.40(2H,s),4.70(1H,d,J=15.9Hz),7.39(2H,d,J=8.8Hz), 7.82(2H,d,J=8.8Hz),8.75(1H,dd,J=10.1,2.2Hz), 9.00(0.5H,d,J=7.8Hz),9.08(0.5H,d,J=8.3Hz), 10.1(1H,d,J=4.9Hz),11.45(1H,br.s).
MS (FAB) m/z: 561$(M+H)^+$.

[Example 26]

N^1-(5-Bromopyridin-2-yl)-N^2-((1S,2R,4S) -4-{[ethyl(methyl)amino]carbonyl}-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1056]



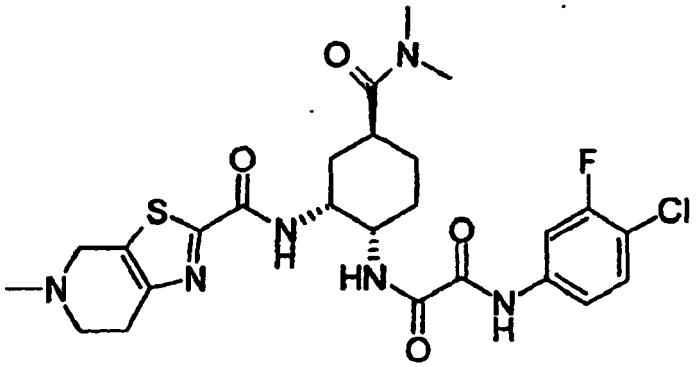
[1057] The title compound was obtained by converting the compound obtained in Referential Example 404 into an

amine, condensing the amine with the compound obtained in Referential Example 375 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 24.
^{1}H-NMR (DMSO-d_6) δ: 1.02(1.5H,t,J=6.9Hz), 1.08(1.5H,t,J=6.9Hz),1.49-1.60(1H,m),1.60-1.86(3H,m), 2.00-2.20(2H,m) 2.81(3H,s) 2.97(3H,s) 3.15-3.42 (6H,m), 3.50-3.60(1H,m),3.70-3.82(1H,m),4.48(2H,s), 4.77(1H,d,J=15.9Hz),8.04(1H, d,J=8.8Hz),8.17(1H,d,J=8.8Hz), 8.58(1H,s),8.78(1H,dd,J=10.1,2.2Hz),9.21(0.5H,d,J=7.8Hz), 9.29(0.5H,d,J=8.3Hz), 10.29(0.5H,s),10.33(0.5H,s), 11.53 (0.5H,br.s), 11.65(0.5H,br.s) .
MS (FAB) m/z: 607 $(M+H)^+$.

[Example 27]

N^1-(4-Chlroro-3-fluorophenyl) -N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1058]

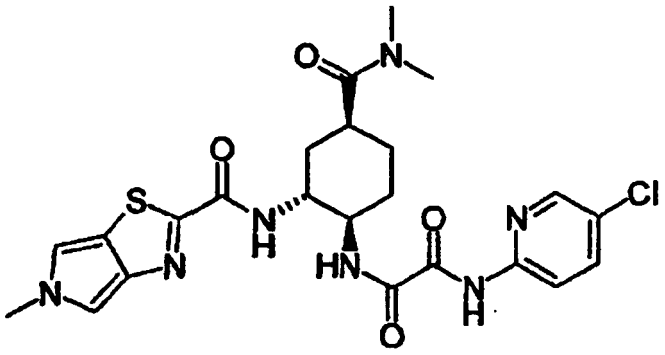


[1059] The title compound was obtained by converting the compound obtained in Referential Example 252 into an amine, condensing the amine with the compound obtained in Referential Example 378 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 24.
^{1}H-NMR (DMSO-d_6) δ: 1.44-1.52(1H,m),1.65-1.76(3H,m), 2.01-2.07(2H,m),2.77(3H,s),2.93(6H,s),2.94-3.00(1H,m), 3.10-3.38(3H,m),3.68-3.70(1H,m),3.96-4.05(1H,m),4.42(2H,s), 4.70(1H,d,J=15.9Hz),7.56(1H,t,J=8.8Hz),7.68(1H,d,J= 8.8Hz), 7.90(1H,dd,J=11.7,1.5Hz),8.73(1H,dd,J=12.5,7.3Hz), 9.06(1H,dd,J=12.5,8,1Hz),11.01(1H,d,J.5.8Hz), 11.30-11.42(1H,m).
MS (FAB) m/z: 565$(M+H)^+$.

[Example 28]

N^1- (5-Chlroropyridin-2-yl)-N^2-((1R,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-5H-pyrxolo[3,4-d]-thiazol-2-yl) carbonyl]amino}cyclohexyl)ethanediamide:

[1060]



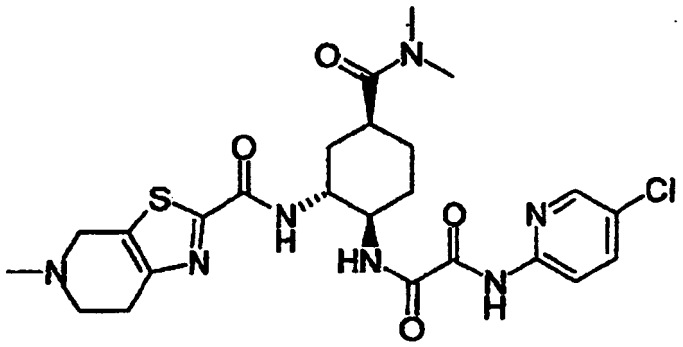
[1061] The title compound was obtained by deprotecting the compound obtained in Referential Example 386 by

hydrochloric acid treatment, and condensing the deprotected compound with the compound obtained in Referential Example 293 in a similar manner to the process described in Example D.
^{1}H-NMR (DMSO-d_6) δ:1.00-2.35(7H,m),2.96(3H,s),3.04(3H,s) . 3.85-3.95(1H,m),3.88(3H,s),4.60-4.75(1H,m), 6.68(1H, d,J=2.0Hz), 7.17(1H,d,J=2.0Hz),7.20-7.32(1H,m), 7.67(1H,dd,J=8.8,2.8Hz),7.99(1H,d,J=8.4Hz), 8.21(1H,d,J=8.8Hz), 8.25(1H,d,J=2.8Hz),9.64(1H,s).
HRMS (FAB) m/z: 532.1520(M+H)$^+$.
(Calculated; $C_{23}H_{27}ClN_7O_4S$: 532.1534).

[Example 29]

N^1-[(5-Chlroropyridin-2-yl)amino]-N^2- ((1R,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1062]

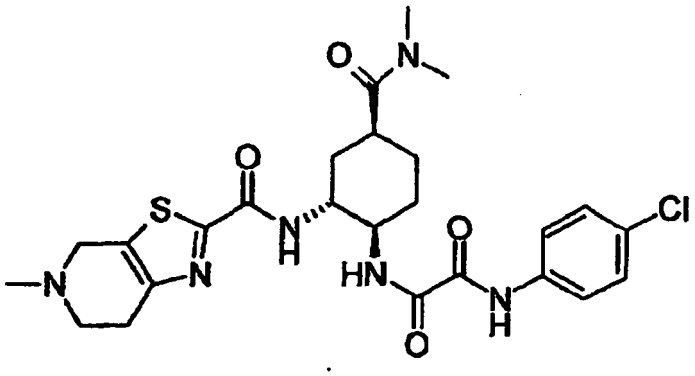


[1063] The title compound was obtained by reducing the compound obtained in Referential Example 387 in a similar manner to the process described in Referential Example 253, and condensing the reduction product with the compound obtained in Referential Example 266 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 18.
^{1}H-NMR (DMSO-d_6) δ: 1.50-1.98(6H,m), 2.82(3H,s),2.91(3H,s), 2.95(3H,s),2.86-3.92(7H,m),4.30-4.81(2H,m),7.92-8.09 (2H,m), 8.39-8.47(1H,m),8.56-8.72(2H,m),10.17(1H,s).
MS (ESI) m/z: 548(M+H)$^+$.

[Example 30]

N^1-(4-Chlorophenyl)-N^2-((1R,2R,4S)-4-[(dimethylamino)-carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide:

[1064]



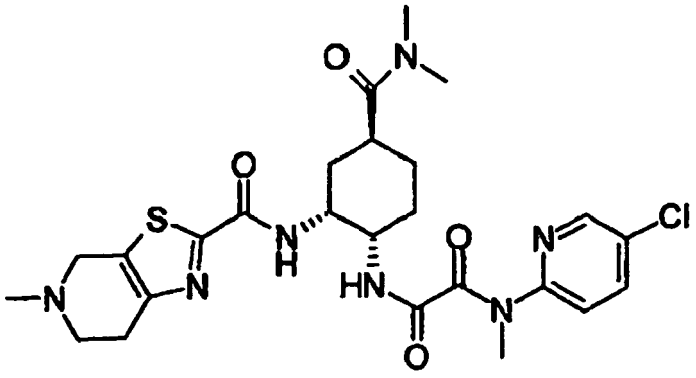
[1065] The title compound was obtained by reducing the compound obtained in Referential Example 387 in a similar

manner to the process described in Referential Example 253, and condensing the reduction product with the lithium salt obtained by hydrolyzing the compound obtained in Referential Example 242 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.50-1.97(6H,m), 2.82(3H,s),2.91(3H,s), 2.98(3H,s),2.83-3.88(7H,m),4.30-4.79(2H,m), 7.37(2H, d,J=8.8Hz), 7.89(2H,d,J=8.8Hz), 8.34(1H,d,J=8.4Hz),8.63(1H,d,J=8.8Hz),10.72(1H,s).
MS (ESI) m/z: 547$(M+H)^+$.

[Example 31]

N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridin-2-yl)carbonyl]-amino}cyclohexyl))-N^1-methylethanediamide hydrochloride:

[1066]

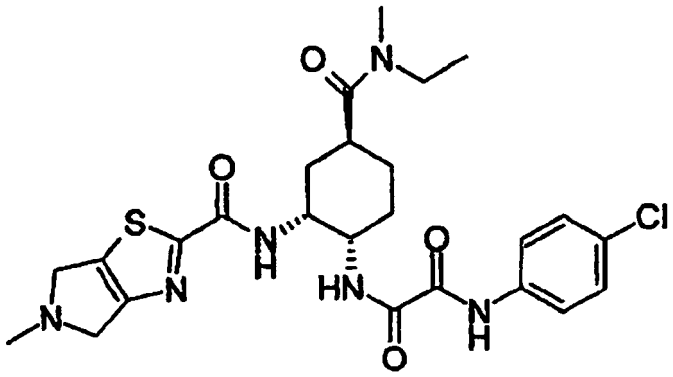


[1067] The title compound was obtained by hydrolyzing the compound obtained in Referential Example 390, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 1.
^{1}H-NMR (DMSO-d_6) δ: 1.32-1.97(6H,m), 2.42-2.51(1H,m), 2.76(3H,s), 2.91(3H,s),2.93(3H,s),3.27(3H,s), 3.00-4.80(8H, m), 7.45(1H,br.s),7.88-7.97(1H,m), 8.25-8.41(2H,m),8.78-8.91(1H,m).
MS (FAB) m/z: 562$(M+H)^+$.

[Example 32]

N^1-(4-chlorophenyl)-N^2-((1S,2R,4S)-4-{[ethyl(methyl)amino]-carbonyl}-2-{[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazol-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:

[1068]



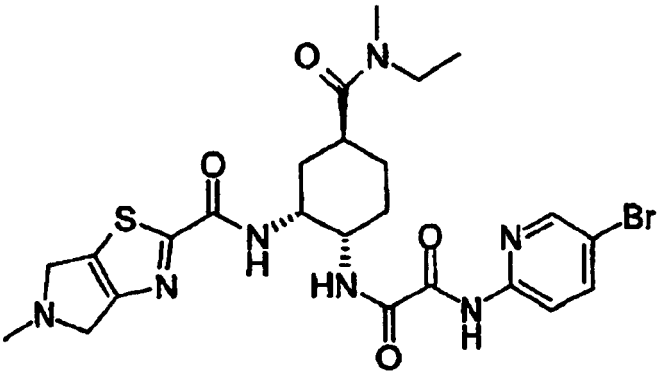
[1069] The title compound was obtained by reducing the compound obtained in Referential Example 392 in a similar manner to the process described in Referential Example 253, and condensing the reduction product with the carboxylic

acid obtained by hydrolyzing the compound obtained in Referential Example 242 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 5.
^{1}H-NMR (DMSO-d_6) δ: 0.96,1.02(3H, each t,J=7.0Hz), 1.47-1.58(1H,m),1.65-1.77(3H,m),1.98-2.08(2H,m), 2.76-2.91 (4H,m),3.07(3H,s),3.19-3.41(2H,m),3.98-4.04(1H,m), 4.42(1H,br.s),4.46-4.94(4H,m),7.41(2H,d,J=8.8Hz), 7.83(2H,d, J=8.8Hz),8.74-8.80(1H,m),9.02(1H,d,J=7.3Hz), 10.82(1H,s),12.41(1H,br.s).
MS (FAB) m/z: 547$(M+H)^+$.

[Example 33]

N^1-(5-Bromopyridin-2-yl)-N^2-((1S,2R,4S)-4-{[ethyl(methyl)amino]carbonyl}-2-{[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d] thiazol-2-yl)carbonyl]amino}cyclohexyl)-ethanediamide hydrochloride:

[1070]

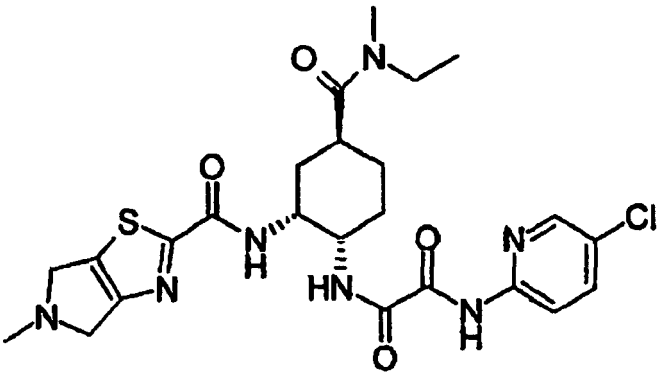


[1071] The title compound was obtained from the compound obtained in Referential Example 392 and the compound obtained in Referential Example 262 in a similar manner to the process described in Example 32.
^{1}H-NMR (DMSO-d_6) δ: 0.90-1.08(3H,m),1.40-2.13(6H,m), 2.70-3.53(13H,m),3.92-4.08(1H,m),4.35-4.47(1H,m), 7.95 (1H,d,J=8.8Hz),8.10(1H,dd,J=8.8,2.4Hz),8.50-8.55(1H,m), 8.68-8.78(1H,m),9.12-9.18(1H,m),10.26(1H,s).
MS (FAB) m/z: 592$(M+H)^+$.

[Example 34]

N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-{[ethyl(methyl)amino]carbonyl}-2-{[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d] thiazol-2-yl)carbonyl]amino}cyclohexyl)-ethanediamide hydrochloride:

[1072]



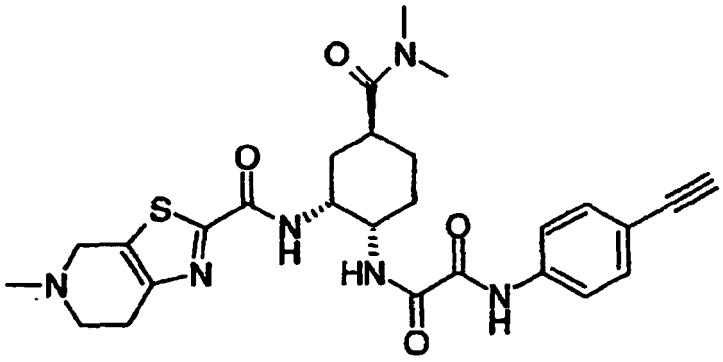
[1073] The title compound was obtained from the compound obtained in Referential Example 392 and the compound obtained in Referential Example 243 in a similar manner to the process described in Example 32.
^{1}H-NMR (DMSO-d_6) δ: [0.95(t,J=7.0Hz),1.01(t,J=6.8Hz),3H] , 1.45-1.72(4H,m),1.96-2.07(2H,m),2.74-2-90(4H,m),3.06

(3H,s), 3.18-3.40(2H,m),3.95-4.02(1H,m),4.41(1H,br.s),4.54-4.90(4H,m), 8.00(2H,br.s),8.45(1H,s),8.70-8.75(1H,m), 9.15(1H,br.s),10.27(1H,br.s),12.29(1H,br.s).
MS (ESI) m/z: 548$(M+H)^+$.

[Example 35]

N^1-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)-N^2-(4-ethynylphenyl)ethanediamide:

[1074]

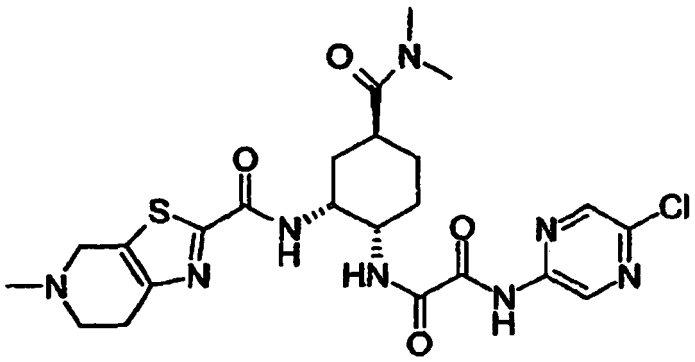


[1075] The title compound was obtained by condensing the compound obtained in Referential Example 252 with the compound obtained in Referential Example 397 in a similar manner to the process described in Example 24.
^{1}H-NMR ($CDCl_3$) δ: 1.67-2.16(6H,m),2.51(3H,s),2.76-2.91(5H,m), 2.94(3H,s),3.04(3H,s),3.07(1H,s),[3.65(1H,d,J=15.5 Hz), 3.73(1H,d,J=15.5Hz)AB pattern] 4.09-4.16(1H,m),4.72-4.75(1H,m),7.42-7.46(3H,m),7.58(2H,d,J=8.5Hz) , 8.02 (1H,d,J=8.1Hz),9.36(1H,s).
MS (FAB) m/z: 537$(M+H)^+$.

[Example 36]

N^1-(5-Chloropyrazin-2-yl)-N^2- ((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1076]

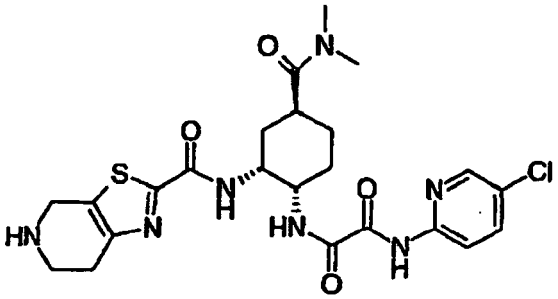


[1077] The title compound was obtained by condensing the compound obtained in Referential Example 253 with the compound obtained in Referential Example 399 in a similar manner to the process described in Referential Example 97 and then treating the condensation product with hydrochloric acid.
^{1}H-NMR (DMSO-d_6) δ: 1.44-1.52(1H,m),1.65-1.77(3H,m), 2.00-2.10(2H,m)2,77(3H,s)2.91-2.97(7H,m),3.20(2H,br.s), 3.48(1H,br.s),3.68(1H,br.s),3.97-4.02(1H,m),4.40-4.46(2H,m), 4.68(1H,br.s),8.64(1H,d,J=1.2Hz),8.70(1H,d,J=7.3Hz), 9.02(1H,s),9.21(1H,br.s),10.91(1H,br.s),11.50(1H,br.s).
MS (FAB) m/z : 549$(M+H)^+$.

[Example 37]

N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S) -4-[(dimethylamino)carbonyl]-2-{[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:

[1078]

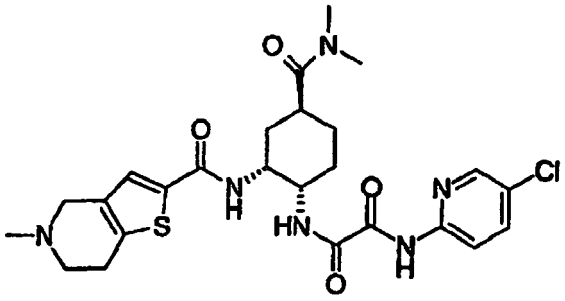


[1079] The title compound was obtained by condensing the compound obtained in Referential Example 34 with the compound obtained in Referential Example 420 and then treating the condensation product with hydrochloric acid in a similar manner to the process described Example B.
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.55(1H,m),1.60-1.80(3H,m), 1.95-2.10(2H,m),2.78(3H,s),2.85-3.00(4H,m), 3.11(2H,br s), 3.40-3.55(2H,m),3.95-4-07(1H,m),4.37-4.45(1H,m),4.48(2H,br s),8.00-8.01(2H,m), 8.10(1H,d,J=7.1Hz), 8.43-8.47(1H, m), 9.16(1H,d,J=7.8Hz),9.43(2H,br s), 10.27(1H,s).
MS (FAB) m/z: 534$(M+H)^+$.

[Example 38]

N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]amino}-cyclohexyl)ethanediamide hydrochloride:

[1080]

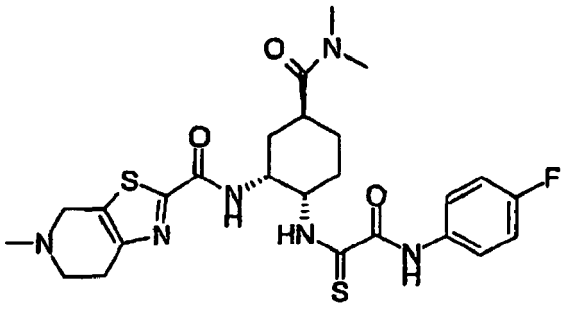


[1081] The title compound was obtained by deprotecting the compound obtained in Referential Example 421 with hydrochloric acid, methylating the deprotected compound in a similar manner to the process described in Example C and treating it with hydrochloric acid.
^{1}H-NMR (DMSO-d_6) δ: 1.42-1.58(1H,m),1.59-1.80(3H,m), 1.83-1.95(1H,m),1.97-2.10(1H,m),2.78(3H,s), 2.89(3H,s), 2.96(3H,s),3.00-3.10(1H,m),3.10-3.20(2H, m), 3.45-3.80(1H, m),3.90-4.00(2H,m),4.00-4.50(3H,m), 7.77(1H,s),7.95-8.05(3H,m),8.44(1H,t,J=1.6Hz), 8.90(1H,d,J=8.6Hz),10.25(1H,s),11.12(1H,br s).
MS (ESI) m/z: 547$(M+H)^+$.

[Example 39]

N-((1R,2S,5S)-5-[(Dimethylamino)carbonyl]-2-{[2-(4-fluoroanilino)-2-oxoethanethioyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

[1082]

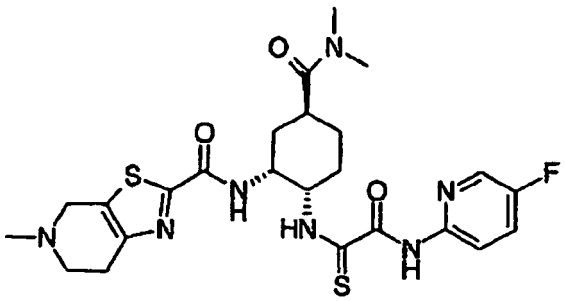


[1083] The title compound was obtained by treating the compound obtained in Referential Example 424 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then subjecting the condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example E.
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.60(1H,m),1.60-1.80(3H,m), 2.00-2.10(1H,m),2.20-2.35(1H,m),2.79(3H,s),2.93(3H,s), 2.95(3H,s),2.95-3.10(1H,m),3.10-3.30(2H,m),3.40-3.60(1H,m), 3.60-3.80(1H,m),4.35-4.50(1H,m),4.50-4.60(1H,m), 4.60-4.80(2H,m), 7.20(2H,t,J=8.8Hz), 7.77(2H,dd,J=9.0, 5.1Hz), 8.80(1H,br) 10.42(1H,s), 10.93(1H,br), 11.28(1H,br).
MS (ESI) m/z: 547$(M+H)^+$.

[Example 40]

N-[(1R,2S,5S)-5-[(Dimethylamino)carbonyl]-2-({2-[(5-fluoropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:

[1084]

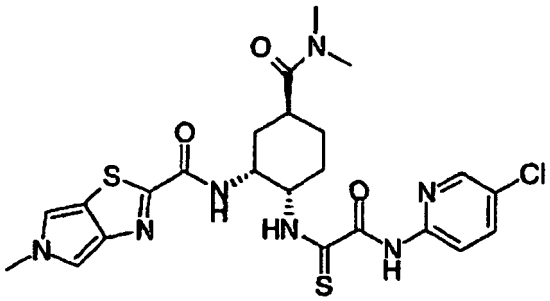


[1085] The title compound was obtained by treating the compound obtained in Referential Example 427 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then subjecting the condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example E.
^{1}H-NMR (DMSO-d_6) δ: 1.43-1.57(1H,m),1,64-1.87(3H,m), 2.00(1H,br s),2.17-2.34(1H, m),2.78(3H,s),2.90(3H,s), 2.95 (3H,s),2.95-3.10(1H,m), 3.10-3.30(2H,m), 3.40-3.60(1H,m), 3.68(1H,br s),4.44(1H,br s),4.45-4.56(1H,m),4.60-4.73(2H, m),7.80-7.90(1H,m),8.08(1H,dd,J=9.1,3.9Hz), 8.41(1H,d,J=2.9Hz),8.79(1H.d,J=6.6Hz),10.49(1H,s), 11.07(1H,br s), 11.69(1H,br).
MS (ESI) m/z: 548$(M+H)^+$.

[Example 41]

N-{(1R,2S,5S)-2-({2-[(5-Chloropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-5H-pyrrolo[3,4-d]thiazole-2-carboxamide:

[1086]

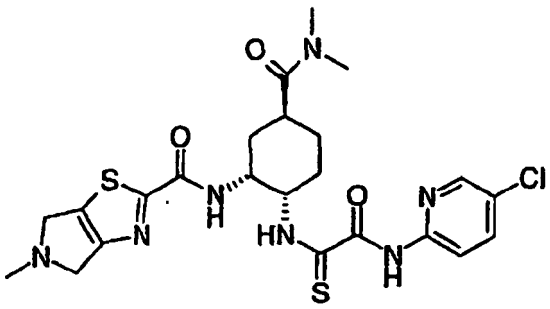


[1087] The title compound was obtained by treating the compound obtained in Referential Example 428 with hydrochloric acid to deprotect it and then condensing the deprotected compound with the compound obtained in Referential Example 293 in a similar manner to the process described in Example E.
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.58(1H,m),1.63-1.73(2H,m),1.73-1.87(2H,m),2.00-2.10(1H,m),2.20-2.35(1H,m),2.79(3H, s), 2.95(3H,s),2.96-3.10(1H,m),3.89(3H,s),4.48-9.58(1H,m),4.60-4.70(1H,m),7.05(1H,d,J=1.7Hz), 7.55(1H,d,J=1.7Hz), 8.00(1H,dd,J=8.9.2.4Hz), 8.05(1H,d,J=8.9Hz),8.44(1H,d,J=2.4Hz),8.71(1H,d,J=7.3Hz), 10.57(1H,s), 11.13(1H,d,J= 7.8Hz).
MS (FAB) m/z : 548(M+H)$^+$.

[Example 42]

N-{(1R,2S,5S)-2-({2-[(5-Chloropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl] - cyclohexyl]-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazole-2-carboxamide hydrochloride:

[1088]

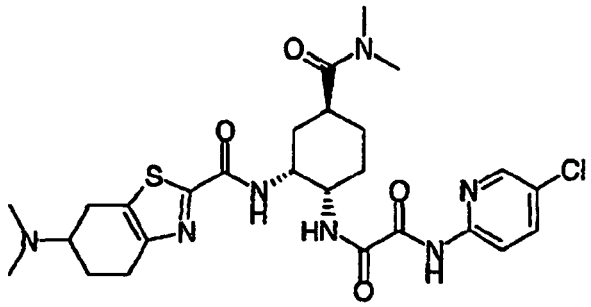


[1089] The title compound was obtained by treating the compound obtained in Referential Example 428 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 293 under an argon atmosphere and then subjecting the condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example E.
^{1}H-NMR (DMSO-d_6) : 1.42-1.58(1H,m),1.65-1.87(3H,m), 1.97-2.10(1H,m) ,2.17-2.30(1H,m),2.80(3H,s),2.96(3H,s), 2.98-3.10(1H,m),3.07(3H,s),4.30-5.00(6H,m),8.00-8.10(1H,m), 8.46(1H,d,J=2.4Hz),8.79(1H,t,J=7.3Hz).10.54(1H,s), 11.04(1H,d,J=7.8Hz),12.24(1H,br s).
MS (ESI) m/z: 550(M+H)$^+$.

[Example 43]

N^1-(5-Chloropyridin-2-yl)-N^2-[(1S,2R,4S) -4-[(dimethylamino)carbonyl]-2-({[6-(dimethylamino)-4,5,6,7-tetrahydrobenzothiazol-2-yl]carbonyl}amino)cyclohexyl]-ethanediamide:

[1090]

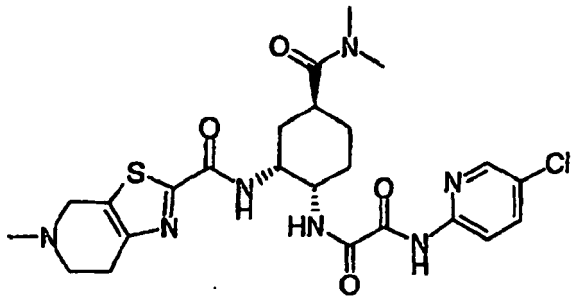


[1091] The title compound was obtained by deprotecting the compound obtained in Referential Example 431 with hydrochloric acid, methylating the deprotected compound in a similar manner to the process described in Example C and treating it with hydrochloric acid.
^{1}H-NMR (DMSO-d_6) δ: 1.42-1.58(1H,m),1.59-1.80(3H,m),1.90-2.12(3H,m),2.30-2.45(1H,m),2.70-3.00(1H,m),2.92(3H, s), 3.00-3.20(2H,m),3.25-3.45(1H,m),3.63-3.80(1H,m),3.88-4.02(1H,m),4.35-4.47(1H,m),8.02(1H,s),8.42-8.55(1H,m), 8.60-8.68(1H,m),8,93(1H,dd,J=14.5,8.2Hz), 9.19(1H,dd,J=17.7,8.2Hz),10.28(1H,s),10.91(1H,br s).
MS (ESI) m/z: 576$(M+H)^+$.

[Example 44]

N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide:

[1092]

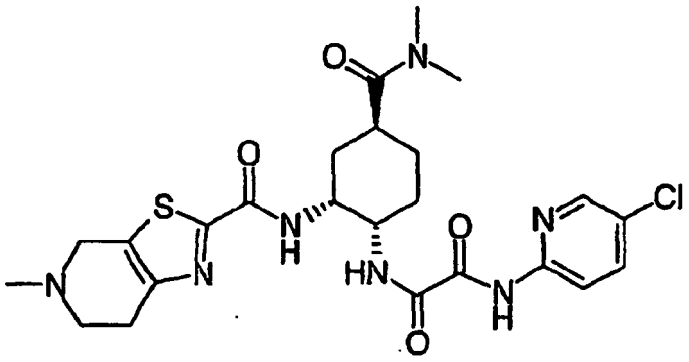


[1093] The title compound was obtained from the compound obtained in Referential Example 435 and the compound obtained in Referential Example 10 in a similar manner to Example A.
^{1}H-NMR ($CDCl_3$) δ: 1.60-1.98(3H,m),2.00-2.16(3H,m), 2.52(3H,s),2.78-2.90(3H,m),2.92-2.98(2H,m),2.95(3H,s), 3.06 (3H,s),3.69(1H,d,J=15.4Hz),3.75(1H,d,J=15.4Hz), 4.07-4.15(1H,m),4.66-4.72(1H,m),7.40(1H,d,J=8.8,0.6Hz), 7.68(1H, dd,J=8.8,2.4Hz),8.03(1H,d,J=7.8Hz), 8.16(1H,dd,J=8.8,0.6Hz),8.30(1H,dd,J=2.4,0.6Hz),9.72(1H,s).
MS (ESI) m/z: 548$(M+H)^+$.

[Example 45]

N^1-(5-Chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide p-toluenesulfonate monohydrate:

[1094]



[1095] The compound (6.2 g) obtained in Example 44 is dissolved in methylene chloride (120 ml), a 1 mol/L ethanol solution (11.28 ml) of p-toluenesulfonic acid was added to the solution, and the solvent was distilled off. Ethanol (95 ml) containing 15% water was added to the residue, and the mixture was stirred at 60°C to dissolve it. The solution was then cooled to room temperature and stirred for a day. Crystals deposited were collected by filtration, washed with ethanol and dried at room temperature for 2 hours under reduced pressure to obtain the title compound (7.4 g).
^{1}H-NMR (DMSO-d_6) δ: 1.45-1.54(1H,m),1.66-1.78(3H,m),2.03-2.10(2H,m),2.28(3H,s),2.79(3H,s),2.91-3.02(1H,m), 2.93(3H,s),2.99(3H,s),3.13-3.24(2H,m),3.46-3.82(2H,m), 3.98-4.04(1H,m),4.43-4:80(3H,m),7.11(2H,d,J-7.8Hz), 7.46 (2H,d,J=8.2Hz),8.01(2H,d,J-1.8H2),8.46(1H,t,J=1.8Hz), 8.75(1H,d,J=6.9Hz),9.10-9.28(1H,br),10.18(1H,br), 10.29(1H, s).
MS (ESI) m/z: 548$(M+H)^+$.
Elemental analysis: $C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$.
Calculated: C;50.43,H;5.46,N;13.28,Cl;4.80,S;8.69.
Found: C;50.25,H;5.36,N;13.32,Cl;4.93,S;8.79.
mp (decomposed) : 245~248°C.

[Test Example 1]

Determination of human FXa-inhibiting effect (IC_{50} value):

[1096] 5% DMSO solutions (10 μl) of each test compound, the concentrations of which were suitably set stepwise, Tris buffer (100 mM Tris, 200 mM potassium chloride, 0.2% BSA, pH 7.4) (40 μl) and 0.0625 U/ml human FXa (Enzyme Research Labolatories, Inc., dissolved and diluted with Tris buffer) (10 μl) were respectively put in wells of a 96-well microplate, and a 750 μM aqueous solution (40 μl) of S-2222 (Chromogenix Co.) was added. Absorbance at 405 nm was measured for 10 minutes at room temperature to determine an increase in absorbance (ΔOD/min). As a control, Tris buffer was used in place of the test compound.
[1097] The percent inhibition (%) calculated using the following equation at the final concentration of the test compound and the final concentration of the test compound were plotted on the axis of ordinate and the axis of abscissa of logarithmic normal probability paper, respectively, to determine the 50% inhibition concentration (IC_{50} value).

$$\text{Percent inhibition (\%)} = \left[1 - (\Delta OD/\text{min of test compound}) \div (\Delta OD/\text{min of control})\right] \times 100$$

(Result)

[1098] In Table 1, it is demonstrated that the compounds according to the present invention have a potent FXa-inhibiting effect.

Table 1

Compound	Human FXa-inhibiting effect (IC_{50}) : nM
Ex. 1	1.2
Ex. 2	2.0
Ex. 4	5.0
Ex. 14	1.5
Ex. 19	3.1
Ex. 20	1.9
Ex. 21	5.4

[Test Example 2]

[1099] Determination of anti-FXa activity in rat plasma after oral administration:

(A) Administration and blood collection:

A drug solution (1 mg/ml) obtained by dissolving or suspending a test compound (10 mg) in 0.5% methyl cellulose (MC) was orally administered to rats (10 ml/kg). After 0.5, 1, 2 and 4 hours from the drug administration, the blood (0.5 ml) was collected through the jugular vein using a syringe which is containing a 3.13% (w/v) aqueous solution (50 μl) of trisodium citrate dihydrate (amount of blood collected: 0.45 ml). For rats of a control group, the same blood collection was conducted after a 0.5% MC solution was administered. Each blood sample was centrifuged at 1500 x g for 10 minutes at 4°C to separate plasma, and the plasma was preserved at -40°C until it was used in the following determination of anti-FXa activity in plasma.

(B) Determination of FXa-inhibiting activity in plasma:

In the determination of anti-FXa activity in plasma, S-2222 was used as a substrate. Tris buffer (100 mM Tris, 200 mM potassium chloride, 0.2% BSA, pH 7.4) (5456 μl), human FXa (2.5 U/ml, 44 μl) and water (550 μl) were mixed. The resultant human FXa solution was used in the following test.

[1100] Rat plasma (5 μl) obtained in accordance with the procedure (A) described above was put in wells of a 96-well microplate, and the above-described human FXa solution (55 μl) and a 750 μM aqueous solution (40 μl) of S-2222 were sequentially added. Immediately after that, absorbance at 405 nm was measured at room temperature by means of a spectrophotometer SPECTRAmax 340 or 190 (Molecular Devices Co., U.S.A.), thereby determining a rate of reaction (ΔOD/min).

[1101] The anti-FXa activity, i.e., percent inhibition (%) was calculated in accordance with the following equation:

$$\text{Percent inhibition (\%)} = [1 - (\Delta OD/min \text{ of sample}) \div (\text{average value of } \Delta OD/min \text{ of the control group})] \times 100$$

(Result)

[1102] The compounds described in Examples 1, 2, 4 and 14 exhibited a potent FXa-inhibiting activity of 62 to 96% at an oral dose of 10 mg/kg.

INDUSTRIAL APPLICABILITY

[1103] The cyclicdiamine derivatives according to the present invention exhibit a potent inhibitory effect on activated blood coagulation factor X and are useful as medicines, activated blood coagulation factor X inhibitors, anticoagulants,

agents for preventing and/or treating thrombosis or embolism, agents for preventing and/or treating thrombotic disease and agents for preventing and/or treating cerebral infarction, cerebral embolism, myocardial infarction, angina pectoris, pulmonary infarction, pulmonary embolism, Buerger's disease, deep venous thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve or joint replacement, thrombus formation and reocclusion after angioplasty, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), thrombus formation during extracorporeal circulation, or blood clotting upon blood drawing.

Claims

1. A compound represented by the general formula (1):

$$Q^1\text{-}Q^2\text{-}T^0\text{-}N(R^1)\text{-}Q^3\text{-}N(R^2)T^1\text{-}Q^4 \quad (I)$$

wherein

R^1 and R^2, independently of each other, represent a hydrogen atom, hydroxyl group, linear, branched or cyclic alkyl group having 1 to 6 carbon atoms or linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms;
Q^1 represents a saturated or unsaturated, bicyclic or tricyclic fused heterocyclic group which is selected from 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl,4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-cyclopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-carboxymethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-butyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl,5-(4-pyridyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl, 5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-2-yl, 6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl, 5-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl, 5-methyl-4,6-dihydro-5H-pyrrolo[3,4-d]thiazol-2-yl,5,7-dihydro-6-methylpyrrolo[3,4-d]pyrimidin-2-yl. 5.6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazin-2-yl, 5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[4,5-d]pyridazin-2-yl, 5-dimethylamino-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl, and 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl groups:
Q^2 represents a single bond;
Q^3 represents the following group:

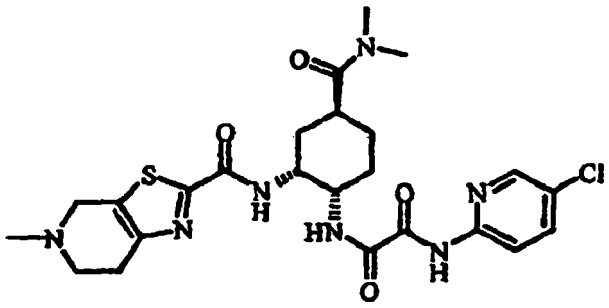
in which Q^5 means an alkylene group having 4 carbon atoms, R^3 is a hydrogen atom, and R^4 is an N,N-dialkylcarbamoyl group having two linear, branched or cyclic C1-C6 alkyl groups
Q^4 represents a phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl, 4-ethynylphenyl, 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl, 3-ethynylphenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chloro-2-fluorophenyl, 2-chloro-4-fluorophenyl, 4-bromo-2-fluorophenyl, 2-bromo-4-fluorophenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dibromophenyl, 4-chloro-3-methylphenyl, 4-fluoro-3-methylphenyl, 4-bromo-3-methylphenyl, 4-chloro-2-methylphenyl, 4-fluoro-2-methylphenyl, 4-bromo-2-methylphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,-4-dibromophenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-chloro-2-pyridyl, 4-fluoro-2-pyridyl, 4-bromo-2-pyridyl, 4-ethynyl-2-pyridyl, 4-chloro-3-pyridyl, 4-fluoro-3-pyridyl, 4-bromo-3-pyridyl, 4-ethynyl-3-pyridyl, 5-chloro-2-pyridyl, 5-fluoro-2-pyridyl, 5-bromo-2-pyridyl, 5-ethynyl-2-pyridyl, 4-chloro-5-fluoro-2-pyridyl, 5-chloro-4-fluoro-2-pyridyl, 5-chloro-3-pyridyl, 5-fluoro-3-pyridyl, 5-bromo-3-pyridyl, 5-ethynyl-3-pyridyl, 6-chloro-3-pyridazinyl, 6-fluoro-3-pyridazinyl, 6-bromo-3-pyridazinyl, 6-ethynyl-3-pydazinyl, 4-chloro-2-thienyl, 4-fluoro-2-thienyl, 4-bromo-2-thienyl, 4-ethynyl-2-thienyl, 4-chloro-2-pyrrolyl, 4-fluoro-2-pyrrolyl, 4-bromo-2-pyrrolyl, 4-ethynyl-2-pyrrolyl, 4-chloro-2-furyl, 4-fluoro-2-furyl, 4-bromo-2-furyl, 4-ethynyl-2-furyl, 5-chloro-2-thienyl, 5-fluoro-2-thienyl, 5-bromo-2-thienyl, 5-ethynyl-2-thienyl, 5-chloro-2-thiazolyl, 5-fluoro-2-thiazolyl, 5-bromo-2-thiazolyl, 5-ethynyl-2-thiazolyl, 5-chloro-2-oxazolyl, 5-fluoro-2-oxazolyl, 5-bromo-2-oxazolyl or 5-ethynyl-2-oxazolyl;
T^0 represents a carbonyl or thiocarbonyl group; and
T^1 represents group -C(=O)-C(=O)-N(R')-, group -C(=S)-C(-O)-N(R')-, group -C(=O)-C(=S)-N(R')-, or group -C(=S)-C(=S)-N(R')-, in which R' means a hydrogen atom, hydroxyl group, linear, branched or cyclic alkyl group having 1 to 6 carbon atoms or linear, branched or cyclic alkoxy group having 1 to 6 carbon atoms,

a salt thereof, a solvate thereof, or an N-oxide thereof.

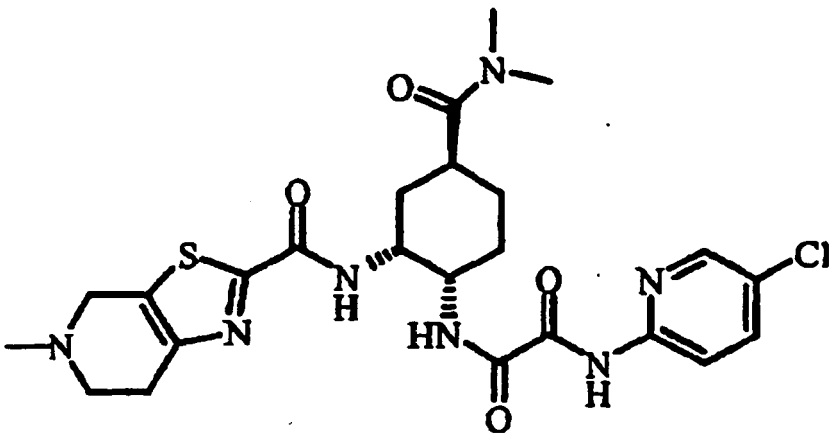
2. The compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to claim 1, wherein the group Q^3 is

wherein Q^5 means an alkylene group having 4 carbon atoms, R^3 is a hydrogen atom, and R^4 is an N,N-dimethylcarbamoyl group.

3. The compound, the salt thereof, or the hydrate thereof according to claim 1, which is N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino} cyclohexyl)ethanediamide of the following formula, a salt thereof, or a hydrate thereof:

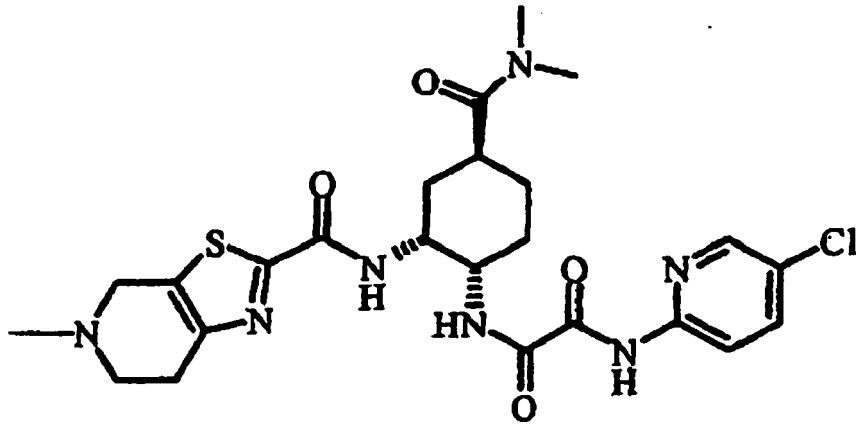


4. The compound, the salt thereof, or the hydrate thereof according to claim 1, which is N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino} cyclohexyl)ethanediamide p-toluenesulfonate:



p-toluenesulfonate.

5. N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide p-toluenesulfonate monohydrate:



p-toluenesulfonate - monohydrate.

6. A medicine comprising the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5.

7. An activated blood coagulation factor X inhibitor comprising the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5.

8. An anticoagulant comprising the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5.

9. An agent for preventing and/or treating thrombosis or embolism, comprising the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5.

10. An agent for preventing and/or treating cerebral infarction, cerebral embolism, myocardial infarction, angina pectoris, pulmonary infarction, pulmonary embolism, Buerger's disease, deep venous thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve or joint replacement, thrombus formation and reocclusion after angioplasty, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), thrombus formation during extracorporeal circulation, or blood clotting upon blood drawing, comprising the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5.

11. A medicinal composition comprising the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5, and a pharmaceutically acceptable carrier.

12. The composition according to claim 11, wherein said composition further comprises at least one pharmaceutically acceptable additive selected from the group consisting of fillers, extenders, binders, disintegrating agents, dissolution aids/accelerators, suspending agents, emulsifying agents, wetting agents, stabilizers, and preservatives.

13. The composition according to claim 11, wherein said composition is in the form of a tablet, a granule, a capsule, a powder, a solution, a suspension, an emulsion, an oil, a syrup, an elixir, an ointment, a gel, a cream, a lotion, a spray, or a plaster.

14. The composition according to claim 11, wherein said composition is suitable for oral, topical, or injection administration.

15. The composition according to any one of claims 11 to 14 for use in the treatment of thrombosis or embolism by administering to a mammal in need thereof a effective amount of a compound according to claim 1.

16. The composition according to claim 15, wherein said effective amount ranges from 1 mg to 1000 mg per day of said at least one compound present within said composition.

17. The composition according to claim15, wherein said effective amount ranges from 0.1 mg to 200 mg per kg of body weight of said mammal per day of said at least one compound present within said composition.

18. The composition according to clam 15, wherein the administration of said composition ranges from one to four times per day.

19. A process for preparing a composition comprising combining at least one compound according to claim 1 to 5 with a pharmaceutically acceptable carrier.

20. The process according to claim 19, wherein said process further comprises combining with said at least one compound and said pharmaceutically acceptable carrier, at least one pharmaceutically acceptable additive selected from the group consisting of fillers, extenders, binders, disintegrating agents, dissolution aidstaccolerators, suspending agents, emulsifying agents, wetting agents, stabilizers, and preservatives.

21. Use of the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5 for preparation of a medicine.

22. Use of the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5 for preparation of an activated blood coagulation factor X inhibitor.

23. Use of the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5 for preparation of an anticoagulant.

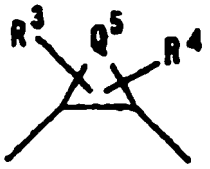
24. Use of the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5 for preparation of an agent for preventing and/or treating thrombosis or embolism.

25. Use of the compound, the salt thereof, the solvate thereof, or the N-oxide thereof according to any one of claims 1 to 5 for preparation of an agent for preventing and/or treating cerebral infarction, cerebral embolism, myocardial infarction, angina pectoris, pulmonary infarction, pulmonary embolism, Buerger's disease, deep venous thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve or joint replacement, thrombus formation and reocclusion after angioplasty, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), thrombus formation during extracorporeal circulation, or blood clotting upon blood drawing.

26. A compound represented by the following general formula (4):

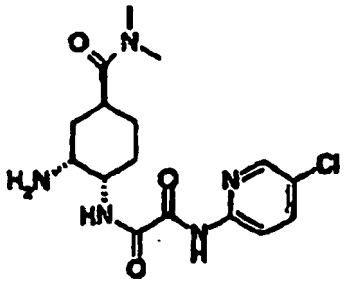
$$HN(R^1)\text{-}Q^3\text{-}N(R^2)\text{-}T^1\text{-}Q^4 \quad (4)$$

wherein R^1, R^2 and T^1 have the same meanings as defined in claim 1, Q^3 represents the following group:



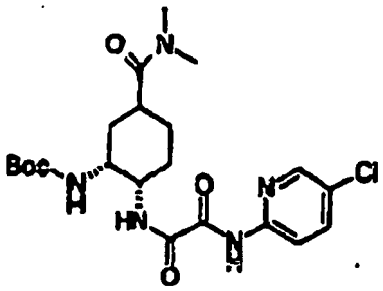
wherein Q^5, R^3 and R^4 have the same meanings as defined in claim 1, and Q^4 has the same meaning as in claim 1; a salt thereof, a solvate thereof, or an N-oxide thereof.

27. The compound according to claim 26, which is N^1-{(1S, 2R, 4S)-2-amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(5-chloropyridin-2-yl)ethanediamide hydrochloride:



hydrochloride.

28. tert.-Butyl (1R, 2S, 5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



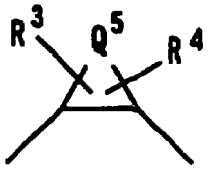
Patentansprüche

1. Verbindung der allgemeinen Formel (1):

$$Q^1\text{-}Q^2\text{-}T^0\text{-}N(R^1)\text{-}Q^3\text{-}N(R^2)\text{-}T^1\text{-}Q^4 \quad (1)$$

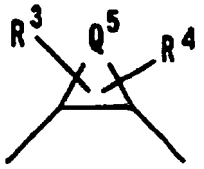
wobei

R^1 und R^2 unabhängig voneinander für ein Wasserstoffatom, eine Hydroxylgruppe, eine lineare, verzweigte oder zyklische Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder eine lineare, verzweigte oder zyklische Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen stehen;
Q^1 für eine gesättigte oder ungesättigte bizyklische oder trizyklische annelierte heterozyklische Gruppe steht, die ausgewählt ist aus 5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 5-Cyclopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl-, 5-Carboxymethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl-, 5-Butyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl-, 5-(4-Pyridyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl-, 5-Methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-2-yl-, 6-Methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl, 5-Methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl-, 5-Methyl-4,6-dihydro-5H-pyrrolo[3,4-d]thiazol-2-yl-, 5,7-Dihydro-6-methylpyrrolo[3,4-d]pyrimidin-2-yl-, 5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazin-2-yl-, 5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[4,5-d]pyridazin-2-yl-, 5-Dimethylamino-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl- und 6,7-Dihydro-4H-pyrano[4,3-d]thiazol-2-yl Gruppen;
Q^2 für eine Einfachbindung steht;
Q^3 für die folgende Gruppe steht:



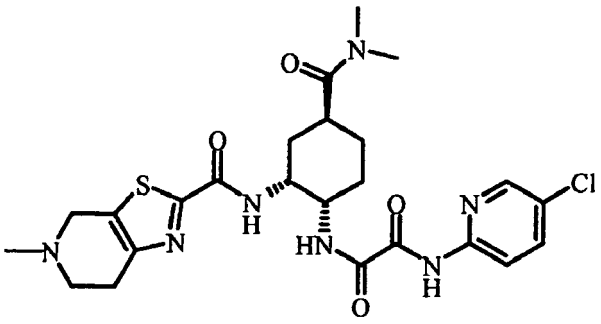
in der Q^5 eine Alkylengruppe mit 4 Kohlenstoffatomen bedeutet, R^3 ein Wasserstoffatom bedeutet und R^4 für eine N,N-Dialkylcarbamoylgruppe mit zwei linearen, verzweigten oder zyklischen C1-C6 Alkylgruppen, steht;
Q^4 für Phenyl, 4-Chlorphenyl, 4-Fluorphenyl, 4-Bromphenyl, 4-Ethynylphenyl, 3-Chlorphenyl, 3-Fluorphenyl, 3-Bromphenyl, 3-Ethynylphenyl, 3-Chlor-4-fluorphenyl, 4-Chlor-3-fluorphenyl, 4-Chlor-2-fluorphenyl, 2-Chlor-4-fluorphenyl, 4-Brom-2-fluorphenyl, 2-Brom-4-fluorphenyl, 2,4-Dichlorphenyl, 2,4-Difluorphenyl, 2,4-Dibromphenyl, 4-Chlor-3-methylphenyl, 4-Fluor-3-methylphenyl, 4-Brom-3-methylphenyl, 4-Chlor-2-methylphenyl, 4-Fluor-2-methylphenyl, 4-Brom-2-methylphenyl, 3,4-Dichlorphenyl, 3,4-Difluorphenyl, 3,4-Dibromphenyl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 4-Chlor-2-pyridyl, 4-Fluor-2-pyridyl, 4-Brom-2-pyridyl, 4-Ethynyl-2-pyridyl, 4-Chlor-3-pyridyl, 4-Fluor-3-pyridyl, 4-Brom-3-pyridyl, 4-Ethynyl-3-pyridyl, 5-Chlor-2-pyridyl, 5-Fluor-2-pyridyl, 5-Brom-2-pyridyl, 5-Ethynyl-2-pyridyl, 4-Chlor-5-fluor-2-pyridyl, 5-Chlor-4-fluor-2-pyridyl, 5-Chlor-3-pyridyl, 5-Fluor-3-pyridyl, 5-Brom-3-pyridyl, 5-Ethynyl-3-pyridyl, 6-Chlor-3-pyridazinyl, 6-Fluor-3-pyridazinyl, 6-Brom-3-pyridazinyl, 6-Ethynyl-3-pyridazinyl, 4-Chlor-2-thienyl, 4-Fluor-2-thienyl, 4-Brom-2-thienyl, 4-Ethynyl-2-thienyl, 4-Chlor-2-pyrrolyl, 4-Fluor-2-pyrrolyl, 4-Brom-2-pyrrolyl, 4-Ethynyl-2-pyrrolyl, 4-Chlor-2-furyl, 4-Fluor-2-furyl, 4-Brom-2-furyl, 4-Ethynyl-2-furyl, 5-Chlor-2-thienyl, 5-Fluor-2-thienyl, 5-Brom-2-thienyl, 5-Ethynyl-2-thienyl , 5-Chlor-2-thiazolyl, 5-Fluor-2-thiazolyl, 5-Brom-2-thiazolyl, 5-Ethynyl-2-thiazolyl, 5-Chlor-2-oxazolyl, 5-Fluor-2-oxazolyl, 5-Brom-2-oxazolyl oder 5-Ethynyl-2-oxazolyl steht;
T^0 für eine Carbonyl- oder Thiocarbonylgruppe steht; und
T^1 für eine Gruppe -C(=O)-C(=O)-N(R')-, Gruppe -C(=S)-C(=O)-N(R')-, Gruppe -C(=O)-C(=S)-N(R')-, oder Gruppe -C(=S)-C(=S)-N(R')-, in denen R' für ein Wasserstoffatom, eine Hydroxylgruppe, eine lineare, verzweigte oder zyklische Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder eine lineare, verzweigte oder zyklische Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen steht, ein Salz davon, ein Solvat davon oder ein N-Oxid davon.

2. Die Verbindung, das Salz davon, das Solvat davon oder das N-Oxid davon nach Anspruch 1, wobei die Gruppe Q^3 für

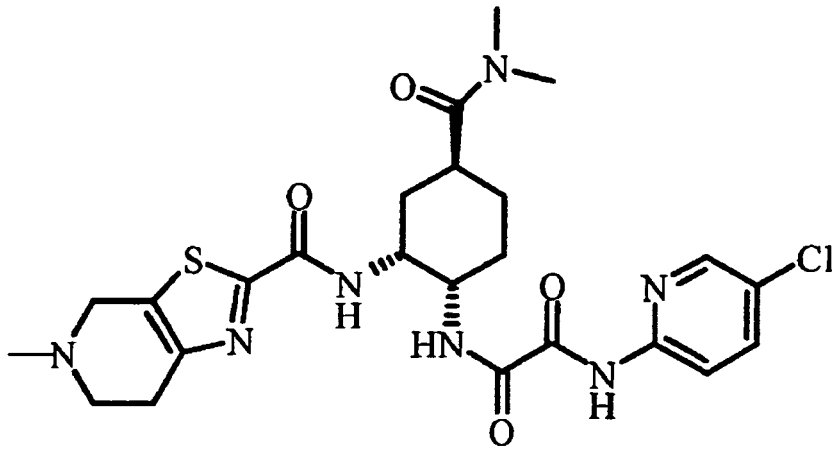


steht, wobei Q^5 für eine Alkylengruppe mit 4 Kohlenstoffatomen steht, R^3 für ein Wasserstoffatom steht und R^4 für eine N,N-Dimethylcarbamoylgruppe steht.

3. Die Verbindung, das Salz davon, oder das Hydrat davon nach Anspruch 1, die N^1-(5-Chlorpyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)ethandiamid der folgenden Formel, ein Salz davon oder ein Hydrat davon:

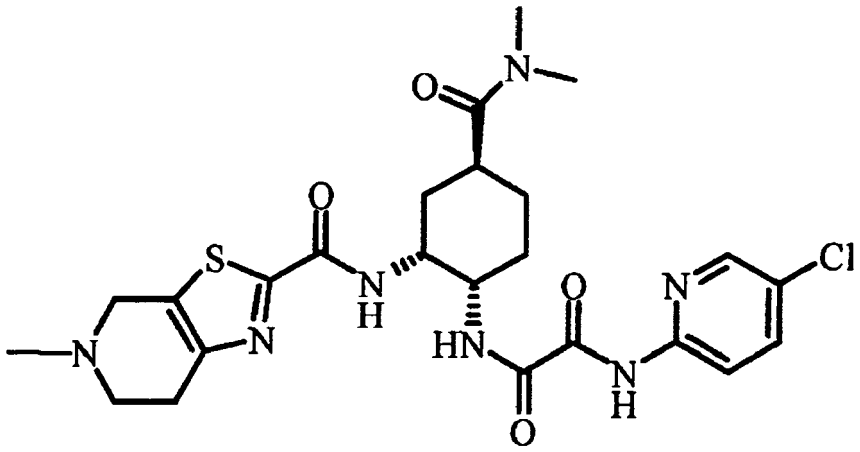


4. Die Verbindung, das Salz davon oder das Hydrat davon nach Anspruch 1, bei der es sich um N^1-(5-Chlorpyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)ethandiamid-p-toluolsulfonat:



p-Toluolsulfonat.

5. N^1-(5-Chlorpyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)ethandiamid-p-toluolsulfonat:



p-Toluolsulfonat ·Monohydrat.

6. Medikament, umfassend die Verbindung, das Salz davon, das Solvat davon oder das N-Oxid davon nach einem der Ansprüche 1 bis 5.

7. Inhibitor des aktivierten Blutkoagulationsfaktors X, der umfasst die Verbindung, das Salz davon, das Solvat davon oder das N-Oxid davon nach einem der Ansprüche 1 bis 5.

8. Antikoagulanz, umfassend die Verbindung, das Salz davon, das Solvat davon oder das N-Oxid davon nach einem der Ansprüche 1 bis 5.

9. Mittel zur Prävention und/oder Behandlung von Thrombose oder Embolie, umfassend die Verbindung, das Salz davon, das Solvat davon oder das N-Oxid davon nach einem der Ansprüche 1 bis 5.

10. Mittel zur Prävention und/oder Behandlung von zerebralem Infarkt, zerebraler Embolie, Myokardinfarkt, Angina Pectoris, Lungeninfarkt, Lungenembolie, Buerger'scher Krankheit, tiefer Venenthrombose, disseminiertem intravasalen Gerinnungssyndrom, Thrombusbildung nach Herzklappen- oder Gelenktransplantation, Thrombusbildung und Reokklusion nach Angioplastie, systemischem entzündlichen Reaktionssyndrom (SIRS), multiplem Organversagen (MODS), Thrombusbildung während extrakorporealer Zirkulation oder Blutgerinnung nach Blutabnahme, umfassend die Verbindung, das Salz davon, das Solvat davon oder das N-Oxid davon nach einem der Ansprüche 1 bis 5.

11. Eine medizinische Zusammensetzung, umfassend die Verbindung, das Salz davon, das Solvat davon oder das N-Oxid davon nach einem der Ansprüche 1 bis 5 sowie einen pharmazeutisch unbedenklichen Träger.

12. Die Zusammensetzung nach Anspruch 11, wobei die Zusammensetzung ferner umfasst mindestens ein pharmazeutisch unbedenkliches Additiv, ausgewählt aus der Gruppe, bestehend aus Füllstoffen, Extendern, Bindemitteln, Sprengmitteln, Auflösungshilfen/Beschleunigern, Suspensionsmitteln, Emulgatoren, Benetzungsmitteln, Stabilisatoren und Konservierungstoffen.

13. Die Zusammensetzung nach Anspruch 11, wobei die Zusammensetzung in Form einer Tablette, einer Granule, einer Kapsel, eines Pulvers, einer Lösung, einer Suspension, einer Emulsion, eines Öls, eines Sirups, eines Elexiers, einer Salbe, eines Gels, einer Creme, einer Lotion, eines Sprays oder eines Pflasters vorliegt.

14. Die Zusammensetzung nach Anspruch 11, wobei die Zusammensetzung zur oralen, topischen oder Injektionsverabreichung geeignet ist.

15. Die Zusammensetzung nach einem der Ansprüche 11 bis 14 zur Verwendung bei der Behandlung von Thrombose oder Embolie durch Verabreichung einer wirksamen Menge einer Verbindung nach Anspruch 1 an ein Säugetier, das diese benötigt.

16. Die Zusammensetzung nach Anspruch 15, wobei die wirksame Menge im Bereich von 1 mg bis 1000 mg pro Tag mindestens einer Verbindung, die in der Zusammensetzung vorliegt, liegt.

17. Die Zusammensetzung nach Anspruch 15, wobei die wirksame Menge im Bereich von 0,1 mg bis 200 mg pro kg Körpergewicht des Säugetiers pro Tag der mindestens einen Verbindung, die in der Zusammensetzung vorliegt, liegt.

18. Die Zusammensetzung nach Anspruch 15, wobei die Verabreichung der Zusammensetzung ein- bis viermal pro Tag erfolgt.

19. Verfahren zur Herstellung einer Zusammensetzung, umfassend ein Vereinigen mindestens einer Verbindung nach Anspruch 1 bis 5 mit einem pharmazeutisch unbedenklichem Träger.

20. Das Verfahren nach Anspruch 19, wobei das Verfahren ferner umfasst ein Kombinieren mit dieser mindestens einen Verbindung und dem pharmazeutisch unbedenklichem Träger von mindestens einem pharmazeutisch unbedenklichem Additiv, ausgewählt aus der Gruppe, bestehend aus Füllstoffen, Extendern, Bindemitteln, Sprengmitteln, Auflösungshilfen/Beschleunigern, Suspensionsmitteln, Emulgatoren, Benetzungsmitteln, Stabilisatoren und Konservierungstoffen.

21. Verwendung der Verbindung des Salzes davon, des Solvats davon oder des N-Oxids davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Medikaments.

22. Verwendung der Verbindung des Salzes davon, des Solvats davon oder des N-Oxids davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Inhibitors des aktivierten Blutkoagulationsfaktors X.

23. Verwendung der Verbindung, des Salzes davon, des Solvats davon oder des N-Oxids davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Antikoagulanzes.

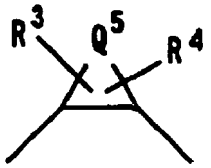
24. Verwendung der Verbindung, des Salzes davon, des Solvats davon oder des N-Oxids davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Mittels zur Prävention und/oder Behandlung von Thrombose oder Embolie.

25. Verwendung der Verbindung, des Salzes davon, des Solvats davon oder des N-Oxids davon nach einem der Ansprüche 1 bis 5 zur Herstellung eines Mittels zur Prävention und/oder Behandlung von zerebralem Infarkt, zerebraler Embolie, Myokardinfarkt, Angina Pectoris, Lungeninfarkt, Lungenembolie, Buerger'scher Krankheit, tiefer Venenthrombose, disseminiertem intravasalen Gerinnungssyndrom, Thrombusbildung nach Herzklappen- oder Gelenktransplantation, Thrombusbildung und Reokklusion nach Angioplastie, systemischem entzündlichen Reaktionssyndrom (SIRS), multiplem Organversagen (MODS), Thrombusbildung während extrakorporealer Zirkulation oder Blutgerinnung nach Blutabnahme.

26. Verbindung der folgenden allgemeinen Formel (4):

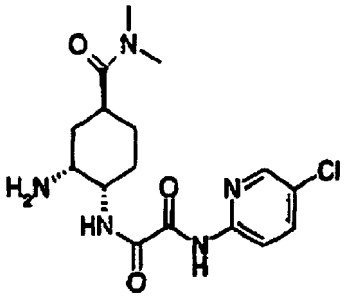
$HN(R^1)\text{-}Q^3\text{-}N(R^2)\text{-}T^1\text{-}Q^4$ (4)

wobei R^1, R^2 und T^1 die gleiche Bedeutung wie in Anspruch 1 haben, Q^3 die folgende Gruppe bedeutet:



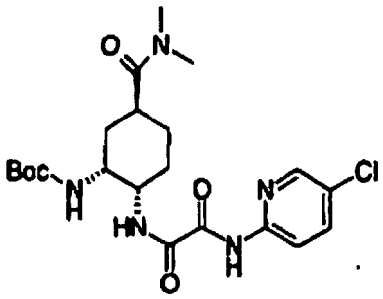
wobei Q^5, R^3 und R^4 die gleichen Bedeutungen wie in Anspruch 1 haben und Q^4 dieselbe Bedeutung wie in Anspruch 1 hat, ein Salz davon, ein Solvat davon oder ein N-Oxid davon.

27. Die Verbindung nach Anspruch 26, bei der es sich um N^1-{(1S,2R,4S)-2-amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(5-chloropyridin-2-yl)ethandiamidhydrochlorid handelt:



Hydrochlorid.

28. tert.-Butyl(1R,2S,5S)-2-({2-[5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl]-carbamat:



Revendications

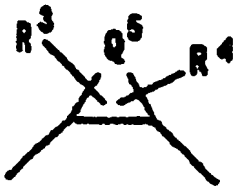
1. Composé représenté par la formule générale (1) :

$Q^1\text{-}Q^2\text{-}T^0\text{-}N(R^1)\text{-}Q^3\text{-}N(R^2)\text{-}T^1\text{-}Q^4$ (1)

dans laquelle

R^1 et R^2 indépendamment l'un de l'autre, représentent un atome d'hydrogène, un groupe hydroxyle, un groupe alkyle linéaire, ramifié ou cyclique ayant de 1 à 6 atomes de carbone ou un groupe alcoxy linéaire, ramifié ou cyclique ayant de 1 à 6 atomes de carbone ;
Q^1 représente un groupe hétérocyclique condensé bicyclique ou tricyclique, saturé ou insaturé, choisi parmi

les groupes 5-méthyl-4,5,6,7-tétrahydrothiazolo[5,4-c]pyridin-2-yle, 4,5,6,7-tétrahydrothiazolo[5,4-c]pyridin-2-yle, 5-cyclopropyl-4,5,6,7-tétrahydrothiazolo[5,4-c]pyridin-2-yle, 5-carboxyméthyl-4,5,6,7-tétrahydrothiazolo [5,4-c]-pyridin-2-yle, 5-butyl-4,5,6,7-tétrahydrothiazolo[5,4-c]-pyridin-2-yle, 5-(4-pyridyl)-4,5,6,7-tétrahydrothiazolo-[5,4-c]pyridin-2-yle, 5-méthyl-4,5,6,7-tétrahydrothiazolo-[4,5-c]pyridin-2-yle, 6-méthyl-4,5,6,7-tétrahydrothiéno-[2,3-c]pyridin-2-yle, 5-méthyl-4,5,6,7-tétrahydrooxazolo-[5,4-c]pyridin-2-yle, 5-méthyl-4,6-dihydro-5H-pyrrolo[3,4-d]thiazol-2-yle, 5,7-dihydro-6-méthylpyrrolo[3,4-d]-pyrimidin-2-yle, 5,6-diméthyl-4,5,6,7-tétrahydrothiazolo-[4,5-d]pyridazin-2-yle, 5,6-diméthyl-4,5,6,7-tétrahydro-oxazolo[4,5-d]pyridazin-2-yle, 5-diméthylamino-4,5,6,7-tétrahydrobenzo[d]thiazol-2-yle, et 6,7-dihydro-4H-pyrano-[4,3-d]thiazol-2-yle ;
Q^2 représente une liaison simple ;
Q^3 représente le groupe suivant :



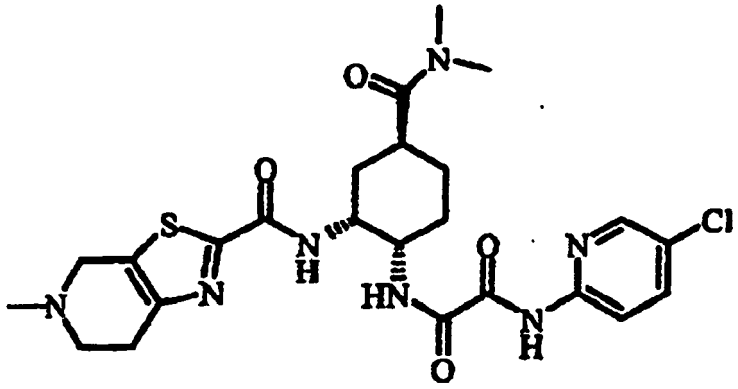
dans lequel Q^5 signifie un groupe alkylène ayant 4 atomes de carbone, R^3 est un atome d'hydrogène, et R^4 est un groupe N,N-dialkylcarbamoyle ayant deux groupes alkyle en C_1 à C_6 linéaires, ramifiés ou cycliques ;
Q_4 représente un radical phényle, 4-chlorophényle, 4-fluorophényle, 4-bromophényle, 4-éthynylphényle, 3-chlorophényle, 3-fluorophényle, 3-bromophényle, 3-éthynylphényle, 3-chloro-4-fluorophényle, 4-chloro-3-fluorophényle, 4-chloro-2-fluorophényle, 2-chloro-4-fluorophényle, 4-bromo-2-fluorophényle, 2-bromo-4-fluorophényle, 2,4-dichlorophényle, 2,4-difluorophényle, 2,4-dibromophényle, 4-chloro-3-méthylphényle, 4-fluoro-3-méthylphényle, 4-bromo-3-méthylphényle, 4-chloro-2-méthylphényle, 4-fluoro-2-méthylphényle, 4-bromo-2-méthylphényle, 3,4-dichlorophényle, 3,4-difluorophényle, 3,4-dibromophényle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 4-chloro-2-pyridyle, 4-fluoro-2-pyridyle, 4-bromo-2-pyridyle, 4-éthynyl-2-pyridyle, 4-chloro-3-pyridyle, 4-fluoro-3-pyridyle, 4-bromo-3-pyridyle, 4-éthynyl-3-pyridyle, 5-chloro-2-pyridyle, 5-fluoro-2-pyridyle, 5-bromo-2-pyridyle, 5-éthynyl-2-pyridyle, 4-chloro-5-fluoro-2-pyridyle, 5-chloro-4-fluoro-2-pyridyle, 5-chloro-3-pyridyle, 5-fluoro-3-pyridyle, 5-bromo-3-pyridyle, 5-éthynyl-3-pyridyle, 6-chloro-3-pyridazinyle, 6-fluoro-3-pyridazinyle, 6-bromo-3-pyridazinyle, 6-éthynyl-3-pyridazinyle, 4-chloro-2-thiényle, 4-fluoro-2-thiényle, 4-bromo-2-thiényle, 4-éthynyl-2-thiényle, 4-chloro-2-pyrrolyle, 4-fluoro-2-pyrrolyle, 4-bromo-2-pyrrolyle, 4-éthynyl-2-pyrrolyle, 4-chloro-2-furyle, 4-fluoro-2-furyle, 4-bromo-2-furyle, 4-éthynyl-2-furyle, 5-chloro-2-thiényle, 5-fluoro-2-thiényle, 5-bromo-2-thiényle, 5-éthynyl-2-thiényle, 5-chloro-2-thiazolyle, 5-fluoro-2-thiazolyle, 5-bromo-2-thiazolyle, 5-éthynyl-2-thiazolyle, 5-chloro-2-oxazolyle, 5-fluoro-2-oxazolyle, 5-bromo-2-oxazolyle ou 5-éthynyl-2-oxazolyle ;
T^0 représente un groupe carbonyle ou thiocarbonyle ; et
T^1 représente un groupe -C(=O)-C(=O)-N(R')-, un groupe -C(=S)-C(=O)-N(R')-, un groupe -C(=O)-C(=S)-N(R')- ou un groupe -C(=S)-C(=S)-N(R')-, où R' signifie un atome d'hydrogène, un groupe hydroxyle, un groupe alkyle linéaire, ramifié ou cyclique ayant de 1 à 6 atomes de carbone ou un groupe alcoxy linéaire, ramifié ou cyclique ayant de 1 à 6 atomes de carbone,
un sel de celui-ci, un solvate de celui-ci, ou un N-oxyde de celui-ci.

2. Composé, son sel, son solvate, ou son N-oxyde, selon la revendication 1, dans lequel le groupe Q^3 est

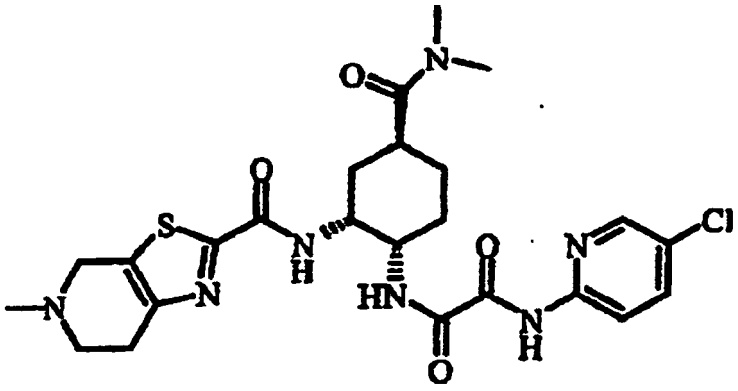
où Q^5 signifie un groupe alkylène ayant 4 atomes de carbone, R^3 est un atome d'hydrogène, et R^4 est un groupe N,N-diméthylcarbamoyle.

3. Composé, son sel, ou son hydrate, selon la revendication 1, qui est le N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(diméthylamino)carbonyl]-2-{[(5-méthyl-4,5,6,7-tétrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclo-

hexyl)éthanediamide de formule suivante, un sel de celui-ci, ou un hydrate de celui-ci :

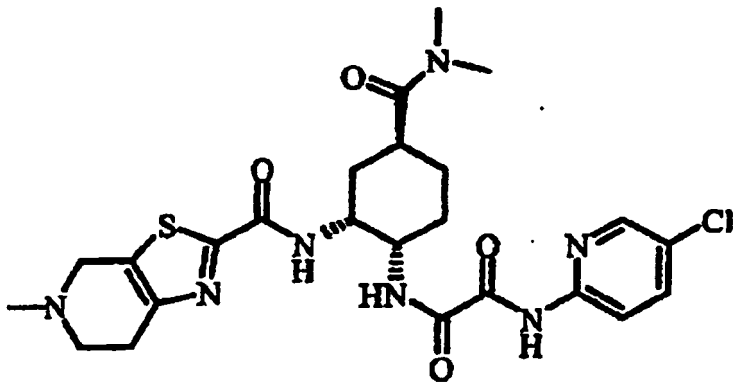


4. Composé, son sel, ou son hydrate, selon la revendication 1, qui est le p-toluènesulfonate de N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(diméthylamino)-carbonyl]-2-{[(5-méthyl-4,5,6,7-tétrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)éthanediamide :



p-toluènesulfonate.

5. p-toluènesulfonate de N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(diméthylamino)carbonyl]-2-{[(5-méthyl-4,5,6,7-tétrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)éthanediamide monohydraté :



p-toluènesulfonate monohydraté.

6. Médicament comprenant le composé, son sel, son solvate, ou son N-oxyde, selon l'une quelconque des revendications 1 à 5.

7. Inhibiteur du facteur X de coagulation du sang activé, comprenant le composé, son sel, son solvate, ou son N-oxyde, selon l'une quelconque des revendications 1 à 5.

8. Anticoagulant comprenant le composé, son sel, son solvate, ou son N-oxyde, selon l'une quelconque des revendications 1 à 5.

9. Agent pour prévenir et/ou traiter une thrombose ou une embolie, comprenant le composé, son sel, son solvate, ou son N-oxyde, selon l'une quelconque des revendications 1 à 5.

10. Agent pour prévenir et/ou traiter un infarctus cérébral, une embolie cérébrale, un infarctus du myocarde, une angine de poitrine, un infarctus pulmonaire, une embolie pulmonaire, la maladie de Buerger, une thrombose veineuse profonde, un syndrome de coagulation intravasculaire disséminée, une formation de thrombus après remplacement de valvule ou d'articulation, une formation de thrombus et une réocclusion après angioplastie, un syndrome de réponse inflammatoire systémique (SIRS), un syndrome de dysfonctionnement d'organes multiples (MODS), une formation de thrombus durant une circulation extracorporelle, ou une coagulation du sang après prise de sang, comprenant le composé, son sel, son solvate, ou son N-oxyde, selon l'une quelconque des revendications 1 à 5.

11. Composition médicale comprenant le composé, son sel, son solvate, ou son N-oxyde, selon l'une quelconque des revendications 1 à 5, et un véhicule pharmaceutiquement acceptable.

12. Composition selon la revendication 11, laquelle composition comprend en outre au moins un additif pharmaceutiquement acceptable choisi dans l'ensemble constitué par les charges, les agents de remplissage, les liants, les agents délitants, les auxiliaires/accélérateurs de dissolution, les agents de mise en suspension, les agents émulsionnants, les agents mouillants, les stabilisants, et les conservateurs.

13. Composition selon la revendication 11, laquelle composition est sous la forme d'un comprimé, d'un granule, d'une capsule, d'une poudre, d'une solution, d'une suspension, d'une émulsion, d'une huile, d'un sirop, d'un élixir, d'une pommade, d'un gel, d'une crème, d'une lotion, d'un spray, ou d'un emplâtre.

14. Composition selon la revendication 11, laquelle composition convient pour une administration par voie orale, topique, ou par injection.

15. Composition selon l'une quelconque des revendications 11 à 14, pour utilisation dans le traitement d'une thrombose ou d'une embolie, par administration, à un mammifère en ayant besoin, d'une quantité efficace d'un composé selon la revendication 1.

16. Composition selon la revendication 15, dans lequel ladite quantité efficace est située dans la plage allant de 1 mg à 1000 mg par jour dudit au moins un composé présent dans ladite composition.

17. Composition selon la revendication 15, dans lequel ladite quantité efficace est située dans la plage allant de 0,1 mg à 200 mg par kg de poids corporel dudit mammifère et par jour dudit au moins un composé présent dans ladite composition.

18. Composition selon la revendication 15, dans laquelle l'administration de ladite composition est effectuée une à quatre fois par jour.

19. Procédé pour préparer une composition, comprenant la combinaison d'au moins un composé selon les revendications 1 à 5 avec un véhicule pharmaceutiquement acceptable.

20. Procédé selon la revendication 19, lequel procédé comprend en outre la combinaison, avec ledit au moins un composé et ledit véhicule pharmaceutiquement acceptable, d'au moins un additif pharmaceutiquement acceptable choisi dans l'ensemble constitué par les charges, les agents de remplissage, les liants, les agents délitants, les auxiliaires/accélérateurs de dissolution, les agents de mise en suspension, les agents émulsionnants, les agents mouillants, les stabilisants, et les conservateurs.

21. Utilisation du composé, de son sel, de son solvate, ou de son N-oxyde, selon l'une quelconque des revendications 1 à 5, pour la préparation d'un médicament.

22. Utilisation du composé, de son sel, de son solvate, ou de son N-oxyde, selon l'une quelconque des revendications 1 à 5, pour la préparation d'un inhibiteur du facteur X de coagulation du sang activé.

23. Utilisation du composé, de son sel, de son solvate, ou de son N-oxyde, selon l'une quelconque des revendications 1 à 5, pour la préparation d'un anticoagulant.

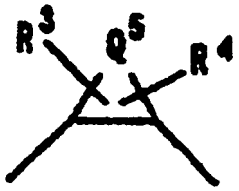
24. Utilisation du composé, de son sel, de son solvate, ou de son N-oxyde, selon l'une quelconque des revendications 1 à 5, pour la préparation d'un agent pour prévenir et/ou traiter une thrombose ou une embolie.

25. Utilisation du composé, de son sel, de son solvate, ou de son N-oxyde, selon l'une quelconque des revendications 1 à 5, pour la préparation d'un agent pour prévenir et/ou traiter un infarctus cérébral, une embolie cérébrale, un infarctus du myocarde, une angine de poitrine, un infarctus pulmonaire, une embolie pulmonaire, la maladie de Buerger, une thrombose veineuse profonde, un syndrome de coagulation intravasculaire disséminée, une formation de thrombus après remplacement de valvule ou d'articulation, une formation de thrombus et une réocclusion après angioplastie, un syndrome de réponse inflammatoire systémique (SIRS), un syndrome de dysfonctionnement d'organes multiples (MODS), une formation de thrombus durant une circulation extracorporelle, ou une coagulation du sang après prise de sang.

26. Composé représenté par la formule générale (4) :

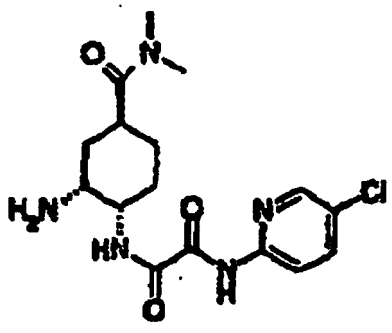
$$HN(R^1)\text{-}Q^3\text{-}N(R^2)\text{-}T^1\text{-}Q^4 \quad (4)$$

dans laquelle R^1, R^2 et T^1 ont les mêmes significations que celles définies dans la revendication 1, Q^3 représente le groupe suivant :



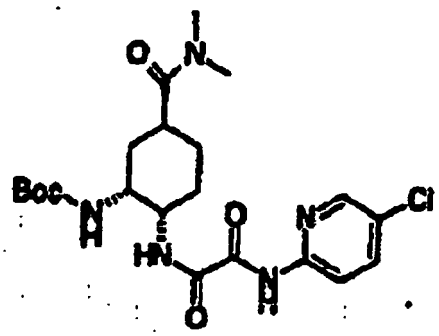
dans lequel Q^5, R^3 et R^4 ont les mêmes significations que celles définies dans la revendication 1, et Q^4 a la même signification que dans la revendication 1,
un sel de celui-ci, un solvate de celui-ci, ou un N-oxyde de celui-ci.

27. Composé selon la revendication 26, qui est le chlorhydrate de N^1-{(1S,2R,4S)-2-amino-4-[(diméthylamino)-carbonyl] cyclohexyl}-N^2-(5-chloropyridin-2-yl)éthanediamide :



chlorhydrate.

28. (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacétyl}amino)-5-[(diméthylamino)carbonyl]cyclohexylcarbamate de tert-butyle :



REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 0009480 A **[0002] [0040]**
- WO 9610022 A **[0040]**
- WO 9830574 A **[0046] [0049] [0245]**
- JP 7138264 A **[0078]**
- JP 7149723 A **[0171]**
- JP 4321691 A **[0178]**
- WO 9532965 A **[0210]**
- US 5726126 A **[0214]**
- WO 9421599 A **[0962] [0995]**

Non-patent literature cited in the description

- *Thrombosis Research,* 1992, vol. 68, 507-512 **[0003] [0006]**
- *Thrombosis Research,* 1979, vol. 15, 617-629 **[0004]**
- *Journal of Clinical Investigation,* 1983, vol. 71, 1383-1389 **[0006]**
- *Mebio,* vol. 14, 92-97 **[0006]**
- *Science,* 1990, vol. 248, 593-596 **[0006]**
- *Journal of Biological Chemistry,* 1988, vol. 263, 10162-10167 **[0006]**
- *J. Org. Chem.,* 1998, vol. 63, 6094 **[0049]**
- *Tetrahedron: Asymmetry,* 1996, vol. 7, 843 **[0052]**
- *J. Org. Chem.,* 1985, vol. 50, 4154 **[0052]**
- *J. Med. Chem.,* 1998, vol. 41, 38 **[0052]**
- *Tetrahedron Lett.,* 1996, vol. 37, 7457 **[0073]**
- *Tetrahedron: Symmetry,* 1997, vol. 8, 1861 **[0078]**
- *J. Org. Chem.,* 1996, vol. 61, 581 **[0084]**
- *J. Org. Chem.,* 1992, vol. 57, 6279 **[0084]**
- *J. Org. Chem.,* 1998, vol. 63, 7263 **[0084]**
- *Can. J. Chem.,* 1993, vol. 71, 1047 **[0086]**
- *Tetrahedron Lett.,* 2000, vol. 41, 1141 **[0087]**
- *Heterocycles,* 2000, vol. 53, 173 **[0087]**
- *J. Org. Chem.,* 1996, vol. 61, 8687-8691 **[0098]**
- **PANEK.** *J. Org. Chem.,* 1996, vol. 61, 6496 **[0149]**
- *Tetrahedron,* 1983, vol. 39, 3767 **[0174]**
- *Helv. Cim. Acta,* 1994, vol. 77, 1256 **[0184]**
- *Yakugaku Zasshi,* 1966, vol. 86, 300 **[0194]**
- *J. Org. Chem.,* 1989, vol. 54, 1815 **[0200]**
- *J. Med. Chem.,* 1998, vol. 41, 4723-4732 **[0241]**
- *J. Am. Chem. Soc.,* 1942, vol. 64, 2696-2700 **[0243]**
- *J. Heterocycl. Chem.,* 1989, vol. 26, 451 **[0293]**
- *J. Org. Chem.,* 1996, vol. 61, 8687 **[0299] [0311]**
- *J. Am. Chem. Soc.,* 1978, vol. 100, 5199 **[0340]**
- *J. Org. Chem.,* 1981, vol. 53, 3841-3843 **[0420]**
- *J. Am. Chem. Soc.,* 1978, vol. 100, 5199-5203 **[0608]**
- **M. AL. HARIRI ; O. GALLEY ; F. PAUTET ; H. FILLION.** *Eur. J. Org. Chem.,* 1998, 593-594 **[0700]**
- *Eur. J. Chem-Chim. Ther.,* 1984, vol. 19, 205-214 **[0708]**
- *Bull. Chem. Soc. Jpn.,* 1989, vol. 62, 2668 **[0720]**
- *Acta. Chem. Scand.,* 1999, vol. 53, 258 **[0730]**
- *J. Org. Chem.,* 1978, vol. 43, 1256 **[0730]**
- *Helv. Chim. Acta,* 1998, vol. 81, 303 **[0743]**
- *J. Chem. Soc. Perkin Trans. 1,* 1992, 973 **[0753]**
- *Monatsh. Chem.,* 1989, vol. 120, 53 **[0802]**
- **GILCHRIST, T. L. ; PEEK, M. E. ; REES, C. W.** *J. Chem. Soc. Chem. Commun.,* 1975, 913 **[0851]**
- **SATO, NOBUHIRO et al.** *J. Heterocycl. Chem.,* 1982, vol. 19 (3), 673-4 **[0917]**
- *Helv. Cim. Acta.,* 1994, vol. 77, 1256 **[0978]**