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(54) **5-amino-2,4,7-trioxo-3,4,7,8-tetrahydro-2H-pyrido[2,3-d]pyrimidine derivatives and related compounds for the treatment of cancer**

5-amino-2,4,7-trioxo-3,4,7,8-tetrahydro-2H-pyrido[2,3-d]pyrimidin Derivate und verwandte Verbindungen zur Behandlung von Krebs

Dérivés 5-amino-2,4,7-trioxo-3,4,7,8-tetrahydro-2H-pyrido[2,3-d]pyrimidine et composés similaires pour le traitement de cancer

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WO-A-02/03997 **WO-A-02/094824**
WO-A-03/062236
- **DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1996, KHATTAB, AHMED F. A. ET AL: "Ring closure reaction of 5-hydroxypyrido[2,3-d]pyrimidine-2,4,7- triones to benzo[b]pyrimido[4,5-h]1,6-naphthyridine-1 ,3,6-triones", XP002343581, retrieved from STN Database accession no. 1996: 147520 & JOURNAL FÜR PRAKTISCHE CHEMIE - CHEMIKER-ZEITUNG, vol. 338, no. 2, 1996, pages 151-156, ISSN: 0941-1216**

Description

[0001] The present invention relates to a novel pyrimidine compound or a pharmaceutically acceptable salt thereof useful as an agent for the prophylaxis or treatment of diseases caused by undesirable cell proliferation, particularly, an antitumor agent. Moreover, the present invention relates to novel use of a certain kind of pyrimidine compound or a pharmaceutically acceptable salt thereof as an agent for the prophylaxis or treatment of a disease. caused by undesirable cell proliferation, particularly, as an antitumor agent. More particularly, the present invention relates to a pharmaceutical agent comprising a pyrimidine compound showing a p15 protein inducing action and/or a p27 protein inducing action and/or an MEK inhibitory action, or a pharmaceutically acceptable salt thereof.

[0002] A "cell cycle" means a cycle wherein the period for a cell to divide and once again divide is one cycle, and this cycle, is also referred to as a "cell division cycle".

[0003] A cell cycle includes four phases in a determined order. They are DNA duplication preparation phase.(G1 phase), DNA duplication phase (S phase), division preparation phase (G2 phase) and division phase (M phase), and are regulated by many factors. Among them, the kinase activity of a cyclin/cyclin dependent kinase (CDK) complex is essential for the regulation of the cell cycle.

[0004] As a protein to inhibit the kinase activity, a CDK inhibitory protein is known. The CDK inhibitory proteins of mammalian cells are p21 family and p16 family, both of which are considered to negatively regulate the progress of cell cycle and responsible for cell differentiation, apoptosis and repair of DNA damage due to irradiation of X ray and the like. At present, p21, p27 and p57 have been reported as a p21 family, and p16, p15, p18 and p19 have been reported as a p16 family.

[0005] When these CDK inhibitory proteins are highly expressed in the cell, the cell proliferation is arrested at G1 phase.

[0006] The p21 family shows an inhibitory activity on a relatively wide range and plural cyclin/CDK complexes. For example, cyclin E/CDK 2 which is an important cyclin /CDK complex from G1 phase to G1/S transition phase, cyclin B/Cdc2 which is important for M phase and the like can be mentioned. The p16 family is a specific inhibitory factor against cyclin D/CDK 4 and cyclin D/CDK 6, which are one of the cyclin/CDKs in the G1 phase, and is considered to dissociate the cyclin/CDK complex by binding with CDK 4 and CDK 6, respectively.

[0007] From the examination of clinical materials of cancer of esophagus, pancreatic cancer, non-small cell lung cancer, skin cancer and the like, highly frequent incidence of genetic abnormality of P16 has been reported, and high cancer incidence in p16 knock out mice has been demonstrated, and therefore, clinical application of p16 inducer has been tried.

[0008] Under such situation, p15 protein (aka:INK4B, also simply referred to as p15) has been found as a p16 family. In 1994, induction of p15 expression by TGF- β stimulation was confirmed in human keratinocyte cell (HaCaT), and p15 was considered to be one of the factors negatively regulating the cell cycle. It is known that induction of G1 phase cell cycle arrest in HaCaT by TGF- β leads to the suppression of cell proliferation (Letters to Nature, September 15, 1994, vol. 371, pp. 257-261).

[0009] While the histone deacetylase (HDAC) inhibitor is known to arrest cell cycles at G1 phase or G2 phase in human cancer cell, it has been found recently that trichostatin A, which is an HDAC inhibitor, induces p15 gene in human colon cancer cell (HCT116p21(-/-)), and the induction of p15 by trichostatin A is involved in the inhibition of the cell proliferation of the cancer cells (FEBS Letters, 2003, vol. 554, pp. 347-350).

[0010] In this way, a compound that induces p15 and/or p27 is expected to inhibit the cell proliferation of cancer cells and the like.

[0011] In the meantime, Mitogen-activated protein (MAP) Kinase/extracellular signal-regulated kinase (ERK) kinase (hereinafter to be referred to as MEK) is known to be involved in the regulation of cell proliferation as a kinase that mediates Raf-MEK-ERK signal transduction pathway, and the Raf family (B-Raf, C-Raf etc.) activates the MEK family (MEK-1, MEK-2 etc.) and the MEK family activates the ERK family (ERK-1 and ERK-2).

[0012] Activation of Raf-MEK-ERK signal transduction pathway in cancer, particularly colorectal cancer, pancreatic cancer, lung cancer, breast cancer and the like, has been frequently observed.

[0013] In addition, since the signals produced by signal molecules such as growth factor, cytokine and the like converge to the activation of MEK-ERK, inhibition of these functions is considered to more effectively suppress Raf-MEK-ERK signal transduction than the suppression of the function of RTK, Ras, Raf and the like in the upstream.

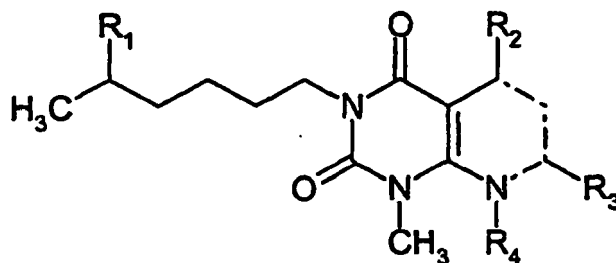
[0014] Moreover, it is also known in recent years that a compounds having an MEK inhibitory activity extremely effectively induces inhibition of ERK1/2 activity and suppression of cell proliferation (The Journal of Biological Chemistry, vol.276, No.4, pp.2686-2692, 2001), and the compound is expected to show effects on the disease caused by undesirable cell proliferation, such as tumor and the like. In addition, an MEK inhibitor is expected to inhibit infiltration or metastaticity of cells via promotion of expression of Matrix metalloproteinase (MMP) and CD44, and angiogenesis via promotion of expression of vascular endothelial growth factor (VEGF).

[0015] WO 02/03997 A1 describes a purine nucleoside analog including a pyrido[2,3-d]pyrimidine or a pyrimido[4,5-d]pyrimidine and further has a sugar moiety that is optionally modified at the C2', C3', C4' and/or C5' position. Particularly

contemplated compounds also include prodrug forms of the purine nucleoside analogs, and both purine nucleoside analogs and the corresponding prodrugs are employed in the reduction of growth of neoplastic cells.

[0016] WO 03/062236 A1 provides substituted 2-aminopyridines useful in treating cell proliferative disorders. The compounds are described to be potent inhibitors of cyclin-dependent kinases 4.

[0017] WO 02/094824 A1 describes a therapeutic compound, including resolved enantiomers, diastereomers, tautomers, salts and solvates thereof, having the following formula:

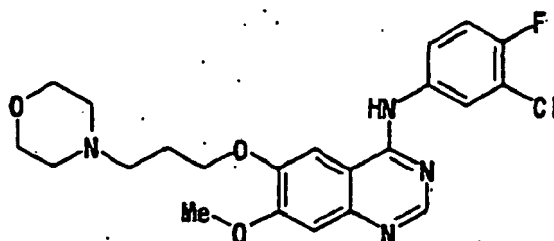


[0018] KHATTAB ET AL discloses ring closure reaction of 5-hydroxypyrido [2,3-d]pyrimidine-2,4,7-triones to benzo[b]pyrimido[4,5-h]1,6-naphthyridine-1,3,6-triones (Journal für Praktische Chemie-Chemiker Zeitung, 1996, No. 2, vol. 338, pp. 151-156).

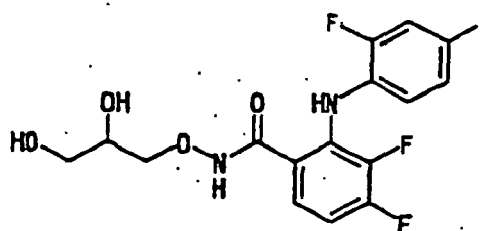
[0019] Furthermore, application to chronic pain (JP 2003-504401: WO 01/005393), application to diseases or symptoms mediated by neutrophile (JP2002-332247: CA-2385412), application to graft rejection (JP 2002-532414: WO 00/35435), application to arthritis (JP 200-2-532415: WO 00/35436), application to asthma (JP 2002-534380: WO 00/40235), application to viral diseases (JP 2002-534381: WO 00/40237), application to diseases caused by deformation or injury of cartilage (W02002/087620: US 2004/138285), application to Peutz-Jeghers syndrome (WO02/006520) are expected.

[0020] However, such pharmaceutical agent has not been marked heretofore.

[0021] As an already commercially available antitumor agent, the following compound (Gefitinib) and the like are known (Iressa tablet 250 package insert).



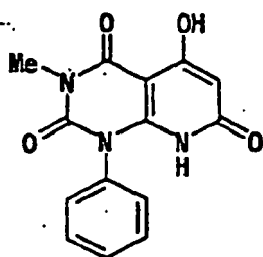
[0022] JP-A-2004-504294 (patent family: WO2002/006213) describes the following compound and the like as compounds having an antitumor activity. In addition, the MEK inhibitory activity of such compounds is described (JP-A-2004-504294, pp. 123-124, Example 39, Example 241).



[0023] Known compounds relatively similar to the pharmaceutical agent of the present invention are described below.

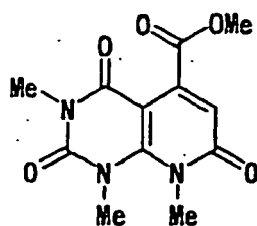
[0024] In the literatures issued in 1991, the antitumor activity of pyrido[2,3-d]pyrimidine derivative has been studied and it is described, for example, that some of the following compounds and the like have an inhibitory activity in sarcoma, leukemia cells (Khimia geterotsiklicheskikh soedinenii, 1991, No. 5, pp. 674-680 (English translation p. 542, lines 4-7;

p. 538, compound IIIa)).



[0025] In the literatures issued in 1973, novel synthetic methods of the following compound and the like are disclosed and the antitumor activity of pyrido[2,3-d]pyrimidine derivative is described (Chem. Pharm. Bull., 1973, No. 21, vol. 9, pp. 2014-2018 (p. 2015, chart 2, compound VIII)).

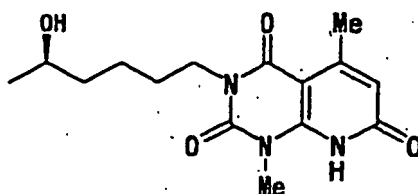
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[0026] In these literatures, however, the compound of the present invention is not disclosed, nor is there found a description suggestive thereof.

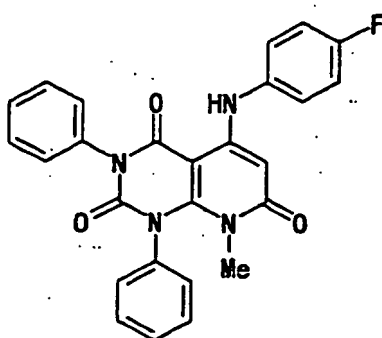
[0027] Furthermore, WO2002/094824 discloses the following compound and the like (W02002/094824, p. 55, Example 9) as a therapeutic agent having a cytokine regulating action for immune, inflammatory or allergic disease.

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[0028] In the literatures issued in 1996, synthetic methods of the following compound and the like are disclosed (Journal fur Praktische Chemie, 1996, vol. 338, pp. 151-156 (p. 154, Table 1, compound 8f)).

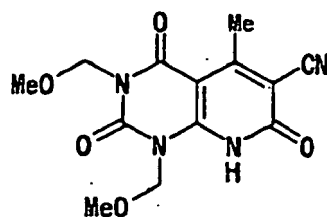
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[0029] In the literatures issued in 1986, synthetic methods of the following compound and the like as a synthetic intermediate for aminopterin analog having an antitumor activity are disclosed (Journal of Medicinal Chemistry, 1986,

vol. 29, No. 5, pp. 709-715 (p. 709 abstract; p. 712, Table 1, compound 9b)).

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[0030] However, this literature does not contain a description relating to the use of these compounds as antitumor agents, the compound of the present invention is not disclosed and a description suggestive thereof is not found.

15 [0031] An object of the present invention is to provide a pharmaceutical agent containing a pyrimidine compound showing undesirable cell proliferation inhibitory action, particularly an antitumor action or a pharmaceutically acceptable salt thereof.

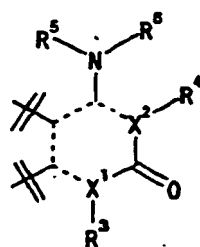
[0032] The present inventors have conducted intensive studies in an attempt to find a compound having such action and completed the present invention.

20 [0033] More particularly, the present invention is as defined in the appended claims.

[0034] The definitions of each substituent and each moiety used in the present specification are as follows.

[0035] X¹ and X² are the same or different, and each is a carbon atom or a nitrogen atom, a

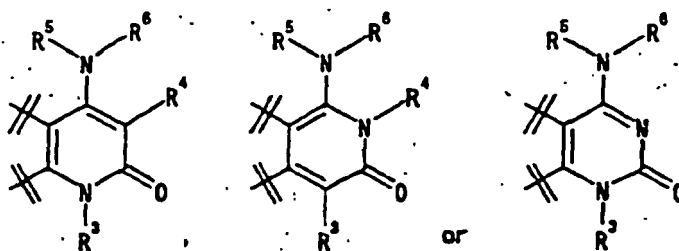
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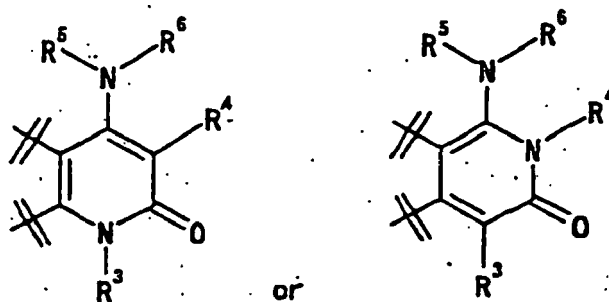


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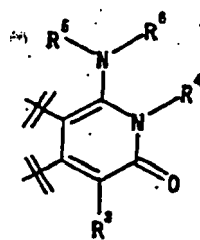
preferably,

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, and particularly preferably



[0036] The "halogen atom" is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, which is preferably a fluorine atom, a chlorine atom or a bromine atom for 1) of group A and 1) of group C, more preferably a fluorine atom for 1) of group A, more preferably a fluorine atom or a bromine atom for 1) of group C, and preferably a fluorine atom or an iodine atom for 1) of group B.

[0037] The "C₁₋₆ alkyl group" is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, and specifically, a methyl group, ethyl group, propyl group, isopropyl group, 2,2-dimethylpropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, hexyl group and the like can be mentioned.

[0038] As R¹, R^{1'}, R², R^{2'} and R⁶, a methyl group, ethyl group, propyl group, isopropyl group, 2,2-dimethylpropyl group, butyl group and isobutyl group are preferable, methyl group and ethyl group are more preferable, and methyl group is particularly preferable. As R³, R⁴ and R⁵, a methyl group, ethyl group, propyl group and isobutyl group are preferable, and a methyl group is more preferable.

[0039] The "C₁₋₄ alkyl group" is a straight chain or branched chain alkyl group having 1 to 4 carbon atoms, and specifically, a methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group and the like can be mentioned.

[0040] As 4) of group A and 3) of group C, a methyl group and ethyl group are preferable and methyl group is more preferable. As R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} and R^{A9}, a methyl group, ethyl group R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} and R^{A9}, a methyl group, ethyl group and butyl group are preferable and methyl group is more preferable. As R^{B1} to R^{B31}, a methyl group, ethyl group, propyl group, isopropyl group and butyl group are preferable and methyl group, ethyl group and propyl group are more preferable. As R^{C1}, R^{C2}, R^{C3}, R^{C4} and R^{C5}, a methyl group and ethyl group are preferable and methyl group is more preferable.

[0041] The "C₁₋₈ alkyl group" is a straight chain or branched chain alkyl group having 1 to 8 carbon atoms, and specifically, a methyl group, ethyl group, propyl group, isopropyl group, 1-ethyl-1-propyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, 3-methylbutyl group, 1-propyl-1-butyl group, pentyl group, isopentyl group, hexyl group, heptyl group, octyl group and the like can be mentioned.

[0042] As 2) of group B, a methyl group, ethyl group, propyl group, isopentyl group, 1-ethyl-1-propyl group, 3-methylbutyl group and 1-propyl-1-butyl group are preferable and methyl group and ethyl group are more preferable.

[0043] The "C₂₋₆ alkenyl group" is a straight chain or branched chain alkenyl group having 2 to 6 carbon atoms, and specifically, a vinyl group, 1-propenyl group, 2-propenyl group, isopropenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 1-methyl-1-propenyl group, 1-methyl-2-propenyl group, 2-methyl-2-propenyl group, 1-ethylvinyl group, 1-pentenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 1,2-dimethyl-1-propenyl group, 1,2-dimethyl-2-propenyl group, 1-ethyl-1-propenyl group, 1-ethyl-2-propenyl group, 1-methyl-1-butenyl group, 1-methyl-2-butenyl group, 2-methyl-1-butenyl group, 1-isopropylvinyl group, 2,4-pentadienyl group, 1-hexenyl group, 2-hexenyl group, 3-hexenyl group, 4-hexenyl group, 5-hexenyl group, 2,4-hexadienyl group, 1-methyl-1-pentenyl group and the like can be mentioned.

[0044] As R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁵ and R⁶, vinyl group, 1-propenyl group and 2-propenyl group are preferable and 2-propenyl group is more preferable.

[0045] The "C₂₋₄ alkenyl group" is a straight chain or branched chain alkenyl group having 2 to 4 carbon atoms, and specifically, vinyl group, 1-propenyl group, 2-propenyl group, isopropenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 1-methyl-1-propenyl group, 1-methyl-2-propenyl group, 2-ethyl-2-propenyl group, 1-ethylvinyl group and the like can be mentioned.

[0046] As 5) of group B, vinyl group and 1-propenyl group are preferable, and vinyl group is more preferable.

[0047] The "C₂₋₄ alkynyl group" is a straight chain or branched chain alkynyl group having 2 to 4 carbon atoms, and specifically, ethynyl group, 1-propynyl group, 2-propynyl group, isopropynyl group, 1-butylnyl group, 2-butylnyl group, 3-butylnyl group, 1-methyl-1-propynyl group, 1-methyl-2-propynyl group, 2-methyl-2-propynyl group, 1-ethylethylnyl group and the like can be mentioned.

[0048] As 6) of group B, an ethynyl group, 1-propynyl group and 1-butylnyl group are preferable, and ethynyl group is more preferable.

[0049] The "C₁₋₄ alkylene group" optionally formed by R² in junction with R³ and the "C₁₋₄ alkylene group" optionally formed by R⁴ in junction with R⁵ is a straight chain or branched chain alkylene group having 1 to 4 carbon atoms, and specifically, a methylene group, ethylene group, trimethylene group, 2-methyltrimethylene group, tetramethylene group and the like can be mentioned.

[0050] The "C₁₋₄ alkylene group" optionally formed by R² in junction with R³ is preferably a methylene group, ethylene group or trimethylene group, more preferably a trimethylene group.

[0051] The "C₁₋₄alkylene group" optionally formed by R⁴ in junction with R⁵ is preferably a methylene group, ethylene group or trimethylene group, more preferably an ethylene group.

[0052] As m, preferred is 0 or an integer of 1 or 2, more preferably 0.

[0053] The "C₃₋₁₂ carbon ring group" is a saturated or unsaturated cyclic hydrocarbon group having 3 to 12 carbon atoms, which means a phenyl group, naphthyl group, C₃₋₈cycloalkyl group, or a fused ring group of C₃₋₈ cycloalkyl and benzene.

[0054] The "C₃₋₈ cycloalkyl group" is a saturated cyclic hydrocarbon group having 3 to 8 carbon atoms, and specifically, a cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, norbornanyl group and the like can be mentioned, and preferably cyclopropyl group, cyclobutyl group, cyclopentyl group or cyclohexyl group.

[0055] As the "fused ring group of C₃₋₈cycloalkyl group and benzene", an indanyl group, 1,2,3,4-tetrahydronaphthyl group (1,2,3,4-tetrahydro-2-naphthyl group, 5,6,7,8-tetrahydro-2-naphthyl group etc.) and the like can be specifically mentioned, which is preferably indanyl group, 1,2,3,4-tetrahydronaphthyl group and the like, and more preferably indanyl group.

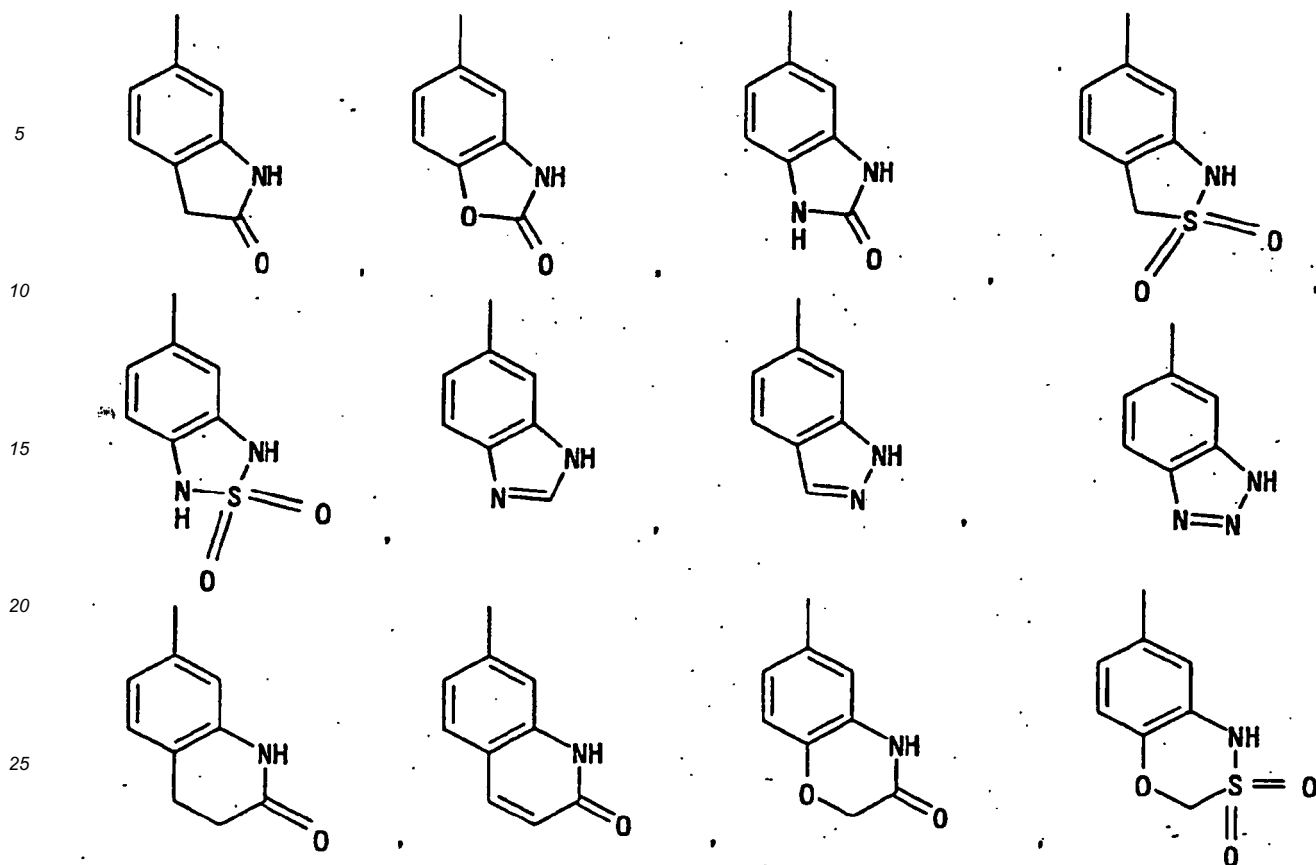
[0056] As R¹, R², R³, R⁴, R⁵ and R⁶, a phenyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group are preferable, and phenyl group and cyclopropyl group are more preferable. As R¹, a cyclopropyl group is particularly preferable, and as R² and R⁶, a phenyl group is particularly preferable. As 11) of group A, R^{A7}, 22) of group B, R^{B3}, R^{B6} and R^{B16}, a phenyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group are preferable, and phenyl group and cyclopropyl group are more preferable.

[0057] The "heterocyclic group" is a saturated monocyclic ring or an unsaturated monocyclic ring having 5 or 6 ring-constituting atoms, which contains, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, as a ring-constituting atom, a fused ring of the monocycle and a benzene ring or a spiro ring of these monocycles or fused rings and the above-mentioned C₃₋₁₂ carbon ring, each of which may have 1 to 4, preferably 1 or 2, oxo groups.

[0058] as the "heterocyclic group", which is a monocycle of a saturated ring, a pyrrolidinyl group, tetrahydrofuryl group, tetrahydrothienyl group, imidazolidinyl group, 2-oxoimidazolidinyl group, 2,4-dioxoimidazolidinyl group, pyrazolidinyl group, 1,3-dioxolanyl group, 1,3-oxathiolanyl group, oxazolidinyl group, 2-oxooxazolidinyl group, thiazolidinyl group, piperidinyl group, piperazinyl group, 2-oxopiperazinyl group, tetrahydropyranyl group, tetrahydrothiopyranyl group, dioxanyl group, morpholinyl group, thiomorpholinyl group, 2-oxopyrrolidinyl group, 2-oxopiperidinyl group, 4-oxopiperidinyl group, 2,6-dioxopiperidinyl group, thiadiazolidinyl group (e.g., 1,1-dioxo-1,2,5-thiadiazolidin-2-yl group etc.) and the like can be mentioned. Preferably, pyrrolidinyl group, piperidinyl group, piperazinyl group and morpholinyl group can be mentioned.

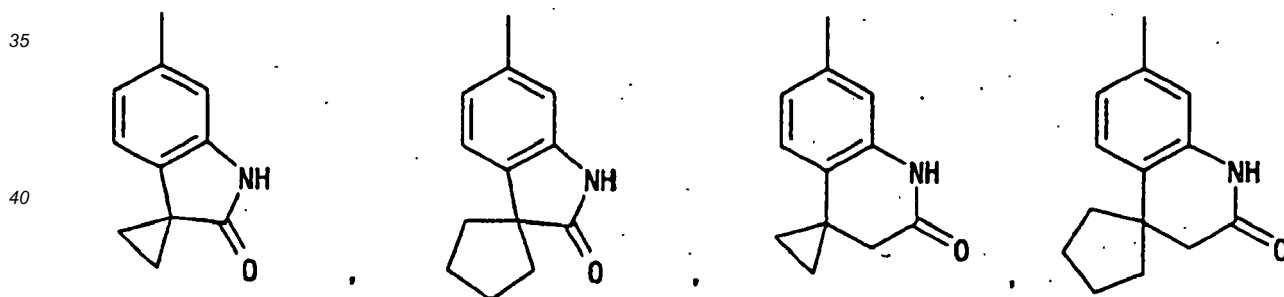
[0059] As the "heterocyclic group", which is a monocycle of unsaturated ring, a pyrrolyl group (e.g., 2-pyrrolyl group etc.), furyl group, thienyl group, imidazolyl group (e.g., 4-imidazolyl group etc.), 1,2-dihydro-2-oxoimidazolyl group, pyrazolyl group (e.g., 5-pyrazolyl group etc.), diazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, 1,2,4-triazolyl group, 1,2,3-triazolyl group, tetrazolyl group, 1,3,4-oxadiazolyl group, 1,2,4-oxadiazolyl group, 1,3,4-thiadiazolyl group, 1,2,4-thiadiazolyl group, furazanyl group, pyridyl group (e.g., 3-pyridyl group etc.), pyrimidinyl group, 3,4-dihydro-4-oxopyrimidinyl group, pyridazinyl group, pyrazinyl group, 1,3,5-triazinyl group, imidazoliny group (e.g., 2-imidazoliny group etc.) pyrazolinyl group, oxazoliny group (2-oxazoliny group, 3-oxazoliny group, 4-oxazoliny group), isoxazoliny group, thiophenyl group, thiazoliny group, isothiazoliny group, pyranyl group, 2-oxopyranyl group, 2-oxo-2,5-dihydrofuranly group, 1,1-dioxo-1H-isothiazolyl group and the like can be mentioned. Preferably, pyrrolyl group, thienyl group, imidazolyl group, pyrazolyl group, oxazolyl group, isooxazolyl group, thiophenyl group, thiazolyl group, isothiazolyl group and pyridyl group can be mentioned.

[0060] As the "heterocyclic group" which is a fused ring of monocycle and a benzene ring, indolyl groups (e.g., 4-indolyl group, 5-indolyl group, 6-indolyl group, 7-indolyl group etc.), an isoindolyl group, 1,3-dihydro-1,3-dioxoisoindolyl group and benzofuranly groups (e.g., 4-benzofuranly group, 7-benzofuranly group etc.), indazolyl group, isobenzofuranly group and benzothiophenyl groups (e.g., 4-benzothiophenyl group, 5-benzothiophenyl group, 7-benzothiophenyl group etc.), benzoxazolyl groups (e.g., 4-benzoxazolyl group, 7-benzoxazolyl group etc.), benzimidazolyl groups (e.g., 4-benzimidazolyl group, 5-benzimidazolyl group, 7-benzimidazolyl group etc.), benzothiazolyl groups (e.g., 4-benzothiazolyl group, 7-benzothiazolyl group etc.), quinolyl group, isoquinolyl group, 1,2-dihydro-2-oxoquinolyl group, quinazoliny group, quinoxaliny group, cinnoliny group, phthalazinyl group, 2,3-dihydroindolyl group, isoindoliny group, 1,2,3,4-tetrahydroquinolyl group, 2-5 oxo-1,2,3,4-tetrahydroquinolyl group, benzo[1,3]dioxolyl group, chromanyl group, isochromanyl group,



30 and the like can be mentioned.

[0061] As the spiro ring of the above-mentioned monocycle or fused ring and the above-mentioned C₃₋₁₂ carbon ring, for example, groups represented by the following formulas can be mentioned.



45 **[0062]** Preferably, it is a fused ring group of monocyclic 5- or 6-membered heterocycle and a benzene ring, which is specifically, indolyl group; indazolyl group, benzothienyl group, benzimidazolyl group, 2,3-dihydroindolyl group, 1,2,3,4-tetrahydroquinolyl group, benzo[1,3]dioxolyl group and the like.

50 **[0063]** As R¹, R², R³, R⁴, R⁵ and R⁶, a pyrrolidinyl group, piperidinyl group, piperazinyl group, morpholinyl group, pyridinyl group, thiophenyl group, thiazolyl group, indolyl group, indazolyl group, benzothienyl group, benzimidazolyl group, 2,3-dihydroindolyl group, 1,2,3,4-tetrahydroquinolyl group and benzo[1,3]dioxolyl group are preferable and piperidinyl group, pyridinyl group, thiophenyl group, thiazolyl group, indolyl group, indazolyl group, benzothienyl group, benzimidazolyl group, 2,3-dihydroindolyl group, 1,2,3,4-tetrahydroquinolyl group, benzo[1,3]dioxolyl group are more preferable. As 12) of group A, R^{A7} and 23) of group B, R¹³, R¹⁶, R^{B16} and R^{B17}, pyrrolidinyl group, piperidinyl group, piperazinyl group, morpholinyl group, pyridyl group and oxazolynyl group are preferable, and pyrrolidinyl group, piperidinyl group, piperazinyl group and morpholinyl group are more preferable.

55 **[0064]** The "C₁₋₆ alkyl group" and "C₂₋₆ alkenyl group" for R¹, R² and R⁶, and R³, R⁴ and R⁵ are optionally substituted by 1 to 3 substituents selected from group A. That is, the above-defined "C₁₋₆ alkyl group" and "C₂₋₆ alkenyl group," may be substituted by 1 to 3 substituents selected from group A, and include unsubstituted "C₂₋₆ alkyl" group" and

unsubstituted "C₂₋₆ alkenyl group".

[0065] Each of the above-defined "C₁₋₉ alkyl group" for the below-defined 4) of group B, and the above-defined "C₁₋₄ alkyl group" for R^{B1} to R^{B31} is optionally substituted by the same or different 1 to 3 substituents selected from group A.

[0066] Each of the above-defined "C₂₋₄ alkenyl group" for the below-defined 5) of group B and the above-defined "C₂₋₄ alkynyl group" for 6) is optionally substituted by the same or different 1 to 3 substituents selected from group A.

[0067] The "group A" is a group consisting of 1) the above-defined "halogen atom", 2) nitro group, 3) cyano group, 4) the above-defined "C₁₋₄ alkyl group", 5) "-OR^{A1}", 6) "-SR^{A2}", 7) "-NR^{A3}RA⁴", 8) "-COOR^{A5}", 9) "-NR^{A6}COR^{A7}", 10) "-NR^{A8}COOR^{A9}", 11) the above-defined "C₃₋₁₂ carbon ring group" and 12) the above-defined "heterocyclic group", wherein RA¹, RA², RA³, RA⁴, RA⁵, RA⁶, RA⁸ and RA⁹ are the same or different and each is a hydrogen atom, or, the above-defined "C₁₋₄ alkyl group", RA⁷ is the above-defined "C₁₋₄ alkyl group", the above-defined "C₃₋₁₂ carbon ring group" or the above-defined "heterocyclic group".

[0068] As the "-OR^{A1}", a hydroxyl group, methoxy group, ethoxy group, propoxy group, isopropoxy group, tert-butoxy group and the like can be specifically mentioned.

[0069] As the "-SR^{A2}", a mercapto group, methylsulfanyl group, ethylsulfanyl group, propylsulfanyl group, isopropylsulfanyl group, tert-butylsulfanyl group, and the like can be specifically mentioned.

[0070] As the "-NR^{A3}RA⁴", an amino group, methylamino group, ethylamino group, propylamino group, isopropylamino group, tert-butylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-isopropyl-N-methylamino group and the like can be specifically mentioned.

[0071] As the "-COOR^{A5}", carboxyl group, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, tert-butoxycarbonyl group and the like can be specifically mentioned.

[0072] As the "-NR^{A6}COR^{A7}", an acetylamino group, propionylamino group, butyrylamino group, isobutyrylamino group, pivaloylamino group, N-acetyl-N-methylamino group, butylcarbonylamino group and the like can be specifically mentioned.

[0073] As the "-NR^{A8}COOR^{A9}", a carboxyamino group, carboxymethylamino group, carboxyethylamino group, methoxycarbonylamino group, methoxycarbonylmethylamino group and the like can be specifically mentioned.

[0074] As the group A", preferably, a fluorine atom, chlorine atom, bromine atom, methyl group, ethyl group, propyl group, hydroxyl group, methoxy group, ethoxy group, propoxy group, amino group, methylamino group, ethylamino group, dimethylamino group, diethylamino group, carboxyamino group, butylcarbonylamino group, carboxy group, phenyl group, 4-morpholinyl group, 1-pyrrolidinyl group, 1-piperidinyl group and 1-piperazinyl group can be mentioned.

[0075] As the "group A", particularly preferably, a fluorine atom, chlorine atom, methyl group, hydroxyl group, methoxy group, amino group, dimethylamino group, diethylamino group, carboxyamino group, butylcarbonylamino group, carboxy group, phenyl group, 4-morpholinyl group, 1-pyrrolidinyl group, 1-piperidinyl group and 1-piperazinyl group can be mentioned.

[0076] The preferable number of the substituent is 1, and the substituent may be used at any substitutable position.

[0077] The "C₃₋₁₂ carbon ring group" and "heterocyclic group" for ring Cy, and "C₃₋₁₂ carbon ring group" and "heterocyclic group" for R³, R⁴ or R⁵ are optionally substituted by 1 to 5 substituents selected from group B. That is, the above-defined "C₃₋₁₂ carbon ring group" and "heterocyclic group" may be substituted by 1 to 5 substituents selected from group B, and includes unsubstituted "C₃₋₁₂ carbon ring group" and unsubstituted "heterocyclic group".

[0078] The "group B" is a group consisting of 1) the above-defined "halogen atom", 2) a nitro group, 3) a cyano group, 4) the above-defined "C₁₋₈ alkyl group", 5) the above-defined "C₂₋₄ alkenyl group", 6) the above-defined "C₂₋₄ alkynyl group", 7) "-OR^{B1}", 8) "-SR^{B2}", 9) "-NR^{B3}RB⁴", 10) "-NR^{B5}COR^{B6}", 11) "-NR^{B7}COOR^{B8}", 12) "-NR^{B9}CONR^{B10}RB¹¹", 13) "-NR^{B12}CONR^{B13}ORB¹⁴", 14) "-NR^{B15}SO₂RB¹⁶", 15) "-SO₂-RB¹⁷", 16) "-SO₂NR^{B18}RB¹⁹", 17) "-P(=O) (RB²⁰) (RB²¹)", 18) "-COOR^{B22}", 19) "-CONR^{B23}RB²⁴", 20) "-NR^{B25}SO₂NR^{B26}RB²⁷", 21) "-NR^{B28}SO₂NR^{B29}CONR^{B30}RB³¹", 22) the above-defined "C₃₋₁₂ carbon ring group" and 23) the above-defined "heterocyclic group", wherein RB¹, RB², RB⁴, RB⁵, RB⁷, RB⁸, RB⁹, RB¹⁰, RB¹¹, RB¹², RB¹³, RB¹⁴, RB¹⁵, RB¹⁸, RB¹⁹, RB²², RB²³, RB²⁴, RB²⁵, RB²⁶, RB²⁷, RB²⁸, RB²⁹, RB³⁰ and RB³¹ are the same or different and each is a hydrogen atom or the above-defined "C₁₋₄ alkyl group", RB³ and RB⁶ are each a hydrogen atom, the above-defined "C₁₋₄ alkyl group", the above-defined "C₃₋₁₂ carbon ring group" or the above-defined "heterocyclic group", RB¹⁶ is the above-defined "C₁₋₄ alkyl group", the above-defined "C₃₋₁₂ carbon ring group" or the above-defined "heterocyclic group", RB¹⁷ is the above-defined "C₁₋₄ alkyl group" or the above-defined "heterocyclic group", and RB²⁰ and RB²¹ are the same or different and each is the above-defined "C₁₋₄ alkyl group".

[0079] as the "-OR^{B1}", a hydroxyl group, methoxy group, ethoxy group, propoxy group, isopropoxy group, tert-butoxy group and the like can be specifically mentioned.

[0080] As the "-SR^{B2}", a mercapto group, methylsulfanyl group, ethylsulfanyl group, propylsulfanyl group, isopropylsulfanyl group, tert-butylsulfanyl group and the like can be specifically mentioned.

[0081] As the "-NR^{B3}RB⁴", an amino group, methylamino group, ethylamino group, 2-aminoethylamino group, propylamino group, isopropylamino group, tert-butylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-isopropyl-N-methylamino group, N-(imidazolin-2-yl)amino group and the like can be specifically mentioned.

[0082] As the "-NR^{B5}COR^{B6}", an amino group, formylamino group, acetylamino group, hydroxyacetylamino group, propionylamino group, butyrylamino group, isobutyrylamino group, pivaloylamino group, N-acetyl-N-methylamino group, 3-aminopropionylamino group, 3-(pentanoylamino)propionylamino group, 4-imidazolylcarbonylamino group, (1-methylpyrrol-2-yl)carbonylamino group, 4-pyrazolylcarbonylamino group and the like can be specifically mentioned.

[0083] As the "-NR^{B7}COOR^{B8}", a carboxyamino group, carboxymethylamino group, carboxyethylamino group, methoxycarbonylamino group, methoxycarbonylmethylamino-group and the like can be specifically mentioned.

[0084] As the "-NR^{B9}CONR^{B10}R^{B11}", an aminocarbonylamino group, methylaminocarbonylamino group, dimethylaminocarbonylamino group, (methylaminocarbonyl) (methyl) amino group, (dimethylaminocarbonyl) (methyl) amino group, [(2-hydroxyethyl)carbamoyl]amino and the like can be specifically mentioned.

[0085] As the "-NR^{B11}CONR^{B13}OR^{B14}", a methoxyaminocarbonylamino group, (methylmethoxyaminocarbonyl)(methyl)amino group, (methylmethoxyaminocarbonyl) amino group and the like can be specifically mentioned.

[0086] As the "-NR^{B15}SO₂R^{B16}", a sulfonylamino group, methylsulfonylamino group, ethylsulfonylamino group, propylsulfonylamino group, N-methyl-N-sulfonylamino group, N-methyl-N-methylsulfonylamino group, N-ethyl-N-sulfonylamino group, N-ethyl-N-methylsulfonylamino group, 3-pyridylsulfonylamino group, morpholin-sulfonylamino group, piperidinomorpholin-sulfonylamino group, 2-morpholinoethylsulfonylamino group and the like can be specifically mentioned.

[0087] As the "-SO₂-R^{B17}", a sulfonyl group, methylsulfonyl group, ethylsulfonyl group, propylsulfonyl group, butylsulfonyl group and the like can be specifically mentioned.

[0088] As the "-SO₂NR^{B18}R^{B19}", an aminosulfonyl group, methylaminosulfonyl group, dimethylaminosulfonyl group, ethylmethylaminosulfonyl group and the like can specifically be mentioned.

[0089] As the "-P(=O)(R^{B20})(R^{B21})", a phosphinoyl group, methylphosphinoyl groups, dimethylphosphinoyl group, ethylphosphinoyl group, diethylphosphinoyl group and the like can be specifically mentioned.

[0090] As the "-COOR^{B22}", a carboxyl group, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, tert-butoxycarbonyl group and the like can be specifically mentioned.

[0091] As the "-CONR^{B23}R^{B24}", a carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl, butylcarbamoyl and the like can be specifically mentioned.

[0092] As the "-NR^{B25}SO₂NR^{B26}R^{B27}", a sulfamoylamino group, dimethylsulfamoylamino group and the like can be specifically mentioned.

[0093] As the "-NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31}", a {[[(2-hydroxyethyl)carbamoyl] (2-hydroxyethyl)sulfamoyl]amino group and the like can be specifically mentioned.

[0094] As the "group B", preferably, a fluorine atom, chlorine atom, bromine atom, iodine atom, nitro group, cyano group, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, pentyl group, isopentyl group, hexyl group, 1-ethylpropyl group; 1-propylbutyl group, vinyl group, 1-propenyl group, ethynyl group, 1-propynyl group, 1-butynyl group, hydroxyl group, methoxy group, ethoxy group, propoxy group, isopropoxy group, methylthio group, ethylthio group, amino group, methylamino group, ethylamino group, dimethylamino group, diethylamino group, ethylmethylamino group, methylcarbonylamino group, ethylcarbonylamino group, propylcarbonylamino group, isopropylcarbonylamino group, (methylcarbonyl)(methyl) amino group, ethoxycarbonylamino group, methylaminocarbonylamino group, dimethylaminocarbonylamino group, methoxyaminocarbonylamino group, methylsulfonylamino group, ethylsulfonylamino group, propylsulfonylamino group, isopropylsulfonylamino group, phenylsulfonylamino group, (methylsulfonyl) (methyl) amino group, methylsulfonyl group, piperazin-1-ylsulfonyl group, morpholin-4-ylsulfonyl group, piperidin-4-ylsulfonyl group, pyrrolidin-4-ylsulfonyl group, aminosulfonyl group, methylaminosulfonyl group, ethylaminosulfonyl group, dimethylaminosulfonyl group, dimethylphosphinoyl group, carboxy group, methoxycarbonyl group, carbamoyl group, methylaminocarbonyl group, ethylaminocarbonylamino group, dimethylaminosulfonylamino group, cyclopropyl group, cyclohexyl group, phenyl group, piperidinyl group, pyrrolidinyl group, piperidinyl group, piperazinyl group and morpholinyl group can be mentioned.

[0095] As the group B", particularly preferably, a fluorine atom, chlorine atom, bromine atom, iodine atom, nitro group, cyano group, methyl group, ethyl group, propyl group, isopropyl group, butyl group, 1-ethylpropyl group, 1-propylbutyl group, butyl group, isobutyl group, isopentyl group, vinyl group, ethynyl group, 1-propynyl group, 1-butynyl group, hydroxyl group, methoxy group, propoxy group, isopropoxy group, methylthio group, amino group, methylamino group, ethylamino group, dimethylamino group, diethylamino group, ethylmethylamino group, methylcarbonylamino group, ethylcarbonylamino group, propylcarbonylamino group, isopropylcarbonylamino group, (methylcarbonyl) (methyl)amino group, ethoxycarbonylamino group, methylaminocarbonylamino group, dimethylaminocarbonylamino group, methoxyaminocarbonylamino group, methylsulfonylamino group, ethylsulfonylamino group, propylsulfonylamino group, isopropylsulfonylamino group, phenylsulfonylamino group, (methylsulfonyl) (methyl)amino group, methylsulfonyl group, piperazin-1-ylsulfonyl group, morpholin-4-ylsulfonyl group, piperidin-4-ylsulfonyl group, pyrrolidin-4-ylsulfonyl group, aminosulfonyl group, methylaminosulfonyl group, ethylaminosulfonyl group, dimethylaminosulfonyl group, dimethylphosphinoyl group, carboxy group, methoxycarbonyl group, carbamoyl group, methylaminocarbonyl group, ethylaminocarbonylamino group, dimethylaminosulfonylamino group, cyclopropyl group, phenyl group, piperidinyl group, pyrrolidinyl group, piperidinyl

group, piperazinyl group and morpholinyl group can be mentioned.

[0096] The preferable number of substituent is 1 or 2, and when the "C₃₋₁₂ carbon ring group" is a phenyl group, ring Cy is preferably mono-substituted at the 2-position, mono-substituted at the 3-position, mono-substituted at the 4-position, di-substituted at the 2,3-position, di-substituted at the 2,4-position, di-substituted at the 2,5-position or di-substituted at the 2,6-position, and particularly preferably mono-substituted at the 4-position or di-substituted at the 2,4-position, R² is more preferably mono-substituted at the 3-position, and R⁶ is more preferably di-substituted at the 2,4-position.

[0097] Each of the above-defined "C₁₋₄ alkyl group" for 4) of the above-defined group A, and the above-defined "C₁₋₄ alkyl group" for R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} or R^{A9} is optionally substituted by the same or different 1 to 3 substituents selected from the below-defined "group C".

[0098] Each of the above-defined "C₃₋₁₂ carbon ring group" for 11) of group A and R^{A7}, and the above-defined "heterocyclic group" for 12) and R^{A7} is optionally substituted by the same or different 1 to 5 substituents selected from the below-defined "group C".

[0099] Each of the above-defined "C₃₋₁₂ carbon ring group" for the above-mentioned 22) of group B, R^{B3}, R^{B6} and R^{B16}, and the above-defined "heterocyclic group" for the above-mentioned 23), R^{B3}, R^{B6}, R^{B16} and R^{B17} is optionally substituted by the same or different 1 to 5 substituents selected from the below-defined "group C".

[0100] The "group C" is a group consisting of 1) the above-defined "halogen atom", 2) a cyano group, 3) the above-defined "C₁₋₄ alkyl group", 4) "-OR^{C1}", 5) "-NRC²R^{C3}", 6) "-COOR^{C4}" and 7) an oxo group, wherein R^{C1}, R^{C2}, R^{C3} and R^{C4} are the same or different and each is a hydrogen atom or the above-defined "C₁₋₄ alkyl group".

[0101] As the -OR^{C1}, a hydroxyl group, methoxy group, ethoxy group, propoxy group, isopropoxy group, tert-butoxy group and the like can be specifically mentioned.

[0102] As the "-NRC²R^{C3}", an amino group, methylamino group, ethylamino group, propylamino group, isopropylamino group, tert-butylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-isopropyl-N-methylamino group and the like can be specifically mentioned.

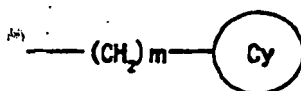
[0103] As the "-COOR^{C4}", a carboxyl group, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, tert-butoxycarbonyl group and the like can be specifically mentioned.

[0104] As the "group C", the group consisting of 1) the above-defined "halogen atom", 2) a cyano group, 3) the above-defined "C₁₋₄alkyl group", 4) "-OR^{C1}", 5) "-NRC¹-2R^{C3}" and 6) "-COOR^{C4}" are preferable, and specifically, a fluorine atom, chlorine atom, bromine atom, cyano group, methyl group, ethyl group, propyl group, hydroxyl group, methoxy group, ethoxy group, amino group, dimethylamino group, diethylamino group, carboxyl group and methoxycarbonyl group can be mentioned.

[0105] As the "group C", a methyl group is particularly preferable.

[0106] The preferable number of the substituent is 1, and the substituent may be used at any substitutable position.

[0107] As the "R¹", preferably, a C₁₋₆ alkyl group (wherein the C₂₋₆ alkyl group is optionally substituted by 1 to 3 substituents selected from group A) or



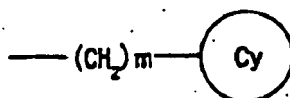
wherein each symbol is as defined above, can be mentioned.

[0108] Here, m is preferably 0, the "ring Cy" is preferably a C₃₋₁₂ carbon ring group, and the "carbon ring group" is preferably cycloalkyl group (wherein the "C₃₋₁₂ carbon ring group" and "cycloalkyl group" are optionally substituted by 1 to 5 substituents selected from group B).

[0109] Specifically, as the "R¹", a methyl group, ethyl group, 2,2,2-trifluoroethyl group, propyl group, isopropyl group, butyl group, 2-propenyl group, cyclopropyl group, 2-methylcyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, phenyl group, 4-chlorophenyl group, 4-fluorophenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 4-methoxyphenyl group, thiophen-3-yl group, cyclopropylmethyl group, 2-methoxyethyl, carboxymethyl, 2-hydroxyethyl, 2-(dimethylamino)ethyl and benzyl group are preferable.

[0110] More preferably, a methyl group, ethyl group, 2,2,2-trifluoroethyl group, propyl group, isopropyl group, butyl group, cyclopropyl group, 2-methylcyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, phenyl group, 4-chlorophenyl group, 4-fluorophenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 4-methoxyphenyl group, thiophen-3-yl group, 2-methoxyethyl, carboxymethyl, 2-hydroxyethyl and 2-(dimethylamino)ethyl, particularly preferably, methyl group or cyclopropyl group can be mentioned.

[0111] As the "R²",

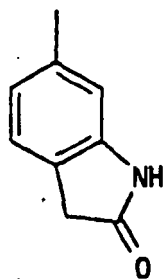


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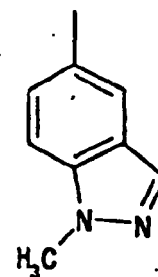
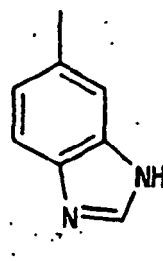
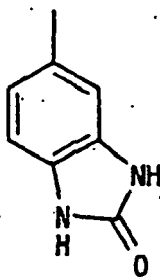
wherein each symbol is as defined above, is preferable. Here, m is preferably 0, the "ring Cy" is preferably a C_{3-12} carbon ring group, and the "carbon ring group" is preferably a phenyl group (wherein the " C_{3-12} carbon ring group" and "phenyl group" are optionally substituted by 1 to 5 substituents selected from group B, and as the "group B", $-NR^{B3}R^{B4}$, $-NR^{B5}COR^{B6}$, $-NR^{B7}COOR^{B8}$, $-NR^{B9}CONR^{B10}R^{B11}$, $-NR^{B12}CONR^{B13}OR^{B14}$, $-NR^{B15}SO_2R^{B16}$, $-NR^{B25}SO_2NR^{B26}R^{B27}$ and $-NR^{B28}OSO_2NR^{B29}CONR^{B30}R^{B31}$ are preferable).

[0112] Specifically, as the " R^2 ", a hydrogen atom, methyl group, ethyl group, 2,2,2-trifluoroethyl group, isopropyl group, butyl group, isobutyl group, 2-propenyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, phenyl group, 4-chlorophenyl group, 2-fluorophenyl group, 4-fluorophenyl group, 4-bromophenyl group, 2,6-difluorophenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,6-dimethylphenyl group, 2-ethylphenyl group, 3-(3-hydroxypropyl)phenyl group, 3-(2-carboxyethyl)phenyl group, 3-(3-morpholin-4-ylpropyl)phenyl group, 3-dimethylaminopropylphenyl group, 3-hydroxyphenyl group, 4-hydroxyphenyl group, 2-methoxyphenyl group, 3-methoxyphenyl group, 4-methoxyphenyl group, 3-dimethylaminoethoxyphenyl group, 3-carboxymethoxyphenyl group, 3-(3-dimethylaminopropoxy)phenyl group, 3-(2-morpholin-4-ylethoxy) phenyl group, 3-(2-pyrrolidin-1-ylethoxy)phenyl group, 3-(2-piperidin-1-ylethoxy)phenyl group, 3-(2-diethylaminoethoxy)phenyl group, 3-(3-(4-methylpiperazin-1-yl)propoxy)phenyl group, 3-aminophenyl group, 3-methylaminophenyl group, 3-dimethylaminophenyl group, 3-(methanesulfonyl)methylaminophenyl group, 3-methylcarbonylamino phenyl group, 3-methanesulfonylamino phenyl group, 4-chloro-3-methanesulfonylamino phenyl group, 3-ethanesulfonylamino phenyl group, 3-(propane-1-sulfonylamino) phenyl group, 3-(propane-2-sulfonylamino)phenyl group, 3-chloromethanesulfonylamino phenyl group, 3-trifluoromethanesulfonylamino phenyl group, 3-(2,2,2-trifluoroethanesulfonylamino)phenyl group, 3-(2-methoxyethyl)methylaminophenyl group, 3-methylcarbonylamino phenyl group, 3-ethylcarbonylamino phenyl group, 3-propylcarbonylamino phenyl group, 3-isopropylcarbonylamino phenyl group, 3-ethoxycarbonylamino phenyl group, 3-(hydroxymethylcarbonyl) amino phenyl group, 3-(2-hydroxyethylcarbonylamino) phenyl group, 3-ethylaminocarbonylamino phenyl group, 3-(2-dimethylaminoethylcarbonylamino)phenyl group, 3-(3-dimethylaminopropylcarbonylamino)phenyl group, 3-(methoxymethylcarbonylamino)phenyl group, 3-(butylcarbonylamino methylcarbonylamino)phenyl group, 3-(2-butylcarbonylaminoethylcarbonylamino)phenyl group, 3-methylaminocarbonylamino phenyl group, 3-methoxyaminocarbonylamino phenyl group, 3-dimethylaminocarbonylamino phenyl group, 3-(dimethylaminomethylcarbonylamino)phenyl group, 3-(2-morpholin-4-ylethylamino)phenyl group, 3-(2-benzyloxycarbonylaminoethyl)sulfonylamino phenyl group, 3-(2-aminoethyl)sulfonylamino phenyl group, 3-(2-butylcarbonylaminoethyl)sulfonylamino phenyl group, 3-dimethylaminosulfonylamino phenyl group, 3-carboxyphenyl group, 3-carbamoylphenyl group, 3-methanesulfonylphenyl group, 4-methanesulfonylphenyl group, 3-ethanesulfonylphenyl group, 3-methylaminosulfonylphenyl group, 3-ethylaminosulfonylphenyl group, 3-benzenesulfonylamino phenyl group, 3-aminosulfonylphenyl group, 3-dimethylaminosulfonylphenyl group, 4-dimethylaminosulfonylphenyl group, 3-(4-methylpiperazine-1-sulfonyl) phenyl group, 3-(morpholine-4-sulfonyl)phenyl group, 3-(piperidine-1-sulfonyl)phenyl group, 3-(pyrrolidine-1-sulfonyl)phenyl group, 3-methylaminocarbonylphenyl group, 3-morpholin-4-ylphenyl group, 3-pyrrolidin-1-ylphenyl group, 3-piperidin-1-ylphenyl group, 3-(4-methylpiperazin-1-yl)phenyl group, 3-(2-oxopyrrolidin-1-yl)phenyl group, 3-(3-oxomorpholin-4-yl)phenyl group, thiophen-3-yl group, pyridin-3-yl group, benzyl group and the following groups:

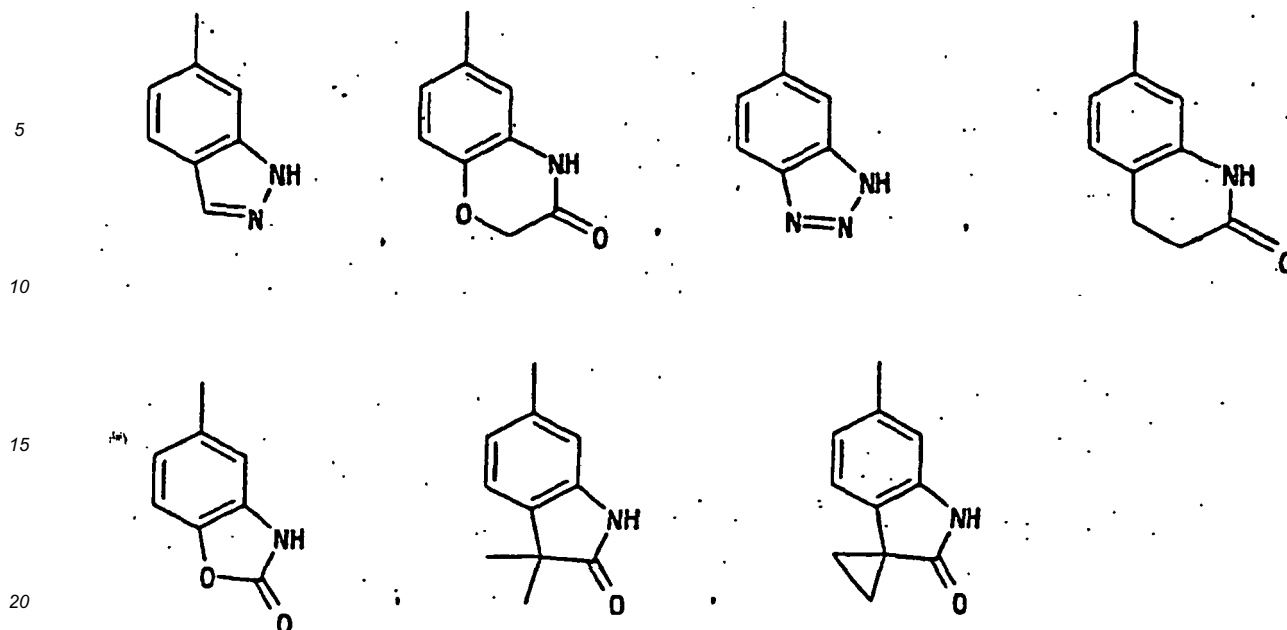
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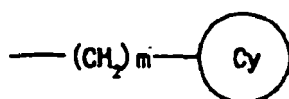


are preferable.

25 **[0113]** More preferably, a phenyl group, 4-chlorophenyl group, 2-fluorophenyl group, 4-fluorophenyl group, 4-bromophenyl group, 2,6-difluorophenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,6-dimethylphenyl group, 2-ethylphenyl group, 3-(3-hydroxypropyl) phenyl group, 3-(2-carboxyethyl)phenyl group, 3-(3-morpholin-4-ylpropyl)phenyl group, 3-dimethylaminopropylphenyl group, 3-hydroxyphenyl group, 4-hydroxyphenyl group, 2-methoxyphenyl group, 3-methoxyphenyl group, 4-methoxyphenyl group, 3-dimethylaminoethoxyphenyl group, 3-carboxymethoxyphenyl group, 3-(3-dimethylaminopropoxy)phenyl group, 3-(2-morpholin-9-ylethoxy)phenyl group, 3-(2-pyrrolidin-1-ylethoxy)phenyl group, 3-(2-piperidin-1-ylethoxy)phenyl group, 3-(2-diethylaminoethoxy)phenyl group, 3-[3-(4-methylpiperazin-1-yl)propoxy]phenyl group, 3-aminophenyl group, 3-methylaminophenyl group, 3-dimethylaminophenyl group, 3-(methanesulfonyl)methylaminophenyl group, 3-methylcarbonylaminophenyl group, 3-methanesulfonylaminophenyl group, 4-chloro-3-methanesulfonylaminophenyl group, 3-ethanesulfonylaminophenyl group, 3-(propane-1-sulfonylamino)phenyl group, 3-(propane-2-sulfonylamino)phenyl group, 3-chloromethanesulfonylaminophenyl group, 3-trifluoromethanesulfonylaminophenyl group, 3-(2,2,2-trifluoroethanesulfonylamino)phenyl group, 3-(2-methoxyethyl)methylaminophenyl group, 3-methylcarbonylaminophenyl group, 3-ethylcarbonylaminophenyl group, 3-propylcarbonylaminophenyl group, 3-isopropylcarbonylaminophenyl group, 3-ethoxycarbonylaminophenyl group, 3-(hydroxymethylcarbonyl)aminophenyl group, 3-(2-hydroxyethylcarbonylamino)phenyl group, 3-ethylaminocarbonylaminophenyl group, 3-(2-dimethylaminoethylcarbonylamino)phenyl group, 3-(3-dimethylaminopropylcarbonylamino)phenyl group, 3-(methoxymethylcarbonylamino)phenyl group, 3-(butylcarbonylaminomethylcarbonylamino)phenyl group, 3-(2-butylcarbonylaminoethylcarbonylamino)phenyl group, 3-methylaminocarbonylaminophenyl group, 3-methoxyaminocarbonylaminophenyl group, 3-dimethylaminocarbonylaminophenyl group, 3-(dimethylaminomethylcarbonylamino)phenyl group, 3-(2-morpholin-4-ylethylamino)phenyl group, 3-(2-benzyloxycarbonylaminoethyl)sulfonylaminophenyl group, 3-(2-aminoethyl)sulfonylaminophenyl group, 3-(2-butylcarbonylaminoethyl)sulfonylaminophenyl group, 3-dimethylaminosulfonylaminophenyl group, 3-carboxyphenyl group, 3-carbamoylphenyl group, 3-methanesulfonylphenyl group, 4-methanesulfonylphenyl group, 3-ethanesulfonylphenyl group, 3-methylaminosulfonylphenyl group, 3-ethylaminosulfonylphenyl group, 3-benzenesulfonylaminophenyl group, 3-aminosulfonylphenyl group, 3-dimethylaminosulfonylphenyl group, 4-dimethylaminosulfonylphenyl group, 3-(4-methylpiperazine-1-sulfonyl)phenyl group, 3-(morpholine-4-sulfonyl)phenyl group, 3-(piperidine-1-sulfonyl)phenyl group, 3-(pyrrolidine-1-sulfonyl)phenyl group, 3-methylaminocarbonylphenyl group, 3-morpholin-4-ylphenyl group, 3-pyrrolidin-1-ylphenyl group, 3-piperidin-1-ylphenyl group, 3-(4-methylpiperazin-1-yl)phenyl group; 3-(2-oxopyrrolidin-1-yl)phenyl group and 3-(3-oxomorpholin-4-yl)phenyl group can be mentioned.

[0114] As the "R⁶",

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wherein each symbol is as defined above, is preferable. Here, m is preferably, 0, the "ring Cy" is preferably a C₃₋₁₂ carbon ring group and the "carbon ring group" is preferably a phenyl group (wherein the "C₃₋₁₂ carbon ring group" and "phenyl group" are optionally substituted by 1 to 5 substituents selected from group B, where the "group B" preferably includes the above-defined "halogen atom", the above-defined "C₁₋₈ alkyl group" and the above-defined "C₂₋₄ alkynyl group").

[0115] Specifically, as the "R⁶", a 2-methoxyethyl group, 2,2-dimethylpropyl group, 3-dimethylaminopropyl group, cyclopropyl group, cyclohexyl group, phenyl group, 2-chlorophenyl group, 3-chlorophenyl group, 4-chlorophenyl group, 2,4-dichlorophenyl group, 3,4-dichlorophenyl group, 4-bromophenyl group, 2-fluorophenyl group, 4-fluorophenyl group, 4-iodophenyl group, o-tolyl group, p-tolyl group, methylphenyl group, 4-ethylphenyl group, 2-propylphenyl group, 2-isopropylphenyl group, 4-isopropylphenyl group, 2-butylphenyl group, 4-butylphenyl group, 2-isobutylphenyl group, 4-tert-butylphenyl group, 2-(3-methylbutyl)phenyl group, 4-trifluoromethylphenyl group, 4-(2-fluoroethyl)phenyl group, 4-(2,2-difluoroethyl) phenyl group, 4-(2,2,2-trifluoroethyl)phenyl group, 4-(1-ethylpropyl)phenyl group, 4-(1-propylbutyl) phenyl group, 4-ethynylphenyl group, 2,4-difluorophenyl group, 2,6-difluorophenyl group, 2,4-dichlorophenyl group, 4-bromo-2-fluorophenyl group, 4-bromo-3-fluorophenyl group, 4-bromo-2-chlorophenyl group, 4-chloro-2-fluorophenyl group, 2-fluoro-4-iodophenyl group, 2-chloro-4-methylphenyl group, 4-chloro-2-methylphenyl group, 4-bromo-2-methylphenyl group, 4-bromo-3-methylphenyl group, 2-fluoro-4-methylphenyl group, 2-fluoro-4-trifluoromethylphenyl group, 4-bromo-2-ethylphenyl group, 4-ethyl-2-fluorophenyl group, 4-(2-carboxyethyl)-2-fluorophenyl group, 2-fluoro-4-propylphenyl group, 2-fluoro-4-vinylphenyl group, 4-(2-carboxyvinyl)-2-fluorophenyl group, 4-ethynyl-2-fluorophenyl group, 2-fluoro-4-(prop-1-ynyl)phenyl group, 2-fluoro-4-(3-hydroxyprop-1-ynyl)phenyl group, 2-fluoro-4-(3-methoxyprop-1-ynyl) phenyl group, 4-cyclopropyl-2-fluorophenyl group, 2-fluoro-4-(3-hydroxy-3-methylbut-1-ynyl)phenyl group, 4-(3-dimethylaminoprop-1-ynyl)-2-fluorophenyl group, 4-chloro-2-dimethylaminomethylphenyl group, 4-dimethylamino-2-methylphenyl group, 4-hydroxyphenyl group, 2-methoxyphenyl group, 4-methoxyphenyl group, 4-trifluoromethoxyphenyl group, 4-isopropoxyphenyl group, 2,4-dimethoxyphenyl group, 4-methoxy-2-methylphenyl group, 2-fluoro-4-methoxyphenyl group, 4-bromo-2-hydroxyphenyl group, 4-bromo-2-methoxyphenyl group, 2-bromo-4-methoxyphenyl group, 4-methylthiophenyl group, 4-trifluoromethylthiophenyl group, 2-fluoro-4-methylthiophenyl group, 4-aminophenyl group, 4-methylaminophenyl group, 2-dimethylaminophenyl group, 3-dimethylaminophenyl group, 4-dimethylaminophenyl group, 4-ethylaminophenyl group, 4-diethylaminophenyl group, 4-ethylmethylamino-2-fluorophenyl group, 4-nitrophenyl group, 4-cyanophenyl group, 6-aminopyridin-3-yl group, 6-dimethylaminopyridin-3-yl group, 6-chloropyridin-2-yl group, 4-chloropyridin-3-yl group, 4-carboxyphenyl group, 4-methoxycarbonylphenyl group, 4-ethylaminophenyl group, 4-(methylcarbonyl)methylaminophenyl group, 4-methanesulfonylphenyl group, 4-trifluoromethanesulfonylphenyl group, 4-dimethylamino-2-methylphenyl group, 4-dimethylamino-3-methylphenyl group, 4-dimethylamino-3-trifluoromethylphenyl group, 4-dimethylamino-2-propylphenyl group, 4-dimethylamino-2-fluorophenyl group, 4-dimethylamino-3-fluorophenyl group, 4-dimethylphosphinoyl phenyl group, benzo[1,3]dioxol-5-yl group, 1,1'-biphenyl-4-yl group, 4-(piperidin-1-yl)phenyl group, 4-benzylphenyl group, 4-(morpholin-4-yl)phenyl group, 1-methylpiperidin-4-yl group, 1-isopropylpiperidin-4-yl group, thiazol-2-yl group, 2-dimethylaminothiazol-4-yl group, 1-methyl-1,2,3,4-tetrahydroquinolin-6-yl group, 1H-indol-5-yl group, 1-methyl-1H-indol-5-yl group, 1-ethyl-1H-indol-5-yl group, 1-methyl-1H-indol-6-yl group, 1-methyl-1H-indol-7-yl group, 1,2-dimethyl-1H-indol-5-yl group, 1,2,3-trimethyl-1H-indol-5-yl group, 6-fluoro-1H-indol-5-yl group, 1-methyl-1H-benzimidazol-5-yl group, 1-methyl-1H-indazol-5-yl group, 1-methyl-2,3-dihydro-1H-indol-5-yl group, benzo[b]thiophen-5-yl group, 4-chlorobenzyl group, 2-bromobenzyl group, 3-bromobenzyl group, 4-bromobenzyl group, 5-bromo-2-fluorobenzyl group, 2-morpholin-4-ylethyl group and pyridin-3-ylmethyl group are preferable.

[0116] More preferably, a phenyl group, 2-chlorophenyl group, 3-chlorophenyl group, 4-chlorophenyl group, 2,4-dichlorophenyl group, 3,4-dichlorophenyl group, 4-bromophenyl group, 2-fluorophenyl group, 4-fluorophenyl group, 4-iodophenyl group, o-tolyl group, p-tolyl group, 2-ethylphenyl group, 4-ethylphenyl group, 2-propylphenyl group, 2-isopropylphenyl group, 4-isopropylphenyl group, 2-butylphenyl group, 4-butylphenyl group, 2-isobutylphenyl group, 4-tert-butylphenyl group, 2-(3-methylbutyl)phenyl group, 4-trifluoromethylphenyl group, 4-(2-fluoroethyl)phenyl group, 4-(2,2-difluoroethyl)phenyl group, 4-(2,2,2-trifluoroethyl)phenyl group, 4-(1-ethylpropyl)phenyl group, 4-(1-propylbutyl)phenyl group, 4-ethynylphenyl group, 2,4-difluorophenyl group, 2,6-difluorophenyl group, 2,4-dichlorophenyl group, 4-bromo-2-fluorophenyl group, 4-bromo-3-fluorophenyl group, 4-bromo-2-chlorophenyl group, 4-chloro-2-fluorophenyl group, 2-fluoro-4-iodophenyl group, 2-chloro-4-methylphenyl group, 4-chloro-2-methylphenyl group, 4-bromo-2-methylphenyl group, 4-bromo-3-methylphenyl group, 2-fluoro-4-methylphenyl group, 2-fluoro-4-trifluoromethylphenyl group, 4-bromo-2-ethylphenyl group, 4-ethyl-2-fluorophenyl group, 4-(2-carboxyethyl)-2-fluorophenyl group, 2-fluoro-4-propylphenyl group, 2-fluoro-4-vinylphenyl group, 4-(2-carboxyvinyl)-2-fluorophenyl group, 4-ethynyl-2-fluorophenyl group, 2-fluoro-4-(prop-1-ynyl)phenyl group, 2-fluoro-4-(3-hydroxyprop-1-ynyl)phenyl group, 2-fluoro-4-(3-methoxyprop-1-ynyl)phenyl group, 4-cyclopropyl-2-fluorophenyl group, 2-fluoro-4-(3-hydroxy-3-methylbut-1-ynyl)phenyl group, 4-(3-dimethylamino-prop-1-ynyl)-2-fluorophenyl group, 4-chloro-2-dimethylaminomethylphenyl group, 4-dimethylamino-2-methylphenyl group, 4-hydroxyphenyl group, 2-methoxyphenyl group, 4-methoxyphenyl group, 4-trifluoromethoxyphenyl group, 4-isopropoxyphenyl group, 2,4-dimethoxyphenyl group, 4-methoxy-2-methylphenyl group, 2-fluoro-4-methoxyphenyl group, 4-bromo-2-hydroxyphenyl group, 4-bromo-2-methoxyphenyl group, 2-bromo-4-methoxyphenyl group, 4-methyl-

thiophenyl group, 4-trifluoromethylthiophenyl group, 2-fluoro-4-methylthiophenyl group, 4-aminophenyl group, 4-methylaminophenyl group, 2-dimethylaminophenyl group, 3-dimethylaminophenyl group, 4-dimethylaminophenyl group, 4-ethylaminophenyl group, 4-diethylaminophenyl group, 4-ethylmethylamino-2-fluorophenyl group, 4-nitrophenyl group, 4-cyanophenyl group, 6-aminopyridin-3-yl group, 6-dimethylaminopyridin-3-yl group, 6-chloropyridin-2-yl group, 4-chloropyridin-3-yl group, 4-carboxyphenyl group, 4-methoxycarbonylphenyl group, 4-ethylaminophenyl group, 4-(methylcarbonyl)methylaminophenyl group, 4-methanesulfonylphenyl group, 4-trifluoromethanesulfonylphenyl group, 4-dimethylamino-2-methylphenyl group, 4-dimethylamino-3-methylphenyl group, 4-dimethylamino-3-trifluoromethylphenyl group, 4-dimethylamino-2-propylphenyl group, 4-dimethylamino-2-fluorophenyl group, 4-dimethylamino-3-fluorophenyl group, 4-dimethylphosphinoylphenyl group, 1,1'-biphenyl-4-yl group, 4-(piperidin-1-yl)phenyl group, 4-benzylphenyl group and 4-(morpholin-4-yl)phenyl group can be mentioned.

[0117] As the "R³" preferably, a C₁₋₆ alkyl group (wherein the C₁₋₆ alkyl group is optionally substituted by 1 to 3 substituents selected from group A) can be mentioned.

[0118] Specifically, a hydrogen atom, methyl group, ethyl group, propyl group, isobutyl group, 2-methoxyethyl group, cyclopropyl group, 2-dimethylaminoethyl group and 2-propenyl group are preferable, and methyl group is particularly preferable.

[0119] As the "R⁴", preferably, a C₁₋₆ alkyl group (wherein the C₁₋₆ alkyl group is optionally substituted by 1 to 3 substituents selected from group A) can be mentioned.

[0120] Specifically, a hydrogen atom, methyl group, propyl group and hydroxy group are preferable, and methyl group is particularly preferable.

[0121] As the "R⁵", a hydrogen atom and methyl group are preferable, and a hydrogen atom is particularly preferable.

[0122] The "pharmaceutically acceptable salt thereof" may be any salt as long as it forms a non-toxic salt with the compounds of the above-mentioned formula [I], [I'] and [I-1]-[I-3] and can be obtained by a reaction with an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; an organic acid such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, gluconic acid, ascorbic acid, methanesulfonic acid, benzenesulfonic acid and the like; an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like; an organic base such as methylamine, diethylamine, triethylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, guanidine, choline, cinchonine and the like; or an amino acid such as lysine, arginine, alanine and the like. The present invention also encompasses hydrate and solvate of each compound.

[0123] By the "prodrug" is meant a derivative of the compound of the present invention, which has a chemically or metabolically decomposable group and which, after administration to a body, restores to the original compound to show its inherent efficacy, including a complex and a salt, not involving a covalent bond.

[0124] The prodrug is utilized for, for example, improving absorption by oral administration or targeting of a target site.

[0125] As the site to be modified, highly reactive functional groups in the compound of the present invention, such as hydroxyl group, carboxyl group, amino group, thiol group and the like, are mentioned.

[0126] For example, a compound wherein a hydroxyl group is substituted by -CO-alkyl, -CO₂-alkyl, -CONH-alkyl, -CO-alkenyl, -CO₂-alkenyl, -CONH-alkenyl, -CO-aryl, -CO₂-aryl, -CONH-aryl, -CO-heterocycle, -CO₂-heterocycle, -CONH-heterocycle (wherein alkyl, alkenyl, aryl and heterocycle are optionally substituted by a halogen atom, alkyl group, hydroxyl group, alkoxy group, carboxy group, amino group, amino acid residue, -PO₃H₂, -SO₃H, -OPO₃H₂, -OSO₃H and the like) or -PO₃H₂ and the like, a compound wherein an amino group is substituted by -CO-alkyl, -CO₂-alkyl, -CO-alkenyl, -CO₂-alkenyl, -CO₂-aryl, -CO-aryl, -CO-heterocycle, -CO₂-heterocycle (wherein alkyl, alkenyl, aryl and heterocycle are optionally substituted by halogen atom, alkyl group, hydroxyl group, alkoxy group, carboxy group, amino group, amino acid residue, -PO₃H₂, -SO₃H, -OPO₃H₂, -OSO₃H and the like) or -PO₃H₂ and the like can be mentioned.

[0127] Specifically, as the modifying group of a hydroxyl group, acetyl group, propionyl group, isobutyryl group, pivaloyl group, palmitoyl group, benzoyl group, 4-methylbenzoyl group, dimethylcarbamoyl group, dimethylaminomethylcarbonyl group, sulfo group, alanyl group, fumaryl group and the like can be mentioned. The sodium salt of a 3-carboxybenzoyl group or 2-carboxyethylcarbonyl group and the like can be also mentioned.

[0128] Specifically, as the modifying group of a carboxyl group, a methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, tert-butyl group, pivaloyloxymethyl group, carboxymethyl group, dimethylaminomethyl group, 1-(acetyloxy)ethyl group, 1-(ethoxycarbonyloxy)ethyl group, 1-(isopropylloxycarbonyloxy)ethyl group, 1-(cyclohexyloxycarbonyloxy)ethyl group, carboxylmethyl group, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group, benzyl group, phenyl group, o-tolyl group, morpholinoethyl group, N,N-diethylcarbamoylmethyl group, phthalidyl group and the like can be mentioned.

[0129] Specifically, as the modifying group of an amino group, a tert-butyl group, docosanoyl group, pivaloylmethoxy group, alanyl group, hexylcarbamoyl group, pentylcarbamoyl group, 3-methylthio-1-(acetylamino)propylcarbonyl group, 1-sulfo-1-(3-ethoxy-4-hydroxyphenyl)methyl group, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group, (5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl group, tetrahydrofuranyl group, pyrrolidylmethyl group and the like can be mentioned.

[0130] The "tumor" used in the present specification includes malignant tumor, and the "antitumor agent" contains an

anticancer agent and is a compound having an antitumor activity.

[0131] The compound of the present invention can be administered to a mammal (human, mouse, rat, hamster, rabbit, cat, dog, cattle, sheep, monkey etc.) and the like as an antitumor agent and the like.

[0132] When the compound of the present invention is used as a pharmaceutical preparation, it is generally admixed with pharmaceutically acceptable carriers, excipients, diluents, extending agents, disintegrants, stabilizers, preservatives, buffers, emulsifiers, flavoring agents, coloring agents, sweetening agents, thickeners, corrigents, dissolution aids, and other additives, that are known per se, such as water, vegetable oil, alcohol (e.g., ethanol, benzyl alcohol etc.), polyethylene glycol, glycerol triacetate, gelatin, carbohydrate (e.g., lactose, starch etc.), magnesium stearate, talc, lanolin, petrolatum and the like, formed into tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like by a conventional method, and administered systemically or topically, and orally or parenterally.

[0133] While the dose varies depending on age, body weight, symptom, treatment effect, administration method and the like, it is generally 0.01 mg to 1 g per dose for an adult, which is given once to several times a day orally or in a dosage form of an injection such as intravenous injection and the like.

[0134] An antitumor agent is generally required to sustain its effect for a long time, so that can be effective not only for temporal suppression of the proliferation of cancer cells but also for the inhibition of the re-inhibition of cancer cells. This means that a prolonged administration is necessary and that a high single dose may be frequently inevitable to sustain effect for a longer period through the night. Such prolonged and high dose administration increases the risk of causing side effects.

[0135] In view of this, one of the preferable embodiments of the pyrimidine compound of the present invention is such a compound that permits high absorption by oral administration, and such a compound capable of maintaining blood concentration of the administered compound for an extended period of time.

[0136] A compound capable of showing p15 protein induction and/or p27 protein induction and/or MEK inhibition in combination is preferable.

[0137] This compound is useful for the treatment of diseases caused by undesirable cell proliferation.

[0138] As the "diseases caused by undesirable cell proliferation", for example, tumor, specifically cerebral tumor (neuroglioma having a component of malignant astroglioma and oligodendroglioma and the like), cancer of esophagus, stomach cancer, liver cancer, pancreatic cancer, colorectal cancer (colon cancer, rectal cancer etc.), lung cancer (non-small cell lung cancer, small cell lung cancer, primary and metastatic squamous cancer etc.), renal cancer, breast cancer, ovarian cancer, prostate cancer, skin cancer, neuroblastoma, sarcoma, osteochondroma, osteoma, osteosarcoma, seminoma, extragonadal tumor, testicle tumor, uterine cancer (cervical cancer, endometrial cancer and the like), head and neck tumor (maxillary cancer, larynx cancer, pharyngeal cancer, lingual cancer, intraoral cancer and the like), multiple myeloma, malignant lymphoma (reticulosarcoma, lymphosarcoma, Hodgkin's disease etc.), polycythemia vera, leukemia (acute myeloid leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia etc.), goiter, renal pelvic cancer, ureteral tumor, bladder tumor, gallbladder cancer, bile duct cancer, chorioma, malignant melanoma, pediatric tumor (sarcoma of the ewing's family, Wilms' tumor, rhabdomyosarcoma, vascular sarcoma, embryonal testicle cancer, neuroblastoma, retinoblastoma, hepatoblastoma, nephroblastoma etc.) and the like can be mentioned.

[0139] Application to a cerebral tumor (neuroglioma having a component of malignant astroglioma and oligodendroglioma etc.), cancer of esophagus, stomach cancer, liver cancer, pancreatic cancer, colorectal cancer (colon cancer, rectal cancer etc.), lung cancer (non-small cell lung cancer, small cell lung cancer etc.), renal cancer, breast cancer, ovarian cancer, prostate cancer, skin cancer, neuroblastoma, sarcoma and the like can be mentioned. More preferably, colon cancer, pancreas cancer, renal cancer, lung cancer, and breast cancer is preferable, and application to colon cancer and pancreas cancer is particularly preferable.

[0140] In addition, treatment of chronic pain, specifically, neuropathic pain, cataplectic pain, pain associated with chronic alcoholism, vitamin deficiency, uremia and hypothyroidism can be mentioned. Furthermore, neutrophile-mediated disease or symptoms, specifically, ischemia reperfusion injury, chronic obstructive pulmonary disease, acute respiratory disease syndrome, cystic fibrosis, cataplectic pulmonary fibrosis, sepsis, endotoxemia, lung emphysema and pulmonary asbestosis can be mentioned. Furthermore, graft rejection can be mentioned. Moreover, arthritis, specifically, rheumatoid arthritis and osteoarthritis, can be mentioned. In addition, asthma can be mentioned. Moreover, viral diseases, specifically, herpes virus (HSV-1) infection, human cytomegalovirus (HCMV) infection, human immunodeficiency virus (HIV) infection can be mentioned. Furthermore, disease caused by denaturation or injury of cartilage, specifically, osteoarthritis, rheumatoid arthritis, osteochondrosis dissecans and disease requiring chondrogenesis can be mentioned.

[0141] Besides the above, application to restenosis, psoriasis, atherosclerosis, cardiac failure, apoplexia and the like can be mentioned.

[0142] As the "diseases caused by undesirable cell proliferation", tumor and rheumatism are preferable.

[0143] As other "antitumor agent" used for multiple drug therapy, an alkylating agent, platinum complex, metabolism antagonist, antibiotics, plant alkaloid, interferon, cyclooxygenase-2 (COX-2) inhibitor, hormonal anticancer agent, cancer

cell vaccine, bacterial preparation, mushroom extract polysaccharides, cytokine agonist, interleukin preparation, antibody drug, immunomodulator, angiogenesis inhibitor, intracellular tube formation inhibitor, cell proliferation inhibitor, cell cycle regulator, apoptosis inducer, cancer gene therapy agent and the like can be mentioned.

[0144] As the alkylating agent, cyclophosphamide, ifosfamide, melpharan, buslfan, nimustine, ranimustine (MCNU), nitrogen mustard-N-oxide hydrochloride, thiotepea, procarbazine hydrochloride, carboquone, mitobronitol, improsulfan tosylate, estramustine phosphate sodium, dacarbazine, temozolomide, dacarbazine(DTIC), mustine hydrochride, treosulfan, temozolomide, MS-247, (-)-(S)-bromofosfamide and the like can be mentioned.

[0145] As the platinum complex, cisplatin, carboplatin, nedaplatin, paraplalin, etoposide, oxaliplatin, eptaplalin, miriplatin, lobaplalin, picoplalin, oxaliplatin, satraplatin, SLIT-cisplatin and the like can be mentioned.

[0146] As the metabolism antagonist, methotrexate, 6-mercaptapurine, cytosine-arabinoside, encitabine (BHAC), 5-fluorouracil, tegafur, tegafur-uracil (UFT), carmofur (HCFU), doxifluridine, gemcitabine hydrochloride, hydroxyl carbamide, procarbazine hydrochloride, pemetrexed disodium, L-MDAM, mercaptopurine riboside, fludarabine phosphate, tegafur-gimestat-otastat, levofolinate-fluorouracil, folinate calcium levofolinate, bemcitabine, calcium levoleucovorin, capecitabine, cytarabine, cytarabine ocfosfate, CS-682, 3'-ethynylcytidine, TAS-102, capecitabine, fulvestrant, idoxuridine, hydroxyurea, pemetrexedisodium, 3-AP, bensem, lometrexol, troxacitabine, ABT-510, AP-2/09, AR-726, AVI-4126, belimumab, CA4P, colorectal cancer vaccine, COU-1, degarelix, DJ-927, DPC-974, EKB-569, enzastaurin hydrochloride, fentanyl citrate, fulvestrant, gallium maltolate, HuMax-EGFR, IDD-1, LE-AON, MDX-070, MT-201, NK-911, NV-07, Oncomyc-NG, pertuzumab, PX-103.1, renal cancer vaccine, SN-4071, TL-139, topixantrone dihydrochloride, ZYC-101a and the like can be mentioned.

[0147] As the antibiotics, actinomycin D, daunomycin, doxorubicin (adriamycin), epirubicin, aclacinomycin A, mitomycin C, bleomycin, pirarubicin hydrochloride, idarubicin hydrochloride, aclarubicin hydrochloride, amrubicin hydrochloride, peplomycin sulfate, neocarzinostatine, zinostatin stimalamer, valrubicin, liposomal doxorubicin, NK911, BMS-247550 (epothilone derivative), KRN5500, KW-2170, annamycin, becatecarin, PK1, sabarubicin hydrochloride, CVS-10290 and the like can be mentioned.

[0148] As the plant alkaloid, vincristine, vinblastine, vindesine, etoposide, docetaxel, paclitaxel, irinotecan hydrochloride, vinorelbine tartrate, mitoxantrone hydrochloride, noscapine, vinflunine, docetaxel, E-7010, polyglutamated paclitaxel, soblidotin, Bay59-8862, E-7389, DJ-927, HTI-286, AC-7700, T-3782, ABI-007, batabulin sodium, DHA-paclitaxel, deoxyepothilone B, ixabepilone, MBT-0206, ortataxel, SB-715992, AI-850, synthadotin, Ixabepilone, rubitecan, nogitecan hydrochloride, topotecan hydrochloride, sobuzoxane, etoposide phosphate disodium salt, dexrazoxane hydrochloride, rubitecan IST-622, exatecan mesylate, TOP-53, edotecarin, karenitecan, AG-7352, TAS-103, T-0128, NK-314, CKD-602, BNP-1350, lurtotecan, pegamotecan, rubitecan, LE-SN38, CPT-11 and the like can be mentioned.

[0149] As interferon, interferon α , interferon α -2a, interferon α -2b, interferon β and interferon γ , interferon γ -1a, interferon γ -1b, interferon γ -n1 and the like can be mentioned.

[0150] As the cyclooxygenase-2 inhibitor, rofecoxib, celecoxib, lumiracoxib, tiracoxib (tilmacozib), CS-502, CS-706, valdecoxib, parecoxib, R-109339, deguelin, ajulemic acid, p-54, E-6087, LM-4108, R-109339, CBX-AC, CBX-PR, CBX-BU, L-748706, DMNQ-S64, ON-09250, ON-09300 and the like can be mentioned.

[0151] As the hormonal anticancer agent, leuprorelin acetate, goserelin acetate, aminoglutethimide, triptorelin, goserelin, formestane, fabrozole monohydrochloride, letrozole, exemestane, deslorelin, buserelin acetate, cetorelix acetate, histrelin acetate, abarelix, atrigel-leuprolide, estramustine phosphate sodium, chlormadinone acetate, fosfetrol, flutamide, bicartamide, cyproterone acetate, medroxyprogesterone acetate, tamoxifen citrate, toremifene citrate, mepithiostane, epithiostanol, medroxyprogesterone acetate, fluevestrant, ormeloxifene, raloxifene hydrochloride, miproxifene phosphate, TAS-108, FMPA, fadrozole, anastrozole, exemestan, letrozole, formestane, bosentan, atrasentan, dutasteride, ESI, KT5555, KAT-682 and the like can be mentioned.

[0152] As the cancer cell vaccine, cancer vaccine, activated lymphocyte, UL56 deficient HSV, vaccine for colorectal cancer treatment, cancer peptide vaccine and the like can be mentioned.

[0153] As the bacterial preparation, BCG, anti-malignant tumor streptococcal preparation, LC9018, tubercle bacillus hot water an extract and the like can be mentioned.

[0154] As the mushroom extract polysaccharides, lentinan, Coriolus versicolor polysaccharides (krestin), sizofiran, CM6271 and the like can be mentioned.

[0155] As the cytokine agonist, ubenimex and the like can be mentioned.

[0156] As the interleukin preparation, interleukin-2, teceleukin, interleukin-12 and the like can be mentioned.

[0157] As the antibody pharmaceutical agent, an immunomodulator, trastuzumab, rituximab, gemtuzumab ozogamicin, iburimumab tiuxetan, cetuximab, bevacizumab, caprpmab pendetide, capromab pendetide indium, pemetrexed disodium, yttrium 90 ibritumab tiuxetan, votumumab, humanized IL-6 receptor antibody, anti-TA226 human monoclonal antibody, F(ab') human antibody GAH, EMD72000, partuzumab, alemtuzumab, VEGF receptor FLT-1 antibody, KW-2871, humanized anti-GM2 antibody, humanized anti-GD2 antibody, KM2760, TRAIL receptor-2 monoclonal antibody, anti-TRAIL receptor DR5 antibody, TRAIL-R1mAb, humanized anti-HM1.24 antibody, humanized FasL antibody, humanized anti-CD26 monoclonal antibody, α -galactosylceramide, diphtheria toxin modified transferrin bond, CD47 mon-

oclonal antibody, anti-human melanoma monoclonal antibody, HoAKs-1 (anti-lung cancer monoclonal antibody) and the like can be mentioned.

[0158] As the angiogenesis inhibitor, gefitinib (Iressa), thalidomide, cetuximab, semaxanib, TSU-68, KRN633, KRN951, marimastat, S-3304, erlotinib hydrochloride, ZD6474, GW572016, S-3304, E7820, SU6668, E7080, NK4, TAS-101, lapatinib, priomastat, RPI-4610, thalidomide, WX-UK1, 2-methoxyestradiol, SG-292, FYK-1388 and the like can be mentioned.

[0159] As the intracellular tube formation inhibitor, TAC-01, E-7820 and the like can be mentioned.

[0160] As the cell proliferation inhibitor, imatinib mesylate, trastuzumab, rituximab, gemtuzumab, AHM, mubritinib/TAK-165, KW-2871, KM8969, CP-724714 and the like can be mentioned.

[0161] As the cell cycle regulator, Boltezomib (NF- κ B Activation inhibitor), histone deacetylase HDAC inhibitor (FK-228, SARA, CI-994, LAQ-824, pyroxamide, AN-9, PBA, MS-275 and the like), E-7070, flavopiritol, UCN-01, CGP41251, CCI-779, KT5555, HMN-214, Y-27632, vatalanib/PTK-787A, MGCD0130, temsirolimus, (R)-roscovitine, indisulam and the like can be mentioned.

[0162] As the apoptosis inducer, bortezomib, arglabin, R-115777, KW-2401, BMS-214662, tipifarnib, lonafarnib, arglabin, bexarotene, exisulind, glufosfamide, irofulven, MX-126374, MX-2167, GRN163, GM95, MST-312, (-)-EGCG (Teavigo) and the like can be mentioned.

[0163] As the cancer gene therapy agent, A-007, Ad/Q5-H-sDd, apaziquone, AVE-8062, MS-214662, combretastatin A-4, didox, dolastatin-10, ganglioside vaccine, GivaRex, ILX-23-7553, interleukins, itriglumide, KW-2401, MCC-465, miriplatin, MUC-1 vaccine, OSI-7904L, platelet factor 4, SR-271425, ZK-230211 and the like can be mentioned.

[0164] As other antitumor agents, anticancer agents, L-asparaginase, tretinoin, levoleucovorin calcium, celmoleukin, ¹¹¹In-pentetreotide, ibandronate sodium hydrate, aminolevulinic acid hydrochloride, ukrain, Stem cell factor, denileukin diftitox, menatetrenone, methoxsalen, trimetrexate glucuronate, IOR-R3, everolimus, cytokeatin 19, doxercalciferol, alitretinoin, bexarotene, verteporfin, morphine sulfate sustained-release, Bacillus Calmette Guerin, megestrol acetate, menadione, floxuridine, thyrotropin alfa, inositol hexaphosphate, augmerosen, Thio TEPA, chorionic gonadotropin, histamine dihydrochloride, lycopene, talaporfin sodium, tasonermin, arsenic trioxide, levamisole hydrochloride, folic acid, teniposide, mebendazole, morphine hydrochloride, ALA Me ester, anethole dithiolethion, testosterone propionate, cinalcacet hydrochloride, anethole dithiolethione, testosterone, mitotane, sodium thiosulfate, zevalin, bexxar, salmon calcitonin, novobiocin, aminoglutethimide, eflornithine hydrochloride, lonidamine, amoxnox, pirarubicin, vesnarinone, pamidronate sodium, clodronate disodium, zoledronic acid monohydrate, ambamustine hydrochloride, ubestatin, amifostine hydrate, deoxyspergualin hydrochloride, pentostatin, bisantrene, peplomycin, iobenguane, amsacrine, trilostane, tramadol hydrochloride, elliptinium acetate, ladakamycin, bromebrate sodium, nitracrin dihydrochloride hydrate, altretamine, OROS-oxydone, fentanyl citrate, aspirin, AERx Morphine sulfate, carmustine, metoclopramide hydrochloride, loperamide hydrochloride, nilutamide, polysaccharide K, ranimustine, atvogen, pipobroman, imiquimod (interferon inducers), cladribine, tibolone, suramin sodium, leflunomide, fentanyl, octreotide acetate, inositol, ursodiol, feverfew, lentinan, tetranabinex, (cannabinoid receptor agonists), pegaspargase, triclosan, carbohydrate antigen 19-9, angiopeptin acetate, fotemustine, gallium nitrate, trabectebin, raltitrexed, zinostatin stimalamer, hexadecylphosphocholine, tazarotene, finasteride, clofarabine, temoporfin, SY-801, human angiotensin II, efaproxiral sodium, amonafide (DNA-Intercalating Drug), SP-1053C (DNA-Intercalating Drug), antineoplaston AS2-1, fenretinide (retinoids), trabectebin, mammastatin, DOS-47, ECO-04601, thymectacin, rhIGFBP-3, carboxyamidotriazole, CoFactor, davanat-1, tariquidar, ONT-093, minobronic acid, minodronic acid, dofequidar fumarate (MDR-1 inhibitors), tariquidar (MDR-1 Inhibitors), Davanat-1, ranpirnase, atrasentan, meclintertant, tacediniline, troxacitabine, DN-101, EB-1627, ACO-04601, MX-116407, STA-4783, Davanat-1, moverastin, mitoxantrone hydrochloride, procarbazine hydrochloride, octreotide acetate, porfimer sodium, pentostatin, cladribine, sobuzoxane, tretinoin, aceglatone, mitotane, porfimer sodium, elliptinium Acetate, AZD6126, tirapazamine, Bay43-9006, tipifarnib/R115777, midostaurin, BMS-214662, EKB-569, E7107, CBP501, HMN-214, FK-866, WF-536, SU-11248, MKT-077, phenoxodiol, NSC-330507, G-CSF, Edrecolomab (Monoclonal Antibodies), satumomab, sargramostin (GM-CSF), tamibarotene (retinoid derivative), arsenic trioxide, dutasteride, menatetrenone, ZD4054, NIK-333, NS-9, ABT-510, S-2678, methioninase, TAS-105, metastin, TOP-008, NCO-700, BCA and the like can be mentioned.

[0165] As "other antitumor agents" used for the multiple drug therapy with the compound of the present invention, platinum complex, alkylating agent and metabolism antagonist are preferable. It is possible to use 2 or 3 or more pharmaceutical agents in combination, wherein a combination of pharmaceutical agents having different action mechanism is one of the preferable embodiments. Moreover, selection of pharmaceutical agents having non-overlapping side effects is preferable.

[0166] For a combined use of the compound of the present invention with "other antitumor agents", these two or more kinds of compounds may be contained in the same composition. In addition, a composition containing the compound of the present invention and a composition containing "other antitumor agents" may be simultaneously or sequentially administered.

[0167] When two agents are simultaneously administered, "simultaneous" includes administration of 2 agents, with administration of one agent and then the other agent in several minutes after the first administration. By "sequentially"

is meant a lapse of a given time. For example, administration of the other agent several minutes to several dozen minutes after the administration of the first agent, and administration of the other agent several hours to several days after the administration of the first agent are included, wherein the lapse of time is not limited. For example, one agent may be administered once a day, and the other agent may be administered 2 or 3 times a day, or one agent may be administered once a week, and the other agent may be administered once a day and the like.

[0168] When the compound of the present invention is used as an antitumor agent, and when the compound of the present invention is used in combination with "other antitumor agents", radiotherapy, activation lymphocyte therapy and the like may be further added.

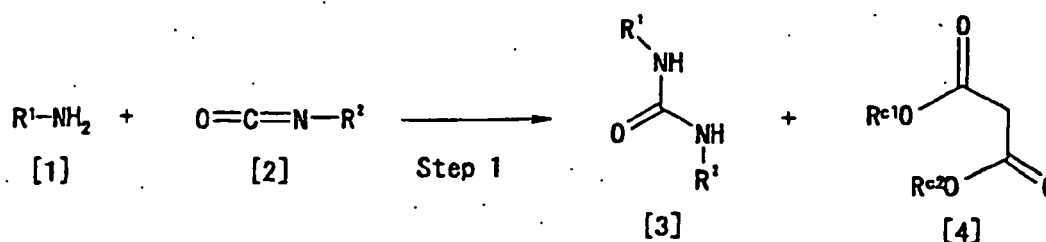
[0169] Some examples of the Production Methods of the compound used for embodiment of the present invention are shown in the following. However, the Production Methods of the compound of the present invention are not limited to these examples.

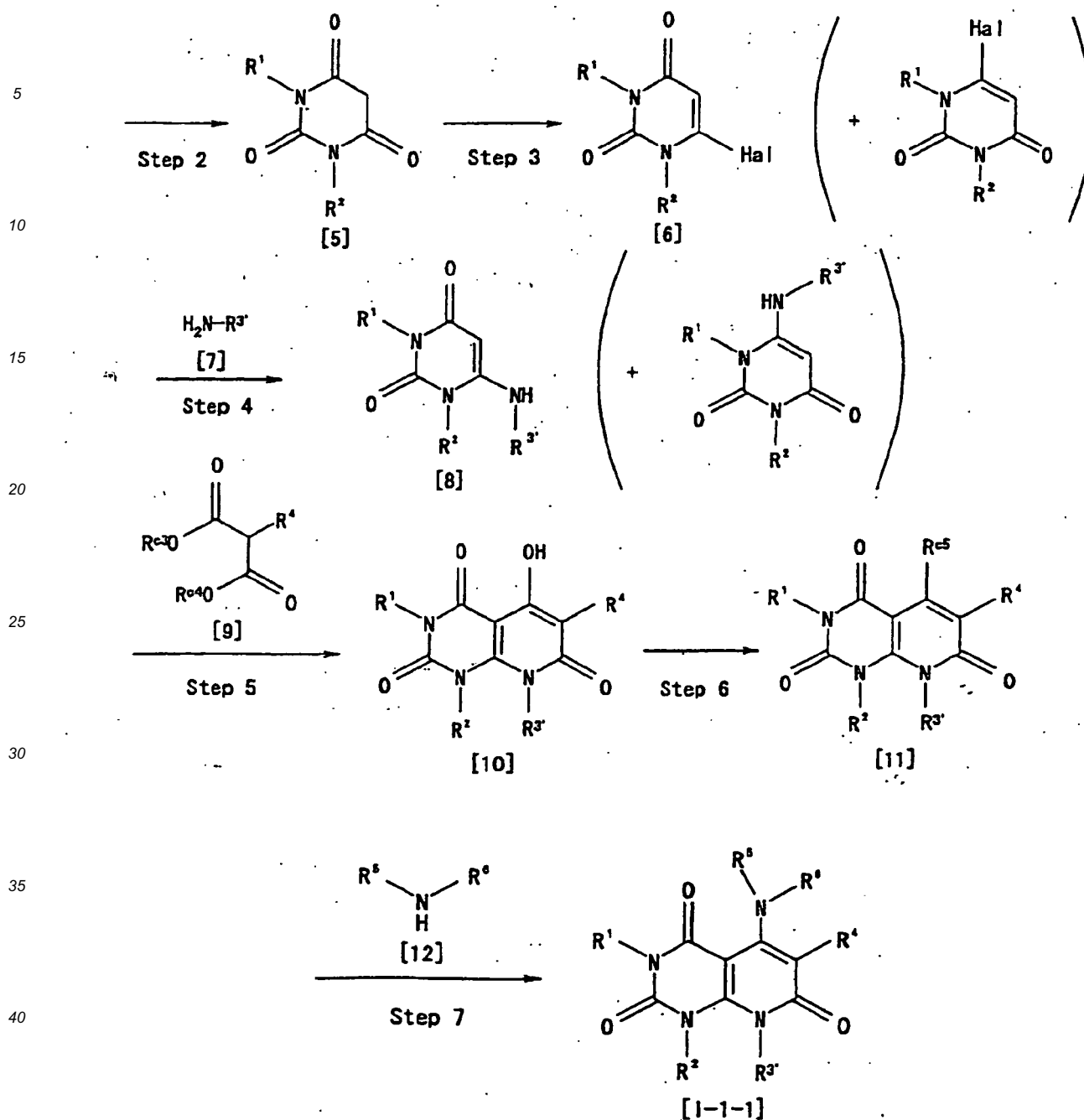
[0170] Even in the absence of description in the Production Methods, efficient production can be afforded by designs such as introducing, where necessary, a protecting group into a functional group followed by deprotection in a subsequent step; subjecting a functional group to each step as a precursor and converting the group to a desired functional group in a suitable step; exchanging the order of respective Production Methods and steps; and the like.

[0171] The work-up treatment in each step can be applied by a typical method, wherein isolation and purification is performed as necessary by selecting or combining conventional methods, such as crystallization, recrystallization, distillation, partitioning, silica gel chromatography, preparative HPLC and the like.

Production Method 1

[0172]





wherein Hal is a halogen atom such as chlorine atom, bromine atom and the like, R^{c1} , R^{c2} , R^{c3} and R^{c4} are the same or different and each is a hydrogen atom or the above-defined "C₁₋₆ alkyl group", R^3 is R³ other than a hydrogen atom, R^{c5} is a leaving group such as a halogen atom, p-toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy and the like, and other symbols are as defined above.

Step 1

[0173] The compound [3] can be obtained by reacting compound [1] with compound [2] in a solvent preferably under a nitrogen atmosphere from cooling to room temperature.

[0174] As the solvent, ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran (THF) and the like; hydrocarbon solvents such as benzene, toluene, xylene, hexane and the like; and the like can be mentioned.

Step 2

[0175] The compound [5] can be obtained by reacting compound [3] with compound [4] in a solvent preferably under a nitrogen atmosphere under heating.

[0176] As the solvent, acetic anhydride, acetyl chloride, phosphorus oxychloride and the like can be mentioned.

Step 3

[0177] Here, Hal is preferably a bromine atom or chlorine atom. The compound [6] can be obtained by reacting compound [5] with a halogenating agent such as phosphorus oxychloride, N-bromosuccinimide, N-iodosuccinimide and the like, in a solvent such as trifluoromethanesulfonic acid, acetic acid, concentrated sulfuric acid, N,N-dimethylformamide (DMF), water and the like, at room temperature to under heating.

Step 4

[0178] The compound [8] can be obtained by reacting compound [6] with compound [7] in a solvent under heating.

[0179] As the solvent, alcohol solvents such as water-containing or nonaqueous methanol, ethanol and the like; ether solvents such as 1,4-dioxane, tetrahydrofuran (THF) and the like, and the like can be mentioned.

Step 5

[0180] The compound [10] can be obtained by reacting compound [8] with compound [9] in a solvent under heating.

[0181] As the solvent, ether solvents such as diphenylether and the like; acetic anhydride, acetyl chloride and the like can be mentioned.

Step 6

[0182] The compound [11] can be obtained by introducing a leaving group into compound [10] by a conventional method.

[0183] For example, compound [11] can be obtained by reacting compound [10] with methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride and the like, in the presence of base such as trimethylamine hydrochloride, triethylamine, pyridine and the like as necessary in a solvent.

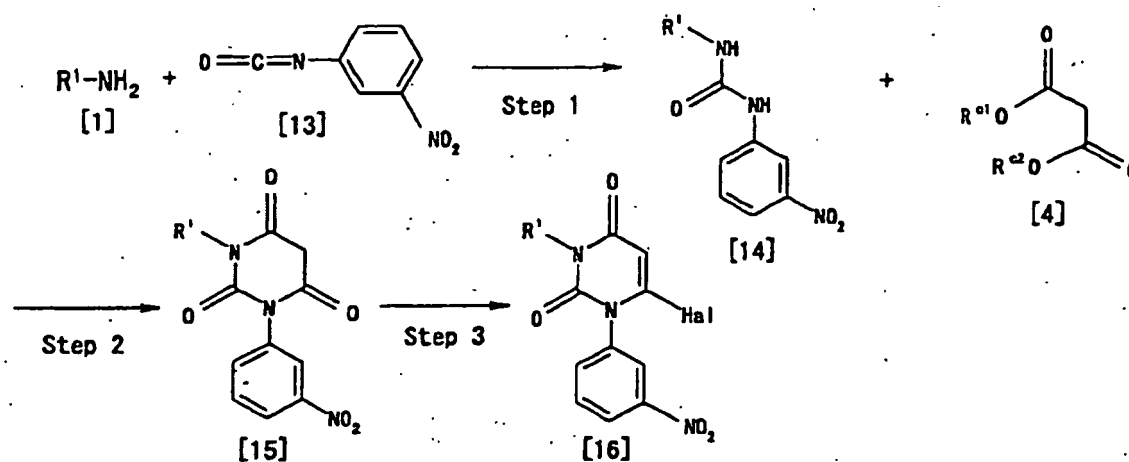
[0184] As the solvent, acetonitrile; ether solvents such as tetrahydrofuran and the like; halogen solvents such as dichloromethane and the like, and the like can be mentioned.

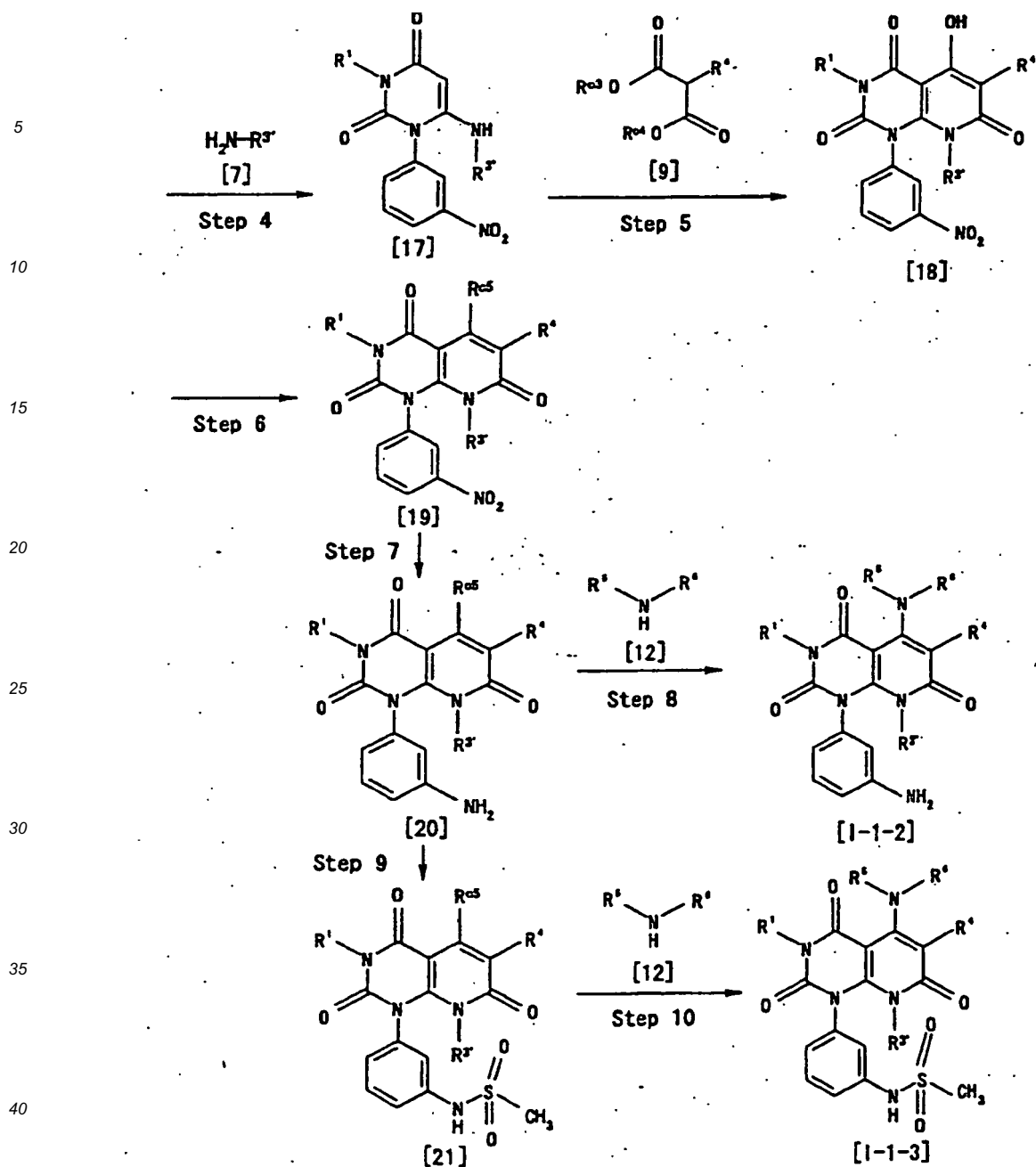
Step 7

[0185] The compound [I-1-1] can be obtained by reacting compound [11] with compound [12] under heating as necessary in a solvent. As the solvent, N,N-dimethylacetamide, chloroform and the like can be mentioned.

[0186] To improve reaction efficiency, 2,6-lutidine may be added.

[0187] Production Method 1-1





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45 wherein each symbol is as defined above.

Step 1

50 [0188] The compound [14] can be obtained by reacting compound [1] with compound [13] in the same manner as in Production Method 1, Step 1.

Step 2

55 [0189] The compound [15] can be obtained by reacting compound [14] with compound [4] in the same manner as in Production Method 1, Step 2.

Step 3

5 **[0190]** The compound [16] can be obtained by reacting compound [15] in the same manner as in Production Method 1, Step 3.

Step 4

10 **[0191]** The compound [17] can be obtained by reacting compound [16] with compound [7] in the same manner as in Production Method 1, Step 4.

Step 5

15 **[0192]** The compound [18] can be obtained by reacting compound [17] with compound [9] in the same manner as in Production Method 1, Step 5.

Step 6

20 **[0193]** The compound [19] can be obtained by reacting compound [18] in the same manner as in Production Method 1, Step 6.

Step 7

25 **[0194]** The compound [20] can be obtained by reducing compound [19] by a conventional method such as reduction with zinc or iron in a neutral or alkaline condition; iron and acid; tin or tin (II) chloride and concentrated hydrochloric acid; alkali sulfide; alkaline hydrosulfite and the like, or hydrogenation under hydrogen atmosphere and the like.

30 **[0195]** For example, compound [20] can be obtained by adding acetic acid and zinc powder to compound [19] under cooling to allow to react at room temperature. Alternatively, compound [20] can be obtained by adding palladium-carbon to a solution of compound [19] in a mixed solvent of THF and methanol under hydrogen atmosphere to allow to react at room temperature.

Step 8

35 **[0196]** The compound [I-1-2] can be obtained by reacting compound [20] with compound [12] in the same manner as in Production Method 1, Step 7.

Step 9

40 **[0197]** The compound [21] can be obtained by reacting compound [20] with methanesulfonyl chloride in a solvent in the presence of base such as triethylamine, pyridine and the like under cooling.

[0198] As the solvent, acetonitrile; ether solvents such as tetrahydrofuran and the like; halogen solvents such as dichloromethane and the like, and the like can be mentioned.

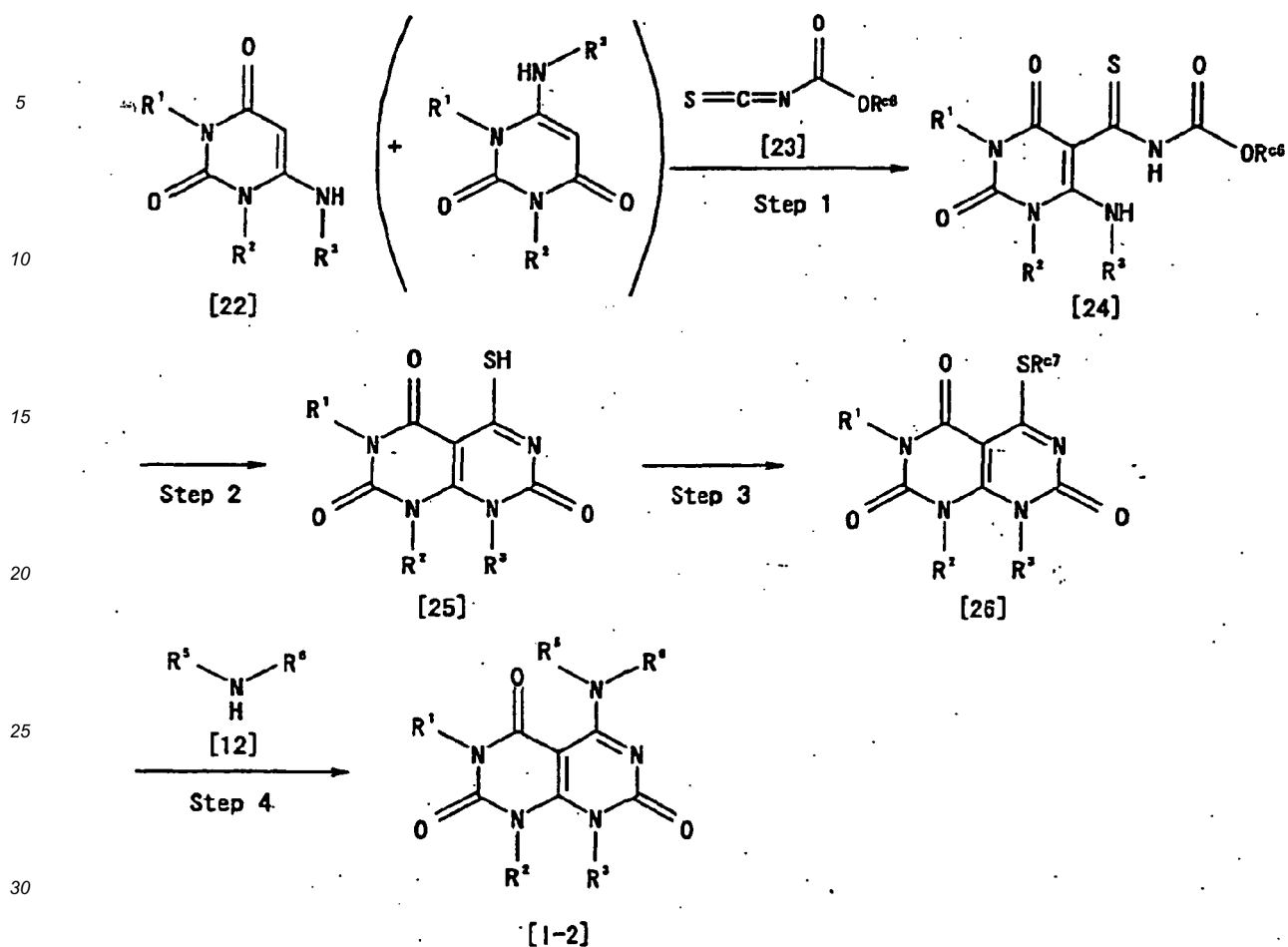
Step 10

45 **[0199]** The compound [I-1-3] can be obtained by reacting compound [21] with compound [12] in the same manner as in Production Method 1, Step 7.

Production Method 2

50 **[0200]**

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wherein R^{c6} is a hydrogen atom or an C_{1-4} alkyl group, SR^{c7} (R^{c7} is lower alkyl such as methyl, ethyl and the like or benzyl) is a leaving group, and other symbols are as defined above.

Step 1

[0201] The compound [24] can be obtained by reacting compound [22] obtained in the same manner as in Production Method 1, Step 1 to Step 4 with compound [23].

Step 2

[0202] The compound [25] can be obtained by cyclizing compound [24] by a conventional method. For example, compound [25] can be obtained by stirring compound [24] in a solvent such as *N,N*-dimethylformamide and the like in the presence of triethylamine at room temperature.

Step 3

[0203] The compound [26] can be obtained by reacting compound [25] with lower alkyl halide or benzyl halide in the presence of base.

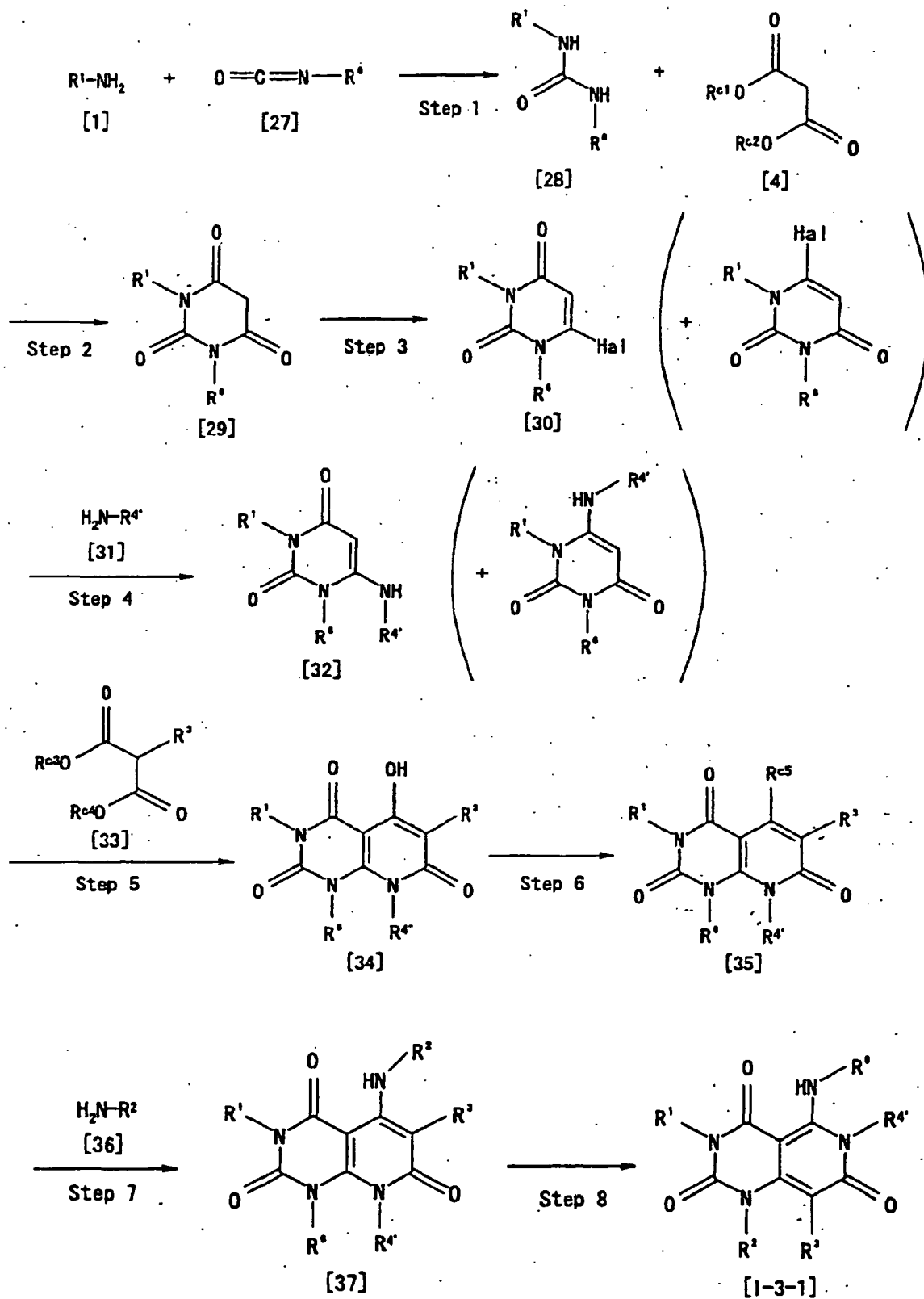
[0204] As the base, potassium carbonate, sodium carbonate, lithium hydride, sodium hydride, potassium hydride and the like can be mentioned, potassium carbonate is preferable.

[0205] As the lower alkyl halide, methyl iodide, ethyl iodide, benzyl iodide and the like can be mentioned, methyl iodide is preferable.

Step 4

[0206] The compound [1-2] can be obtained by reacting compound [26] with compound [12] in the same manner as in Production Method 1, Step 7.

[0207] Production Method 3



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wherein R⁴ is R⁴ other than a hydrogen atom, and other symbols are as defined above.

Step 1

5 **[0208]** The compound [28] can be obtained by reacting compound [1] with compound [27] in the same manner as in Production Method 1, Step 1.

Step 2

10 **[0209]** The compound [29] can be obtained by reacting compound [28] with compound [4] in the same manner as in Production Method 1, Step 2.

Step 3

15 **[0210]** The compound [30] can be obtained by reacting compound [29] in the same manner as in Production Method 1, Step 3.

Step 4

20 **[0211]** The compound [32] can be obtained by reacting compound [30] with compound [31] in the same manner as in Production Method 1, Step 4.

Step 5

25 **[0212]** The compound [34] can be obtained by reacting compound [32] with compound [33] in the same manner as in Production Method 1, Step 5.

Step 6

30 **[0213]** The compound [35] can be obtained by reacting compound [34] in the same manner as in Production Method 1, Step 6.

Step 7

35 **[0214]** The compound [37] can be obtained by reacting compound [35] with compound [36] in the same manner as in Production Method 1, Step 7.

Step 8

40 **[0215]** The compound [I-3-1] can be obtained by stirring compound [37] in a solvent, in the presence of base at room temperature to under reflux.

[0216] As the base, potassium carbonate, sodium carbonate, lithium hydride, sodium hydride, potassium hydride, sodium methoxide and the like can be mentioned, potassium carbonate and sodium methoxide are preferable.

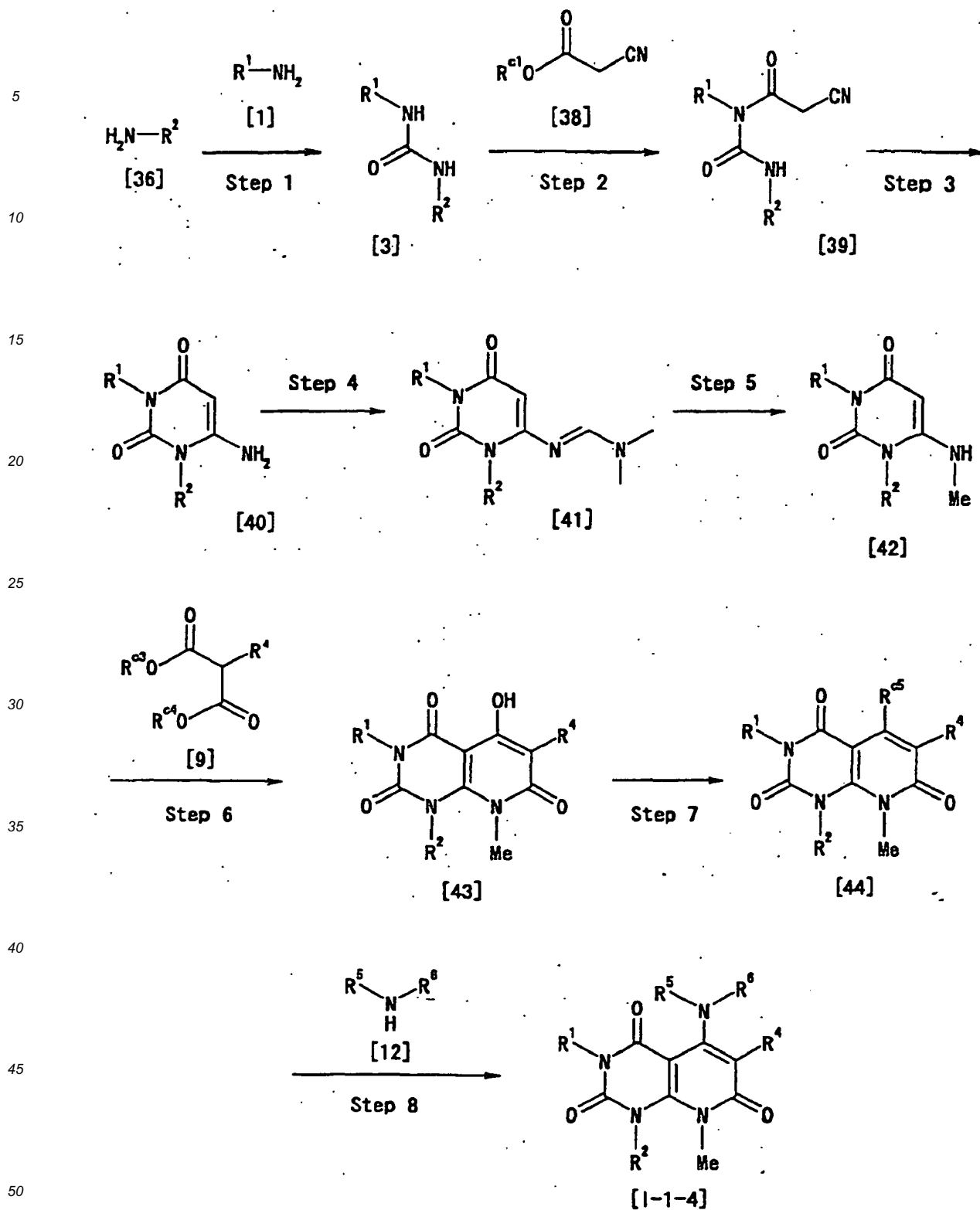
45 **[0217]** As the solvent, alcohol solvents such as methanol, ethanol, n-propanol, isopropanol and the like; mixed solvents of these solvent and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, halogen solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like or ether solvents such as tetrahydrofuran (THF) and the like, and the like can be mentioned.

Production Method 4-1

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[0218]

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wherein each symbol is as defined above.

55 Step 1

[0219] The compound [3] can be obtained by reacting compound [36] with carbonyldiimidazole in a solvent in the presence of tertiary amine such as triethylamine and the like under nitrogen or argon atmosphere from cooling to room

temperature, and then reacting with compound [1].

[0220] As the solvent, N,N-dimethylformamide, chloroform, dichloromethane, tetrahydrofuran and the like can be mentioned.

5 Step 2

[0221] The compound [39] can be obtained by acylating compound [3] with compound [38] preferably under a nitrogen atmosphere by a conventional method.

10 **[0222]** For example, when R^{c1} is hydrogen, compound [38] can be condensed with compound [3] using acetic anhydride, acetyl chloride, pivaloyl chloride, methanesulfonyl chloride and the like, particularly methanesulfonyl chloride in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide and the like.

Step 3

15 **[0223]** The compound [40] can be obtained by reacting compound [39] in a solvent in the presence of base at room temperature to heating temperature.

[0224] As the solvent, water, ethanol-water, tetrahydrofuran-water and the like can be mentioned, water is preferable.

20 **[0225]** As the base, potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, lithium hydride, sodium hydride, potassium hydride and the like can be mentioned, sodium hydroxide is preferable.

Step 4

25 **[0226]** The compound [41] can be obtained by reacting compound [40] with N,N-dimethylformamide dimethylacetal in a N,N-dimethylformamide solvent preferably under a nitrogen atmosphere.

Step 5

[0227] The compound [42] can be obtained by reducing compound [41] by a conventional method.

30 **[0228]** For example, compound [42] can be obtained by treating with a reducing agent such as sodium borohydride, sodium cyanoborohydride and the like in an alcohol solvent such as methanol, ethanol, isopropanol, tert-butanol and the like or a mixed solvent thereof under a nitrogen atmosphere.

Step 6

35 **[0229]** The compound [43] can be obtained by reacting compound [42] with compound [9] in the same manner as in Production Method 1, Step 5.

Step 7

40 **[0230]** The compound [44] can be obtained by reacting compound [43] in the same manner as in Production Method 1, Step 6.

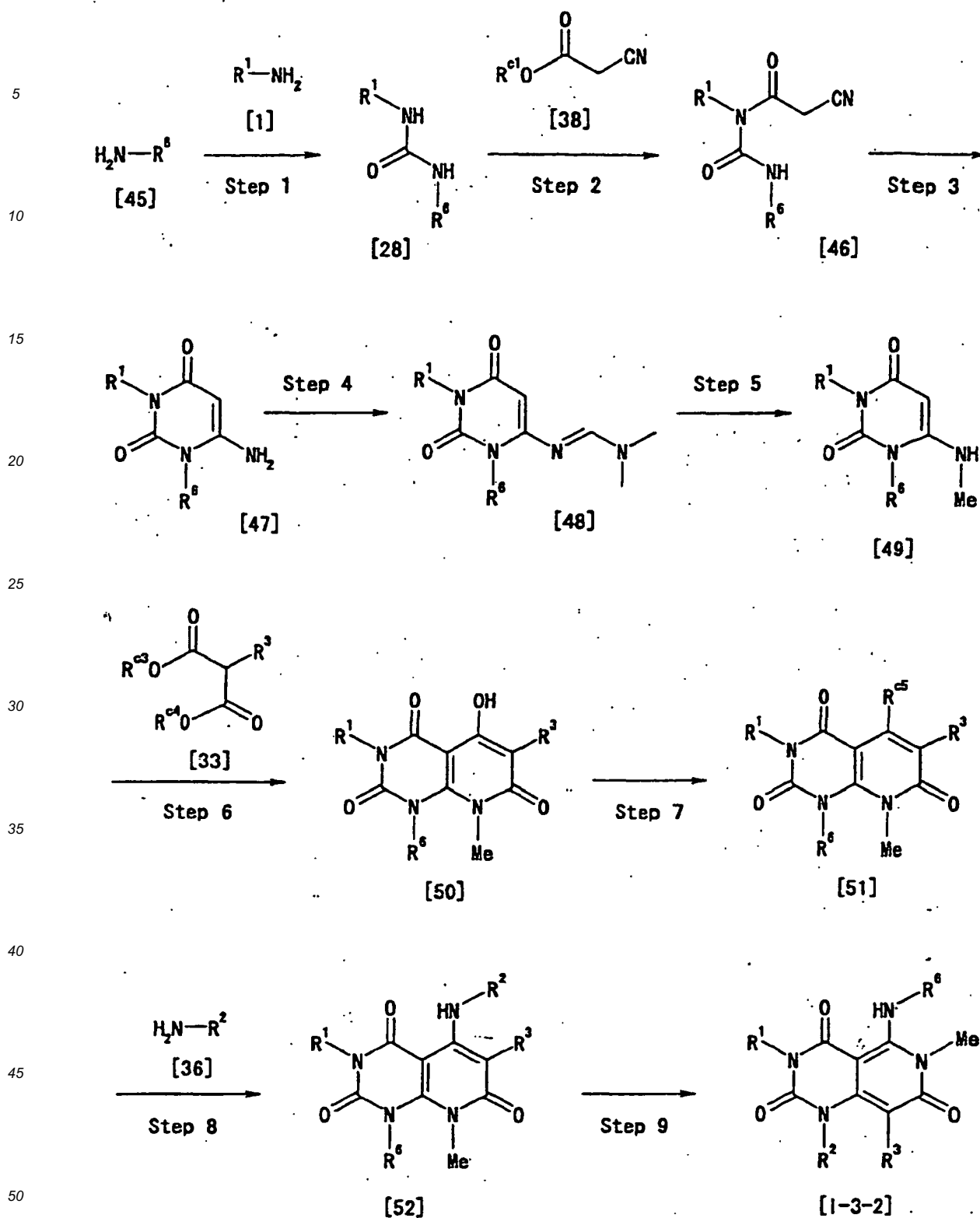
Step 8

45 **[0231]** The compound [I-1-4] can be obtained by reacting compound [44] with compound [12] in the same manner as in Production Method 1, Step 7.

[0232] Production Method 4-2

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wherein each symbol is as defined above.

55 Step 1

[0233] The compound [28] can be obtained by reacting compound [45] with compound [1] in the same manner as in Production Method 4-1, Step 1.

Step 2

[0234] The compound [46] can be obtained by reacting compound [28] with compound [38] in the same manner as in Production Method 4-1, Step 2.

Step 3

[0235] The compound [47] can be obtained by reacting compound [46] in the same manner as in Production Method 4-1, Step 3.

Step 4

[0236] The compound [48] can be obtained by reacting compound [47] in the same manner as in Production Method 4-1, Step 4.

Step 5

[0237] The compound [49] can be obtained by reacting compound [48] in the same manner as in Production Method 4-1, Step 5.

Step 6

[0238] The compound [50] can be obtained by reacting compound [49] with compound [33] in the same manner as in Production Method 1, Step 5.

Step 7

[0239] The compound [51] can be obtained by reacting compound [50] in the same manner as in Production Method 1, Step 6.

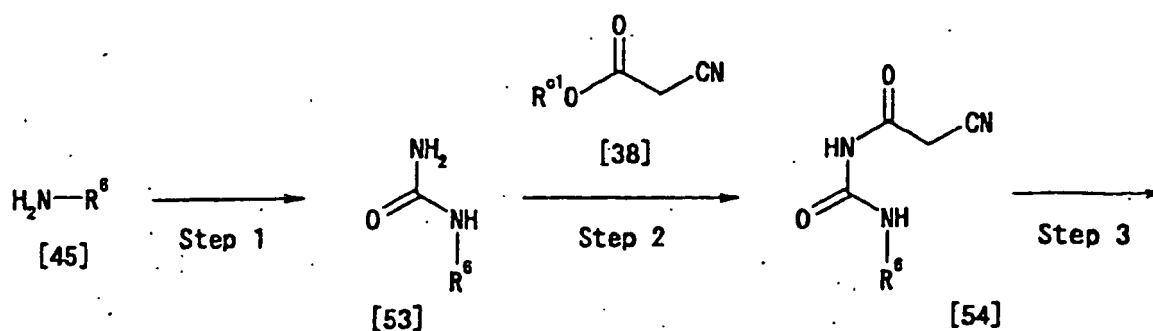
Step 8

[0240] The compound [52] can be obtained by reacting compound [51] with compound [36] in the same manner as in Production Method 1, Step 7.

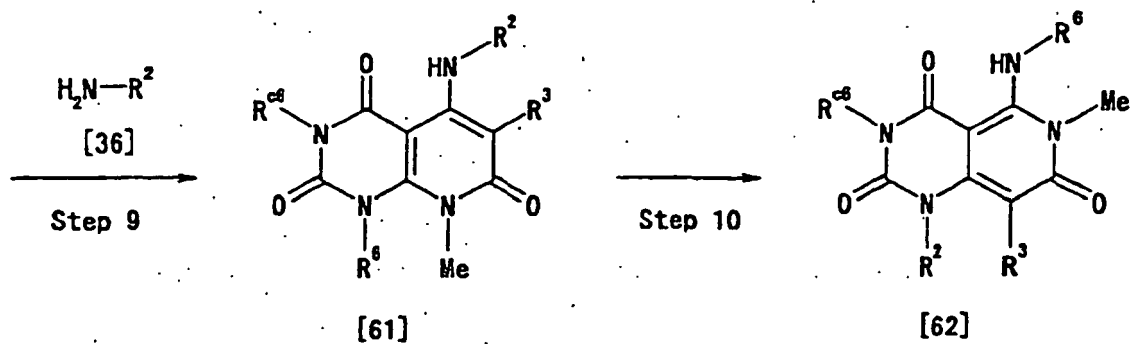
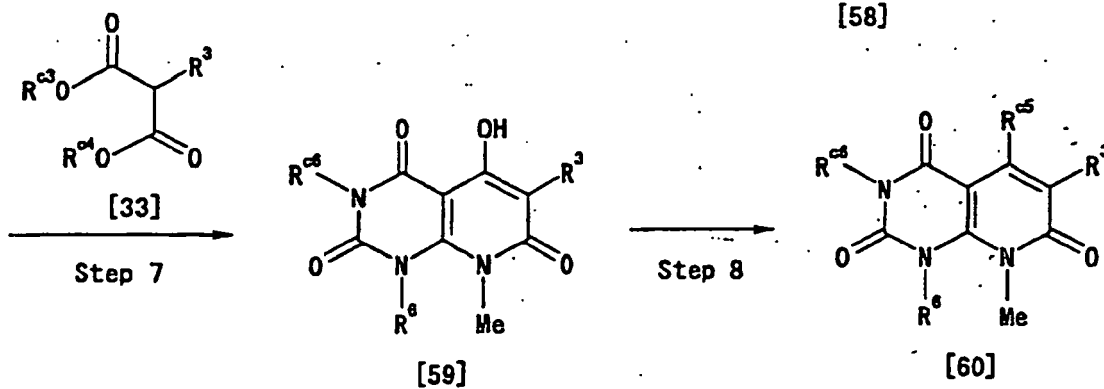
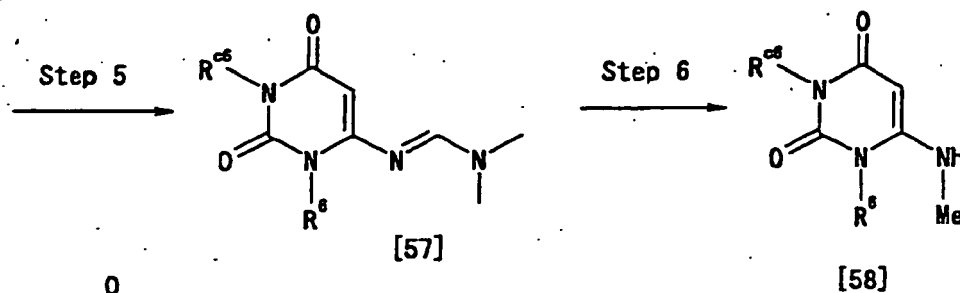
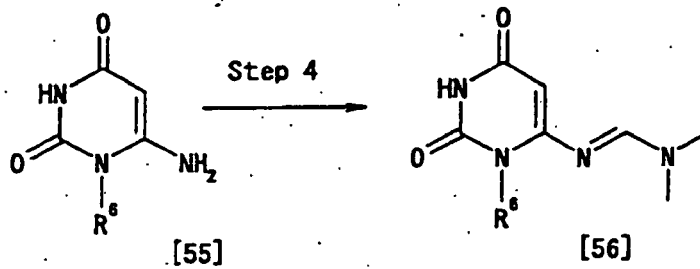
Step 9

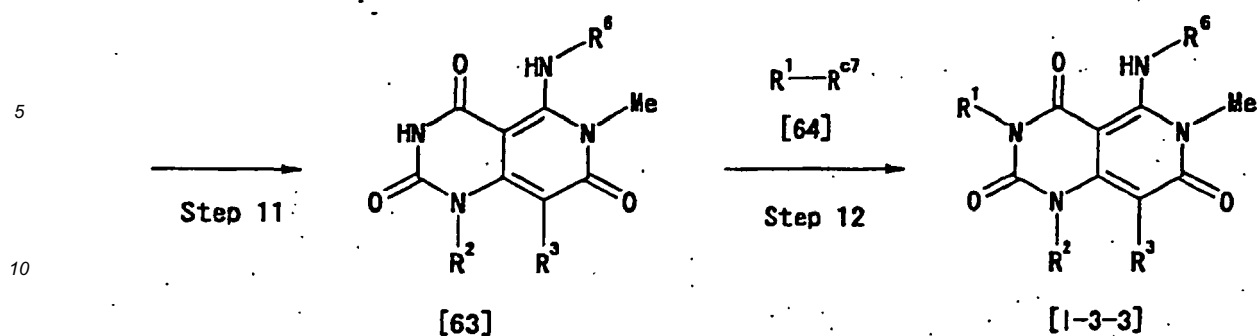
[0241] The compound [I-3-2] can be obtained by reacting compound [52] in the same manner as in Production Method 3, Step 8.

[0242] Production Method 4-3



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15 wherein R^{c7} is a halogen atom such as bromine atom, chlorine atom and the like or a hydroxyl group and the other symbols are as defined above.

Step 1

20 [0243] The compound [53] can be obtained by reacting compound [45] with carbonyldiimidazole in a solvent in the presence of tertiary amine such as triethylamine and the like under a nitrogen or argon atmosphere from cooling to room temperature, and then reacting with ammonia.

[0244] As the solvent, N,N-dimethylformamide, chloroform, dichloromethane, tetrahydrofuran and the like can be mentioned.

25 Step 2

[0245] The compound [54] can be obtained by reacting compound [53] with compound [38] in the same manner as in Production Method 4-1, Step 2.

30 Step 3

[0246] The compound [55] can be obtained by reacting compound [54] in the same manner as in Production Method 4-1, Step 3.

35 Step 4

[0247] The compound [56] can be obtained by reacting compound [55] in the same manner as in Production Method 4-1, Step 4.

40 Step 5

[0248] The compound [57] can be obtained by introducing a protecting group into compound [56] by a conventional method.

45 Step 6

[0249] The compound [58] can be obtained by reacting compound [57] in the same manner as in Production Method 4-1, Step 5.

50 Step 7

[0250] The compound [59] can be obtained by reacting compound [58] with compound [33] in the same manner as in Production Method 1, Step 5.

55 Step 8

[0251] The compound [60] can be obtained by reacting compound [59] in the same manner as in Production Method 1; Step 6.

Step 9

[0252] The compound [61] can be obtained by reacting compound [60] with compound [36] in the same manner as in Production Method 1, Step 7.

Step 10

[0253] The compound [62] can be obtained by reacting compound [61] in the same manner as in Production Method 3, Step 8.

Step 11

[0254] The compound [63] can be obtained by deprotecting compound [62] by a conventional method.

Step 12

[0255] The compound [I-3-3] can be obtained by reacting compound [63] with compound [64] by a conventional method.

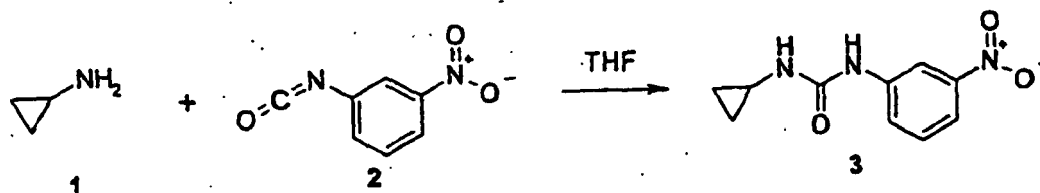
[0256] For example, when R⁷ is a hydroxyl group, compound [63] is reacted with a condensing agent such as diethyl azodicarboxylate, diisopropyl azodicarboxylate and the like and triphenylphosphine in a solvent such as N,N-dimethylformamide, acetonitrile, tetrahydrofuran and the like under a nitrogen or argon atmosphere according to Mitsunobu reaction.

Examples

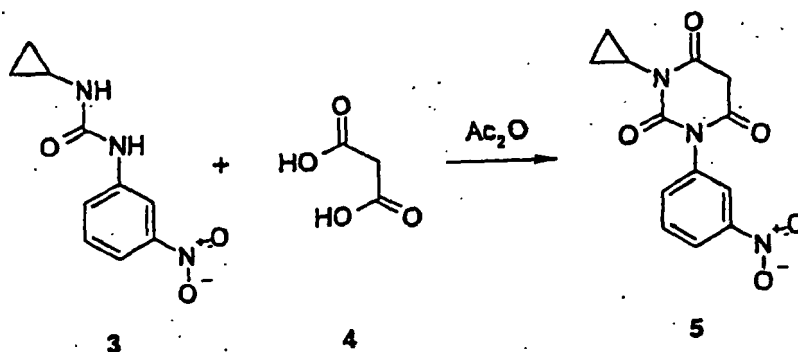
Example 1-1

Synthesis of N-{3-[5-(4-bromo-2-fluoro-phenylamino)-3-cyclopropyl-8-methyl-2,4,7-trioxo-3,4,7,8-tetrahydro-2H-pyrido[2,3-d]pyrimidin-1-yl]phenyl}-methanesulfonamide Step 1 Synthesis of 1-cyclopropyl-3-(nitrophenyl)urea

[0257]



[0258] To a solution of cyclopropylamine 1 (9 g) in tetrahydrofuran (250 ml) was added 3-nitrophenylisocyanate 2 (25 g) by small portions, and the mixture was stirred at room temperature for 1 hr. The solid precipitated from the reaction nature was filtered by suction, washed with ethyl acetate, and dried to give 1-cyclopropyl-3-(nitrophenyl) urea 3 (33 g, 99%) as a yellow solid. Step 2 Synthesis of 1-cyclopropyl-3-(3-nitrophenyl)pyrimidine-2,4,6-trione

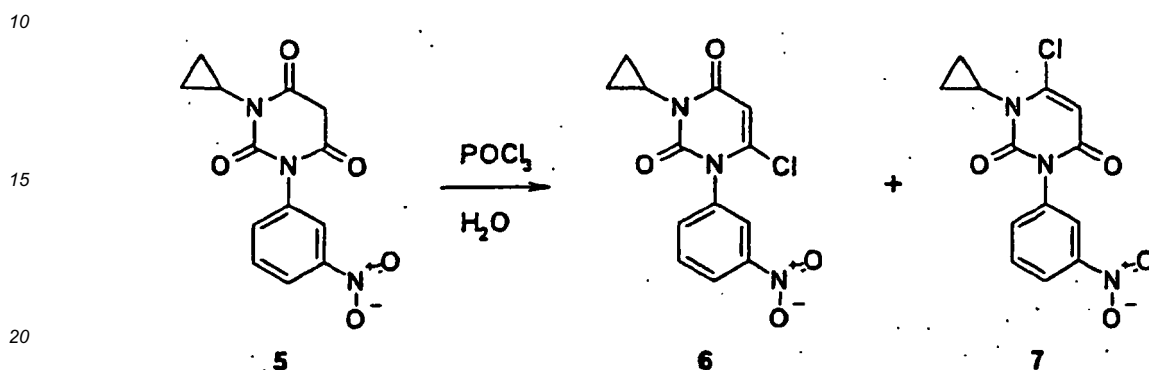


[0259] To 1-cyclopropyl-3-(nitrophenyl)urea 3 (33 g) obtained in Step 1 were added acetic anhydride (99 ml) and

malonic acid **4** (17 g), and the mixture was stirred under heating at 110°C for 4 hrs. The reaction mixture was concentrated under reduced pressure. Chloroform was added to the residue, and the mixture was stirred at room temperature for 10 min. Chloroform insoluble material was filtered by suction and dried to give 1-cyclopropyl-3-(3-nitrophenyl)pyrimidine-2,4,6-trione **5** (28 g, 65%) as a brown solid.

Step 3 Synthesis of 6-chloro-3-cyclopropyl-1-(3-nitrophenyl)-1H-pyrimidine-2,4-dione

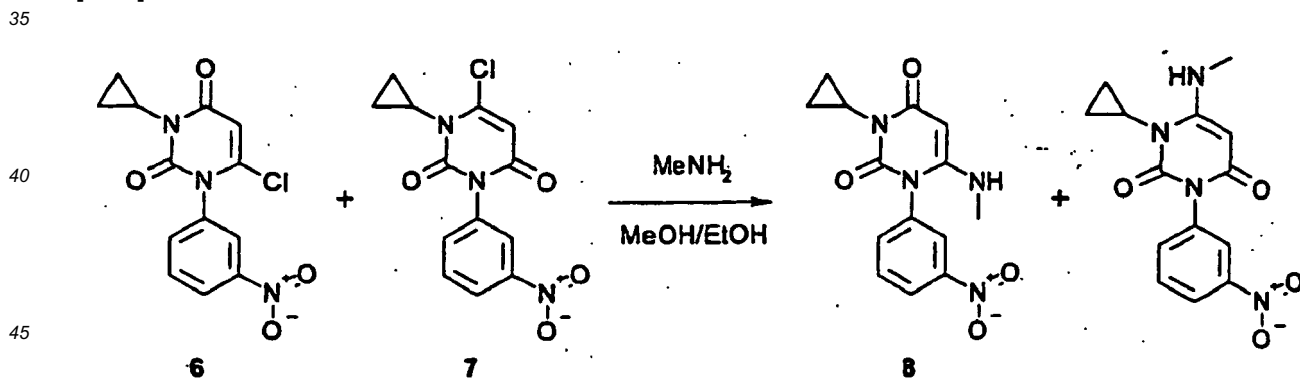
[0260]



[0261] To 1-cyclopropyl-3-(3-nitrophenyl)pyrimidine-2,4,6-trione **5** (28 g) obtained in Step 2 was added water (3 ml), phosphorus oxychloride (72 ml) was added dropwise by small portions with stirring, and the mixture was stirred with heating at 110°C for 1 hr. The reaction mixture was poured into ice water by small portions, and the precipitated solid was filtered by suction. The filtrate was dissolved in chloroform (300 ml), washed with water (30 ml) and brine (30 ml), and the organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (chloroform : acetone=9:1) to give a 2:1 mixture (10 g, 34%) of 6-chloro-3-cyclopropyl-1-(3-nitrophenyl)-1H-pyrimidine-2,4-dione **6** and 4-chloro-3-cyclopropyl-1-(3-nitrophenyl)-1H-pyrimidine-2,6-dione **7** as a white solid.

Step 4 Synthesis of 3-cyclopropyl-6-methylamino-1-(3-nitrophenyl)-1H-pyrimidine-2,4-dione

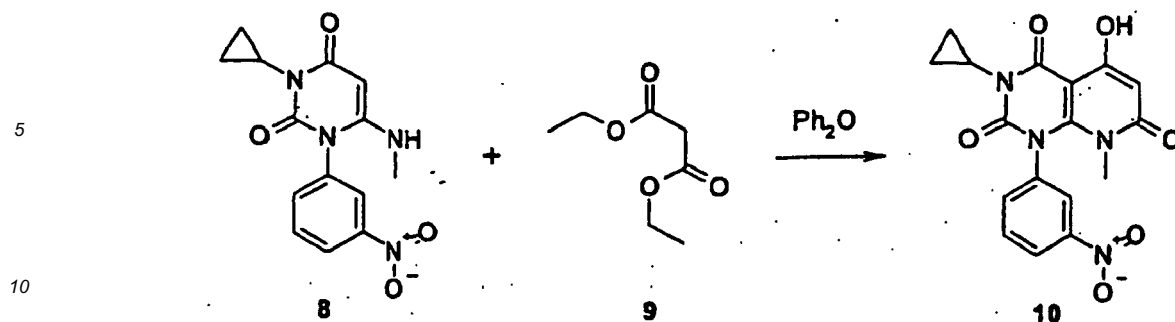
[0262]



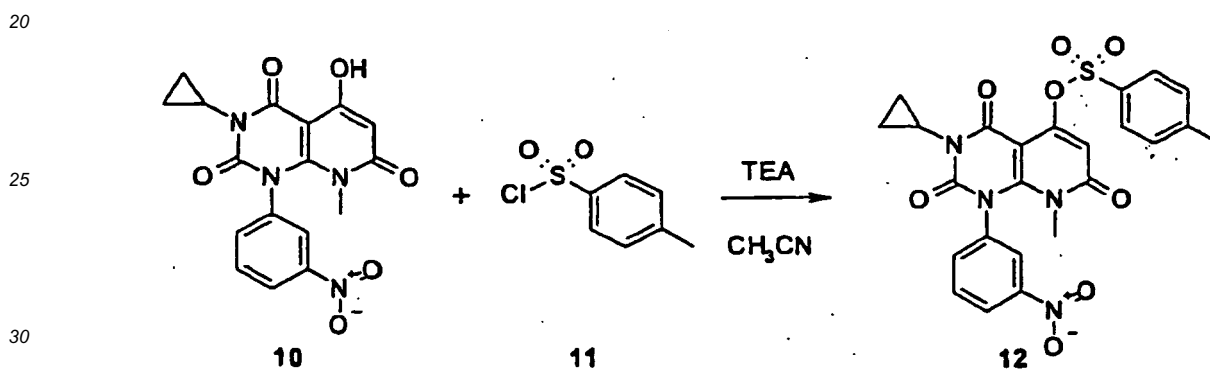
[0263] To the mixture (30 g) of 6-chloro-3-cyclopropyl-1-(3-nitrophenyl)-1H-pyrimidine-2,4-dione **6** and 4-chloro-3-cyclopropyl-1-(3-nitrophenyl)-1H-pyrimidine-2,6-dione **7** obtained in Step 3 were added ethanol (300 ml) and a 40% solution (150 ml) of methylamine in methanol, and the mixture was stirred with heating at 80°C for 4.5 hrs, ice-cooled and the precipitated solid was filtered by suction. The residue was washed with water (1 liter) and dried to give 3-cyclopropyl-6-methylamino-1-(3-nitrophenyl)-1H-pyrimidine-2,4-dione **8** (16 g, 55%) as a white solid.

Step 5 Synthesis of 3-cyclopropyl-5-hydroxy-8-methyl-1-(3-nitrophenyl)-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione

[0264]



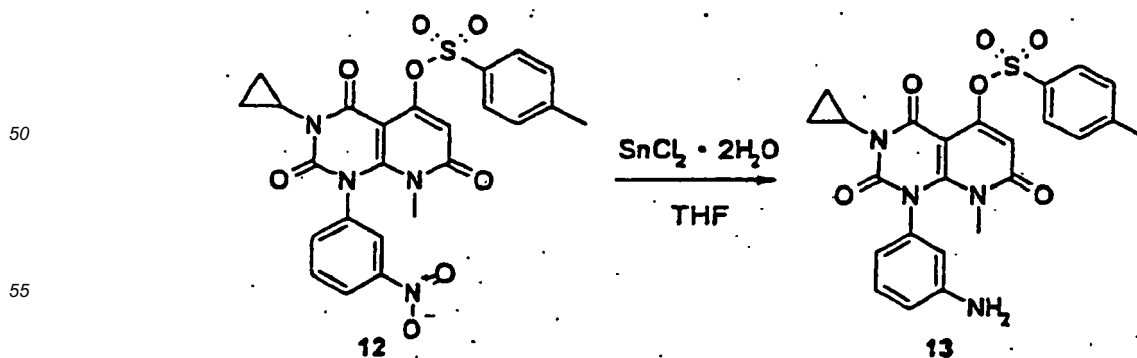
[0265] To 3-cyclopropyl-6-methylamino-1-(3-nitrophenyl)-1H-pyrimidine-2,4-dione **8** (16 g) obtained in Step 4 were added diphenyl ether (160 ml) and diethyl malonate **9** (40 ml), and the mixture was stirred under heating at 230°C for 11 hrs while evaporating the resulting ethanol. The reaction mixture was purified by column chromatography (chloroform→chloroform:acetone=9:1) to give 3-cyclopropyl-5-hydroxy-8-methyl-1-(3-nitrophenyl)-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione **10** (10 g, 51%) as a brown foamy oil. **Step 6** Synthesis of toluene-4-sulfonic acid 3-cyclopropyl-8-methyl-1-(3-nitrophenyl)-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl ester



[0266] To 3-cyclopropyl-5-hydroxy-8-methyl-1-(3-nitrophenyl)-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione **10**, (18 g) obtained in Step 5 were added acetonitrile (180 ml), tosyl chloride **11** (11 g) and triethylamine (8 ml), and the mixture was stirred with heating under reflux at 110°C for 1 hr. The reaction mixture was concentrated under reduced pressure. Water (100 ml) was added to the residue and the mixture was extracted with chloroform (800 ml). The organic layer was washed with brine (50 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from chloroform: diethyl ether=1:5 to give toluene-4-sulfonic acid 3-cyclopropyl-8-methyl-1-(3-nitrophenyl)-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester **12** (21 g, 82%) as a white solid.

Step 7 Synthesis of toluene-4-sulfonic acid 1-(3-aminophenyl)-3-cyclopropyl-8-methyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester

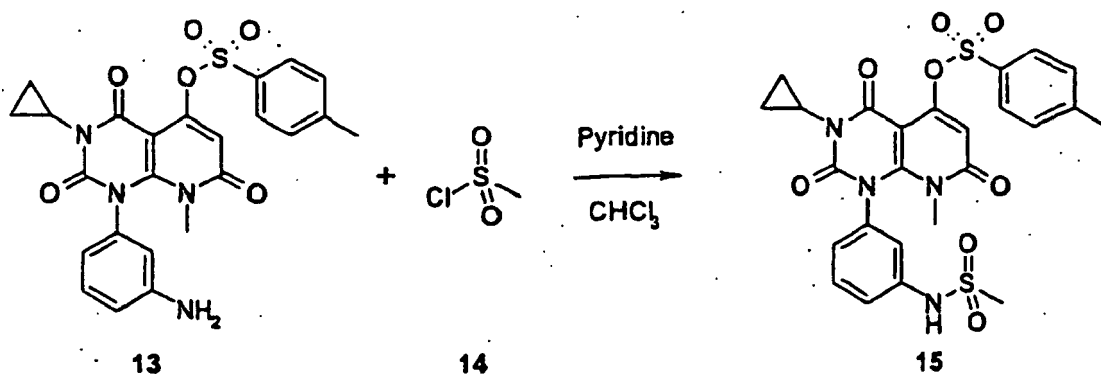
[0267]



[0268] To a suspension of toluene-4-sulfonic acid 3-cyclopropyl-8-methyl-1-(3-nitrophenyl)-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl ester **12** (21 g) obtained in Step 6 in tetrahydrofuran was added stannous chloride dihydrate (45 g), and the mixture was stirred at room temperature for 4 hrs. The reduction mixture was alkali-fied with saturated aqueous sodium hydrogen carbonate, an insoluble inorganic product was filtered off by suction using celite as a filter aid, and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (chloroform:acetone=9:1) to give toluene-4-sulfonic acid 1-(3-aminophenyl)-3-cyclopropyl-8-methyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester **13** (15 g, 74%) as a white solid.

Step 8 Synthesis of toluene-4-sulfonic acid 3-cyclopropyl-1-(3-methanesulfonylamino-phenyl)-8-methyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester

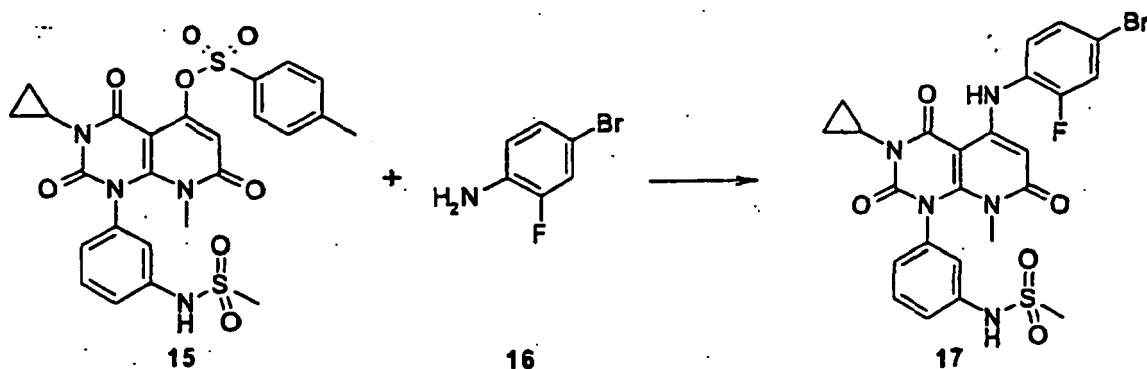
[0269]



[0270] To toluene-4-sulfonic acid 1-(3-aminophenyl)-3-cyclopropyl-8-methyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester **13** (5 g) obtained in Step 7 was added pyridine (40 ml), a solution of methanesulfonyl chloride **14** (0.9 ml) in chloroform (10 ml) was added dropwise with stirring under ice-cooling, and the mixture was stirred for 3 hrs in an ice bath. The reaction mixture was concentrated under reduced pressure, 2N hydrochloric acid was added and the mixture was extracted with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resultant solid was suspended in diethyl ether:hexane=1:1, and filtered by suction to give toluene-4-sulfonic acid 3-cyclopropyl-1-(3-methanesulfonylamino-phenyl)-8-methyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester **15** (5.5 g, 95%) as a white solid.

Step 9 Synthesis of N-{3-[5-(4-bromo-2-fluoro-phenylamino)-3-cyclopropyl-8-methyl-2,4,7-trioxo-3,4,7,8-tetrahydro-2H-pyrido[2,3-d]pyrimidin-1-yl]phenyl}-methanesulfonamide

[0271]



[0272] To toluene-4-sulfonic acid 3-cyclopropyl-1-(3-methanesulfonylamino-phenyl)-8-methyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester **15** (3.5 g) obtained in Step 8 was added 2-fluoro-4-bromoaniline **16** (23 g), and the mixture was stirred under heating at 135°C for 3 hrs. The reaction mixture was purified by column chromatography

(chloroform:acetone=9:1) to give N-{3-[5-(4-bromo-2-fluoro-phenylamino)-3-cyclopropyl-8-methyl-2,4,7-trioxo-3,4,7,8-tetrahydro-2H-pyrido[2,3-d]pyrimidin-1-yl]phenyl}-methanesulfonamide **17** (3.0 g, 83%) as a white solid.

MS ESI m/e: 590, 592 (M+H), 588, 590 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.08 (m, 2H), 2.66 (s, 1H), 3.02 (s, 1H), 5.36 (s, 1H), 7.13 (d, J=9.0Hz, 1H), 7.24-7.30 (m, 2H), 7.43-7.54 (m, 3H), 7.74 (d, J=9.0Hz, 1H), 10.00 (brs, 1H), 10.53 (brs, 1H).

Examples 1-2 to 1-343

[0273] In the same manner as in Example 1-1, the compounds of Examples 1-2 to 1-343 were obtained. The structural formulas thereof are shown in Tables 1-1 to 1-58 with Example 1-1.

Table 1-1

Ex. No.	structural formula	Ex. No.	structural formula
1-1		1-2	
1-3		1-4	
1-5		1-6	

Table 1-2

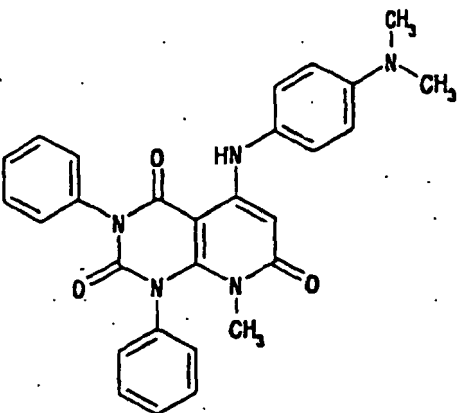
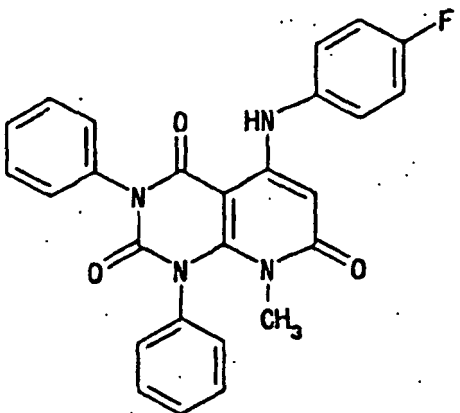
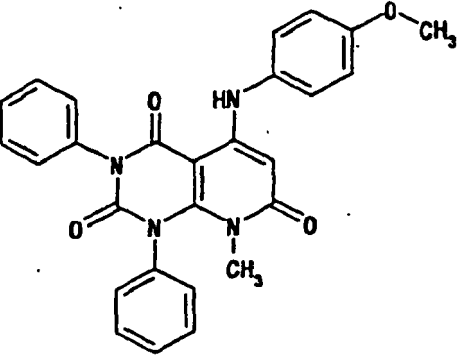
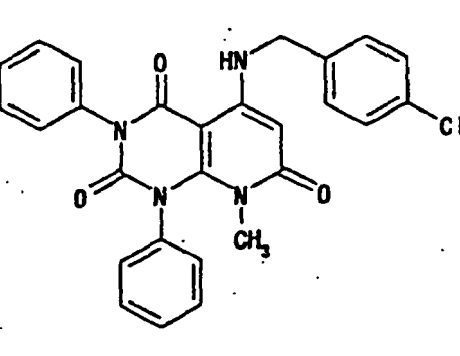
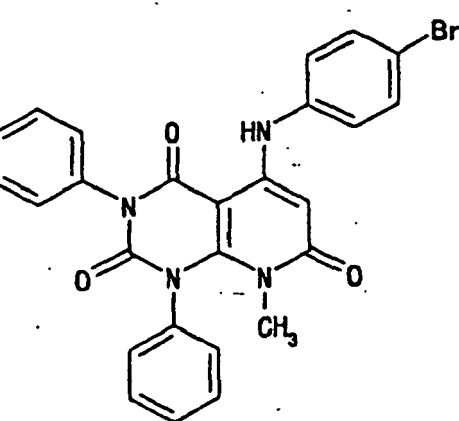
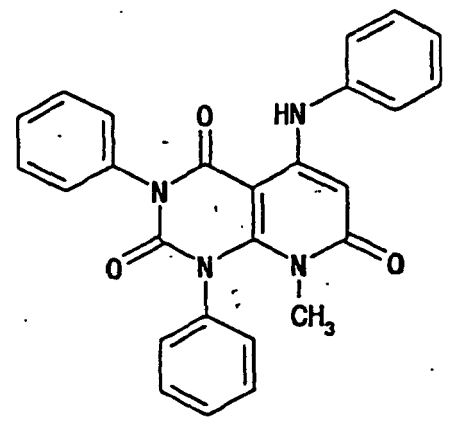
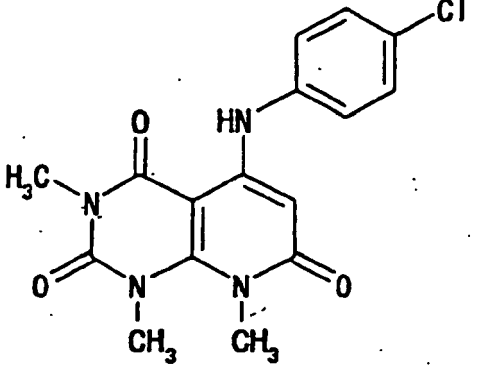
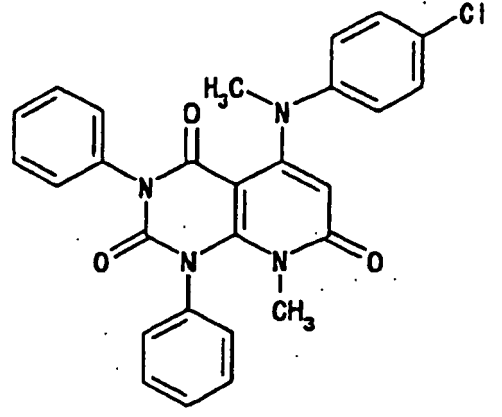
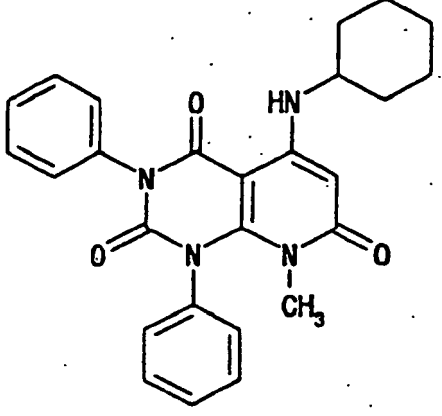
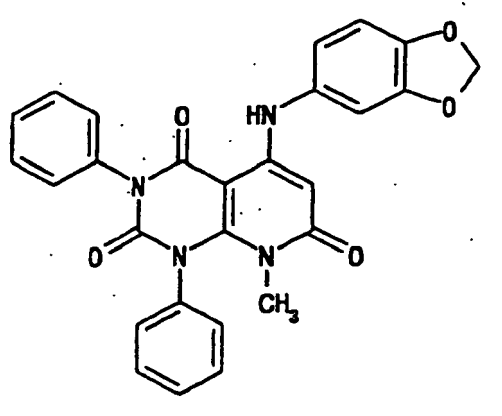
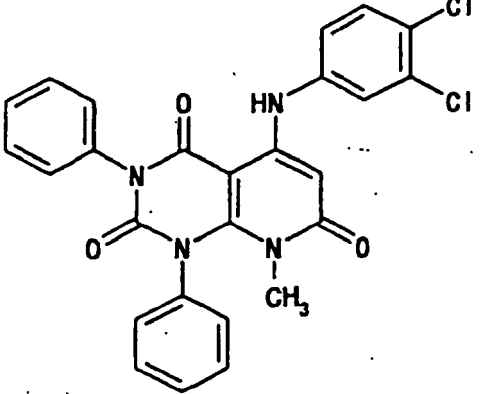
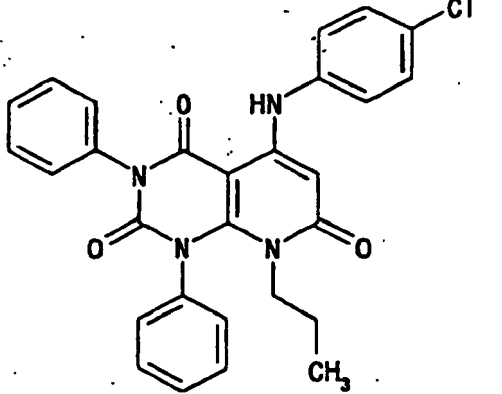
Ex. No.	structural formula	Ex. No.	structural formula
1-7		1-8	
1-9		1-10	
1-11		1-12	

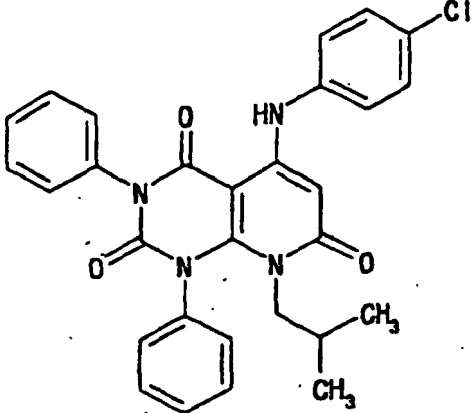
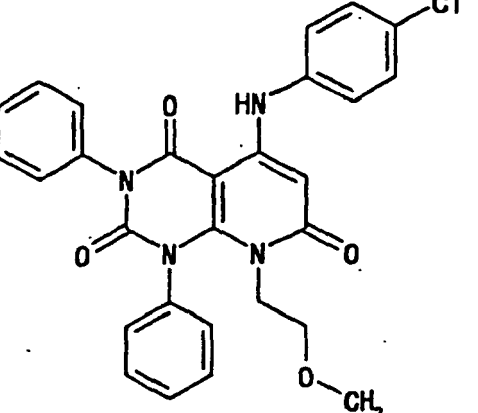
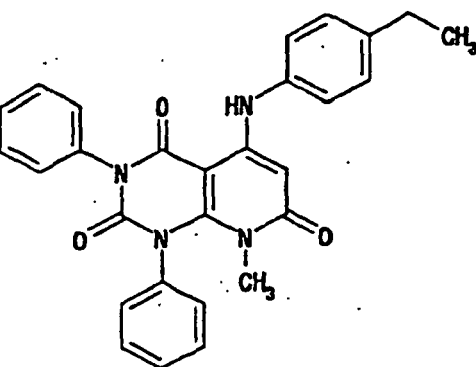
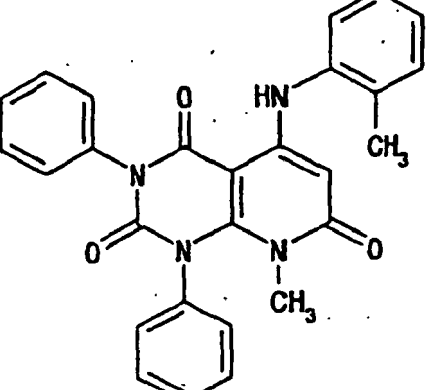
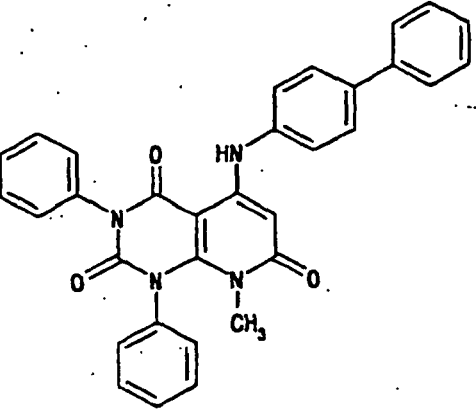
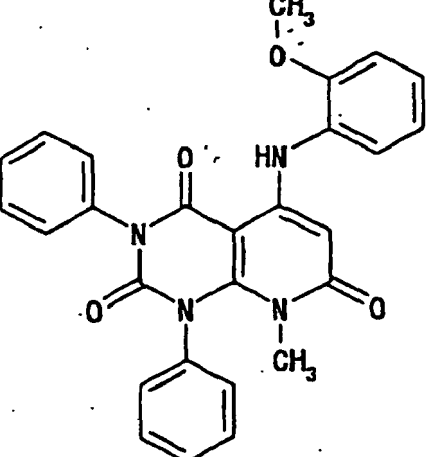
Table 1-3

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-13		1-14	
20 25 30 1-15		1-16	
35 40 45 1-17		1-18	

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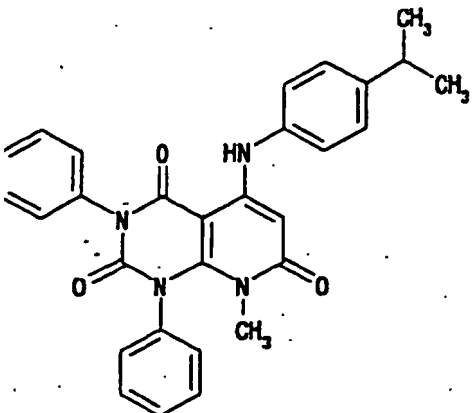
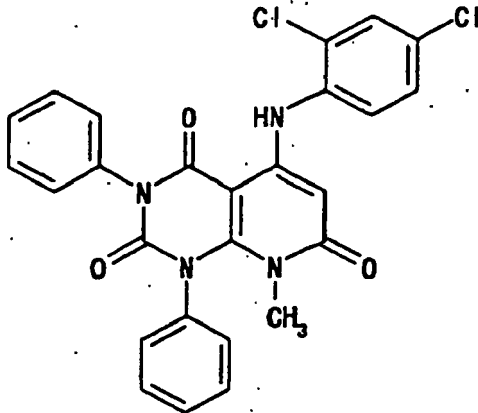
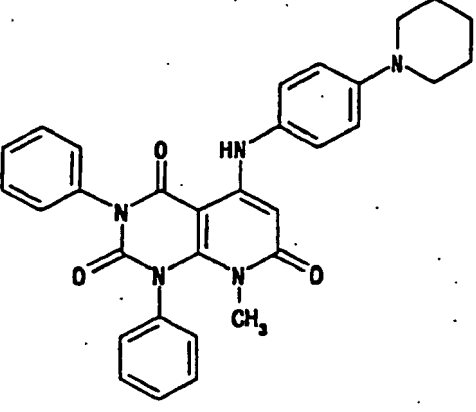
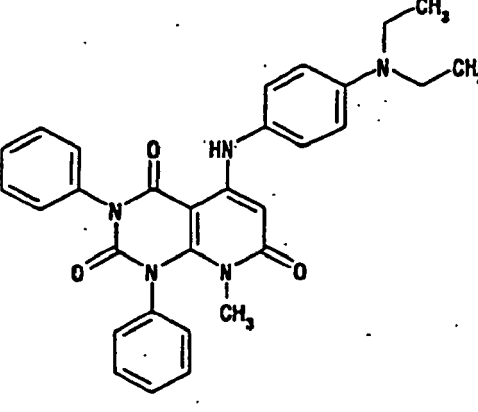
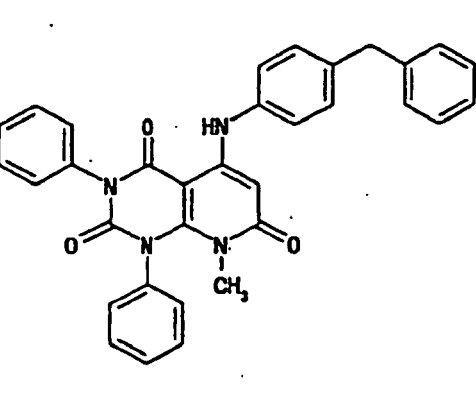
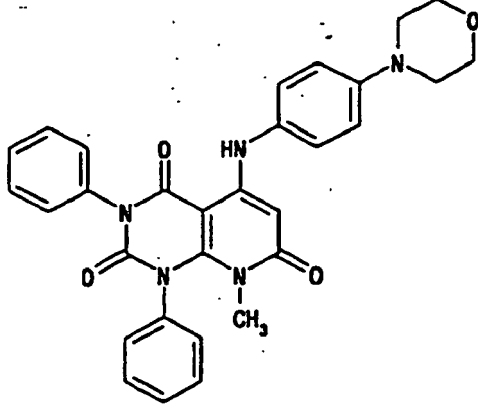
Table 1-4

Ex. No.	structural formula	Ex. No.	structural formula
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20 25 30 1-21		1-22	
35 40 45 1-23		1-24	

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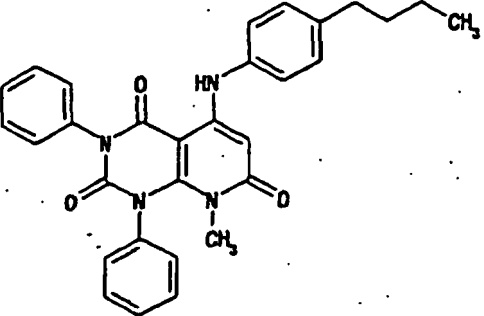
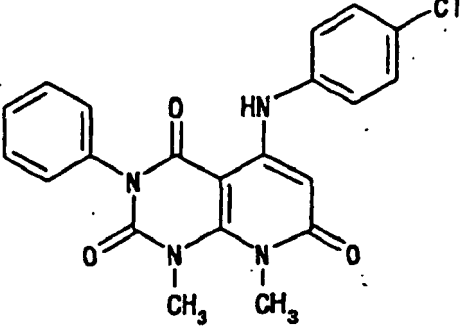
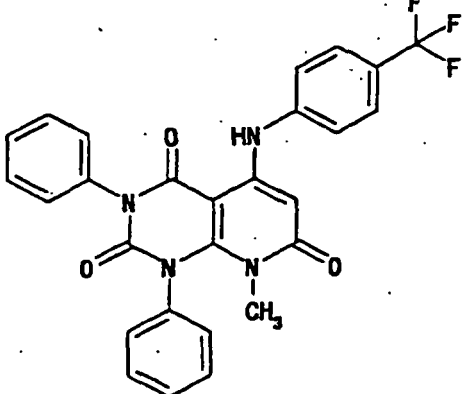
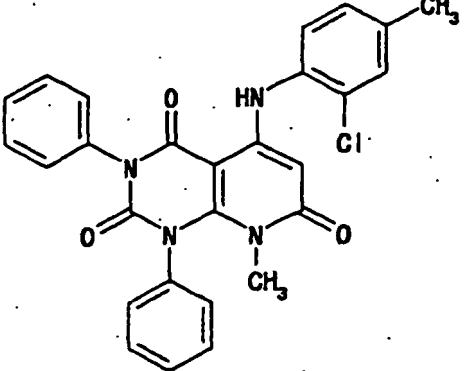
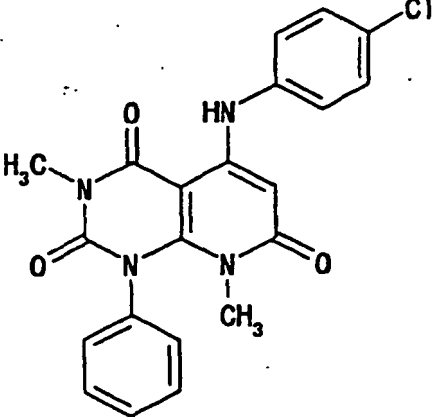
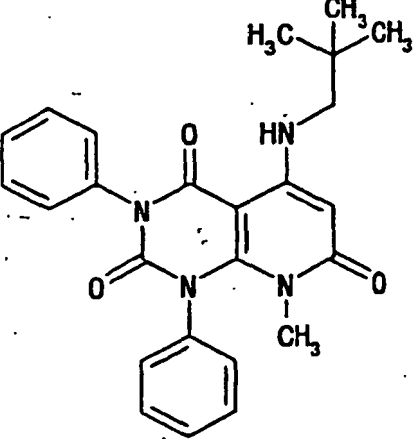
Table 1-5

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-25		1-26	
20 25 30 1-27		1-28	
35 40 45 1-29		1-30	

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Table 1-6

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-31		1-32	
20 25 30 1-33		1-34	
35 40 45 1-35		1-36	

50

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Table 1-7

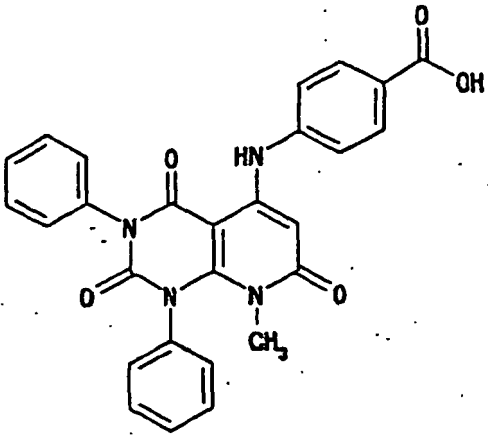
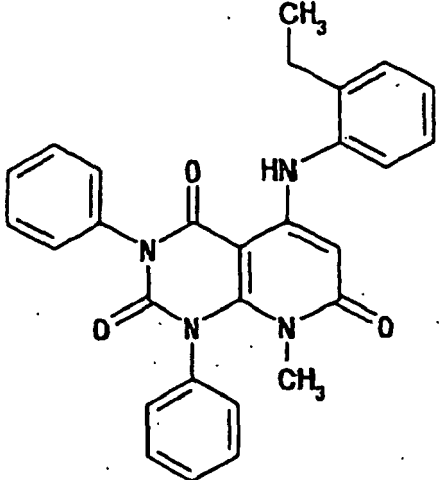
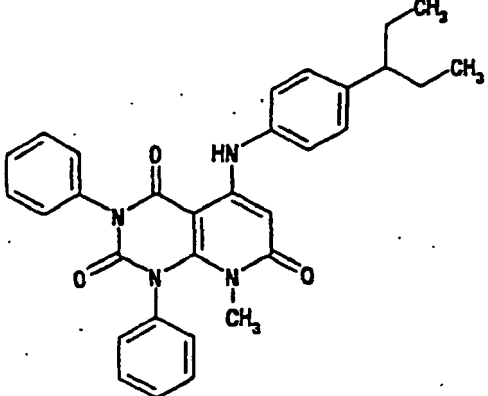
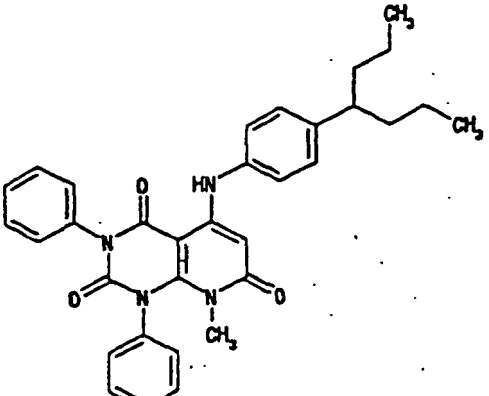
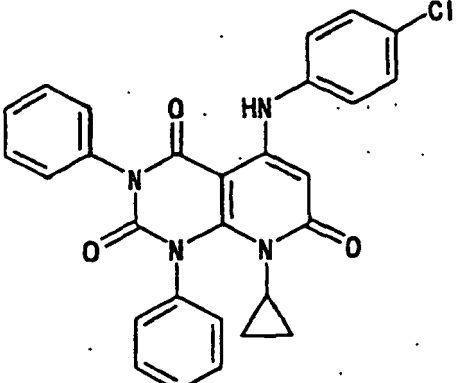
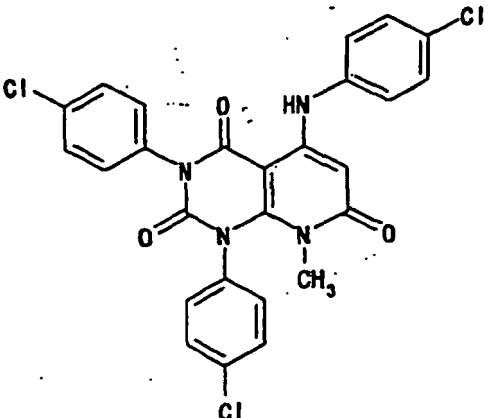
Ex. No.	structural formula	Ex. No.	structural formula
1-37		1-38	
1-39		1-40	
1-41		1-42	

Table 1-8

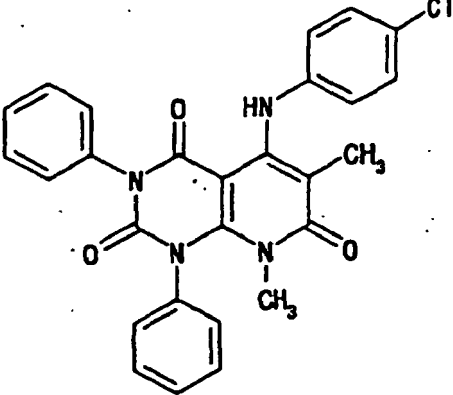
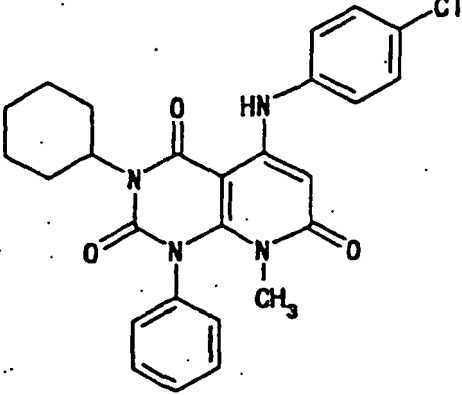
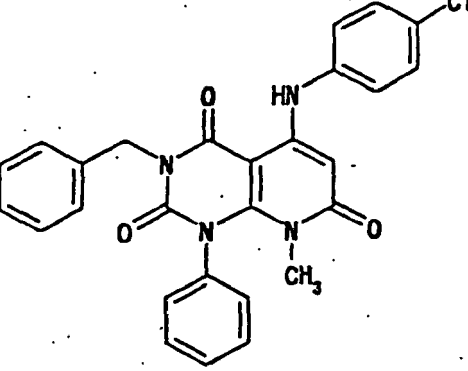
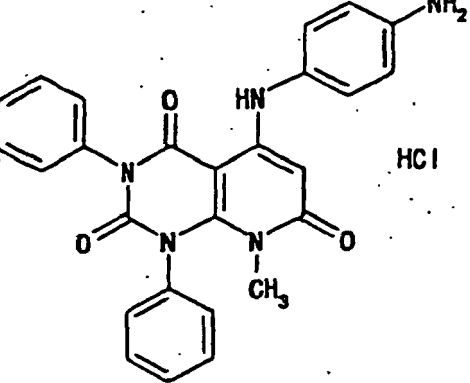
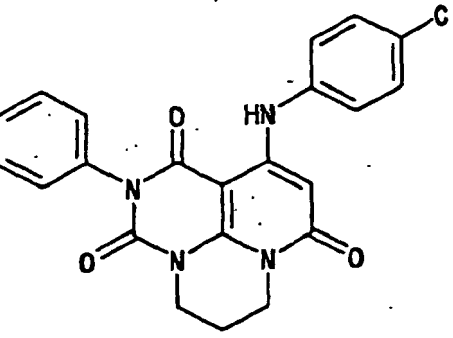
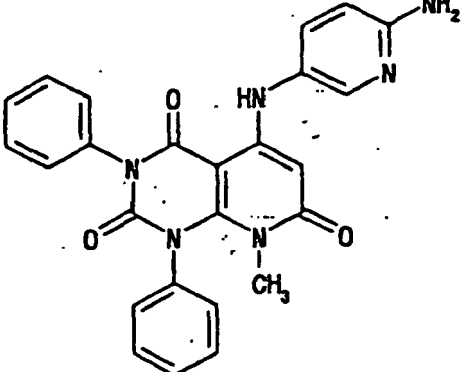
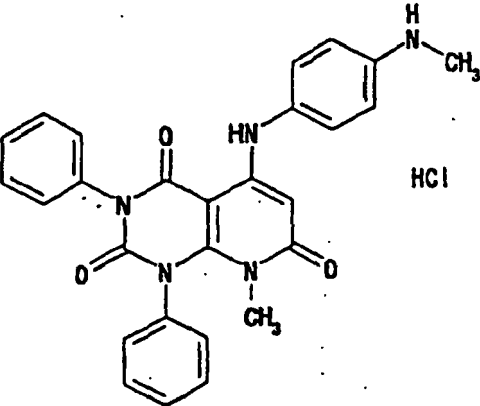
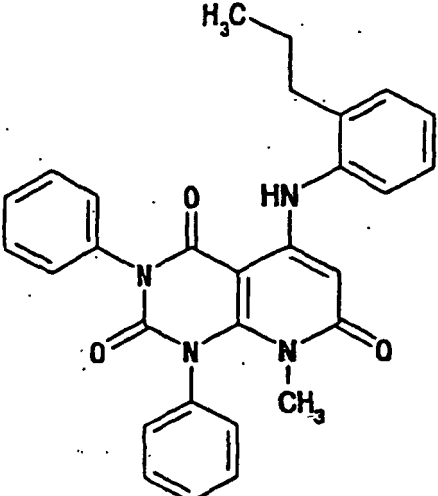
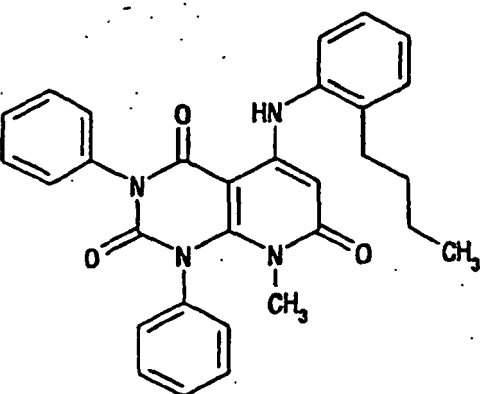
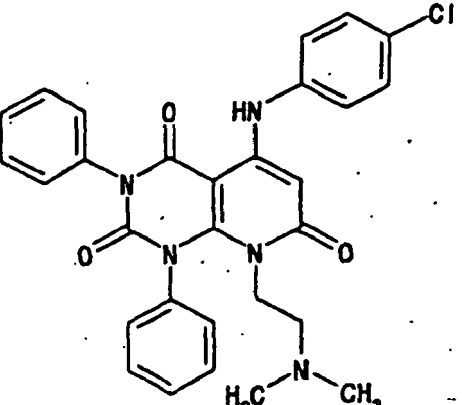
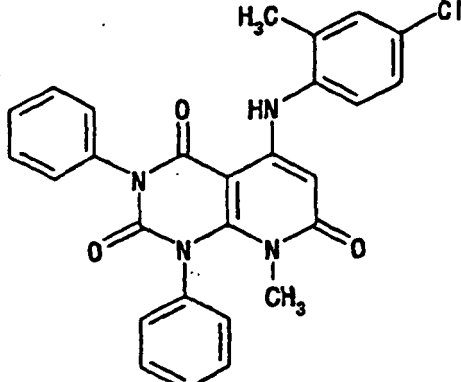
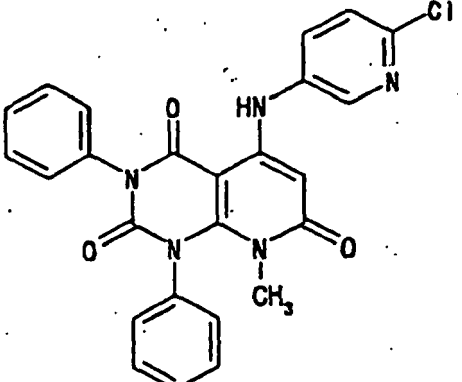
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-43		1-44	
20 25 30 1-45		1-46	
35 40 45 1-47		1-48	

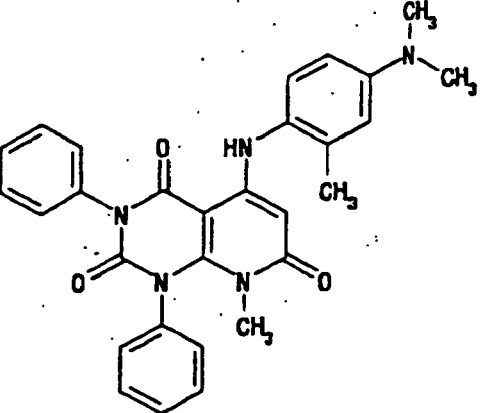
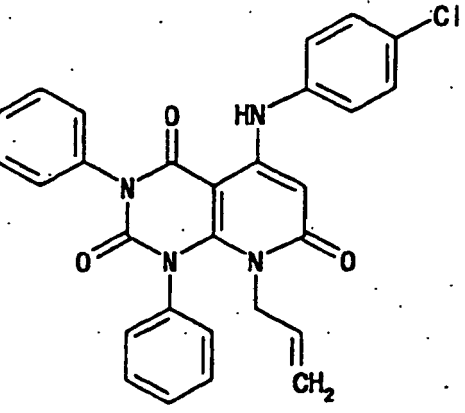
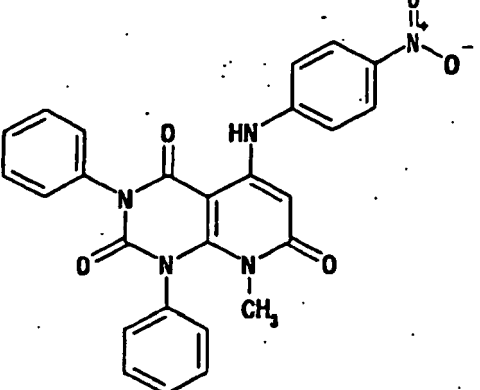
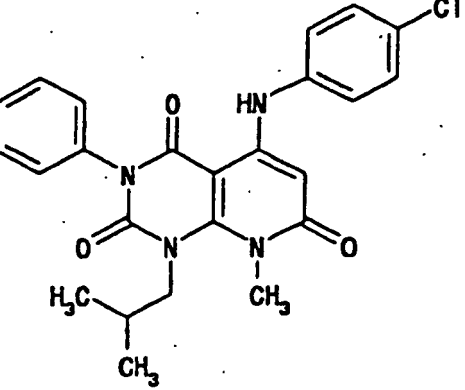
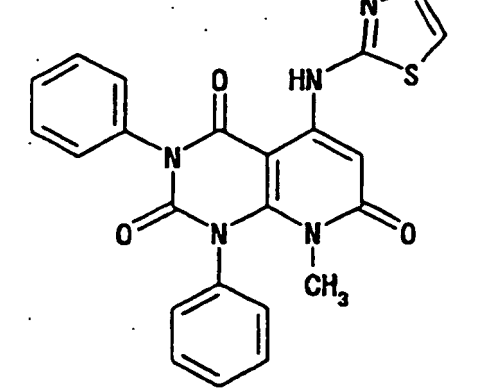
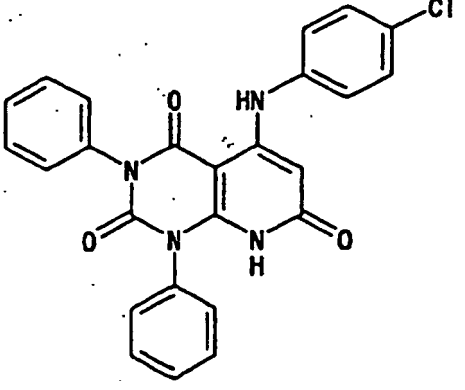
Table 1-9

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-49		1-50	
25 30 35 1-51		1-52	
40 45 1-53		1-54	

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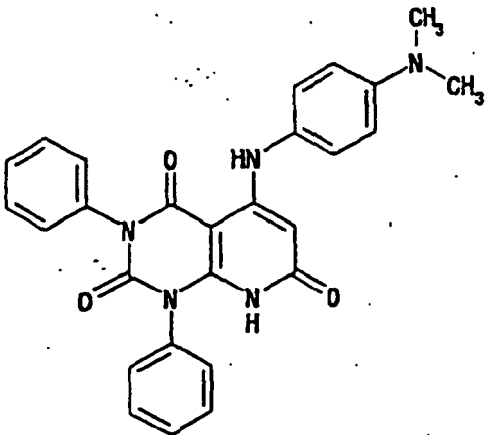
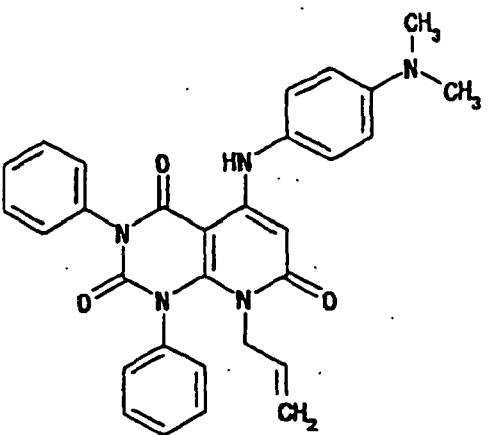
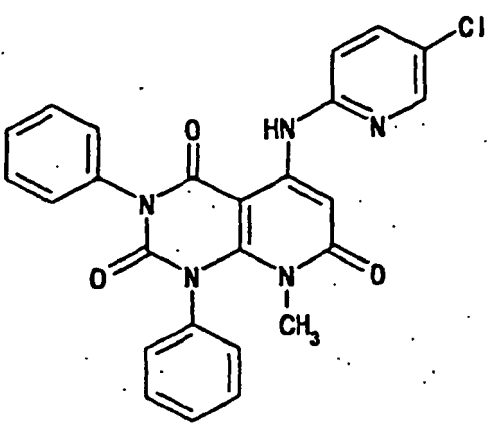
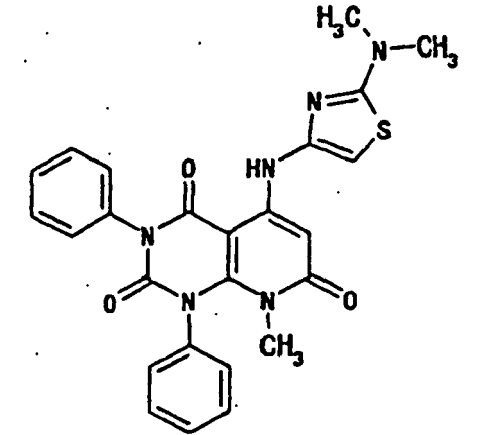
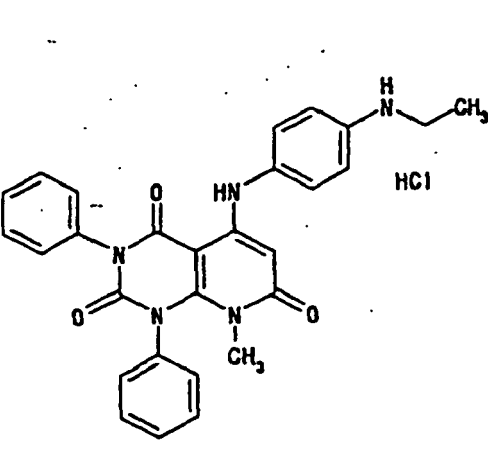
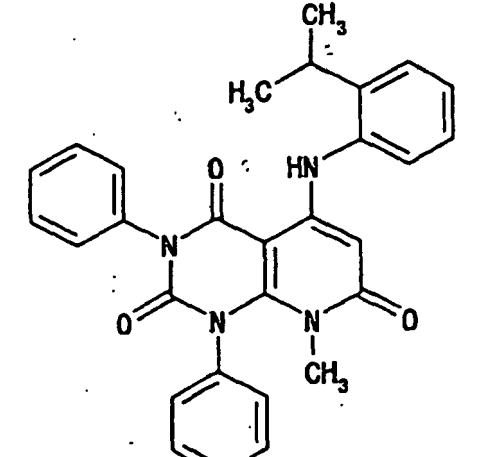
Table 1-10

Ex. No..	structural formula	Ex. No.	structural formula
5 10 15 1-55		1-56	
20 25 30 1-57		1-58	
35 40 45 1-59		1-60	

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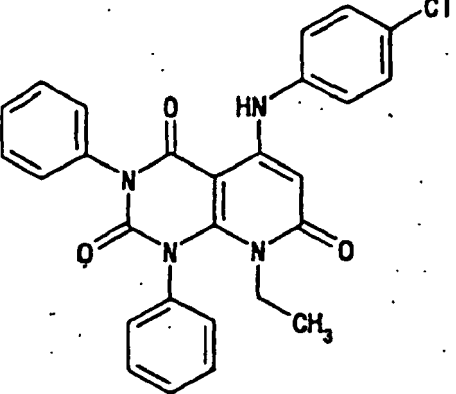
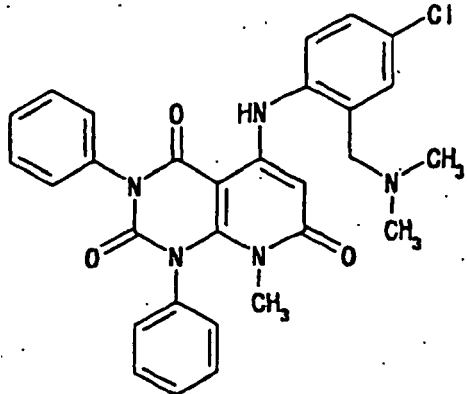
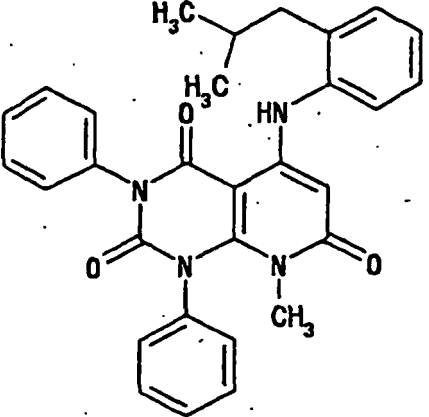
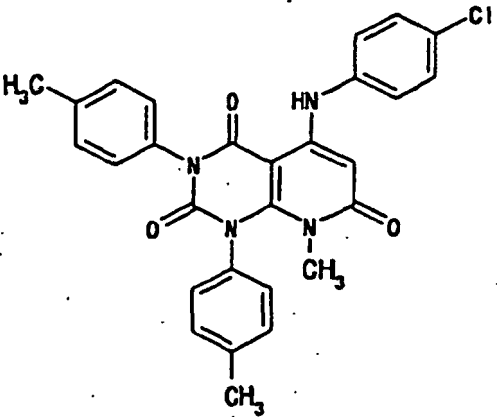
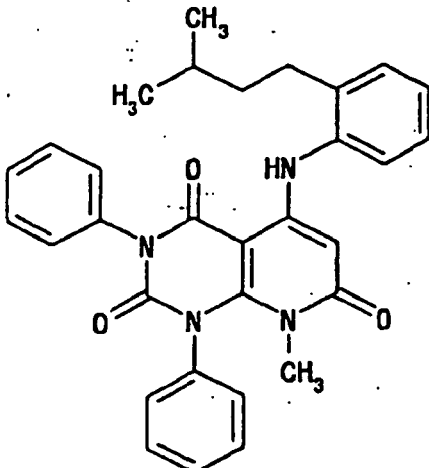
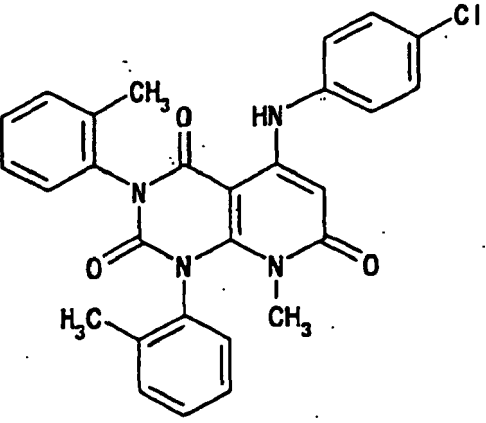
Table 1-11

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-61		1-62	
20 25 30 1-63		1-64	
35 40 45 1-65		1-66	

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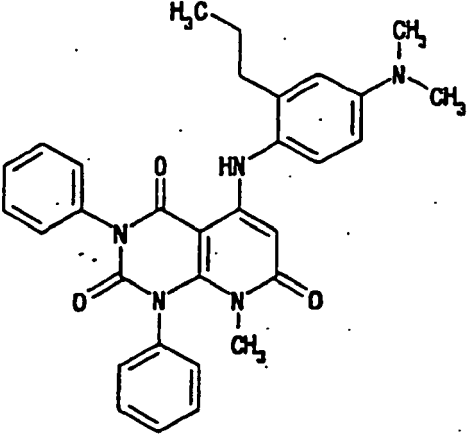
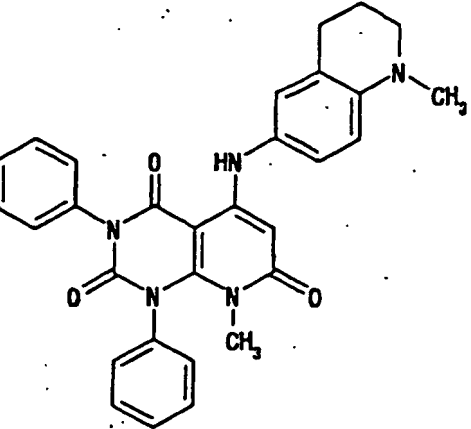
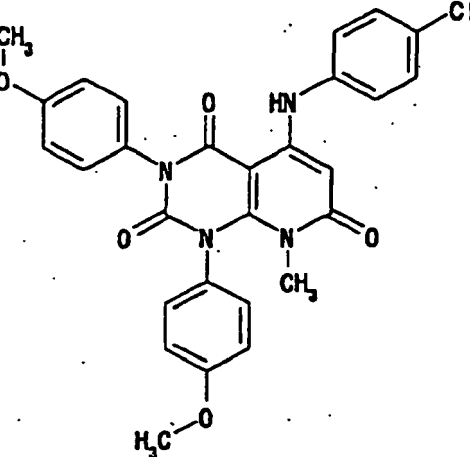
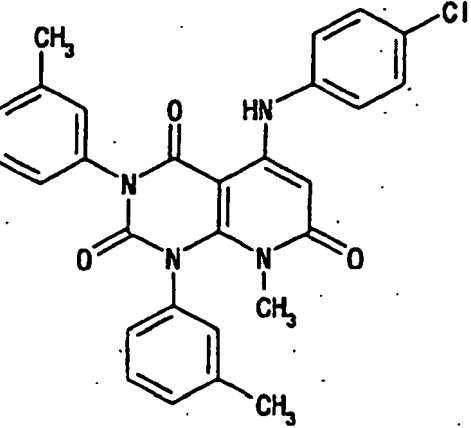
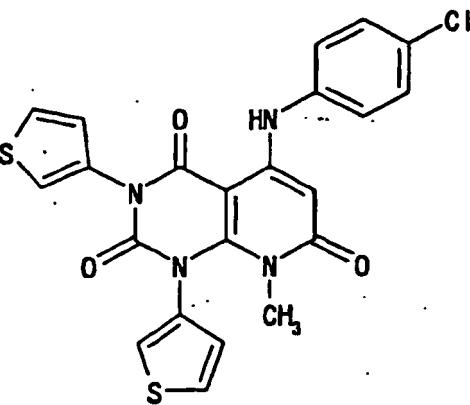
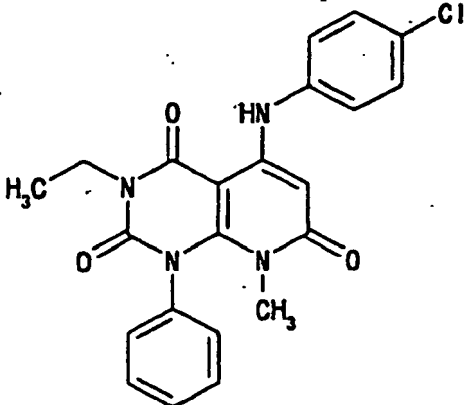
Table 1-12

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-67		1-68	
20 25 30 1-69		1-70	
35 40 45 1-71		1-72	

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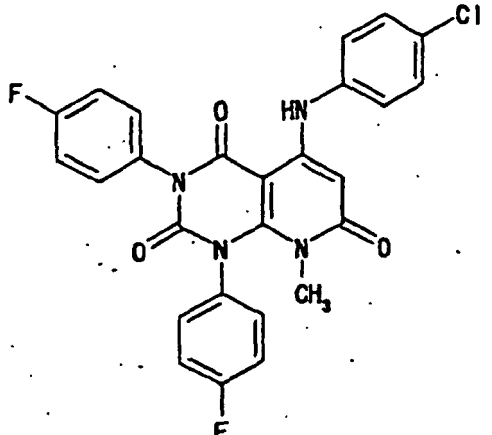
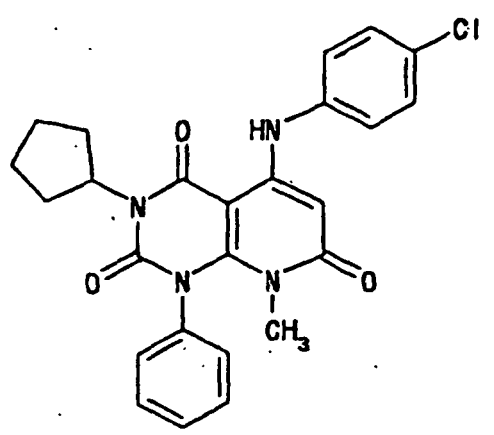
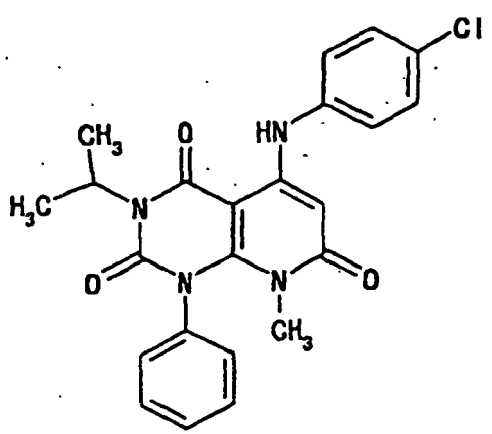
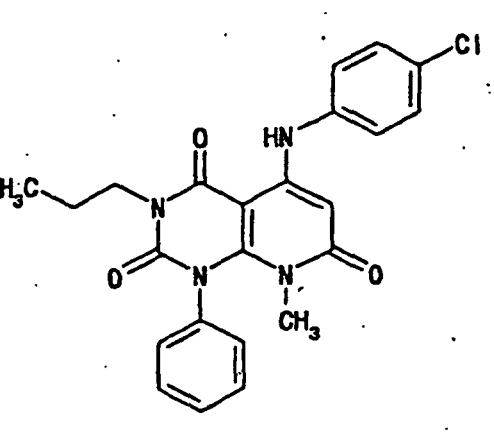
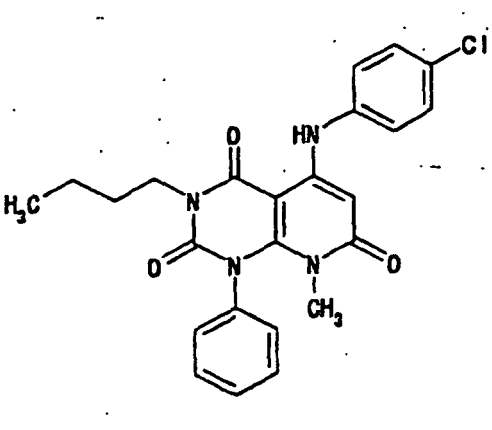
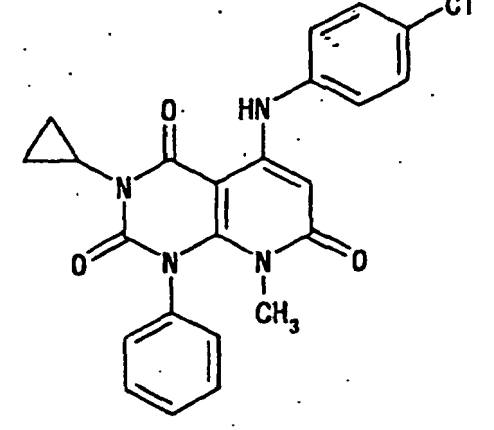
Table 1-13

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-73		1-74	
20 25 30 1-75		1-76	
35 40 45 1-77		1-78	

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Table 1-14

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-79		1-80	
20 25 30 1-81		1-82	
35 40 45 1-83		1-84	

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Table 1-15

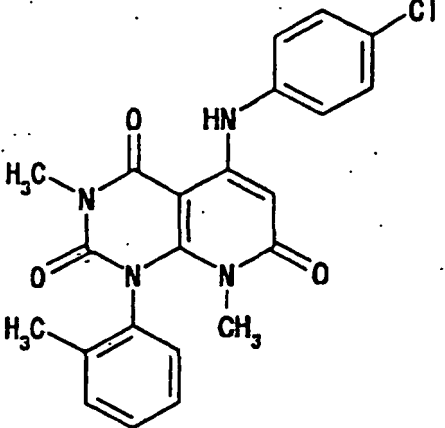
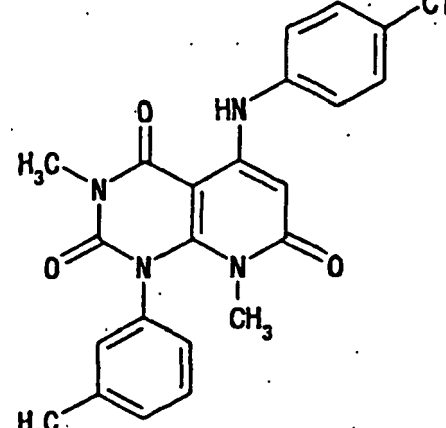
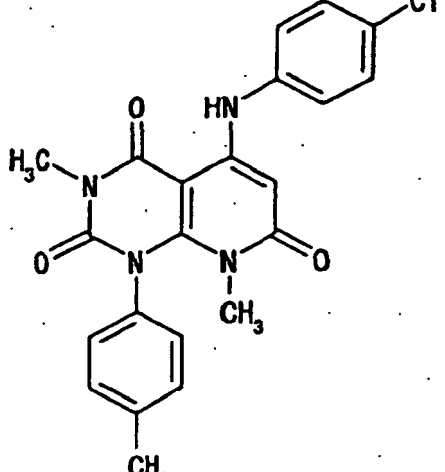
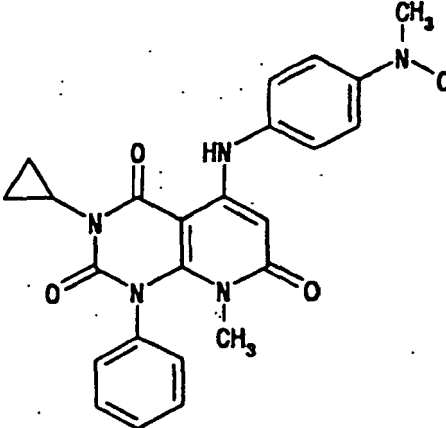
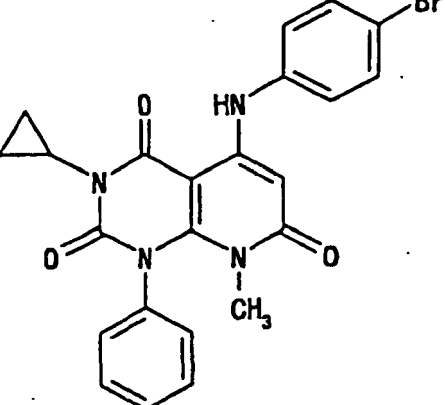
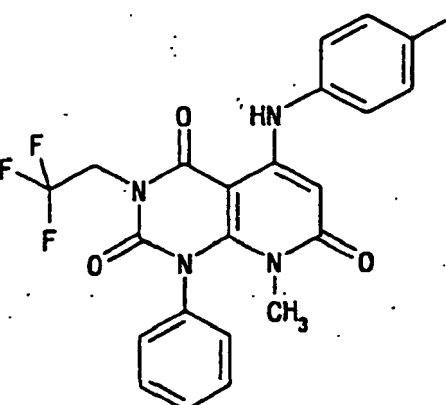
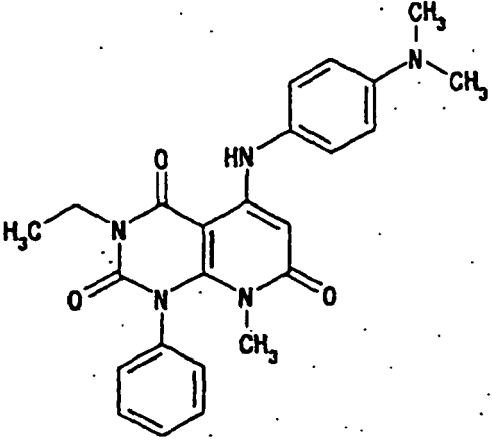
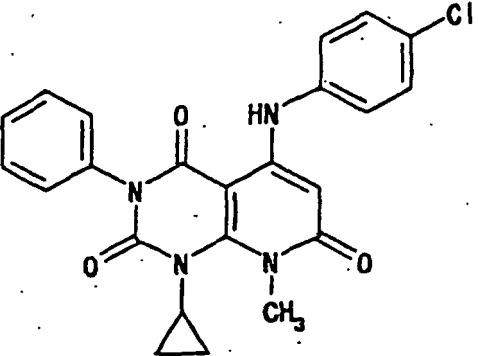
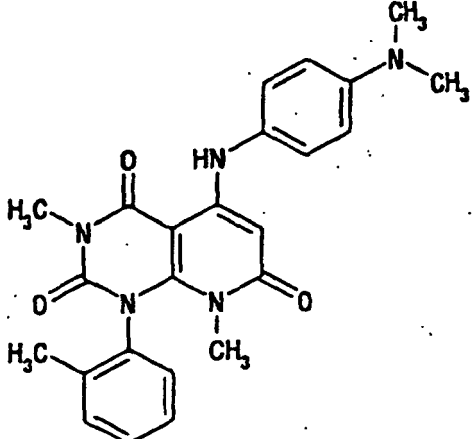
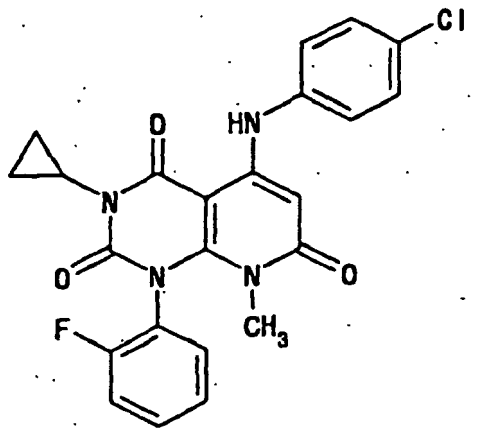
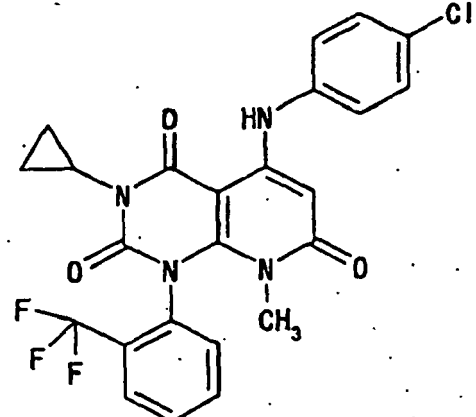
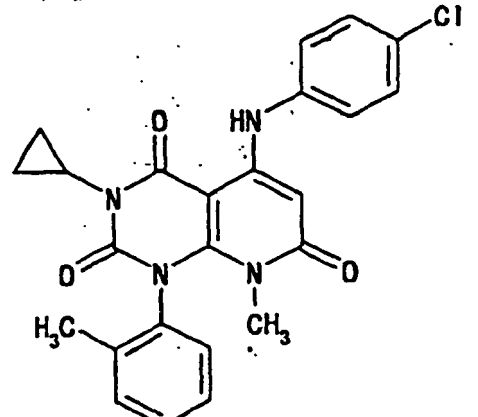
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-85		1-86	
20 25 30 35 1-87		1-88	
40 45 50 55 1-89		1-90	

Table 1-16

Ex. No.	structural formula	Ex. No.	structural formula
1-91		1-92	
1-93		1-94	
1-95		1-96	

Table 1-17

Ex. No.	structural formula	Ex. No.	structural formula
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1-99		1-100	
1-101		1-102	

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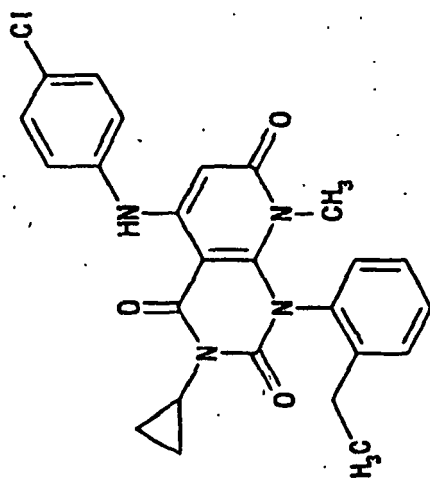
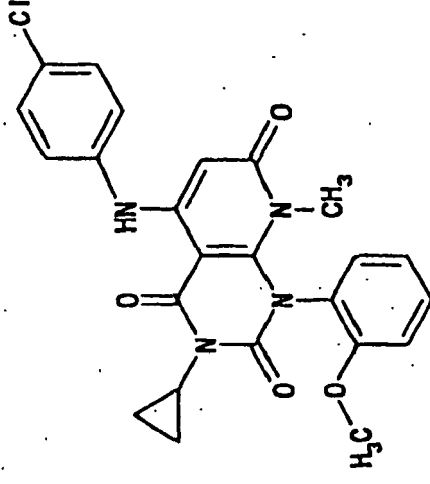
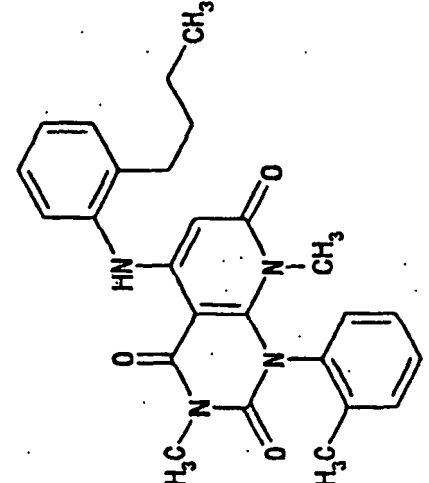
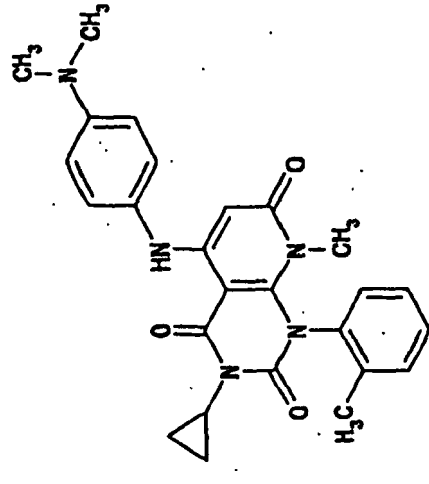
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Table 1-18

Ex. No.	structural formula	Ex. No.	structural formula
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1-105		1-106	

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(continued)

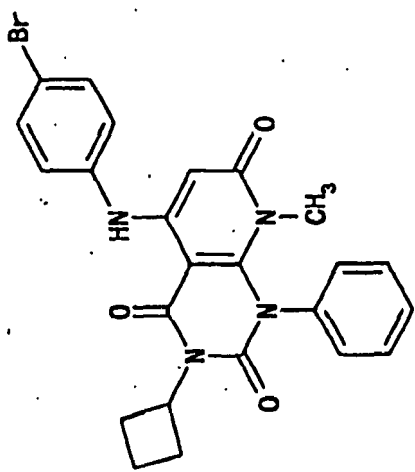
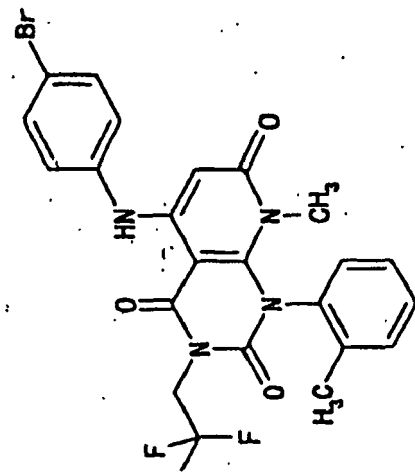
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Ex. No.	structural formula	Ex. No.	structural formula
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Table 1-19

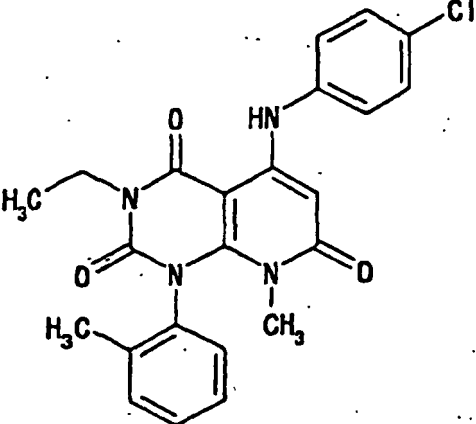
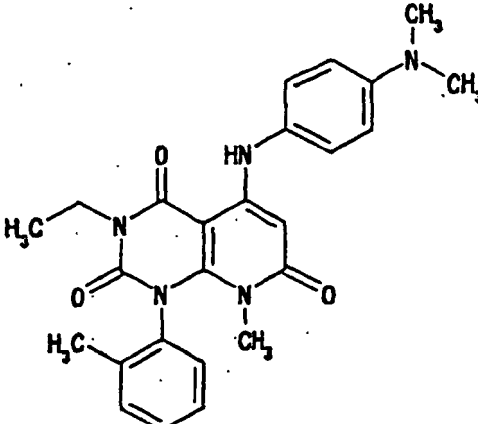
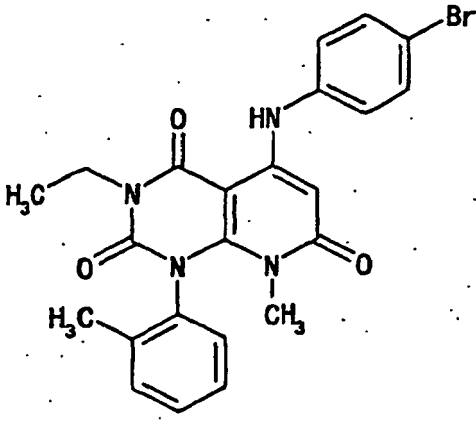
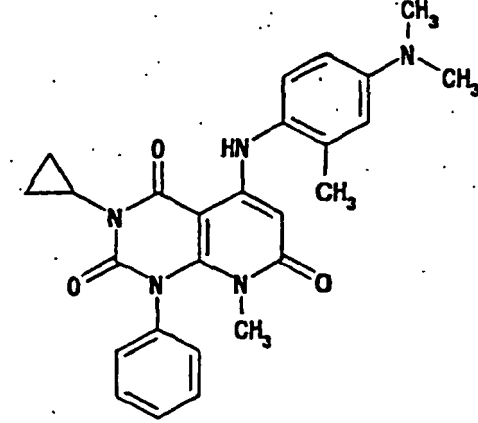
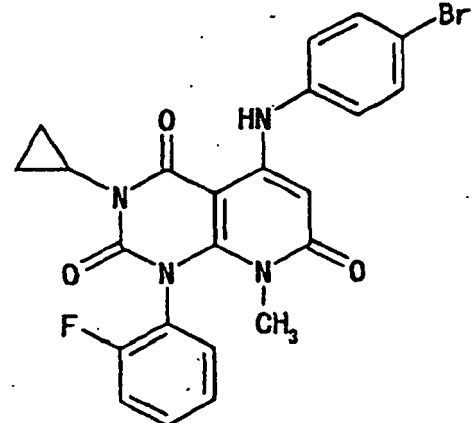
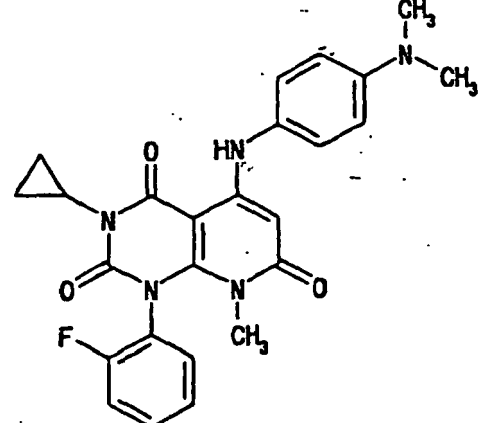
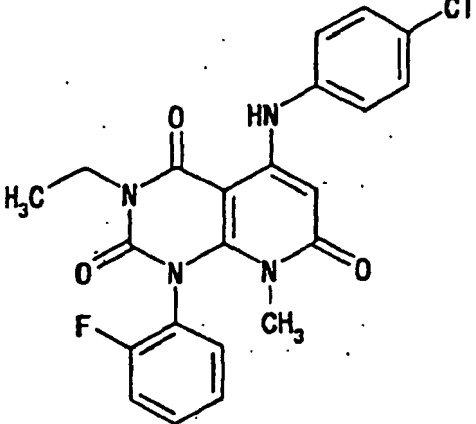
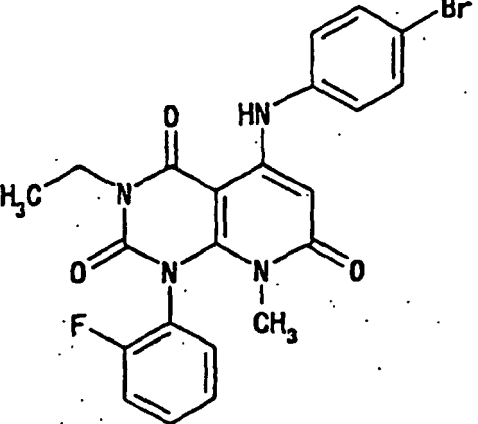
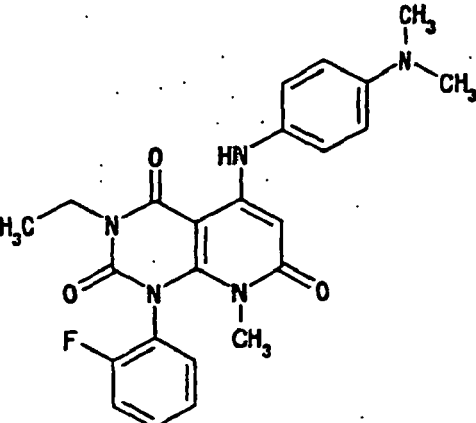
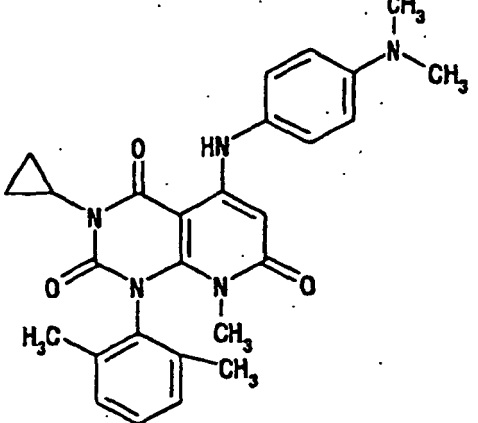
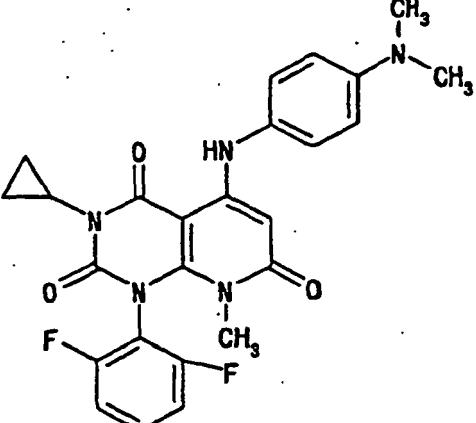
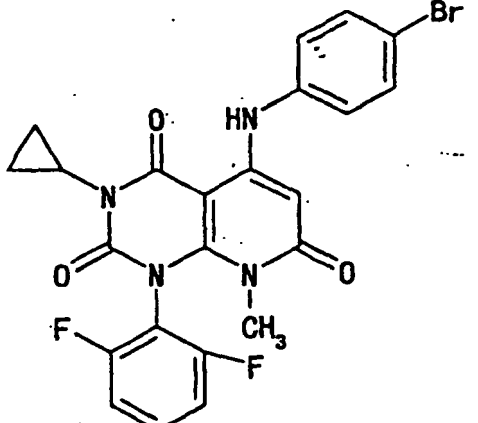
Ex. No.	structural formula	Ex. No.	structural formula
1-109		1-110	
1-111		1-112	
1-113		1-114	

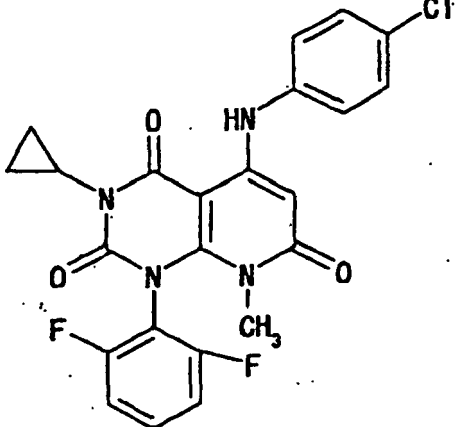
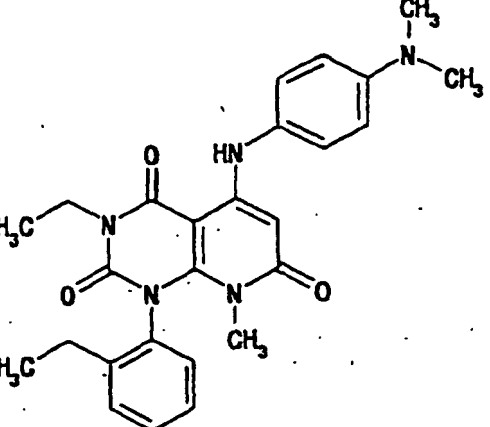
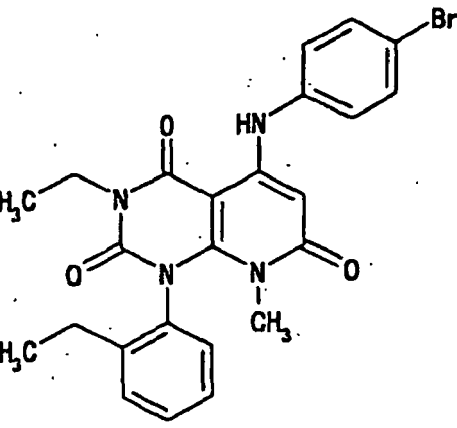
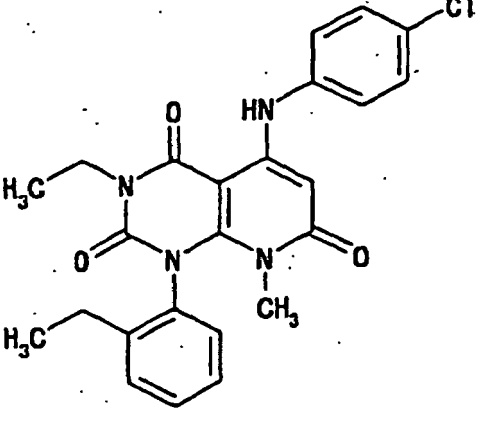
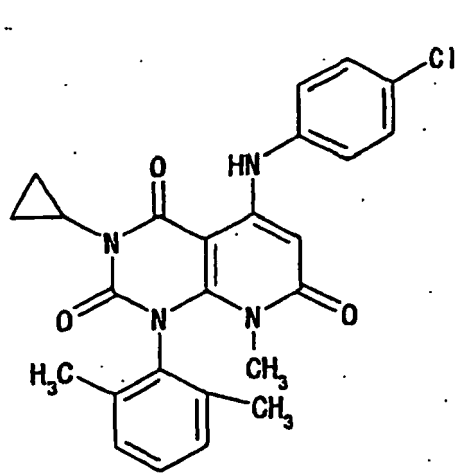
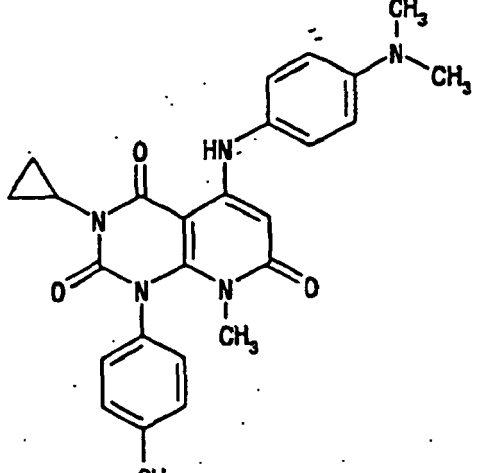
Table 1-20

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-115		1-116	
20 25 30 1-117		1-118	
35 40 45 1-119		1-120	

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Table 1-21

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-121		1-122	
20 25 30 1-123		1-124	
35 40 45 50 1-125		1-126	

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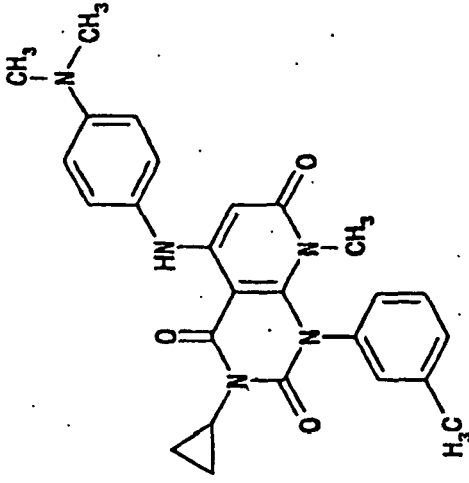
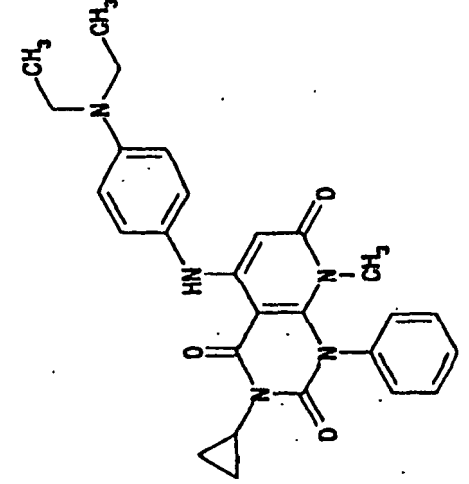
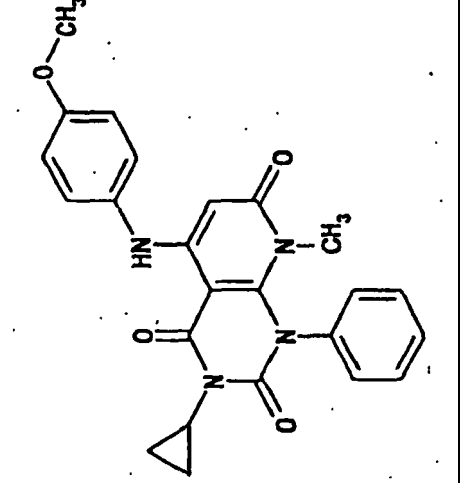
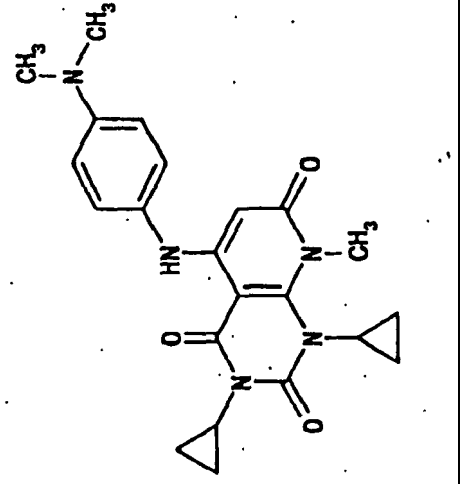
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Table 1-22

Ex. No.	structural formula	Ex. No.	structural formula
1-127		1-128	
1-129		1-130	

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(continued)

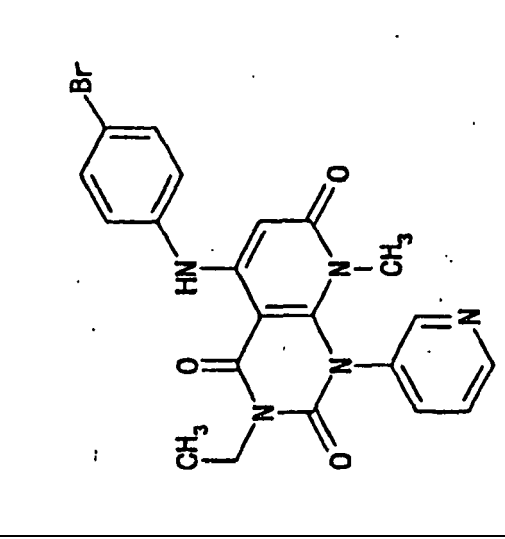
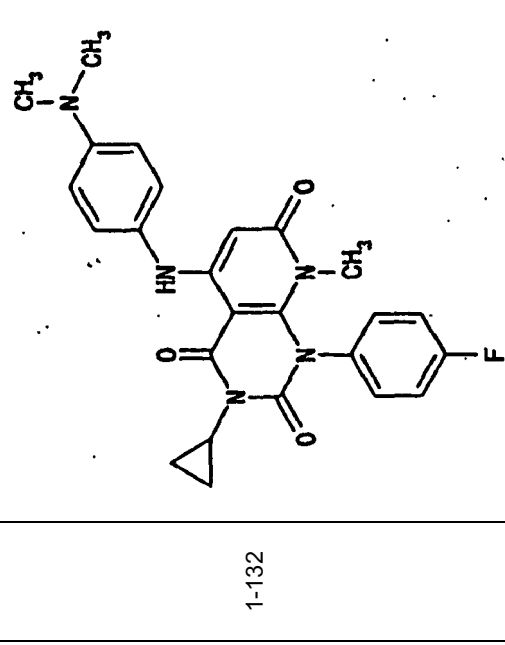
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Ex. No.	structural formula	Ex. No.	structural formula
1-131		1-132	

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Table 1-23

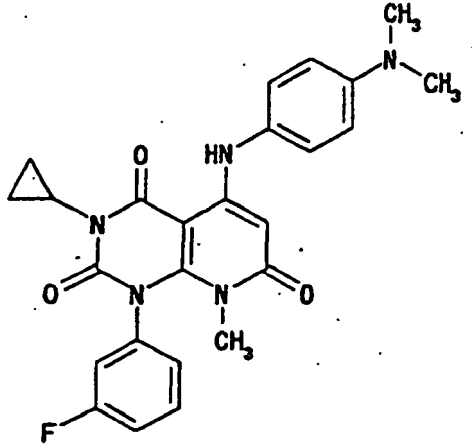
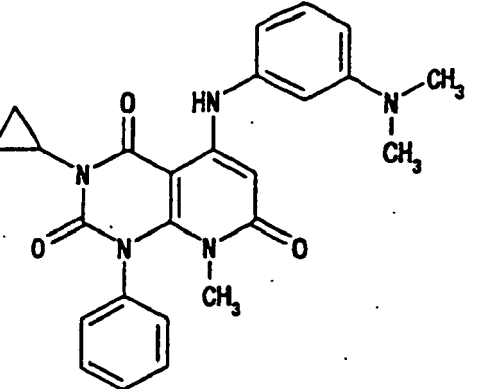
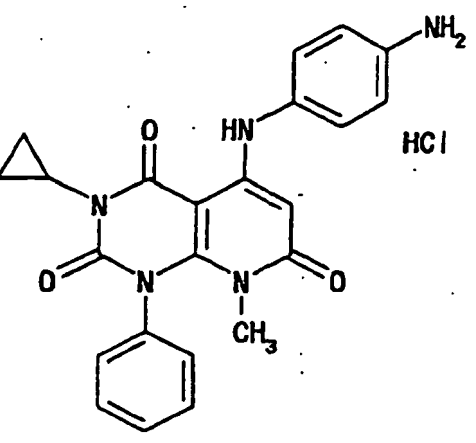
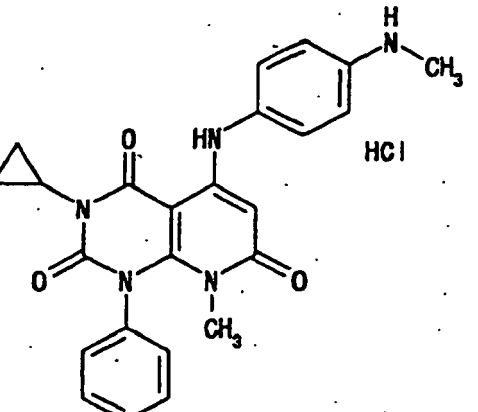
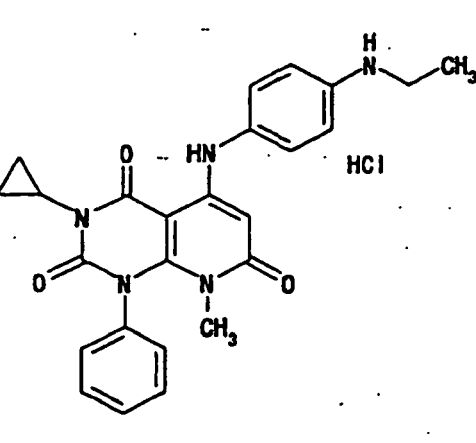
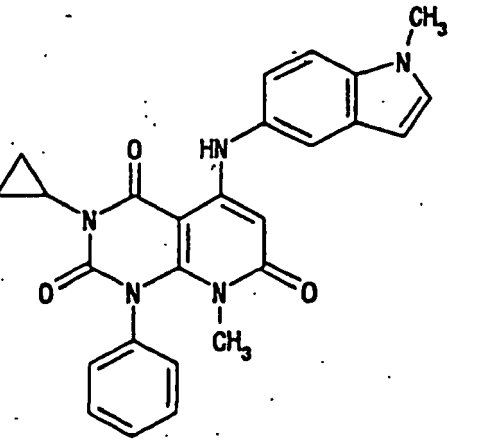
Ex. No.	structural formula No.	Ex. No.	structural formula
1-133		1-134	
1-135		1-136	
1-137		1-138	

Table 1-24

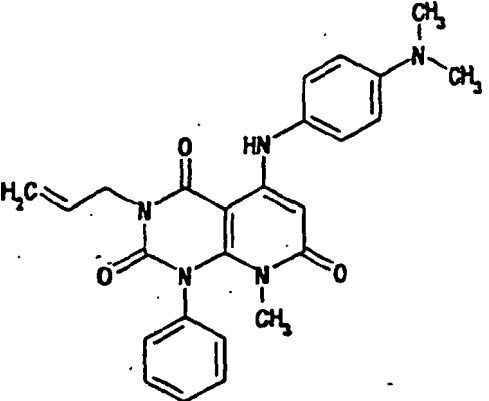
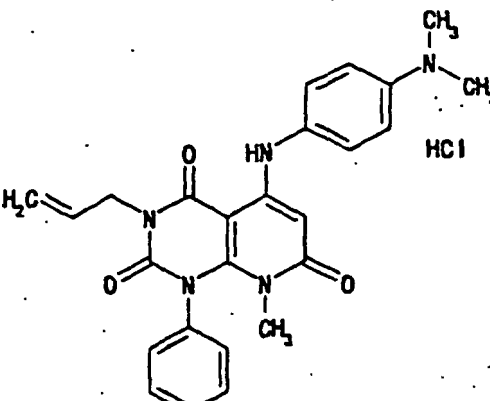
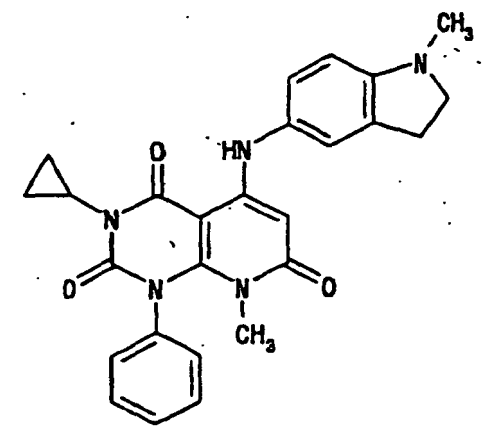
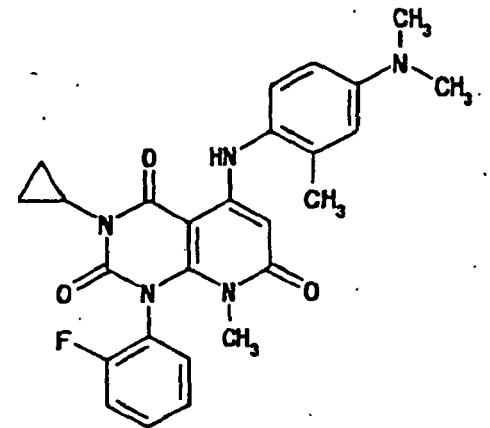
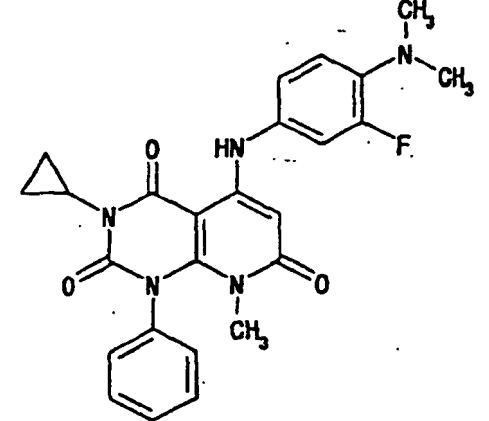
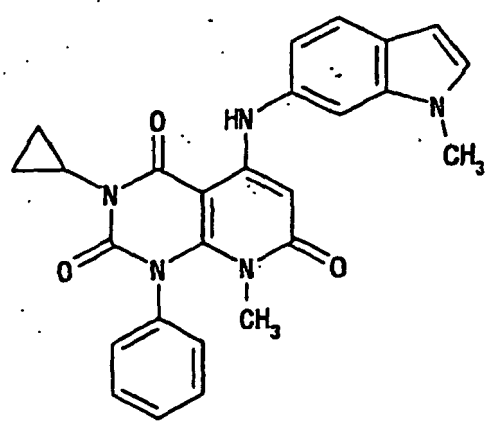
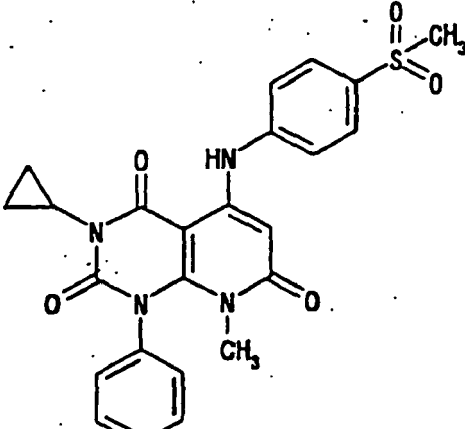
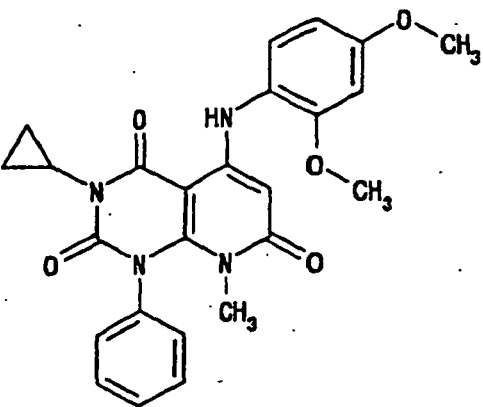
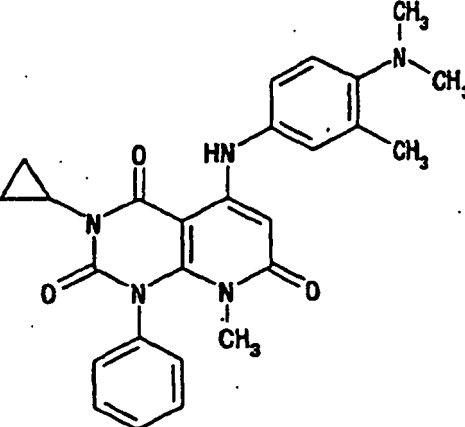
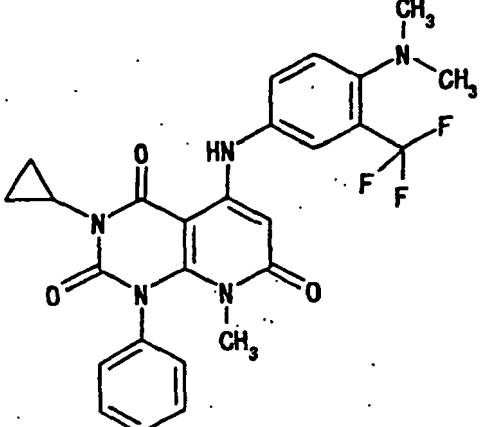
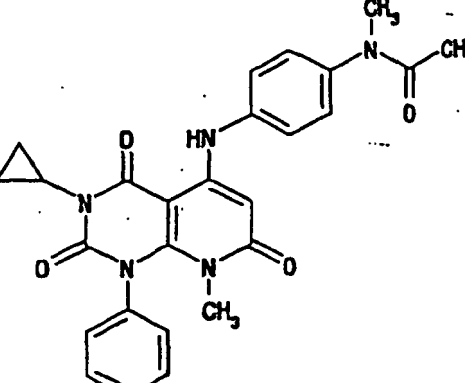
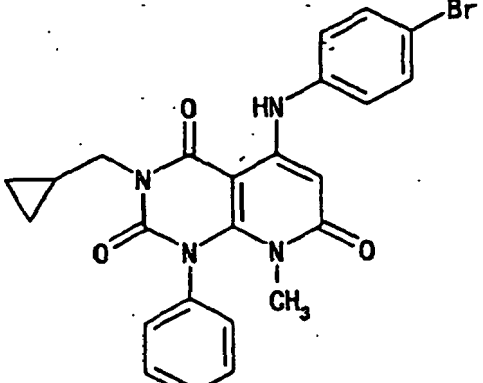
Ex. No.	structural formula	Ex. No.	structural formula
1-139		1-140	
1-141		1-142	
1-143		1-144	

Table 1-25

Ex. No.	structural formula No.	Ex. No.	structural formula
5 10 15 1-145		1-146	
20 25 30 1-147		1-148	
35 40 45 1-149		1-150	

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Table 1-26

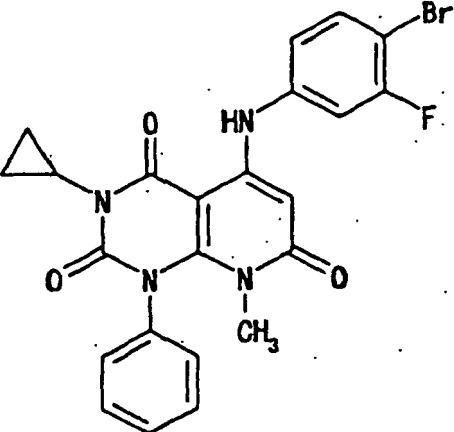
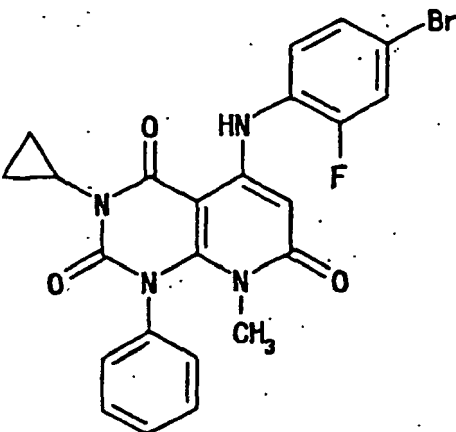
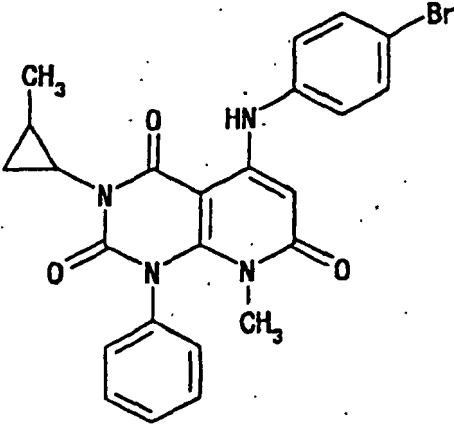
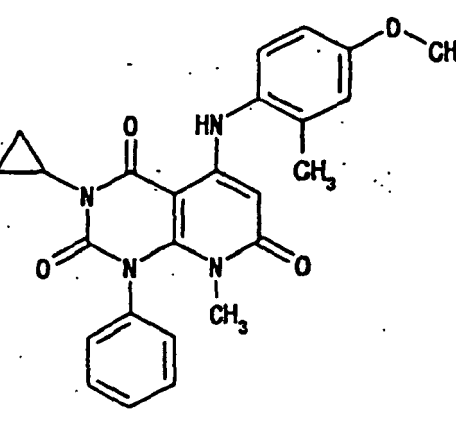
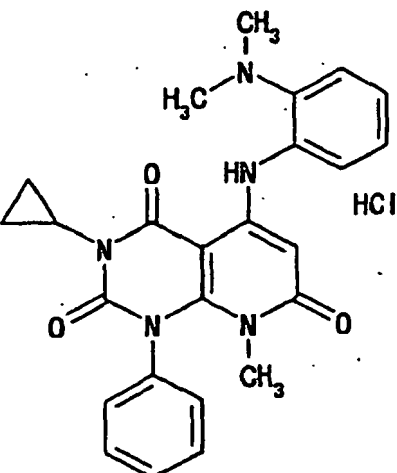
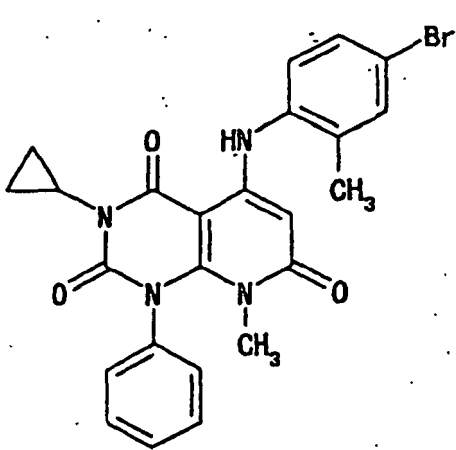
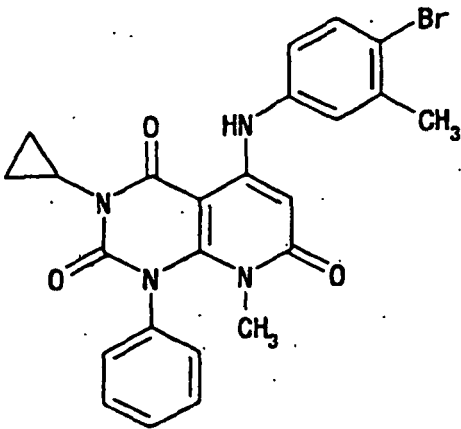
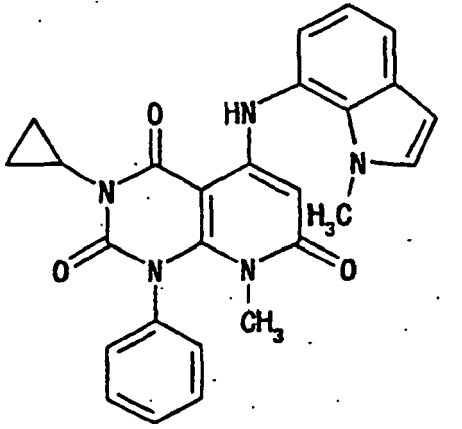
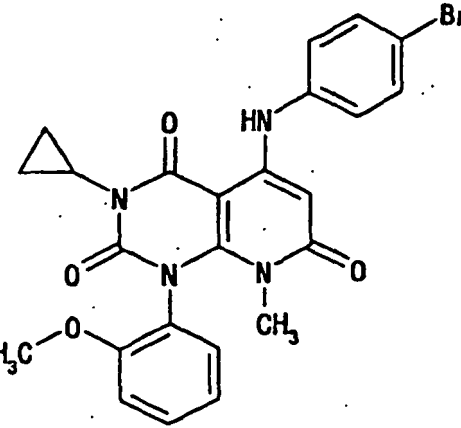
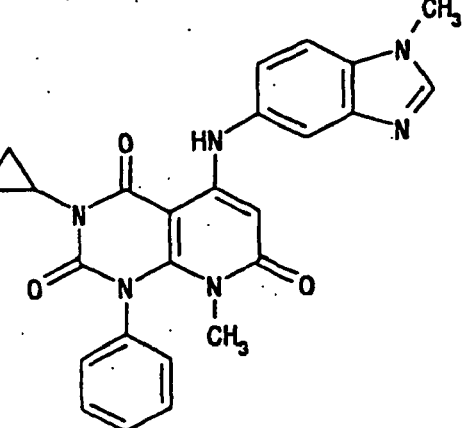
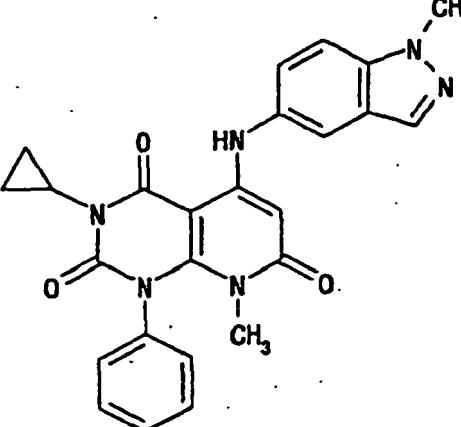
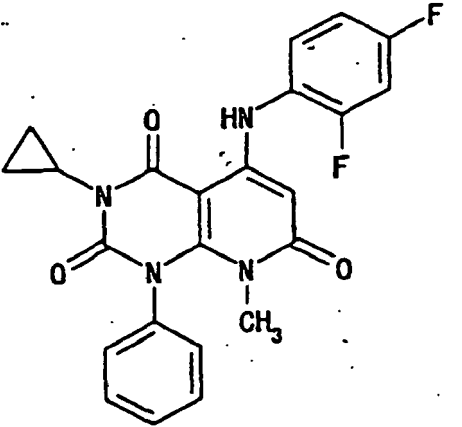
Ex. No.	structural formula No.	Ex. No.	structural formula
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20 25 30 1-153		1-154	
35 40 45 50 1-155		1-156	

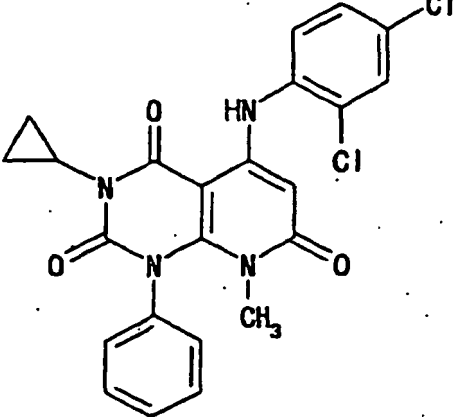
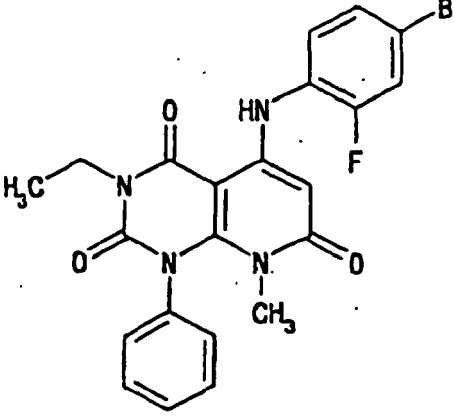
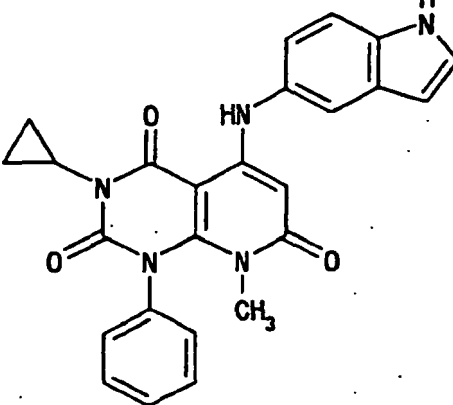
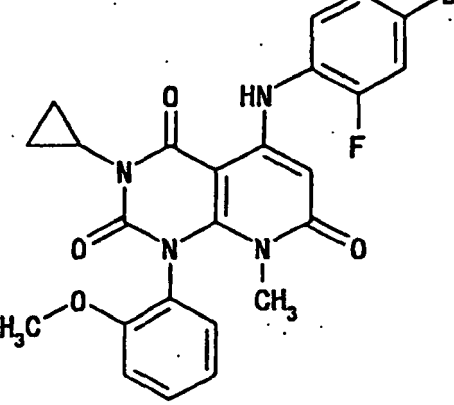
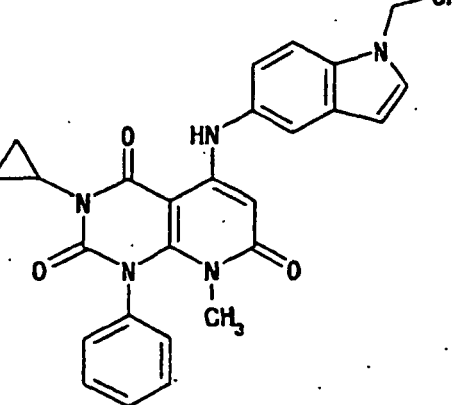
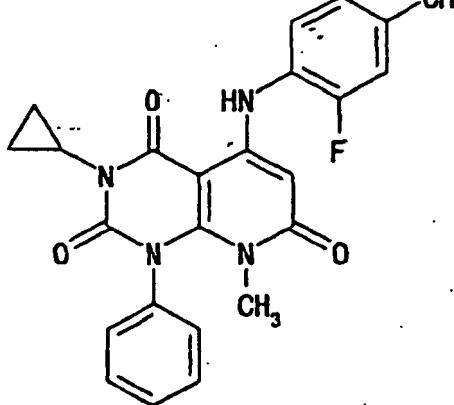
Table 1-27

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-157		1-158	
20 25 30 1-159		1-160	
35 40 45 1-161		1-162	

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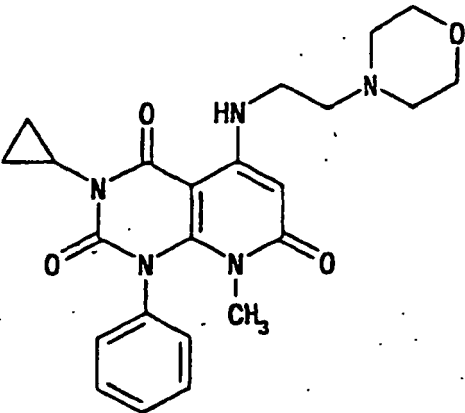
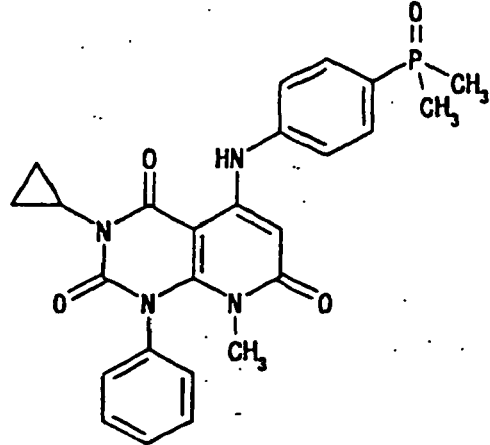
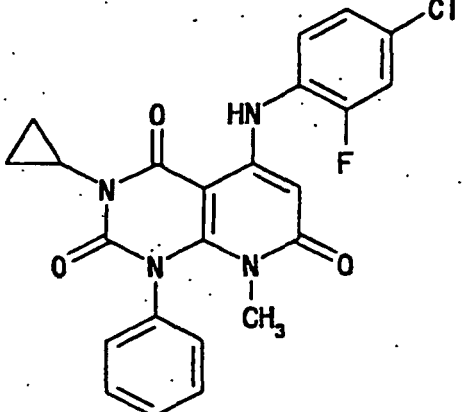
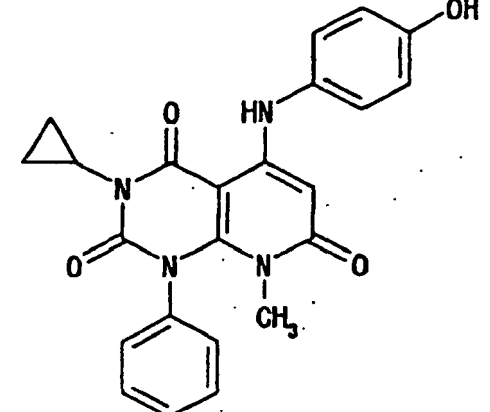
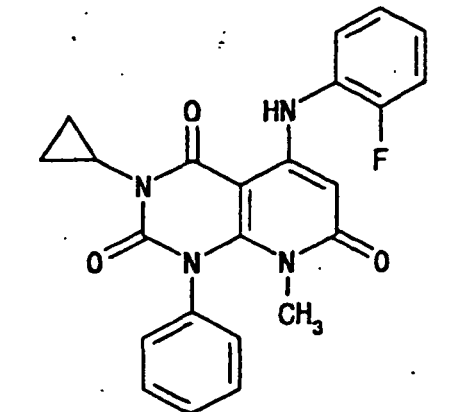
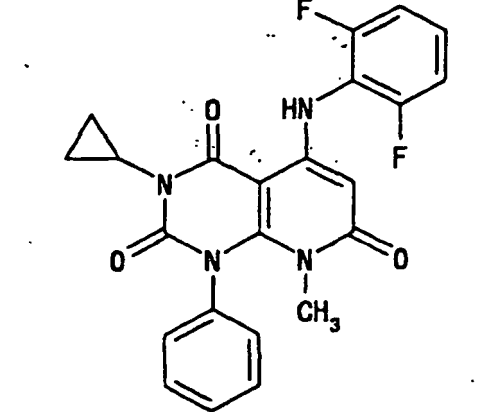
Table 1-28

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-163		1-164	
20 25 30 1-165		1-166	
35 40 45 1-167		1-168	

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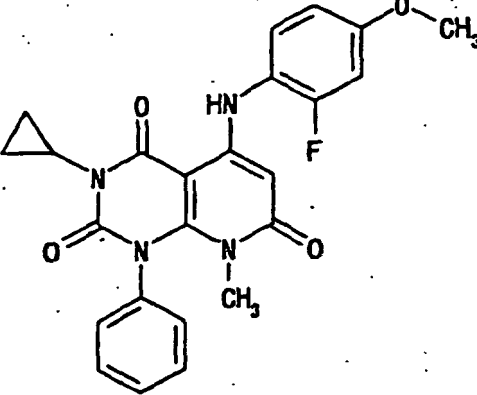
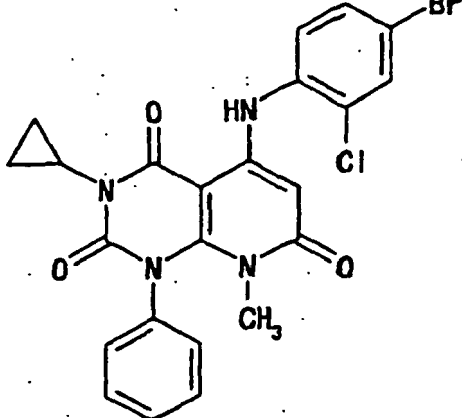
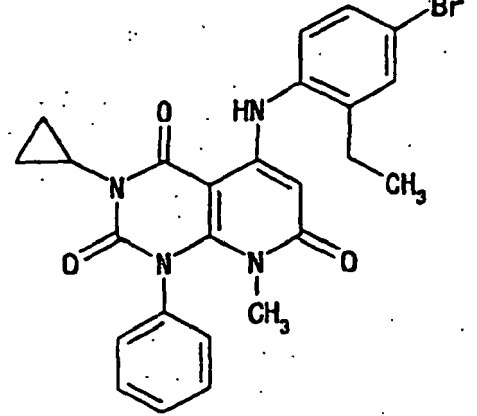
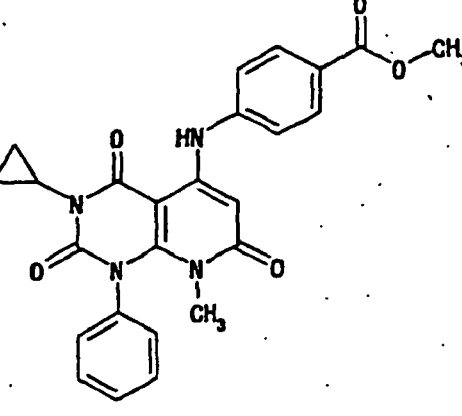
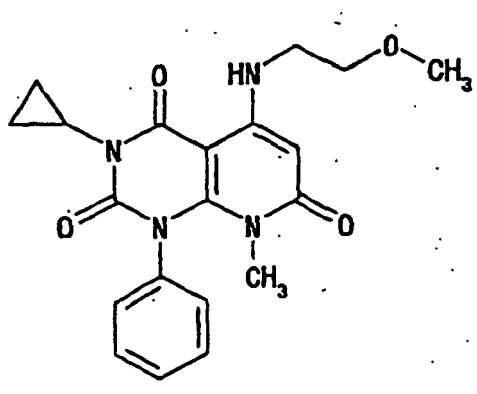
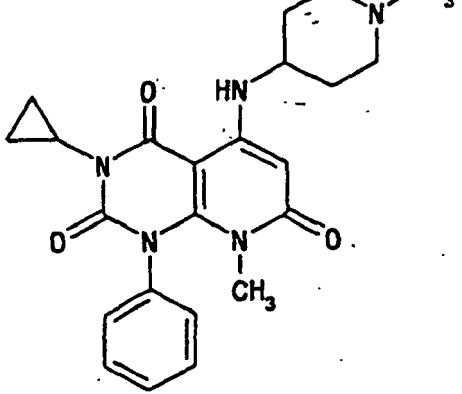
Table 1-29

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-169		1-170	
20 25 30 1-171		1-172	
35 40 45 1-173		1-174	

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Table 1-30

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-175		1-176	
20 25 30 1-177		1-178	
35 40 45 1-179		1-180	

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Table 1-31

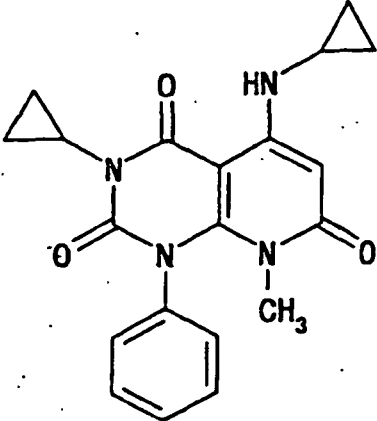
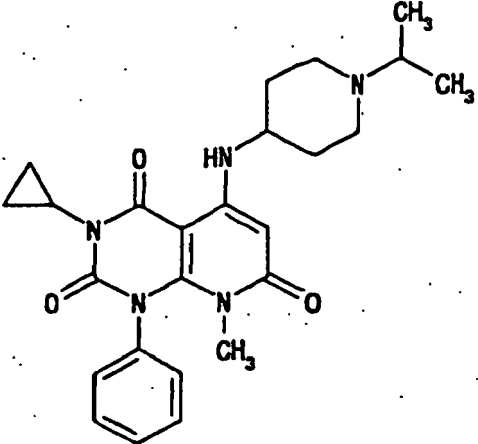
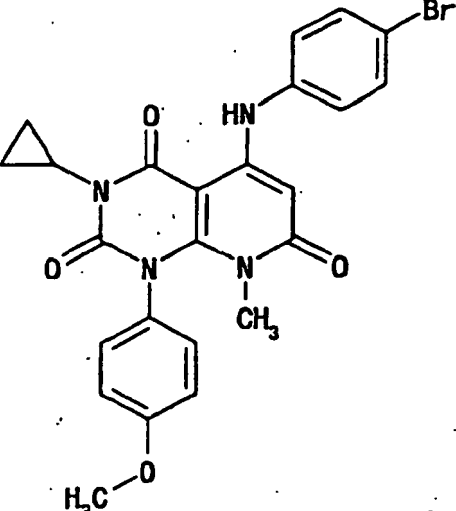
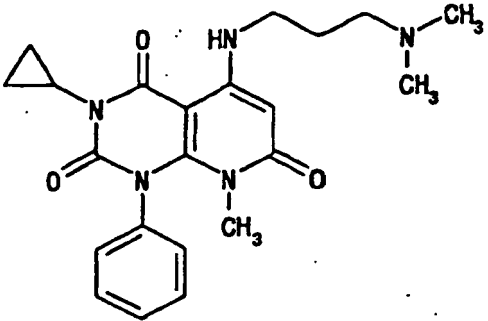
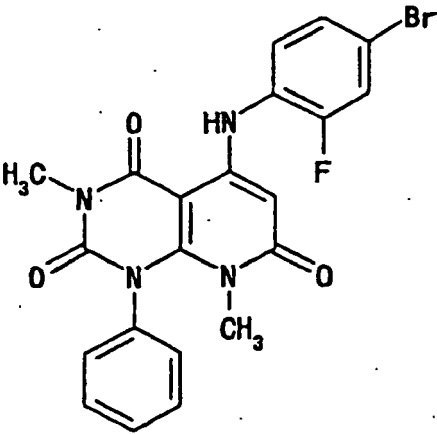
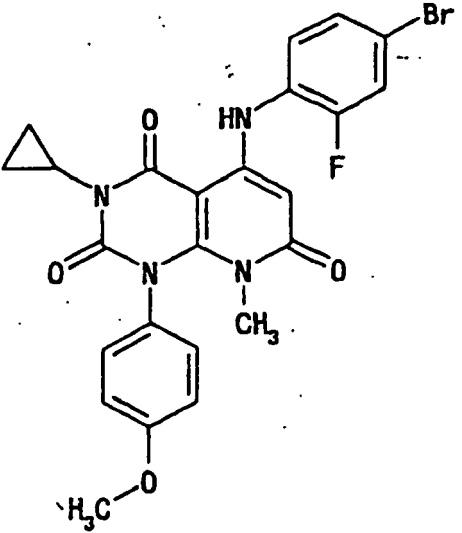
Ex. No.	structural formula	Ex. No.	structural formula
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1-183		1-184	
1-185		1-186	

Table 1-32

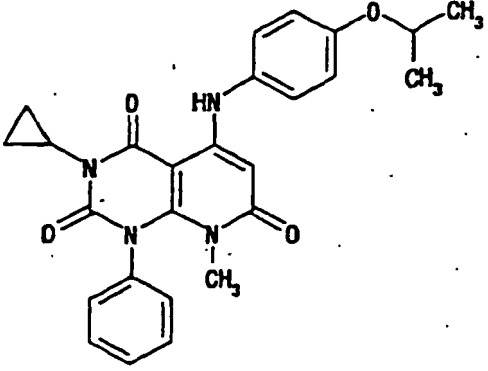
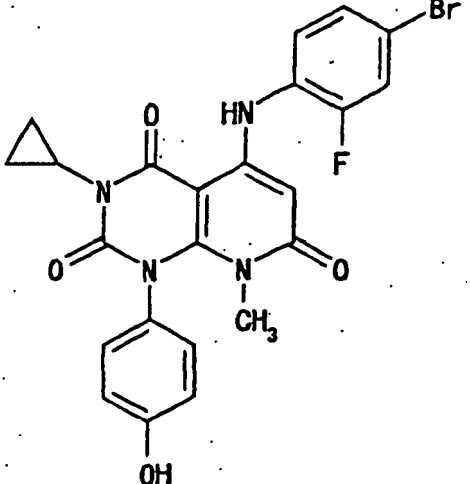
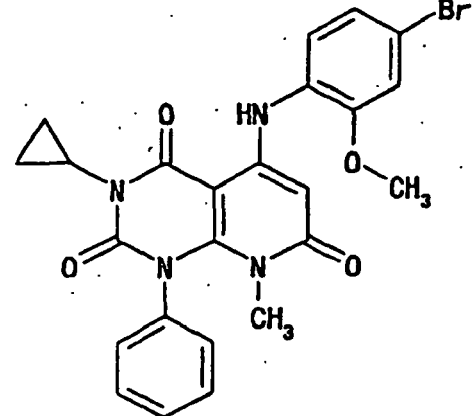
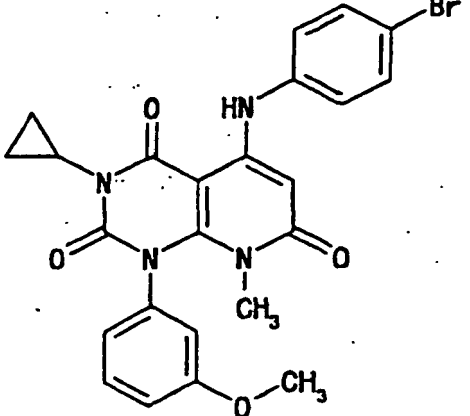
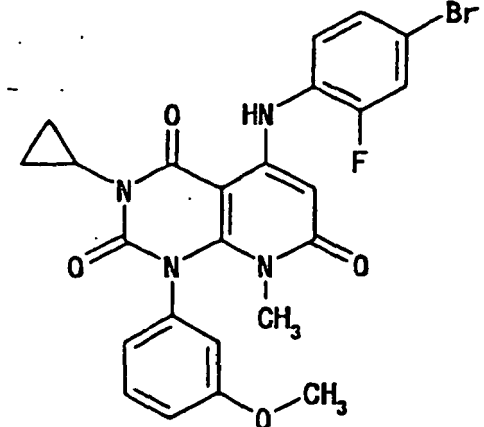
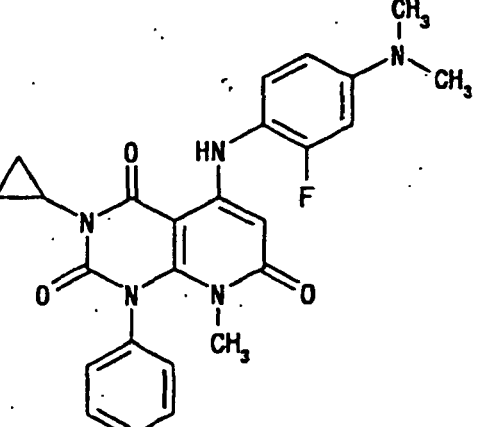
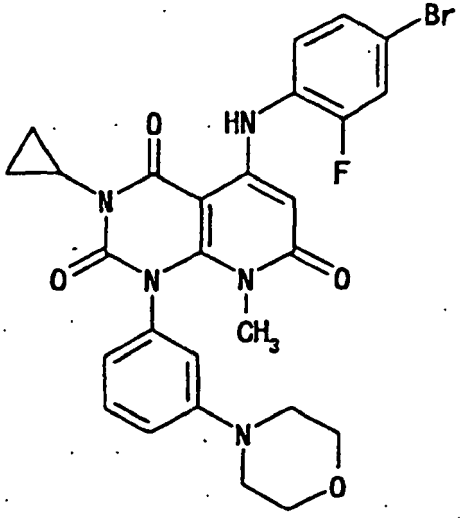
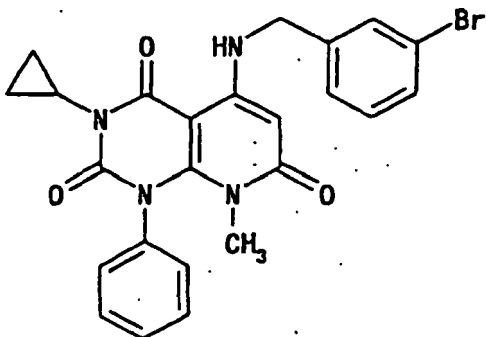
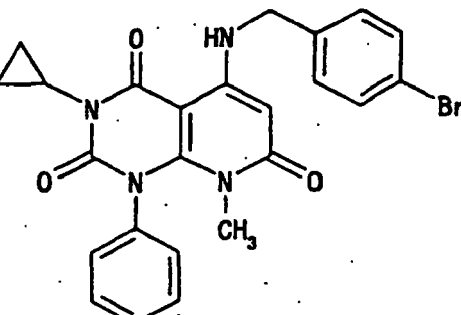
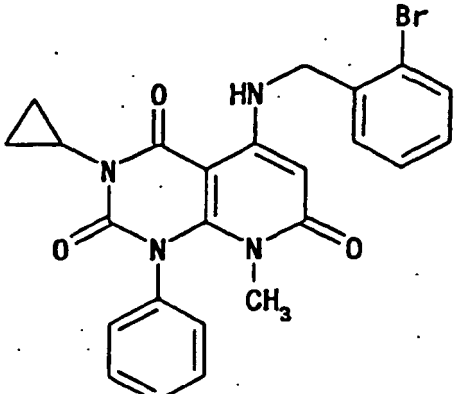
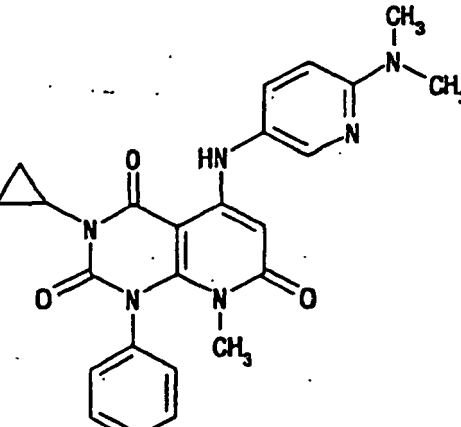
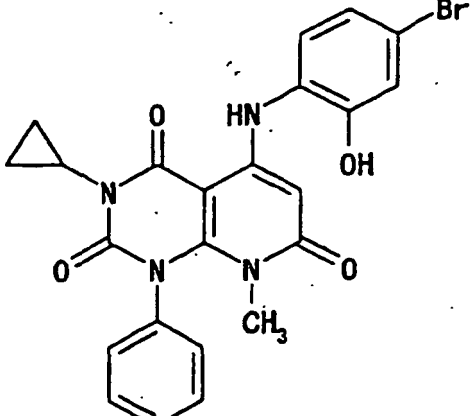
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5 10 15 20 1-187		1-188	
25 30 35 1-189		1-190	
40 45 50 1-191		1-192	

Table 1-33

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-193		1-194	
25 30 35 1-195		1-196	
40 45 50 1-197		1-198	

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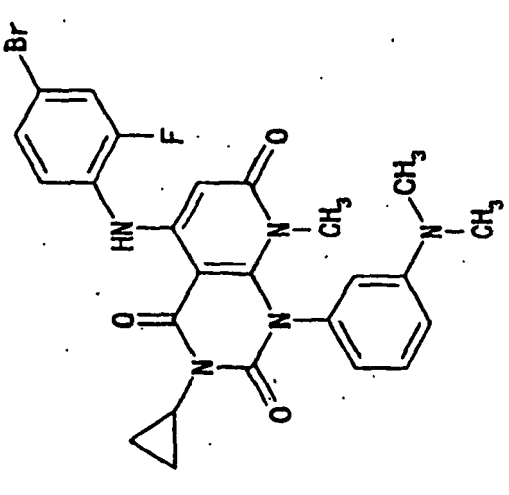
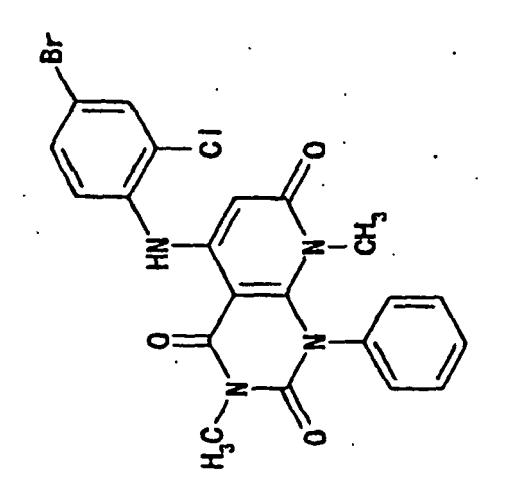
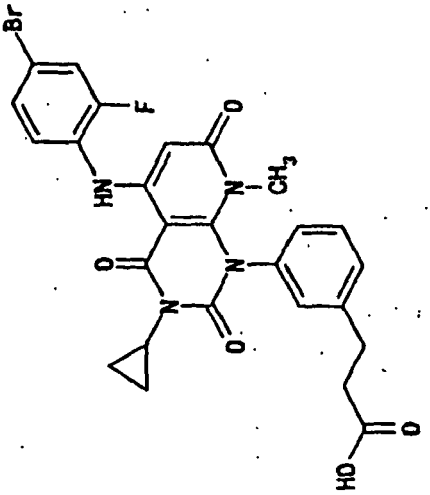
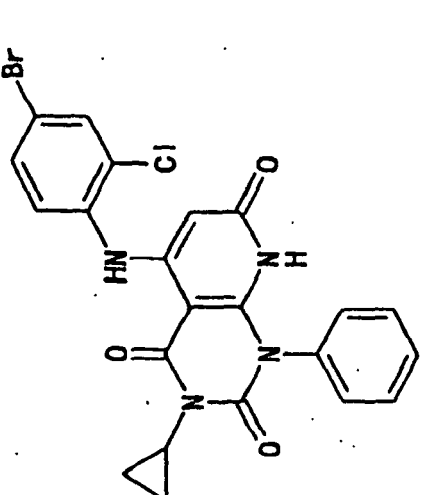
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Table 1-34

Ex. No.	structural formula No.	Ex. No.	structural formula
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1-201		1-202	

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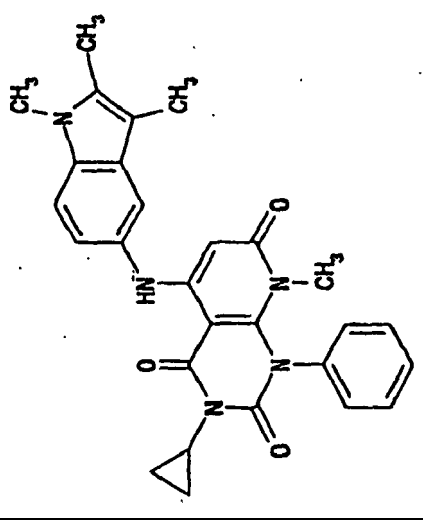
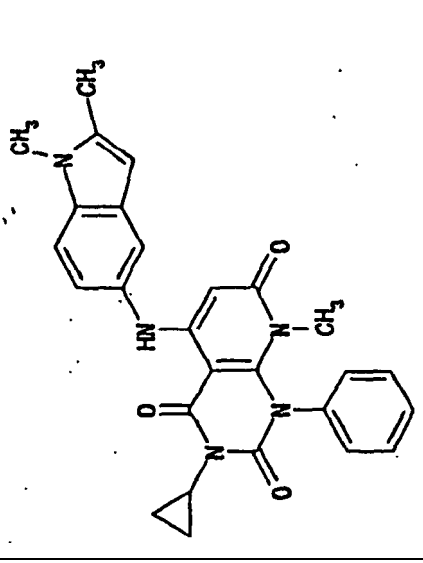
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Ex. No.	structural formula No.	Ex. No.	structural formula
1-203		1-204	

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Table 1-35

Ex. No.	structural formula	Ex. No.	structural formula
1-205		1-206	
1-207		1-208	
1-209		1-210	

Table 1-36

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-211		1-212	
25 30 35 1-213		1-214	
40 45 50 1-215		1-216	

Table 1-37

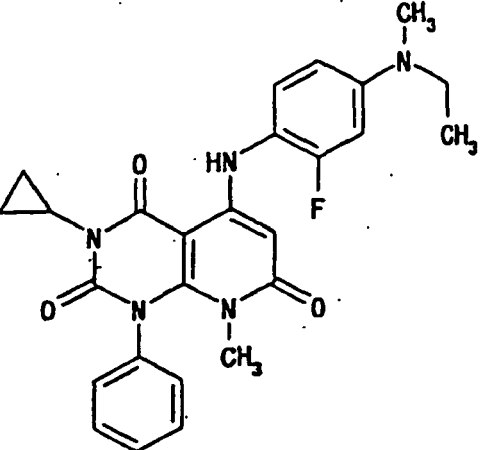
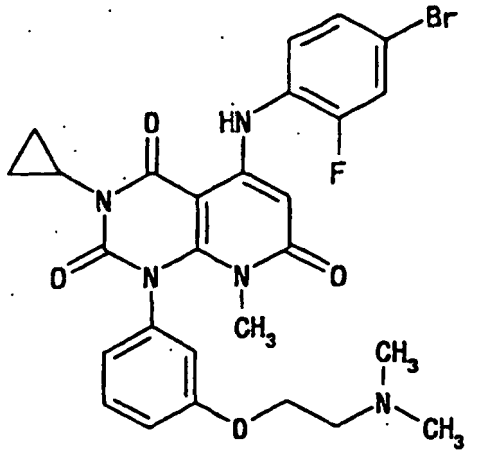
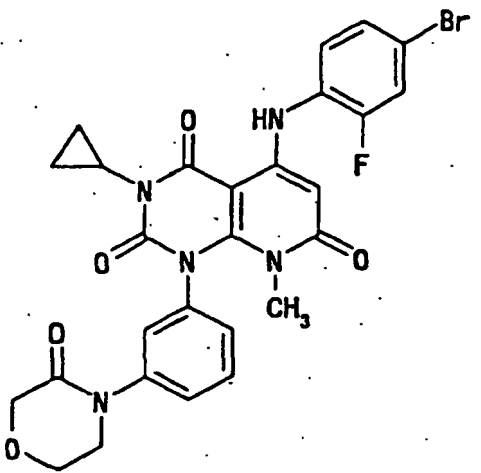
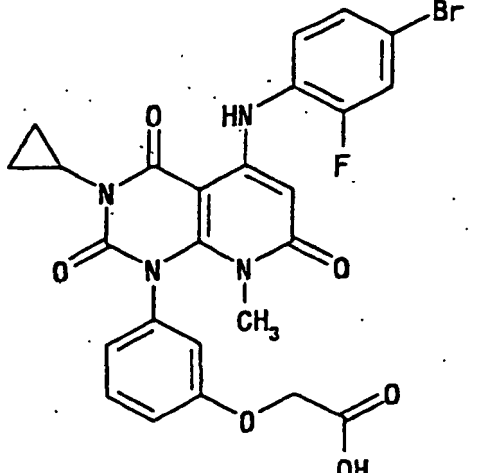
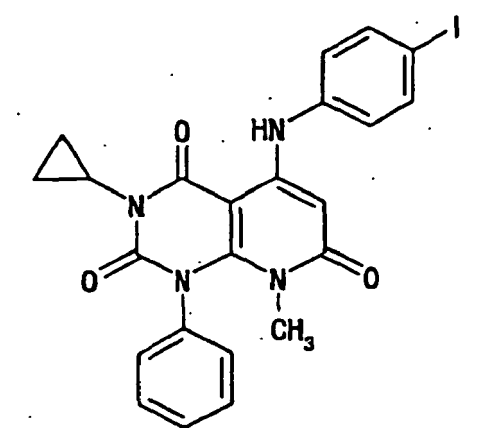
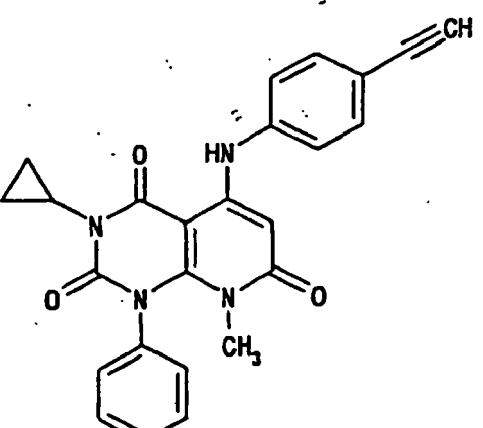
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 25 30 35 40 45 50		1-218	
20 25 30 35		1-220	
40 45 50		1-222	

Table 1-38

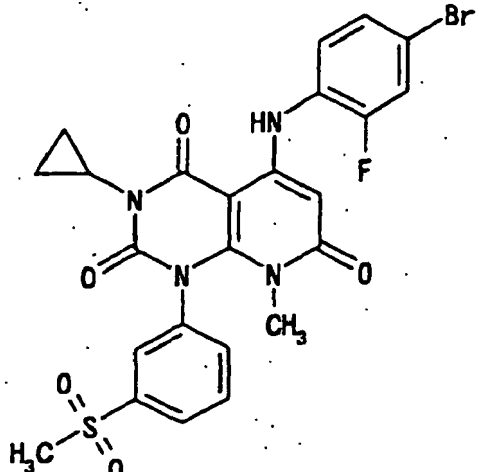
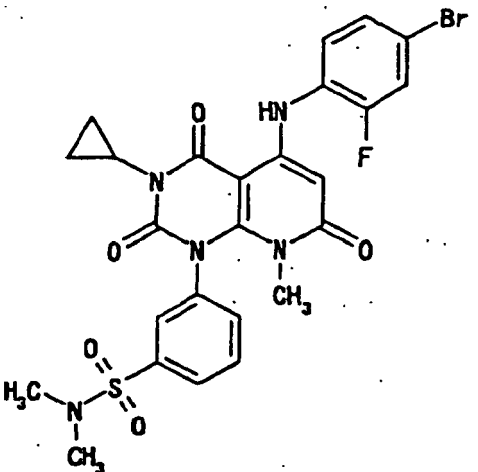
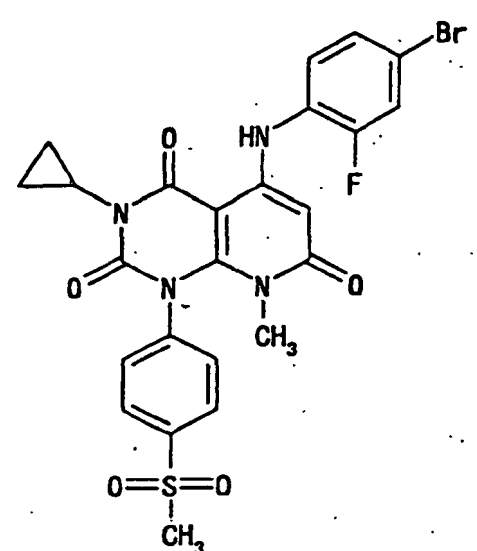
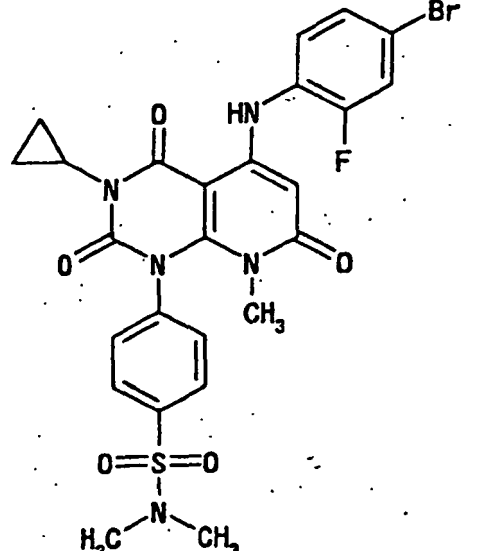
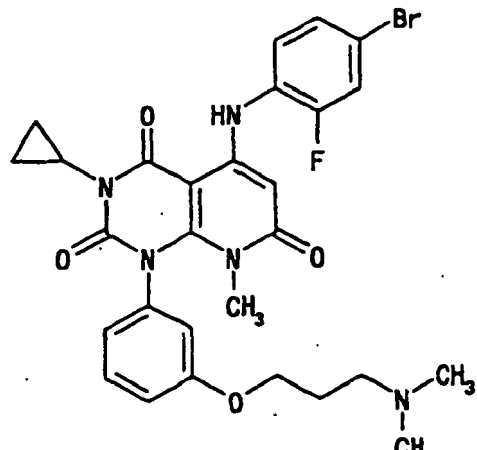
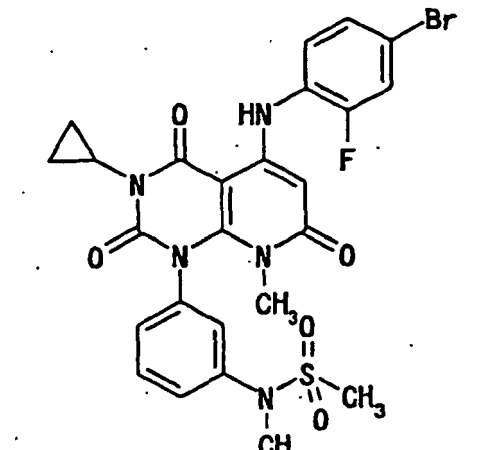
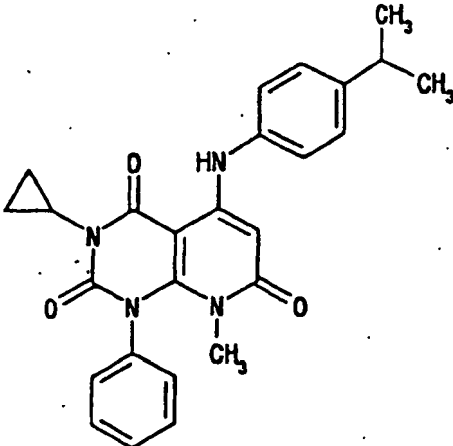
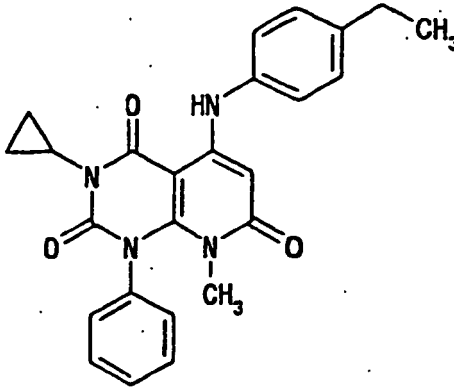
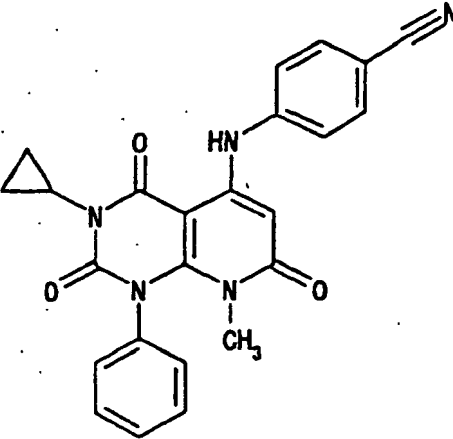
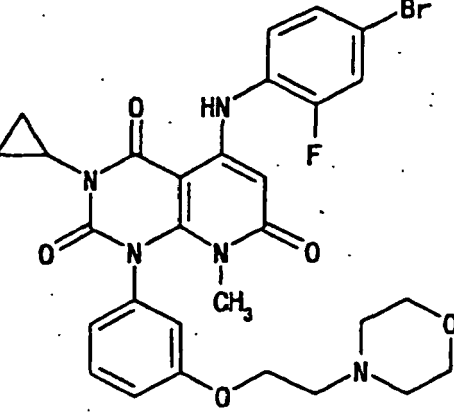
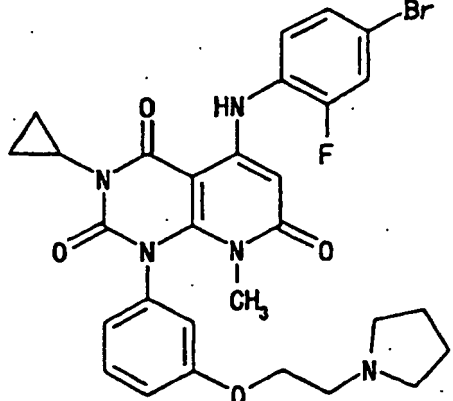
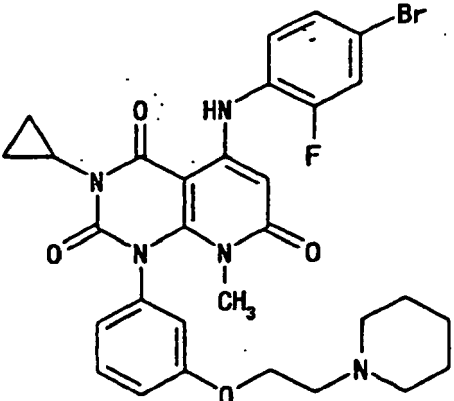
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5 10 15 1-223		1-224	
20 25 30 35 1-225		1-226	
40 45 50 55 1-227		1-228	

Table 1-39

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-229		1-230	
20 25 30 1-231		1-232	
35 40 45 1-233		1-234	

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Table 1-40

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-235		1-236	
20 25 30 1-237		1-238	
35 40 45 1-239		1-240	

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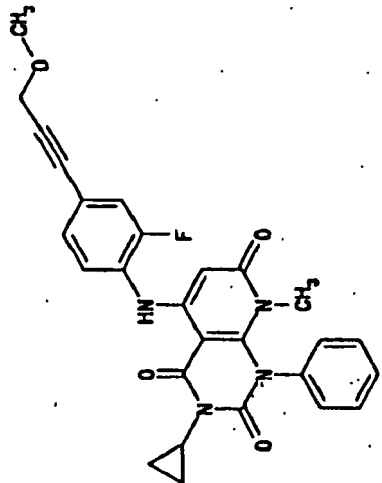
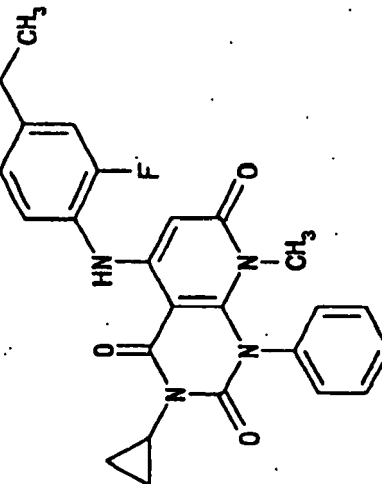
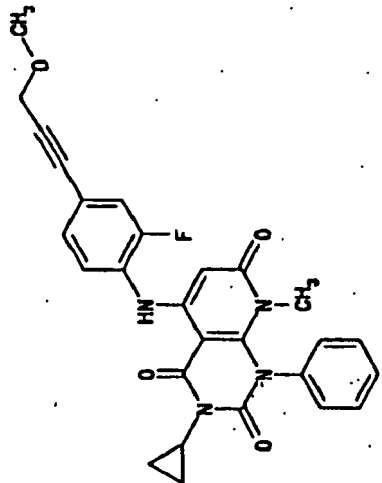
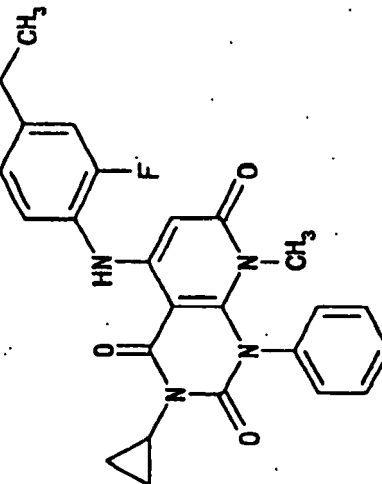
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Table 1-41

Ex. No.	structural formula	Ex. No.	structural formula
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1-243		1-244	

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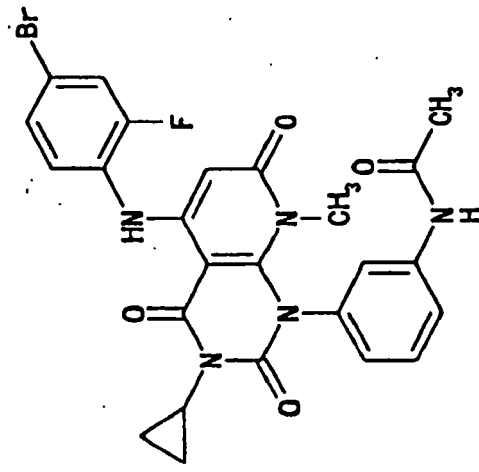
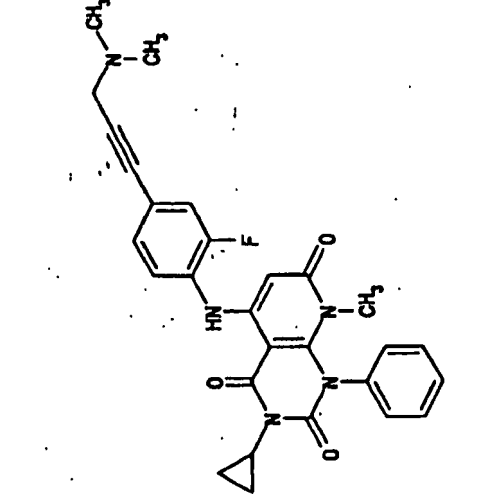
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Ex. No.	structural formula	Ex. No.	structural formula
1-245		1-246	

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Table 1-42

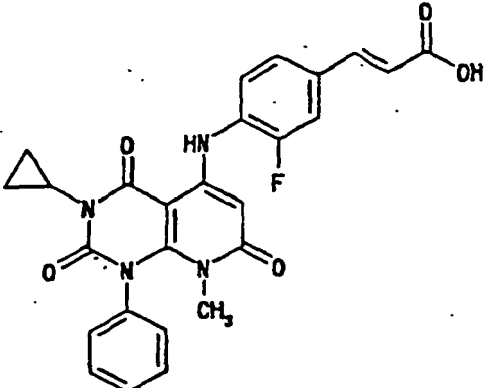
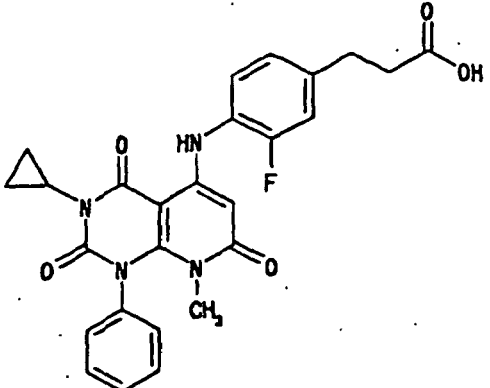
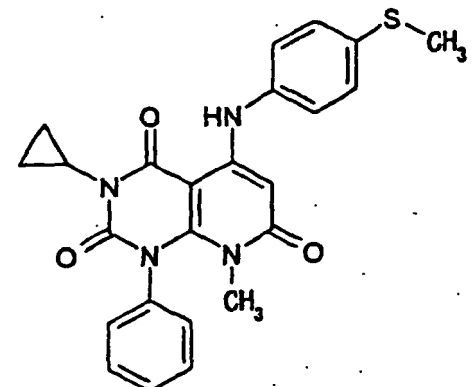
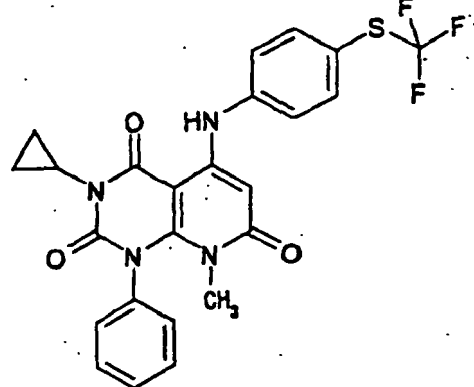
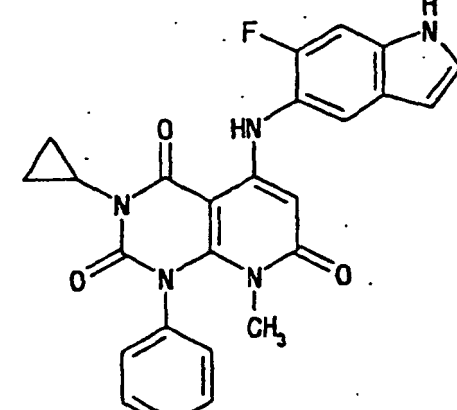
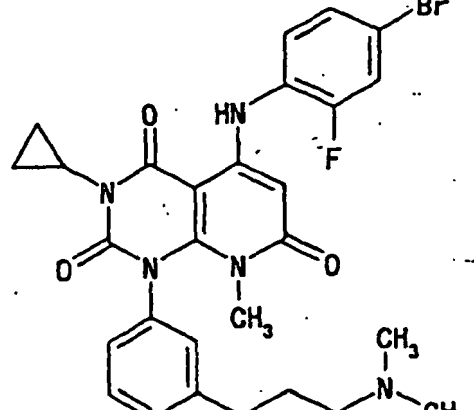
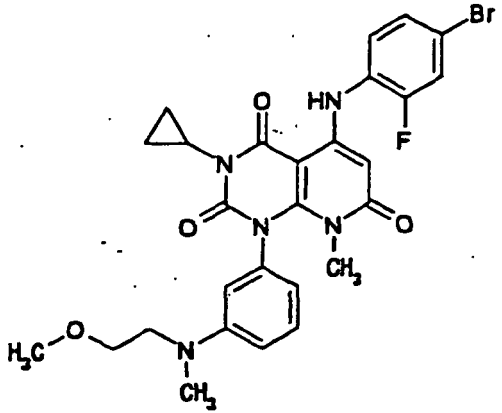
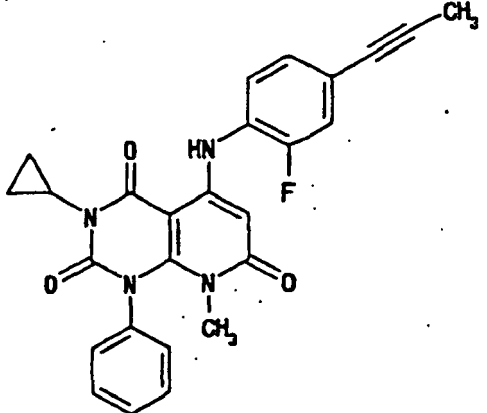
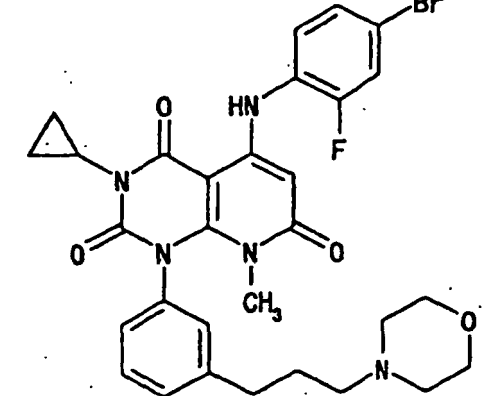
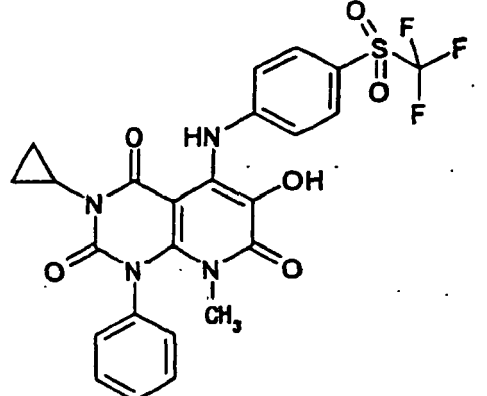
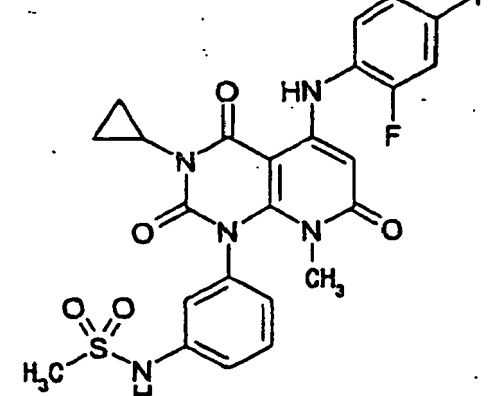
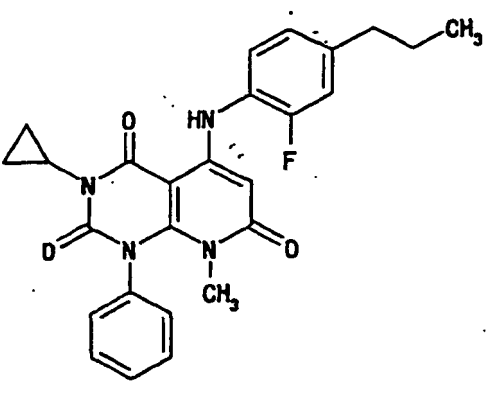
Ex. No.	structural formula	Ex. No.	structural formula
1-247		1-248	
1-249		1-250	
1-251		1-252	

Table 1-43

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-253		1-254	
20 25 30 1-255		1-256	
35 40 45 1-257		1-258	

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Table 1-44

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-259		1-260	
25 30 35 1-261		1-262	
40 45 50 1-263		1-264	

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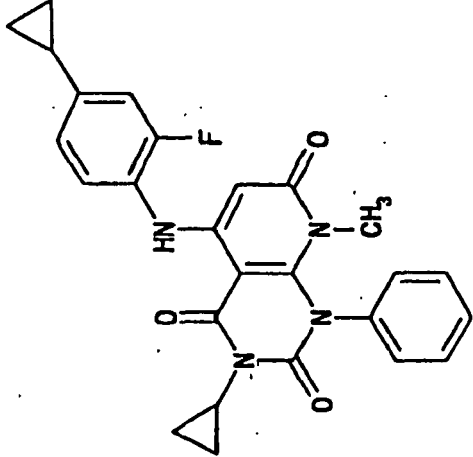
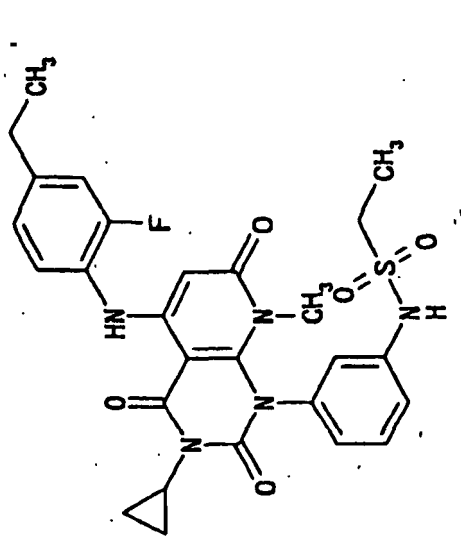
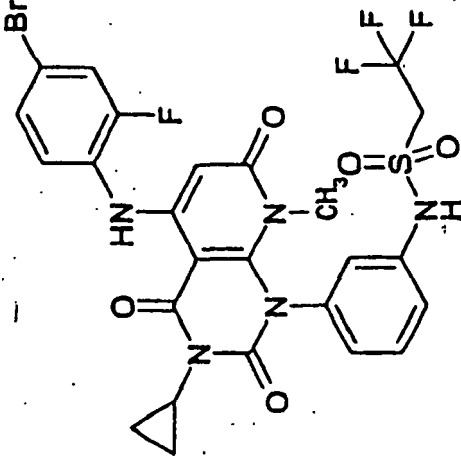
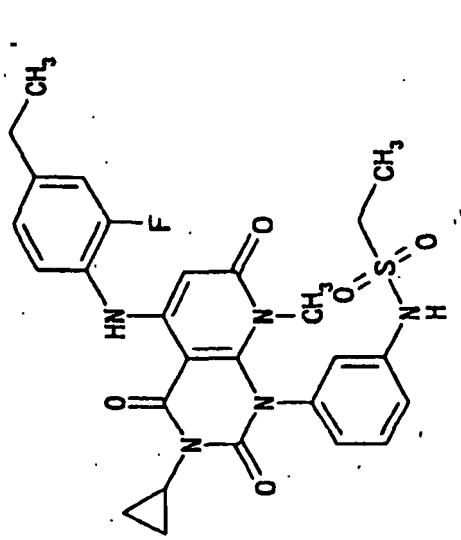
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Table 1-45

Ex. No.	structural formula	Ex. No.	structural formula
1-265		1-266	
1-267		1-268	

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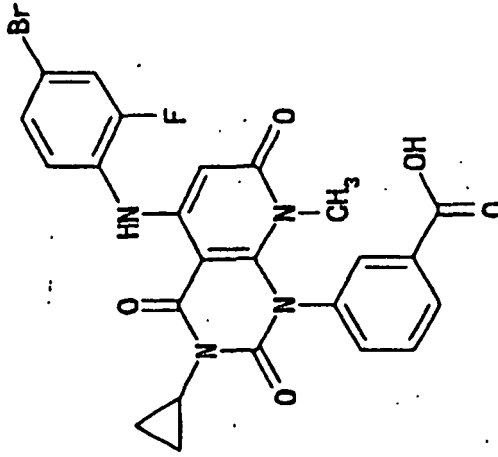
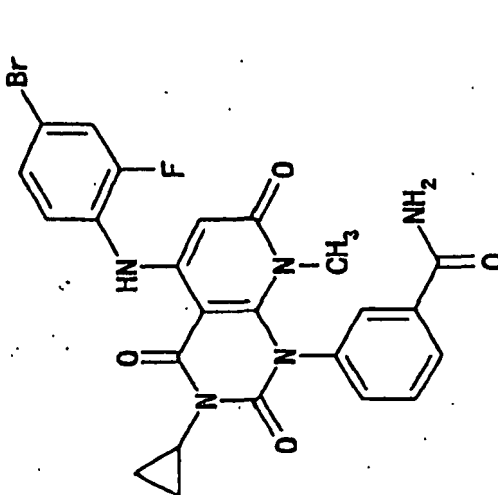
Ex. No.	structural formula	Ex. No.	structural formula
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Table 1-46

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-271		-272	
25 30 35 1-273		1-274	
40 45 50 1-275		1-276	

Table 1-47

Ex. No.	structural formula	Ex. No.	structural formula No.
5 10 15 20 1-277		1-278	
25 30 35 1-279		L-280	
40 45 50 1-281		1-282	

Table 1-48

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-283		1-284	
25 30 35 1-285		1-286	
40 45 50 1-287		1-288	

Table 1-49

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-289		1-290	
25 30 35 1-291		1-292	
40 45 50 55 1-293		1-294	

Table 1-50

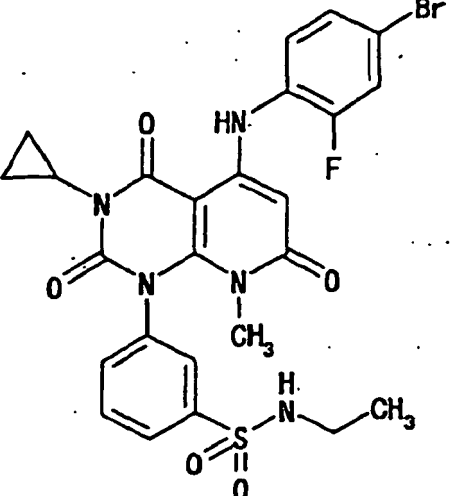
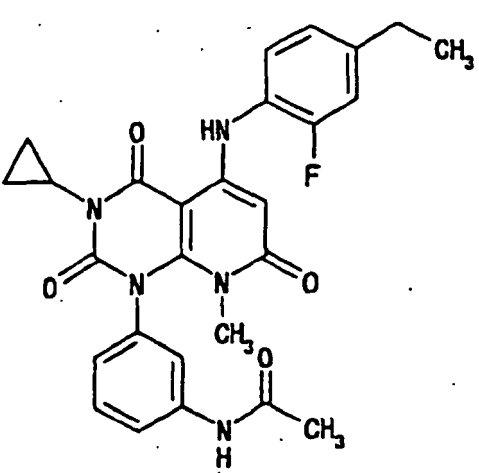
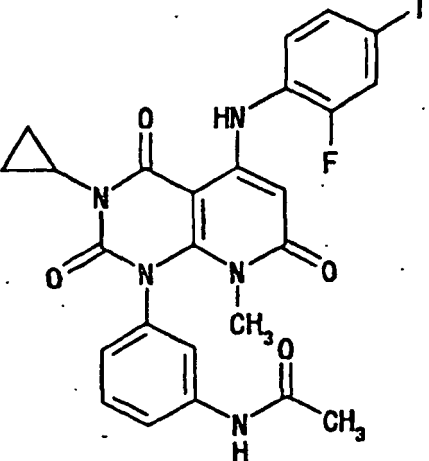
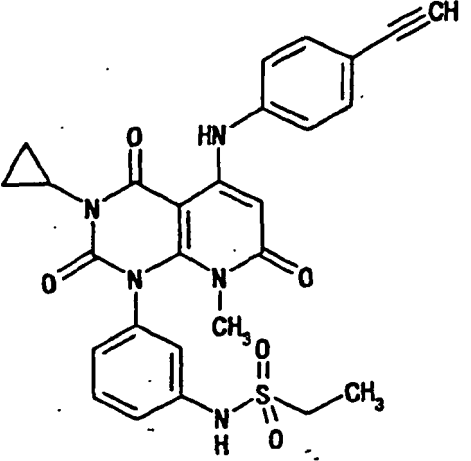
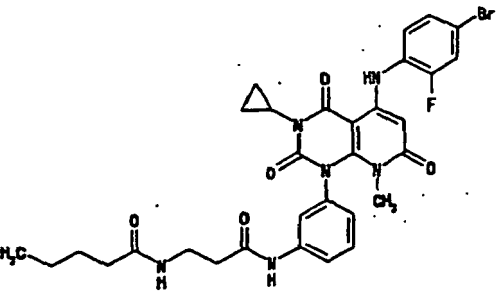
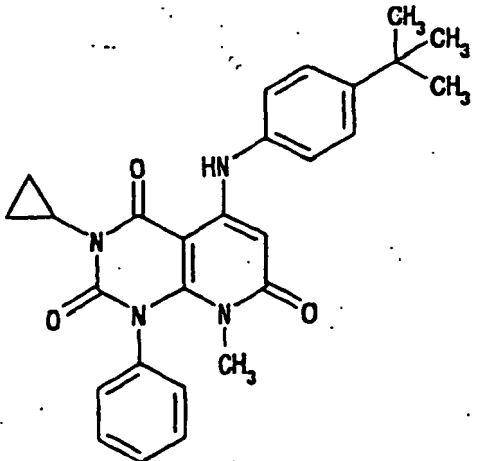
Ex. No.	structural formula No.	Ex. No.	structural formula
5 10 15 20 1-295		1-296	
25 30 35 1-297		1-298	
40 45 50 1-299		1-300	

Table 1-51

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-301		1-302	
25 30 35 1-303		1-304	
40 45 50 55 1-305		1-306	

Table 1-52

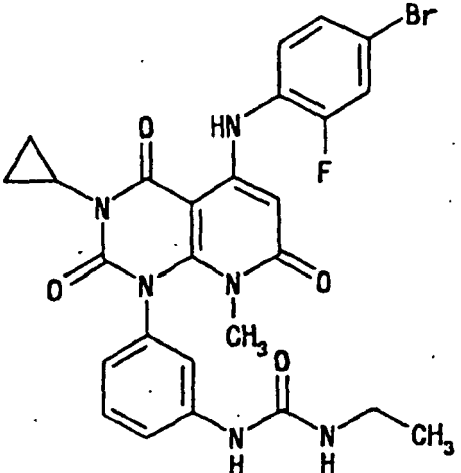
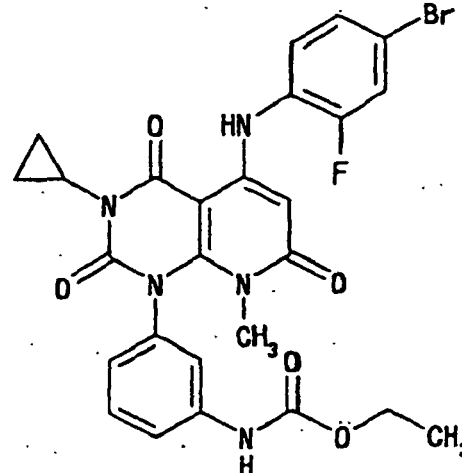
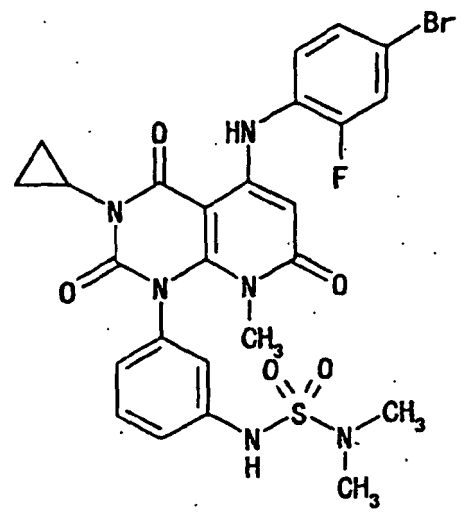
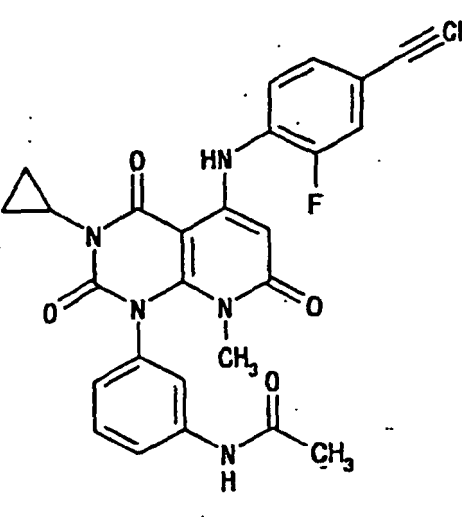
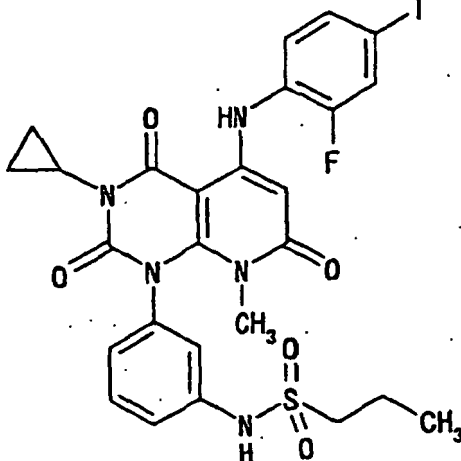
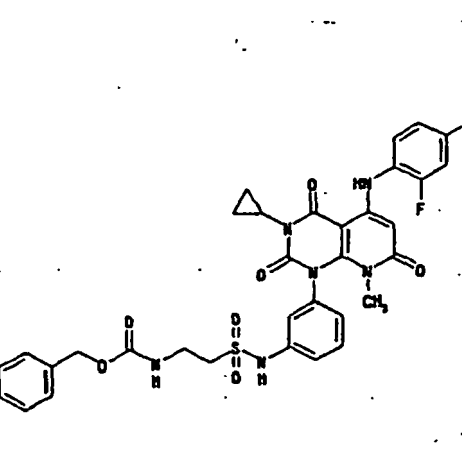
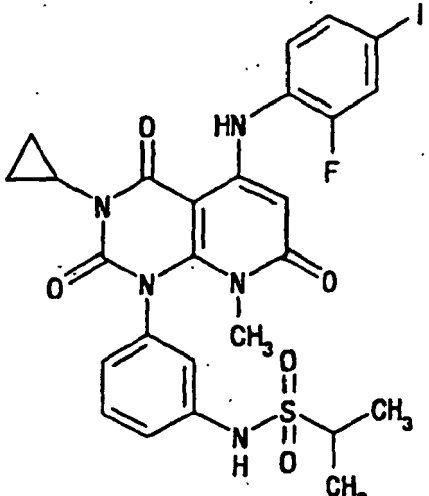
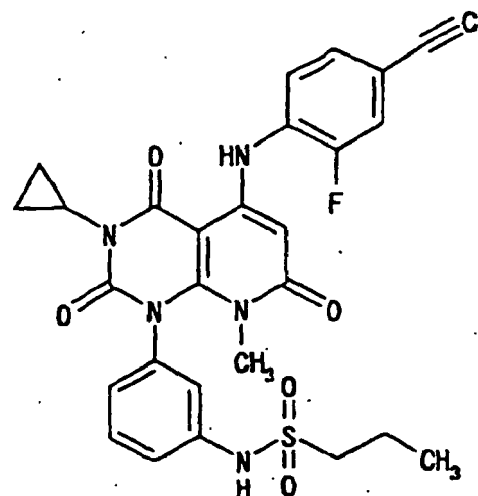
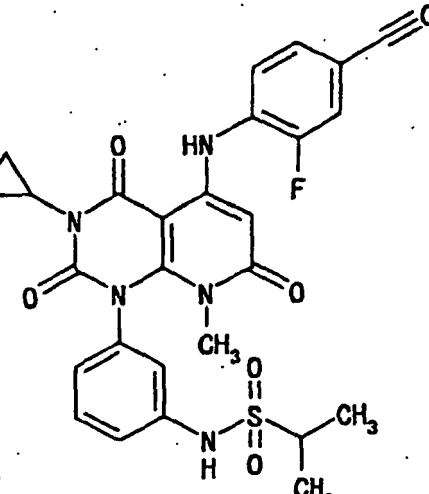
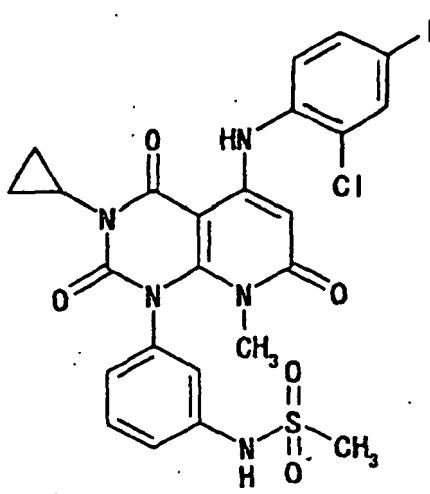
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-307		1-308	
25 30 35 1-309		1-310	
40 45 50 55 1-311		1-312	

Table 1-53

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-313		1-314	
20 25 30 1-315		1-316	
35 40 45 50 1-317		1-318	

Table 1-54

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-319		1-320	
25 30 35 1-321		1-322	

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Table 1-55

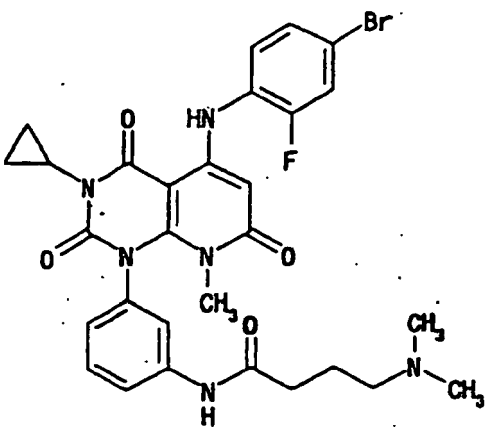
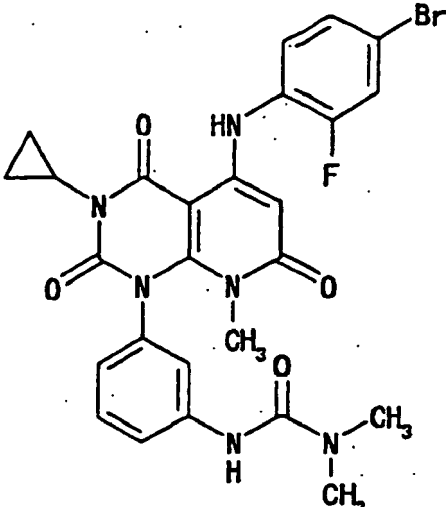
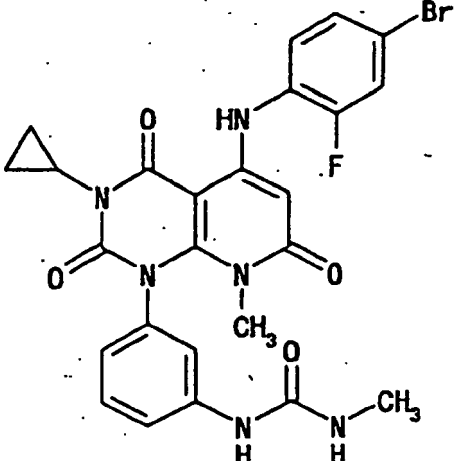
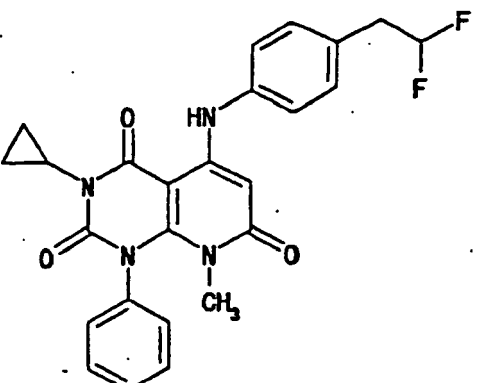
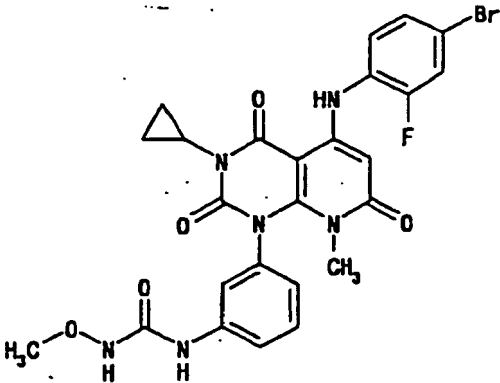
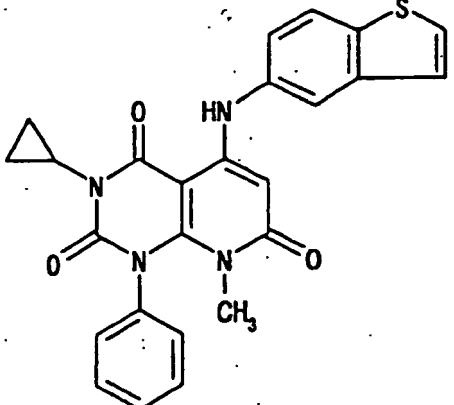
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 1-323		1-324	
25 30 35 1-325		1-326	
40 45 50 1-327		1-328	

Table 1-56

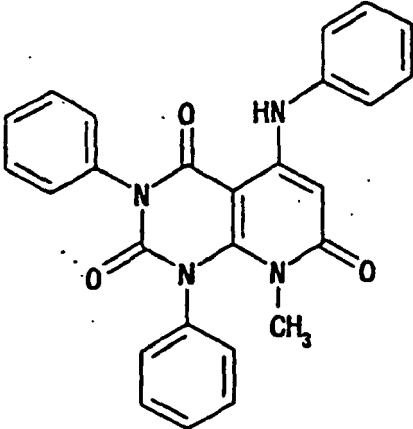
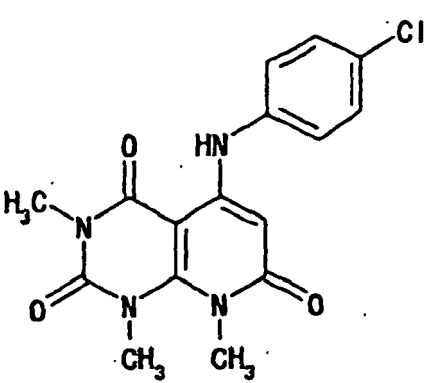
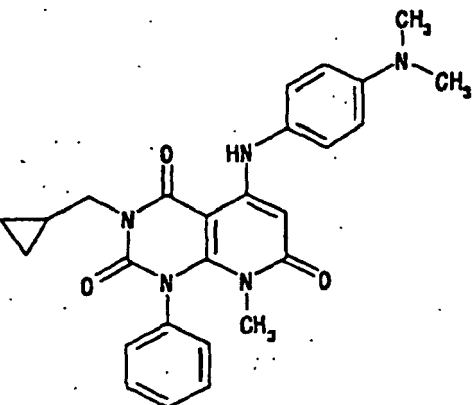
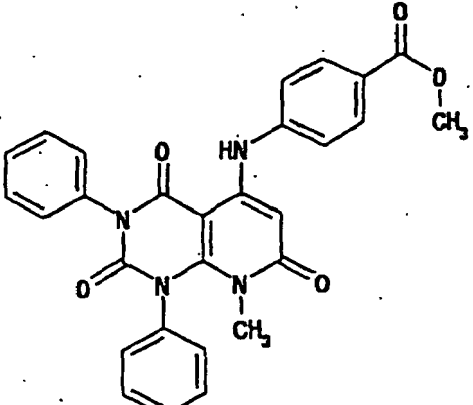
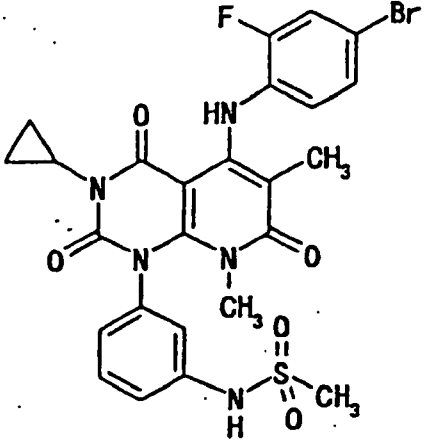
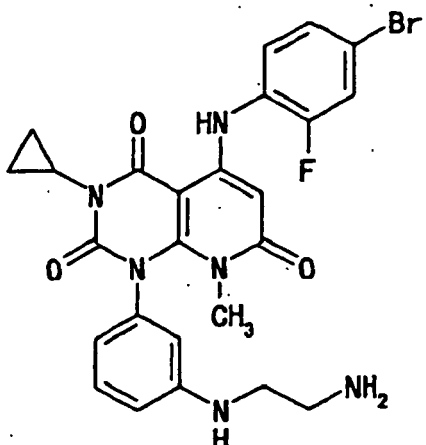
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-329		1-330	
20 25 30 1-331		1-332	

Table 1-57

Ex. No.	structural formula	Ex. No.	structural formula
40 45 50 1-333		1-334	

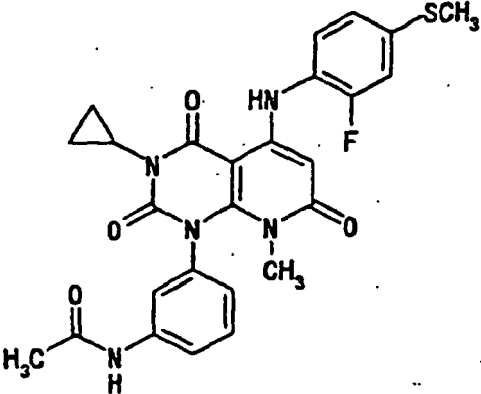
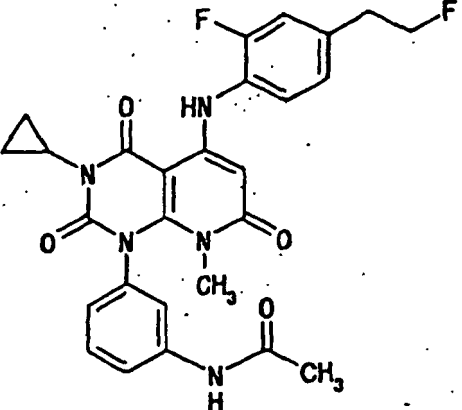
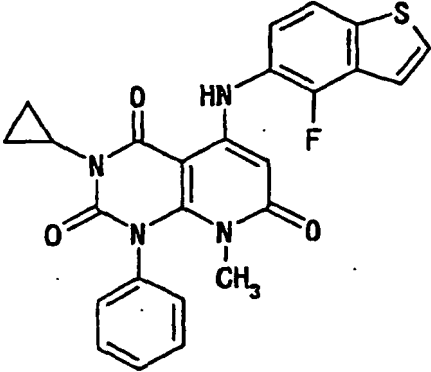
(continued)

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-335		1-336	
20 25 30 1-337		1-338	

Table 1-58

Ex. No.	structural formula	Ex. No.	structural formula
40 45 50 55 1-339		1-340	

(continued)

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 1-341		5 1-342	
20 25 30 1-343			

Example 2-1

35 Synthesis of 5-(4-chloro-phenylamino)-8-methyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione

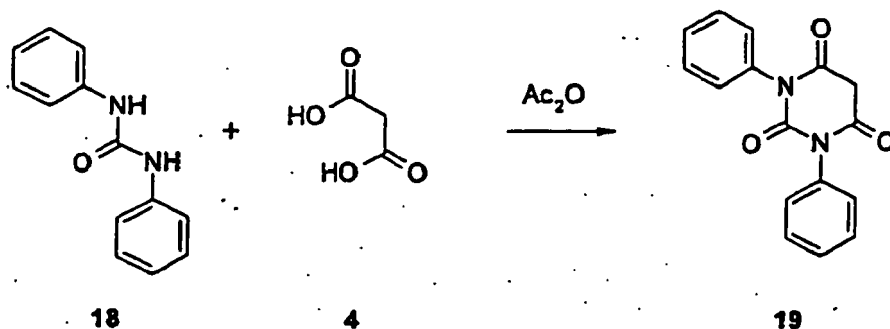
Step 1 Synthesis of 1,3-diphenyl-pyrimidine-2,4,6-trione

[0274]

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[0275] Acetic anhydride (290 ml) was added to 1,3-diphenylurea 18 (148 g), malonic acid 4 (81.6 g) was added under a nitrogen atmosphere, and the mixture was stirred at 90°C for 3 hrs. The mixture was stirred at 100°C for 1.5 hrs and allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure. Ethanol (500 ml) was added to the residue, and the mixture was stirred at 90°C. When the mixture was cooled to 40°C, the crystals were collected by filtration, washed with ethanol and dried to give 1,3-diphenyl-pyrimidine-2,4,6-trione 19 (78.0 g, yield 40%).

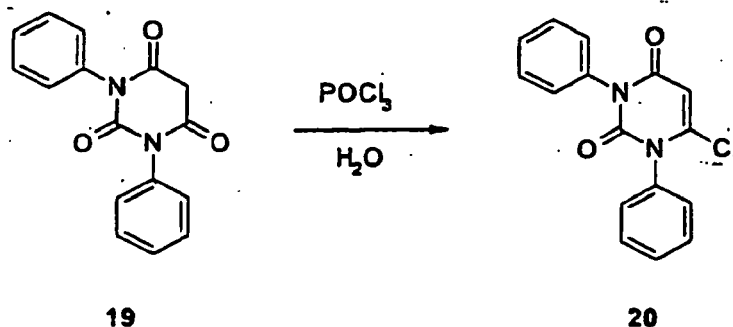
Step 2 Synthesis of 6-chloro-1,3-diphenyl-1H-pyrimidine-2,4-dione

[0276]

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[0277] To 1,3-diphenyl-pyrimidine-2,4,6-trione 19 (78.0 g) obtained in Step 1 was added water (16 ml). Phosphorus oxychloride (422 ml) was added dropwise under stirring at room temperature over 50 min. After the completion of the dropwise addition, the mixture was stirred under heating at 110°C for 3 hrs. After allowing to cool to room temperature, the reaction mixture was added to ice water by small portions and the mixture was stirred at room temperature and extracted with ethyl acetate. The organic layer was washed with brine and saturated aqueous sodium hydrogen carbonate, and dried over anhydrous sodium sulfate. Anhydrous sodium sulfate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate=2:1-3:2) to give 6-chloro-1,3-diphenyl-1H-pyrimidine-2,4-dione 20 (61.5 g, yield 74%) as pale-yellow crystals.

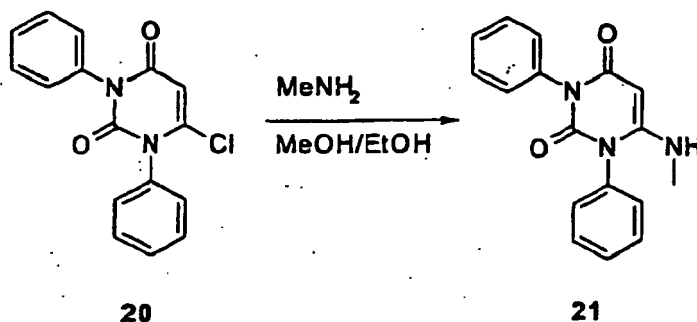
Step 3 Synthesis of 6-methylamino-1,3-diphenyl-1H-pyrimidine-2,4-dione

[0278]

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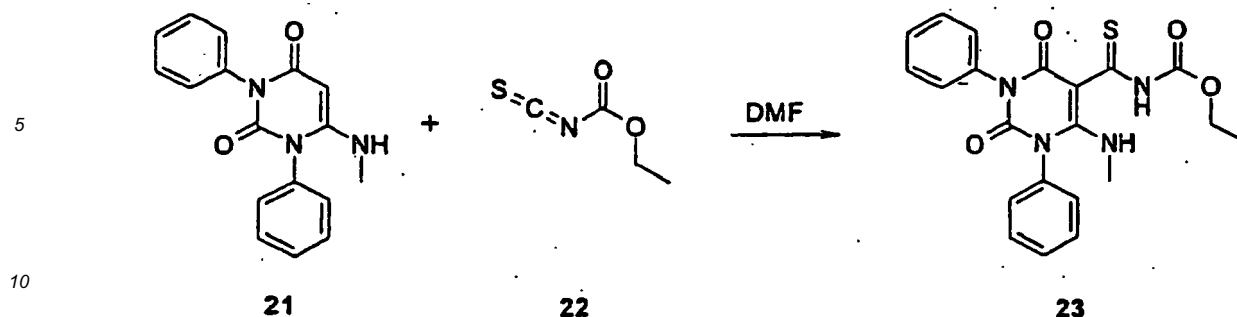
[0279] In the same manner as in Step 4 of Example 1-1 and using 6-chloro-1,3-diphenyl-1H-pyrimidine-2,4-dione 20 (5.0 g) obtained in Step 2, ethanol (25 ml), a 40% solution (21.7 ml) of methylamine in methanol, 6-methylamino-1,3-diphenyl-1H-pyrimidine-2,4-dione 21 (4.42 g, yield 90%) was obtained as colorless crystals.

Step 4 Synthesis of ethyl (6-methylamino-2,4-dioxo-1,3-diphenyl-1,2,3,4-tetrahydro-pyrimidine-5-thiocarbonyl)-carbamate

[0280]

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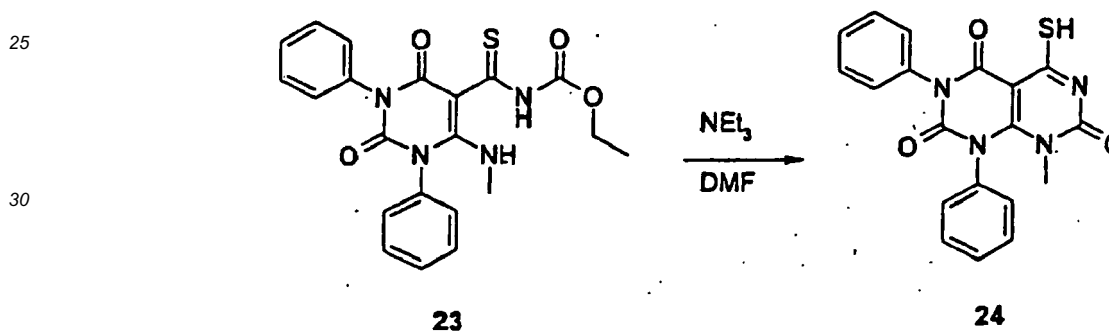
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15 [0281] To 6-methylamino-1,3-diphenyl-1H-pyrimidine-2,4-dione 21 (1.18 g) obtained in Step 3 was added N,N-dimethylformamide (5.9 ml), ethyl isothiocyanate formate 22 (0.52 ml) was added under a nitrogen atmosphere, and the mixture was stirred at room temperature for 1 hr. Water (30 ml) was added to the reaction mixture, and the crystals were collected by filtration and washed with water to give crude ethyl (6-methylamino-2,4-dioxo-1,3-diphenyl-1,2,3,4-tetrahydro-pyrimidine-5-thiocarbonyl)-carbamate 23 (1.68 g) as pale-yellow crystals, which were used for the next step without purification.

20 Step 5 Synthesis of 5-mercapto-8-methyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione

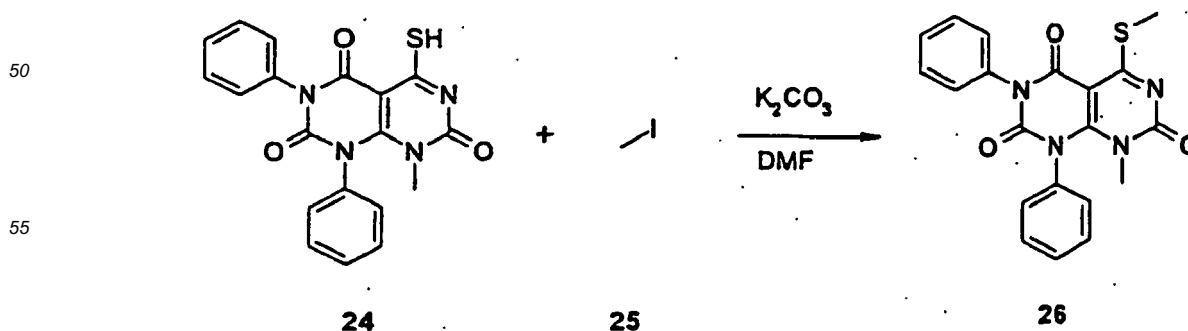
[0282]



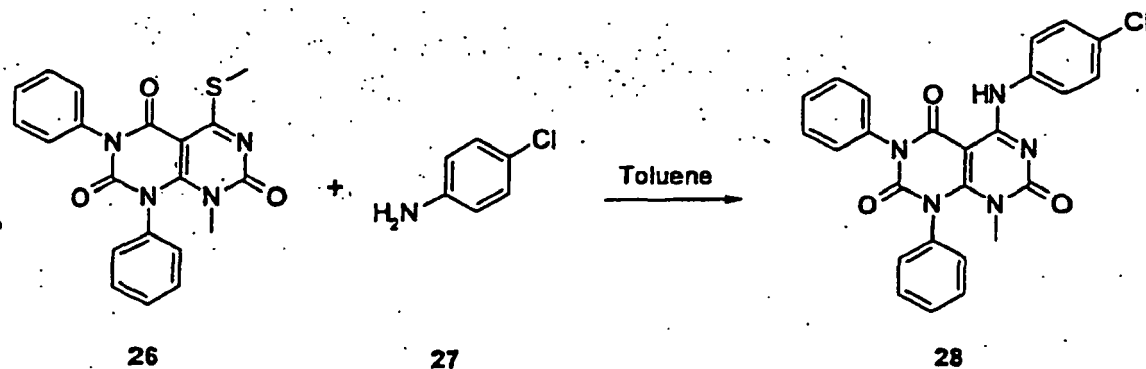
35 [0283] To crude ethyl (6-methylamino-2,4-dioxo-1,3-diphenyl-1,2,3,4-tetrahydro-pyrimidine-5-thiocarbonyl)-carbamate 23 (1.58 g) obtained in Step 4 was added N,N-dimethylformamide (8.4 ml) triethylamine (0.63 ml) was added under a nitrogen atmosphere, and the mixture was stirred at room temperature for 30 min. Water (25 ml) was added, the mixture was stirred, 1N hydrochloric acid (5.0 ml) was added, and the mixture was stirred at room temperature for 1 hr. The crystals were collected by filtration, washed with water and dried to give crude 5-mercapto-8-methyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione 24 (1.53 g, over weight) as yellow crystals, which were used for the next step without purification.

45 Step 6 Synthesis of 8-methyl-5-methylsulfanyl-1,3-diphenyl-1H, 8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione

[0284]



[0285] To crude 5-mercapto-8-methyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione 24 (100 mg) obtained in Step 5 was added N,N-dimethylformamide (0.5 ml). Under a nitrogen atmosphere, potassium carbonate (44 mg) and methyl iodide 25 (20 μ l) were successively added, and the mixture was stirred at room temperature for 3 hrs. Water was added, and the mixture was extracted with chloroform. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. Anhydrous sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate=4:1 \rightarrow 3:1) to give 8-methyl-5-methylsulfanyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione 26 (91 mg, yield 89%) as brown crystals. **Step 7** Synthesis of 5-(4-chloro-phenylamino)-8-methyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione



[0286] To 8-methyl-5-methylsulfanyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione 26 (149 mg) obtained in Step 6 was added toluene (2 ml), 4-chloroaniline 27 (97 mg) was added, and the mixture was stirred under reflux for 3.5 hrs. After allowing to cool to room temperature, diethyl ether was added. The crystals were collected by filtration, washed with diethyl ether and dried to give 5-(4-chloro-phenylamino)-8-methyl-1,3-diphenyl-1H,8H-pyrimido[4,5-d]pyrimidine-2,4,7-trione 28 (94 mg, yield 53%) as colorless crystals.

MS ESI m/e: 472 (M+H), 470 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 2.68 (s, 3H), 7.34-7.39 (m, 2H), 7.41-7.61 (m, 10H), 7.80-7.87 (m, 2H), 11.34 (s, 1H).

Example 2-2

[0287] In the same manner as in Example 2-1, the compounds of Example 2-2 were obtained. The structural formulas thereof are shown in Table 2-1 with Example 2-1.

Table 2-1

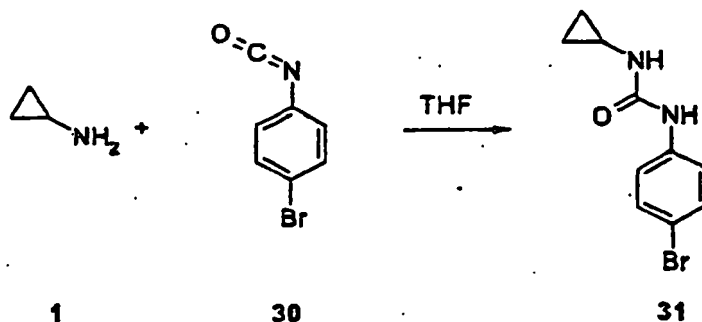
Ex. No.	structural formula	Ex. No.	structural formula
2-1		2-2	

Example 3-1

Synthesis of 5-(4-bromo-phenylamino)-3-cyclopropyl-6,8-dimethyl-1-phenylamino-1H,6H-pyrido[4,3-d]pyrimidine-2,4,7-trione

Step 1 Synthesis of 1-(4-bromo-phenyl)-3-cyclopropyl-urea

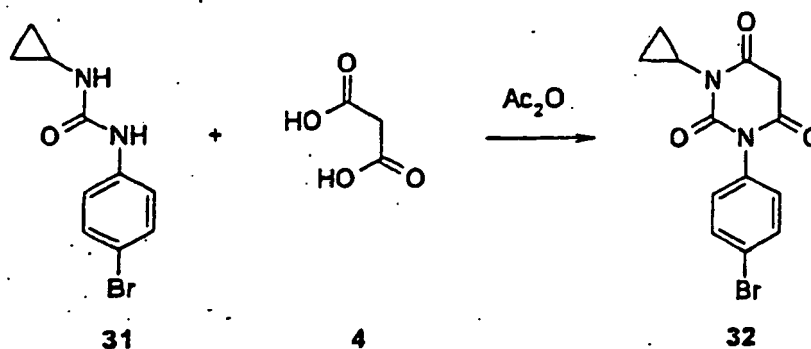
[0288]



[0289] Under a nitrogen atmosphere, tetrahydrofuran (80 ml) was added to 4-bromophenyl isocyanate **30** (10.0 g), and a solution of cyclopropylamine **1** (3.17 g) in tetrahydrofuran (20 ml) was added dropwise with stirring under ice-cooling: After the completion of the dropwise addition, the mixture was stirred at room temperature for 3 hrs, and the reaction mixture was concentrated under reduced pressure. Diethyl ether-hexane [1:1 (volume ratio), 100 ml] was added to the residue and, after stirring, the crystals were collected by filtration and dried to give 1-(4-bromo-phenyl)-3-cyclopropyl-urea **31** (12.9 g, excess) as colorless crystals, which were used for the next step without purification.

Step 2 Synthesis of 1-(4-bromo-phenyl)-3-cyclopropyl-pyrimidine-2,4,6-trione

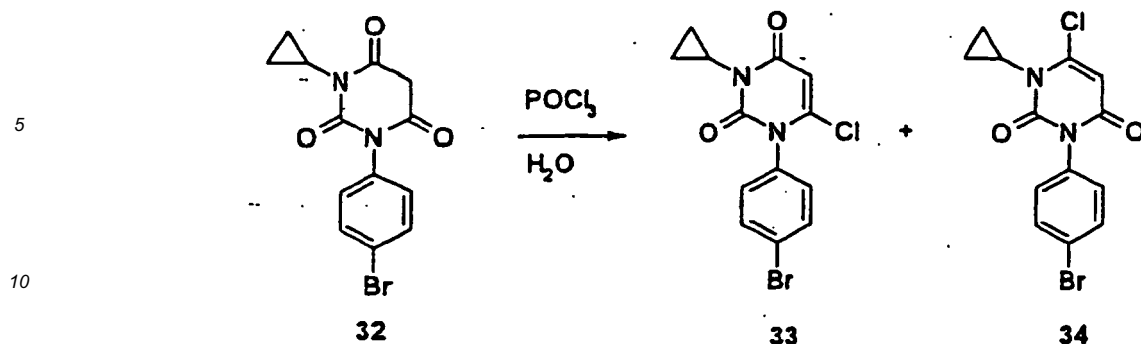
[0290]



[0291] To 1-(4-bromo-phenyl)-3-cyclopropyl-urea **31** (12.9 g) obtained in Step 1 was added acetic anhydride (25.8 ml), malonic acid **4** (5.79 g) was added under a nitrogen atmosphere, and the mixture was stirred at 100°C for 3 hrs. After allowing to cool to room temperature, the reaction mixture was concentrated under reduced pressure. Diethyl ether-ethanol [4:1 (volume ratio), 100 ml] was added to the residue and, after stirring, the crystals were collected by filtration and dried to give 1-(4-bromo-phenyl)-3-cyclopropyl-pyrimidine-2,4,6-trione **32** (11.9 g, yield 73%) as pale-yellow crystals.

Step 3 Synthesis of 1-(4-bromo-phenyl)-6-chloro-3-cyclopropyl-1H-pyrimidine-2,4-dione

[0292]

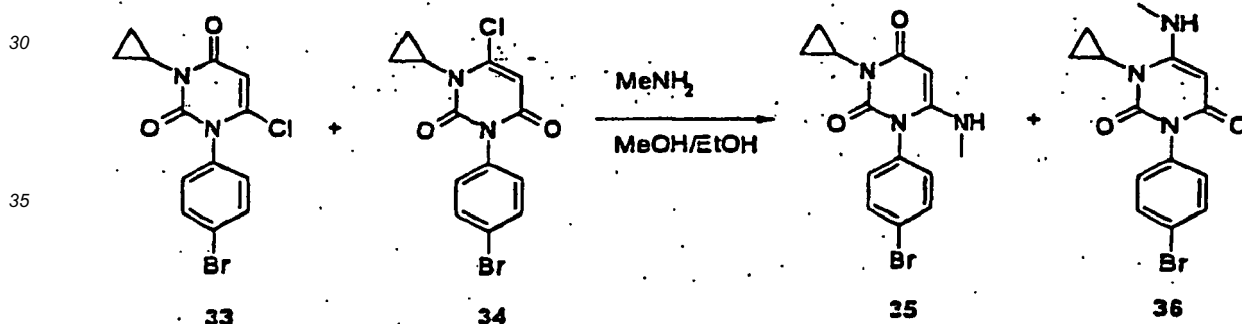


15 **[0293]** To 1-(4-bromo-phenyl)-3-cyclopropyl-pyrimidine-2,4,6-trione 32 (11.8 g) obtained in Step 2 was added water (1.31 ml) and phosphorus oxychloride (17.0 ml) was added dropwise with stirring at room temperature. After the completion of the dropwise addition, the mixture was stirred at 110°C for 3 hrs. After allowing to cool to room temperature, the reaction mixture was added to ice water by small portions and the mixture was stirred. The mixture was stirred at room temperature and extracted with chloroform. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. Anhydrous magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate=2:1-chloroform:acetone=30:1) to give a 1:1.4 mixture (11.6 g, yield 93%) of 1-(4-bromo-phenyl)-6-chloro-3-cyclopropyl-1H-pyrimidine-2,4-dione 33 and 3-(4-bromo-phenyl)-6-chloro-1-cyclopropyl-1H-pyrimidine-2,4-dione 34 as a pale-yellow foamy oil.

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25 **Step 4** Synthesis of 1-(4-bromo-phenyl)-3-cyclopropyl-6-methylamino-1H-pyrimidine-2,4-dione

[0294]



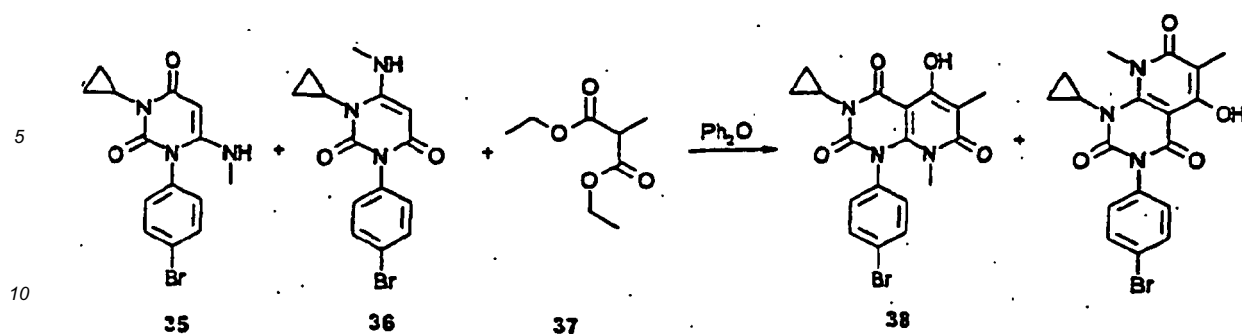
40 **[0295]** A 1:1.3 mixture (5.34 g, yield 78%) of 1-(4-bromo-phenyl)-3-cyclopropyl-6-methylamino-1H-pyrimidine-2,4-dione 35 and 3-(4-bromo-phenyl)-1-cyclopropyl-6-methylamino-1H-pyrimidine-2,4-dione 36 was obtained as colorless crystals in the same manner as the synthesis of compound 8 and using a 1:1.4 mixture (7.00 g) of 1-(4-bromo-phenyl)-6-chloro-3-cyclopropyl-1H-pyrimidine-2,4-dione 33 and 3-(4-bromo-phenyl)-6-chloro-1-cyclopropyl-1H-pyrimidine-2,4-dione 34 obtained in Step 3, ethanol (20.9 ml) and a 40% solution (10.5 ml) of methylamine in methanol.

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Step 5 Synthesis of 1-(4-bromo-phenyl)-3-cyclopropyl-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione

50 **[0296]**

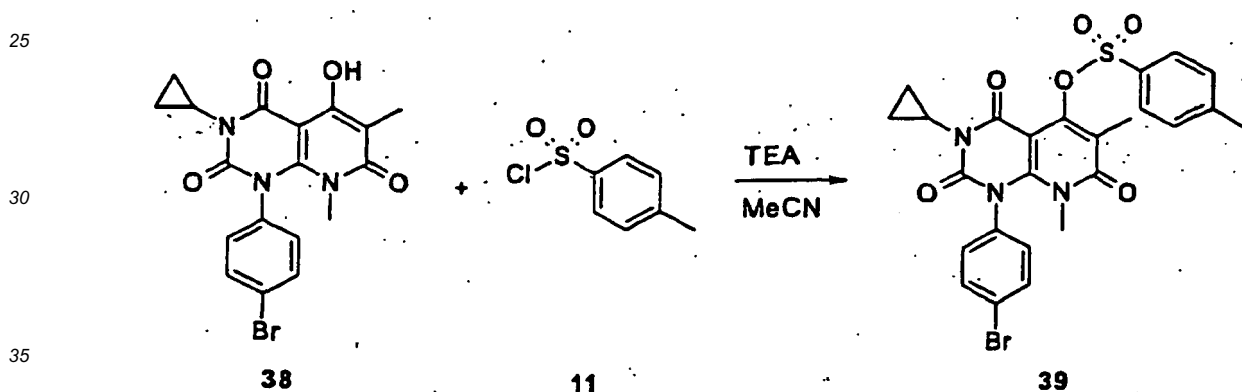
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15 **[0297]** 1-(4-Bromo-phenyl)-3-cyclopropyl-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 38 (0.40 g, yield 32%) was obtained as pale-yellow crystals in the same manner as in Step 5 of Example 1-1 and using a 1:1.3 mixture (1.00 g) of 1-(4-bromo-phenyl)-3-cyclopropyl-6-methylamino-1H-pyrimidine-2,4-dione 35 and 3-(4-bromo-phenyl)-1-cyclopropyl-6-methylamino-1H-pyrimidine-2,4-dione 36 obtained in Step 4, 2-methyl-diethyl malonate 37 (2.56 ml) and diphenyl ether (1.49 g).

20 **Step 6** Synthesis of toluene-4-sulfonic acid 1-(4-bromo-phenyl)-3-cyclopropyl-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl ester

25 **[0298]**

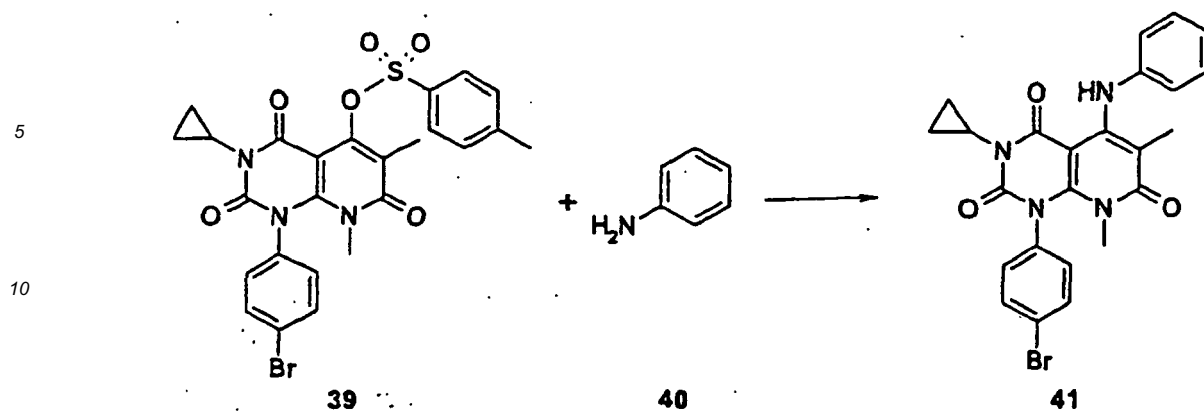


40 **[0299]** To 1-(4-bromo-phenyl)-3-cyclopropyl-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 38 (400mg) obtained in Step 5 was added acetonitrile (8.0 ml), tosyl chloride 11 (458 mg) and triethylamine (0.34 ml) were added under a nitrogen atmosphere, and the mixture was stirred under reflux for 30 hrs. After allowing to cool to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (chloroform:acetone=25:1→20:1) to give toluene-4-sulfonic acid 1-(4-bromo-phenyl)-3-cyclopropyl-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester 39 (407 mg, yield 74%) as other crystals. **Step 7** Synthesis of 1-(4-bromo-phenyl)-3-cyclopropyl-6,8-dimethyl-5-phenylamino-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione

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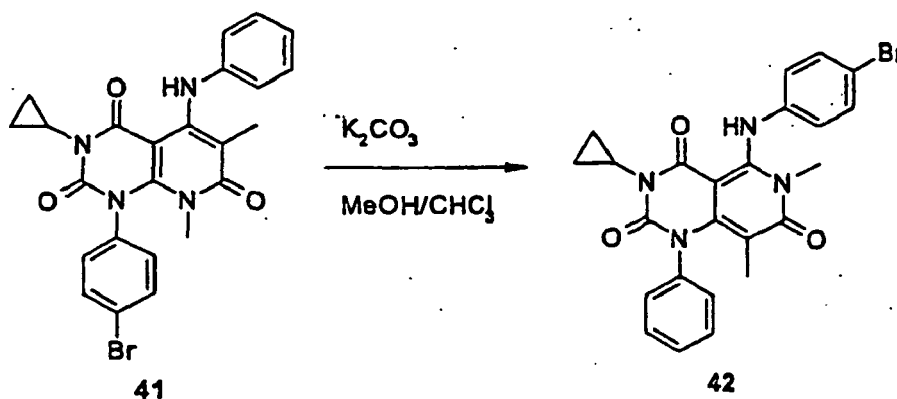
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[0300] To toluene-4-sulfonic acid 1-(4-bromo-phenyl)-3-cyclopropyl-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester 39 (100 mg) obtained in Step 6 was added aniline 40 (0.64 ml), and the mixture was stirred at 150°C for 2.5 hrs. After allowing to cool to room temperature, diethyl ether-hexane [1:1 (volume ratio), 30 ml] was added to the reaction mixture, and the crystals were collected by filtration. The obtained crystals were purified by column chromatography (chloroform:acetone=15:1) to give 1-(4-bromo-phenyl)-3-cyclopropyl-6,8-dimethyl-5-phenylamino-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 41 (81 mg, yield 93%) as pale-yellow crystals.

Step 8 Synthesis of 5-(4-bromo-phenylamino)-3-cyclopropyl-6,8-dimethyl-1-phenylamino-1H,6H-pyrido[4,3-d]pyrimidine-2,4,7-trione

[0301]



[0302] To 1-(4-bromo-phenyl)-3-cyclopropyl-6,8-dimethyl-5-phenylamino-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 41 (78 mg) obtained in Step 7 was added chloroform-methanol [1:1 (volume ratio), 2.0 ml], potassium carbonate (22 mg) was added, and the mixture was stirred at room temperature for 10 hrs. The mixture was further stirred under reflux for 3 hrs, and allowed to cool to room temperature. The mixture was concentrated under reduced pressure and purified by column chromatography (chloroform: acetone=50:1) to give 5-(4-bromo-phenylamino)-3-cyclopropyl-6,8-dimethyl-1-phenylamino-1H,6H-pyrido[4,3-d]pyrimidine-2,4,7-trione 42 (23 mg, yield 26%) as colorless crystals.

MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

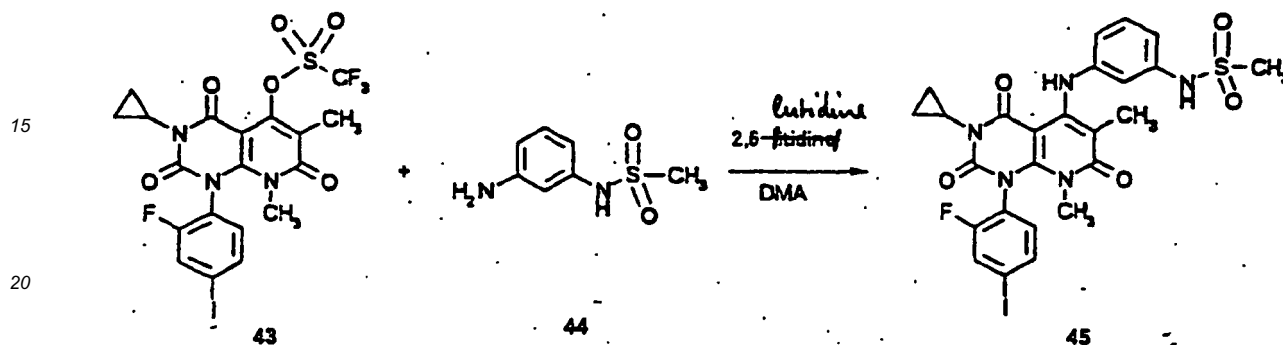
¹H-NMR (CDCl₃, 400MHz) δ 0.77-0.82 (m, 2H), 1.09-1.15 (m, 2H), 1.36 (s, 3H), 2.72-2.74 (m, 1H), 3.20 (s, 3H), 6.86 (d, 2H), 7.28-7.32 (m, 2H), 7.34-7.51 (m, 5H), 11.36 (s, 1H).

Example 3-7

Synthesis of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide

Step 1 Synthesis of N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-ylamino]phenyl}methanesulfonamide

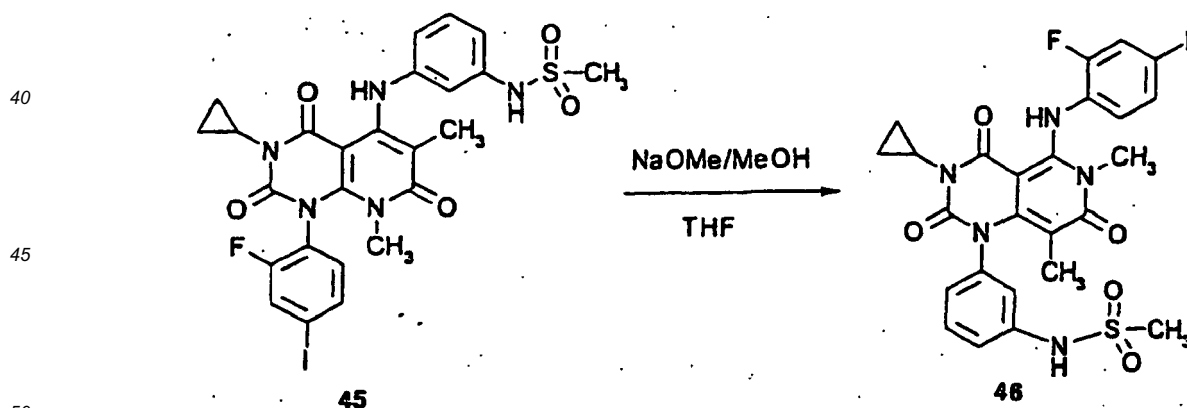
[0303]



[0304] To trifluoromethanesulfonic acid 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl ester 43 (30.0 g) obtained in the same manner in Example 4-2, Step 6 to be mentioned later and N-(3-aminophenyl) methanesulfonamide 44 (10.9 g) were added N,N-dimethylacetamide (60.0 ml) and 2,6-lutidine (6.82 ml), and the mixture was stirred at 130°C for 3.5 hrs. After allowing to cool to room temperature, methanol (60 ml) was added with stirring and the mixture was stirred for 2 hrs. The crystals were collected by filtration and dried to give N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-ylamino]phenyl}methanesulfonamide 45 (30.5 g, yield 96%) as colorless crystals.

Step 2 Synthesis of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide

[0305]



[0306] Under a nitrogen atmosphere, to a solution (18.5 g) of 28% sodium methoxide in methanol was added tetrahydrofuran (284 ml), N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]phenyl}methanesulfonamide 45 (28.4 g) obtained in Step 1 was added, and the mixture was stirred at room temperature for 1 hr. Acetic acid (12.5 ml) was added, and the mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure. A 9:1 mixed solvent (426 mL) of 1-butanol and water was added to the obtained solid, and the mixture was stirred with heating under reflux for 3 hrs. The mixture was allowed to return to room temperature and stirred overnight, and the crystals were collected by filtration and dried. A 9:1 mixed solvent (426

mL) of 1-butanol and water was added again to the obtained crystals, and the mixture was stirred with heating under reflux for 3 hrs. The mixture was allowed to return to room temperature and stirred overnight. The crystals were collected by filtration and washed with a 9:1 mixed solvent of methanol and water and dried to give N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide 46 (26.35 g, yield 93%) as white crystals.

MS ESI m/e: 652 (M+H), 650 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.72 (m, 2H), 0.91-1.01 (m, 2H), 1.25 (s, 3H), 2.57-2.67 (m, 1H), 3.01 (s, 3H), 3.08 (s, 3H), 6.92 (t, J=9.0Hz, 1H), 7.09-7.14(m, 1H), 7.20-7.26(m, 2H), 7.37-7.45(m, 1H), 7.52-7.58 (m, 1H), 7.79 (dd, J=1.8, 9.0Hz, 1H), 9.89(s, 1H), 11.08 (s, 1H).

Examples 3-2 to 3-6, 3-8 and 3-9

[0307] In the same manner as in Examples 3-1 and 3-7, the compounds of Examples 3-2 to 3-6, 3-8 and 3-9 were obtained. The structural formulas thereof are shown in Table 3-1 to 3-2 with Examples 3-1 and 3-7.

Table 3-1

Ex. No.	structural formula	Ex. No.	structural formula
3-1		3-2	
3-3		3-4	

(continued)

Ex. No.	structural formula	Ex. No.	structural formula
3-5		3-6	

Table 3-2

Ex. No.	structural formula	Ex. No.	structural formula
3-7		3-8	
3-9			

Example 3-10

[0308] By treating N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide **46** according to conventional methods, sodium salt and potassium salt thereof were obtained. N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide sodium salt:

¹H-NMR (DMSO-d₆, 300 MHz) δ 0.47 (brs, 2H), 0.70-0.90 (m, 2H), 1.23 (s, 3H), 2.35 (brs, 1H), 2.82 (s, 3H), 3.22 (s, 3H), 6.69 (t, J=8.8Hz, 1H), 6.81 (d, J=8.1Hz, 1H), 6.98 (s, 1H), 7.02 (d, J=8.8Hz, 1H), 7.10-7.30 (m, 2H), 7.38 (d, J=9.2Hz, 1H), 10.22 (brs, 1H).

MS (ESI) *m/z* 652 [MH]⁺.

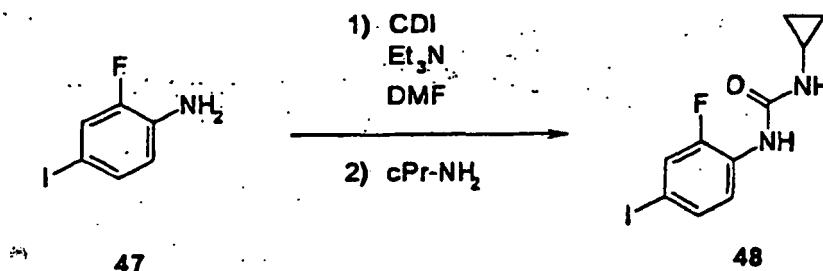
N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide potassium salt:

Example 4-1

N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide

Step 1 Synthesis of 1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)urea

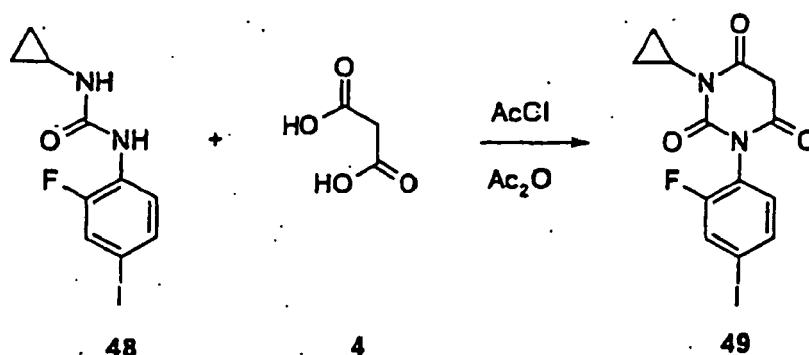
[0309]



[0310] Under a nitrogen atmosphere, to N,N-carbonyldimidazole (39.9 g) were added N,N-dimethylformamide (200 ml) and triethylamine (34.3 ml) and a solution of 2-fluoro-4-iodoaniline **47** (48.5 g) in N,N-dimethylformamide (50 ml) was added dropwise with stirring under ice-cooling. After the completion of the dropwise addition, the mixture was stirred at room temperature for 18 hrs. The reaction mixture was ice-cooled, and cyclopropylamine (21.3 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 hr and added dropwise to water-toluene [2:1 (volume ratio), 750 ml] with stirring. The precipitated crystals were collected by filtration and dried to give 1-cyclopropyl-3-(2-fluoro-4-iodophenyl)urea **48** (61.3 g, yield 93.4%) as colorless crystals.

Step 2 Synthesis of 1-cyclopropyl-3-(2-fluoro-4-iodophenyl)pyrimidine-2,4,6-trione

[0311]

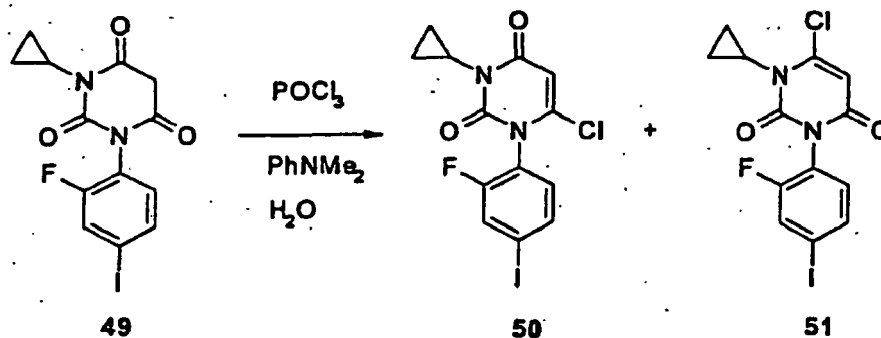


[0312] To 1-cyclopropyl-3-(2-fluoro-4-iodophenyl)urea **48** (61.0 g) obtained in Step 1 and malonic acid **4** (19.9 g) were

added acetic anhydride (300 ml) and acetyl chloride (27.2 ml), and the mixture was stirred under a nitrogen atmosphere at 60°C for 3 hrs. After allowing to cool to room temperature, the reaction mixture was added dropwise to water-toluene [2:1 (volume ratio), 900 ml] with stirring. The precipitated crystals were collected by filtration and dried to give 1-cyclopropyl-3-(2-fluoro-4-iodophenyl)pyrimidine-2,4,6-trione 49 (60.9 g, yield 82%) as pale-yellow crystals.

Step 3 Synthesis of 6-chloro-3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione

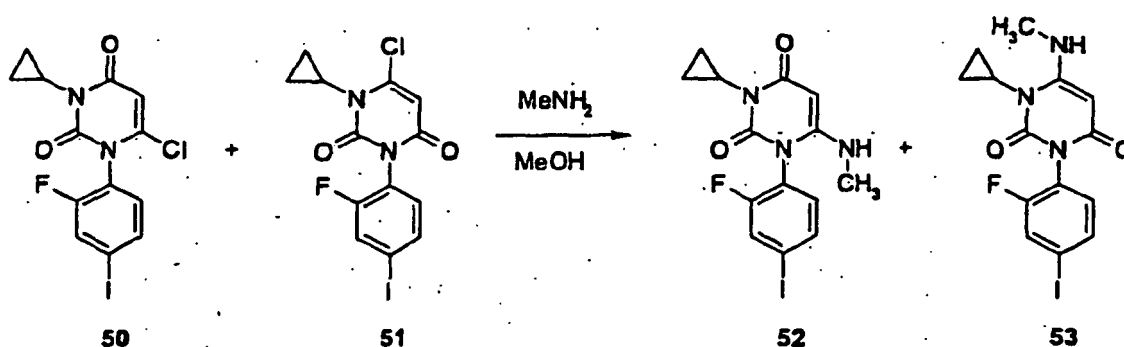
[0313]



To 1-cyclopropyl-3-(2-fluoro-4-iodophenyl)pyrimidine-2,4,6-trione 49 (59.0 g) obtained in Step 2 were added phosphorus oxychloride (85.0 ml) and dimethylaniline (29.0 ml), and water (8.3 ml) was added dropwise to the mixture at room temperature with stirring. After the completion of the dropwise addition, the mixture was stirred with heating at 110°C for 1 hr. After allowing to cool to room temperature, the reaction mixture was added dropwise to ice water-toluene [2:1 (volume ratio), 900 ml] with stirring. The mixture was stirred at room temperature for 1 hr. The organic layer was separated, and washed successively with water (300 ml) and brine (300 ml). Anhydrous magnesium sulfate and activated carbon were added and the mixture was stirred. Anhydrous magnesium sulfate and activated carbon were filtered off, and the filtrate was concentrated under reduced pressure to give a 1:2 mixture (62.9 g) of 6-chloro-3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione 50 and 6-chloro-1-cyclopropyl-3-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione 51 as a yellow foamy oil, which was used for the next step without purification.

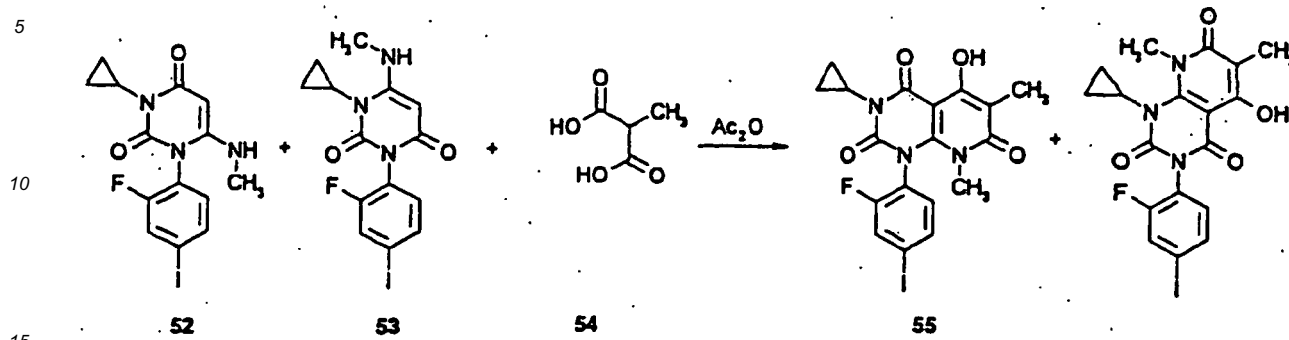
Step 4 Synthesis of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6-methylamino-1H-pyrimidine-2,4-dione

[0315]



To a 1:2 mixture (62.9 g) of 6-chloro-3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione 50 and 6-chloro-1-cyclopropyl-3-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione 51 obtained in Step 3 were added methanol (189 ml) and a solution (126 ml) of 40% methylamine in methanol, and the mixture was stirred at room temperature for 2 hrs. The precipitated crystals were filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with chloroform (200 ml) and water (200 ml), and the organic layer was washed with brine (200 ml) and dried over anhydrous magnesium sulfate. Anhydrous magnesium sulfate was filtered off and the filtrate was concentrated under reduced pressure to give a 2:1 mixture (34.55 g) of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6-methylamino-1H-pyrimidine-2,4-dione 52 and 1-cyclopropyl-3-(2-fluoro-4-iodophenyl)-6-methylamino-1H-pyrimidine-2,4-dione 53 as yellow crystals.

low crystals, which were used for the next step without purification. **Step 5** Synthesis of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione



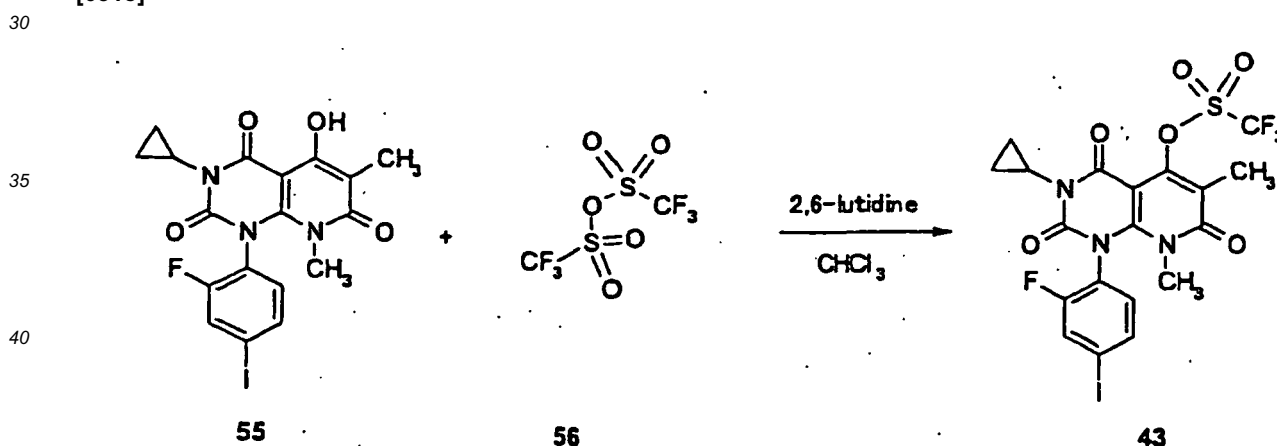
[0317] To a 2:1 mixture (34.6 g) of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6-methylamino-1H-pyrimidine-2,4-dione 52 and 1-cyclopropyl-3-(2-fluoro-4-iodophenyl)-6-methylamino-1H-pyrimidine-2,4-dione 53 obtained in Step 4, and 2-methylmalonic acid 54 (10.2 g) was added acetic anhydride (173 ml), and the mixture was stirred at 100°C for 2 hrs. After allowing to cool to room temperature, the reaction mixture was concentrated under reduced pressure. Acetone (104 ml) was added to the residue, and the mixture was stirred with heating under reflux for 30 min. After allowing to cool to room temperature, the precipitated crystals were collected by filtration and dried to give 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 55 (15.1 g, yield from 48, 21%) as colorless crystals.

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Step 6 Synthesis of trifluoromethanesulfonic acid 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester

[0318]



[0319] Under a nitrogen atmosphere, to 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 55 (33.0 g) obtained in Step 5 were added chloroform (165 ml) and 2,6-lutidine (10.4 ml), and trifluoromethanesulfonic anhydride 56 (14.4 ml) was added dropwise under ice-cooling with stirring. After the completion of the dropwise addition, the mixture was stirred at the same temperature for 30 min and at room temperature for 2 hrs. The reaction mixture was washed successively with aqueous sodium hydrogen carbonate (165 ml), 1N hydrochloric acid (165 ml) and brine (165 ml) and dried over anhydrous magnesium sulfate. Anhydrous magnesium sulfate was filtered off and the filtrate was concentrated under reduced pressure. 2-Propanol (198 ml) was added to the residue, and the mixture was stirred with heating under reflux, and allowed to return to room temperature. The crystals were collected by filtration and dried to give trifluoromethanesulfonic acid 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester 43 (31.9 g, yield 93%) as colorless crystals

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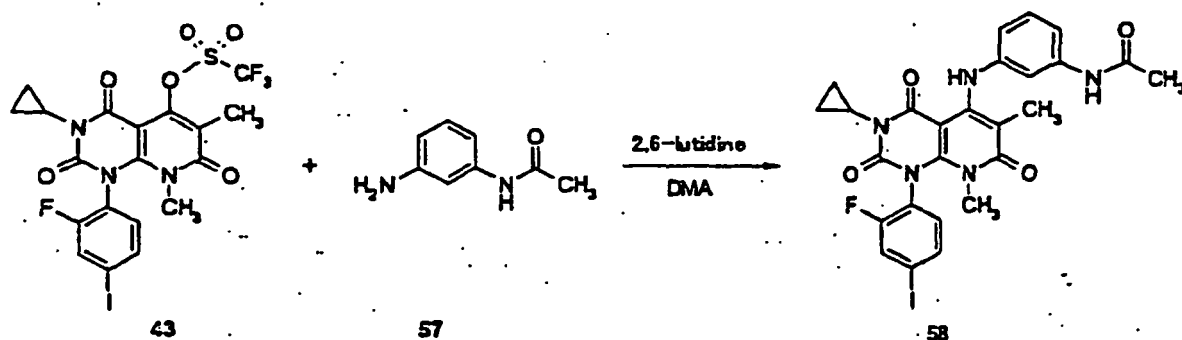
Step 7 Synthesis of N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]phenyl}acetamide

[0320]

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[0321] To trifluoromethanesulfonic acid 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester 43 (25.0 g) obtained in Step 6 and 3'-aminoacetanilide 57 (7.33 g) were added N,N-dimethylacetamide (50.0 ml) and 2,6-lutidine (5.68 ml), and the mixture was stirred at 130°C for 5 hrs. After allowing to cool to room temperature, methanol-water [1:2 (volume ratio), 150 ml] was added with stirring. The crystals were collected by filtration and dried to give N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]phenyl}acetamide 58 (24.8 g, yield 99%) as colorless crystals.

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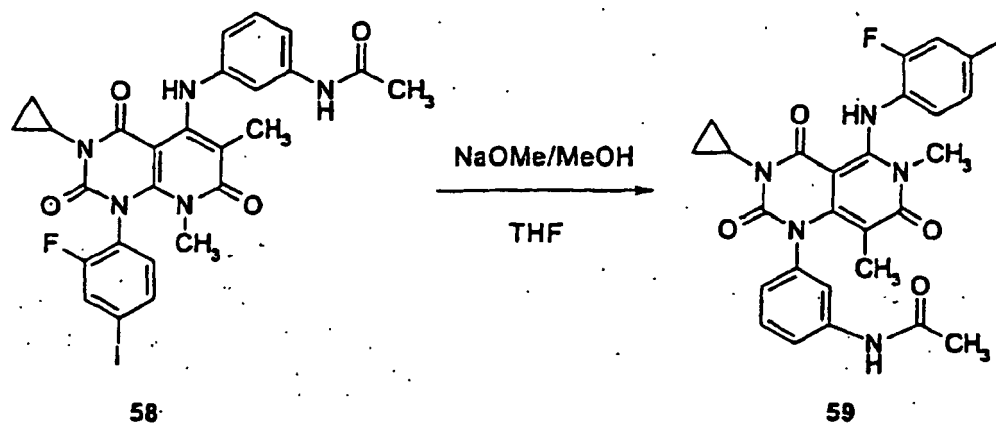
Step 8 Synthesis of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide

[0322]

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[0323] Under a nitrogen atmosphere, to a solution (1.57 g) of 28% sodium methoxide in methanol was added tetrahydrofuran (40 ml), N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]phenyl}acetamide 58 (5.00 g) obtained in Steep 7 was added, and the mixture was stirred at room temperature for 4 hrs. Acetic acid (0.56 ml) was added, and the mixture was stirred at room temperature for 30 min. Water (40 ml) was added and the mixture was further stirred for 1 hr. The crystals were collected by filtration and dried to give N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide 59 (4.75 g, yield 95%) as colorless crystals.

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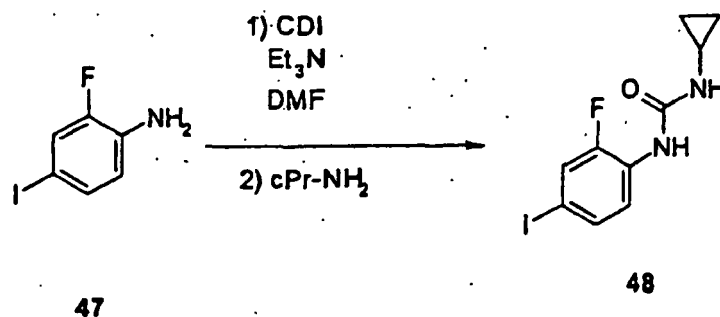
MS ESI m/e: 616 (M+H), 614 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 0.63-0.70 (m, 2H), 0.91-1.00 (m, 2H), 1.25 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 6.92 (t, J=8.8Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J=8.2Hz, 1H), 7.52-7.63 (m, 3H), 7.79(dd, J=2.0, 10.4Hz, 1H), 10.10(s, 1H), 11.08(s, 1H).

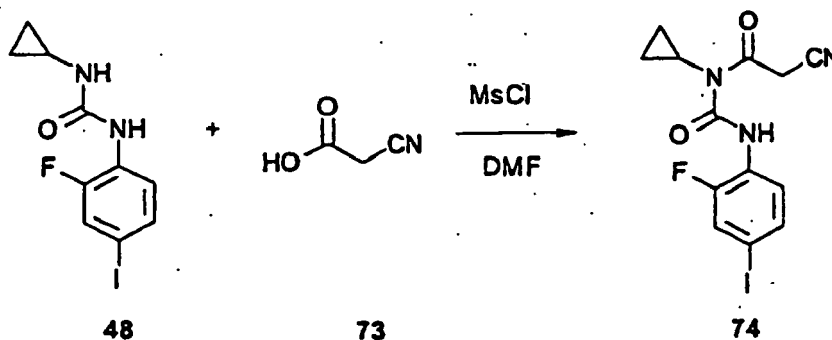
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Example 4-1 (alternative method)

N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide

Step 1 Synthesis of 1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-urea**[0324]**

[0325] Under a nitrogen atmosphere, to N,N-carbonyldiimidazole (82.1 g) were added N,N-dimethylformamide (400 ml) and triethylamine (70.5 ml), and a solution of 2-fluoro-4-iodoaniline 47 (100 g) in N,N-dimethylformamide (100 ml) was added dropwise under ice-cooling. After the completion of the dropwise addition, the mixture was stirred at room temperature for 5 hrs. The reaction mixture was ice-cooled, and cyclopropylamine (44.0 ml) was added dropwise. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was added dropwise to water-toluene [2:1 (volume ratio), 1500 ml] with stirring. The precipitated crystals were collected by filtration and dried to give 1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-urea 48 (129 g, yield 95.5%) as colorless crystals.

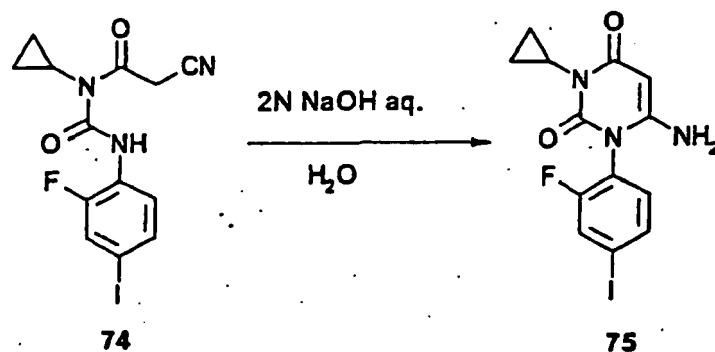
Step 2 Synthesis of 1-(2-cyano-acetyl)-1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-urea**[0326]**

[0327] Under a nitrogen atmosphere, to 1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-urea 48 (167 g) and cyanoacetic acid 73 (80.0 g), was added N,N-dimethylformamide (836 ml), and methanesulfonyl chloride (72.8 ml) was added dropwise with stirring at room temperature. The mixture was stirred at room temperature for 4 hrs. The reaction mixture was cooled with water, and water-isopropanol [2:1 (volume ratio), 1670 ml] was added dropwise. The mixture was stirred under water-cooling for 1 hr, and the precipitated crystals were collected by filtration and dried to give 1-(2-cyano-acetyl)-1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-urea 74 (192 g).

Step 3 Syntheses of 6-amino-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-1H-pyrimidine-2,4-dione**[0328]**

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[0329] To 1-(2-cyanoacetyl)-1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-urea **74** (192 g) were added water (962 ml) and 2N aqueous sodium hydroxide solution (24.9 ml), and the mixture was stirred with heating at 80°C for 1 hr. After allowing to cool to room temperature, the crystals were collected by filtration and dried to give 6-amino-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-1H-pyrimidine-2,4-dione **75** (178g, yield from **48**, 88%) as pale-yellow crystals.

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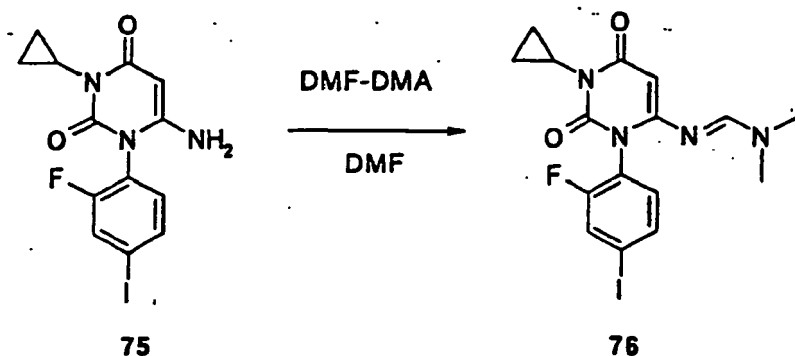
Step. 4 Synthesis of N'-[1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]-N,N-dimethyl-formamide

[0330]

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[0331] Under a nitrogen atmosphere, to 6-amino-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-1H-pyrimidine-2,4-dione **75** (178 g) were added N,N-dimethylformamide (356 ml) and N,N-dimethylformamide dimethylacetal (178 ml), and the mixture was stirred at room temperature for 2 hrs. Isopropanol (178 ml) was added with stirring at room temperature, and water (1068 ml) was added dropwise. The mixture was stirred at room temperature for 2 hrs, and the precipitated crystals were collected by filtration and dried to give N'-[1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]-N,N-dimethyl-formamide **76** (188 g, yield 92%) as yellow crystals.

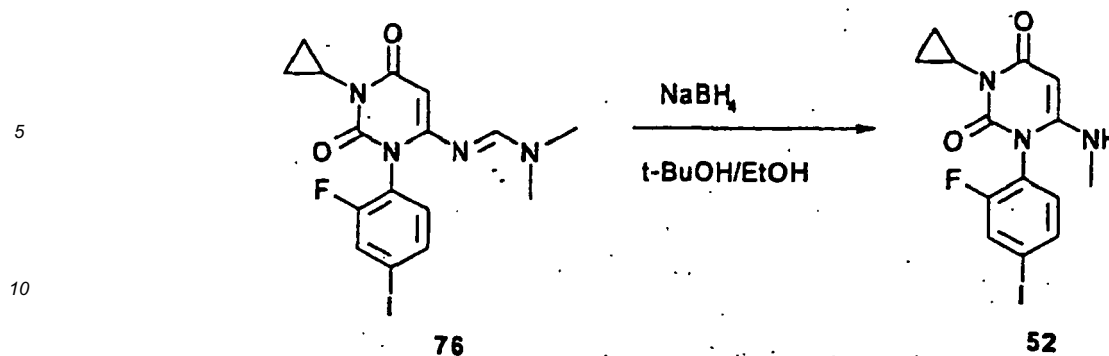
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Step 5 Synthesis of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6-methylamino-1H-pyrimidine-2,4-dione

[0332]

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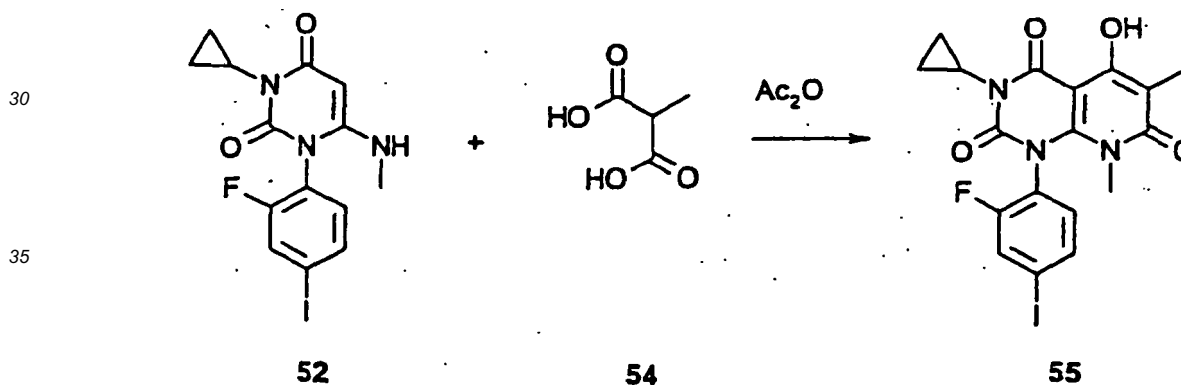


15 [0333] Under a nitrogen atmosphere, to t-butanol-ethanol [2:1 (volume ratio), 250 ml] was added sodium borohydride (6.41 g), and the mixture was stirred at room temperature for 1 hr. Under water-cooling, N'-[1-cyclopropyl-3-(2-fluoro-4-iodo-phenyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]-N,N-dimethyl-formamidine 76 (50.0 g) was added, and the mixture was stirred for 2.5 hrs. Under water-cooling, water (225 ml) and 10% aqueous citric acid solution (175 ml) were successively added dropwise, and the mixture was stirred for 3 hrs. The precipitated crystals were collected by filtration and dried to give crude crystals (34.5 g, LC purity 91%) of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6-methylamino-1H-pyrimidine-2,4-dione 52, which were used for the next reaction without purification.

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Step 6 Synthesis of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione

25 [0334]



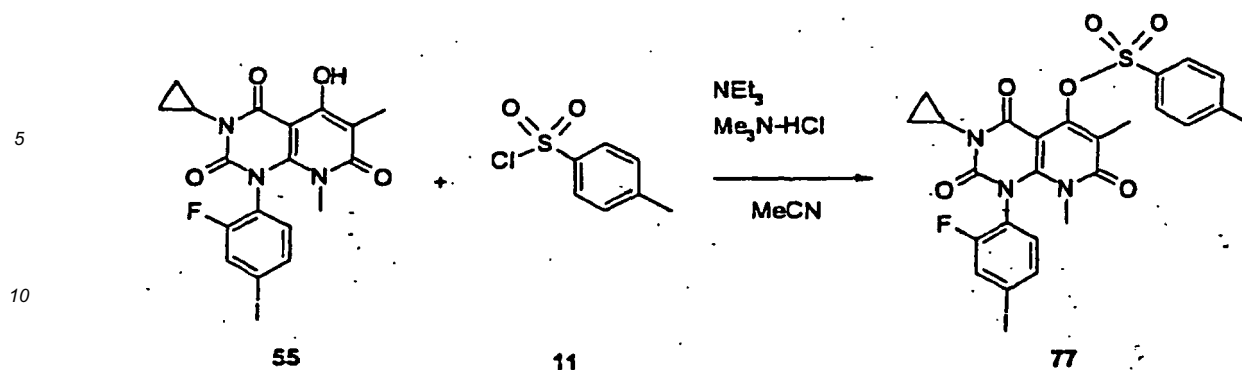
40 [0335] Under a nitrogen atmosphere, to 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6-methylamino-1H-pyrimidine-2,4-dione 52 (34.4 g) and 2-methyl-malonic acid 54 (15.2 g) was added acetic anhydride (34.4 ml), and the mixture was stirred with heating at 100°C for 3 hrs. After allowing to cool to 50°C, acetone (68.8 ml) was added dropwise, and the mixture was stirred as it was for 30 min. Water (172 ml) was further added dropwise, and the mixture was stirred for 1 hr. After allowing to cool to room temperature with stirring, the precipitated crystals were collected by filtration and dried to give crude crystals (37.7 g, LC purity 91%) of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 55. Isopropanol (92.0 ml) was added to the obtained crude crystals (30.7 g), and the mixture was stirred at room temperature for 4 hrs. The crystals were collected by filtration and dried to give 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 55 (25.9 g, yield from 76, 58%) as pale-yellow crystals.

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Step 7 Synthesis of p-toluenesulfonic acid 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester

55 [0336]

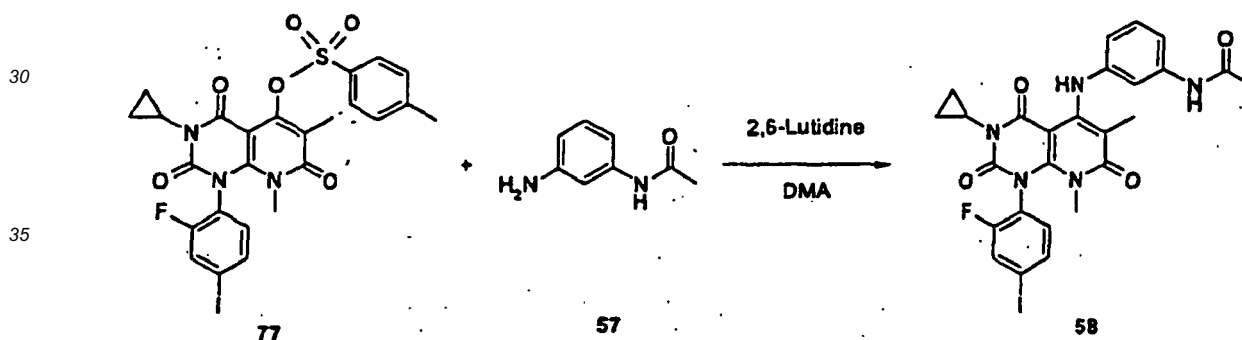


15 [0337] Under a nitrogen atmosphere, to 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione 55 (23.9 g) was added acetonitrile (167 ml), and the mixture was stirred under ice-cooling. Triethylamine (11.0 ml) and trimethylamine hydrochloride (2.37 g) were added, and a solution of p-toluenesulfonyl chloride 11 (12.3 g) in acetonitrile (72.0 ml) was added dropwise. The mixture was stirred under ice-cooling for 1 hr, and stirred at room temperature for 3 hrs. Methanol (239 ml) was added, and the mixture was stirred at room temperature for 1 hr. The crystals were collected by filtration and dried to give p-toluenesulfonic acid 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester 77 (28.7 g, yield 91%) as colorless crystals.

20

25 **Step 8** Synthesis of N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]-phenyl}-acetamide

30 [0338]

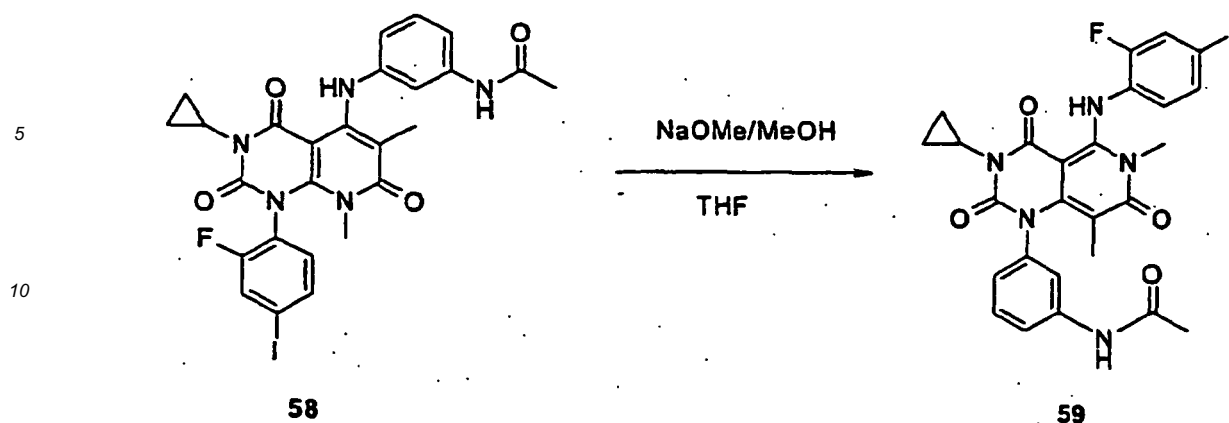


40 [0339] To p-toluenesulfonic acid 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester 77 (28.0 g) and 3'-aminoacetanilide 57 (13.2 g) were added N,N-dimethylacetamide (84.0 ml) and 2,6-lutidine (15.3 ml), and the mixture was stirred at 130°C for 4 hrs. After allowing to cool with stirring, methanol (196 ml) was added dropwise, and the mixture was stirred at room temperature. The crystals were collected by filtration and dried to give N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]-phenyl}-acetamide 58 (25.2 g, yield 93%) as colorless crystals.

45

50 **Step 9** Synthesis of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide

55 [0340]



[0341] Under a nitrogen atmosphere, to N-{3-[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]-phenyl}-acetamide **58** (45.7 g) was added tetrahydrofuran (366 ml), and a solution (15.7 g) of 28% sodium methoxide in ethanol was added dropwise with stirring at room temperature and the mixture was stirred at room temperature for 4 hrs. Acetic acid (5.61 ml) was added, and the mixture was stirred at room temperature for 30 min. With stirring at 70°C in an oil bath, water (366 ml) was added dropwise, and the mixture was stirred for 1 hr. After allowing to cool with stirring, the crystals were collected by filtration and dried to give crystal 1 (46.0 g) of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **59**.

[0342] N,N-Dimethylacetamide (184 ml) was added to crystal 1 (46.0 g), and the mixture was stirred with heating at 130°C. After complete dissolution, the solution was filtered by suction using with paper (5H), and washed with N,N-dimethylacetamide (92.0 ml). The filtrate was stirred under heating at 130°C, 1-butanol (138 ml) and water (96.0 ml) were successively added dropwise, and the mixture was stirred for 30 min. Water (46.0 ml) was further added dropwise, and the mixture was stirred for 30 min and allowed to cool with stirring. The crystals were collected by filtration and dried to give crystal 2 (41.7 g) of N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **59** as colorless crystals.

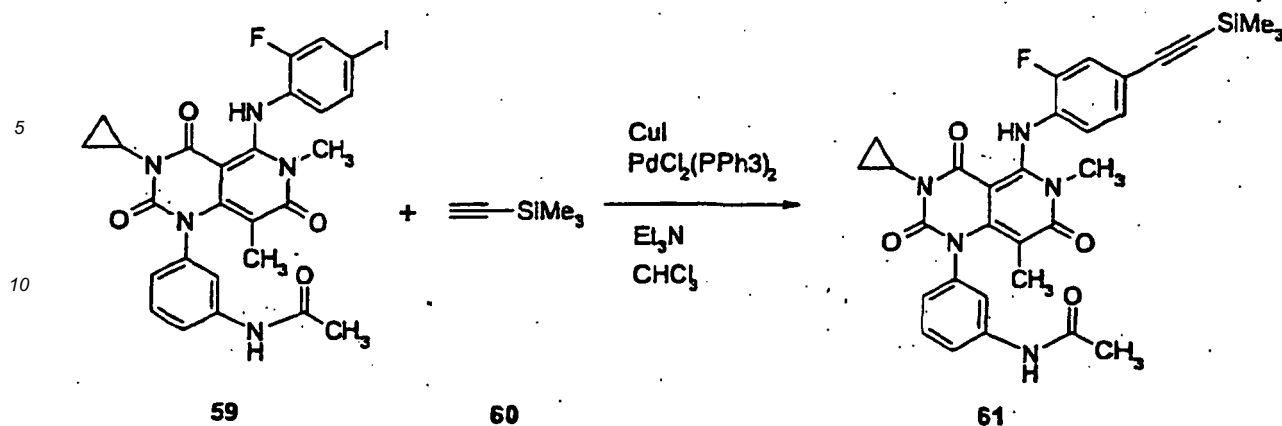
[0343] To crystal 2 (41.5 g) was added 1-butanol-water [19:1 (volume ratio), 415 ml], and the mixture was stirred at 130°C for 18 hrs. After allowing to cool with stirring, the crystals were collected by filtration and dried to give N-(3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl)-acetamide **59** (40.7 g, yield 89%) as colorless crystals.

Example 4-3

N-{3-[3-cyclopropyl-5-(4-ethynyl-2-fluorophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide

Step 1 Synthesis of N-{3-[3-cyclopropyl-5-(2-fluoro-4-trimethylsilanylethynylphenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide

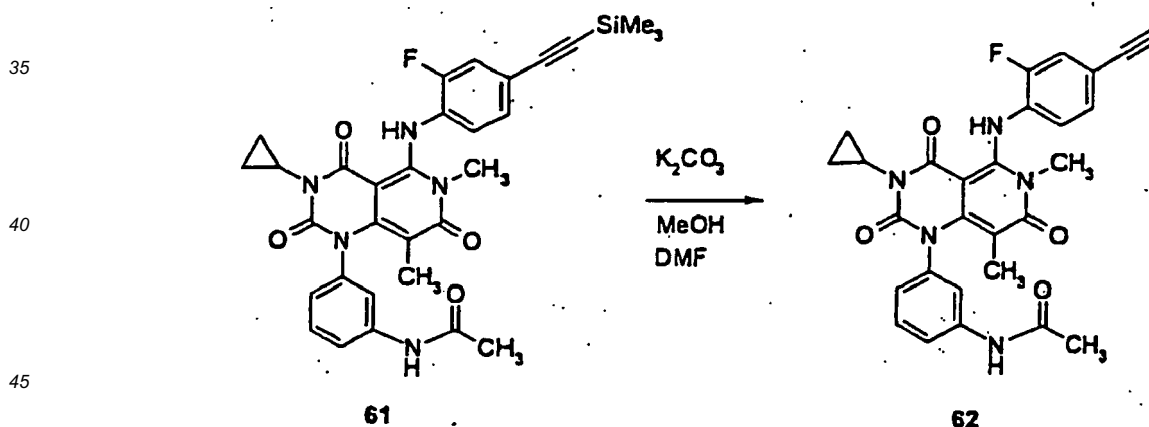
[0344]



[0345] Under a nitrogen atmosphere, to N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide **59** (14.5 g) obtained in Example 4-1 were added chloroform (145 ml), trimethylsilylacetylene **60** (4.99 ml) and triethylamine (13.1 ml). Copper (I) iodide (22 mg) and bis (triphenylphosphine)palladium(II)chloride(83 mg) were added, and the mixture was stirred at room temperature for 20 hrs. The mixture was concentrated under reduced pressure, activated carbon (435 mg) and methanol (435 ml) were added to the residue, and the mixture was stirred with heating at reflux for 2 hrs. Activated carbon was filtered off while it was hot, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (chloroform:acetone=10:1-4:1) and toluene-acetone [5:1 (volume ratio), 87 ml] was added to the obtained crystals. The mixture was stirred at 80°C for 1 hr. After allowing to cool to room temperature, the crystals were collected by filtration and dried to give N-{3-[3-cyclopropyl-5-(2-fluoro-4-trimethylsilyl-ethynylphenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide **61** (12.9 g, yield 93%) as pale-yellow crystals.

Step 2 Synthesis of N-{3-[3-cyclopropyl-5-(4-ethynyl-2-fluorophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide

[0346]



[0347] To N-{3-[3-cyclopropyl-5-(2-fluoro-4-trimethylsilyl-ethynylphenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide **61** (1.00 g) obtained in Step 2 and potassium carbonate (236 mg) was added methanol/N,N-dimethylformamide. [1:1 (volume ratio), 10.0 ml], and the mixture was stirred at room temperature for 20 hrs. The mixture was neutralized with 2N hydrochloric acid, water (10.0 ml) was added, and the mixture was stirred at room temperature for 1 hr. The crystals were collected by filtration and dried to give N-{3-[3-cyclopropyl-5-(4-ethynyl-2-fluorophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide **62** (815 mg, yield 93%) as pale-yellow crystals.

MS ESI m/e: 514 (M+H), 512 (M-H).

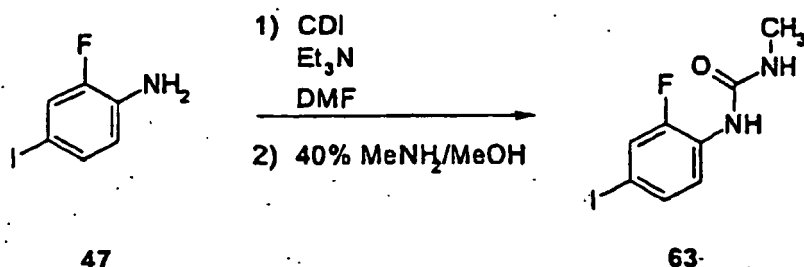
¹H-NMR(DMSO-d₆, 400MHz) δ 0.63-0.70 (m, 2H), 0.91-0.99 (m, 2H), 1.26 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.10 (s, 3H), 4.30 (s, 3H), 7.01-7.06 (m, 1H), 7.09 (t, J=8.4Hz, 1H), 7.31 (dd, J=1.6, 8.4 Hz, 1H), 7.36 (t, J=7.8Hz, 1H), 7.52 (dd, J=1.6, 11.6Hz, 1H), 7.57-7.63 (m, 2H), 10.10 (s, 1H), 11.10 (s, 1H).

Example 4-16

N-{3-[5-(2-fluoro-4-iodophenylamino)-3,6,8-trimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido [4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide

Step 1 Synthesis of 1-(2-fluoro-4-iodophenyl)-3-methylurea

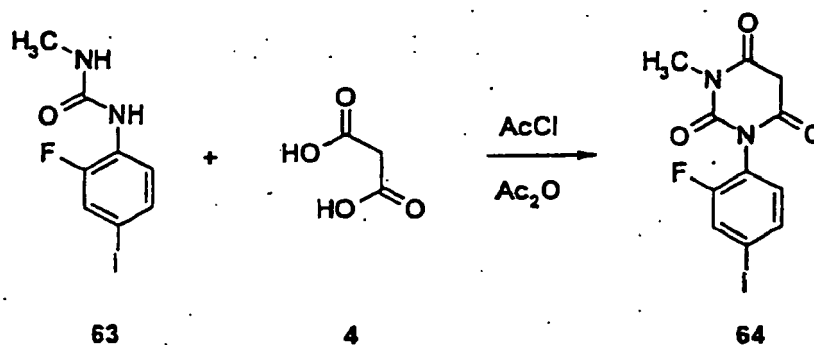
[0348]



[0349] Under a nitrogen atmosphere, to N,N-carbonyldiimidazole (61.4 g) were added N,N-dimethylformamide (300 ml) and triethylamine (52.8 ml) and a solution of 2-fluoro-4-iodoaniline **47** (74.8 g) in N,N-dimethylformamide (75 ml) was added dropwise with stirring under ice-cooling. After the completion of the dropwise addition, the mixture was stirred at room temperature for 5 hrs. The reaction mixture was ice-cooled, and a solution (60 ml) of 40% methylamine in methanol was added dropwise. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was added dropwise to water-toluene [2:1 (volume ratio), 1125 ml] under stirring. The precipitated crystals were collected by filtration and dried to give 1-(2-fluoro-4-iodophenyl)-3-methylurea **63** (87.9 g, yield 94.8%) as colorless crystals.

Step 2 Synthesis of 1-(2-fluoro-4-iodophenyl)-3-methylpyrimidine-2,4,6-trione

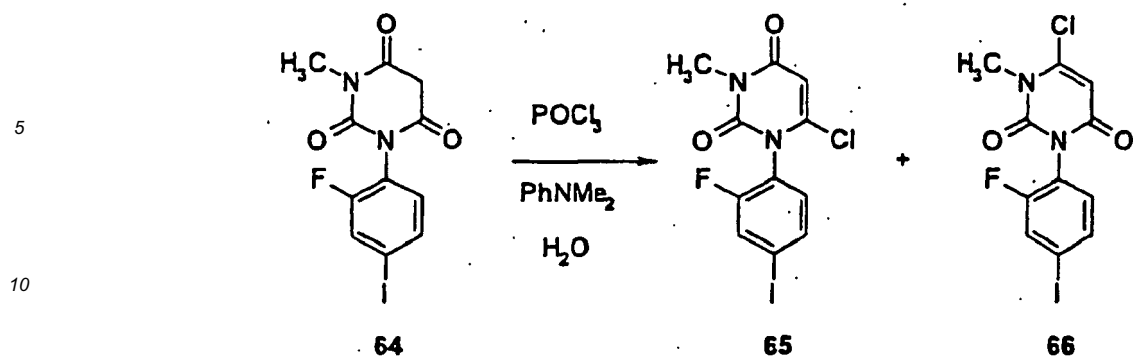
[0350]



[0351] Under a nitrogen atmosphere, to 1-(2-fluoro-4-iodophenyl)-3-methylurea **63** (87.9 g) obtained in Step 1 and malonic acid **4** (31.1 g) were added acetic anhydride (264 ml) and acetyl chloride (42.5 ml) and the mixture was stirred at 65°C for 3 hrs. After allowing to cool to room temperature, the reaction mixture was added dropwise to water-toluene [2:1 (volume ratio), 800 ml] with stirring, and hexane (132 ml) was successively added. The precipitated crystals were collected by filtration and dried to give 1-(2-fluoro-4-iodophenyl)-3-methylpyrimidine-2,4,6-trione **64** (75.3 g, yield 69.5%) as pale-yellow crystals.

Step 3 Synthesis of 6-chloro-1-(2-fluoro-4-iodophenyl)-3-methyl-1H-pyrimidine-2,4-dione

[0352]

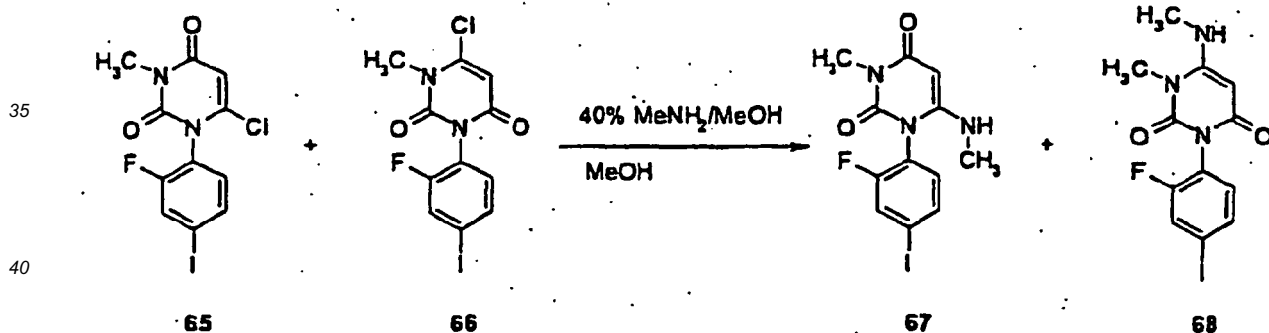


15 **[0353]** Under a nitrogen atmosphere, to 1-(2-fluoro-4-iodophenyl)-3-methylpyrimidine-2,4,6-trione **64** (75.3 g) were added phosphorus oxychloride (116.3 ml) and dimethylaniline (39.5 ml) and water (11.6 ml) was added dropwise with stirring under room temperature. After the completion of the dropwise addition, the mixture was stirred at 125°C for 1 hr. After, allowing to cool to room temperature, the reaction mixture was added dropwise with stirring to ice water (500 ml/chloroform (150 ml)). The mixture was stirred at room temperature for 1 hr, and chloroform (150 ml) was added. The organic layer was separated, washed successively with water (300 ml) and brine (300 ml), and dried over anhydrous sodium sulfate.

20 **[0354]** Anhydrous sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. To a solution of the residue in chloroform (250 ml), silica gel (200 ml) was added and the mixture was stirred. Silica gel was filtered off and washed with chloroform/ethyl acetate [10:1 (volume ratio), 11]. The filtrate was concentrated under reduced pressure to give a 6:5 mixture (75.7 g, yield 95.6%) of 6-chloro-1-(2-fluoro-4-iodophenyl)-3-methyl-1H-pyrimidine-2,4-dione **65** and 6-chloro-3-(2-fluoro-4-iodophenyl)-1-methyl-1H-pyrimidine-2,4-dione **66** as pale-yellow crystals.

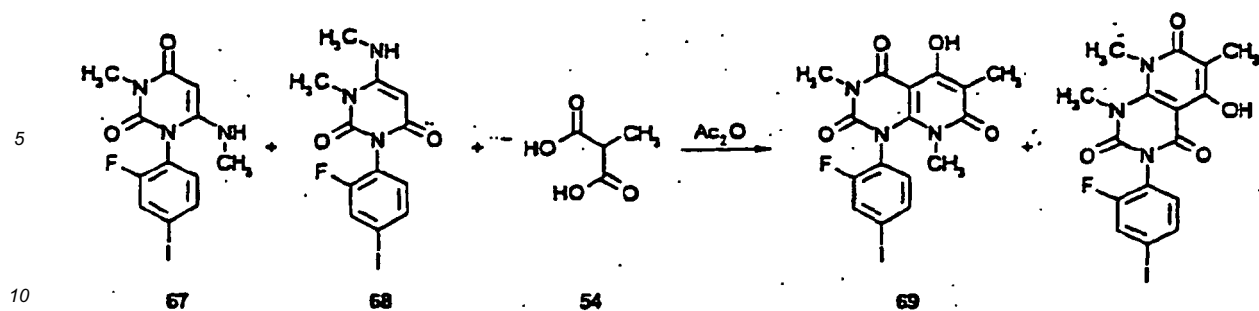
Step 4 Synthesis of 1-(2-fluoro-4-iodophenyl)-3-methyl-6-methylamino-1H-pyrimidine-2,4-dione

30 **[0355]**



45 **[0356]** To a 6:5 mixture (75.7 g) of 6-chloro-1-(2-fluoro-4-iodophenyl)-3-methyl-1H-pyrimidine-2,4-dione **65** and 6-chloro-3-(2-fluoro-4-iodophenyl)-1-methyl-1H-pyrimidine-2,4-dione **66** obtained in Step 3 were added methanol (227 ml) and a 40% solution (152 ml) of methylamine in methanol, and the mixture was stirred at room temperature for 2.5 hrs. The reaction mixture was concentrated under reduced pressure, and toluene (150 ml) and water (150 ml) were added to the residue, and the mixture was stirred under heating at reflux for 30 min. After allowing to return to room temperature, the crystals were collected by filtration and dried to give a 6:5 mixture (59.6 g, yield 79.9%) of 1-(2-fluoro-4-iodophenyl)-3-methyl-6-methylamino-1H-pyrimidine-2,4-dione **67** and 3-(2-fluoro-4-iodophenyl)-1-methyl-6-methylamino-1H-pyrimidine-2,4-dione **68** as pale-yellow crystals. **Step 5** Synthesis of 1-(2-fluoro-4-iodophenyl)-5-hydroxy-3,6,8-trimethyl-1H, 8H-pyrido[2,3-d]pyrimidine-2,4,7-trione

55



[0357] To a 6:5 mixture (59.6 g) of 1-(2-fluoro-4-iodophenyl)-3-methyl-6-methylamino-1H-pyrimidine-2,4-dione **67** and 3-(2-fluoro-4-iodophenyl)-1-methyl-6-methylamino-1H-pyrimidine-2,4-dione **68** obtained in Step 4 and 2-methylmalonic acid **54** (20.7 g) was added acetic anhydride (180 ml), and the mixture was stirred with heating at 95°C for 1 hr. After allowing to cool to room temperature, the mixture was concentrated under reduced pressure. Tetrahydrofuran (350 ml) was added to the residue, and the mixture was stirred with heating under reflux for 1 hr. After allowing to cool to room temperature, the crystals were filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (chloroform:tetrahydrofuran=18:1). Toluene (150 ml) was added to the obtained solid, and the mixture was stirred with heating under reflux for 30 min. After allowing to return to room temperature, the crystals were collected by filtration and dried to give 1-(2-fluoro-4-iodophenyl)-5-hydroxy-3,6,8-trimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione **69** (27.0 g, yield 37%) as colorless crystals.

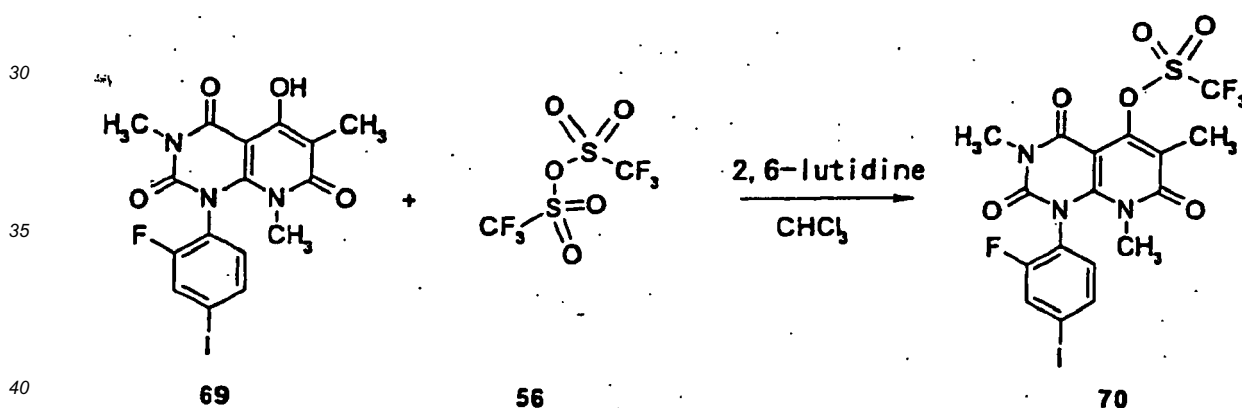
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Step 6 Synthesis of trifluoromethanesulfonic acid 1-(2-fluoro-4-iodophenyl)-3,6,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester

25

[0358]



[0359] Under a nitrogen atmosphere, to 1-(2-fluoro-4-iodophenyl)-5-hydroxy-3,6,8-trimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione **69** (27.0 g) obtained in Step 5 were added chloroform (200 ml) and 2,6-lutidine (11.1 ml) and trifluoromethanesulfonic anhydride **56** (14.9 ml) was added dropwise under ice-cooling with stirring. After the completion of the dropwise addition, the mixture was stirred at the same temperature for 30 min, and at room temperature for 3 hrs. With stirring under ice-cooling, water (200 ml) was added to the reaction mixture. The organic layer was separated, washed successively with water (300 ml) and brine (300 ml), and dried over anhydrous magnesium sulfate. Anhydrous magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. 2-Propanol (150 ml) was added to the residue, and seed crystals were added at room temperature to allow precipitation of the crystals. The mixture was stirred with heating under reflux for 30 min, and allowed to cool to room temperature. The crystals were collected by filtration and dried to give trifluoromethanesulfonic acid 1-(2-fluoro-4-iodophenyl)-3,6,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester **70** (22.9 g, yield 66%) as colorless crystals.

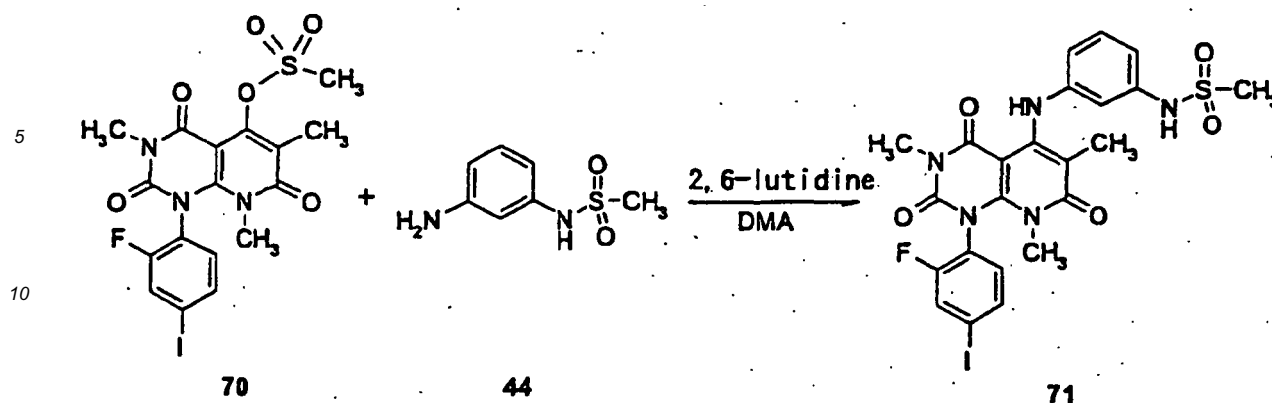
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Step 7 Synthesis of N-{3-[1-(2-fluoro-4-iodophenyl)-3,6,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]phenyl}methanesulfonamide

55

[0360]

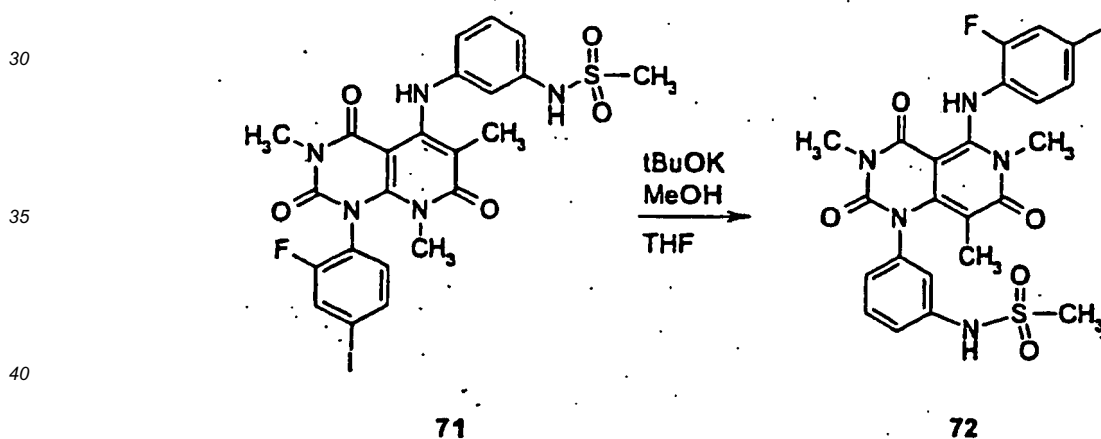


15 **[0361]** To trifluoromethanesulfonic acid 1-(2-fluoro-4-iodophenyl)-3,6,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-yl ester **70** (3.00 g obtained in Step 6 and N-(3-aminophenyl)methanesulfonamide **44** (1.14 g) were added N,N-dimethylacetamide (6.00 ml) and 2,6-lutidine (0.712 ml), and the mixture was stirred at 130°C for 4 hrs. After allowing to cool to room temperature, methanol/water [1:2 (volume ratio), 180 ml] was added under stirring. The crystals were collected by filtration and dried to give N-(3-[1-(2-fluoro-4-iodophenyl)-3,6,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]phenyl)methanesulfonamide **71** (3.13 g, yield 98%) as a pale-gray solid.

20

25 **Step 8** Synthesis of N-(3-[5-(2-fluoro-4-iodophenylamino)-3,6,8-trimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl)methanesulfonamide

30 **[0362]**



45 **[0363]** Under ice-cooling, to a suspension of N-(3-[1-(2-fluoro-4-iodophenyl)-3,6,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidin-5-ylamino]-phenyl)methanesulfonamide **71** (3.10 g) obtained in Step 7 in tetrahydrofuran (31.0 ml) was added dropwise a mixture of potassium t-butoxide (1.33g), methanol (0.482 ml) and tetrahydrofuran (15.5 ml), and the mixture was stirred under ice-cooling for 2 hrs. Acetic acid (1.36 ml) was added, the mixture was allowed to warm to room temperature and stirred for 1 hr. The reaction mixture was concentrated, methanol/water [1:2 (volume ratio), 45.0 ml] was added, and the mixture was further stirred at room temperature for 1 hr. The crystals were collected by filtration and dried to give N-(3-[5-(2-fluoro-4-iodophenylamino)-3,6,8-trimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl)methanesulfonamide **72** (3.01 g, yield 97%) as a pale-gray solid.

50

MS ESI m/e: 626 (M+H), 624 (M-H).

¹H-NMR(DMSO-d₆, 300MHz)δ 1.26(s, 3H), 3.01(s, 3H), 3.09(s, 3H), 3.21(s, 3H), 6.93(t, J=8.3Hz, 1H), 7.11-7.15(m, 1H), 7.20-7.28(m, 2H), 7.42 (t, J=8.3Hz, 1H), 7.52-7.57 (m, 1H), 7.76-7.81 (m, 1H), 9.94 (brs, 1H), 11.21(brs, 1H).

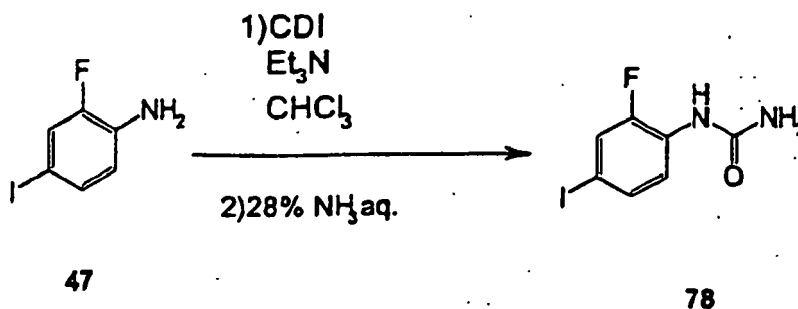
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Example 4-144

N-(3-[5-(2-Fluoro-4-iodophenylamino)-3-(4-hydroxybutyl)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl)-acetamide

Step 1 Synthesis of (2-fluoro-4-iodophenyl)-urea

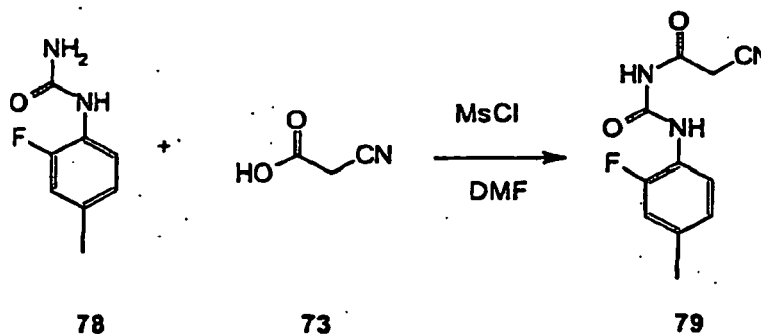
[0364]



[0365] Under argon atmosphere, to a solution of 2-fluoro-4-iodoaniline **47** (20.0 g) and triethylamine (23.6 ml) in chloroform (200 ml) was added N,N-carbonyldiimidazole (27.4 g) with stirring under ice-cooling. After the completion of the addition, the mixture was stirred under ice-cooling for 15 min and at room temperature for 4 hrs. The reaction mixture was ice-cooled, and 28% aqueous ammonia (100 ml) was added dropwise. The mixture was stirred at room temperature for 1.5 hrs. The precipitated crystals were collected by filtration, washed with water and dried to give (2-fluoro-4-iodophenyl)-urea **78** (23.5 g, yield 98.8%) as pale-pink crystals.

Step 2 Synthesis of 1-(2-cyanoacetyl)-3-(2-fluoro-4-iodophenyl)-urea

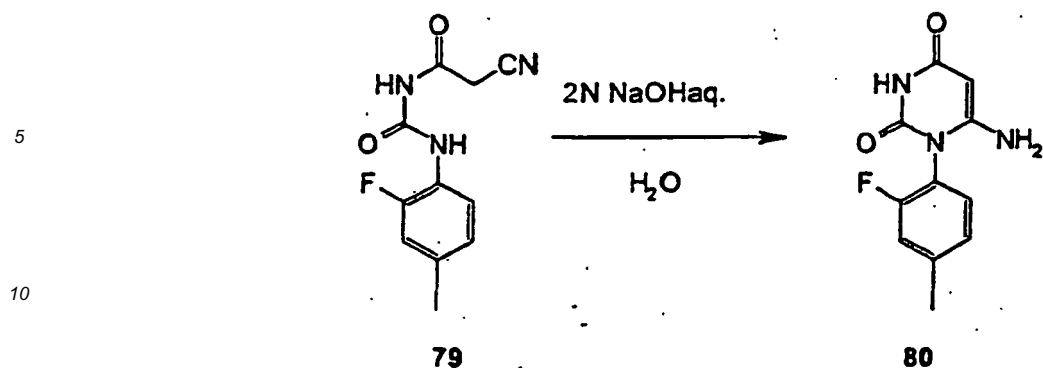
[0366]



[0367] To a mixture of (2-fluoro-4-iodophenyl)-urea **78** (21.7 g) and cyanoacetic acid **73** (7.88 g) in N,N-dimethylformamide (108 ml) was added, and methanesulfonyl chloride (7.17 ml) was added dropwise with stirring at room temperature. The mixture was stirred at room temperature for 2 hrs, and water-isopropyl alcohol [1:2 (volume ratio), 210 ml] was added dropwise. The mixture was stirred at room temperature for 1 hr. The precipitated crystals were collected by filtration and washed with water to give 1-(2-cyanoacetyl)-3-(2-fluoro-4-iodophenyl)-urea **79** (wet crystals), which was used for the next reaction in the form of wet crystals.

Step 3 Synthesis of 6-amino-1-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione

[0368]

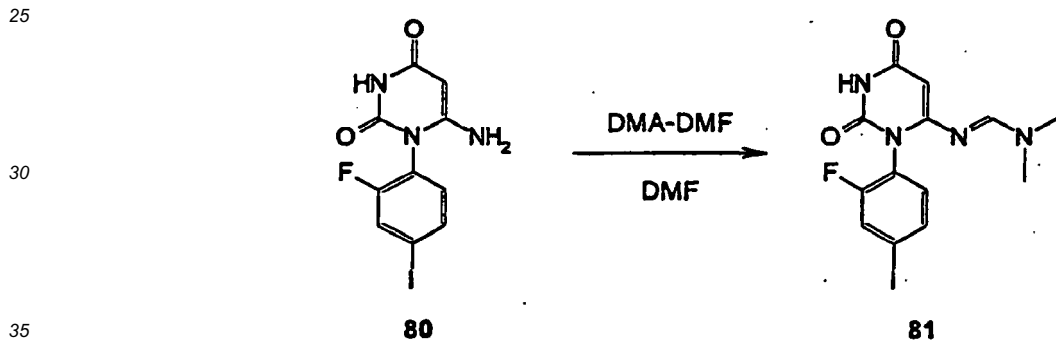


15 **[0369]** To a suspension of 1-(2-cyanoacetyl)-3-(2-fluoro-4-iodophenyl)-urea **79** (wet crystals) in water (110 ml) was added 2N aqueous sodium hydroxide solution (3.96 ml), and the mixture was stirred with heating at 85°C for 1 hr. After allowing to cool to room temperature, 2N hydrochloric acid (3.96 ml) and isopropyl alcohol (44.0 ml) were successively added dropwise. The mixture was stirred at room temperature for 1.5 hrs, the precipitated; crystals were collected by filtration, washed with isopropyl alcohol, and dried to give a mixture of 6-amino-1-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione **80** and **78** (21.8 g) as colorless crystals, which were used for the next reaction without purification.

20

Step 4 Synthesis of N'-[3-(2-fluoro-4-iodophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-N,N-dimethylformamide

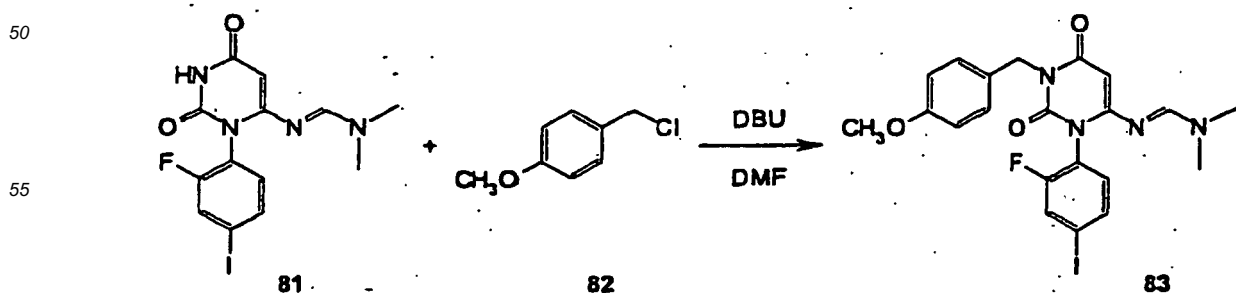
[0370]



40 **[0371]** To a mixture (21.8 g) of 6-amino-1-(2-fluoro-4-iodophenyl)-1H-pyrimidine-2,4-dione **80** and **78** was added N,N-dimethylformamide (42.0 ml) and N,N-dimethylformamidedimethylacetal (21.0 ml) and the mixture was stirred at room temperature for 4.5 hrs. With stirring at room temperature, isopropyl alcohol (20.0 ml) was added, and water (100 ml) was added dropwise. The mixture was stirred at room temperature for 45 min, and the precipitated crystals were collected by filtration, washed with water and dried to give N'-[3-(2-fluoro-4-iodophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-N,N-dimethylformamide **81** (21.7 g, yield 67.7% from **78**) as colorless crystals.

45 **Step 5** Synthesis of N'-[3-(2-fluoro-4-iodophenyl)-1-(4-methoxybenzyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-N,N-dimethylformamide

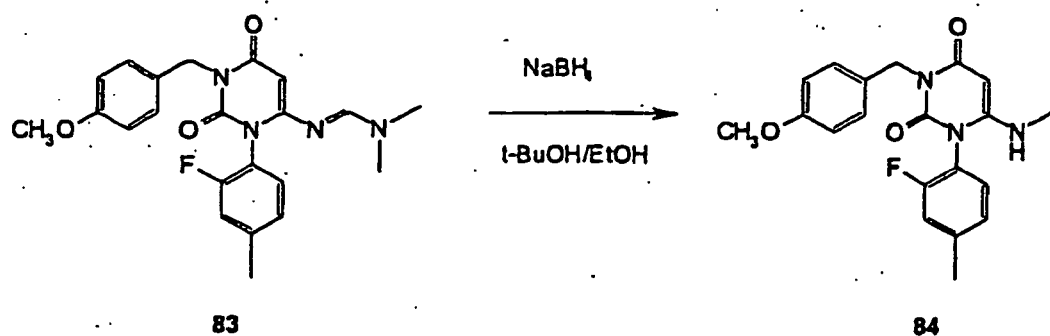
[0372]



[0373] To a solution of N'-[3-(2-fluoro-4-iodophenyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-N,N-dimethylformamide **81** (20.0 g) in N,N-dimethylformamide (150 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-en (14.9 ml) and 4-methoxybenzyl chloride **82** (10.1 ml) at room temperature. The mixture was stirred with heating at 75°C for 2.5 hrs, 1,8-diazabicyclo[5.4.0]undec-7-en (7.50 ml) and 4-methoxybenzyl chloride (4.00 ml) were added, and the mixture was stirred with heating at the same temperature for 2.5 hrs. After allowing to cool to room temperature, isopropyl alcohol (150 ml) and water (300 ml) were successively added dropwise. The mixture was stirred overnight at room temperature, and the precipitated crystals were collected by filtration and dried to give N'-[3-(2-fluoro-4-iodophenyl)-1-(4-methoxybenzyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-N,N-dimethylformamide **83** (20.2 g, yield 77.8%) as yellow crystals.

Step 6 Synthesis of 1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6-methylamino-1H-pyrimidine-2,4-dione

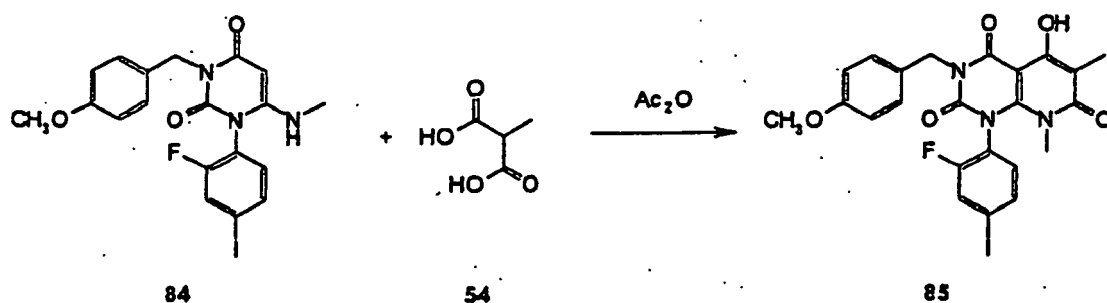
[0374]



[0375] To a suspension of sodium borohydride (326 mg) in t-butanol/ethanol [2:1 (volume ratio), 18.0 ml] was added N'-[3-(2-fluoro-4-iodophenyl)-1-(4-methoxybenzyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-N,N-dimethylformamide **83** (3.00 g) with stirring at room temperature. The mixture was stirred at room temperature for 1 hr, and at 65°C for 2 hrs. With stirring at the same temperature, water (30.0 ml) and ammonium chloride (461 mg) were successively added, and the mixture was stirred to allow to cool to room temperature. The reaction solution was extracted twice with ethyl acetate. The organic layers were combined, washed successively with saturated aqueous hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained crude product was purified by column chromatography to give 1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6-methylamino-1H-pyrimidine-2,4-dione **84** (2.57 g, yield 93.1%) as a pale-yellow solid.

Step 7 Synthesis of 1-(2-fluoro-4-iodophenyl)-5-hydroxy-3-(4-methoxybenzyl)-6,8-dimethyl-1H,5H-pyrido[2,3-d]pyrimidine-2,4,7-trione

[0376]



[0377] To a suspension of 1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6-methylamino-1H-pyrimidine-2,4-dione **84** (13.3 g) in acetic anhydride (13.0 ml) was added 2-methylmalonic acid **54** (4.90 g), and the mixture was stirred with heating at 90°C for 3 hrs and at 104°C for 1 hr. After allowing to cool to about 50°C, acetone (13.3 ml) was added dropwise, and water (75.0 ml) was further added. After seeding with compound **85**, acetone (30.0 ml) was added, and the mixture was stirred for 1.5 hrs. Water (30.0 ml) was added and the mixture was stirred for 45 min, and allowed to cool to room temperature. The precipitated crystals were collected by filtration, washed with water and dried to give 1-(2-

fluoro-9-iodophenyl)-5-hydroxy-3-(4-methoxybenzyl)-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidine-2,4,7-trione **85** (14.1 g, yield 90.7%) as pale-ocher crystals.

Step 8 Synthesis of trifluoromethanesulfonic acid 1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl ester

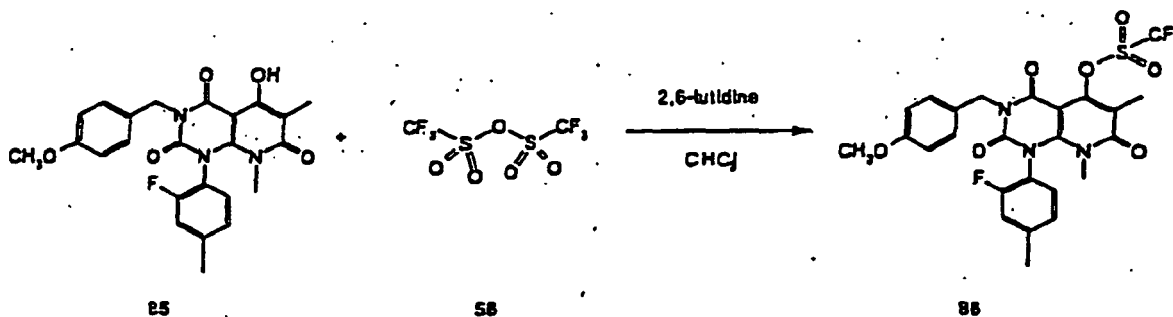
[0378]

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[0379] Under argon atmosphere, to a solution of 1-(2-fluoro-4-iodophenyl)-5-hydroxy-3-(4-methoxybenzyl)-6,8-dimethyl-1H,8H-pyrido[2,3-d]pyrimidin-2,4,7-trione **85** (14.1 g) in chloroform (70.0 ml) was added 2,6-lutidine (3.79 ml) and trifluoromethanesulfonic anhydride **56** (5.47 ml) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hr, and at room temperature for 1.5 hrs. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution and chloroform to allow partitioning. The organic layer was washed once with saturated aqueous sodium hydrogen carbonate solution, twice with 1N hydrochloric acid, once with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. To the obtained crude product was added isopropyl alcohol (35.0 ml), and the mixture was stirred with heating at an outer temperature of 95°C for 30 min. After allowing to cool with stirring to room temperature, isopropyl alcohol (35.0 ml) was added, and the mixture was stirred for 1 hr. The precipitated crystals were collected by filtration, washed with isopropyl alcohol and dried to give trifluoromethanesulfonic acid 1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl ester **86** (14.4 g, yield 82.8%) as brown crystals.

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Step 9 Synthesis of N-{3-[1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-ylamino]-phenyl}-acetamide

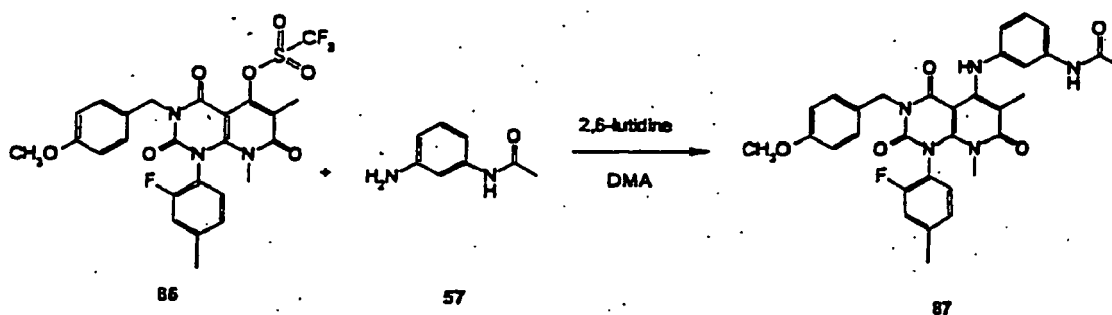
[0380]

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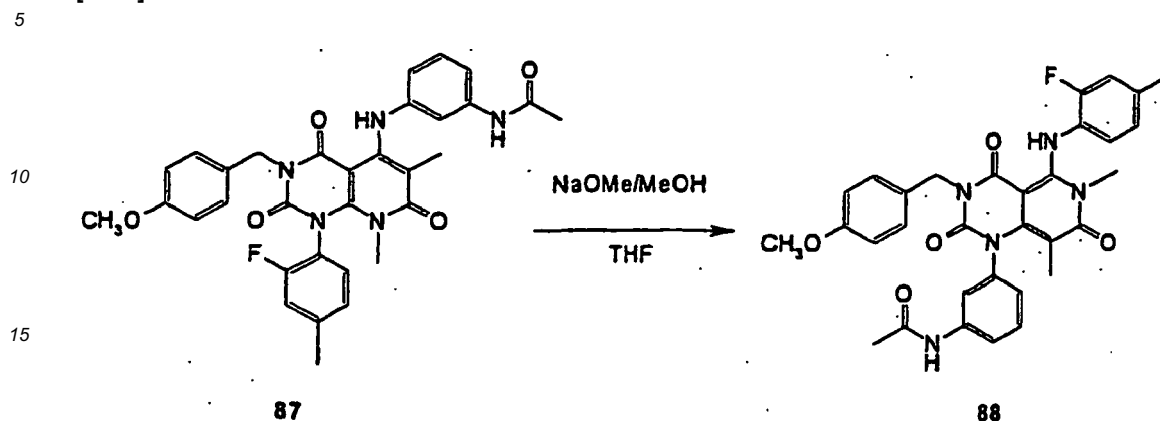


[0381] To trifluoromethanesulfonic acid 1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl ester **86** (1.10 g) and 3'-aminoacetanilide **57** (285 mg) were added, N,N-dimethylacetamide (2.20 ml) and 2,6-lutidine (221 μ l), and the mixture was stirred at 130°C for 2 hrs. After allowing to return to room temperature, methanol (12.0 ml) was added dropwise with stirring. The precipitated crystals were collected by filtration, washed with methanol and dried to give N-{3-[1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-ylamino]-phenyl}-acetamide **87** (1.04 g, yield 94.6%) as colorless crystals.

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Step 10 Synthesis of N-{3-[5-(2-fluoro-4-iodophenylamino)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide

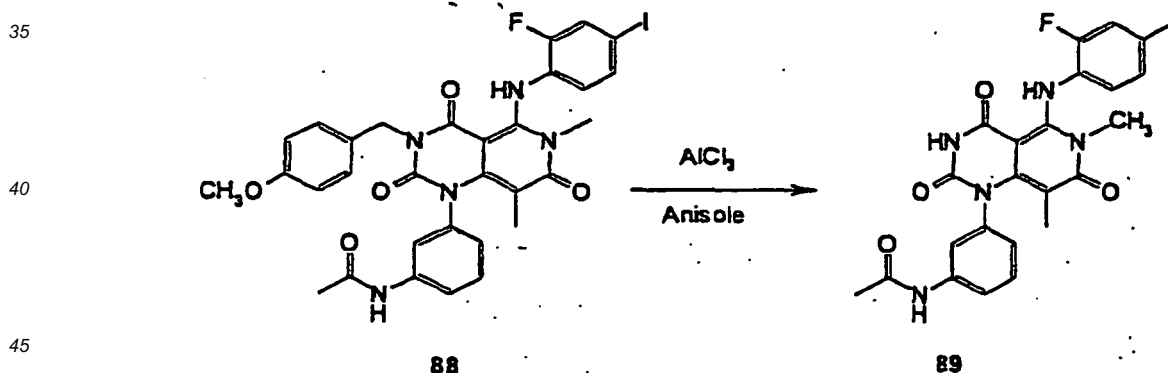
[0382]



[0383] To a solution (305 mg) of 28% sodium methoxide in methanol were added tetrahydrofuran (4.00 ml) and N-{3-[1-(2-fluoro-4-iodophenyl)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-2H-pyrido[2,3-d]pyrimidin-5-ylamino]-phenyl}-acetamide **87** (1.00 g). The inner wall was washed with tetrahydrofuran (4.00 ml). The mixture was stirred at room temperature for 1.5 hrs., 2N hydrochloric acid (900 μ l) was added, and the mixture was concentrated under reduced pressure. To the residue was added isopropyl alcohol, methanol and water, and after refluxing, the mixture was allowed to cool to room temperature with stirring. The precipitated crystals were collected by filtration, washed with methanol, and dried to give N-{3-[5-(2-fluoro-4-iodophenylamino)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **88** (974 mg, yield 97.2%) as colorless crystals.

Step 11 Synthesis of N-{3-[5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide

[0384]



[0385] To a suspension of N-{3-[5-(2-fluoro-4-iodophenylamino)-3-(4-methoxybenzyl)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **88** (960 mg) in anisole (10.0 ml) was added aluminum chloride (1.94 g) with stirring in a water bath. The mixture was stirred at room temperature for 37 hrs, methanol (12.0 ml) was added dropwise, and the mixture was concentrated under reduced pressure. The obtained residue was dissolved in methanol (12.0 ml), and 2N hydrochloric acid (20.0 ml) was added dropwise with stirring in a water bath. The mixture was stirred at room temperature for 1 hr, hexane (10.0 ml) was added, and the mixture was stirred for 1 hr. The precipitated crystals were collected by filtration, washed with hexane, water and methanol, and dried to give N-{3-[5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **89** (620 mg, yield 78.1%) as colorless crystals.

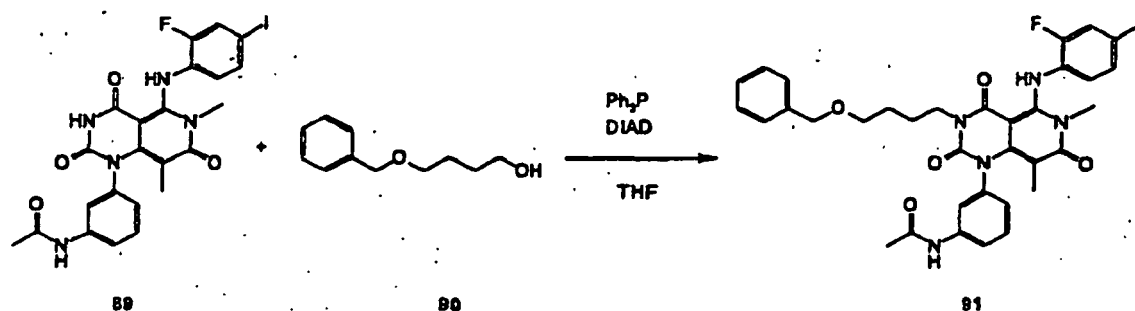
Step 12 Synthesis of N-{3-[3-(4-benzyloxybutyl)-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide

[0386]

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[0387] Under argon atmosphere, to a suspension of N-{3-[5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **89** (75.0 mg), 4-benzyloxybutyl alcohol **90** (25.0 μ l) and triphenylphosphine (37.0 mg) in tetrahydrofuran (1.00 ml) was added diisopropyl azodicarboxylate (28.0 μ l) with stirring under ice cooling. The mixture was stirred at the same temperature for 2 hrs, and 4-benzyloxybutyl alcohol (13.0 μ l), triphenylphosphine (19.0 mg) and diisopropyl azodicarboxylate (14.0 μ l) were added. The mixture was stirred at the same temperature for 1 hr, and water and ethyl acetate were added to allow partitioning. The organic layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (chloroform:ethyl acetate=2:1 \rightarrow 1:1) and thin layer chromatography (hexane:acetone=1:1) for further purification to give N-{3-[3-(4-benzyloxybutyl)-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **91** (74 mg, yield 77%) as a pale-yellow amorphous form.

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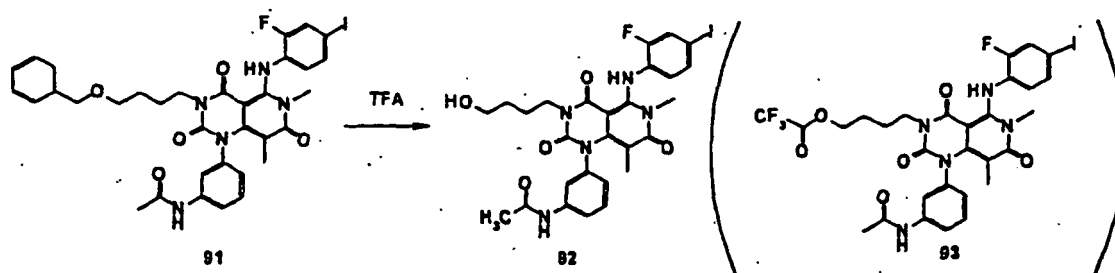
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Step 13 Synthesis of N-{3-[5-(2-fluoro-4-iodophenylamino)-3-(4-hydroxybutyl)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide

[0388]

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[0389] N-{3-[3-(4-Benzyloxybutyl)-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **91** (74 mg) was stirred under reflux for 5.5 hrs in trifluoroacetic acid (1.00 ml). The reaction mixture was concentrated under reduced pressure, and ethyl acetate and saturated aqueous sodium hydrogen carbonate solution were added to the residue to allow partitioning. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. To the residue was added diisopropyl ether (1.00 ml), and the mixture was stirred at 60°C to allow cooling to room temperature with stirring. The crystals were collected by filtration, washed with diisopropyl ether, and dried to give compound **93** (26 mg) as colorless crystals. Compound **93** was stirred in a mixed solution of saturated aqueous sodium hydrogen carbonate solution (300 μ l), methanol (300 μ l) and ethyl acetate (300 μ l) at room temperature for 1 hr, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. To the residue were added ethyl acetate, hexane and diethyl ether, and the mixture was stirred at room temperature for 1 hr. The precipitated crystals were collected by filtration, washed with hexane and dried to give N-{3-[5-(2-fluoro-4-iodophenylamino)-3-(4-hydroxybutyl)-6,8-dimethyl-2,4,7-tri-

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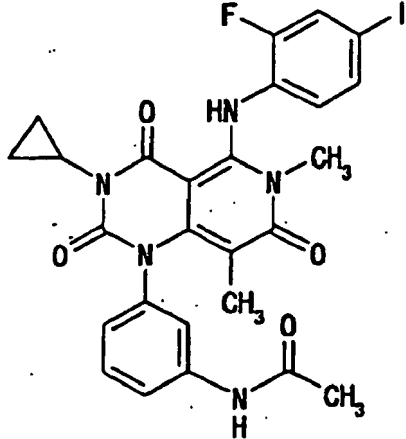
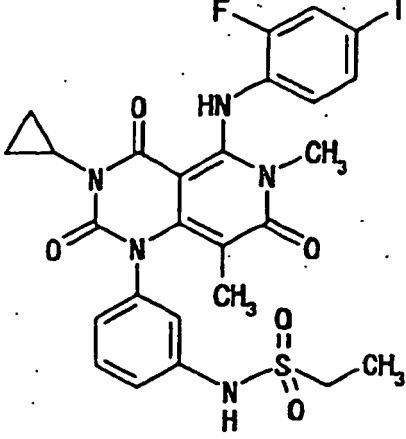
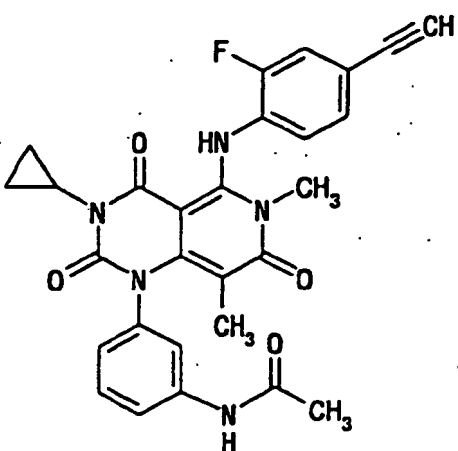
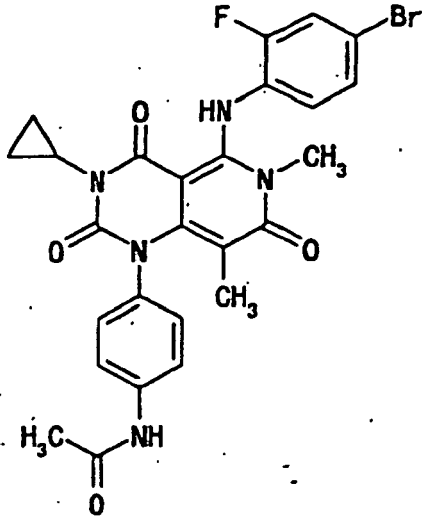
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oxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl)-phenyl)-acetamide **92** (5 mg, yield 8%) as colorless crystals.

Examples 4-2, 4-4-15, 4-17-143 and 4-145-148

5 **[0390]** In the same manner as in Examples 4-1, 4-3 and 4-16, the compounds of Examples 4-2, 4-4-15, 4-17-133 and 4-138-4-140 were obtained. In addition, in the same manner as in Example 4-144, the compounds of Examples 4-83-86, Examples 4-134-137, 4-141-143 and 4-145-148 were obtained. The structural formulas thereof are shown in Table 4-1 to 4-25 with Examples 4-1, 4-3, 4-16 and 4-144.

10 Table 4-1

Ex. No.	structural formula	Ex. No.	structural formula
4-1		4-2	
4-3		4-4	

(continued)

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-5		4-6	

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Table 4-2

Ex. No.	structural formula	Ex. No.	structural formula
25 30 35 40 4-7		4-8	
45 50 55 4-9		4-10	

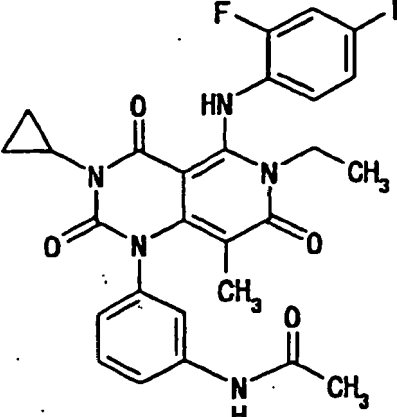
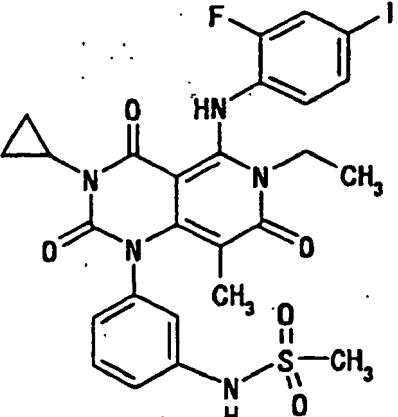
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Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-11		4-12	

Table 4-3

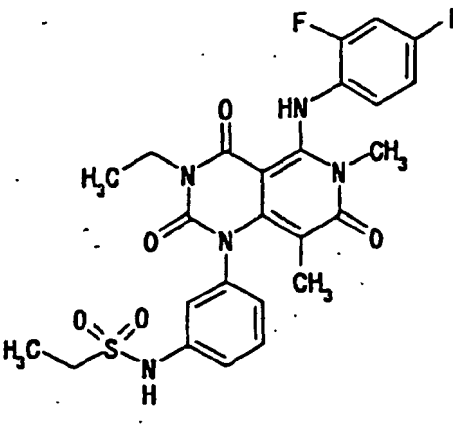
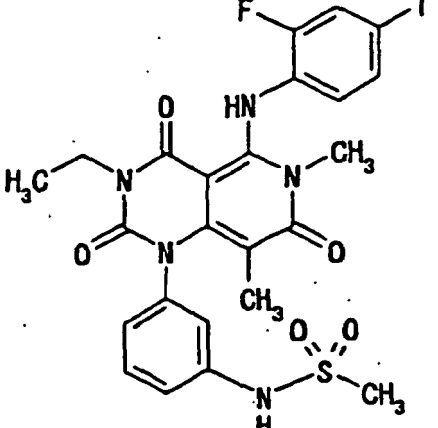
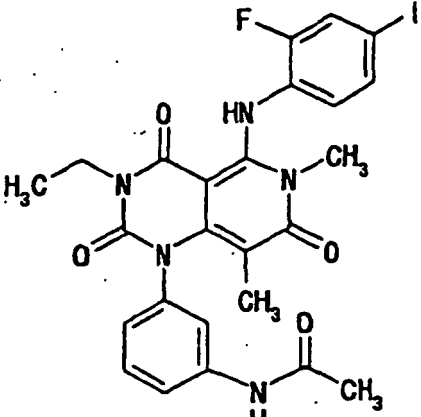
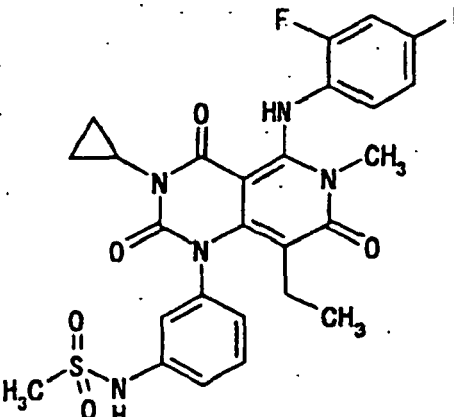
Ex. No.	structural formula	Ex. No.	structural formula
25 30 35 4-13		4-14	
40 45 50 4-15		4-16	

(continued)

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-17		4-18	

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Table 4-4

Ex. No.	structural formula	Ex. No.	structural formula
25 30 35 4-19		4-20	
40 45 50 4-21		4-22	

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(continued)

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-23		4-24	

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Table 4-5

Ex. No.	structural formula	Ex. No.	structural formula
25 30 35 4-25		4-26	
40 45 50 4-27		4-28	

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(continued)

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-29		4-30	

Table 4-6

Ex. No.	structural formula	Ex. No.	structural formula
20 25 30 35 4-31		4-32	
40 45 50 4-33		4-34	

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(continued)

Ex. No.	structural formula	Ex. No.	structural formula
4-35	<p>HCl</p>	4-36	<p>HCl</p>

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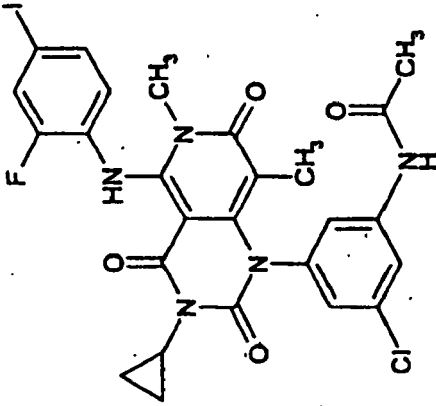
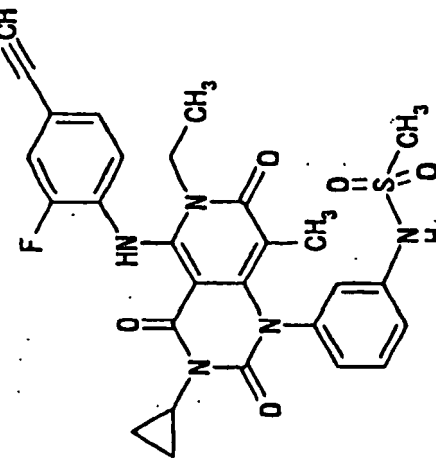
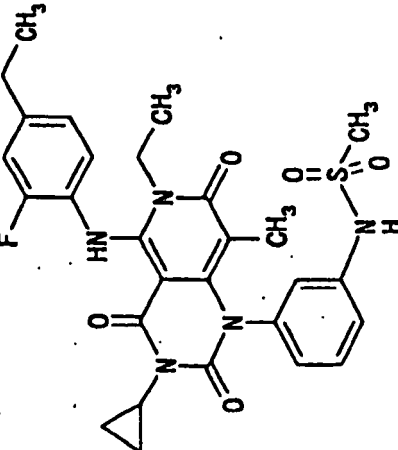
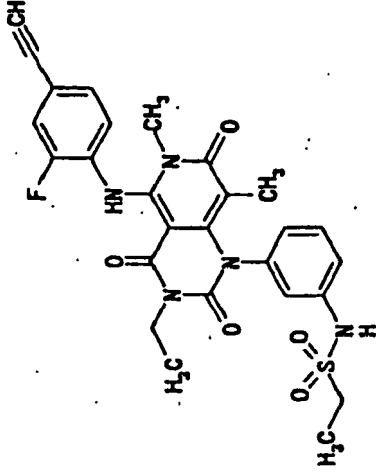
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Table 4-7

Ex. No.	structural formula	Ex. No.	structural formula
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4-39		4-40	

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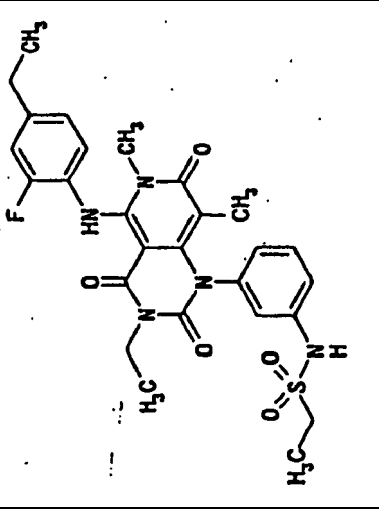
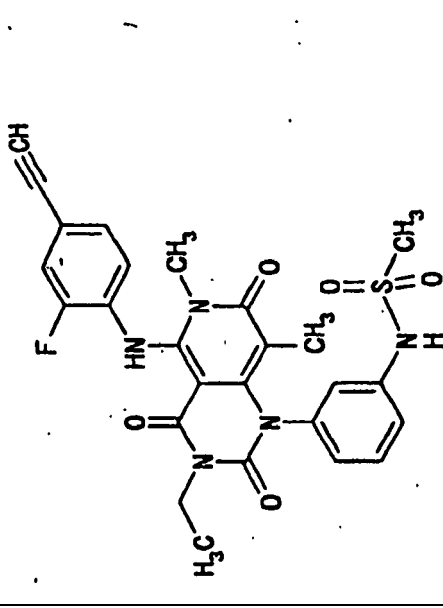
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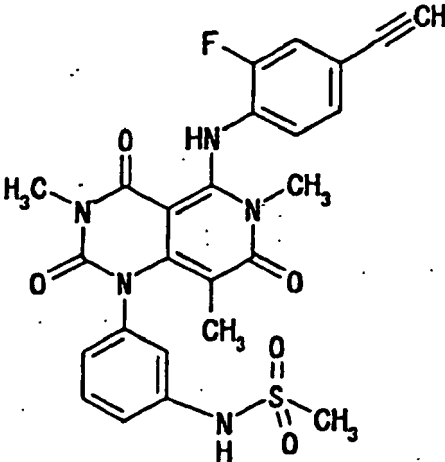
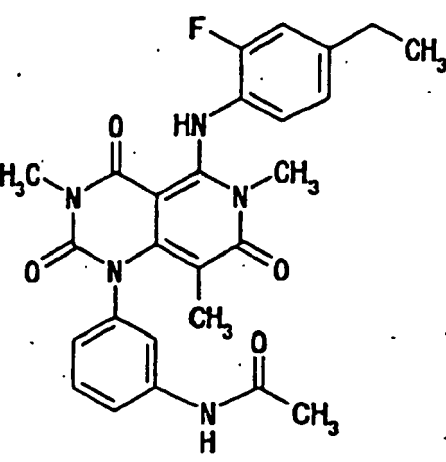
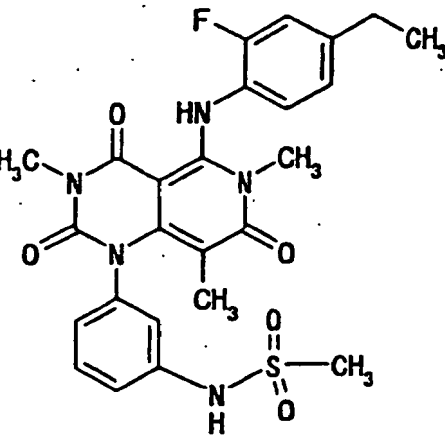
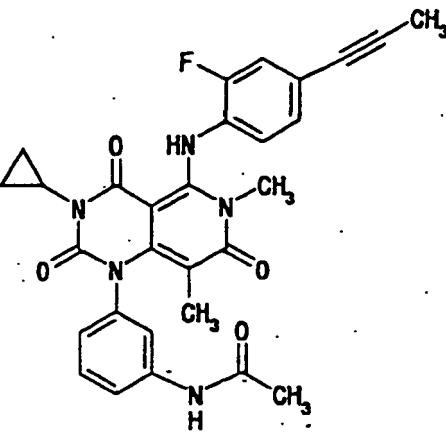
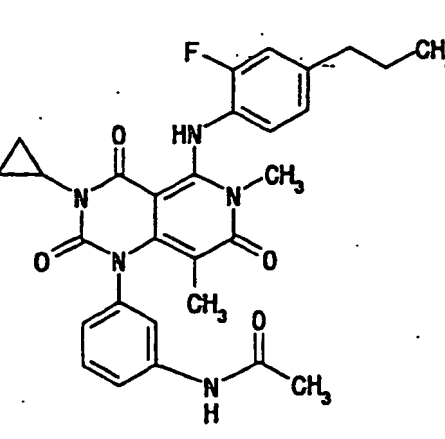
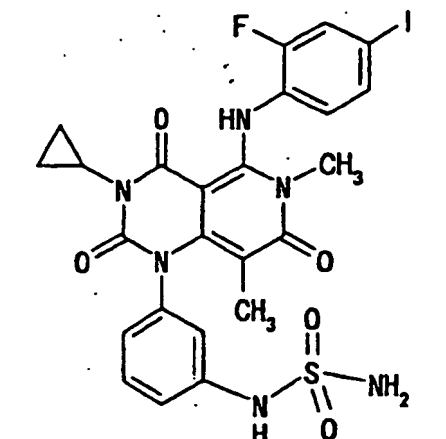
Ex. No.	structural formula	Ex. No.	structural formula
4-41		4-42	

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Table 4-8

Ex. No.	structural formula	Ex. No.	structural formula
4-43		4-44	
4-45		4-46	
4-47		4-48	

Table 4-9

Ex. No.	structural formula	Ex. No.	structural formula
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<p>20</p> <p>25</p> <p>30</p> <p>4-51</p>		<p>4-52</p>	
<p>35</p> <p>40</p> <p>45</p> <p>4-53</p>		<p>4-54</p>	

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Table 4-10

Ex No.	structural formula	Ex. No.	structural formula
5 10 15 4-55		4-56	
20 25 30 4-57		4-58	
35 40 45 50 4-59		4-60	

Table 4-11

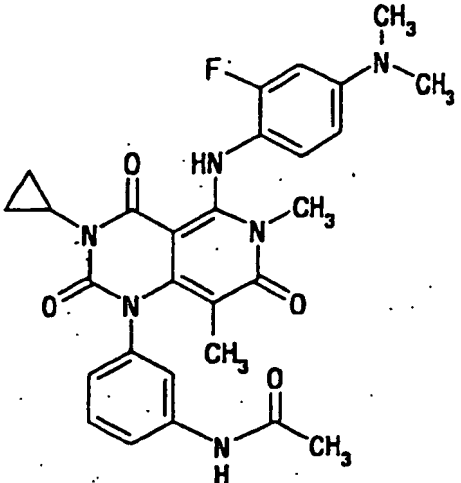
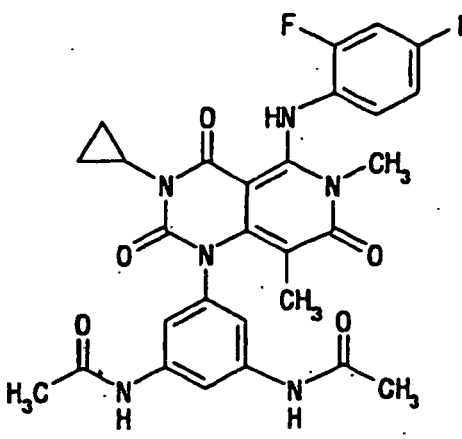
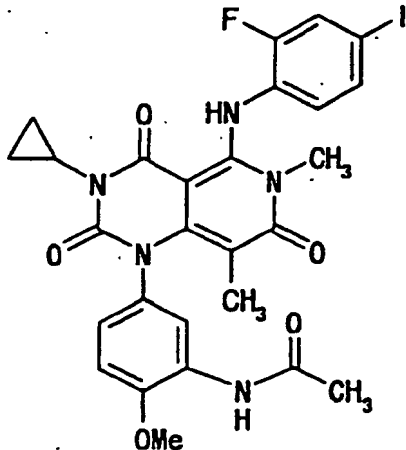
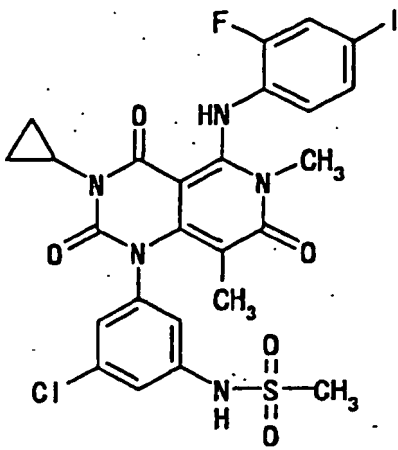
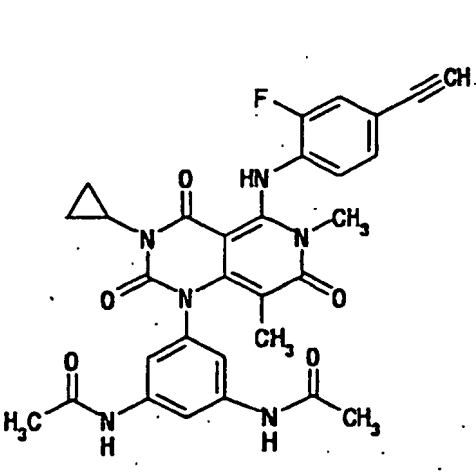
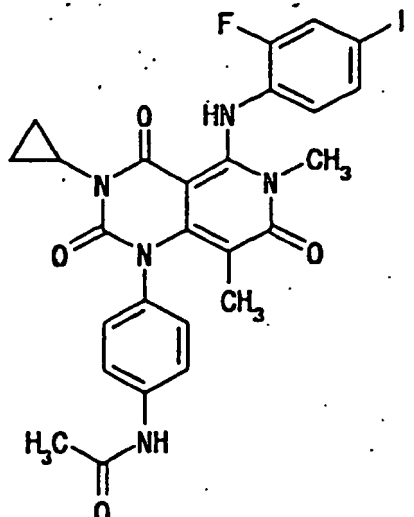
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20	<p>4-61</p> 	<p>4-62</p> 	
25 30	<p>4-63</p> 	<p>4-64</p> 	
35 40 45 50	<p>4-65</p> 	<p>4-66</p> 	

Table 4-12

Ex. No.	structural formula	Ex. No.	structural formula
4-67		4-68	
4-69		4-70	
4-71		4-72	

Table 4-13

Ex. No.	structural formula	Ex. No.	structural formula
4-73		4-74	
4-75		4-76	
4-77		4-78	

Table 4-14

Ex. No.	structural formula	Ex. No.	structural formula
4-79		4-80	
4-81		4-82	
4-83		4-84	

Table 4-15

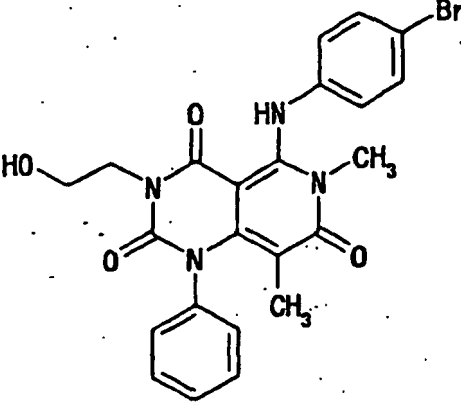
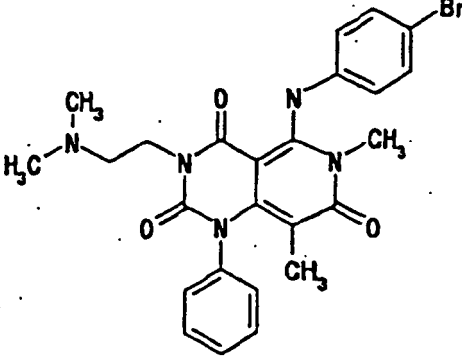
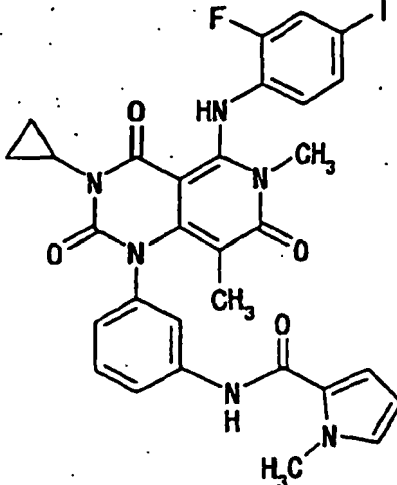
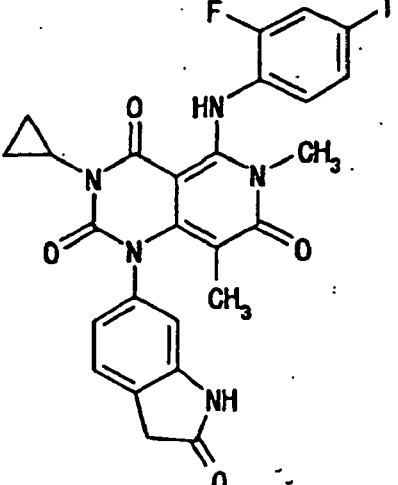
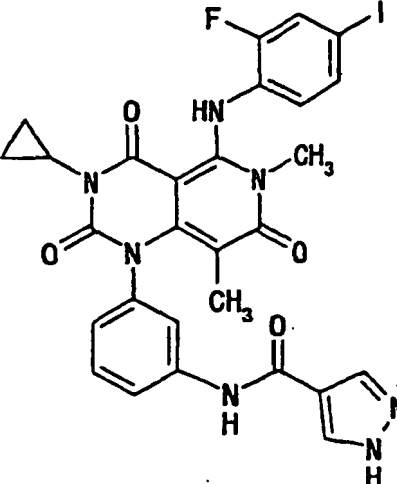
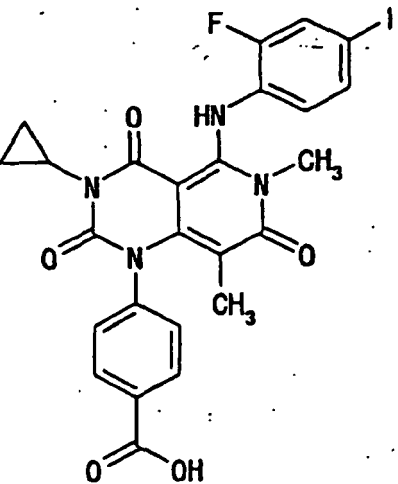
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-85		4-86	
20 25 30 35 4-87		4-88	
40 45 50 55 4-89		4-90	

Table 4-16

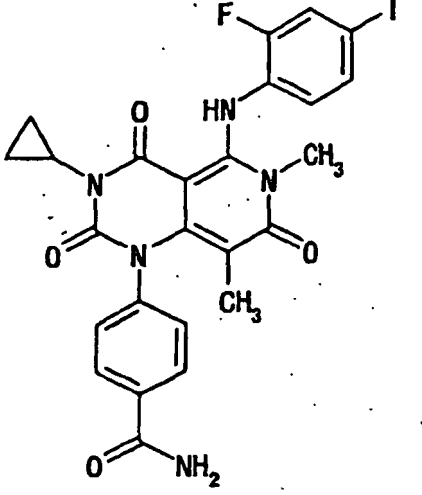
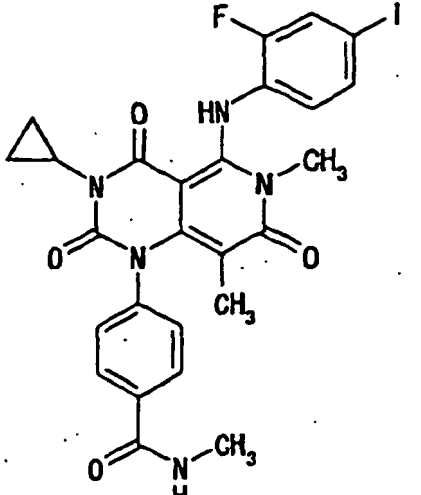
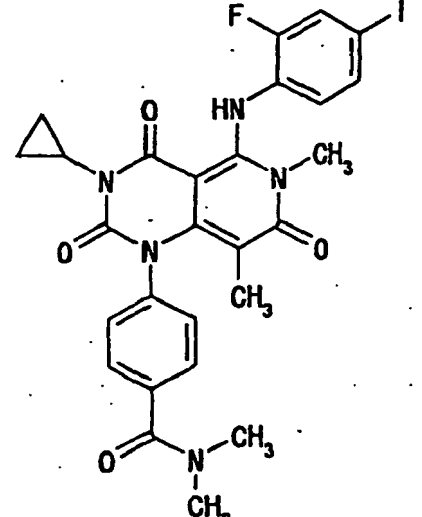
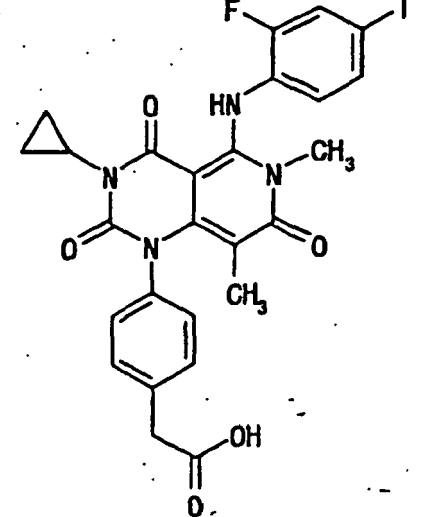
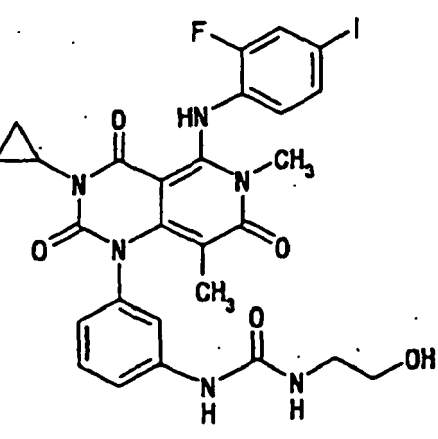
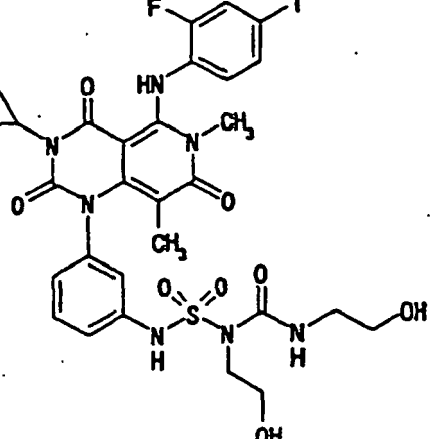
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 4-91		4-92	
25 30 35 4-93		4-94	
40 45 50 55 4-95		4-96	

Table 4-17

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-97		4-98	
20 25 30 4-99		4-100	
35 40 45 4-101		4-102	

50

55

Table 4-18

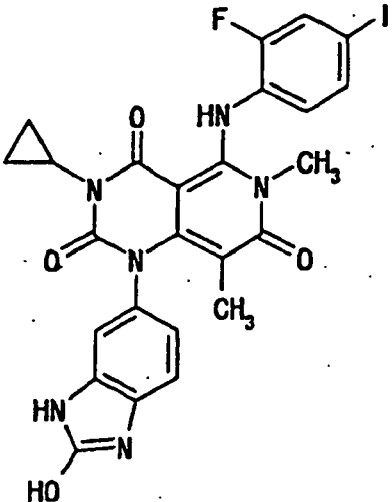
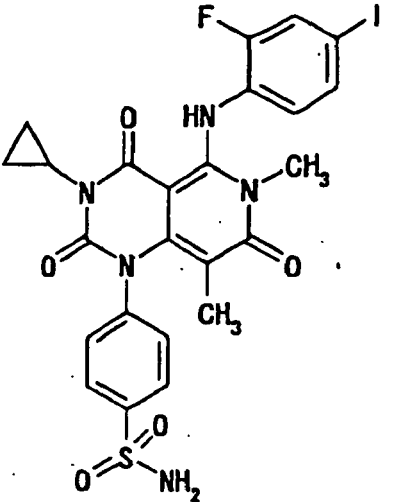
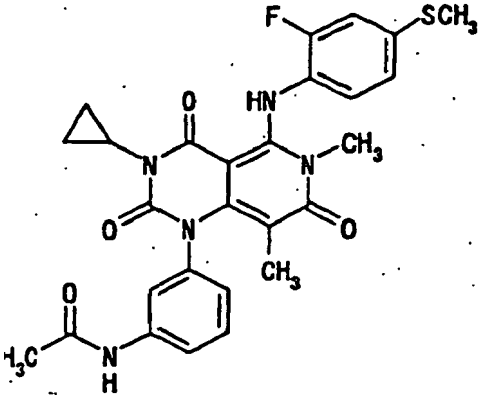
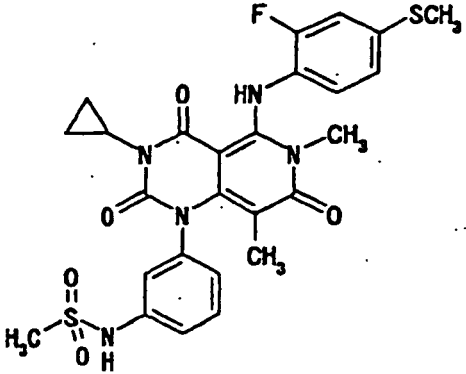
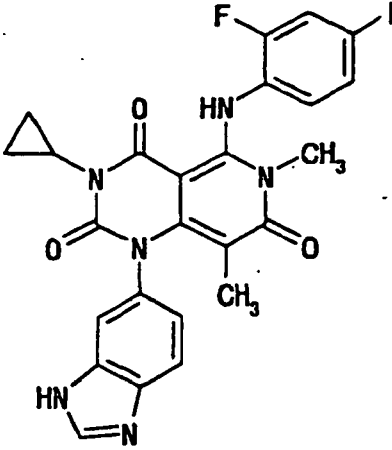
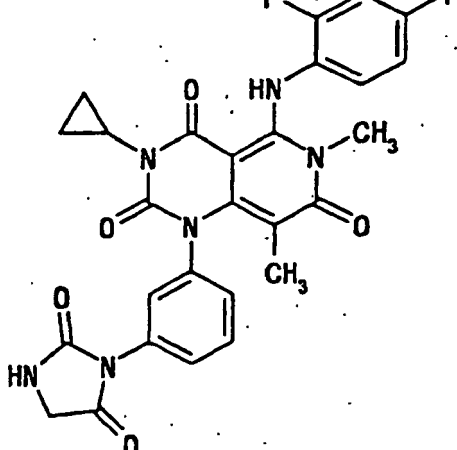
Ex. No.	structural formula	Ex. No.	structural formula
4-103		4-104	
4-105		4-106	
4-107		4-108	

Table 4-19

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 4-109		4-110	
25 30 35 4-111		4-112	
40 45 50 55 4-113		4-114	

Table 4-20

Ex. No.	structural formula	Ex. No.	structural formula
4-115		4-116	
4-117		4-118	
4-119		4-120	

Table 4-21

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-121		4-122	
20 25 30 35 4-123		4-124	
40 45 50 55 4-125		4-126	

Table 4-22

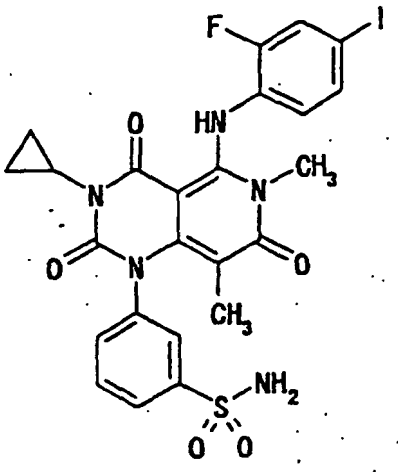
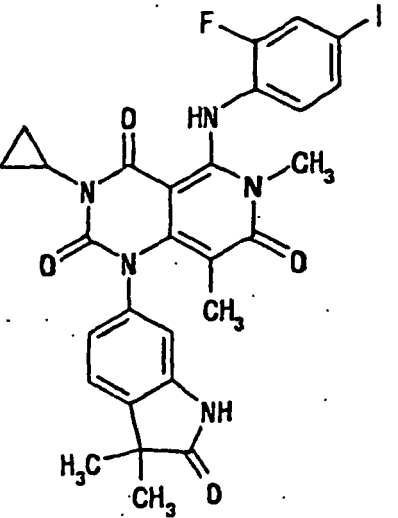
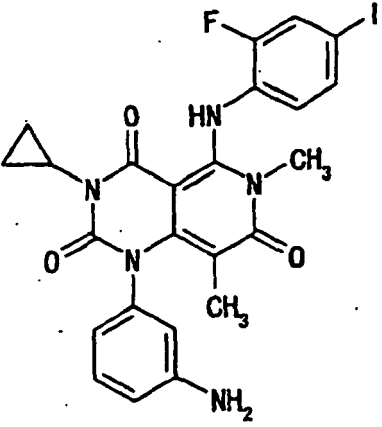
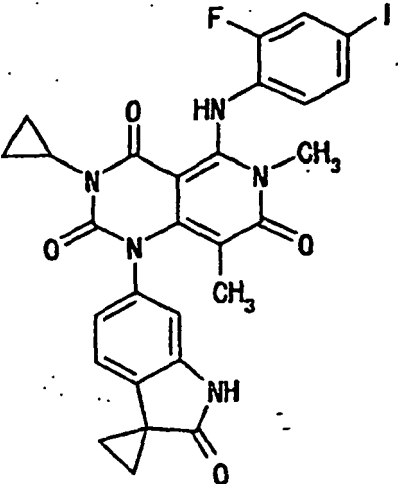
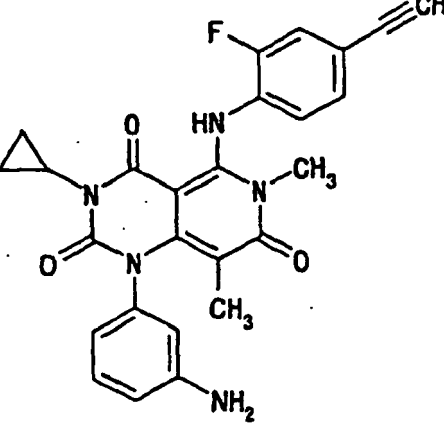
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 4-127		4-128	
25 30 35 4-129		4-130	
40 45 50 4-131			

Table 4-23

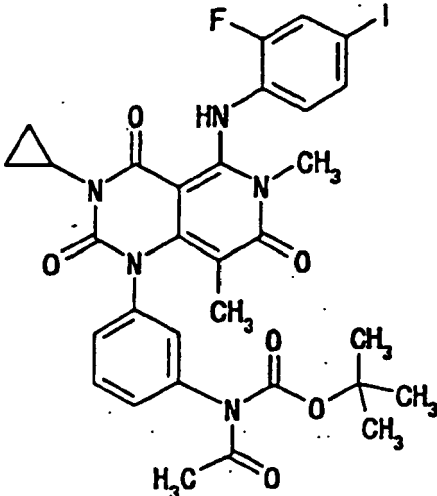
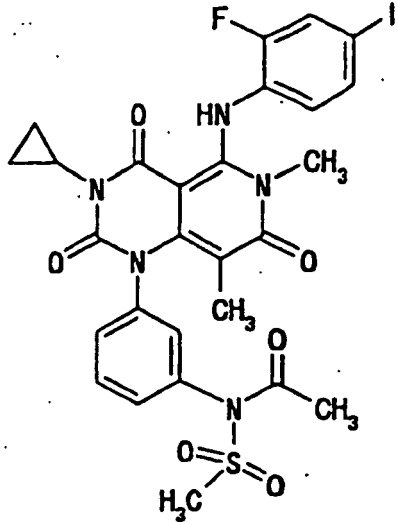
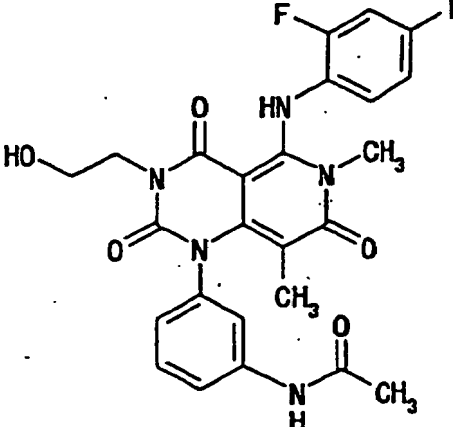
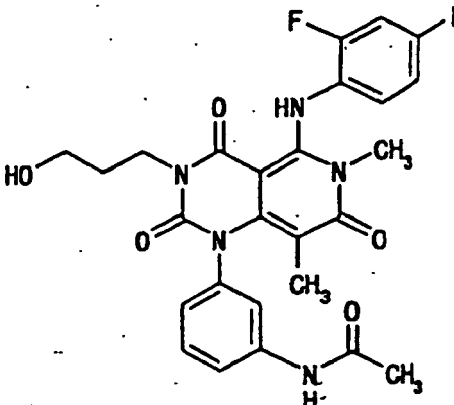
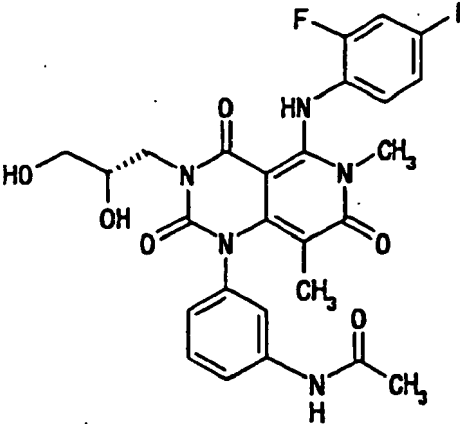
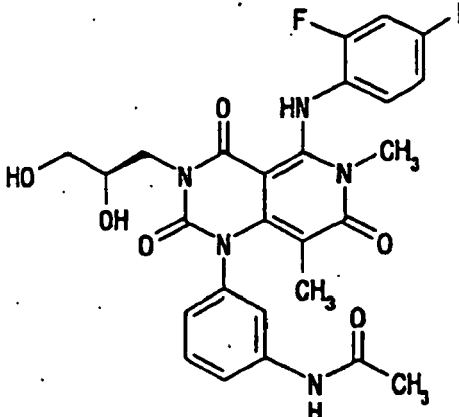
Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 4-132		4-133	
25 30 35 4-134		4-135	
40 45 50 4-136		4-137	

Table 4-24

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 20 4-138		4-139	
25 30 35 4-140		4-141	
40 45 50 4-142		4-143	

Table 4-25

Ex. No.	structural formula	Ex. No.	structural formula
5 10 15 4-144		4-145	
20 25 30 4-146		4-147	
35 40 45 4-148			

Example 4-149

[0391] By treating N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide **59** by a conventional method, the sodium salt, hydrate, acetic acid solvate, dimethylsulfoxide solvate, ethanol solvate, nitromethane solvate, chlorobenzene solvate, 1-pentanol solvate, isopropyl alcohol solvate, ethylene glycol solvate and 3-methylbutanol solvate thereof were obtained.

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide sodium salt:

$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ 0.35-0.41 (m, 2H), 0.71-0.77 (m, 2H), 1.16 (s, 3H), 2.02 (s, 3H), 2.18-2.24 (m, 1H),

3.32 (s, 3H), 6.59 (t, J=8.8Hz, 1H), 6.94 (d, J=8.6Hz, 1H), 7.04 (d, J=10.2Hz, 1H), 7.19 (d, J=11.1Hz, 1H), 7.27 (t, J=8.0Hz, 1H), 7.34 (s, 1H), 7.64 (d, J=8.3Hz, 1H), 10.00 (s, 1H).

MS (ESI) *m/z* 616 [MH]⁺.

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide hydrate:

¹H-NMR (DMSO-*d*₆, 400 MHz) δ 0.63-0.70 (m, 2H), 0.91-1.00 (m, 2H), 1.25 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.08 (s, 3H), 6.92 (t, J = 8.8 Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J = 8.2 Hz, 1H), 7.52-7.63 (m, 3H), 7.79 (dd, J = 2.0, 10.4 Hz, 1H), 10.09 (s, 1H), 11.08 (s, 1H).

MS (ESI) *m/z* 616 [MH]⁺.

N-(3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl)-acetamide acetic acid solvate:

¹H-NMR (DMSO-*d*₆, 400 MHz) δ 0.63-0.70 (m, 2H), 0.92-0.98 (m, 2H), 1.25 (s, 3H), 1.91 (s, 3H), 2.04 (s, 3H), 2.59-2.65 (m, 1H), 3.08 (s, 3H), 6.92 (t, J=8.6Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J=7.6Hz, 1H), 7.53-7.62 (m, 3H), 7.79 (dd, J=10.4Hz; 1H), 10.08 (s, 1H), 11.07 (s, 1H), 11.94 (s, 1H).

MS (ESI) *m/z* 616 [MH]⁺.

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide dimethyl sulfoxide solvate:

¹H-NMR (CDCl₃, 400 MHz) δ 0.76-0.82 (m, 2H), 1.09-1.15 (m, 2H), 1.41 (s, 3H), 2.14 (s, 3H), 2.62 (s, 6H), 2.71-2.77 (m, 1H), 3.20 (s, 3H), 6.70 (t, J = 8.4 Hz, 1H), 7.00 (brs, 1H), 7.32 (brs, 2H), 7.43-7.47 (m, 1H), 7.52 (dd, J = 2.0, 9.6 Hz, 1H), 7.71 (brs, 2H), 11.30 (s, 1H).

MS (ESI) *m/z* 616 [MH]⁺.

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide ethanol solvate:

¹H-NMR (DMSO-*d*₆, 300 MHz) δ 0.63-0.70 (m, 2H), 0.91-1.00 (m, 2H), 1.06 (t, J = 7.1 Hz, 3H), 1.25 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 3.40-3.49 (m, 2H), 4.33 (t, J = 5.1 Hz, 1H), 6.92 (t, J = 8.8 Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J = 8.2 Hz, 1H), 7.52-7.63 (m, 3H), 7.79 (dd, J = 2.0, 10.4 Hz, 1H), 10.08 (s, 1H), 11.07 (s, 1H).

MS (ESI) *m/z* 616 [MH]⁺.

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide nitromethane solvate:

¹H-NMR (DMSO-*d*₆, 300 MHz) δ 0.63-0.70 (m, 2H), 0.91-1.00 (m, 2H), 1.25 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 4.42 (s, 2H), 6.92 (t, J = 8.8 Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J = 8.2 Hz, 1H), 7.52-7.63 (m, 3H), 7.79 (dd, J = 2.0, 10.4 Hz, 1H), 10.08 (s, 1H), 11.07 (s, 1H).

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3'-d]pyrimidin-1-yl]-phenyl}-acetamide chlorobenzene solvate:

¹H-NMR (DMSO-*d*₆, 300 MHz) δ 0.63-0.70 (m, 2H), 0.91-1.00 (m, 2H), 1.25 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 6.92 (t, J = 8.8 Hz, 1H), 7.00-7.05 (m, 1H), 7.29-7.45 (m, 5H), 7.50-7.63 (m, 3H), 7.79 (dd, J = 2.0, 10.4 Hz, 1H), 10.08 (s, 1H), 11.07 (s, 1H).

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide 1-pentanol solvate

¹H-NMR (DMSO-*d*₆, 300 MHz) δ 0.62-0.70 (m, 2H), 0.86 (t, J=7.0Hz, 1.5H), 0.90-0.99 (m, 2H), 1.22-1.30 (m, 5H), 1.35-1.44 (m, 1H), 2.04 (s, 3H), 2.56-2.67 (m, 1H), 3.08 (s, 3H), 3.33-3.41 (m, 1H), 4.30 (t, J=5.1Hz, 0.5H), 6.91 (t, J=8.5Hz, 1H), 7.00-7.06 (m, 1H), 7.36 (t, J=8.3Hz, 1H), 7.52-7.62 (m, 3H), 7.74-7.81 (m, 1H), 10.08 (s, 1H), 11.07 (s, 1H).

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide isopropyl alcohol solvate:

¹H-NMR (DMSO-*d*₆, 400 MHz) δ 0.63-0.69 (m, 2H), 0.91-0.98 (m, 2H), 1.04 (d, J=6.0Hz, 6H), 1.25 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 3.73-3.81 (m, 1H), 4.34 (d, J=4.2Hz, 1H), 6.92 (t, J=8.7Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J=8.3Hz, 1H), 7.52-7.62 (m, 3H), 7.79 (dd, J=1.8, 10.2Hz, 1H), 10.10 (s, 1H), 11.08 (s, 1H).

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide ethylene glycol solvate:

¹H-NMR (DMSO-*d*₆, 300 MHz) δ 0.63-0.70 (m, 2H), 0.91-1.00 (m, 2H), 1.24 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 3.36-3.41 (m, 4H), 4.37-4.44 (m, 2H), 6.92 (t, J = 8.8 Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J = 8.2 Hz, 1H), 7.52-7.63 (m, 3H), 7.79 (dd, J = 2.0, 10.4 Hz, 1H), 10.10 (s, 1H), 11.08 (s, 1H).

N-{3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]-phenyl}-acetamide 3-methyl-1-butanol solvate:

¹H-NMR (DMSO-*d*₆, 400 MHz) δ 0.64-0.69 (m, 2H), 0.85 (d, J=6.7Hz, 6H), 0.92-0.98 (m, 2H), 1.25 (s, 3H), 1.31 (q, J=6.7Hz, 2H), 1.60-1.70 (m, 1H), 2.04 (s, 3H), 2.59-2.66 (m, 1H), 3.08 (s, 3H), 3.38-3.44 (m, 2H), 4.26 (t, J=5.1Hz, 1H), 6.92 (t, J=8.7Hz, 1H), 7.01-7.05 (m, 1H), 7.35 (t, J=8.0Hz, 1H), 7.52-7.62 (m, 3H), 7.78 (dd, J=1.9, 10.2Hz, 1H), 10.08

(s, 1H), 11.07 (s, 1H).

Example 4-150

5 **[0392]** By treating N-{3-[3-cyclopropyl-5-(4-ethynyl-2-fluorophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide 62 according to a conventional method, acetic acid solvate was obtained. N-{3-[3-cyclopropyl-5-(4-ethynyl-2-fluorophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide acetic acid solvate:

10 ¹H-NMR (DMSO-d₆, 400 MHz) δ 0.60-0.70 (m, 2H), 0.90-1.00 (m, 2H), 1.26(s, 3H), 1.91 (s, 3H), 2.04(s, 3H), 2.59-2.66 (m, 1H), 3.10(s, 3H), 4.29(s, 1H), 7.01-7.05 (m, 1H), 7.08(t, J=8.6Hz, 1H), 7.31(dd, J=1.6, 8.3Hz, 1H), 7.36 (t, J=8.1Hz, 1H), 7.52(dd, J=1.6, 11.3Hz, 1H), 7.57-7.62 (m, 2H), 10.09 (s, 1H), 11.09(s, 1H), 11.94 (s, 1H).
MS (ESI) *m/z* 514 [MH]⁺.

Examples 4-151

15 **[0393]** By treating N-{3-[5-(2-fluoro-4-iodophenylamino)-3,6,8-trimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide 72 according to a conventional method, a sodium salt was obtained. N-{3-[5-(2-fluoro-4-iodophenylamino)-3,6,8-trimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}methanesulfonamide sodium salt:

20 ¹H-NMR (DMSO-d₆, 300 MHz) δ 1.25 (s, 3H), 2.78(s, 3H), 2.97(s, 3H), 3.24 (s, 3H), 6.68 (t, J=8.7Hz, 1H), 6.77 (d, J=7.5Hz, 1H), 6.90-7.00(m, 2H), 7.10-7.30(m, 2H), 7.37(d, J=10.0Hz, 1H), 10.30(brs, 1H).
MS (ESI) *m/z*, 626 [MH]⁺.

Example 5 (evaluation of growth inhibitory effect against cancer cell lines)

25 **[0394]** Renal cancer cell line ACHN cell or colorectal cancer cell line HT-29 cells were cultured in a 96 well plate at 1.0×10^4 cells/90 μL/well for 24 hrs, then a test substance dissolved in DMSO (dimethyl sulfoxide) was added. After 18 hrs, ³H-thymidine (0.25 μCi/well) was added and the cells were cultured for 6 hrs. Using a cell harvester, the cells were recovered on a UniFilter-96 GF/B glass filter and the ³H radioactivity uptaken by the cells was measured by TopCount (Packard). As a control, DMSO was used and the activity of the test substance was expressed in the concentration (IC₅₀) necessary for inhibiting ³H radioactivity uptaken by the cell to 50% of that of the control group. The measurements were made in triplicate.

30 **[0395]** The results are shown in Tables 5-1 to 5-8 according to the following.

35 A: not less than 0.1 μM and less than 1 μM
B: not less than 0.01 μM and less than 0.1 μM
C: less than 0.01 μM

40 Table 5-1

Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-1	B	C	1-117		A
1-2		A	1-126		A
1-7		A	1-127		A
1-11		A	1-129		A
1-55		A	1-132		A
1-88	A	A	1-133		A
1-89	A	B	1-136		A
1-95		A	1-138		A
1-96		A	1-140		A
1-97		A	1-142		A

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(continued)

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Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-99		A	1-143		A
1-100		A	1-151		A
1-106	A	A	1-152	A	B
1-111		A	1-153		A
1-112	A	B	1-156		A
1-113	A	A	1-159		A
1-114	A	A	1-163		A
1-116		A	1-164		B

Table 5-2

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Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-165		A	1-205	A	C
1-166		B	1-206		A
1-168		B	1-207	B	C
1-171		B	1-208	B	C
1-175		A	1-211		A
1-176	A	B	1-212	A	C
1-183		A	1-213	A	B
1-185	A	B	1-214		B
1-186		B	1-215		A
1-188	A	B	1-216		A
1-189		A	1-217		A
1-190		A	1-218		B
1-191	A	B	1-219	A	B
1-192	A	B	1-221	B	C
1-193	A	C	1-222	A	B
1-199	A	B	1-223	A	B
1-200	A	B	1-224	A	C
1-201		A	1-225		A

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Table 5-3

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Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-226	A	B	1-253	A	B
1-227		B	1-255		A

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(continued)

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Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-228	A	B	1-257	C	C
1-229		A	1-258		A
1-230		A	1-259	A	C
1-232	A	B	1-260	C	C
1-233		A	1-262	B	C
1-234		A	1-263	A	C
1-235		A	1-264	A	B
1-236		A	1-265	A	B
1-240	B	B	1-266	A	C
1-242	A	B	1-267	A	B
1-243	A	B	1-268	B	B
1-244		A	1-270	A	B
1-245	B	C	1-271	B	C
1-246	A	B	1-272	B	B
1-249	A	B	1-273		A
1-252		B	3-1	A	A

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Table 5-4

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Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-274	C	C	1-295	A	B
1-275	B	C	1-296	A	C
1-276	A	B	1-297	B	C
1-277		B	1-298	B	C
1-278	A	B	1-299	A	B
1-279	A	B	1-301	A	B
1-282	A	B	1-302	B	C
1-283	A	B	1-303	A	B
1-284	A	B	1-304	A	B
1-285	B	B	1-305		B
1-286	B	C	1-307	A	B
1-287	A	B	1-308	A	B
1-288		B	1-309	B	C
1-289	C	C	1-310	B	C
1-290	B	C	1-311	C	C
1-292		B	1-313		B
1-293	A	A	1-313		B

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(continued)

Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-294	B		1-315	A	B

Table 5-5

Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
1-316	A	B	1-339	A	
1-317	A	B	1-340	B	C
1-318	A	C	1-341	B	C
1-319	C	C	1-342	A	C
1-320	B	C	1-343	A	B
1-321	B	C	3-4	B	C
1-322	B	C	3-5	B	C
1-324		B	3-6	A	C
1-325	A	B	3-7	C	C
1-326		A	3-8	B	C
1-327	A	B	4-1	C	C
1-328	A	B	4-2	C	C
1-333	B	C	4-3	B	C
1-334		A	4-4		A
1-335	A	B	4-5	A	B
1-336	B	C	4-6	B	C
1-337	B	C	4-7		A
1-338	B	C	4-9	B	C

Table 5-6

Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
4-10	A	B	4-42	B	C
4-11	B	C	4-43	A	B
4-12	B	C	4-44	A	B
4-13		A	4-45	A	B
4-15	B	C	4-46	A	B
4-16	C	C	4-47	A	
4-19	B	C	4-48	B	C
4-20	B	C	4-49	B	C
4-21	B	C	4-50	A	B

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(continued)

Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
4-25	B	C	4-51	B	C
4-26	B	C	4-52	A	A
4-27	A		4-53	A	B
4-33	C	C	4-54	c	C
4-34	C	C	4-55	B	C
4-37	A	B	4-56	A	B
4-39	A		4-57		A
4-40	B	C	4-58	B	C
4-41	B	B	4-59	B	C

Table 5-7

Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
4-60	B	C	4-85		A
4-61	B	B	4-87	A	B
4-63		B	4-88	C	C
4-64	A	B	4-89	A	B
4-66	A	B	4-90	A	B
4-67	B	C	4-91	B	C
4-70	B	C	4-92	B	C
4-71	A	B	4-93	B	C
4-72	B	C	4-94	A	B
4-73	B	C	4-95	A	B
4-74	B	C	4-96	A	B
4-75		B	4-97	B	C
4-76	B	C	4-98	B	C
4-77	B	C	4-99	A	C
4-78	A	B	4-101	B	C
4-80	B	C	4-102	A	B
4-81	B	C	4-103	A	C
4-82	B	C	4-104	C	C

Table 5-8

Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
4-105	B	C	4-121	B	C

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(continued)

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Example No.	IC ₅₀		Example No.	IC ₅₀	
	ACHN cell	HT-29 cell		ACHN cell	HT-29 cell
4-106	B	c	4-122	B	C
4-107	B	C	4-123	A	C
4-108	B	C	4-124	B	C
4-109	B	C	4-125	C	C
4-110	B	C	4-126	C	C
4-111	A	B	4-127	B	C
4-112	A	C	4-128	B	C
4-113	c	C	4-133		A
4-114	B	C	4-135		A
4-115	B	C	4-138		A
4-116	A	C	4-140		A
4-117	A	C	4-145		A
4-118	B	C	4-146		A
4-119	B	C	4-147		A
4-120	B	C	4-148		A

Example 6 (evaluation of p15 induction activity)

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[0396] ACHN cells or HT-29 cells were cultured in a 6 well plate at 2.5×10^5 cells/1.8 mL/well for 24 hrs, then a test substance (0.1 μ M) dissolved in DMSO was added. After 24 hrs, cells were detached using trypsin-EDTA (ethylene diamine tetraacetic acid) and solubilized with NuPAGE LDS sample buffer (Invitrogen). Using an RC DC protein assay kit (BIO-RAD), the protein concentration of the sample was quantitated, and a sample in an amount corresponding to 10 μ g of BSA (bovine serum albumin) was analyzed by Western blotting using an anti-p15 antibody. The density of the band stained with the anti-p15 antibody was measured by a densitometer to quantify the amount of p15 protein. As a control, DMSO was used and the test was performed with n=2 and the average protein amount was determined.

[0397] The results are shown in Tables 6-1 to 6-6 according to the following.

Table 6-1

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Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
1-1	+	1-43	+
1-4	+	1-46	+
1-6	+	1-49	+
1-7	+	1-51	+
1-8	+	1-53	+
1-9	+	1-55	+
1-11	+	1-65	+
1-12	+	1-77	+
1-16	+	1-78	+
1-17	+	1-79	+
1-26	+	1-80	+
1-33	+	1-81	+

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(continued)

Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
1-34	+	1-84	+
1-35	+	1-85	+
1-36	+	1-86	+
1-37	+	1-88	+
1-38	+	1-89	+
1-40	+	1-92	+
+: As compared to DMSO, not less than 1.5-fold induction of p15 protein			

Table 6-2

Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
1-93	+	1-114	+
1-94	+	1-116	+
1-95	+	1-117	+
1-96	+	1-126	+
1-97	+	1-127	+
1-99	+	1-131	+
1-100	+	1-132	+
1-102	+	1-133	+
1-103	+	1-136	+
1-104	+	1-137	+
1-106	+	1-138	+
1-107	+	1-142	+
1-108	+	1-143	+
1-109	+	1-146	+
1-110	+	1-151	+
1-111	+	1-152	+
1-112	+	1-153	+
1-113	+	1-154	+

Table 6-3

Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
1-156	+	1-199	+
1-157	+	1-200	+
1-162	+	1-205	+
1-163	+	1-207	+
1-165	+	1-208	+
1-166	+	1-212	+

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(continued)

Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
1-167	+	1-213	+
1-168	+	1-218	+
1-172	+	1-219	+
1-173	+	1-221	+
1-175	+	1-222	+
1-176	+	1-223	+
1-183	+	1-224	+
1-185	+	1-226	+
1-186	+	1-240	+
1-188	+	1-242	+
1-191	+	1-243	+
1-192	+	1-245	+
1-193	+	1-246	+

Table 6-4

Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
1-264	+	1-301	+
1-265	+	1-317	+
1-266	+	1-318	+
1-268	+	1-319	+
1-271	+	1-320	+
1-272	+	1-321	+
1-282	+	1-322	+
1-283	+	1-325	+
1-284	+	1-327	+
1-285	+	1-328	+
1-286	+	1-333	+
1-287	+	1-336	+
1-289	+	1-337	+
1-290	+	1-338	+
1-293	+	1-340	+
1-295	+	1-341	+
1-296	+	1-342	+
1-297	+	3-4	+
1-298	+	3-6	+

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Table 6-5

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Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
3-7	+	4-53	+
3-8	+	4-54	+
4-1	+	4-55	+
4-2	+	4-56	+
4-3	+	4-58	+
4-6	+	4-59	+
4-9	+	4-60	+
4-10	+	4-61	+
4-11	+	4-64	+
4-12	+	4-66	+
4-15	+	4-67	+
4-16	+	4-70	+
4-21	+	4-71	+
4-43	+	4-72	+
4-45	+	4-73	+
4-48	+	4-74	+
4-49	+	4-76	+
4-50	+	4-77	+
4-51	+	4-78	+

Table 6-6

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Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
4-80	+	4-110	+
4-81	+	4-111	+
4-82	+	4-112	+
4-88	+	4-113	+
4-89	+	4-114	+
4-90	+	4-115	+
4-91	+	4-116	+
4-92	+	4-117	+
4-93	+	4-118	+
4-97	+	4-119	+
4-98	+	4-120	+
4-101	+	4-121	+
4-102	+	4-122	+
4-103	+	4-123	+
4-104	+	4-124	+
4-105	+	4-125	+

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(continued)

Example No.	Induction of p15 protein	Example No.	Induction of p15 protein
4-106	+	4-126	+
4-107	+	4-127	+
4-108	+	4-128	+
4-109	+		

Example 7 (cell cycle analysis)

[0398] ACHN cells or HT-29 cells were cultured in a 6 well plate at 2.5×10^5 cells/1.8 mL/well for 24 hrs, then a test substance (less than 10 μ M) dissolved in DMSO was added. After 24 hrs, cells were detached using trypsin-EDTA and the DNA content of single cell was analyzed by flow cytometry method using a CycleTEST PLUS (BECKTON DICKINSON) kit, and the proportion of the cells in the G0/G1 phase-S phase-G2/M phase was calculated. As a control, DMSO was used and the test was performed with n=2.

[0399] The results are shown in Tables 7-1 and 7-2 according to the following.

Table 7-1

Example No.	CELL RATIO OF G0/G1 PHASE	Example No.	CELL RATIO OF G0/G1 PHASE
1-2	G1	1-78	G1
1-4	G1	1-84	G1
1-6	G1	1-85	G1
1-7	G1	1-86	G1
1-9	G1	1-88	G1
1-11	G1	1-89	G1
1-21	G1	1-90	G1
1-25	G1	1-91	G1
1-26	G1	1-92	G1
1-33	G1	1-93	G1
1-34	G1	1-94	G1
1-38	G1	1-95	G1
1-43	G1	1-97	G1
1-49	G1	1-99	G1
1-50	G1	1-100	G1
1-51	G1	1-101	G1
1-55	G1	1-102	G1
1-69	G1	1-103	G1
1-77	G1	1-104	G1

G1: the ratio of the cells in the G0/G1 phase was not less than 1.2-fold as compared to that of DMSO.

Table 7-2

Example No.	CELL RATIO OF G0/G1 PHASE	Example No.	CELL RATIO OF G0/G1 PHASE
3-7	G1	4-70	G1
4-1	G1	4-82	G1

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(continued)

Example No.	CELL RATIO OF G0/G1 PHASE	Example No.	CELL RATIO OF G0/G1 PHASE
4-3	G1	4-104	G1
4-16	G1	4-126	G1

Example 8 (evaluation on the nude-mouse xenograft model)

[0400] HT-29 cells (5.0×10^6 cells/100 μ L/head, suspended in HBSS (Hanks' solution)) in the logarithmic growth phase were implanted in a mouse (Balb/c-nu/nu) at the right lateral abdomen under ether anesthesia. After 5 days of implantation, the long diameter and short diameter of the tumor were measured, and the mice were divided into groups such that each group has an equivalent average tumor volume. For grouping, a grouping soft (general grouping system (Visions) was used. From the next day of the grouping, a test substance suspended in 0.5% MC (methyl cellulose) was repeatedly orally administered twice a day for 10 days (30 mg/kg). The tumor volume was measured twice a week and used as an index of antitumor activity. As a control, 0.5% MC was used and the test was performed with n=6-8.

[0401] The index (T/C (%)) of the antitumor activity was calculated according to the following formula.

$$T/C (\%) = \frac{\text{(The average tumor volume of the group treated with a test substance)}}{\text{(The average tumor volume of the Vehicle group)}} \times 100$$

[0402] The tumor volume was calculated according to the following formula.

$$\text{Tumor volume (mm}^3\text{)} = L \times W \times W / 2 \quad (L: \text{long diameter (mm) of tumor, } W: \text{short diameter (mm) of tumor})$$

Table 8

Example No.	T/C (%)
1-257	26
3-8	27
4-1	3
4-15	31
4-16	10
4-49	35
4-54	11
4-70	31

Example 9 (p27 protein induction test)

[0403] ACHN cells or HT-29 cells were cultured in a 6 well plate at 2.5×10^5 cells/1.8 mL/well for 24 hrs, a test substance (0.1 μ M) dissolved in DMSO was added. After 24 hrs, cells were detached using trypsin-EDTA (ethylene diamine tetraacetic acid) and solubilized with NuPAGE LDS sample buffer (Invitrogen). Using an RC DC protein assay kit (BIO-RAD), the protein concentration of the sample was quantitated, and a sample in an amount corresponding to 10 μ g of BSA (bovine serum albumin) was analyzed by Western blotting using an anti-p27 antibody. The density of the band stained with the anti-p27 antibody was measured by a densitometer to quantify the amount of p27 protein. As a control, DMSO was used and the test was performed with n=2 and the average protein amount was determined.

[0404] The results are shown in Tables 9-1 to 9-4 according to the following.

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Table 9-1

Example No.	Induction of p27 protein	Example No.	Induction of p27 protein
1-1	+	1-243	+
1-89	+	1-245	+
1-112	+	1-249	+
1-114	+	1-253	+
1-142	+	1-257	+
1-152	+	1-259	+
1-175	+	1-260	+
1-182.	+	1-262	+
1-185	+	1-263	+
1-186	+	1-264	+
1-218	+	1-265	+
1-219	+	1-266	+
1-221	+	1-268	+
1-222	+	1-271	+
1-224	+	1-272	+
1-226	+	1-274	+
1-228	+	1-275	+
1-240	+	1-279	+
1-242	+	1-282	+
+: As compared to DMSO, not less than 1.5-fold induction of p27 protein			

Table 9-2

Example No.	Induction of p27 protein	Example No.	Induction of p27 protein
1-283	+	1-311	+
1-284	+	1-315	+
1-285	+	1-316	+
1-286	+	1-317	+
1-287	+	1-318	+
1-289	+	1-319	+
1-290	+	1-320	+
1-293	+	1-322	+
1-295	+	1-325	+
1-296	+	1-327	+
1-297	+	1-328	+
1-298	+	1-336	+
1-299	+	1-337	+
1-301	+	1-338	+

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(continued)

Example No.	Induction of p27 protein	Example No.	Induction of p27 protein
1-302	+	1-340	+
1-303	+	1-341	+
1-307	+	1-342	+
1-309	+	3-4	+
1-310	+	3-5	+

Table 9-3

Example No.	Induction of p27 protein	Example No.	Induction of p27 protein
3-6	+	4-51	+
3-7	+	4-53	+
3-8	+	4-54	+
4-1	+	4-55	+
4-2	+	4-56	+
4-3	+	4-58	+
4-6	+	4-59	+
4-9	+	4-60	+
4-10	+	4-61	+
4-11	+	4-64	+
4-12	+	4-66	+
4-15	+	4-67	+
4-16	+	4-70	+
4-1	+	4-71	+
4-43	+	4-72	+
4-45	+	4-73	+
4-48	+	4-74	+
4-49	+	4-76	+
4-50	+	4-77	+

Table 9-4

Example No.	Induction of p27 protein	Example No.	Induction of p27 protein
4-78	+	4-108	+
4-80	+	4-109	+
4-81	+	4-110	+
4-82	+	4-113	+
4-88	+	4-114	+
4-89	+	4-115	+
4-90	+	4-116	+

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(continued)

Example No.	Induction of p27 protein	Example No.	Induction of p27 protein
4-91	+	4-117	+
4-92	+	4-118	+
4-93	+	4-119	+
4-97	+	4-120	+
4-98	+	4-121	+
4-99	+	4-122	+
4-101	+	4-123	+
4-102	+	4-124	+
4-103	+	4-125	+
4-104	+	4-126	+
4-105	+	4-127	+
4-106	+	4-128	+
4-107	+		

Example 10 (evaluation of MEK enzyme inhibitory activity)

[0405] To an evaluation system where Raf (B-Raf or c-Raf) and MEK (MEK1 or MEK2) were mixed, or MEK (MEK1 or MEK2) and ERK2 were mixed was added a test substance dissolved in DMSO, and an ATP solution containing [γ -³²P]-ATP was added to start the enzyme reaction. After reacting at 30°C for 20 min, the reaction mixture was subjected to SDS-PAGE (sodium dodecylsulfate - polyacrylamide gel electrophoresis) and radioactivity of phosphorylated MEK or ERK2 was measured by Bio Imaging Analyzer (BAS2000, Fuji photo film).

[0406] With the radioactivity of the solvent added control as 100%, inhibitory rate (%) by the test substance was determined, and IC₅₀ value was calculated.

[0407] The test was performed with n=1 and the average values of two or three times of testing are shown. The results are summarized in Table 10.

Table. 10 IC₅₀ of various enzyme reaction system (μ M)

enzyme	Example 1-257	Example 4-1
B-Raf MEK1	0.0060	0.0067
B-Raf MEK2	0.0188	0.0128
c-Raf MEK1	-	-
c-Raf MEK2	0.0078	0.0130
MEK1 ERK2	1.3	0.290
MEK2 ERK2	1.6	0.190

Example 11 (evaluation on the mouse collagen arthritis model)

[0408] Bovine type II collagen (100 μ g) was resuspended with Freund's complete adjuvant and intracutaneously administered (initial immunization) to the tail head of mouse (DBA/1). Three weeks later, the same collagen was given

to the tail head as boost, whereby multiple arthritis was induced.-The test substance was oral administered forcibly once a day for 38 days from immediately before the initial immunization, and arthritis score after boost was calculated twice a week to examine the arthritis onset suppressing effect. For arthritis scores, the level of swelling of each of the four limbs of the mice was scored in 4 .; levels, and the average of the scores of four limbs was taken as the arthritis score of each individual. The test was performed with n = 16.

[0409] The arthritis score at 17 days after boost (after consecutive administration for 38 days) was 2.2 for the medium administration group, and 0.57 (p<0.001, wilcoxon test) for the 1 mg/kg acetic acid solvate of compound of Example 4-1 administration group, thus showing a significant suppressive effect on the arthritis onset.

Example 12 (evaluation on inflammatory cytokine production)

[0410] the compounds of Example 4-1 and Example 4-16 suppressed production of TNF- α or IL-6 upon stimulation of human peripheral blood-derived mononuclear cell (PBMC) with LPS.

[0411] The compounds shown in Tables 11-1 to 11-9 can be further obtained in same as in Examples 1-1 to 1-148 or by the other conventional method employed as necessary.

Table 11-1

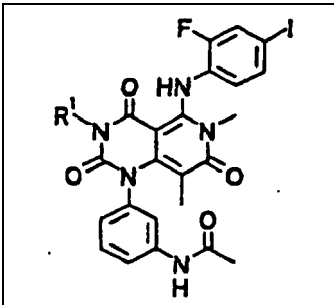
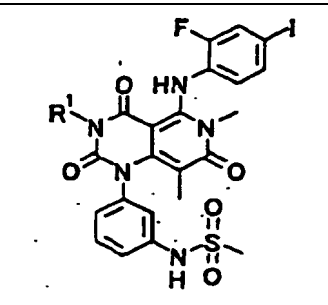
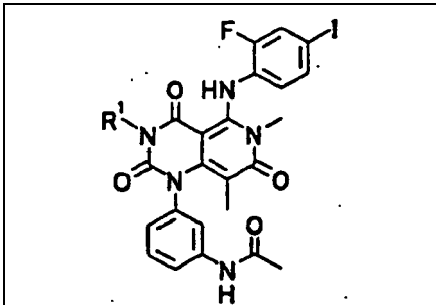
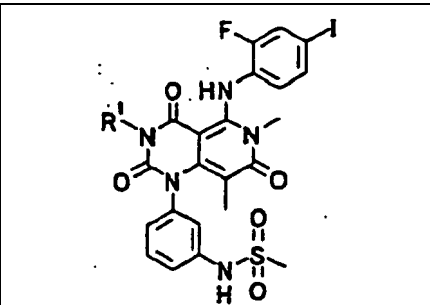
			
Example No.	R ¹	Example No.	R ¹
1001	2-F-Ph-	1002	2-F-Ph-
1003	3-F-Ph-	1004	3-F-Ph-
1005	4-F-Ph-	1006	4-F-Ph-
1007	2-Me-Ph-	1008	2-Me-Ph-
1009	3-Me-Ph-	1010	3-Me-Ph-
1011	4-Me-Ph-	1012	4-Me-Ph-
1013	2-MeO-Ph-	1014	2-MeO-Ph-
1015	3-MeO-Ph-	1016	3-MeO-Ph-
1017	4-MeO-Ph-	1018	4-MeO-Ph-
1019	2-Py-	1020	2-Py-
1021	3-Py-	1022	3-Py-

Table 11-2

			
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(continued)

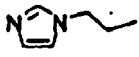
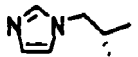
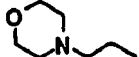
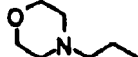
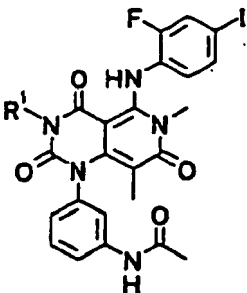
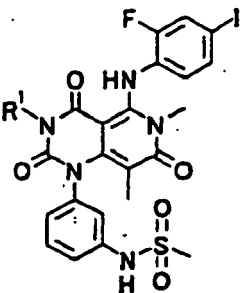
Example No.	R ¹	Example No.	R ¹
1023	4-Py-	1024	4-Py-
1025	2-MeS (CH ₂) ₂ -	1026	2-MeS (CH ₂) ₂ -
1027	2-HS (CH ₂) ₂ -	1028	2-HS (CH ₂) ₂ -
1029	4- (Me) ₂ N-Bzl-	1030	4- (Me) ₂ N-Bzl-
1031	3- (Me) ₂ N-Bzl-	1032	3- (Me) ₂ N-Bzl-
1033	2- (Me) ₂ N-Bzl-	1034	2-(Me) ₂ N-Bzl-
1035	4- (Me) ₂ N-Phenethyl-	1036	4- (Me) ₂ N-Phenethyl-
1037	4-HO-Phenethyl-	1038	4-HO-Phenethyl-
1039	4-HO-Bzl-	1040	4-HO-Bzl-
1041	3-HO-Bzl-	1042	3-HO-Bzl-
1043	2-HO-Bzl-	1044	2-HO-Bzl-
1045	4-MeO-Bzl-	1046	4-MeO-Bzl-
1047	4-Py-(CH ₂) ₂ -	1048	4-Py- (CH ₂) ₂ -
1049	3-Py- (CH ₂) ₂ -	1050	3-Py- (CH ₂) ₂ -
1051	2-Py- (CH ₂) ₂ -	1052	2-Py- (CH ₂) ₂ -
1053		1054	
1055		1056	
1057	Allyl-	1058	Allyl-
1059	CF ₃ CH ₂ -	1060	CF ₃ CH ₂ -
1061	n-Propyl-	1062	n-Propyl-
1063	Cyclopropylmethyl-	1064	Cyclopropylmethyl-
1065	HO-	1066	HO-

Table 11-3

			
Example No.	R ¹	Example No.	R ¹
1067	HO- (CH ₂) ₂ -O-	1068	HO- (CH ₂) ₂ -O-
1069	HO- (CH ₂) ₃ -O-	1070	HO- (CH ₂) ₃ -O-

(continued)

Example No.	R ¹	Example No.	R ¹
1071		1072	
1073		1074	
1075		1076	
1077		1078	
1079		1080	
1081		1082	
1083		1084	

Py: Pyridyl, Ph: Phenyl Bzl: Benzyl

Table 11-4

Example No.	R ²	Example No.	R ²
2001		2002	
2003		2004	
2005		2006	
2007		2008	

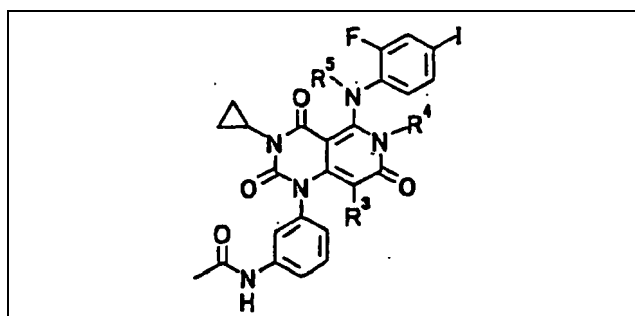
(continued)

Example No.	R ²	Example No.	R ²
2009		2010	

Table 11-5

Example No.	R ²	Example No.	R ²
2011		2012	
2013		2014	
2015		2016	
2017		2018	
2019		2020	

Table 11-6



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(continued)

Example No.	R ³	R ⁴	R ⁵
3001	Allyl-	Me-	H
3002	n-Propyl-	Me-	H
3003	CF ₃ CH ₂ -	Me-	H
3004	MeO(CH ₂) ₂ -	Me-	H
3005	(Me) ₂ N-(CH ₂) ₂ -	Me-	H
3006	Ph-	Me-	H
3007	3-Py	Me-	H
3008	Me-	Allyl-	H
3009	Me-	MeO-	H
3010	Me-	Cyclopropyl	H
3011	Me-	Me-	HO-
3012	Me-	Me-	MeO-

Table 11-7

Example No.	R ³	R ⁴	R ⁵
4001	Allyl-	Me-	H
4002	n-Propyl-	Me-	H
4003	CF ₃ CH ₂ -	Me-	H
4004	MeO(CH ₂) ₂ -	Me-	H
4005	(Me) ₂ N-(CH ₂) ₂ -	Me-	H
4006	Ph-	Me-	H
4007	3-Py	Me-	H
4008	Me-	Allyl-	H
4009	Me-	MeO-	H
4010	Me-	cyclopropyl	H
4011	Me-	Me-	HO-
4012	Me-	Me-	MeO-

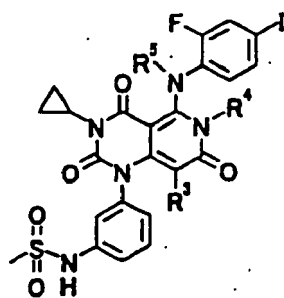


Table 11-8

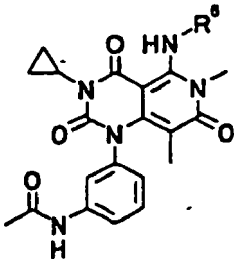
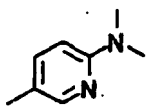
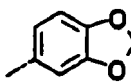
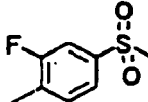
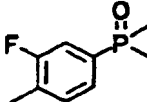
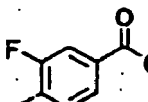
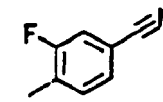
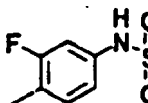
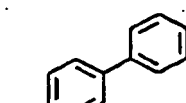
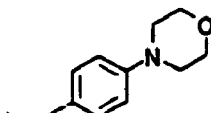
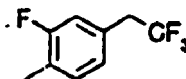
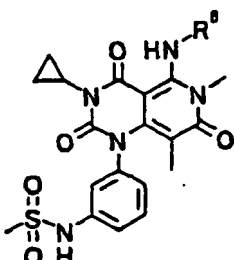
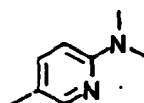
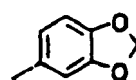
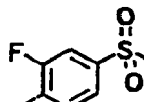
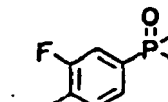
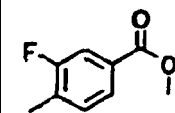
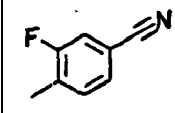
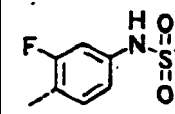
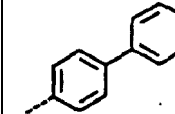
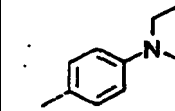
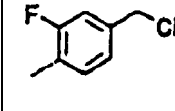
			
Example No.	R ⁶	Example No.	R ⁶
5001		5002	
5003		5004	
5005		5006	
5007		5008	
5009		5010	

Table 11-9

			
Example No.	R ⁶	Example No.	R ⁶
6001		6002	
6003		6004	

(continued)

Example No.	R ⁶	Example No.	R ⁶
6005		6006	
6007		6008	
6009		6010	

[0412] The MS and NMR data of the Example compounds shown in the above-mentioned Table 1-1 to Table 4-25 are shown below.

Example 1-1

[0413] MS ESI m/e: 590, 592 (M+H), 588, 590 (M-H)

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.08 (m, 2H), 2.64-2.70 (m, 4H), 3.02 (s, 3H), 5.36 (s, 1H), 7.13 (d, J=9.0Hz, 1H), 7.24-7.30 (m, 2H), 7.43-7.54 (m, 3H), 7.74 (d, J=9.0Hz, 1H), 10.00 (brs, 1H), 10.53 (brs, 1H).

Example 1-2

Example 1-3

Example 1-4

[0414] MS ESI m/e: 470, 471 (M+H), 473, 474, 469 (M-H), 470, 471.

¹H-NMR (DMSO-d₆, 300MHz) δ 2.68 (s, 3H), 5.47 (s, 1H), 7.24-7.63 (m, 14H), 10.63 (brs, 1H).

Example 1-5

[0415] MS ESI m/e: 470, 471 (M+H), 473, 474, 469 (M-H), 470, 471.

¹H-NMR (DMSO-d₆, 300MHz) δ 2.68 (s, 3H), 5.60 (s, 1H), 7.25-7.57 (m, 14H), 10.52 (brs, 1H).

Example 1-6

[0416] MS ESI m/e: 451 (M+H), 449 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 2.34 (s, 3H), 2.88 (s, 3H), 5.79 (s, 1H), 7.08-7.18 (m, 4H), 7.27-7.32 (m, 2H), 7.37-7.54 (m, 8H), 10.24 (s, 1H).

Example 1-7.

[0417] MS. ESI m/e: 480 (M+H).

¹H-NMR (CDCl₃, 400MHz) δ 2.87 (s, 3H), 2.95 (s, 6H), 5.66 (s, 1H), 6.67-6.73 (m, 2H), 7.05-7.11 (m, 2H), 7.27-7.32 (m, 2H), 7.37-7.55 (m, 8H), 10.24 (s, 1H).

Example 1-8

[0418] MS ESI m/e: 455 (M+H), 453 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 2.88 (s, 3H), 5.69 (s, 1H), 7.03-7.10 (m, 2H), 7.17-7.23 (m, 2H), 7.27-7.32 (m, 2H), 7.37-7.55 (m, 8H), 10.24 (s, 1H).

Example 1-9

[0419] MS ESI m/e: 467 (M+H), 465 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 2.88 (s, 3H), 3.81 (s, 3H), 5.67 (s, 1H), 6.86-6.95 (m, 2H), 7.12-7.20 (m, 2H), 7.28-7.34 (m, 2H), 7.37-7.58 (m, 8H), 10.14 (s, 1H).

Example 1-10

[0420] MS ESI m/e: 485 (M+H), 4.83 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 2.86 (s, 3H), 4.32 (d, J=4.0Hz, 2H), 5.39 (s, 1H), 7.23-7.31 (m, 6H), 7.34-7.38 (m, 2H), 7.39-7.52 (m, 6H), 9.03 (t, J=6.0Hz, 1H).

Example 1-11

[0421] MS ESI m/e: 515, 517 (M+H), 513, 515 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 2.67 (s, 3H), 5.56 (s, 1H), 7.25-7.29 (m, 2H), 7.34-7.38 (m, 2H), 7.41-7.55 (m, 8H), 7.57-7.61 (m, 2H), 10.48 (s, 1H).

Example 1-12

Example 1-13

Example 1-14

[0422] MS ESI m/e: 485 (M+H).

¹H-NMR (DMSO-d₆, 400MHz) δ 2.74 (s, 3H), 3.22 (s, 3H), 6.03 (s, 1H), 6.99-7.05 (m, 4H), 7.21-7.25 (m, 2H), 7.32-7.40 (m, 3H), 7.44-7.54 (m, 5H).

Example 1-15

[0423] MS ESI m/e: 443 (M+H)

¹H-NMR (DMSO-d₆, 300MHz) δ 1.17-1.95 (m, 11H), 2.63 (s, 3H), 5.28 (s, 1H), 7.31-7.55 (m, 10H), 8.76 (d, J=6.0Hz, 1H).

Example 1-1.6

[0424] MS ESI m/e: 481 (M+H), 479 (M-H)

¹H-NMR (CDCl₃, 300MHz) δ 2.88 (s, 3H), 5.69 (s, 1H), 5.99 (s, 2H), 6.85-6.82 (m, 3H), 7.28-7.34 (m, 2H), 7.37-7.58 (m, 8H), 10.12 (s, 1H).

Example 1-17

[0425] MS ESI m/e: 505, 507 (M+H), 503, 505 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 2.90 (s, 3H), 5.87 (s, 1H), 7.07-7.11 (m, 1H), 7.26-7.31 (m, 2H), 7.35-7.56 (m, 10H), 10.45 (s, 1H).

Example 1-18

[0426] MS ESI m/e: 499 (M+H), 497 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.56 (t, J=7.5Hz, 3H), 1.05-1.12. (m, 2H), 3.30-3.40 (m, 2H), 5.54 (s, 1H), 7.31-7.56 (m, 14H), 10.52 (s, 1H).

Example 1-19

[0427] MS ESI m/e: 513 (M+H), 511 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.62 (s, 3H), 0.64 (s, 3H), 1.04 (d, J=6.0Hz, 1H), 1.94-2.06 (m, 1H), 3.13 (brs, 1H), 5.56 (s, 1H), 7.32-7.60 (m, 14H), 10.58 (s, 1H).

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Example 1-20 -

[0428] MS ESI m/e: 515 (M+H), 513 (M-H).

5 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 3.04 (t, J=6.0Hz, 2H), 3.09 (s, 3H), 3.61 (t, J=4.5Hz, 2H), 5.53 (s, 1H), 7.32-7.60 (m, 14H), 10.52 (s, 1H).

Example 1-21

[0429] MS ESI m/e: 465 (M+H), 463 (M-H).

10 $^1\text{H-NMR}$ (DMSO-d_6 , 400MHz) δ 1.19 (t, J=8.0Hz, 3H), 2.61 (q, J=8.0Hz, 2H), 2.66 (s, 3H), 5.46 (s, 1H), 7.17-7.21 (m, 2H), 7.25-7.29 (m, 2H), 7.34-7.38 (m, 2H), 7.41-7.55 (m, 8H), 10.37 (s, 1H).

Example 1-22

[0430] MS ESI m/e: 451 (M+H), 449 (M-H).

15 $^1\text{H-NMR}$ (DMSO-d_6 , 400MHz) δ 2.21 (s, 3H), 2.66 (s, 3H), 5.12 (s, 1H), 7.18-7.55 (m, 14H), 10.22 (s, 1H).

Example 1-23

[0431] MS ESI m/e: 513 (M+H), 511 (M-H).

20 $^1\text{H-NMR}$ (DMSO-d_6 , 400MHz) δ 2.68 (s, 3H), 5.65 (s, 1H), 7.33-7.56 (m, 15H), 7.66-7.74 (m, 4H), 10.56 (s, 1H).

Example 1-24.

[0432] MS ESI m/e: 467 (M+H), 465 (M-H).

25 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 2.89 (s, 3H), 3.82 (s, 3H), 5.83 (s, 1H), 6.91-6.98 (m, 2H), 7.13-7.19 (m, 1H), 7.27-7.33 (m, 2H), 7.37-7.54 (m, 9H), 10.21 (s, 1H).

Example 1-25.

[0433] MS ESI m/e: 479 (M+H), 477 (M-H).

30 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 1.25 (d, J=6.7Hz, 6H), 2.85-2.95 (m, 1H), 2.88 (s, 3H), 5.80 (s, 1H), 7.12-7.17 (m, 2H), 7.19-7.24 (m, 2H), 7.27-7.32 (m, 2H), 7.37-7.55 (m, 8H), 10.24 (s, 1H).

Examples 1-26)

[0434] MS ESI m/e: 505, 507 (M+H), 503, 505 (M-H).

35 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 2.89 (s, 3H), 5.70 (s, 1H), 7.22-7.32 (m, 3H), 7.37-7.55 (m, 10H), 10.39 (s, 1H).

Example 1-27

[0435] MS ESI m/e: 520 (M+H).

40 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 1.54-1.62 (m, 4H), 1.67-1.75 (m, 4H), 2.87 (s, 3H), 3.14 (t, J=5.6Hz, 2H), 5.70 (s, 1H), 6.87-6.93 (m, 2H), 7.06-7.11 (m, 2H), 7.27-7.32 (m, 2H), 7.37-7.54 (m, 8H), 10.09 (s, 1H).

Example 1-28

[0436] MS ESI m/e: 508 (M+H), 506 (M-H).

45 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 1.16 (t, J=7.1Hz, 6H), 2.87 (s, 3H), 3.34 (q, J=7.1Hz, 4H), 5.65 (s, 1H), 6.60-6.65 (m, 2H), 7.00-7.06 (m, 2H), 7.27-7.31 (m, 2H), 7.36-7.54 (m, 8H), 9.98 (s, 1H).

Example 1-29

[0437] MS ESI m/e: 527 (M+H), 525 (M-H).

55 $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 2.88 (s, 3H), 3.97 (s, 2H), 5.83 (s, 1H), 7.12-7.58 (m, 19H), 10.29 (s, 1H).

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Example 1-30

[0438] MS ESI m/e: 522 (M+H), 520 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.66 (s, 3H), 3.10-3.13 (m, 4H), 3.73-3.76 (m, 4H), 5.32 (s, 1H), 7.01 (d, J=9.0Hz, 2H), 7.15 (d, J=9.0Hz, 2H), 7.35-7.57 (m, 10H), 10.20 (brs, 1H).

Example 1-31

[0439] MS ESI m/e: 493 (M+H), 491 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 0.90 (t, J=8.0Hz, 3H), 1.26-1.36 (m, 2H), 1.52-1.60 (m, 2H), 2.58 (t, J=8.0Hz, 2H), 2.66 (s, 3H), 5.46 (s, 1H), 7.18 (d, J=8.0Hz, 2H), 7.25 (d, J=8.0Hz, 2H), 7.35-7.37 (m, 2H), 7.41-7.54 (m, 8H), 10.36 (brs, 1H).

Example 1-32

[0440] MS ESI m/e: 409 (M+H), 407 (M-H)

¹H-NMR (DMSO-d₆, 300MHz) δ 3.446 (s, 3H), 3.48 (s, 3H), 5.49 (s, 1H), 7.28-7.34 (m, 4H), 7.41-7.53 (m, 5H), 10.44 (brs, 1H).

Example 1-33.

[0441] MS ESI m/e: 505 (M+H), 503 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 2.67 (s, 3H), 5.78 (s, 1H), 7.34 (d, J=8.0Hz, 2H), 7.40-7.53 (m, 10H), 7.73 (d, J=8.0Hz, 2H), 10.75 (brs, 1H).

Example 1-34

[0442] MS ESI m/e: 485 (M+H), 483 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.32 (s, 3H), 2.67 (s, 3H), 5.35 (s, 1H), 7.23-7.56 (m, 13H), 10.48 (brs, 1H).

Example 1-35

[0443] MS ESI m/e: 409 (M+H), 407 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.61 (s, 3H), 3.26 (s, 3H), 5.50 (s, 1H), 7.35 (d, J=6.0Hz, 2H), 7.44-7.54 (m, 5H), 1.49 (d, J=6.0Hz, 2H), 10.62 (brs, 1H).

Example 1-36

[0444] MS ESI m/e: 431 (M+H).

¹H-NMR (CDCl₃, 400MHz) δ 1.00 (s, 9H), 2.86 (s, 3H), 2.92 (d, J=8.0Hz, 2H), 5.43 (s, 1H), 7.24-7.29 (m, 2H), 7.34-7.53 (m, 8H), 8.78 (t, J=6.0Hz, 1H).

Example 1-37

[0445] MS ESI m/e: 481 (M+H), 479 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.70 (s, 3H), 5.85 (s, 1H), 7.36-7.54 (m, 10H), 7.43 (d, J=9.0Hz, 2H), 7.97 (d, J=9.0Hz, 2H), 10.81 (brs, 1H).

Example 1-38

[0446] MS ESI m/e: 465 (M+H), 463 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 1.18 (t, J=7.5Hz, 3H), 2.63 (q, J=7.5Hz, 2H), 2.88 (s, 3H), 5.43 (s, 1H), 7.20-7.36 (m, 6H), 7.39-7.57 (m, 8H), 10.07 (s, 1H).

Example 1-39

[0447] MS ESI m/e: 507 (M+H), 505 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.78 (t, J=7.3Hz, 6H), 1.44-1.77 (m, 4H), 2.2.5-2.38 (m, 1H), 2.89 (s, 3H), 5.85 (s, 1H), 7.10-7.19 (m, 4H), 7.28-7.34 (m, 2H), 7.38-7.57 (m, 8H), 10.28 (s, 1H).

Example 1-40

[0448] MS ESI m/e: 535 (M+H), 533 (M-H).

5 $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.85 (t, J=7.4Hz, 6H), 1.08-1.24 (m, 4H), 1.45-1.64 (m, 4H), 2.45-2.58 (m, 1H), 2.89 (s, 3H), 5.84 (s, 1H), 7.10-7.18 (m, 4H), 7.28-7.34 (m, 2H), 7.38-7.57 (m, 8H), 10.27 (s, 1H).

Example 1-41

[0449] MS ESI m/e: 497 (M+H), 495 (M-H).

10 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.79-1.00 (m, 4H), 1.70-1.78 (m, 1H), 5.73 (s, 1H), 7.12-7.18 (m, 2H), 7.26-7.34 (m, 4H), 7.35-7.55 (m, 8H), 10.35 (s, 1H).

Example 1-42

[0450] MS ESI m/e: 539, 541 (M+H), 537, 539 (M-H).

15 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 2.92 (s, 3H), 5.80 (s, 1H), 7.14-7.19 (m, 2H), 7.19-7.24 (m, 2H), 7.30-7.36 (m, 4H), 7.45-7.51 (m, 4H), 10.24 (s, 1H).

Example 1-43

[0451] MS ESI m/e: 485(M+H), 483 (M-H).

20 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 1.57 (s, 3H), 2.76 (s, 3H), 6.93 (d, J=9.0Hz, 2H), 7.31-7.54 (m, 12H), 10.07 (brs, 1H).

Example 1-44

[0452] MS ESI m/e: 477(M+H), 475 (M-H).

25 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 1.07-1.85 (m, 11H), 2.60 (s, 3H), 4.65-4.65 (m, 1H), 5.49 (s, 1H), 7.35-7.54 (m, 5H), 10.63 (brs, 1H).

Example 1-45

[0453] MS ESI m/e: 485 (M+H), 483 (M-H).

30 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 2.63 (s, 3H), 5.10 (brs, 2H), 5.51 (s, 1H), 7.24-7.56 (m, 14H), 10.57 (s, 1H).

Example 1-46

[0454] MS ESI m/e: 452 (M+H).

35 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 2.67 (s, 3H), 5.47 (s, 1H), 7.19 (d, J=9.0Hz, 2H), 7.29 (d, J=6.0Hz, 2H), 7.35-7.40 (m, 2H), 7.41-7.57 (m, 8H), 10.40 (s, 1H).

Example 1-47

[0455] MS ESI m/e: 421 (M+H), 419 (M-H).

40 $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 2.19-2.30 (m, 2H), 4.09-4.20 (m, 4H), 5.73 (s, 1H), 7.11-7.19 (m, 2H), 7.23-7.36 (m, 4H), 7.45-7.60 (m, 3H), 10.49 (s, 1H).

Example 1-48

[0456] MS ESI m/e: 453(M+H), 451 (M-H).

50 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 2.65 (s, 3H), 5.08 (s, 1H), 6.07 (brs, 2H), 6.52 (d, J=9.0Hz, 1H), 7.29-7.57 (m, 1H), 7.80 (d, J=3.0Hz, 1H), 9.94 (brs, 1H).

Example 1-49

[0457] MS ESI m/e: 466 (M+H).

55 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 2.67 (s, 3H), 2.86 (s, 3H), 5.50 (s, 1H), 7.33-7.57 (m, 14H), 10.44 (brs, 1H).

Example 1-50

[0458] MS ESI m/e: 479 (M+H), 477 (M-H).

5 $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.90 (t, J=7.3Hz, 3H), 1.51-1.66 (m, 2H), 2.57 (t, J=7.5Hz, 2H), 2.88 (s, 3H), 5.43 (s, 1H), 7.17-7.30 (m, 4H), 7.30-7.37 (m, 2H), 7.39-7.58 (m, 8H), 10.07 (s, 1H).

Example 1-51

[0459] MS ESI m/e: 493 (M+H), 491 (M-H).

10 $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.88 (t, J=6.0Hz, 3H), 1.26-1.38 (m, 2H), 1.49-1.61 (m, 2H), 2.55-2.61 (m, 2H), 2.88 (s, 3H), 5.43 (s, 1H), 7.14-7.34 (m, 6H), 7.39-7.56 (m, 8H), 10.07 (brs, 1H).

Example 1-52

15 **[0460]** MS ESI m/e: 528 (M+H), 526 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 2.15 (s, 6H), 2.12-2.22 (m, 2H), 3.72 (t, J=6.5Hz, 2H), 5.81 (s, 1H), 7.15-7.21 (m, 2H), 7.26-7.35 (m, 4H), 7.40-7.56 (m, 8H), 10.35 (s, 1H).

Example 1-53

20 **[0461]** MS ESI m/e: 485 (M+H), 483 (M-H)
 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 2.24 (s, 3H), 2.88 (s, 3H), 5.39 (s, 1H), 7.17-7.20 (m, 2H), 7.28-7.33 (m, 2H), 7.37-7.55 (m, 9H), 10.04 (s, 1H).

25 Example 1-54

[0462] MS ESI m/e: 472 (M+H), 470 (M-H).

30 $^1\text{H-NMR}$ (DMSO-d_6 , 400MHz) δ 2.68 (s, 3H), 5.50 (s, 1H), 7.34-7.38 (m, 2H), 7.41-7.57 (m, 9H), 7.87 (dd, J=4.0, 8.0Hz, 1H), 8.37 (d, J=4.0Hz, 1H), 10.49 (s, 1H).

Example 1-55

[0463] MS ESI m/e: 494 (M+H), 492 (M-H).

35 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 2.15 (s, 3H), 2.64 (s, 3H), 2.90 (s, 6H), 4.92 (s, 1H), 6.63 (dd, J=3.0, 9.0Hz, 1H), 6.69 (d, J=3.0Hz, 1H), 7.03 (d, J=9.0Hz, 1H), 7.36-7.57 (m, 10H), 9.89 (s, 1H).

Example 1-56

[0464] MS ESI m/e: 497 (M+H), 495 (M-H).

40 $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 4.24 (d, J=4.2Hz, 2H), 4.87 (d, J=16.9Hz, 1H), 5.02 (d, J=10.4Hz, 1H), 5.40-5.51 (m, 1H), 5.83 (s, 1H), 7.16-7.21 (m, 2H), 7.26-7.30 (m, 2H), 7.31-7.36 (m, 2H), 7.36-7.41 (m, 2H), 7.43-7.55 (m, 6H), 10.40 (s, 1H).

Example 1-57

45 **[0465]** MS ESI m/e: 482 (M+H), 480 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 2.93 (s, 3H), 6.20 (s, 1H), 7.28-7.33 (m, 2H), 7.35-7.44 (m, 4H), 7.46-7.59 (m, 6H), 8.20-8.27 (m, 2H), 10.95 (s, 1H).

Example 1-58

50 **[0466]** MS ESI m/e: 451 (M+H), 449 (M-H).
 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.83 (d, J=9.0Hz, 6H), 1.90-2.04 (m, 1H), 3.45 (s, 3H), 3.98 (d, J=9.0Hz, 2H), 5.50 (s, 1H), 7.28-7.34 (m, 4H), 7.43-7.55 (m, 5H), 10.30 (brs, 1H).

55 Example 1-59

[0467] MS ESI m/e: 444 (M+H), 442 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 3.14 (s, 3H), 5.22 (s, 1H), 6.96-7.03 (m, 2H), 7.17-7.41 (m, 5H), 7.41-7.55 (m, 3H), 7.60

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(d, J=3.7Hz, 1H), 7.89 (d, J=3.7Hz, 1H), 11.57 (s, 1H) .

Example 1-60

5 **[0468]** MS ESI m/e: 457 (M+H), 455 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 5.70 (s, 1H), 7.14-7.12 (m, 2H), 7.30-7.43 (m, 6H), 7.43-7.65 (m, 6H), 10.48 (s, 1H).

Example 1-61

10 **[0469]** MS ESI m/e: 466 (M+H), 464 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 2.95 (s, 3H), 5.56 (s, 1H), 6.65-6.75 (m, 2H), 7.02-7.14 (m, 2H), 7.29-7.67 (m, 10H), 10.18 (s, 1H).

Example 1-62

15 **[0470]** MS ESI m/e: 506 (M+H), 504 (M-H) .
¹H-NMR (CDCl₃, 300MHz) δ 2.96 (6H, s), 4.23 (d, J=4.7Hz, 2H), 4.88 (d, J=17.3Hz, 1H), 5.02 (d, J=10.6Hz, 1H), 5.40-5.55 (m, 1H), 5.69 (s, 1H), 6.68-6.75 (m, 2H), 7.07-7.14 (m, 2H), 7.27-7.33 (m, 2H), 7.37-7.56 (m, 8H), 10.10 (s, 1H).

20 Example 1-63

[0471] MS ESI m/e: 472 (M+H).
¹H-NMR (DMSO-d₆, 300MHz) δ 2.72 (s, 3H), 7.16 (d, J=9.0Hz, 1H), 7.34-7.42 (m, 2H), 7.43-7.60 (m, 10H), 7.82 (dd, J=3.0, 6.0Hz, 1H), 8.42 (d, J=3.0Hz, 1H), 11.68 (s, 1H) .

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Example 1-64

[0472] MS ESI m/e: 487 (M+H)
¹H-NMR (CDCl₃, 400MHz) δ 2.94 (s, 3H), 3.12 (s, 6H), 7.26-7.32 (m, 2H), 7.34-7.54 (m, 8H), 7.68 (s, 1H), 9.00 (d, J=4.8Hz, 1H), 10.26 (d, J=5.8Hz, 1H).

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Example 1-65

[0473] MS ESI m/e: 480 (M+H), 478 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 1.24 (t, J=7.3Hz, 3H), 2.68 (s, 3H), 3.27 (q, J=7.3Hz, 2H), 5.53 (s, 1H), 7.29-7.60 (m, 16H), 10.46 (s, 1H).

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Example 1-66

[0474] MS ESI m/e: 478 (M+H), 477(M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 1.16 (d, J=6.8Hz, 6H), 2.65 (s, 3H), 3.05-3.15 (m, 1H), 5.00 (s, 1H), 7.27-7.54 (m, 14H), 10.19 (brs, 1H).

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Example 1-67

[0475] MS ESI m/e: 485 (M+H), 483(M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.56 (t, J=7.0Hz, 3H), 3.55 (q, 2H, J=7.0Hz), 5.53 (s, 1H), 7.10-7.13 (m, 2H), 7.32-7.56 (m, 12H), 10.49 (brs, 1H) .

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Example 1-68

[0476] MS ESI m/e: 528 (M+H), 526 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 2.15 (s, 6H), 2.88 (s, 3H), 3.31 (s, 2H), 5.65 (s, 1H), 7.21-7.54 (m, 13H), 10.50 (s, 1H) .

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Example 1-69

[0477] MS ESI m/e: 493 (M+H), 491(M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.84 (d, J=6.6Hz, 6H), 1.78-1.88 (m, 1H), 2.45 (d, J=7.2Hz, 2H), 2.67 (s, 3H), 5.15 (s,

55

1H), 7.20-7.53 (m, 14H), 10.24 (brs, 1H).

Example 1-70

5 **[0478]** MS ESI m/e: 499, 501 (M+H), 497, 499 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 2.37 (s, 3H), 2.38 (s, 3H), 2.70 (s, 3H), 5.54 (s, 1H), 7.21-7.50 (m, 12H), 10.51 (brs, 1H) .

Example 1-71

10 **[0479]** MS ESI m/e: 507, 508 (M+H), 505, 506 (M-H) .
¹H-NMR (DMSO-d₆, 300MHz) δ 0.85 (d, J=6.5Hz, 6H), 1.37-1.42 (m, 2H), 1.49-1.53(m, 1H), 2.50-2.58 (m, 2H), 2.67 (s, 3H), 5.12 (s, 1H), 7.24-7.55 (m, 14H), 10.23 (brs, 1H) .

Example 1-72

15 **[0480]** MS ESI m/e: 499 (M+H), 497 (M-H)
¹H-NMR (CDCl₃, 300MHz) δ 2.12-2.44 (m, 6H), 2.84 (s, 3H), 5.83 (brs, 1H), 7.05-7.48 (m, 12H), 10.47-10.57 (m, 1H) .

Example 1-73

20 **[0481]** MS ESI m/e: 522 (M+H), 520 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.91 (t, J=7.3Hz, 3H), 1.49-1.66 (m, 2H), 2.50 (t, J=7.7Hz, 2H), 2.87 (s, 3H), 2.95 (s, 6H), 5.33 (s, 1H), 6.54-6.63 (m, 2H), 7.01-7.08 (m, 1H), 7.30-7.37 (m, 2H), 7.38-7.58 (m, 8H), 9.80 (s, 1H) .

25 Example 1-74

[0482] MS ESI m/e: 506 (M+H), 504 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 1.91-2.03 (m 2H), 2.73 (t, J=6.4Hz, 2H), 2.87 (s, 3H), 2.88 (s, 3H), 3.22 (t, J=5.7Hz, 2H), 5.68 (s, 1H), 6.54 (d, J=8.4Hz, 1H), 6.79-6.85 (m, 1H), 6.87-6.93 (m, 1H), 7.28-7.34 (m, 2H), 7.36-7.58 (m, 8H), 10.00 (s, 1H) .

Example 1-75

35 **[0483]** MS ESI m/e: 531, 533 (M+H), 529, 531 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 2.63 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H) , 5.45 (s, 1H), 6.97 (t, J=9.1Hz, 4H), 7.16-7.42 (m, 8H), 10.46 (brs, 1H).

Example 1-76

40 **[0484]** MS ESI m/e: 499, 501 (M+H), 497, 499 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 2.26 (s, 3H), 2.27 (s, 3H), 2.63 (s, 3H), 5.46 (s, 1H), 7.09-7.42 (m, 12H), 10.42 (brs, 1H) .

Example 1-77

45 **[0485]** MS ESI m/e: 483, 485 (M+H), 481, 483 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 2.68 (s, 3H), 5.45 (s, 1H), 7.00-7.64 (m, 10H), 10.35 (brs, 1H).

Example 1-78

50 **[0486]** MS ESI m/e: 423 (M+H), 421 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 1.30 (t, J=6.9Hz, 3H), 2.82 (s, 3H), 4.08 (q, J=7.0Hz, 2H), 5.77 (s, 1H), 7.19-7.25 (m, 2H), 7.31-7.39 (m, 4H), 7.41-7.54 (m, 3H), 10.53 (s, 1H)

Example 1-79

55 **[0487]** MS ESI m/e: 507, 508 (M+H), 505, 503 (M-H) .
¹H-NMR(DMSO-d₆, 300MHz) δ 2.64 (s, 3H), 5.46 (s, 1H), 7.23-7.51 (m, 12H), 10.37 (brs, 1H).

Example 1-80

[0488] MS ESI m/e: 463 (M+H), 461 (M-H) .

¹H-NMR (CDCl₃, 300MHz) δ 1.52-1.67 (m, 2H), 1.82-2.02 (m, 4H), 2.04-2.20 (m, 2H), 2.80 (s, 3H), 5.21-5.37 (m, 1H), 5.75 (s, 1H), 7.18-7.28 (m, 2H), 7.30-7.56 (m, 7H), 10.54 (s, 1H).

Example 1-81

[0489] MS ESI m/e: 437 (M+H), 435 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 1.51 (d, J=7.0Hz, 6H), 2.81 (s, 3H), 5.09-5.23 (m, 1H), 5.75 (s, 1H), 7.18-7.28 (m, 2H), 7.29-7.55 (m, 7H), 10.53 (s, 1H).

Example 1-82

[0490] MS ESI m/e: 437 (M+H), 435 (M-H) .

¹H-NMR (CDCl₃, 400MHz) δ 0.98 (t, J=7.4Hz, 3H), 1.66-1.79 (m, 2H), 2.82 (s, 3H), 3.96 (t, J=7.6Hz, 2H), 5.77 (s, 1H), 7.20-7.25 (m, 2H), 7.32-7.40 (m, 4H), 7.41-7.54 (m, 3H), 10.54 (s, 1H).

Example 1-83

[0491] MS ESI m/e: 451 (M+H), 449 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.96 (t, J=7.4Hz, 3H), 1.34-1.47 (m, 2H), 1.62-1.73 (m, 2H), 2.81 (s, 3H), 3.99 (t, J=7.6Hz, 2H), 5.76 (s, 1H), 7.18-7.24 (m, 2H), 7.31-7.39 (m, 4H), 7.41-7.52 (m, 3H), 10.53 (s, 1H) .

Example 1-84

[0492] MS ESI m/e: 435 (M+H), 433 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.81-0.90 (m, 2H), 1.14-1.24 (m, 2H), 2.71-2.81 (m, 1H), 2.81 (s, 3H), 5.77 (s, 1H), 7.17-7.24 (m, 2H), 7.27-7.39 (m, 4H), 7.39-7.52 (m, 3H), 10.38 (s, 1H) .

Example 1-85

[0493] MS ESI m/e: 423 (M+H), 421 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.25-2.30 (m, 3H), 2.51-2.57 (m, 3H), 3.26-3.31 (m, 3H), 5.48-5.52 (m, 1H), 7.24-7.55 (m, 8H), 10.74 (s, 1H) .

Example 1-86

[0494] MS ESI m/e: 423 (M+H), 421 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.35 (s, 3H), 2.65 (s, 3H), 3.26 (s, 3H), 5.51 (s, 1H), 7.23-7.32 (m, 3H), 7.32-7.45 (m, 3H), 7.46-7.54 (m, 2H), 10.64 (s, 1H).

Example 1-87

[0495] MS ESI m/e: 4.23 (M+H), 421 (M-H) .

¹H-NMR (DMSO-d₆, 300MHz) δ 2.37 (s, 3H), 2.63 (s, 3H), 3.26 (s, 3H), 5.50 (s, 1H), 7.29-7.39 (m, 6H), 7.46-7.53 (m, 2H), 10.64 (s, 1H).

Example 1-88

[0496] MS ESI m/e: 444 (M+H), 442 (M-H) .

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.91 (m, 2H), 1.13-1.23 (m, 2H), 2.71-2.80 (m, 1H), 2.80 (s, 3H), 2.97 (s, 6H), 5.62 (s, 1H), 6.69-6.77 (m, 2H), 7.08-7.16 (m, 2H), 7.29-7.35 (m, 2H), 7.38-7.52 (m, 3H), 10.07 (s, 1H) .

Example 1-89

[0497] MS ESI m/e: 479, 481 (M+H), 477, 479 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.91 (m, 2H), 1.15-1.26 (m, 2H), 2.71-2.82 (m, 1H), 2.82 (s, 3H), 5.80 (s, 1H), 7.13-7.21

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(m, 2H), 7.28-7.36 (m, 2H), 7.39-7.56 (m, 5H), 10.41 (s, 1H) .

Example 1-90

5 **[0498]** MS ESI m/e: 477 (M+H), 475 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 2.84 (s, 3H), 4.75 (q, J=8.4Hz, 2H), 5.76 (s, 1H), 7.19-7.28 (m, 2H), 7.31-7.42 (m, 4H), 7.43-7.57 (m, 3H), 10.20 (s, 1H).

Example 1-91

10 **[0499]** MS ESI m/e: 513 (M+H), 511 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.64 (t, J=6.0Hz, 3H), 1.21-1.41 (m, 2H), 2.15 (t, J=7.5Hz, 2H), 2.76 (s, 3H), 6.93-7.07 (m, 2H), 7.27-7.37 (m, 4H), 7.39-7.64 (m, 8H), 9.92 (s, 1H).

15 Example 1-92

[0500] MS ESI m/e: 521, 523 (M+H), 519, 521 (M-H) .
¹H-NMR (CDCl₃, 300MHz) δ 2.85 (s, 3H), 4.75 (q, J=8.4Hz, 2H), 5.78 (s, 1H), 7.14-7.22 (m, 2H), 7.32-7.40 (m, 2H), 7.44-7.58 (m, 5H), 10.20 (s, 1H) .

20 Example 1-93
[0501] MS ESI m/e: 486 (M+H), 484 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 2.83 (s, 3H), 2.97 (s, 6H), 4.75 (q, J=8.4Hz, 2H), 5.61 (s, 1H), 6.67-6.81 (m, 2H), 7.08-7.18 (m, 2H), 7.32-7.40 (m, 2H), 7.41-7.56 (m, 3H), 9.92 (s, 1H) .

Example 1-94

30 **[0502]** MS ESI m/e: 457 (M+H), 455 (M-H) .
¹H-NMR (DMSO-d₆, 300MHz) δ 1.18 (t, J=6.7Hz, 3H), 2.66 (s, 3H), 3.93 (q, J=6.7Hz, 2H), 5.50 (s, 1H), 7.36 (d, J=9.0Hz, 2H), 7.46-7.56 (m, 4H), 7.57-7.66 (m, 2H), 10.62 (s, 1H).

Example 1-95

35 **[0503]** MS ESI m/e: 467, 469 (M+H), 465, 467 (M-H).
¹H-NMR (DMSO-d₆, 400MHz) δ 2.28 (s, 3H), 2.53 (s, 3H), 3.28 (s, 3H), 5.51 (s, 1H), 7.23-7.35 (m, 4H), 7.38-7.44 (m, 2H), 7.58-7.65 (m, 2H), 10.72 (s, 1H) .

Example 1-96

40 **[0504]** MS ESI m/e: 467, 469 (M+H), 465, 467 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 1.29 (t, J=7.1Hz, 3H), 2.81 (s, 3H), 4.07 (q, J=7.1Hz, 2H), 5.78 (s, 1H), 7.14-7.19 (m, 2H), 7.31-7.36 (m, 2H), 7.40-7.53 (m, 5H), 10.53 (s, 1H) .

45 Example 1-97

[0505] MS ESI m/e: 432 (M+H).
¹H-NMR (CDCl₃, 400MHz) δ 1.29 (t, J=7.1Hz, 3H), 2.80 (s, 3H), 2.96 (s, 6H), 4.07 (q, J=7.0Hz, 2H), 5.59 (s, 1H), 6.69-6.75 (m, 2H), 7.08-7.14 (m, 2H), 7.31-7.36 (m, 2H), 7.38-7.50 (m, 3H), 10.19 (s, 1H) .

50 Example 1-98
[0506] MS ESI m/e: 435 (M+H), 433 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.80-0.91 (m, 2H), 1.25-1.35 (m, 2H), 3.38-3.49 (m, 1H), 3.74 (s, 3H), 5.76 (s, 1H), 7.09-7.18 (m, 2H), 7.20-7.37 (m, 4H), 7.44-7.60 (m, 3H), 10.23 (s, 1H).

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Example 1-99

[0507] MS ESI m/e: 432 (M+H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.27 (s, 3H), 2.51 (s, 3H), 2.92 (s, 6H), 3.27 (s, 3H), 5.21 (s, 1H), 6.76-6.84 (m, 2H), 7.06-7.14 (m, 2H), 7.23-7.38 (m, 2H), 7.38-7.44 (m, 2H), 10.35 (s, 1H).

Example 1-100

[0508] MS ESI m/e: 453 (M+H), 451 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.92 (m, 2H), 1.14-1.24 (m, 2H), 2.74-2.83 (m, 1H), 2.86 (s, 3H), 5.76 (s, 1H), 7.18-7.33 (m, 5H), 7.33-7.40 (m, 2H), 7.45-7.55 (m, 1H), 10.41 (s, 1H).

Example 1-101

[0509] MS ESI m/e: 503 (M+H), 501 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.78-0.91 (m, 2H), 1.14-1.26 (m, 2H), 2.73-2.86 (m, 1H), 2.82 (s, 3H), 5.76 (s, 1H), 7.19-7.29 (m, 2H), 7.32-7.41 (m, 2H), 7.42-7.50 (m, 1H), 7.61-7.79 (m, 2H), 7.80-7.89 (m, 1H), 10.50 (s, 1H).

Example 1-102

[0510] MS ESI m/e: 449 (M+H), 447 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.74-0.96 (m, 2H), 1.11-1.31 (m, 2H), 2.30 (s, 3H), 2.74 (s, 3H), 2.76-2.85 (m, 1H), 5.76 (s, 1H), 7.04-7.12 (m, 1H), 7.18-7.43 (m, 7H), 10.53 (s, 1H).

Example 1-103

[0511] MS ESI m/e: 463 (M+H), 461 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.76-0.90 (m, 2H), 1.11-1.27 (m, 2H), 1.26 (t, J=7.5Hz, 3H), 2.40-2.67 (m, 2H), 2.71-2.84 (m, 1H), 2.75 (s, 3H), 5.76 (s, 1H), 7.08-7.14 (m, 1H), 7.18-7.47 (m, 7H), 10.54 (s, 1H).

Example 1-104

[0512] MS ESI m/e: 465 (M+H), 463 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.79-0.94 (m, 2H), 1.11-1.28 (m, 2H), 2.71-2.83 (m, 1H), 2.84 (s, 3H), 3.84 (s, 3H), 5.76 (s, 1H), 7.00-7.13 (m, 2H), 7.19-7.30 (m, 3H), 7.32-7.40 (m, 2H), 7.41-7.52 (m, 1H), 10.52 (s, 1H).

Example 1-105

[0513] MS ESI m/e: 445 (M+H), 443 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.92 (t, J=7.5Hz, 3H), 1.36 (sext, J=7.5Hz, 2H), 1.59 (quint, J=7.5Hz, 2H), 2.33 (s, 3H), 2.62 (t, J=7.5Hz, 2H), 2.75 (s, 3H), 3.45 (s, 3H), 5.43 (s, 1H), 7.08-7.45 (m, 8H), 10.37 (s, 1H).

Example 1-106

[0514] MS ESI m/e: 458 (M+H).

¹H-NMR (CDCl₃, 300MHz) δ 0.77-0.92 (m, 2H), 1.14-1.27 (m, 2H), 2.30 (s, 3H), 2.72 (s, 3H), 2.74-2.85 (m, 1H), 2.96 (s, 6H), 5.60 (s, 1H), 6.69-6.79 (m, 2H), 7.03-7.18 (m, 3H), 7.22-7.42 (m, 3H), 10.20 (s, 1H).

Example 1-107

[0515] MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 1.68-1.79 (m, 2H), 2.19-2.32 (m, 2H), 2.59 (s, 3H), 2.60-2.75 (m, 2H), 4.88-4.98 (m, 1H), 5.49 (s, 1H), 7.29 (d, J=8.7Hz, 2H), 7.41-7.53 (m, 5H), 7.60 (d, J=8.6Hz, 2H), 10.52 (brs, 1H).

Example 1-108

[0516] MS ESI m/e: 535, 537 (M+H), 533, 535 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.27 (s, 3H), 2.54 (s, 3H), 4.62-4.88 (m, 2H), 5.49 (s, 1H), 7.28-7.30 (m, 4H), 7.41-7.42

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(m, 2H), 7.62 (d, J=9.0Hz, 2H), 10.40 (brs, 1H) .

Example 1-109

5 **[0517]** MS ESI m/e: 437 (M+H), 435 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 1.30 (t, J=6.0Hz, 3H), 2.30 (s, 3H), 2.75 (s, 3H), 4.09 (q, J=6.0Hz, 2H), 5.75 (s, 1H), 7.12 (d, J=6.0Hz, 1H), 7.19-7.43 (m, 7H), 10.65 (s, 1H) .

Example 1-110

10 **[0518]** MS ESI m/e: 446 (M+H), 444 (M-H) .
¹H-NMR (CDCl₃, 300MHz) δ 1.30 (t, J=7.1Hz, 3H), 2.30 (s, 3H), 2.73 (s, 3H), 2.96 (s, 6H), 4.09 (q, J=2.3Hz, 2H), 4.84 (q, J=149.0Hz, 2H), 6.68-6.77 (m, 2H), 7.08-7.17 (m, 3H), 7.25-7.32 (m, 1H), 7.33-7.38 (m, 2H), 10.31 (brs, 1H).

15 Example 1-111

[0519] MS ESI m/e: 481, 483 (M+H), 479, 481 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 1.30 (t, J=6.0Hz, 3H), 2.30 (s, 1H), 2.75 (s, 1H), 4.09 (q, J=7.0Hz, 2H), 5.77 (s, 1H), 7.08-7.22 (m, 3H), 7.26-7.42 (m, 3H), 7.49-7.56 (m, 2H), 10.66 (brs, 1H).

20 Example 1-112

[0520] MS ESI m/e: 458 (M+H), 456 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.93 (m, 2H), 1.14-1.24 (m, 2H), 2.23 (s, 3H), 2.71-2.82 (m, 1H), 2.79 (s, 3H), 2.95 (s, 6H), 5.29 (s, 1H), 6.55-6.64 (m, 2H), 7.02-7.10 (m, 1H), 7.29-7.36 (m, 2H), 7.38-7.53 (m, 3H), 9.86 (s, 1H) .

Example 1-113

30 **[0521]** MS ESI m/e: 497, 499 (M+H), 495, 497 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.92 (m, 2H), 1.14-1.24 (m, 2H), 2.73-2.83 (m, 1H), 2.86 (s, 3H), 5.78 (s, 1H), 7.12-7.21 (m, 2H), 7.21-7.34 (m, 3H), 7.45-7.55 (m, 3H), 10.41 (s, 1H).

Example 1-114

35 **[0522]** MS ESI m/e: 462 (M+H), 460 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.93 (m, 2H), 1.13-1.25 (m, 2H), 2.72-2.84 (m, 1H), 2.84 (s, 3H), 2.96 (s, 6H), 5.60 (s, 1H), 6.69-6.77 (m, 2H), 7.08-7.15 (m, 2H), 7.17-7.31 (m, 3H), 7.43-7.53 (m, 1H), 10.09 (s, 1H) .

Example 1-115

40 **[0523]** MS ESI m/e: 441 (M+H), 439 (M-H) .
¹H-NMR (CDCl₃, 300MHz) δ 1.31 (t, J=7.0Hz, 3H), 2.86 (s, 3H), 4.08 (q, J=7.0Hz, 2H), 5.75 (s, 1H), 7.18-7.40 (m, 7H), 7.46-7.56 (m, 1H), 10.54 (s, 1H) .

45 Example 1-116

[0524] MS ESI m/e: 485, 487 (M+H), 483, 485 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 1.31 (t, J=7.0Hz, 3H), 2.86 (s, 3H), 4.08 (q, J=7.0Hz, 2H), 5.77 (s, 1H), 7.13-7.21 (m, 2H), 7.24-7.34 (m, 3H), 7.46-7.56 (m, 3H), 10.55 (s, 1H).

50 Example 1-117

[0525] MS ESI m/e: 450 (M+H), 448 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 1.31 (t, J=7.0Hz, 3H), 2.85 (s, 3H), 2.96 (s, 6H), 4.08 (q, J=7.1Hz, 2H), 5.59 (s, 1H), 6.69-6.77 (m, 2H), 7.08-7.17 (m, 2H), 7.22-7.34 (m, 3H), 7.43-7.54 (m, 1H), 10.21 (s, 1H).

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Example 1-118

[0526] MS ESI m/e: 472 (M+H),

5 $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.79-0.89 (m, 2H), 1.14-1.25 (m, 2H), 2.16 (s, 6H), 2.71 (s, 3H), 2.77-2.87 (m, 1H), 2.96 (s, 6H), 5.59 (s, 1H), 6.68-6.77 (m, 2H), 7.08-7.19 (m, 4H), 7.23-7.31 (m, 1H), 10.31 (s, 1H).

Example 1-119

[0527] MS ESI m/e: 480 (M+H).

10 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.10 (m, 2H), 2.68-2.79 (m, 1H), 2.71 (s, 1H), 5.21 (s, 1H), 6.79 (d, J=9.0Hz, 2H), 7.12 (d, J=9.0Hz, 2H), 7.39 (t, J=9.0Hz, 2H), 7.65-7.75 (m, 1H), 10.11 (brs, 1H) .

Example 1-120

15 **[0528]** MS ESI m/e: 515, 517 (M+H), 513, 515 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.71-0.79 (m, 2H), 1.00-1.10 (m, 2H), 2.71-2.80 (m, 1H), 2.74 (s, 3H), 5.51 (s, 1H), 7.32 (d, J=9.0Hz, 2H), 7.41 (t, J=7.5Hz, 2H), 7.62 (d, J=6.0Hz, 2H), 7.64-7.76 (m, 1H), 10.47 (brs, 1H).

Example 1-121

20 **[0529]** MS ESI m/e: 471 (M+H), 469 (M-H).
 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.71-0.79 (m, 2H), 1.03-1.07 (m, 2H), 2.70-2.80 (m, 1H), 2.74 (s, 3H), 5.49 (s, 1H), 7.36-7.43 (m, 4H), 7.50 (d, J=9.0Hz, 2H), 7.65-7.76 (m, 1H), 10.47 (brs, H).

25 Example 1-122

[0530] MS ESI m/e: 460 (M+H), 458 (M-H).

30 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 1.16 (t, J=7.5Hz, 3H), 1.18 (t, J=6.0Hz, 3H), 2.52 (q, J=4.0Hz, 2H), 2.50 (s, 3H), 2.92 (s, 6H), 3.94 (q, J=5.0Hz, 2H), 5.20 (s, 1H), 6.79 (d, J=9.0Hz, 2H), 7.12 (d, J=9.0Hz, 2H), 7.33 (d, J=3.0Hz, 2H), 7.47 (s, 2H), 10.35 (brs, H).

Example 1-123

[0531] MS ESI m/e: 495, 497 (M+H), 493, 495 (M-H) .

35 $^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 1.16 (t, J=7.5Hz, 3H), 1.18 (t, J=6.0Hz, 3H), 2.50-2.56 (m, 2H), 2.53 (s, 3H), 3.96 (q, J=7.0Hz, 2H), 5.51 (s, 1H), 7.29-7.34 (m, 4H), 7.46-7.48 (m, 2H), 7.62 (d, J=6.0Hz, 2H), 10.74 (brs, H).

Example 1-124

40 **[0532]** MS ESI m/e: 451 (M+H), 499 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 1.16 (t, J=6.0Hz, 3H), 1.18 (t, J=6.0Hz, 3H), 2.50-2.55 (m, 2H), 2.56 (s, 3H), 3.95 (q, J=8.0Hz, 2H), 5.49 (s, 1H), 7.33-7.38 (m, 4H), 7.48-7.51 (m, 4H), 10.73 (brs, H).

Example 1-125

45 **[0533]** MS ESI m/e: 463 (M+H), 461 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.78-0.88 (m, 2H), 1.16-1.29 (m, 2H), 2.15 (s, 6H), 2.72 (s, 3H), 2.77-2.88 (m, 1H), 5.74 (s, 1H), 7.11-7.40 (m, 7H), 10.64 (s, 1H).

50 Example 1-126

[0534] MS ESI m/e: 458 (M+H).

55 $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.83-0.90 (m, 2H), 1.13-1.23 (m, 2H), 2.39 (s, 3H), 2.71-2.78 (m, 1H), 2.81 (s, 3H), 2.96 (s, 6H), 5.60 (s, 1H), 6.68-6.78 (m, 2H), 7.07-7.32 (m, 6H), 10.08 (brs, 1H) .

Example 1-127

[0535] MS ESI m/e: 458 (M+H).

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$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.81-0.93 (m, 2H), 1.13-1.23 (m, 2H), 2.39 (s, 3H), 2.71-2.81 (m, 1H), 2.83 (s, 3H), 2.96 (s, 6H), 5.62 (s, 1H), 6.70-6.76 (m, 2H), 7.08-7.16 (m, 4H), 7.20-7.25 (m, 1H), 7.31-7.39 (m, 1H), 10.08 (brs, 1H).

Example 1-128

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[0536] MS ESI m/e: 472 (M+H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.82-0.92 (m, 2H), 1.14-1.25 (m, 2H), 1.18 (t, J=7.0Hz, 6H), 2.71-2.82 (m, 1H), 2.80 (s, 3H), 3.36 (q, J=7.0Hz, 4H), 5.62 (s, 1H), 6.63-6.71 (m, 2H), 7.03-7.13 (m, 2H), 7.28-7.36 (m, 2H), 7.37-7.53 (m, 3H), 10.03 (s, 1H).

10

Example 1-129

[0537] MS ESI m/e: 431 (M+H), 429 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.84-0.90 (m, 2H), 1.15-1.23 (m, 2H), 2.72-2.80 (m, 1H), 2.80 (s, 3H), 3.82 (s, 3H), 5.61 (s, 1H), 6.88-6.94 (m, 2H), 7.14-7.21 (m, 2H), 7.28-7.33 (m, 2H), 7.38-7.50 (m, 3H), 10.15 (s, 1H).

15

Example 1-130

[0538] MS ESI m/e: 40.8 (M+H) .

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.68-0.73 (m, 4H), 0.96-1.02 (m, 2H), 1.05-1.12 (m, 2H), 2.54-2.63 (m, 1H), 2.91 (s, 6H), 3.30-3.40 (m, 1H), 3.48 (s, 3H), 5.14 (s, 1H), 6.77 (d, J=9.0Hz, 2H), 7.06 (d, J=9.0Hz, 2H), 10.04 (brs, H) .

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Example 1-131

[0539] MS ESI m/e: 468, 470 (M+H), 466, 468 (M-H) .

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 1.20 (t, J=7.5Hz, 3H), 2.62 (s, 3H), 3.95 (q, J=7.0Hz, 2H), 5.53 (s, 1H), 7.32 (d, J=9.0Hz, 2H), 7.52-7.64 (m, 3H), 7.97 (d, J=9.0Hz, 1H), 8.67 (d, J=15Hz, 1H), 8.68 (d, J=15Hz, 1H), 10.62 (brs, H).

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Example 1-132

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[0540] MS ESI m/e: 462 (M+H), 460 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.82-0.89 (m, 2H), 1.15-1.22 (m, 2H), 2.72-2.79 (m, 1H), 2.82, (s, 3H), 2.96 (s, 6H), 5.60 (s, 1H), 6.69-6.75 (m, 2H), 7.07-7.21 (m, 4H), 7.27-7.33 (m, 2H), 10.03 (s, 1H) .

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Example 1-133

[0541] MS ESI m/e: 462 (M+H), 460 (M-H) .

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.83-0.89 (m, 2H), 1.15-1.23 (m, 2H), 2.72-2.80 (m, 1H), 2.85 (s, 3H), 2.96 (s, 6H), 5.61 (s, 1H), 6.69-6.75 (m, 2H), 7.03-7.19 (m, 5H), 7.39-7.46 (m, 1H), 10.01 (s, 1H).

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Example 1-134

[0542] MS ESI m/e: 444 (M+H), 442 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.82-0.93 (m, 2H), 1.13-1.24 (m, 2H), 2.72-2.82 (m, 1H), 2.82 (s, 3H), 2.96 (s, 6H), 5.90 (s, 1H), 6.55-6.62 (m, 2H), 6.63-6.69 (m, 1H), 7.19-7.24 (m, 1H), 7.30-7.35 (m, 2H), 7.38-7.53 (m, 3H), 10.31 (s, 1H).

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Example 1-135

[0543] MS ESI m/e: 416 (M+H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.70-0.82 (m, 2H), 0.99-1.09 (m, 2H), 2.60 (s, 3H), 2.63-2.74 (m, 1H), 5.52 (s, 1H), 7.36-7.57 (m, 9H), 10.61 (s, 1H).

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Example 1-136

[0544] MS ESI m/e: 430 (M+H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.71-0.80 (m, 2H), 0.98-1.08 (m, 2H), 2.60 (s, 3H), 2.63-2.72 (m, 1H), 2.89 (s, 3H), 5.51 (d, J=2.9Hz, 1H), 7.38-7.56 (m, 9H), 10.59 (brs, 1H).

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Example 1-137

[0545] MS ESI m/e: 444 (M+H), 442 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.80 (m, 2H), 0.98-1.08 (m, 2H), 1.27 (t, J=7.5Hz, 3H), 2.61 (s, 3H), 2.64-2.72 (m, 1H), 3.31 (q, J=7.0Hz, 2H), 5.54 (s, 1H), 7.07-7.19 (m, 2H), 7.38-7.57 (m, 9H), 10.62 (brs, 1H).

Example 1-138

[0546] MS ESI m/e: 454 (M+H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.80 (m, 2H), 0.99-1.08 (m, 2H), 2.57 (s, 3H), 2.62-2.75 (m, 1H), 3.81 (s, 3H), 5.26 (s, 1H), 6.44 (d, J=3.0Hz, 1H), 7.06 (dd, J=3.0, 3.0Hz, 1H), 7.37-7.52 (m, 8H), 10.37 (brs, H).

Example 1-139

[0547] MS ESI m/e: 444 (M+H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.59 (s, 3H), 2.92 (s, 6H), 4.49 (d, J=3.0Hz, 2H), 5.15 (d, J=9.0Hz, 1H), 5.22 (dd, J=3.0, 9.0Hz, 2H), 6.78 (d, J=6.0Hz, 2H), 7.10 (d, J=6.0Hz, 2H), 7.48-7.50 (m, 5H), 10.19 (brs, H).

Example 1-140

[0548] MS ESI m/e: 444 (M+H), 442 (M-H) .

¹H-NMR (DMSO-d₆, 300MHz) δ 2.60 (s, 3H), 3.03 (s, 6H), 4.50 (d, J=3.0Hz, 2H), 5.17 (dd, J=21.0, 24.0Hz, 2H), 5.38 (s, 1H), 5.79-5.92 (m, 1H), 7.19-7.38 (m, 4H), 7.41-7.55 (m, 5H), 10.42 (brs, H) .

Example 1-141

[0549] MS ESI m/e: 456 (M+H), 454 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.99-1.08 (m, 2H), 2.55 (s, 3H), 2.61-2.68 (m, 1H), 2.71 (s, 3H), 2.89 (t, J=9.0Hz, 2H), 3.28 (t, J=7.5Hz, 2H), 5.18 (s, 1H), 6.54 (d, J=9.0Hz, 1H), 6.90 (d, J=6.0Hz, 1H), 6.96 (s, 1H), 7.39-7.50 (m, 5H), 10.13 (brs, H).

Example 1-142

[0550] MS ESI m/e: 476 (M+H).

¹H-NMR (CDCl₃, 300MHz) δ 0.85-0.93 (m, 2H), 1.14-1.24 (m, 2H), 2.23 (s, 3H), 2.74-2.83 (m, 1H), 2.83 (s, 3H), 2.95 (s, 6H), 5.27 (s, 1H), 6.55-6.65 (m, 2H), 7.02-7.09 (m, 1H), 7.18-7.32 (m, 3H), 7.43-7.54 (m, 1H), 9.89 (s, 1H).

Example 1-143

[0551] MS ESI m/e : 462 (M+H), 460 (M-H) .

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.92 (m, 2H), 1.14-1.25 (m, 2H), 2.71-2.81 (m, 1H), 2.81 (s, 1H), 2.87 (s, 6H), 5.71 (s, 1H), 6.86-7.02 (m, 3H), 7.27-7.35 (m, 2H), 7.41-7.54 (m, 3H), 10.22 (brs, 1H).

Example 1-144

[0552] MS ESI m/e: 454 (M+H), 452 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.80 (m, 2H), 1.00-1.09 (m, 2H), 2.58 (s, 3H), 2.64-2.71 (m, 1H), 3.78 (s, 3H), 5.40 (s, 1H), 6.45 (d, J=3.0Hz, 1H), 6.97 (d, J=6.0Hz, 1H), 7.34-7.51 (m, 7H), 7.60 (d, J=9.0Hz, 1H), 8.30 (brs, H).

Example 1-145

[0553] MS ESI m/e: 479 (M+H), 477 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.91 (m, 2H), 1.15-1.26 (m, 2H), 2.73-2.83 (m, 1H), 2.85 (s, 3H), 3.08 (s, 3H), 6.08 (s, 1H), 7.29-7.37 (m, 2H), 7.41-7.56 (m, 5H), 7.92-8.00 (m, 2H), 10.87 (s, 1H).

Example 1-146

[0554] MS ESI m/e: 461 (M+H), 459 (M-H).

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$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.82-0.92 (m, 2H), 1.13-1.24 (m, 2H), 2.72-2.83 (m, 1H), 2.80 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 5.60 (s, 1H), 6.45-6.58 (m, 2H), 7.19-7.26 (m, 1H), 7.28-7.35 (m, 2H), 7.38-7.52 (m, 3H), 10.01 (s, 1H).

Example 1-147

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[0555] MS ESI m/e: 458 (M+H), 456 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.81-0.91 (m, 2H), 1.13-1.23 (m, 2H), 2.32 (s, 3H), 2.67-2.84 (m, 1H), 2.71, (s, 6H), 2.81 (s, 3H), 5.72 (s, 1H), 6.99-7.10 (m, 3H), 7.28-7.36 (m, 2H) 7.38-7.53 (m, 3H), 10.19 (s, 1H).

10 Example 1-148

[0556] MS ESI m/e: 512 (M+H), 510 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.84-0.90 (m, 2H), 1.16-1.24 (m, 2H), 2.73-2.79 (m, 1H), 2.75 (s, 6H), 2.81 (s, 3H), 5.66 (s, 1H), 7.29-7.37 (m, 3H), 7.39-7.52 (m, 5H), 10.33 (brs, 1H).

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Example 1-149

[0557] MS ESI m/e: 472 (M+H), 470 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.84-0.91 (m, 2H), 1.17-1.25. (m, 2H), 1.91 (s, 3H), 2.74-2.81 (m, 1H), 2.83 (s, 3H), 3.28 (s, 3H), 5.84 (s, 1H), 7.18-7.24 (m, 2H), 7.29-7.35 (m, 4H), 7.40-7.52 (m, 3H), 10.47 (s, 1H).

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Example 1-150

[0558] MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.39-0.57 (m, 4H), 1.24-1.36 (m, 1H), 2.83 (s, 3H), 3.91 (d, J=7.0Hz, 2H), 5.80 (s, 1H), 7.15-7.21 (m, 2H), 7.33-7.39 (m, 2H), 7.42-7.55 (m, 5H), 10.57 (s, 1H).

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Example 1-151

[0559] MS ESI m/e: 497, 499 (M+H), 495, 497 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.73-0.79 (m, 2H), 1.01-1.09 (m, 2H), 2.61 (s, 3H), 2.68-2.71 (m, 1H), 5.65 (s, 1H), 7.19 (d, J=9.0Hz, 1H), 7.40-7.52 (m, 6H), 7.73 (t, J=9.0Hz, 1H), 10.67 (brs, H).

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Example 1-152

[0560] MS ESI m/e: 497, 499 (M+H), 495, 497 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.72-0.79 (m, 2H), 1.01-1.09 (m, 2H), 2.60 (s, 3H), 2.62-2.72 (m, 1H), 5.37 (s, 1H), 7.42-7.52 (m, 7H), 7.73 (d, J=12.0Hz, 1H), 10.55 (brs, H).

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Example 1-153

[0561] MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.81-1.17 (m, 6H), 2.29-2.35 (m, 1H), 2.58 (s, 3H), 5.50 (s, 1H), 7.29 (d, J=6.0Hz, 2H), 7.39-7.52 (m, 5H), 7.61 (d, J=9.0Hz, 2H), 10.56 (brs, H).

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Example 1-154

[0562] MS ESI m/e: 445 (M+H), 443 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.84-0.93 (m, 2H), 1.16-1.24 (m, 2H), 2.26 (s, 3H), 2.74-2.80 (m, 1H), 2.80 (s, 3H), 3.81 (s, 3H), 5.27 (s, 1H), 6.73-6.84 (m, 2H), 7.14 (d, J=9.0Hz, 1H), 7.30-7.35 (m, 2H), 7.39-7.52 (m, 3H), 9.94 (brs, 1H).

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Example 1-155

[0563] MS ESI m/e: 444 (M+H), 442 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.71-0.79 (m, 2H), 1.00-1.10 (m, 2H), 2.60 (s, 3H), 2.64-2.76 (m, 1H), 2.76 (brs, 6H), 5.51 (brs, 1H), 7.09-7.58 (m, 8H), 10.46 (brs, 1H).

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Example 1-156

[0564] MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.92 (m, 2H), 1.15-1.25 (m, 2H), 2.29 (s, 3H), 2.73-2.85 (m, 1H), 2.8T (s, 3H), 5.41 (s, 1H), 7.16 (d, J=8.4Hz, 1H), 7.30-7.39 (m, 3H), 7.40-7.53 (m, 4H), 10.13 (s, 1H)

Example 1-157

[0565] MS ESI m/e: 495 (M+H), 491, 493 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.91 (m, 2H), 1.14-1.24 (m, 2H), 2.40 (s, 3H), 2.71-2.82 (m, 1H), 2.82 (s, 3H), 5.81 (s, 1H), 6.99 (dd, J=2.6, 8.4Hz, 1H), 7.17 (d, J=2.6Hz, 1H), 7.28-7.36 (m, 2H), 7.39-7.57 (m, 4H), 10.37 (s, 1H).

Example 1-158

[0566] MS ESI m/e: 454 (M+H), 452 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.80 (m, 2H), 1.01-1.09 (m, 2H), 2.55 (s, 3H), 2.63-2.72 (m, 1H), 3.85 (s; 3H), 4.71 (s, 1H), 6.48 (d, J=3.0Hz, 1H), 6.97 (d, J=15.0Hz, 1H), 7.06 (t, J=9.0Hz, 1H), 7.29 (d, J=3.0Hz, 1H), 7.41-7.56 (m, 6H), 10.37 (brs, H)

Example 1-159

[0567] MS ESI m/e: 509, 511 (M+H), 507, 509 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.61-0.79 (m, 2H), 0.96-1.08 (m, 2H), 2.61 (s, 3H), 2.61-2.74 (m, 1H), 3.77 (s, 3H), 5.49 (s, 1H), 7.07 (t, J=6.0Hz, 1H), 7.20 (d, J=12.0Hz, 1H), 7.29 (d, J=9.0Hz, 2H), 7.38 (d, J=6.0Hz, 1H), 7.48 (t, J=9.0Hz, 1H), 7.60 (d, J=9.0Hz, 2H), 10.60 (brs, H).

Example 1-160

[0568] MS ESI m/e: 455 (M+H), 453 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.85-0.93 (m, 2H), 1.15-1.26 (m, 2H), 2.74-2.84 (m, 1H), 2.81 (s, 3H), 3.88 (s, 3H), 5.65 (s, 1H), 7.22-7.29 (m, 1H), 7.30-7.37 (m, 2H), 7.37-7.54 (m, 4H), 7.70 (d, J=1.8Hz, 1H), 7.90 (s, 1H), 10.36 (s, 1H).

Example 1-161

[0569] MS ESI m/e: 455 (M+H), 453 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.85-0.94 (m, 2H), 1.15-1.26 (m, 2H), 2.74-2.84 (m, 1H), 2.82 (s, 3H), 4.10 (s, 3H), 5.65 (s, 1H), 7.28-7.37 (m, 3H), 7.39-7.54 (m, 4H), 7.60-7.64 (m, 1H), 7.95-7.98 (m, 1H), 10.36 (s, 1H).

Example 1-162

[0570] MS ESI m/e: 437 (M+H), 435 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.83-0.91 (m, 2H), 1.15-1.24 (m, 2H), 2.73-2.81 (m, 1H), 2.81 (s, 3H), 5.49 (s, 1H), 6.88-6.98 (m, 2H), 7.28-7.38 (m, 3H), 7.39-7.52 (m, 3H), 10.15 (s, 1H).

Example 1-163

[0571] MS ESI m/e: 469, 471 (M+H), 467, 469 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.83-0.90 (m, 2H), 1.16-1.24 (m, 2H), 2.74-2.81 (m, 1H), 2.82 (s, 3H), 5.70 (s, 1H), 7.24-7.34 (m, 3H), 7.39-7.52 (m, 5H), 10.50 (s, 1H).

Example 1-164

[0572] MS ESI m/e: 485, 487 (M+H), 483; 485 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 1.30 (t, J=7.1Hz, 3H), 2.82 (s, 3H), 4.08 (q, J=7.0Hz, 2H), 5.66 (s, 1H), 7.28-7.39 (m, 5H), 7.41-7.53 (m, 3H), 10.48 (s, 1H).

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Example 1-165

[0573] MS ESI m/e: 440 (M+H), 438 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.81 (m, 2H), 1.00-1.10 (m, 2H), 2.58 (s, 3H), 2.62-2.78 (m, 1H), 5.28 (s, 1H) 6.46 (s, 1H), 7.01 (d, J=9.0Hz, 1H), 7.40-7.68 (m, 8H), 10.37 (brs, H), 11.22 (brs, H).

Example 1-166

[0574] MS ESI m/e: 527, 529 (M+H), 525, 52-7 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.81 (m, 2H), 0.99-1.09 (m, 2H), 2.63 (s, 3H), 2.66-2.75 (m, 1H), 3.79 (s, 3H), 5.34 (s, 1H), 7.09 (t, J=7.5Hz, 1H), 7.23 (d, J=9.0Hz, 1H), 7.40 (d, J=6.0Hz, 1H), 7.43-7.54 (m, 3H), 7.73 (d, J=9.0Hz, 1H), 10-58 (brs, H).

Example 1-167

[0575] MS ESI m/e: 468 (M+H), 466 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.94 (m, 2H), 1.14-1.26 (m, 2H), 1.49 (t, J=7.4Hz, 3H), 2.72-2.84 (m, 1H), 2.81 (s, 3H), 4.19 (q, J=7.3Hz, 2H), 5.68 (s, 1H), 6.4,7 (d, J=3.0Hz, 1H), 7.10 (dd, J=1.9, 8.6Hz, 1H), 7.16 (d, J=3.0Hz, 1H), 7.29-7.38 (m, 3H), 7.38-7.55 (m, 4H), 10.27 (brs, 1H).

Example 1-168

[0576] MS ESI m/e: 433 (M+H), 431 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.75-0.90 (m, 2H), 1.10-1.25 (m, 2H), 2.37 (s, 3H), 2.77 (m, 1H), 2.81 (s, 3H), 5.59 (s, 1H), 6.90-7.05 (m, 2H), 7.25 (t, J=8.3Hz, 1H), 7.30-7.35 (m, 2H), 7.40-7.50 (m, 3H), 10.16 (s, 1H).

Example 1-169

[0577] MS ESI m/e: 438 (M+H), 436 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.75-0.85 (m, 2H), 1.10-1.25 (m, 2H), 2.50-2.55 (m, 4H), 2.65-2.80 (m, 3H), 2.80 (s, 3H), 3.26 (q, J=5.8Hz, 2H), 3.70-3.80 (m, 4H), 5.37 (s, 1H), 7.25-7.35 (m, 2H), 7.35-7.50 (m, 3H), 8.90 (brs, 1H).

Example 1-170

[0578] MS ESI m/e: 477 (M+H), 475 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.92 (m, 2H), 1.15-1.26 (m, 2H), 1.76 (d, J=12.8Hz, 6H), 2.72-2.82 (m, 1H), 2.84 (s, 3H), 5.99 (s, 1H), 7.29-7.36 (m, 2H), 7.39-7.56 (m, 5H), 7.70-7.82, (m, 2H), 10.67 (s, 1H).

Example 1-171

[0579] MS ESI m/e: 453 (M+H), 451 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.68-0.79 (m, 2H), 0.98-1.09 (m, 2H), 2.58 (s, 3H), 2.61-2.71 (m, 1H), 5.32 (s, 1H), 7.34-7.63 (m, 8H), 10.52 (brs, H).

Example 1-17.2

[0580] MS ESI m/e: 417 (M+H), 415 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.68-0.78 (m, 2H), 0.97-1.06 (m, 2H), 2.55 (s, 3H), 2.61-2.69 (m, 1H), 5.19 (s, 1H), 6.82 (d, J=9.0Hz, 2H), 7.08 (d, J=6.0Hz, 2H), 7.39-7.50 (m, 5H), 9.53 (brs, H), 10.18 (brs, H).

Example 1-173

[0581] MS ESI m/e: 419 (M+H), 417 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.71-2.80 (m, 2H), 1.01-1.09 (m, 2H), 2.60 (s, 3H), 2.64-2.72 (m, 1H) 5.34 (s, 1H), 7.28-7.54 (m, 9H), 10.53 (brs, H).

Example 1-174

[0582] MS ESI m/e: 437 (M+H), 435 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.78 (m, 2H), 0.96-1.08 (m, 2H), 2.57 (s, 3H), 2.61-2.72 (m, 1H), 4.84 (s, 1H), 7.24-7.52 (m, 8H), 10.15 (brs, ..H) .

Example 1-175

[0583] MS ESI m/e: 449 (M+H), 447 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.83-0.92 (m, 2H), 1.15-1.24 (m, 2H), 2.72-2.81 (m, 1H), 2.81 (s, 3H), 3.82 (s, 3H), 5.46 (d, J=1.6Hz, 1H), 6.69-6.79 (m, 2H), 7.19-7.29 (m, 1H), 7.29-7.36 (m, 2H), 7.39-7.54 (m, 3H), 10.01 (brs, 1H).

Example 1-176

[0584] MS ESI m/e: 513, 515 (M+H), 511, 513 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.91 (m, 2H), 1.16-1.24 (m, 2H), 2.75-2.82 (m, 1H), 2.82 (s, 3H), 5.73 (s, 1H), 7.30-7.36 (m, 2H), 7.38-7.53 (m, 4H), 7.41 (d, J=1.8Hz, 1H), 7.66 (d, J=1.8Hz, 1H), 10.53 (brs, 1H).

Example 1-177

[0585] MS ESI m/e: 507, 509 (M+H), 505, 507 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.85-0.89 (m, 2H), 1.17-1.22 (m, 2H), 1.23 (t, J=7.5,Hz, 3H), 2.63 (q, J=7.5Hz, 2H), 2.74-2.79 (m, 1H), 2.80 (s, 3H), 5.40 (s, 1H), 7.15 (d, J=8.4Hz, 1H), 7.29-7.36 (m, 3H), 7.40-7.51 (m, 4H), 10.11 (brs, 1H).

Example 1-178

[0586] MS ESI m/e: 459 (M+H), 457 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.73-0.79 (m, 2H), 1.00-1.09 (m, 2H), 2.63 (s, 3H), 2.65-2.72 (m, 1H), 3.86 (s, 3H), 5.84 (s, 1H), 7.42-7.56 (m, 6H), 7.99-8.03 (m, 2H), 10.96 (brs, 1H).

Example 1-17.9

[0587] MS ESI m/e: 383 (M+H).

¹H-NMR (CDCl₃, 300MHz) δ 0.79-0.87 (m, 2H), 1.12-1.21 (m, 2H), 2.69-2.76 (m, 1H), 2.80 (s, 3H), 3.36 (q, J=5.4Hz, 2H), 3.44 (s, 3H), 3.66 (t, J=5.4Hz, 2H), 5.39 (s, 1H), 7.23-7.31 (m, 2H), 7.37-7.51 (m, 3H) 8.80-8.88 (m, 1H).

Example 1-180

[0588] MS ESI m/e: 422 (M+H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.65-0.74 (m, 2H), 0.95-1.05 (m, 2H), 1.42-1.56 (m, 2H), 1.88-1.98 (m, 2H), 2.10-2.21 (m, 2H), 2.18 (s, 3H), 2.55 (s, 3H), 2.58-2.70 (m, 3H), 3.33-3.44 (m, 1H), 5.23 (s, 1H), 7.34-7.41 (m, 2H), 7.42-7.53 (m, 3H), 8.77-8.84 (m, 1H).

Example 1-181

[0589] MS ESI m/e: 365 (M+H).

¹H-NMR (CDCl₃, 300MHz) δ 0.59-0.67 (m, 2H), 0.77-0.89 (m, 4H), 1.11-1.21 (m, 2H), 2.42-2.50 (m, 1H), 2.66-2.76 (m, 1H), 2.81 (s, 3H), 5.81 (s, 1H), 7.24-7.28 (m, 1H), 7.29-7.31 (m, 1H), 7.37-7.51 (m, 3H), 8.68 (brs, 1H).

Example 1-182

[0590] MS ESI m/e: 450 (M+H).

¹H-NMR (CDCl₃, 300MHz) δ 0.77-0.86 (m, 2H), 1.01-1.12 (m, 6H), 1.12-1.21 (m, 2H), 1.54-1.74 (m, 2H), 2.03-2.15 (m, 2H), 2.25-2.41 (m, 2H), 2.66-2.76 (m, 1H), 2.79 (s, 3H), 2.82-2.94 (m, 2H), 3.25-3.41 (m, 1H), 5.40 (s, 1H), 7.25-7.28 (m, 1H), 7.29-7.32 (m, 1H), 7.37-7.51 (m, 3H), 8.71-8.79 (m, 1H).

Example 1-183

[0591] MS ESI m/e: 509, 511 (M+H), 507, 509 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.90 (m, 2H), 1.13-1.24 (m, 2H), 2.71-2.81 (m, 2H), 2.85 (s, 3H), 3.84 (s, 3H), 5.78 (s, 1H), 6.93-7.00 (m, 2H), 7.13-7.19 (m, 2H), 7.19-7.23 (m, 2H), 7.47-7.53 (m, 2H), 10.42 (brs, 1H).

Example 1-184

[0592] MS ESI m/e: 410 (M+H).

¹H-NMR (CDCl₃, 300MHz) δ 0.75-0.88 (m, 2H), 1.09-1.22 (m, 2H), 1.85 (tt, J=7.0, 14.0Hz, 2H), 2.26 (s, 6H), 2.40 (t, J=7.1Hz, 2H), 2.67-2.77 (m, 1H), 2.79 (s, 3H), 3.22 (dt, J=5.5, 6.2Hz, 3H), 5.40 (s, 1H) 7.25-7.33 (m, 2H), 7.37-7.52 (m, 3H), 8.74 (t, J=4.8Hz, 1H).

Example 1-185

[0593] MS ESI m/e: 471, 473 (M+H), 469, 471 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 2.62 (s, 3H), 3.27 (s, 3H), 5.37 (s, 1H), 7.40-7.60 (m, 7H), 7.70-7.80 (m, 1H), 10.61 (s, 1H).

Example 1-186

[0594] MS ESI m/e: 527, 529 (M+H), 525, 527 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.90 (m, 2H), 1.13-1.24 (m, 2H), 2.71-2.82 (m, 1H), 2.85 (s, 3H), 3.84 (s, 3H), 5.64 (d, J=1.1Hz, 1H), 6.94-7.01 (m, 2H), 7.17-7.24 (m, 2H), 7.29-7.33 (m, 2H), 7.34-7.40 (m, 1H), 10.35 (brs, 1H).

Example 1-187

[0595] MS ESI m/e: 459 (M+H), 457 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.92 (m, 2H), 1.13-1.24 (m, 2H), 1.35 (d, J=6.0Hz, 6H), 2.72-2.82 (m, 1H), 2.81 (s, 3H), 4.54 (sept, J=6.0Hz, 1H), 5.63 (s, 1H), 6.85-6.94 (m, 2H), 7.12-7.20 (m, 2H), 7.29-7.35 (m, 2H), 7.38-7.53 (m, 3H), 10.15 (brs, 1H).

Example 1-188

[0596] MS ESI m/e: 513, 515 (M+H), 511, 513 (M-K).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.79 (m, 2H), 0.99-1.08 (m, 2H), 2.62-2.72 (m, 1H), 2.66 (s, 3H), 5.35 (d, J=1.1Hz, 1H), 6.79-6.89 (m, 2H), 7.15-7.23 (m, 2H), 7.43-7.55 (m, 2H), 7.70-7.76 (m, 1H), 9.90 (brs, 1H), 10.57 (brs, 1H).

Example 1-189

[0597] MS ESI m/e: 509, 511 (M+H), 507, 509 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.90 (m, 2H), 1.14-1.25 (m, 2H), 2.73-2.80 (m, 1H), 2.82 (s, 3H), 3.89 (s, 3H), 5.80 (s, 1H), 7.07-7.13 (m, 2H), 7.23-7.35 (m, 3H), 7.39-7.53 (m, 3H), 10.29 (brs, 1H).

Example 1-190

[0598] MS ESI m/e: 509, 511 (M+H), 507, 509 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.08 (m, 2H), 2.67 (s, 3H), 2.66-2.68 (m, 1H), 3.78 (s, 3H), 5.53 (s, 1H), 6.97-7.06 (m, 3H), 7.31 (d, J=9.0Hz, 2H), 7.41 (dd, J=9.0, 9.0Hz, 1H), 7.62 (d, J=9.0Hz, 2H), 10.58 (brs, H).

Example 1-191

[0599] MS ESI m/e: 527, 529 (M+H), 525, 527 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 1.01-1.09 (m, 2H), 2.67 (s, 3H), 2.66-2.67 (m, 1H), 3.78 (s, 3H), 5.37 (s, 1H), 6.97-7.06 (m, 3H), 7.39-7.51 (m, 3H), 7.73 (d, J=12.0Hz, 1H), 10.55 (brs, H).

Example 1-192

[0600] MS ESI m/e: 462 (M+H).

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$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.08 (m, 2H), 2.55 (s, 3H), 2.60-2.71 (m, 1H), 2.92 (s, 6H), 5.01 (s, 1H), 6.56-6.66 (m, 2H), 7.18 (dd, $J=12.0, 9.0\text{Hz}$, 1H), 7.39-7.51 (m, 5H), 10.00 (brs, H).

Example 1-193

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[0601] MS ESI m/e: 582, 584 (M+H), 580, 582 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.75 (m, 2H), 1.03 (m, 2H), 2.60-2.75 (m, 1H), 2.69 (s, 3H), 3.11 (brs, 4H), 3.73 (brs, 4H), 5.38 (s, 1H), 6.85 (d, $J=7.6\text{Hz}$, 1H), 7.02 (brs, 2H), 7.34 (t, $J=8.5\text{Hz}$, 1H), 7.40-7.55 (m, 2H), 7.73 (d, $J=11.1\text{Hz}$, 1H), 10.57 (s, 1H).

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Example 1-194

[0602] MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.80-0.89 (m, 2H), 1.12-1.23 (m, 2H), 2.68-2.80 (m, 1H), 2.79 (s, 3H), 4.37 (d, $J=6.0\text{Hz}$, 2H), 5.33 (s, 1H), 7.18-7.33 (m, 4H), 7.39-7.52 (m, 5H), 9.14 (t, $J=5.6\text{Hz}$, 1H).

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Example 1-195

[0603] MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.79-0.89 (m, 2H), 1.12-1.22 (m, 2H), 2.68-2.76 (m, 1H), 2.78 (s, 3H), 4.34 (d, $J=5.6\text{Hz}$, 2H), 5.34 (s, 1H), 7.20-7.31 (m, 4H), 7.39-7.53 (m, 5H), 9.11 (t, $J=5.3\text{Hz}$, 1H).

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Example 1-196

MS ESI m/e: 493, 495 (M+H) 491, 493 (M-H).

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[0604] $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.79-0.89 (m, 2H), 1.12-1.22 (m, 2H), 2.69-2.77 (m, 1H), 2.79 (s, 3H), 4.46 (d, $J=5.6\text{Hz}$, 2H), 5.36 (s, 1H), 7.17 (dt, $J=1.9, 7.5\text{Hz}$, 1H), 7.24-7.33 (m, 3H), 7.35 (dt, $J=1.1, 7.7\text{Hz}$, 1H), 7.39-7.51 (m, 3H), 7.59 (dd, $J=1.1, 7.9\text{Hz}$, 1H), 9.16 (t, $J=5.7\text{Hz}$, 1H).

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Example 1-197.

[0605] MS ESI m/e: 445 (M+H), 443 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.83-0.92 (m, 2H), 1.14-1.25 (m, 2H), 2.72-2.83 (m, 1H), 2.80 (s, 3H), 3.11 (s, 6H), 5.44 (s, 1H), 6.53 (d, $J=9.0\text{Hz}$, 1H), 7.29-7.34 (m, 2H), 7.37 (dd, $J=2.6, 9.0\text{Hz}$, 1H), 7.39-7.52 (m, 3H), 8.07 (d, $J=2.6\text{Hz}$, 1H), 9.96 (brs, 1H).

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Example 1-198

[0606] MS ESI m/e: 495, 497 (M+H), 493, 495 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.69-0.78 (m, 2H), 0.98-1.08 (m, 2H), 2.59 (s, 3H), 2.61-2.72 (m, 1H), 5.50 (s, 1H), 7.04 (dd, $J=2.3, 8.3\text{Hz}$, 1H), 7.13 (d, $J=2.3\text{Hz}$, 1H), 7.30 (d, $J=8.3\text{Hz}$, 1H), 7.38-7.55 (m, 5H), 10.45 (s, 1H), 10.48 (brs, 1H).

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Example 1-199.

[0607] MS ESI m/e: 540, 542 (M+H), 538, 540 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.82-0.91 (m, 2H), 1.14-1.23 (m, 2H), 2.71-2.82 (m, 1H), 2.93 (s, 3H), 2.96 (s, 6H), 5.66 (s, 1H), 6.52 (t, $J=2.1\text{Hz}$, 1H), 6.59 (dd, $J=1.9, 8.3\text{Hz}$, 1H), 6.71 (dd, $J=2.6, 8.6\text{Hz}$, 1H), 7.26-7.40 (m, 4H), 10.39 (brs, 1H).

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Example 1-200

[0608] MS ESI m/e: 487, 489 (M+H), 485, 487(M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 2.62 (s, 3H), 3.27 (s, 3H), 5.47 (s, 1H), 7.40-7.60 (m, 6H), 7.63 (dd, $J=2.1, 8.6\text{Hz}$, 1H), 7.91 (d, $J=2.1\text{Hz}$, 1H), 10.83 (s, 1H).

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Example 1-201

[0609] MS ESI m/e: 569, 571 (M+H), 567, 569 (M-H).

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¹H-NMR (DMSO-d₆, 300MHz) δ 0.75 (m, 2H), 1.03 (m, 2H), 2.45-2.60 (m, 2H), 2.60 (s, 3H), 2.67 (m, 1H), 2.85 (t, J=7.4Hz, 2H), 5.36 (s, 1H), 7.24 (d, J=7.9Hz, 1H), 7.32, (brs, 2H), 7.41 (t, J=7.9Hz, 1H), 7.45-7.55 (m, 2H), 7.73 (d, J=9.2Hz, 1H), 10.54 (s, 1H), 12.15 (brs, 1H).

5 Example 1-202

[0610] MS ESI m/e: 499, 501 (M+H), 497, 499 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.74-0.82 (m, 2H), 0.98-1.06 (m, 2H), 2.63-2.70 (m, 1H), 5.74 (s, 1H), 7.25-7.33 (m, 2H), 7.38-7.55 (m, 4H), 7.63 (dd, J=2.2, 8.8Hz, 1H), 7.92 (d, J=2.2Hz, 1H), 10.90 (brs, 1H), 11.14 (brs, 1H).

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Example 1-203

[0611] MS ESI m/e: 482 (M+H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.77-0.79 (m, 2H), 1.02-1.17 (m, 2H), 2.18 (s, 3H), 2.34 (s, 3H), 2.57 (s, 3H), 2.65-2.68 (m, 1H), 3.66 (s, 3H), 5.24 (s, 1H), 6.98 (d, J=6.0Hz, 1H), 7.29 (d, J=3.0Hz, 1H), 7.40-7.56. (m, 6H), 10.35 (brs, H).

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Example 1-204

[0612] MS ESI m/e: 468 (M+H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.80 (m, 2H), 1.00-1.09 (m, 2H), 2.41 (s, 3H), 2.57 (s, 3H), 2.62-2.71 (m, 1H), 3.68 (s, 3H), 5.26 (s, 1H), 6.23 (s, 1H), 6.97 (d, J=12.0Hz, 1H), 7.33 (s, 1H), 7.42-7.52 (m, 6H), 10.35 (brs, H).

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Example 1-205

[0613] MS ESI m/e: 547 (M+H), 545 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.86 (m, 2H), 1.18 (m, 2H), 2.75 (m, 1H), 2.89 (s, 3H), 2.97 (s, 6H), 3.16 (t, J=4.8Hz, 4H), 3.85 (t, J=4.8Hz, 4H), 5.45 (s, 1H), 6.45 (s, 1H), 6.49 (d, J=3.8Hz, 1H), 6.75-6.80 (m, 2H), 6.91 (d, J=8.3Hz, 1H), 7.14 (t, J=9.0Hz, 1H), 7.33 (t, J=8.4Hz, 1H), 9.89 (s, 1H).

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30 Example 1-206

[0614] MS ESI m/e: 595, 597 (M+H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.77 (m, 2H), 0.98-1.07 (m, 2H), 2.21 (s, 3H), 2.40-2.46 (m, 4H), 2.61-2.71 (m, 1H), 2.69 (s, 3H), 3.09-3.16 (m, 4H), 5.37 (s, 1H), 6.79-6.84 (m, 1H), 6.96-7.03 (m, 2H), 7.29-7.34 (m, 1H), 7.44-7.54 (m, 2H), 7.69-7.77 (m, 1H), 10.58 (brs, 1H).

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Example 1-207

[0615] MS ESI m/e: 545 (M+H), 543 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.92 (m, 2H), 1.14-1.25 (m, 2H), 2.72-2.82 (m, 1H), 2.82 (s, 3H), 5.69 (d, J=1.1Hz, 1H), 7.28-7.36 (m, 2H), 7.40-7.59 (m, 6H), 10.36 (s, 1H).

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Example 1-208

[0616] MS ESI m/e: 443 (M+H), 441 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.81-0.91 (m, 2H), 1.16-1.23 (m, 2H), 2.73-2.80 (m, 1H), 2.82 (s, 3H), 3.12 (s, 1H), 5.80 (s, 1H), 7.26-7.33 (m, 3H), 7.35-7.52 (m, 5H), 10.50 (s, 1H).

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Example 1-209

[0617] MS ESI m/e: 416 (M+H), 414 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.79-0.88 (m, 2H), 1.12-1.22 (m, 2H), 2.68-2.77 (m, 1H), 2.79 (s, 3H), 4.42 (d, J=5.6Hz, 2H), 5.37 (s, 1H), 7.26-7.35 (m, 3H), 7.38-7.52 (m, 3H), 7.65-7.72 (m, 1H), 8.57 (dd, J=1.5, 4.9Hz, 1H), 8.63 (d, J=1.9Hz, 1H), 9.15 (t, J=5.3Hz, 1H).

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Example 1-210

[0618] MS ESI m/e: 511, 513 (M+H), 509, 511 (M-H).

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¹H-NMR (CDCl₃, 300MHz) δ 0.80-0.90 (m, 2H), 1.13-1.23 (m, 2H), 2.70-2.78 (m, 1H), 2.79 (s, 3H) 4.43 (d, J=6.0Hz, 2H), 5.33 (s, 1H), 6.98 (dd, J=9.0, 9.1Hz, 1H), 7.28-7.33 (m, 2H), 7.35-7.53 (m, 5H), 9.12 (t, J=6.0Hz, 1H).

Example 1-211

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[0619] MS ESI m/e: 509, 511 (M+H), 507, 509 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.92 (m, 2H), 1.14-1.25 (m, 2H), 2.73-2.84 (m, 1H), 2.81 (s, 3H), 3.83 (s, 3H), 5.46 (s, 1H), 6.89 (dd, J=3.0, 8.7Hz, 1H), 7.21 (d, J=2.6Hz, 1H), 7.29-7.36 (m, 3H), 7.38-7.54 (m, 3H), 10.17 (brs, 1H).

10 Example 1-212

[0620] MS ESI m/e: 580, 581 (M+H), 578, 580 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.87 (m, 2H), 1.18 (m, 2H), 2.20 (m, 2H), 2.63 (t, J=8.1Hz, 2H), 2.77 (m, 1H), 2.88 (s, 3H), 3.88 (t, J=7.1Hz, 2H), 5.66 (s, 1H), 7.07 (d, J=7.9Hz, 1H), 7.30-7.35 (m, 2H), 7.37 (d, J=9.2Hz, 1H), 7.46 (t, J=8.1Hz, 1H), 7.54 (d, J=8.6Hz, 1H), 7.89 (d, J=2.0Hz, 1H), 10.34 (s, 1H).

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Example 1-213

[0621] MS ESI m/e: 513, 515 (M+H), 511, 513 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.09 (m, 2H), 2.68 (s, 3H), 2.61-2.71 (m, 1H), 5.35 (s, 1H), 2.79-2.89 (m, 3H), 7.27 (dd, J=9.0, 9.0Hz, 1H), 7.48-7.52 (m, 2H), 7.72 (d, J=6.0Hz, 1H), 9.83 (brs, H), 10.53 (brs, H).

Example 1-214

25 **[0622]** MS ESI m/e: 594, 596 (M+H), 592, 594 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.75 (m, 2H), 1.03 (m, 2H), 1.85 (brs, 4H), 2.39 (m, 2H), 2.67 (m, 4H), 3.62 (m, 2H), 5.36 (s, 1H), 7.33 (d, J=8.3Hz, 1H), 7.35-7.40 (m, 2H), 7.45-7.55 (m, 3H), 7.74 (d, J=10.2Hz, 1H), 10.54 (s, 1H).

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Example 1-215

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[0623] MS ESI m/e: 566, 568 (M+H), 564, 566 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.80 (m, 2H), 0.99-1.11 (m, 2H), 1.90-2.01 (m, 4H), 2.64-2.74 (m, 1H), 2.74-2.75 (m, 1H), 3.13-3.27 (m, 4H), 5.39 (s, 1H), 6.54-6.65 (m, 3H), 7.20-7.30 (m, 1H), 7.45-7.55 (m, 2H), 7.71-7.78 (m, 1H), 10.60 (brs, 1H).

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Example 1-216

[0624] MS ESI m/e: 580, 582 (M+H), 578, 580 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.78 (m, 2H), 0.98-1.08 (m, 2H), 1.48-1.65 (m, 6H), 2.63-2.71 (m, 1H), 2.69 (s, 3H), 3.09-3.17 (m, 4H), 5.37 (s, 1H), 6.72-6.79 (m, 1H), 6.95-7.02 (m, 2H), 7.25-7.32 (m, 1H), 7.46-7.54 (m, 2H), 7.69-7.77 (m, 1H), 10.59 (brs, 1H).

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Example 1-217

45 **[0625]** MS ESI m/e: 476 (M+H), 474 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.80 (m, 2H), 1.01-1.13 (m, 5H), 2.58 (s, 3H), 2.61-2.72 (m, 1H), 2.90 (s, 3H), 3.42 (q, J=2.0Hz, 2H), 5.04 (s, 1H), 6.62 (dd, J=9.0, 15.0Hz, 2H), 7.18 (t, J=9.0Hz, 1H), 7.40-7.59 (m, 5H), 10.01 (brs, 1H).

Example 1-218

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[0626] MS ESI m/e: 584, 586 (M+H), 582, 584 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.78 (m, 2H), 0.98-1.09 (m, 2H), 2.18 (s, 6H), 2.59 (t, J=3.0Hz, 2H), 2.66 (s, 3H), 2.65-2.66 (m, 1H), 4.01 (t, J=4.5Hz, 2H), 5.37 (s, 1H), 6.96-7.08 (m, 3H), 7.38-7.51 (m, 3H), 7.71 (d, J=12.0Hz, 1H), 10.55 (brs, 1H).

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Example 1-219

[0627] MS ESI m/e: 596, 598 (M+H), 594, 596 (M-H).

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$^2\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.75 (m, 2H), 1.03 (m, 2H), 2.67 (s, 4H), 3.75 (m, 2H), 3.98 (t, $J=4.9\text{Hz}$, 2H), 4.21 (s, 2H), 5.36 (s, 1H), 7.37 (d, $J=7.3\text{Hz}$, 1H), 7.40-7.60 (m, 5H), 7.73 (d, $J=9.4\text{Hz}$, 1H), 10.53 (s, 1H).

Example 1-220

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[0628] MS ESI m/e : 571, 573 (M+H), 569, 571 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.74-0.76 (m, 2H), 0.99-1.10 (m, 2H), 2.65-2.67 (m, 1H), 2.66 (s, 3H), 4.71 (s, 2H), 5.37 (s, 1H), 6.99-7.08 (m, 3H), 7.41 (t, $J=9.0\text{Hz}$, 1H), 7.45-7.52 (m, 2H), 7.74 (d, $J=9.0\text{Hz}$, 1H), 10.55 (brs, 1H), 13.04 (brs, 1H).

10 Example 1-221

[0629] MS ESI m/e : 527 (M+H), 525 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.81-0.91 (m, 2H), 1.14-1.25 (m, 2H), 2.71-2.82 (m, 1H), 2.82 (s, 3H), 5.82 (s, 1H), 7.01-7.09 (m, 2H), 7.28-7.35 (m, 2H), 7.39-7.54 (m, 3H), 7.66-7.74 (m, 2H), 10.42 (s, 1H).

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Example 1-222

[0630] MS ESI m/e : 425 (M+H), 423 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.81-0.91 (m, 2H), 1.15-1.24 (m, 2H), 2.71-2.83 (m, 1H), 2.83 (s, 3H), 3.09 (s, 1H), 5.92 (s, 1H), 7.22-7.29 (m, 2H), 7.29-7.35 (m, 2H), 7.40-7.57 (m, 5H), 10.54 (s, 1H)

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Example 1-223

[0631] MS ESI m/e : 575, 577 (M+H), 573, 575 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.84-0.91 (m, 2H), 1.17-1.26 (m, 2H), 2.73-2.80 (m, 1H), 2.81 (s, 3H), 3.11 (s, 3H), 5.65 (s, 1H), 7.27-7.35 (m, 2H), 7.35-7.40 (m, 1H), 7.51-7.56 (m, 1H), 7.68-7.75 (m, 1H), 8.00-8.05 (m, 2H), 10.22 (s, 1H).

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Example 1-224

[0632] MS ESI m/e : 604, 606 (M+H), 602, 604 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.82-0.91 (m, 2H), 1.15-1.27 (m, 2H), 2.72-2.81 (m, 1H), 2.76 (s, 6H), 2.81 (s, 3H), 5.65 (d, $J=1.1\text{Hz}$, 1H), 7.29-7.34 (m, 2H), 7.35-7.43 (m, 1H), 7.45-7.51 (m, 1H), 7.63-7.72 (m, 1H), 7.83-7.89 (m, 2H), 10.25 (s, 1H).

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Example 1-225

[0633] MS ESI m/e : 575, 577 (M+H), 573, 575 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 0.82-0.91 (m, 2H), 1.16-1.27 (m, 2H), 2.72-2.83 (m, 1H), 2.83 (brs, 3H), 3.10 (s, 3H), 5.63 (brs, 1H), 7.28-7.35 (m, 2H), 7.36-7.42 (m, 1H), 7.58 (d, $J=8.4\text{Hz}$, 2H), 8.10 (d, $J=8.4\text{Hz}$, 2H), 10.22 (s, 1H).

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Example 1-226

[0634] MS ESI m/e : 604, 606 (M+H), 602, 604 (M-H).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 0.83-0.91 (m, 2H), 1.17-1.25 (m, 2H), 2.71-2.81 (m, 1H), 2.75 (s, 6H), 2.84 (brs, 3H), 5.58 (brs, 1H), 7.26-7.35 (m, 2H), 7.35-7.40 (m, 1H), 7.52 (d, $J=8.1\text{Hz}$, 2H), 7.89 (d, $J=8.1\text{Hz}$, 2H), 10.21 (s, 1H).

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Example 1-227

[0635] MS ESI m/e : 598, 600 (M+H), 596, 598 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.70-0.78 (m, 2H), 0.99-1.09 (m, 2H), 1.84 (t, $J=6.0\text{Hz}$, 2H), 2.13 (s, 6H), 2.34 (t, $J=6.0\text{Hz}$, 2H), 2.66-2.68 (m, 1H), 2.67 (s, 3H), 4.00 (t, $J=6.0\text{Hz}$, 2H), 5.37 (s, 1H), 6.96-7.09 (m, 3H), 7.40 (dd, $J=6.0, 6.0\text{Hz}$, 1H), 7.48-7.51 (m, 2H), 7.74 (d, $J=9.0\text{Hz}$, 1H), 10.56 (brs, 1H).

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Example 1-228

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[0636] MS ESI m/e : 604, 606 (M+H), 602, 604 (M-H).

$^1\text{H-NMR}$ (DMSO-d_6 , 300MHz) δ 0.71-0.80 (m, 2H), 0.98-1.10 (m, 2H), 2.61-2.71 (m, 1H), 2.68 (s, 3H), 2.96 (s, 3H), 3.25 (s, 3H), 5.37 (s, 1H), 7.39 (d, $J=6.0\text{Hz}$, 1H), 7.45-7.58 (m, 5H), 7.74 (d, $J=9.0\text{Hz}$, 1H), 10.53 (brs, 1H).

Example 1-229

[0637] MS ESI m/e: 443 (M+H), 441 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.90 (m, 2H), 1.14-1.24 (m, 2H), 1.27 (d, J=7.1Hz, 6H), 2.72-2.81 (m, 1H), 2.81 (s, 3H), 2.92 (sept, J=6.8Hz, 1H), 5.77 (s, 1H), 7.16-7.22 (m, 2H), 7.22-7.28 (m, 2H), 7.29-7.35 (m, 2H), 7.39-7.53 (m, 3H), 10.28 (brs, 1H).

Example 1-230

[0638] MS ESI m/e: 429 (M+H), 427 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.91 (m, 2H), 1.15-1.24 (m, 2H), 1.25 (t, J=7.5Hz, 3H), 2.66 (q, J=7.5Hz, 2H), 2.72-2.81 (m, 1H), 2.81 (s, 3H), 5.76 (s, 1H), 7.15-7.24 (m, 4H), 7.29-7.36 (m, 2H), 7.39-7.53 (m, 3H), 10.29. (brs, 1H).

Example 1-231

[0639] MS ESI m/e: 426 (M+H), 424 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.90 (m, 2H), 1.15-1.25 (m, 2H), 2.72-2.82 (m, 1H), 2.84 (s, 3H), 6.07 (s, 1H), 7.28-7.34 (m, 2H), 7.36-7.42 (m, 2H), 7.44-7.55 (m, 3H) 7.64-7.70 (m, 2H), 10.84 (brs., 1H).

Example 1-232

[0640] MS ESI m/e: 626, 628 (M+H), 624, 626 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 1.01-1.09 (m, 2H), 2.41-2.48 (m, 4H), 2.67 (s, 3H), 2.64-2.70 (m, 3H), 3.45-3.60 (m, 4H), 4.06-4.10 (m, 2H), 5.36 (s, 1H), 7.00 (d, J=3.0Hz, 1H), 7.03-7.05 (m, 2H), 7.38-7.53 (m, 3H), 7.72 (d, J=6.0Hz, 1H), 10.54 (brs, 1H).

Example 1-233

[0641] MS ESI m/e: 610, 612 (M+H), 608, 610 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 1.00-1.09 (m, 2H), 1.62-1.71 (m, 4H), 2.43-2.55 (m, 4H), 2.64 (s, 3H), 2.61-2.70 (m, 1H), 2.77 (t, J=3.0Hz, 2H), 4.06 (t, J=3.0Hz, 2H), 5.37 (s, 1H), 6.99 (d, J=3.0Hz, 1H), 7.02-7.04 (m, 2H), 7.39 (dd, J=3.0, 3.0Hz, 1H), 7.50-7.52 (m, 2H), 7.74 (d, J=3.0Hz, 1H) 10.54 (brs, 1H).

Example 1-234

[0642] MS ESI m/e: 624, 626 (M+H), 622, 624 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 1.01-1.09 (m, 2H), 1.32-1.41 (m, 2H), 1.41-1.52 (m, 4H), 2.37-2.46 (m, 4H), 2.60-2.71 (m, 3H), 2.67 (s, 3H), 4.07 (t, J=6.0Hz, 2H), 5.38 (s, 1H), 7.01 (dd, J=6.0, 9.0Hz, 1H), 7.05-7.06 (m, 2H), 7.40 (dd, J=9.0, 9.0Hz, 1H), 7.49-7.51 (m, 2H), 7.74 (d, J=12.0Hz, 1H), 10.55 (brs, 1H)

Example 1-235

[0643] MS ESI m/e: 612, 614 (M+H), 610, 612 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 0.96 (t, J=7.5Hz, 6H), 0.99-1.09 (m, 2H), 2.46-2.59 (m, 5H), 2.68 (s, 3H), 2.75 (t, J=3.0Hz, 2H), 4.00 (t, J=3.0Hz, 2H), 5.37 (s, 1H), 7.00 (dd, J=3.0, 3.0Hz, 1H), 7.01-7.06 (m, 2H), 7.40, (dd, J=6.0, 3.0Hz, 1H), 7.49-7.52 (m, 2H), 7.74 (d, J=18.0Hz, 1H), 10.56 (brs, 1H).

Example 1-236

[0644] MS ESI m/e: 653, 655 (M+H), 651, 653 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 0.96 (t, J=7.5Hz, 6H), 0.99-1.09 (m, 2H), 1.80-1.91 (m, 2H), 2.13 (s, 3H), 2.46-2.59 (m, 10H), 2.60-2.73 (m, 4H), 4.00 (t, J=3.0Hz, 2H), 5.37 (s, 1H), 7.00 (dd, J=3.0, 3.0Hz, 1H), 7.01-7.06 (m, 2H), 7.40 (dd, J=6.0, 3.0Hz, 1H), 7.49-7.52 (m, 2H), 7.74 (d, J=18.0Hz, 1H), 10.56 (brs, 1H).

Example 1-237

[0645] MS ESI m/e: 444 (M+H), 442 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.92 (m, 2H), 1.16-1.26 (m, 2H), 2.73-2.83 (m, 1H), 2.85 (s, 3H), 6.01 (s, 1H), 7.29-7.35

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(m, 2H), 7.43-7.56 (m, 5H), 7.60-7.70 (m, 1H), 10.93 (s, 1H).

Example 1-238

5 **[0646]** MS ESI m/e: 473 (M+H), 471 (M-H).
¹H-NMR (DMSO-d₆, 400MHz) δ 0.71-0.79 (m, 2H), 1.00-1.08 (m, 2H), 2.60 (s, 3H), 2.63-2.71 (m, 1H), 4.31 (d, J=5.8Hz, 2H), 5.38 (t, J=5.9Hz, 1H), 5.50 (s, 1H), 7.29-7.35 (m, 1H), 7.39-7.58 (m, 7H), 10.71 (s, 1H).

Example 1-239

10 **[0647]** MS ESI m/e: 501 (M+H), 499 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 0.82-0.90 (m, 2H), 1.15-1.24 (m, 2H), 1.63 (s, 6H), 2.07 (s, 1H), 2.73-2.81 (m, 1H), 2.82 (s, 3H), 5.78 (s, 1H), 7.16-7.25 (m, 2H), 7.28-7.33 (m, 2H), 7.34-7.52 (m, 4H), 10.46 (s, 1H).

15 Example 1-240

[0648] MS ESI m/e: 445 (M+H), 443 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 0.84-0.90 (m, 2H), 1.16-1.24 (m, 2H), 2.73-2.82 (m, 1H), 2.82 (s, 3H), 5.31 (d, J=10.9Hz, 1H), 5.74 (d, J=17.6Hz, 1H), 5.72 (s, 1H), 6.66 (dd, J=10.9, 17.8Hz, 1H), 7.14-7.25 (m, 2H), 7.28-7.39 (m, 3H), 7.40-7.51 (m, 3H), 10.34 (s, 1H).

Example 1-241

25 **[0649]** MS ESI m/e: 487 (M+H), 485 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.91 (m, 2H), 1.15-1.24 (m, 2H), 2.73-2.83 (m, 1H), 2.83 (s, 3H), 3.47 (s, 3H), 4.33 (s, 2H), 5.79 (s, 1H), 7.22-7.35 (m, 4H), 7.35-7.56 (m, 4H), 10.49 (s, 1H)

Example 1-242

30 **[0650]** MS ESI m/e: 447 (M+H), 445 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 0.84-0.90 (m, 2H), 1.15-1.22 (m, 2H), 1.25 (t, J=7.6Hz, 3H), 2.66 (q, J=7.6Hz, 2H), 2.73-2.81 (m, 1H), 2.81 (s, 3H), 5.59 (d, J=1.2Hz, 1H), 6.96-7.04 (m, 2H), 7.23-7.34 (m, 3H), 7.39-7.51 (m, 3H), 10.16 (s, 1H).

Example 1-243

35 **[0651]** MS ESI m/e: 555, 557 (M+H), 553, 555 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.92 (m, 2H), 1.14-1.25 (m, 2H), 1.43 (t, J=4.9Hz, 1H), 1.88 (quint, J=7.3Hz, 2H), 2.72-2.81 (m, 1H), 2.76 (t, J=7.7Hz, 2H), 2.82 (s, 3H), 3.65 (q, J=5.7Hz, 2H), 5.66 (s, 1H), 7.10-7.19 (m, 2H), 7.26-7.33 (m, 3H), 7.35-7.45 (m, 2H), 10.34 (brs, 1H).

Example 1-244

40 **[0652]** MS ESI m/e: 486, 488 (M+H), 484, 486 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 1.19 (t, J=6.0Hz, 3H), 2.50-2.53 (m, 1H), 2.62 (s, 3H), 3.95 (q, J=7.0Hz, 2H), 5.37 (s, 1H), 7.48-7.52 (m, 2H), 7.60 (dd, J=3.0, 3.0Hz, 1H), 7.74 (d, J=12.0Hz, 1H), 7.97 (d, J=6.0Hz, 1H), 8.73 (d, J=45.0Hz, 1H), 10.58 (brs, 1H).

Example 1-245

50 **[0653]** MS ESI m/e: 554, 556 (M+H), 552, 554 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.79 (m, 2H), 0.99-1.09 (m, 2H), 2.04 (s, 3H), 2.63-2.68 (m, 1H), 2.66 (s, 3H), 5.35 (s, 1H), 7.08 (d, J=9.0Hz, 1H), 7.41 (dd, J=6.0, 6.0Hz, 1H), 7.49-7.51 (m, 2H), 7.61-7.77 (m, 3H), 10.18 (brs, 1H), 10.54 (brs, 1H).

55 Example 1-246

[0654] MS ESI m/e: 500 (M+H), 498 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.91 (m, 2H), 1.14-1.25 (m, 2H), 2.38 (s, 6H), 2.72-2.83 (m, 1H), 2.83 (s, 3H), 3.48

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(s, 2H), 5.77 (d, J=0.7Hz, 1H), 7.20-7.55 (m, 8H) 10.45 (s, 1H).

Example 1-247

5 **[0655]** MS ESI m/e: 489 (M+H), 487 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.81 (m, 2H), 0.99-1.10 (m, 2H), 2.61 (s, 3H), 2.64-2.74 (m, 1H), 5.57 (s, 1H), 6.58 (d, J=16.1Hz, 1H), 7.40-7.64 (m, 8H), 7.81 (d, J=12.1Hz, 1H), 10.80 (s, 1H), 12.44 (brs, 1H).

Example 1-248

10 **[0656]** MS ESI m/e: 491 (M+H), 48.9 (M-H).
¹H-NMR (DMSO-d₆, 400MHz) δ 0.72-0.78 (m, 2H), 0.99-1.07 (m, 2H), 2.59 (t, J=7.6Hz, 2H), 2.58 (s, 3H), 2.63-2.70 (m, 1H), 2.86 (t, J=7.5Hz, 2H), 5.25 (d, J=1.2Hz, 1H), 7.12-7.17 (m, 1H), 7.24-7.30 (m, 1H), 7.35-7.54 (m, 6H), 10.40 (s, 1H), 12.18 (s, 1H).

Example 1-249

15 **[0657]** MS ESI m/e: 447 (M+H), 445 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.79 (m, 2H), 0.99-1.07 (m, 2H), 2.59 (s, 3H), 2.63-2.70 (m, 1H), 5.45 (s, 1H),
20 7.25-7.30 (m, 2H), 7.31-7.37 (m, 2H), 7.41-7.55 (m, 5H), 10.49 (brs, 1H).

Example 1-250

25 **[0658]** MS ESI m/e: 501 (M+H), 499 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.78 (m, 2H), 1.00-1.08 (m, 2H), 2.62 (s, 1H), 2.66-2.71 (m, 1H), 5.76 (s, 1H),
7.41-7.55 (m, 7H), 7.76 (d, J=8.3Hz, 2H), 10.86 (brs, 1H)

Example 1-251

30 **[0659]** MS ESI m/e: 458 (M+H), 456 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.72-0.82 (m, 2H), 0.99-1.09 (m, 2H), 2.58 (s, 3H), 2.63-2.74 (m, 1H), 5.13 (d, J=1.1Hz, 1H),
6.45-6.50 (m, 1H), 7.33-7.61 (m, 8H), 10.28 (brs, 1H), 11.28 (brs, 1H).

Example 1-252

35 **[0660]** MS ESI m/e: 582, 584 (M+H), 580, 582 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.91 (m, 2H), 1.14-1.25 (m, 2H), 1.76-1.90 (m, 2H), 2.26-2.38 (m, 2H), 2.26 (brs, 6H),
2.65-2.73 (m, 2H), 2.74-2.80 (m, 1H), 2.83 (s, 3H), 5.65 (d, J=0.7Hz, 1H), 7.10-7.16 (m, 2H), 7.24-7.29 (m, 1H), 7.30-7.34
40 (m, 2H), 7.34-7.44 (m, 2H), 10.34 (brs, 1H).

Example 1-253

[0661] MS ESI m/e: 584, 586 (M+H), 582, 584 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.90 (m, 2H), 1.15-1.23 (m, 2H), 2.73-2.80 (m, 1H), 2.93 (s, 3H), 2.97 (s, 3H), 3.34
45 (s, 3H), 3.44-3.56 (m, 4H), 5.66 (d, J=1.1Hz, 2H), 6.55-6.60 (m, 2H), 6.70-6.76 (m, 1H), 7.22-7.40 (m, 4H), 10.39 (brs, 1H).

Example 1-254

[0662] MS ESI m/e: 457 (M+H), 455 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 0.82-0.89 (m, 2H), 1.15-1.23 (m, 2H), 2.06 (s, 3H), 2.72-2.80 (m, 1H), 2.82 (s, 3H), 5.74
50 (s, 1H), 7.14-7.21 (m, 2H), 7.28-7.36 (m, 3H), 7.39-7.51 (m, 3H), 10.38 (s, 1H).

Example 1-255

55 **[0663]** MS ESI m/e: 624, 626 (M+H), 622, 624 (M-H).
¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.91 (m, 2H), 1.13-1.24 (m, 2H), 1.74-1.90 (m, 2H), 2.28-2.38 (m, 2H), 2.38-2.46 (m,
4H), 2.65-2.72 (m, 2H), 2.73-2.80 (m, 1H), 2.83 (s, 3H), 3.68-3.74 (m, 4H), 5.65 (d, J=1.1Hz, 1H), 7.10-7.17 (m, 2H),
7.23-7.28 (m, 1H), 7.29-7.33 (m, 2H), 7.34-7.44 (m, 2H), 10.33 (brs, 1H).

Example 1-256

[0664] MS ESI m/e: 549 (M+H), 547 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.66-0.77 (m, 2H), 0.89-1.05 (m, 2H), 2.54-2.61 (m, 1H), 2.56 (s, 3H), 7.36-7.45 (m, 4H), 7.53-7.63 (m, 3H), 7.65-7.71 (m, 2H), 12.88 (brs, 1H).

Example 1-257

[0665] MS ESI m/e: 638 (M+H), 636 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.74 (m, 2H), 1.03 (m, 2H), 2.65 (s, 4H), 3.02 (s, 3H), 5.38 (s, 1H), 7.13 (d, J=8.6Hz, 1H), 7.20-7.40 (m, 3H), 7.46 (t, J=8.1Hz, 1H), 7.63 (d, J=9.3Hz, 1H), 7.81 (d, J=10.1Hz, 1H), 10.00 (s, 1H), 10.54 (s, 1H).

Example 1-258

[0666] MS ESI m/e: 461 (M+H), 459 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.91 (m, 2H), 0.96 (t, J=7.3Hz, 3H), 1.14-1.25 (m, 2H), 1.58-1.72 (m, 2H), 2.60 (t, J=7.7Hz, 2H), 2.72-2.82 (m, 1H), 2.82 (s, 3H), 5.61 (d, J=1.1Hz, 1H), 6.94-7.04 (m, 2H), 7.24-7.36 (m, 3H), 7.41-7.53 (m, 3H), 10.18 (s, 1H).

Example 1-259

[0667] MS ESI m/e: 521 (M+H), 519 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.92 (m, 2H), 1.17-1.27 (m, 2H), 2.72-2.82 (m, 1H), 2.82 (s, 3H), 3.12 (s, 3H), 3.14 (s, 1H), 5.80 (d, J=0.7Hz, 1H), 7.28-7.36 (m, 2H), 7.37-7.45 (m, 1H), 7.51-7.57 (m, 1H), 7.68-7.77 (m, 1H), 8.01-8.07 (m, 2H), 10.40 (s, 1H).

Example 1-260

[0668] MS ESI m/e: 536 (M+H), 534 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.82-0.93 (m, 2H), 1.29-1.28 (m, 2H), 2.71-2.81 (m, 1H), 2.89 (s, 3H), 3.10 (s, 3H), 3.15 (s, 1H), 5.82 (s, 1H), 6.81-6.88 (m, 1H), 7.08 (d, J=9.0Hz, 1H), 7.21-7.39 (m, 3H), 7.39-7.51 (m, 2H), 10.49 (brs, H).

Example 1-261

[0669] MS ESI m/e: 499, 501 (M+H).

¹H-NMR (CDCl₃, 300MHz) δ 1.30 (t, J=7.0Hz, 3H), 3.63 (s, 3H), 4.13 (q, J=7.0Hz, 2H), 5.57 (s, 2H), 5.78 (s, 1H), 7.20-7.50 (m, 8H), 10.33 (s, 1H).

Example 1-262

[0670] MS ESI m/e: 604, 606 (M+H), 602, 604 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.78 (m, 2H), 0.99-1.07 (m, 2H), 1.18 (t, J=7.5Hz, 3H), 2.61-2.70 (m, 4H), 3.13 (q, J=7.0Hz, 2H), 5.35 (s, 1H), 7.08-7.14 (m, 1H), 7.25-7.34 (m, 2H), 7.41-7.54 (m, 3H), 7.71-7.77 (m, 1H), 10.04 (brs, 1H), 10.53 (s, 1H).

Example 1-263

[0671] MS ESI m/e: 570, 572 (M+H), 568, 570 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.07 (m, 2H), 2.63-2.73 (m, 1H), 2.66 (s, 3H), 3.99 (d, J=6.0Hz, 2H), 5.36 (s, 1H), 5.65 (t, J=6.0Hz, 1H), 7.10-7.15 (m, 1H), 7.39-7.52 (m, 3H), 7.71-7.85 (m, 3H), 9.91 (brs, 1H), 10.54 (brs, 1H).

Example 1-264

[0672] MS ESI m/e: 512, 514 (M+H), 510, 512 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.77 (m, 2H), 0.97-1.08 (m, 2H), 2.62-2.71 (m, 1H), 2.74 (s, 3H), 5.35 (d, J=1.5Hz, 1H), 5.38 (brs, 2H), 6.47-6.53 (m, 1H), 6.54-6.57 (m, 1H), 6.58-6.63 (m, 1H), 7.11 (t, J=7.9Hz, 1H), 7.44-7.53 (m, 2H), 7.70-7.77 (m, 1H), 10.55 (brs, 1H).

Example 1-265

[0673] MS ESI m/e: 459 (M+H), 457 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.66-0.74 (m, 2H), 0.83-0.91 (m, 2H), 0.97-1.06 (m, 2H), 1.14-1.24 (m, 2H), 1.85-1.96 (m, 1H), 2.72-2.81 (m, 1H), 2.81 (s, 3H), 5.58 (d, J=1.1Hz, 1H), 6/82-6.92 (m, 2H), 7.21-7.29 (m, 1H), 7.29-7.36 (m, 2H), 7.39-7.53 (m, 3H), 10.16 (s, 1H).

Example 1-266

[0674] MS ESI m/e: 584, 586 (M+H), 582, 584 (M-H).

¹H-NMR. (DMSO-d₆, 300MHz) δ 0.71-0.78, (m, 2H), 0.9-1.08 (m, 2H), 2.63-2.71 (m, 1H), 2.66 (s, 3H), 3.32 (s, 3H), 3.37 (s, 3H), 4.00 (brs, 2H), 5.36 (d, J=0.8Hz, 1H), 7.10-7.16 (m, 1H), 7.40-7.52 (m, 3H), 7.71-7.80 (m, 3H), 10.00 (brs, 1H), 10.54 (brs, 1H).

Example 1-267

[0675] MS ESI m/e: 658, 660 (M+H), 656, 658 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.70-0.79 (m, 2H), 0.99-1.10 (m, 2H), 2.62-2.76 (m, 1H), 2.66 (s, 3H), 4.48-4.64 (m, 2H), 5.36 (s, 1H), 7.17 (d, J=9.0Hz, 1H), 7.28-7.33 (m, 2H), 7.43-7.52 (m, 3H), 7.74 (d, J=12.0Hz, 1H), 10.52 (brs, 1H), 10.72 (brs, 1H).

Example 1-268

[0676] MS ESI m/e: 554 (M+H), 552 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.833-0.92 (m, 2H), 1.14-1.24 (m, 2H), 1.26 (t, J=7.7Hz, 3H), 1.37 (t, J=7.3Hz, 3H), 2.67 (q, J=7.6Hz, 2H), 2.71-2.81 (m, 1H), 2.85 (s, 3H), 3.17 (q, J=7.5Hz, 2H), 5.60 (d, J=1.1Hz, 1H), 6.94-7.08 (m, 4H), 7.22-7.33 (m, 3H), 7.38-7.47 (m, 1H), 10.15 (s, 1H).

Example 1-269

[0677] MS ESI m/e: 541, 543 (M+H), 539, 541 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.98-1.10 (m, 2H), 2.60 (s, 3H), 2.62-2.71 (m, 1H), 5.37 (d, J=1.1Hz, 1H), 7.43-7.57 (m, 2H), 7.61-7.78 (m, 3H), 7.95-8.05 (m, 2H), 10.54 (brs, 1H), 13.34 (brs, 1H).

Example 1-270

[0678] MS ESI m/e: 540, 542 (M+H), 538, 540 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.80 (m, 2H), 0.98-1.09 (m, 2H), 2.61 (s, 3H), 2.63-2.74 (m, 1H), 5.38 (s, 1H), 7.45-7.58 (m, 3H), 7.58-7.65 (m, 2H), 7.70-7.78 (m, 1H), 7.90 (brs, 1H), 7.94-8.00 (m, 1H), 8.11 (brs, 1H), 10.54 (brs, 1H).

Example 1-271

[0679] MS ESI m/e: 618, 620 (M+H), 616, 618 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.77 (m, 2H), 0.92 (t, J=7.5Hz, 3H), 1.00-1.07 (m, 2H), 1.66 (q, J=7.0Hz, 2H), 2.62-2.70 (m, 4H), 3.05-3.13 (m, 2H), 5.36 (s, 1H), 7.09-7.13 (m, 1H), 7.23-7.32 (m, 2H), 7.41-7.53 (m, 3H), 7.71-7.77 (m, 1H), 10.05 (brs, 1H), 10.53 (s, 1H).

Example 1-272

[0680] MS ESI m/e: 618, 620 (M+H), 616, 618 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.78 (m, 2H), 0.99-1.08 (m, 2H), 1.23 (d, J=6.0Hz, 6H), 2.62-2.70 (m, 4H), 3.19-3.29 (m, 1H), 5.36 (s, 1H), 7.07-7.13 (m, 1H), 7.26-7.34 (m, 2H), 7.39-7.54 (m, 3H), 7.71-7.76 (m, 1H), 10.00 (brs, 1H), 10.53 (s, 1H).

Example 1-273

[0681] MS ESI m/e: 469 (M+H), 467 (M-1).

¹H-NMR (CDCl₃, 300MHz) δ 0.80-0.90 (m, 2H), 1.10-1.30 (m, 2H), 2.78 (m, 1H), 2.83 (s, 3H), 5.97 (s, 1H), 7.30-7.35

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(m, 2H), 7.35-7.55 (m, 5H) 7.65 (d, J=8.5Hz, 2H), 10.67 (s, 1H).

Example 1-274

5 **[0682]** MS ESI m/e: 652 (M+H), 650 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.98-1.08 (m, 2H), 1.17 (t, J=7.3Hz, 3H), 2.61-2.71 (m, 1H), 2.64 (s, 3H), 3.13 (q, J=7.3Hz, 2H), 5.38 (brs, 1H), 7.09-7.15 (m, 2H), 7.24-7.38 (m, 3H), 7.40-7.49 (m, 1H), 7.60-7.67 (m, 1H), 7.81 (dd, J=1.8, 9.9Hz, 1H), 10.04 (s, 1H).

10 Example 1-275

[0683] MS ESI m/e: 540 (M+H), 538 (M-H).
¹H-NMR (CDCl₃, 400MHz) δ 0.83-0.91 (m, 2H), 1.15-1.23 (m, 2H), 1.26 (t, J=7.6Hz, 3H), 2.67 (q, J=7.6Hz, 2H), 2.72-2.80 (m, 1H), 2.85 (s, 3H), 3.05 (s, 3H), 5.60 (d, J=1.2Hz, 1H), 6.98-7.05 (m, 2H), 7.05-7.10 (m, 1H), 7.23-7.31 (m, 4H),
15 7.40-7.47 (m, 1-H), 10.16 (s, 1H).

Example 1-276

[0684] MS ESI m/e: 653, 655 (M+H).
20 ¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.87 (t, J=7.2Hz, 3H), 1.00-1.08 (m, 2H), 1.22-1.36 (m, 2H), 1.43-1.54 (m, 2H), 2.15 (t, J=7.3Hz, 2H), 2.63-2.72 (m, 1H) 2.66 (s, 3H), 3.86 (d, J=5.3Hz, 2H), 5.36 (s, 1H), 7.05-7.12 (m, 1H), 7.40-7.52 (m, 3H), 7.61-7.77 (m, 3H), 8.08-8.15 (m, 1H), 10.20 (brs, 1H), 10.54 (brs, 1H).

Example 1-277

25 **[0685]** MS ESI m/e: 597, 599 (M+H), 595, 597 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.78 (m, 2H), 0.99-1.07 (m, 2H), 2.28 (s, 6H), 2.64-2.70 (m, 1H), 2.67 (s, 3H), 3.09 (brs, 2H), 5.36 (d, J=1.1Hz, 1H), 7.10-7.14 (m, 1H), 7.40-7.52 (m, 3H), 7.71-7.79 (m, 3H), 9.97 (brs, 1H), 10.54 (brs, 1H).

30 Example 1-278

[0686] MS ESI m/e: 568, 570 (M+H), 566, 568 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.78 (m, 2H), 0.99-1.11 (m, 5H), 2.33 (q, J=7.0Hz, 2H), 2.63-2.71 (m, 4H), 5.36 (s, 1H), 7.04-7.10 (m, 1H), 7.42 (t, J=7.5Hz, 1H), 7.46-7.54 (m, 2H), 7.61-7.67 (m, 1H), 7.70-7.77 (m, 2H), 10.08 (s, 1H),
35 10.54 (s, 1H).

Example 1-279

[0687] MS ESI m/e: 582, 584 (M+H), 580, 582 (M-H).
40 ¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.78 (m, 2H), 0.91 (t, J=7.5Hz, 3H), 0.99-1.07 (m, 2H), 1.60 (q, J=8.0Hz, 2H), 2.29 (t, J=7.5Hz, 2H), 2.63-2.71 (m, 4H), 5.36 (s, 1H), 7.42 (t, J=7.5Hz, 1H), 7.46-7.54 (m, 2H), 7.62-7.76 (m, 3H), 10.09 (s, 1H), 10.54 (s, 1H).

Example 1-280

45 **[0688]** MS ESI m/e: 644, 646 (M+H), 642, 644 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.68-0.80 (m, 2H), 0.97-1.08 (m, 2H), 2.61-2.72 (m, 1H), 2.64 (s, 3H), 5.36 (d, J=0.7Hz, 1H), 6.88-7.01 (m, 1H), 7.05-7.17 (m, 2H), 7.23-7.34 (m, 1H), 7.47 (dd, J=2.3, 8.7Hz, 1H), 7.52 (t, J=8.1Hz, 1H), 7.73 (dd, J=1.5, 10.2Hz, 1H), 10.56 (brs, 1H).

50 Example 1-281

[0689] MS ESI m/e: 485 (M+H), 483 (M-H).
¹H-NMR (-CDCl₃, 300MHz) δ 0.71-0.81 (m, 2H), 1.00-1.10 (m, 2H), 2.60 (s, 3H), 2.61-2.72 (m, 1H), 5.52 (s, 1H), 7.41-7.56 (m, 9H), 10.62 (brs, 1H).

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Example 1-282

[0690] MS ESI m/e : 624, 626 (M+H), 622, 624 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.71-0.81 (m, 2H), 0.97-1.10 (m, 2H), 2.61-2.72 (m, 1H), 2.65 (s, 3H), 5.07 (s, 2H), 5.36 (s, 1H), 7.19 (d, J=9.0Hz, 1H), 7.28-7.38 (m, 2H), 7.42-7.56 (m, 3H), 7.74 (d, J=9.0Hz, 1H), 10.53 (brs, 1H), 10.64 (brs, 1H).

Example 1-283

[0691] MS ESI m/e: 526, 528 (M+H), 524, 526 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.71-0.79 (m, 2H), 0.99-1.09 (m, 2H), 2.66 (d, J=6.0Hz, 3H), 2.64-2.67 (m, 1H), 2.74 (s, 3H), 5.36 (s, 1H), 5.92-5.98 (m, 1H), 6.50-6.60 (m, 3H), 7.19 (t, J=7.5Hz, 1H), 7.49-7.54 (m, 2H), 7.74 (d, J=12.0Hz, 1H), 10.57 (brs, 1H).

Example 1-284

[0692] MS ESI m/e: 652, 654 (M+H), 650, 652 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.68-0.80 (m, 2H), 0.99-1.09 (m, 2H), 2.33 (s, 3H), 2.61-2.70 (m, 1H), 5.35 (s, 1H), 7.04 (d, J=12.0Hz, 1H), 7.13 (d, J=6.0Hz, 1H), 7.30-7.38 (m, 2H), 7.49-7.62 (m, 5H), 7.73-7.80 (m, 3H), 10.48 (brs, 1H), 10.52 (brs, 1H).

Example 1-285

[0693] MS ESI m/e : 465 (M+H), 463 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.78 (m, 2H), 1.01-1.07 (m, 2H), 2.53 (s, 3H), 2.59 (s, 3H), 2.64-2.72 (m, 1H), 5.25 (d, J=1.1Hz, 1H), 7.17 (dd, J=1.9, 8.7Hz, 1H), 7.32 (dd, J=1.9, 11.3Hz, 1H), 7.39-7.55 (m, 6H), 10.41 (brs, 1H).

Example 1-286.

[0694] MS ESI m/e: 558 (M+H), 556 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.78 (m, 2H), 0.99-1.07 (m, 2H), 2.53 (s, 3H), 2.63-2.69 (m, 1H), 2.65 (s, 3H), 3.02 (s, 3H), 5.25 (d, J=1.1Hz, 1H), 7.11-7.19 (m, 2H), 7.24-7.35 (m, 3H), 7.39-7.50 (m, 2H), 9.99 (brs, 1H), 10.39 (brs, 1H).

Example 1-287

[0695] MS ESI m/e: 582, 584 (M+H), 580, 582 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.78 (m, 2H), 0.99-1.12 (m, 8H), 2.53-2.70 (m, 5H), 5.36 (s, 1H), 7.05-7.11 (m, 1H), 7.42 (t, J=7.5Hz, 1H), 7.46-7.55 (m, 2H), 7.62-7.68 (m, 1H), 7.70-7.77 (m, 2H), 10.05 (s, 1H), 10.54 (s, 1H).

Example 1-288

[0696] MS ESI m/e: 576, 578 (M+H), 574, 576 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.80 (m, 2H), 1.00-1.08 (m, 2H), 2.60-2.70 (m, 4H), 5.37 (s, 1H), 7.47-7.58 (m, 4H), 7.65-7.77 (m, 3H), 7.88-7.93 (m, 2H), 10.52 (s, 1H).

Example 1-289

[0697] MS ESI m/e: 550 (M+H), 548 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.78 (m, 2H), 0.99-1.09 (m, 2H), 1.18 (t, J=7.3Hz, 3H), 2.63-2.71 (m, 1H), 2.66 (s, 3H), 3.13 (q, J=7.5Hz, 2H), 4.32 (s, 1H), 5.51 (s, 1H), 7.09-7.15 (m, 1H), 7.24-7.35 (m, 2H), 7.36-7.41 (m, 1H), 7.41-7.49 (m, 1H), 7.50-7.61 (m, 2H), 10.04 (s, 1H), 10.72 (s, 1H).

Example 1-290

[0698] MS ESI m/e: 518 (M+H), 516 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 0.71-0.78 (m, 2H), 1.00-1.08 (m, 2H), 2.61-2.71 (m, 1H), 2.66 (s, 3H), 3.03 (s, 3H), 4.19 (s, 1H), 5.64 (s, 1H), 7.11-7.16 (m, 1H), 7.24-7.29 (m, 1H), 7.30-7.37 (m, 3H), 7.43-7.49 (m, 1H), 7.51-7.56 (m, 2H), 10.01 (s, 1H), 10.70 (s, 1H).

Example 1-291

[0699] MS ESI m/e: 483 (M+H), 481 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.80 (m, 2H), 0.98-1.10 (m, 2H), 2.60 (s, 3H), 2.62-2.73 (m, 1H), 3.68 (q, J=11.6Hz, 2H), 5.54 (s, 1H), 7.30-7.38 (m, 2H), 7.39-7.56 (m, 7H), 10.60 (brs, 1H).

Example 1-292

[0700] MS ESI m/e: 554, 556 (M+H), 552, 554 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.81 (m, 2H), 0.98-1.09 (m, 2H), 2.60 (s, 3H), 2.63-2.71 (m, 1H), 2.79 (d, J=4.5Hz, 3H), 5.38 (d, J=1.1Hz, 1H), 7.45-7.55 (m, 2H), 7.57-7.65 (m, 2H), 7.71-7.77 (m, 1H), 7.884-7.89 (m, 1H), 7.89-7.95 (m, 1H), 8.57 (q, J=5.3Hz, 1H), 10.53 (brs, 1H).

Example 1-293

[0701] MS ESI m/e: 447 (M+H), 445 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.80 (m, 2H), 0.99-1.08 (m, 2H), 2.59 (s, 3H), 2.62-2.73 (m, 1H), 3.00 (dt, J=25.2, 6.0Hz, 2H), 4.67 (dt, J=47.1, 6.4Hz, 2H), 5.46 (s, 1H), 7.23-7.29 (m, 2H), 7.33-7.39 (m, 2H), 7.40-7.56 (m, 5H), 10.51 (brs, 1H).

Example 1-294

[0702] MS ESI m/e: 590, 592 (M+H), 588, 590 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 1.00-1.09 (m, 2H), 2.42 (s, 3H), 2.58-2.70 (m, 4H), 5.37 (s, 1H), 7.45-7.54 (m, 2H), 7.70-7.80 (m, 3H), 7.82-7.88 (m, 2H), 10.51 (s, 1H).

Example 1-295

[0703] MS ESI m/e: 604, 606 (M+H), 602, 604 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.79 (m, 2H), 0.96 (t, J=6.0Hz, 3H), 1.01-1.08 (m, 2H), 2.58-2.71 (m, 4H), 2.74-2.84 (m, 2H), 5.37 (s, 1H), 7.46-7.55 (m, 2H), 7.69-7.79 (m, 4H), 7.84-7.90 (m, 2H), 10.51 (s, 1H).

Example 1-296

[0704] MS ESI m/e: 504 (M+H), 502 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.91 (m, 2H), 1.12-1.23 (m, 2H), 1.26 (t, J=7.5Hz, 3H), 2.16 (s, 3H), 2.66 (q, J=7.6Hz, 2H), 2.72-2.82 (m, 1H), 2.86 (s, 3H), 5.59 (d, J=1.5Hz, 1H), 6.95-7.08 (m, 3H), 7.22-7.32 (m, 1H), 7.33-7.55 (m, 3H), 7.70 (s, 1H), 10.18 (s, 1H).

Example 1-297

[0705] MS ESI m/e: 602 (M+H), 600 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.68-0.79 (m, 2H), 0.98-1.09 (m, 2H), 2.04 (s, 3H), 2.63-2.71 (m, 1H), 2.66 (s, 3H), 5.38 (d, J=1.5Hz, 1H), 7.04-7.10 (m, 1H), 7.29-7.38 (m, 1H), 7.38-7.46 (m, 1H), 7.60-7.72 (m, 3H), 7.81 (dd, J=1.8, 10.2Hz, 1H), 10.15 (s, 1H), 10.55 (s, 1H).

Example 1-298

[0706] MS ESI m/e: 532 (M+H), 530 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.80 (m, 2H), 0.98-1.09 (m, 2H), 1.18 (t, J=7.3Hz, 3H), 2.61-2.72 (m, 1H), 2.65 (s, 3H), 3.13 (q, J=7.5Hz, 2H), 4.18 (s, 1H), 5.65 (s, 1H), 7.08-7.15 (m, 1H), 7.24-7.31 (m, 1H), 7.31-7.38 (m, 3H), 7.41-7.49 (m, 1H), 7.51-7.57 (m, 2H), 10.04 (s, 1H), 10.70 (s, 1H).

Example 1-299

[0707] MS ESI m/e: 667, 669 (M+H), 665, 667 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.77 (m, 2H), 0.83 (t, J=7.4Hz, 3H), 0.98-1.07 (m, 2H), 1.19-1.29 (m, 2H), 1.39-1.49 (m, 2H), 2.04 (t, J=7.5Hz, 2H), 2.95-2.53 (m, 2H), 2.63-2.70 (m, 1H), 2.66 (s, 3H), 3.27-3.35 (m, 2H), 5.35 (d, J=1.1Hz,

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1H), 7.05-7.11 (m, 1H), 7.42 (t, J=8.1Hz, 1H), 7.47-7.52 (m, 2H), 7.60-7.67 (m, 1H), 7.70-7.77 (m, 2H), 7.87-7.94 (m, 1H), 10.17 (brs, 1H), 10.54 (brs, 1H).

Example 1-300

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[0708] MS ESI m/e: 457 (M+H), 455 (M-1).

¹H-NMR (CDCl₃, 300MHz) δ 0.80-0.90 (m, 2H), 1.10-1.30 (m, 2H), 1.34 (s, 9H), 2.77 (m, 1H), 2.81 (s, 3H), 5.79 (s, 1H), 7.20 (d, J=8.5Hz, 2H), 7.30-7.35 (m, 2H), 7.35-7.55 (m, 5H), 10.29 (s, 1H).

10 Example 1-301

[0709] MS ESI m/e: 580 (M+H), 578 (M-1).

15 ¹H-NMR (DMSO-d₆, 300MHz) δ 0.75 (brs, 2H), 1.05 (m, 2H), 2.68 (s, 4H), 3.03 (s, 3H), 3.32 (s, 3H), 5.68 (s, 1H), 7.15 (d, J=8.9Hz, 1H), 7.27 (d, J=8.1Hz, 1H), 7.47 (t, J=8.0Hz, 1H), 7.64 (d, J=8.4Hz, 1H), 7.75-7.90 (m, 2H), 10.01 (s, 1H), 10.95 (s, 1H).

Example 1-302

[0710] MS ESI m/e: 620 (M+H), 618 (M-H).

20 ¹H-NM (DMSO-d₆, 400MHz) δ 0.71-0.78 (m, 2H), 0.99-1.07 (m, 2H), 2.62-2.69 (m, 1H), 2.65 (s, 3H), 3.02 (s, 3H), 5.54 (s, 1H), 7.10-7.19 (m, 3H), 7.23-7.28 (m, 1H), 7.29-7.32 (m, 1H), 7.42-7.49 (m, 1H), 7.74-7.80 (m, 2H), 10.00 (s, 1H), 10.57 (s, 1H).

Example 1-303

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[0711] MS ESI m/e: 625, 627 (M+H), 623, 625 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.78 (m, 2H), 0.99-1.09 (m, 2H), 2.34-2.56 (m, 6H), 2.61-2.71 (m, 1H), 2.74 (s, 3H), 3.08-3.19 (m, 2H), 3.50-3.62 (m, 4H), 5.36 (s, 1H), 5.77 (brs, 1H), 6.53-6.70 (m, 3H), 7.18 (dd, J=9.0, 6.0Hz, 1H), 7.40-7.50 (m, 2H), 7.74 (d, J=9.0Hz, 1H), 10.56 (bis, 1H).

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Example 1-304

[0712] MS ESI m/e: 572, 574 (M+H), 570, 572 (M-H).

35 ¹H-NMR (DMSO-d₆, 300MHz) δ 0.74-0.79 (m, 2H), 1.00-1.08 (m, 2H), 2.62-2.68 (m, 4H), 3.02 (s, 3H), 5.53 (s, 1H), 7.12-7.14 (m, 1H), 7.22-7.35 (m, 4H), 7.42-7.44 (m, 1H), 7.60-7.62 (m, 2H), 10.00 (brs, 1H), 10.57 (brs, 1H).

Example

[0713] MS ESI m/e: 584, 586 (M+H), 582, 584 (M-H).

40 ¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.80 (m, 2H), 0.97-1.08 (m, 2H), 2.47 (t, J=7.2Hz, 2H), 2.62-2.71 (m, 1H), 2.67 (s, 3H), 3.70 (q, J=5.9Hz, 2H), 4.69 (t, J=5.1Hz, 1H), 5.36 (d, J=1.1Hz, 1H), 7.07 (dd, J=2.6, 7.9Hz, 1H), 7.42 (t, J=8.1Hz, 1H), 7.48-7.55 (m, 2H), 7.62-7.69 (m, 1H), 7.71-7.77 (m, 2H), 10.13 (brs, 1H), 10.54 (brs 1H).

Examples 1-306

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[0714] MS ESI m/e: 611, 613 (M+H), 609, 611 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.79 (m, 2H), 0.98-1.08 (m, 2H), 2.16 (s, 6H), 2.39-2.48 (m, 2H), 2.51-2.59 (m, 2H), 2.63-2.72 (m, 1H), 2.67 (s, 3H), 5.35 (d, J=1.1Hz, 1H), 7.05-7.11 (m, 1H), 7.42 (t, J=8.1Hz, 1H), 7.47-7.55 (m, 2H), 7.61-7.67 (m, 1H), 7.69-7.77 (m, 2H), 10.22 (brs, 1H), 10.54 (brs, 1H).

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Example 1-307

[0715] MS ESI m/e: 583, 585 (M+H), 581, 583 (M-H).

55 ¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.98-1.08 (m, 2H), 1.04 (t, J=7.2Hz, 3H), 2.62-2.74 (m, 1H), 2.68 (s, 3H), 3.09 (quint, J=6.8Hz, 2H), 5.35 (d, J=1.1Hz, 1H), 6.16 (t, J=5.8Hz, 1H), 6.88-6.95 (m, 1H), 7.32 (t, J=7.9Hz, 1H), 7.36-7.42 (m, 1H), 7.45-7.57 (m, 3H), 7.71-7.77 (m, 1H), 8.73 (brs, 1H), 10.55 (brs, 1H).

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Example 1-308

[0716] MS ESI m/e: 584, 586 (M+H), 582, 584 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.78 (m, 2H), 0.98-1.08 (m, 2H), 1.24 (t, J=7.2Hz, 3H), 2.61-2.72 (m, 1H), 2.66 (s, 3H), 4.12 (q, J=6.9Hz, 2H), 5.36 (d, J=1.1Hz, 1H), 7.00-7.05 (m, 1H), 7.39 (t, J=7.9Hz, 1H), 7.43-7.55 (m, 3H), 7.60-7.65 (m, 1H), 7.70-7.78 (m, 1H), 9.85 (brs, 1H), 10.54 (brs, 1H)

Example 1-309

[0717] MS ESI m/e: 619, 621 (M+H), 617, 619 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.68-0.80 (m, 2H), 0.98-1.07 (m, 2H), 2.60-2.71 (m, 1H), 2.63 (s, 3H), 2.67 (s, 6H), 5.35 (d, J=1.1Hz, 1H), 7.09-7.15 (m, 1H), 7.21-7.27 (m, 2H), 7.43 (t, J=8.5Hz, 1H), 7.47-7.54 (m, 2H), 7.70-7.76 (m, 1H), 10.11 (brs, 1H), 10.54 (brs, 1H).

Example 1-310

[0718] MS ESI m/e: 500 (M+H), 498 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.98-1.08 (m, 2H), 2.05 (s, 3H), 2.63-2.72 (m, 1H), 2.67 (s, 3H), 4.32 (s, 1H), 5.51 (brs, 1H), 7.04-7.12 (m, 1H), 7.35-7.46 (m, 2H), 7.50-7.61 (m, 2H), 7.62-7.67 (m, 1H), 7.67-7.72 (m, 1H), 10.16 (s, 1H), 10.75 (s, 1H).

Example 1-311

[0719] MS ESI m/e : 666 (M+H), 664 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 0.71-0.77 (m, 2H), 0.92 (t, J=7.5Hz, 3H), 1.00-1.07 (m, 2H), 1.59-1.71 (m, 2H), 2.62-2.70 (m, 1H), 2.64 (s, 3H), 3.09 (t, J=7.4Hz, 2H), 5.38 (d, J=1.2Hz, 1H), 7.08-7.14 (m, 1H), 7.23-7.37 (m, 3H), 7.41-7.48 (m, 1H), 7.61-7.66 (m, 1H), 7.79-7.84 (m, 1H), 10.54 (s, 1H).

Example 1-312

[0720] MS ESI m/e: 753, 755 (M+H), 751, 753 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.81-0.89 (m, 2H), 1.14-1.22 (m, 2H), 2.70-2.79 (m, 1H), 2.81 (s, 3H), 3.21-3.32 (m, 2H), 3.57-3.68 (m, 2H), 5.07 (s, 2H), 5.57-5.67 (m, 1H), 5.65 (d, J=1.1Hz, 1H), 7.04-7.09 (m, 1H), 7.21-7.40 (m, 11H), 7.74-7.80 (m, 1H), 10.34 (brs, 1H).

Example 1-313

[0721] MS ESI m/e: 619, 621 (M+H), 617, 619 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.79 (m, 2H), 0.99-1.09 (m, 2H), 2.63-2.70 (m, 1H), 2.66 (s, 3H), 3.09-3.19 (m, 2H), 3.37-3.49 (m, 2H), 5.36 (d, J=0.9Hz, 1H), 7.17-7.24 (m, 1H), 7.30-7.39 (m, 2H), 7.47-7.54 (m, 3H), 7.73-7.77 (m, 1H), 7.93-8.14 (m, 3H), 10.39 (brs, 1H), 10.52 (brs, 1H).

Example 1-314

[0722] MS ESI m/e: 703, 705 (M+H), 701, 703 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.78 (m, 2H), 0.82 (t, J=7.2Hz, 3H), 0.99-1.08 (m, 2H), 1.15-1.27 (m, 1H), 1.37-1.47 (m, 2H), 2.01 (t, J=7.5Hz, 2H), 2.62-2.70 (m, 1H), 2.65 (s, 3H), 3.17-3.25 (m, 2H), 3.33-3.43 (m, 2H), 5.36 (d, J=1.1Hz, 1H), 7.11-7.18 (m, 1H), 7.25-7.30 (m, 1H), 7.33-7.36 (m, 1H), 7.42-7.54 (m, 3H), 7.72-7.77 (m, 1H), 7.87-7.94 (m, 1H), 10.08 (brs, 1H), 10.53 (brs, 1H).

Example 1-315

[0723] MS ESI m/e: 659, 661 (M+H), 657, 659 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.79 (m, 2H), 1.01-1.09 (m, 2H), 2.14 (s, 3H), 2.32-2.39 (m, 4H), 2.60-2.72 (m, 4H), 2.83-2.97 (m, 4H), 5.37 (s, 1H), 7.46-7.55 (m, 2H), 7.71-7.87 (m, 5H), 10.51 (s, 1H).

Example 1-316

[0724] MS ESI m/e: 646, 648 (M+H), 644, 646 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.72-0.79 (m, 2H), 1.01-1.10 (m, 2H), 2.60-2.71 (m, 4H), 2.81-2.94 (m, 4H), 3.58-3.67 (m, 4H), 5.38 (s, 1H), 7.47-7.55 (m, 2H), 7.71-7.88 (m, 5H), 10.50 (s, 1H).

Example 1-317

[0725] MS ESI m/e: 644, 646 (M+H), 642, 644 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 1.00-1.09 (m, 2H), 1.32-1.41 (m, 2H), 1.47-1.58 (m, 4H), 2.58-2.73 (m, 4H), 2.82-2.92 (m, 4H), 5.37 (s, 1H), 7.46-7.54 (m, 2H), 7.71-7.84 (m, 5H), 10.51 (s, 1H).

Example 1-318

[0726] MS ESI m/e: 630, 632 (M+H), 628, 630 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.71-0.79 (m, 2H), 1.01-1.10 (m, 2H), 1.59-1.69 (m, 4H), 2.58 (s, 3H), 2.63-2.71 (m, 1H), 3.03-3.22 (m, 4H), 5.37 (s, 1H), 7.46-7.55 (m, 2H), 7.71-7.82 (m, 3H), 7.87-7.92 (m, 2H), 10.51 (s, 1H).

Example 1-319

[0727] MS ESI m/e: 666 (M+H), 664 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.99-1.08 (m, 2H), 1.23 (d, J=6.6Hz, 6H), 2.61-2.71 (m, 1H), 2.64 (s, 3H), 5.38 (s, 1H), 7.08-7.15 (m, 1H), 7.27-7.38 (m, 3H), 7.39-7.47 (m, 1H), 7.60-7.66 (m, 1H), 7.78-7.84 (m, 1H), 9.99 (brs, 1H), 10.54 (s, 1H).

Example 1-320

[0728] MS ESI m/e: 564 (M+H), 562 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.92 (t, J=7.3Hz, 3H), 0.99-1.09 (m, 2H), 1.58-1.74 (m, 2H), 2.62-2.72 (m, 1H), 2.66 (s, 3H), 3.05-3.14 (m, 2H), 4.32 (s, 1H), 5.51 (s, 1H), 7.09-7.16 (m, 1H), 7.24-7.34 (m, 2H), 7.35-7.50 (m, 2H), 7.50-7.61 (m, 2H), 10.04 (brs, 1H), 10.73 (s, 1H).

Example 1-321

[0729] MS ESI m/e: 564 (M+H), 562 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.99-1.08 (m, 2H), 1.23 (d, J=6.6Hz, 6H), 2.62-2.71 (m, 1H), 2.65 (s, 1H), 3.18-3.30 (m, 1H), 4.31 (s, 1H), 5.51 (s, 1H), 7.08-7.14 (m, 1H), 7.26-7.35 (m, 2H), 7.35-7.48 (m, 2H), 7.50-7.61 (m, 2H), 10.00 (brs, 1H), 10.73 (s, 1H).

Example 1-322

[0730] MS ESI m/e: 655 (M+H), 653 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.79 (m, 2H), 0.99-1.09 (m, 2H), 2.61-2.71 (m, 4H), 3.02 (s, 3H), 5.49 (s, 1H), 7.15 (d, J=9.0Hz, 1H), 7.25-7.31 (m, 2H), 7.38-7.49 (m, 2H), 7.74-7.77 (m, 1H), 8.00 (s, 1H), 9.99 (brs, 1H), 10.76 (brs, 1H).

Example 1-323

[0731] MS ESI m/e: 625, 627 (M+H), 623, 625 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.79 (m, 2H), 0.98-1.09 (m, 2H), 1.70 (quint, J=7.2Hz, 2H), 2.11 (s, 6H), 2.21 (t, J=7.2Hz, 2H), 2.33 (t, J=7.3Hz, 2H), 2.62-2.72 (m, 1H), 2.66 (s, 3H), 5.35 (d, JJ=1.1Hz, 1H), 7.04-7.11 (m, 1H), 7.41 (t, J=8.1Hz, 1H), 7.45-7.54 (m, 2H), 7.60-7.67 (m, 1H), 7.69-7.78 (m, 2H), 10.13 (brs, 1H), 10.54 (brs, 1H).

Example 1-324

[0732] MS ESI m/e: 583, 585 (M+H), 581, 583 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.79 (m, 2H), 0.97-1.08 (m, 2H), 2.62-2.74 (m, 1H), 2.69 (s, 3H), 2.92 (s, 6H), 5.35 (d, J=1.1Hz, 1H), 6.94-7.01 (m, 1H), 7.34 (t, J=8.1Hz, 1H), 7.46-7.54 (m, 2H), 7.54-7.61 (m, 2H), 7.70-7.77 (m, 1H), 8.51 (brs, 1H), 10.54 (brs, 1H).

Example 1-325

[0733] MS ESI m/e : 569, 571 (M+H), 567, 569 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.69-0.80 (m, 2H), 0.98-1.09 (m, 2H), 2.63 (d, J=4.9Hz, 3H), 2.65-2.73 (m, 1H), 2.68 (s, 3H), 5.35 (d, J=1.1Hz, 1H), 6.00-6.08 (m, 1H), 6.89-6.95 (m, 1H), 7.33 (t, J=7.9Hz, 1H), 7.38-7.45 (m, 1H), 7.46-7.52 (m, 2H), 7.52-7.56(m, 1H), 7.69-7.77 (m, 1H), 8.77 (brs, 1H), 10.55 (brs, 1H).

Example 1-326

[0734] MS ESI m/e: 465 (M+H), 463 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.80 (m, 2H), 0.99-1.08 (m, 2H), 2.59 (s, 3H), 2.62-2.72 (m, 1H), 3.21 (dt, J=4.5, 18.3Hz, 2H), 5.50 (s, 1H), 6.27 (tt, J=4.3, 56.3Hz, 1H), 7.26-7.34 (m, 2H), 7.34-7.56 (m, 7H), 10.55 (brs, 1H).

Example 1-327

[0735] MS ESI m/e: 585, 587 (M+H), 583, 585 (M-1).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.75 (brs, 2H), 1.03 (m, 2H), 2.68 (s, 4H), 3.61 (s, 3H), 5.36 (s, 1H), 7.00-7.10 (m, 1H), 7.38 (t, J=8.1Hz, 1H), 7.45-7.55 (m, 2H), 7.65-7.80 (m, 3H), 9.12 (s, 1H), 9.63 (s, 1H), 10.54 (s, 1H).

Example 1-328

[0736] MS ESI m/e: 457 (M+H), 455 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.74-0.81 (m, 2H), 1.01-1.10 (m, 2H), 2.60 (s, 3H), 2.65-2.74 (m, 1H), 5.50 (s, 1H), 7.32 (dd, J=1.9, 8.7Hz, 1H), 7.40-7.56 (m, 6H), 7.82-7.87 (m, 2H), 8.07 (d, J=8.3Hz, 1H), 10.63 (brs, 1H).

Example 1-329

[0737] MS ESI m/e: 437 (M+H), 435 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 2.89 (s, 3H), 7.15-7.55 (m, 5H), 10.35 (s, 1H).

Example 1-330

[0738] MS ESI m/e: 347 (M+H) 345 (M-H)

¹H-NMR (CDCl₃, 300MHz) δ 3.41 (s, 3H), 3.53 (s, 3H), 3.56 (s, 3H), 7.15-7.23 (m, 2H), 7.32-7.38 (m, 2H), 10.45 (s, 1H).

Example 1-331

[0739] MS ESI m/e: 458 (M+H), 456 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.40-0.57 (m, 4H), 1.24-1.37(m, 1H), 2.81 (s, 3H), 2.97 (s, 6H), 3.91 (d, J=7.0Hz, 2H), 5.61 (s, 1H), 6.70-6.77 (m, 2H), 7.10-7.17 (m, 2H), 7.33-7.54 (m, 5H), 10.22 (s, 1H).

Example 1-332

[0740] MS ESI m/e: 495 (M+H), 496, 493 (M-H), 494.

¹H-NMR (DMSO-d₆, 300MHz) δ 2.70 (s, 3H), 3.84 (s, 3H), 5.88 (s, 1H), 7.36-7.55 (m, 10H), 7.46 (d, J=9.0Hz, 2H), 7.99 (d, J=9.0Hz, 2H), 10.85 (brs, 1H).

Example 1-333

[0741] MS ESI m/e: 604, 606 (M+H), 602, 604 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 0.66-0.74(m, 2H), 0.98-1.06(m, 2H), 1.56.(s, 3H), 2.60-2.69(m, 1H), 2.74(s, 3H), 3.03 (s, 3H), 6.80(t, J=8.9Hz, 1H), 7.10-7.15 (m, 1H), 7.25-7.36(m, 3H), 7.46 (t, J=8.0Hz, 1H), 7.59-7.64 (m, 1H), 9.99(s, 1H), 10.17 (s, 1H).

Example 1-334

[0742] MS ESI m/e: 556(M+H), 554(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.69-0.78(m, 2H), 0.99-1.08(m, 2H), 2.74(s, 3H), 2.61-2.72 (m, 1H), 2.69-2.79 (m, 2H),

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2.98-3.09(m, 2H), 5.36(s, 1H), 5.92 (brs, 1H), 6.51-6.68(m, 3H), 7.15-7.20(m, 1H), 7.49-7.50(m, 2H), 7.72-7.75(m, 1H), 10.60(brs, 1H).

Example 1-335

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[0743] MS ESI m/e: 654 (M+H), 652(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.67-0.81 (m, 2H), 0.96-1.09 (m, 2H), 2.36(s, 3H), 2.61-2.69 (m, 1H), 5.35 (s, 1H), 7.08 (d, J=9.0Hz, 1H), 7.16(d, J=9.0Hz, 1H), 7.31-7.39(m, 2H), 7.48-7.53(m, 2H), 7.57-7.62(m, 1H), 7.74(d, J=9.0Hz, 1H), 8.10(d, J=9.0Hz, 1H), 8.77-8.80(m, 1H), 6.88-8.90(m, 1H), 10.52(brs, 1H), 10.69(brs, 1H).

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Example 1-336

[0744] MS ESI m/e: 532 (M+H), 530 (M-H).

¹H-NMR(DMSO-d₆, 30.0MHz) δ 0.71-0.80 (m, 2H), 0.99-1.09 (m, 2H), 2.25(s, 3H), 2.61-2.73 (m, 1H), 2.64(s, 3H), 3.01 (s, 3H), 4.17(s, 1H), 5.27 (s, 1H), 7.14-7.48 (m, 7H), 9.98 (brs, 1H), 10.50(brs, 1H).

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Example 1-337

[0745] MS ESI m/e: 552(M+H), 550(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.68-0.78(m, 2H), 0.99-1.10(m, 2H), 2.66(s, 3H), 2.61-2.76 (m, 1H), 3.01 (s, 3H), 4.31 (s, 1H), 5.61 (s, 1H), 7.13(d, J=12.0Hz, 1H), 7.22-7.32(m, 2H), 7.41-7.51(m, 2H), 7.61(d, J=6.0Hz, 1H), 7.74 (s, 1H), 9.98 (brs, 1H), 10.90(brs, 1H).

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Example 1-338

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[0746] MS ESI m/e: 558 (M+H), 556 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.70-0.81 (m, 2H), 0.99-1.08 (m, 2H), 2.61-2.71(m, 1H), 2.65 (s, 3H), 3.02 (dt, J=18.8, 3.4Hz, 2H), 3.02(s, 3H), 4.69 (dt, J=47.1, 3.0Hz, 2H), 5.28(s, 1H), 7.10-7.16(m, 1H), 7.17-7.23(m, 1H), 7.23-7.29(m, 1H), 7.29-7.39(m, 2H), 7.41-7.50 (m, 2H), 10.00 (brs, 1H), 10.43 (s, 1H).

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Example 1-339

[0747] MS ESI m/e: 690(M+H), 688(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.69-0.79 (m, 2H), 0.98-1.09 (m, 2H), 2.22-2.32(m, 4H), 2.64(s, 3H), 2.60-2.71(m, 3H), 3.25-3.41(m, 2H), 3.41-3.51 (m, 4H), 5.34(s, 1H), 7.09(d, J=6.0Hz, 1H), 7.23-7.35 (m, 2H), 7.40-7.51(m, 3H), 7.73(d, J=12.0Hz, 1H), 10.08 (brs, 1H), 10.52(brs, 1H).

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Example 1-340

[0748] MS ESI m/e: 634(M+H), 632(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.70-0.79(m, 2H), 0.98-1.09(m, 2H), 2.22 (s, 3H), 2.60-2.69(m, 1H), 2.63(s, 3H), 3.01 (s, 3H), 5.14(s, 1H), 7.13(d, J=9.0Hz, 2H), 7.22-7.30(m, 2H), 7.41-7.48(m, 1H), 7.61-7.64(m, 1H), 7.74 (s, 1H), 9.98 (brs, 1H), 10.32(brs, 1H).

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Example 1-341

[0749] MS ESI m/e: 522 (M+H), 520 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 0.70-0.80(m, 2H), 0.97-1.09(m, 2H), 2.06(s, 3H), 2.54(s, 3H), 2.63-2.72 (m, 1H), 2.66 (s, 3H), 5.23-5.26 (m, 1H), 7.05-7.20(m, 2H), 7.28-7.49 (m, 3H), 7.61-7.73(m, 2H), 10.17(brs, 1H), 10.41(brs, 1H).

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Example 1-342

[0750] MS ESI m/e: 522 (M+H), 520 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.69-0.79(m, 2H), 0.97-1.10(m, 2H), 2.04(s, 3H), 2.60-2.73 (m, 1H), 2.65 (s, 3H), 3.02 (dt, J=25.2, 2.8Hz, 2H), 4.69(dt, J=47.1, 3.2Hz, 2H), 5.27(s, 1H), 7.02-7.11(m, 1H), 7.16-7.23(m, 1H), 7.29-7.49(m, 3H), 7.61-7.71(m, 2H), 10.16 (brs, 1H), 10.44(brs, 1H).

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Example 1-343

[0751] MS ESI m/e: 475 (M+H), 473 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 0.85-0.94 (m, 2H), 1.16-1.24 (m, 2H), 2.75-2.83(m, 1H), 2.82(s, 3H), 5.54-5.58 (m, 1H), 7.30-7.38 (m, 3H), 7.43-7.54 (m, 5H), 7.63-7.69 (m, 1H), 10.28 (brs, 1H).

Example 2-1

[0752] MS ESI m/e: 472 (M+H), 470 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 2.68 (s, 3H), 7.34-7.39 (m, 2H), 7.41-7.61 (m, 10H), 7.80-7.87 (m, 2H), 11.34 (s, 1H).

Example 2-2

[0753] MS ESI m/e: 592 (M+H), 590 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.70-0.82 (m, 2H), 1.01-1.13 (m, 2H), 2.64-2.75 (m, 1H), 2.67 (s, 3H), 3.05 (s, 3H), 7.19-7.27 (m, 1H), 7.27-7.34 (m, 1H), 7.35-7.39 (m, 1H), 7.45-7.54 (m, 2H), 7.71 (dd, J=3.0, 12.0Hz, 1H), 8.51 (t, J=9.0Hz, 1H), 10.05 (s, 1H), 11.61 (d, J=3.0Hz, 1H).

Example 3-1

[0754] MS ESI m/e: 493, 495 (M+H), 491, 493 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.77-0.82 (m, 2H), 1.09-1.15 (m, 2H), 1.36 (s, 3H), 2.72-2.74 (m, 1H), 3.20 (s, 3H), 6.86 (d, 2H), 7.28-7.32 (m, 2H), 7.34-7.51 (m, 5H), 11.36 (s, 1H).

Example 3-2

[0755] MS ESI m/e: 479, 481 (M+H), 477, 479 (M-H).

¹H-NMR (CDCl₃, 400MHz) δ 0.83-0.90 (m, 2H), 1.10-1.18 (m, 2H), 2.67-2.76 (m, 1H), 3.11 (s, 3H), 5.00 (s, 1H), 7.02 (d, J=8.6Hz, 2H), 7.10-7.15 (m, 2H), 7.19-7.25 (m, 1H), 7.34-7.41 (m, 2H), 7.63-7.70 (m, 2H), 11.71 (s, 1H).

Example 3-3

[0756] MS ESI m/e: 479, 481 (M+H), 477, 479 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.83-0.92 (m, 2H), 1.09-1.19 (m, 2H), 2.67-2.78 (m, 1H), 3.13 (s, 3H), 5.06 (s, 1H), 6.87-6.94 (m, 2H), 7.21-7.28 (m, 2H), 7.45-7.60 (m, 5H), 11.68 (s, 1H).

Example 3-4

[0757] MS ESI m/e: 604 (M+H), 606, 602 (M-H), 604.

¹H-NMR (DMSO-d₆, 300MHz) δ 0.65-0.69 (m, 2H), 0.93-0.98 (m, 2H), 1.25 (s, 3H), 2.59-2.64 (m, 1H), 3.01 (s, 3H), 3.08 (s, 3H), 7.08-7.13 (m, 2H), 7.21-7.25 (m, 2H), 7.39-7.43 (m, 2H), 7.70-7.74 (m, 1H), 9.90 (brs, 1H), 11.09 (brs, 1H).

Example 3-5

[0758] MS ESI m/e: 618 (M+H), 620, 616 (M-H), 618.

¹H-NMR (DMSO-d₆, 300MHz) δ 0.64-0.69 (m, 2H), 0.92-0.98 (m, 2H), 1.19 (t, J=9.8Hz, 3H), 1.24 (s, 3H), 2.58-2.64 (m, 1H), 3.11 (q, J=9.8Hz, 2H), 3.08 (s, 3H), 7.07-7.13 (m, 2H), 7.21-7.25 (m, 2H), 7.37-7.42 (m, 2H), 7.70-7.74 (m, 2H), 9.95 (brs, 1H), 11.09 (brs, 1H).

Example 3-6

[0759] MS ESI m/e: 604 (M+H), 606, 602 (M-H), 604.

¹H-NMR (DMSO-d₆, 300MHz) δ 0.64-0.69 (m, 2H), 0.92-0.99 (m, 2H), 1.25 (s, 3H), 2.04 (s, 3H), 2.58-2.66 (m, 1H), 3.08 (s, 3H), 7.01-7.13 (m, 2H), 7.33-7.43 (m, 2H), 7.58-7.60 (m, 2H), 7.70-7.74 (m, 1H), 10.10 (brs, 1H), 11.09 (brs, 1H).

Example 3-7

[0760] MS.ESI m/e: 652 (M+H), 650 (M-H).

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¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.72 (m, 2H), 0.91-1.01 (m, 2H), 1.25 (s, 3H), 2.57-2.67 (m, 1H), 3.01 (s, 3H), 3.08 (s, 3H), 6.92 (t, J=9.0Hz, 1H), 7.09-7.14 (m, 1H), 7.20-7.26 (m, 2H), 7.37-7.45 (m, 1H), 7.52-7.58 (m, 1H), 7.79 (dd, J=1.8, 9.0Hz, 1H), 9.89 (s, 1H), 11.08 (s, 1H).

5 Example 3-8

[0761] MS ESI m/e: 550 (M+H), 548 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.71 (m, 2H), 0.90-1.01 (m, 2H), 1.26 (s, 3H), 2.56-2.66 (m, 1H), 3.01 (s, 3H), 3.10 (s, 3H), 4.30 (s, 1H), 7.05-7.16 (m, 2H), 7.20-7.27 (m, 2H), 7.32 (dd, J=1.7, 9.0Hz, 1H), 7.37-7.45 (m, 1H), 7.52 (dd, J=1.7, 12.0Hz, 1H), 9.90 (s, 1H), 11.10 (s, 1H).

Example 3-9

[0762] MS ESI m/e: 639 (M+H), 638, 637 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.65-0.73 (m, 2H), 0.93-0.98 (m, 2H), 1.26 (s, 3H), 2.58-2.65 (m, 1H), 3.05 (s, 3H), 3.08 (s, 3H), 7.11 (dd, J=10.1Hz, 13.0Hz, 1H), 7.32 (d, J=11.6Hz, 1H), 7.42 (d, J=10.1Hz, 1H), 7.48 (s, 1H), 7.63 (d, J=11.6Hz, 1H), 7.72 (d, J=13.0Hz, 1H), 9.65 (brs, 1H), 11.08 (brs, 1H).

Example 4-1

[0763] MS ESI m/e: 616 (M+H), 614 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.63-0.70 (m, 2H), 0.91-1.00 (m, 2H), 1.25(s, 3H), 2.04(s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 6.92 (t, J=8.8Hz, 1H), 7.00-7.05 (m, 1H), 7.36 (t, J=8.2Hz, 1H), 7.52-7.63(m, 3H), 7.79(dd, J=2.0, 10.4Hz, 1H), 10.10(s, 1H), 11.08(s, 1H).

Example 4-2

[0764] MS ESI m/e: 666 (M+H), 664 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.62-0.71 (m, 2H), 0.91-1.01(m, 2H), 1.19(t, J=7.2Hz, 3H), 1.24(s, 3H), 2.56-2.67(m, 1H), 3.08(s, 3H), 3.11(q, J=7.2Hz, 2H), 6.92(1, J=8.7Hz, 1H), 7.09(d, J=8.1Hz, 1H), 7.21-7.28(m, 2H), 7.40(t, J=8.3Hz, 1H), 7.55(d, J=8.1Hz, 1H), 7.79(dd, J=1.8, 10.5Hz, 1H), 9.94(s, 1H), 11.08(s, 1H).

Example 4-3

[0765] MS ESI m/e: 514 (M+H), 512 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.63-0.70 (m, 2H), 0.91-0.99 (m, 2H), 1.26(s, 3H), 2.04(s, 3H), 2.58-2.66 (m, 1H), 3.10 (s, 3H), 4.30 (s, 1H), 7.01-7.06(m, 1H), 7.09(t, J=8.4Hz, 1H), 7.31(dd, J=1.6, 8.4Hz, 1H), 7.36 (t, J=7.8Hz, 1H), 7.52 (dd, J=1.6, 11.6Hz, 1H), 7.57-7.63(m, 2H), 10.10(s, 1H), 11.10(s, 1H)

Example 4-4

[0766] MS ESI m/e: 568,570 (M+H), 566,568 (M-H)

¹H-NMR(DMSO-d₆, 300MHz) 0.61-0.65(m, 2H), 0.90-0.95(m, 2H), 1.20(s, 3H), 2.04 (s, 3H), 2.56-2.61(m, 1H), 3.04(s, 3H), 7.07(dd, J=8.6, 10.7Hz, 1H), 7.25(d, J=8.8Hz, 2H), 7.38(d, J=10.7Hz, 1H), 7.60(d, J=8.8Hz, 2H), 7.69(d, J=8.6Hz, 1H), 10.07(s, 1H), 11.05(s, 1H)

Example 4-5

[0767] MS ESI m/e: 556,558(M+1).

¹H-NMR(DMSO-d₆, 400MHz)δ 0.63-0.67(m, 2H), 0.91-0.96(m, 2H), 1.17(s, 3H), 2.56-2.62 (m, 1H), 3.05(s, 3H), 7.11 (dd, J=8.6, 10.4Hz, 1H), 7.40(d, J=8.6Hz, 1H), 7.66 (d, J=9.3Hz, 2H), 7.69(dd, J=2.1, 10.4Hz, 1H), 8.30(d, J=9.3Hz, 2H), 10.94(s, 1H)

Example 4-6

[0768] MS ESI m/e: 564 (M+H), 562 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.64-0.70(m, 2H), 0.92-0.99 (m, 2H), 1.19(t, J=7.4Hz, 3H), 1.25(s, 3H), 2.57-2.65(m, 1H), 3.10(s, 3H), 3.11(q, J=7.4Hz, 2H), 4.31 (s, 1H), 7.06-7.12(m, 2H), 7.22-7.27(m, 2H), 7.32(dd, J=1.6, 8.0Hz, 1H),

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7.40(t, J=8.0Hz, 1H), 7.52(dd, J=1.6, 11.6Hz, 1H), 9.95 (s, 1H), 11.10(s, 1H).

Example 4-7

5 **[0769]** MS ESI m/e: 490 (M+H), 488 (M-H).
¹H-NMR(DMSO-d₆, 400MHz) δ 0.64-0.71 (m, 2H), 0.91-0.99(m, 2H), 1.25(s, 3H), 2.04(s, 3H), 2.60-2.67 (m, 1H), 3.05 (s, 3H), 7.02-7.06(m, 1H), 7.13-7.19 (m, 1H), 7.20-7.29(m, 2H), 7.33-7.41(m, 2H), 7.57-7.63(m, 2H), 10.10(s, 1H), 11.23 (s, 1H).

10 Example 4-8

[0770] MS ESI m/e: 604, 606 (M+H), 602, 604 (M-H).
¹H-NMR(DMSO-d, 300MHz) δ 0.63-0.69 (m, 2H), 0.92-0.99 (m, 2H), 1.23 (s, 3H), 2.57-2.67 (m, 1H), 3.04(s, 3H), 3.07 (s, 3H), 7.08-7.14(m, 1H), 7.26 (d, J=9.0Hz, 2H), 7.34(d, J=9.0Hz, 2H), 7.39-7.44 (m, 1H), 7.70-7.75 (m, 1H), 9.96 (s, 1H), 11.08(s, 1H)

Example 4-9

20 **[0771]** MS ESI m/e: 518 (M+H), 516 (M-H).
¹H-NMR(DMSO-d₆, 400MHz)δ 0.64-0.71(m, 2H), 0.92-1.00(m, 2H), 1.19(t, J=7.6Hz, 3H), 1.24(s, 3H), 2.04(s, 3H), 2.59-2.67(m, 1H), 2.62(q, J=7.6Hz, 2H), 3.03(s, 3H), 7.01-7.11(m, 3H), 7.23(d, J=11.6Hz, 1H), 7.36(t, J=8.2Hz, 1H), 7.56-7.63(m, 2H), 10.10(s, 1H), 11.23(s, 1H).

Example 4-10

25 **[0772]** MS ESI m/e: 603, 605 (M+H), 601, 603 (M-H).
¹H-NMR(CDCl₃, 300MHz) 0.77-0.84(m, 2H), 1.11-1.18(m, 2H), 1.32(t, J=7.3Hz, 3H), 1.33(s, 3H), 2.70-2.78 (m, 1H), 3.15(q, J=7.5Hz, 2H), 3.20(s, 3H), 6.89(1, J=8.3Hz, 1H), 7.28-7.32(m, 1H), 7.36(dd, J=2.3, 9.8Hz, 1H), 7.60-7.69(m, 2H), 7.86-7.93(m, 2H), 11.28(s, 1H).

Example 4-11

35 **[0773]** MS ESI m/e: 516 (M+H), 514 (M-H).
¹H-NMR(DMSO-d₆, 400MHz) δ 0.64-0.71(m, 2H), 0.92-1.00(m, 2H), 1.25(s, 3H), 2.04(s, 3H), 2.59-2.67 (m, 1H), 3.07 (s, 3H), 5.32 (d, J=11.1Hz, 1H), 5.89(d, J=17.6Hz, 1H), 6.73(dd, J=10.9, 17.6Hz, 1H), 7.01-7.06(m, 1H), 7.11(t, J=8.6Hz, 1H), 7.28-7.33(m, 1H), 7.33-7.40 (m, 1H), 7.51-7.57(m, 1H), 7.57-7.63(m, 2H), 10.10(s, 1H), 11.22 (s, 1H).

Example 4-12

40 **[0774]** MS ESI m/e: 729 (M+H), 727 (M-H).
¹H-NMR(DMSO-d₆, 300MHz)δ 0.65-0.68 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H), 0.93-0.97 (m, 2H), 1.23-1.26 (m, 5H), 1.40-1.50 (m, 2H), 2.04 (t, J = 7.5 Hz, 2H), 2.48-2.50 (m, 2H), 2.59-2.64 (m, 1H), 3.08 (s, 3H), 3.28-3.33 (m, 2H), 6.92 (t, J = 8.7 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 8.1 Hz, 1H), 7.56-7.59 (m, 2H), 7.64-7.66 (m, 1H), 7.79 (dd, J = 10.4, 1.7 Hz, 1H), 7.90 (t, J = 5.7 Hz, 1H), 10.10 (s, 1H), 11.08 (s, 1H).

Example 4-13

50 **[0775]** MS ESI m/e: 603 (M+H), 601 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 0.66-0.69 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H), 0.93-0.98 (m, 2H), 1.17-1.29 (m, 5H), 1.40-1.50 (m, 2H), 2.04 (t, J = 7.3 Hz, 2H), 2.47-2.51 (m, 2H), 2.61-2.65 (m, 1H), 3.05 (s, 3H), 3.29-3.33 (m, 2H), 7.04 (d, J = 9.0 Hz, 1H), 7.19-7.34 (m, 5H), 7.59 (d, J = 8.7 Hz, 1H), 7.66 (s, 1H), 7.91 (t, J = 5.3 Hz, 1H), 10.10 (s, 1H), 11.23 (s, 1H).

Example 4-14

55 **[0776]** MS ESI m/e: 685 (M+H), 683-(M-H).
¹H-NMR(DMO-d₆, 300MHz) δ 0.64-0.70(m, 2H), 0.82(t, J=7.3Hz, 3H), 0.90-0.98(m, 2H), 1.14-1.28(m, 4H), 1.25(s, 3H), 1.37-1.49(m, 2H), 1.45(s, 6H), 2.04(t, J=7.3Hz, 2H), 2.58-2.65(m, 1H), 3.07(s, 3H), 3.27-3.34(m, 2H), 5.49(brs, 1H), 6.99-7.11(m, 2H), 7.18-7.25(m, 1H), 7.31-7.42(m, 2H), 7.55-7.67(m, 2H), 7.85-7.93(m, 1H), 10.09(s, 1H), 11.14(s, 1H).

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Example 4-15

[0777] MS ESI m/e: 590 (M+H), 588 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 1.42(s, 3H), 2.16(s, 3H), 3.21(s, 3H), 3.37 (s, 3H), 6.69(t, J=8.3Hz, 1H), 7.04-7.10(m, 1H), 7.31-7.55(m, 5H), 7.70 (s, 1H), 11.41(s, 1H).

Example 4-16

[0778] MS ESI m/e: 626 (M+H), 624 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.26 (s, 3H), 3.01(s, 3H), 3.09 (s, 3H), 3.21(s, 3H), 6.93(t, J=8.3Hz, 1H), 7.11-7.15(m, 1H), 7.20-7.28(m, 2H), 7.42(t, J=8.3Hz, 1H), 7.52-7.57(m, 1H), 7.76-7.81(m, 1H), 9.94(br, 1H), 11.21(br, 1H).

Example 4-17

[0779] MS ESI m/e: 630 (M+H), 628 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 0.75-0.81(m, 2H), 1.05-1.15(m, 5H), 1.41(s, 3H), 2.15(s, 3H), 2.68-2.77(m, 1H), 3.90-4.00 (m, 2H), 6.72(t, J=8.3Hz, 1H), 6.97-7.03(m, 1H), 7.30-7.54(m, 5H), 7.65-7.69(m, 1H), 11.07(s, 1H).

Example 4-18

[0780] MS ESI m/e: 666 (M+H), 664 (M-H)

¹H-NMR(CDCl₃, 300MHz) δ 0.75-0.81(m, 2H), 1.06-1.15(m, 5H), 1.39(s, 3H), 2.68-2.76(m, 1H), 3.02(s, 3H), 3.90-4.00 (m, 2H), 6.74(t, J=8.3Hz, 1H), 6.93-6.99(m, 1H), 7.07-7.13(m, 1H), 7.20-7.26(m, 2H), 7.38-7.54 (m, 3H), 11.07 (s, 1H).

Example 4-19

[0781] MS ESI m/e: 654 (M+H), 652 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.13(t, J=6.8Hz, 3H), 1.20(t, J=7.2Hz, 3H), 1.25(s, 3H), 3.08(s,3H), 3.12(q, J=7.4Hz, 2H), 3.87(d, J=7.1Hz, 2H), 6.94(t, J=8.6Hz, 1H), 7.12(d, J=8.0Hz, 1H), 7.25(d, J=8.4Hz, 1H), 7.29(s, 1H), 7.41(t, J=8.0Hz, 1H), 7.55(d, J=8.5Hz, 1H), 7.79(d, J=10.5Hz, 1H), 9.98 (s,1H), 11.24(s,1H).

Example 4-20

[0782] MS ESI m/e: 640 (M+H), 638 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.13(t, J=6.8Hz, 3H), 1.26(s, 3H), 3.02(s, 3H), 3.09(s, 3H), 3.88(q, J=6.8Hz, 2H), 6.95 (t, J=8.5Hz, 1H), 7.11-7.18(m, 1H), 7.21-7.30(m, 2H), 7.43(t, J=7.7Hz, 1H), 7.55(d, J=9.0Hz, 1H), 7.76-7.82(m, 1H), 9.94(brs, 1H), 11.24 (brs, 1H).

Example 4-21

[0783] MS ESI m/e: 604 (M+H), 602 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.13 (t, J=6.8Hz, 3H), 1.26(s, 3H), 2.04(s, 3H), 3.08(s, 3H), 3.87(q, J=7.5Hz, 2H), 6.94 (t, J=8.5Hz, 1H), 7.05-7.11(m, 1H), 7.37 (t, J=7.9Hz, 1H), 7.51-7.60 (m, 2H), 7.65-7.71 (m, 1H), 7.78(d, J=10.2Hz, 1H), 10.10(brs, 1H), 11.23(brs, 1H).

Example 4-22

[0784] MS ESI m/e: 666 (M+H), 664 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.47 (t, J=7.2Hz, 3H), 0.63-0.69 (m, 2H), 0.90-0.97 (m, 2H), 1.76-1.94 (m, 2H), 2.57-2.63 (m, 1H), 3.00 (s, 3H), 3.07(s, 3H), 6.93 (t, J=8.8Hz, 1H), 7.12-7.16 (m, 1H), 7.23-7.30(m, 2H), 7.42(t, J=8.0Hz, 1H), 7.53-7.58(m, 1H), 7.79(dd, J=1.6, 10.0Hz, 1H), 9.91(s, 1H), 11.07(s, 1H).

Example 4-23

[0785] MS ESI m/e: 680 (M+H), 678 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.47(1, J=7.4Hz, 3H), 0.61-0.70(m, 2H), 0.89-0.98(m, 2H), 1.20(t, J=7.4Hz, 3H), 1.74-1.95(m, 2H), 2.55-2.65 (m, 1H), 3.07(s, 3H), 3.11(q, J=7.4Hz, 2H), 6.92(t, J=8.6Hz, 1H), 7.11(d, J=7.8Hz, 1H), 7.22-7.31 (m, 2H), 7.40 (t, J=7.9Hz, 1H) ; 7.56 (d, J=8.7Hz, 1H), 7.79(d, J=10.2Hz, 1H), 9.97(s, 1H), 11.07(s, 1H).

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Example 4-24

[0786] MS ESI m/e: 630 (M+H), 628 (M-H).

5 $^1\text{H-NMR(DMSO-d}_6, 300\text{MHz)}$ δ 0.47(t, J=7.2Hz, 3H), 0.60-0.69 (m, 2H), 0.87-0.98(m, 2H), 1.79-1.93(m, 2H), 2.04(s, 3H), 2.56-2.66(m, 1H), 3.07(s, 3H), 6.92(t, J=8.6Hz, 1H), 7.07(d, J=8.4Hz, 1H), 7.37(t, J=8.1Hz, 1H), 7.53-7.69(m, 3H), 7.79(d, J=10.2Hz, 1H), 10.09(s, 1H), 11.07(s, 1H).

Example 4-25

10 **[0787]** MS ESI m/e: 554 (M+H), 552 (M-H).

$^1\text{H-NMR(DMSO-d}_6, 300\text{MHz)}$ δ 0.64-0.73(m, 2H), 0.91-1.01(m, 2H), 1.19(t, J=7.5Hz, 3H), 1.24(s, 3H), 2.57-2.68(m, 1H), 2.62(q, J=7.4Hz, 2H), 3.01(s, 3H), 3.03(s, 3H), 7.03-7.15(m, 3H), 7.19-7.27 (m, 3H), 7.41(t, J=8.1Hz, 1H), 9.89(s, 1H), 11.24(s, 1H).

15 Example 4-26

[0788] MS ESI m/e: 568 (M+H), 566 (M-H).

20 $^1\text{H-NMR(DMSO-d}_6, 300\text{MHz)}$ δ 0.62-0.73(m, 2H), 0.91-1.01(m, 2H), 1.18 (t, J=7.5Hz, 3H), 1.19(t, J=7.2Hz, 3H), 1.23 (s, 3H), 2.57-2.68(m, 1H), 2.62(q, J=7.5Hz, 2H), 3.03(s, 3H), 3.11(q, J=7.2Hz, 2H), 7.03-7.13(m, 3H), 7.19-7.27(m, 3H), 7.40(t, J=8.1Hz, 1H), 9.94(s, 1H), 11.24(s, 1H).

Example 4-27

[0789] MS ESI m/e: 528 (M+H), 526 (M-H).

25 $^1\text{H-NMR(DMSO-d}_6, 300\text{MHz)}$ δ 0.48(t, J=7.4Hz, 3H), 0.60-0.70(m, 2H), 0.88-0.98(m, 2H), 1.77-1.92(m, 2H), 2.04(s, 3H), 2.55-2.66(m, 1H), 3.10(s, 3H), 4.30(s, 1H), 7.04-7.14(m, 2H), 7.28-7.41(m, 2H), 7.52(d, J=11.7Hz, 1H), 7.58-7.68(m, 2H), 10.09(s, 1H), 11.08(s, 1H).

Example 4-28

30 **[0790]** MS ESI m/e: 564 (M+H), 562 (M-H).
 $^1\text{H-NMR(DMSO-d}_6, 400\text{MHz)}$ δ 0.48(t, J=7.2Hz, 3H), 0.63-0.69 (m, 2H), 0.90-0.97(m, 2H), 1.78-1.93(m, 2H), 2.56-2.64 (m, 1H), 3.01(s, 3H), 3.10(s, 3H), 4.31(s, 1H), 7.09(t, J=8.4Hz, 1H), 7.13-7.17 (m, 1H), 7.23-7.34(m, 3H), 7.42(t, J=8.0Hz, 1H), 7.52 (dd, J=2.0, 11.6Hz, 1H), 9.92(s, 1H) 11.08(s, 1H).

Example 4-29

[0791] MS ESI m/e: 578 (M+H), 576 (M-H).

40 $^1\text{H-NMR(DMSO-d}_6, 300\text{MHz)}$ δ 0.47(t, J=7.1Hz, 3H), 0.61-0.70 (m, 2H), 0.88-0.98(m, 2H), 1.20(t, J=7.2Hz, 3H), 1.75-1.95 (m, 2H), 2.55-2.64(m, 1H), 3.10(s, 3H), 3.11(q, J=7.2Hz, 2H), 4.30(s, 1H), 7.04-7.14 (m, 2H), 7.23-7.35(m, 3H), 7.40(t, J=7.8Hz, 1H), 7.52(d, J=11.4Hz, 1H), 9.97(s, 1H), 11.08(s, 1H).

Example 4-30

45 **[0792]** MS ESI m/e: 532 (M+H), 530 (M-H).

$^1\text{H-NMR(DMSO-d}_6, 400\text{MHz)}$ δ 0.46(t, J=7.4Hz, 3H), 0.64-0.70(m, 2H), 0.90-0.97(m, 2H), 1.19(t, J=7.6Hz, 3H), 1.80-1.90 (m, 2H), 2.04(s, 3H), 2.57-2.67(m, 1H), 2.63(q, J=7.6Hz, 2H), 3.02 (s, 3H), 7.04-7.13(m, 3H), 7.23(d, J=12.0Hz) 1H), 7.37(t, J=8.0Hz, 1H), 7.61(d, J=7.6Hz, 1H), 7.64(t, J=2.0Hz, 1H), 10.09(s, 1H), 11.24(s, 1H).

50 Example 4-31

[0793] MS ESI m/e: 568 (M+H), 566 (M-H).

55 $^1\text{H-NMR(DMSO-d}_6, 400\text{MHz)}$ δ 0.47(t, J=7.2Hz, 3H), 0.63-0.71(m, 2H), 0.90-0.98(m, 2H), 1.19(t, J=7.4Hz, 3H), 1.74-1.96 (m, 2H), 2.57-2.67(m, 1H), 2.63(q, J=7.4Hz, 2H), 3.01(s, 3H), 3.02(s, 3H), 7.06-7.11(m, 2H), 7.12-7.17(m, 1H), 7.20-7.30 (m, 3H), 7.42(t, J=8.0Hz, 1H), 9.91(s, 1H), 11.24(s, 1H).

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Example 4-32

[0794] MS ESI m/e: 582 (M+H), 580 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.46(t, J=7.2Hz, 3H), 0.64-0.70(m, 2H), 0.90-0.98(m, 2H), 1.19(t, J=7.6Hz, 3H), 1.20(t, J=7.6Hz, 3H), 1.75-1.93(m, 2H), 2.58-2.68(m, 1H), 2.63(q, J=7.6Hz, 2H), 3.02(s, 3H), 3.10(q, J=7.6Hz, 2H), 7.05-7.14(m, 3H), 7.20-7.31(m, 3H), 7.40(t, J=8.0Hz, 1H), 9.97(s, 1H), 11.23(s, 1H).

Example 4-33

[0795] MS ESI m/e: 681(M+H), 679(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.61-0.69(m, 2H), 0.90-1.00(m, 2H), 1.22(s, 3H), 2.52-2.63(m, 1H), 2.67(s, 6H), 3.06(s, 3H), 6.88-6.94(m, 1H), 7.02-7.09(m, 1H), 7.18-7.21(m, 2H), 7.31-7.39(m, 1H), 7.51-7.56(m, 1H), 7.75-7.81(m, 1H), 10.01(brs, 1H), 11.06(brs, 1H).

Example 4-34

[0796] MS ESI m/e: 723 (M+H), 721 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.61-0.70(m, 2H), 0.90-0.99(m, 2H), 1.24(s, 3H), 2.55-2.64(m, 1H), 3.06(s, 3H), 2.99-3.10(m, 4H), 3.43-3.53(m, 4H), 6.88-6.92(m, 1H), 7.05-7.09(m, 2H), 7.14-7.22(m, 1H), 7.31-7.40(m, 1H), 7.51-7.59(m, 1H), 7.75-7.81(m, 1H), 10.21(brs, 1H), 11.08(brs, 1H).

Example 4-35.

[0797] MS ESI m/e: 519 (M+H), 517 (M-H) .

¹H-NMR(DMSO-d₆, 300MHz) δ 0.64-0.71 (m, 2H), 0.92-1.00 (m, 2H), 1.26(s, 3H), 2.59-2.67(m, 1H), 2.73(t, J=7.0Hz, 2H), 3.02-3.12(m, 2H), 3.05(s, 3H), 7.04-7.43(m, 6H), 7.58-7.63 (m, 1H), 7.67(s, 1H), 7.77-7.88(m, 3H), 10.39(s, 1H), 11.23(s, 1H).

Example 4-36

[0798] MS ESI m/e: 645 (M+H) 643 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.62-0.70 (m, 2H), 0.92-0.98(m, 2H), 1.26(s, 3H), 2.59-2.66(m, 1H), 2.72(t, J=7.2Hz, 2H), 3.03-3.13(m, 2H), 3.08(s, 3H), 6.93(t, J=8.4Hz, 1H), 7.03-7.08(m, 1H), 7.39(t, J=8.4Hz, 1H), 7.53-7.68(m, 3H), 7.72-7.85(m, 4H), 10.37 (s, 1H), 11.08(s, 1H).

Example 4-37

[0799] MS ESI m/e: 650 (M+H), 648 (M-H) .

¹H-NMR(DMSO-d₄, 300MHz) δ 0.64-0.69(m, 2H), 0.92-0.99(m, 2H), 1.31(s, 3H), 2.06 (s, 3H), 2.57-2.64(m, 1H), 3.08 (s, 3H), 6.93(dd, J=9.3,11.1Hz, 1H), 7.19(s, 1H), 7.46(s, 1H), 7.55(d, J=9.3Hz, 1H), 7.79 (d, J=11.1Hz, 1H), 7.83(s, 1H), 10.27(s, 1H), 11.03(s, 1H)

Example 4-38

[0800] MS ESI m/e: 564 (M+H), 562 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 0.75-0.81(m, 2H), 1.06-1.16(m, 5H), 1.40(s, 3H), 2.69-2.76(m, 1H), 3.03(s, 3H), 3.13(s, 1H), 3.92-4.01(m, 2H), 6.77-6.84(m, 1H), 6.92(t, J=8.1Hz, 1H), 7.08-7.13(m, 1H), 7.18-7.33(m, 4H), 7.42(t, J=8.1Hz, 1H), 11.11(s, 1H).

Example 4-39.

[0801] MS ESI m/e: 568 (M+H), 566 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 0.75-0.83(m, 2H), 1.02 (t, J=7.0Hz, 3H), 1.07-1.15(m, 2H), 1.24(t, J=7.7Hz, 3H), 1.38(s, 3H), 2.60-2.76(m, 3H), 3.02(s, 3H), 3.90-4.00(m, 2H), 6.77(s, 1H), 6.94-7.03(m, 3H), 7.08-7.13(m, 1H), 7.19-7.27(m, 2H), 7.41(t, J=7.7Hz, 1H), 11.19(s, 1H).

Example 4-40

[0802] MS ESI m/e: 552 (M+H), 550 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.13 (t, J=6.9Hz, 3H), 1.20(t, J=7.3Hz, 3H), 1.26(s, 3H), 3.11(s, 3H), 3.12(q, J=7.4Hz, 2H), 3.87(q, J=7.1Hz, 2H), 4.30(s, 1H), 7.05-7.15(m,2H), 7.20-7.35(m, 3H), 7.41(t, J=8.0Hz, 1H), 7.52(d, J=11.6Hz, 1H), 9.99(s, 1H), 11.25(s, 1H).

Example 4-41

[0803] MS ESI m/e: 556 (M+H), 554 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.10-1.25(m,12H), 2.62(q, J=7.6Hz, 2H), 3.03(s,3H), 3.12(q, J=7.3Hz, 2H), 3.88(q, J=6.9Hz, 2H), 7.05-7.15(m,3H), 7.20-7.30(m,3H), 7.41(t, J=8.0Hz, 1H), 9.98(s,1H), 11.41(s,1H).

Example 4-42

[0804] MS ESI m/e: 538 (M+H), 536 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.13(t, J=7.2Hz, 3H), 1.27(s, 3H), 3.03(s, 3H), 3.11(s, 3H), 3.87(q, J=6.8Hz, 2H), 4.30(s, 1H), 7.05-7.18 (m, 2H), 7.20-7.35(m, 3H), 7.43(t, J=7.9Hz, 1H), 7.52(d, J=11.3Hz, 1H), 9.94(brs, 1H), 11.25 (brs, 1H).

Example 4-43'

[0805] MS ESI m/e: 502 (M+H), 500 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.13(t, J=7.0Hz, 3H), 1.27(s, 3H), 2.05(s, 3H), 3.11(s, 3H), 3.87(q, J=7.1Hz, 2H), 4.30(s, 1H), 7.04-7.15(m, 2H), 7.28-7.34(m, 1H), 7.37(1, J=8.1Hz, 1H), 7.49-7.60(m, 2H), 7.66-7.70 (m, 1H), 10.10(brs, 1H), 11.24 (brs, 1H).

Example 4-44

[0806] MS ESI m/e: 542 (M+H), 540 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.14(t, J=7.2Hz, 3H), 1.19(t, J=7.5Hz, 3H), 1.25(s, 3H), -2.63(q, J=7.5Hz, 2H), 3.02(s, 3H), 3.03(s, 3H), 3.89 (q, J=7.0Hz, 2H), 7.04-7.18(m, 3H), 7.20-7.30(m, 3H), 7.42(t, J=8.1Hz, 1H), 9.93(brs, 1H), 11.41 (brs, 1H).

Example 4-45

[0807] MS ESI m/e: 506 (M+H), 504 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.14 (t, J=6.2Hz, 3H), 1.19 (t, J=7.5Hz, 3H), 1.25(s, 3H), 2.05(s, 3H), 2.63(q, J=7.5Hz, 2H), 3.03(s, 3H), 3.89(q, J=6.8Hz, 2H), 7.04-7.15(m, 3H), 7.23(d, J=12.0Hz, 1H), 7.37(t, J=8.1Hz, 1H), 7.53-7.60(m, 1H), 7.65-7.70(m, 1H), 10.10(brs, 1H), 11.41(brs, 1H).

Example 4-46.

[0808] MS ESI m/e: 528 (M+H), 526 (M-H).

³¹H-NMR(CDCl₃, 300MHz) δ 0.75-0.82(m, 2H), 1.06-1.16(m, 5H), 1.42(s, 3H), 2.17(s, 3H), 2.68-2.78(m, 1H), 3.13(s, 1H), 3.92-4.01 (m, 2H), 6.90(t, J=7.9Hz, 1H), 6.99-7.06(m, 1H), 7.22-7.46(m, 5H), 7.63-7.68(m, 1H), 11.10(s, 1H).

Example 4-47

[0809] MS ESI m/e: 532 (M+H), 530 (M-H).

¹H-NMR (CDCl₃, 300MHz) δ 0.75-0.83 (m, 2H), 1.02 (t, J=7.0Hz, 3H), 1.08-1.16 (m, 2H), 1.24(t, J=7.5Hz, 3H), 1.40(s, 3H), 2.16(s, 3H), 2.61-2.77(m, 3H), 3.91-4.00(m, 2H), 6.93-7.05(m, 4H), 7.26-7.48 (m, 3H), 7.59-7.64(m, 1H), 11.19(s, 1H).

Example 4-48

[0810] MS ESI m/e: 488 (M+H), 486 (M-H).

¹H-NMR(CDCl₃, 300MHz)δ 1.42 (s, 3H), 2.15(s, 3H), 3.13(s, 1H), 3.23(s, 3H), 3.38 (s, 3H), 6.86(t, J=8.7Hz, 1H), 7.03-7.10 (m, 1H), 7.22-7.41(m, 5H), 7.70(s, 1H), 11.46(s, 1H).

Example 4-49

[0811] MS ESI m/e: 524 (M+H), 522 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 1.41(s, 3H), 3.04(s, 3H), 3.14(s, 1H), 3.23(s, 3H), 3.38(s, 3H), 6.75(s, 1H), 6.89 (t, J=8.5Hz, 1H), 7.11-7.17(m, 1H), 7.18-7.33(m, 4H), 7.43(t, J=8.1.Hz, 1H), 11.47(s, 1H).

Example 4-50

[0812] MS ESI m/e: 492 (M+H), 490 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 1.24 (t, J=7.5Hz, 3H), 1.41(s, 3H), 2.15(s, 3H), 2.65(q, J=7.7Hz, 2H), 3.18(s, 3H), 3.38(s, 3H), 6.88-7.11(m, 4H), 7.32-7.46(m, 3H), 7.63-7.69(m, 1H), 11.45(s, 1H).

Example 4-51

[0813] MS ESI m/e: 528 (M+H), 526 (M-H).

¹H-NMR(CDCl₃, 300MHz) δ 1.24(t, J=7.5Hz, 3H), 1.39(s, 3H), 2.65(q, J=7.3Hz, 2H), 3.03(s, 3H), 3.18(s, 3H), 3.38(s, 3H), 6.84(s, 1H), 6.90-7.03(m, 3H), 7.11-7.17(m, 1H), 7.19-7.30(m, 2H), 7.42(t, J=8.1Hz, 1H), 11.46(s, 1H).

Example 4-52

[0814] MS ESI m/e : 528 (M+H), 526 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 0.64-0.70(m, 2H), 0.91-0.99(m, 2H), 1.25(s, 3H), 2.04(s, 3H), 2.05(s, 3H), 2.58-2.66(m, 1H), 3.07(s, 3H), 7.01-7.10(m, 2H), 7.20-7.25(m, 1H), 7.32-7.43(m, 2H), 7.57-7.63(m, 2H), 10.10(s, 1H), 11.14 (s, 1H).

Example 4-53

[0815] MS ESI m/e: 532 (M+H), 530 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.64-0.71(m, 2H), 0.89(t, J=7.4Hz, 3H), 0.92-0.99(m, 2H), 1.24(s, 3H), 1.54-1.65(m, 2H), 2.04(s, 3H), 2.57(t, J=7.5Hz, 2H), 2.60-2.67(m, 1H), 3.02(s, 3H), 7.01-7.12(m, 3H), 7.18-7.24(m, 1H), 7.33-7.39(m, 1H), 7.58-7.62(m, 2H), 10.10(s, 1H), 11.24(s, 1H).

Example 4-54

[0816] MS ESI m/e: 653 (M+H), 651 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.60-0.71(m, 2H), 0.90-1.01(m, 2H), 1.27(s, 3H), 2.58-2.67(m, 1H), 3.08(s, 3H), 6.89-7.01 (m, 2H), 7.09-7.23(m, 4H), 7.30-7.39(m, 1H) 7.51-7.59(m, 1H), 7.73-7.83(m, 1H), 9.69(brs, 1H), 11.09(brs, 1H).

Example 4-55

[0817] MS ESI m/e: 637 (M+H), 635 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.69(m,2H), 0.96(m,2H), 1.17(s,3H), 2.62(m,1H), 3.09(s,3H), 3.26(s,3H), 6.95(t, J=8.6Hz, 1H), 7.56(d, J=8.7Hz, 1H), 7.70-7.85(m,3H), 7.90-8.00 (m, H) , 11.04(s,1H).

Example 4-56

[0818] MS ESI m/e: 504 (M+H), 502 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.65-0.71 (m, 2H), 0.92-0.99(m, 2H), 1/24(s, 3H), 2.04(s, 3H), 2.32(s, 3H), 2.58-2.67(m, 1H), 3.02(s, 3H), 7.00-7.10(m, 3H), 7.20(d, J=12.0Hz, 1H), 7.36(t, J=8.2Hz, 1H), 7.56-7.63(m, 2H), 10.10(s, 1H), 11.24 (s, 1H).

Example 4-57

[0819] MS ESI m/e: 558 (M+H), 556 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.64-0.71(m, 2H), 0.90-0.99(m, 2H), 1.24(s, 3H), 1.46-1.57(m, 2H), 1.58-1.69(m, 2H), 1.71-1.83 (m, 2H), 1.97-2.07(m, 2H), 2.04(s, 3H), 2.58-2.68(m, 1H), 2.93-3.06 (m, 1H), 3.03(s, 3H), 7.00-7.14(m, 3H), 7.24 (dd, J=1.2, 12.0Hz, 1H), 7.36 (t, J=8.2Hz, 1H), 7.57-7.63(m, 1H), 10.10(s, 1H), 11.22(s, 1H).

Example 4-58

[0820] MS ESI m/e: 651 (M+H), 649 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.65-0.71(m, 2H), 0.93-1.00(m, 2H), 1.10(t, J=7.3Hz, 3H), 1.17(s, 3H), 2.56-2.66 (m, 1H), 3.09(s, 3H), 3.29-3.40(m, 2H), 6.95(t, J=8.7Hz, 1H), 7.52-7.58(m, 1H), 7.73-7.82(m, 3H), 7.88-7.95(m, 2H), 11.04 (s, 1H).

Example 4-59

[0821] MS ESI m/e: 721 (M+H), 719(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.61-0.71(m, 2H), 0.91-1.01(m, 2H), 1.26(s, 3H), 1.35-1.60(m, 6H), 2.59-2.67(m, 1H), 2.99-3.12(m, 4H), 3.07(s, 3H), 6.89-6.94(m, 1H), 7.04-7.06(m, 1H), 7.13-7.17(m, 2H), 7.34-7.39 (m, 1H), 7.54-7.57(m, 1H), 7.77-7.80 (m, 1H), 10.06(brs, 1H), 11.06(brs, 1H).

Example 4-60

[0822] MS ESI m/e : 630 (M+H), 628(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.63-0.72(m, 2H), 0.91-1.01(m, 2H), 1.09(t, J=7.5Hz, 3H), 1.27(s, 3H), 2.34(q, J=7.0Hz, 2H), 2.59-2.70(m, 1H), 3.09(s, 3H), 6.91-7.08 (m, 2H), 7.34-7.40 (m, 1H), 7.56-7.69(m, 3H), 7.78-7.82(m, 1H), 10.03 (brs, 1H), 11.09(brs, 1H).

Example 4-61

[0823] MS, ESI m/e: 533 (M+H), 531 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.64-0.73(m, 2H), 0.91-1.01(m, 2H), 1.22(s, 3H), 2.04(s, 3H), 2.58-2.68(m, 1H), 2.92(s, 6H), 2.98(s, 3H), 6.55(dd, J=3.0, 9.1Hz, 1H), 6.62(dd, J=2.6, 14.3Hz, 1H), 6.99-7.11(m, 2H), 7.35(t, J=7.9Hz, 1H), 7.55-7.62(m, 2H), 10.09(brs, 1H), 11.27(brs, 1H).

Example 4-62

[0824] MS ESI m/e: 673(M+H), 671(M-H).

²H-NMR(DMSO-d₆, 300MHz) δ 0.63-0.69(m, 2H), 0.91-0.98(m, 2H), 1.33(s, 3H), 2.03(s, 6H), 3.08(s, 3H), 6.91(dd, J=10.5, 9.6Hz, 1H), 7.28(s, 2H), 7.55(d, J=9.6Hz, 1H), 7.78 (d, J=10.5Hz, 1H), 10.09(s, 1H), 7.92(s, 1H), 11.09(s, 1H)

Example 4-63

[0825] MS ESI m/e: 646.0(M+H), 644.0(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.63-0.69 (m, 2H), 0.91-0.98 (m, 2H), 1.28(s, 3H), 2.08(s, 3H), 2.57-2.65(m, 1H), 3.07 (s, 3H), 3.89(s, 3H), 6.91(dd, J=12.0, 9.0Hz, 1H), 7.07(s, 2H), 7.55(d, J=9.0Hz, 1H), 7.79 (d, J=12.0Hz, 1H), 7.95(s, 1H), 9.27(s, 1H), 11.12(s, 1H)

Example 4-64

[0826] MS ESI m/e: 685.9, 687.9, 684.0, 685.9

¹H-NMR(DMSO-d₆, 300MHz) δ 0.64-0.70(m, 2H), 0.92-0.99(m, 2H) 1-31 (s, 3H), 2.57-2.63(m, 1H), 3.08(s, 6H), 6.94(dd, J=9.0, 12.0Hz, 1H), 7.22-7.22(m, 1H), 7.27-7.27(m, 2H), 7.56(d, J=9.0Hz, 1H), 7.79(d, J=12.0Hz, 1H), 10.16(s, 1H), 11.04(s, 1H)

Example 4-65

[0827] MS ESI m/e: 571.1 (M+H), 569.2 (M-H)

¹H-NMR(DMSO-d₆, 300MHz) δ 0.64-0.69(m, 2H), 0.93-1.00(m, 2H), 1.35(s, 3H), 2.04(s, 6H), 2.59-2.67 (m, 1H), 3.11 (s, 3H), 4.32(s, 1H), 7.09(dd, J=9.0, 12.0Hz, 1H), 7.30 (s, 2H), 7.33(d, J=9.0Hz, 1H), 7.53(d, J=12.0Hz, 1H), 7.94(s, 1H), 10.11(s, 2H), 11.12(s, 1H)

Example 4-66.

[0828] MS ESI m/e: 616.0(M+H), 614.0(M-H).

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$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.63-0.68 (m, 2H), 0.92-0.99 (m, 2H), 1.23(s, 3H), 2.07(s, 3H), 2.58-2.66 (m, 1H), 3.07 (s, 3H), 6.92(dd, J=9.0, 9.0Hz, 1H), 7.28(d, J=9.0Hz, 2H), 7.55(d, J=9.0Hz, 1H), 7.64(d, J=9.0Hz, 2H), 7.79(d, J=9.0Hz, 1H), 10.10(s, 1H), 11.06(s, 1H).

5 Example 4-67

[0829] MS ESI m/e: 530 (M+H), 528 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.62-0.76 (m, 4H), 0.90-1.03(m, 4H), 1.24(s, 3H), 1.88-2.02 (m, 1H), 2.04(s, 3H), 2.58-2.68 (m, 1H), 3.01(s, 3H), 6.92-7.11(m, 4H), 7.35(t, J=8.6Hz, 1H), 7.55-7.64(m, 2H), 10.09(s, 1H), 11.23(s, 1H).

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Example 4-68

[0830] MS ESI m/e: 660 (M+H), 658 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.56-0.64(m, 2H), 0.85-0.95(m, 2H), 1.26(s, 3H), 2.04(s, 3H), 2.46-2.60(m, 1H), 3.20 (brs, 3H), 3.46-3.55(m, 2H), 4.01-4.11(m, 2H), 6.91(t, J=8.5Hz, 1H), 6.97-7.07(m, 1H), 7.35(t, J=7.8Hz, 1H), 7.45(d, J=8.4Hz, 1H), 7.54-7.67(m, 2H), 7.73(d, J=9.9Hz, 1H), 10.09(s, 1H), 10.13(s, 1H).

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Example 4-69

20 **[0831]** MS ESI m/e: 696 (M+H), 694 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.56-0.66(m, 2H), 0.81-0.97(m, 2H), 1.26(s, 3H), 2.50-2.59(m, 1H), 3.00(s, 3H), 3.19(s, 3H), 3.50(t, J=5.3Hz, 2H), 4.05(t, J=5.1Hz, 2H), 6.90(t, J=8.9Hz, 1H), 7.07-7.15(m, 1H), 7.18-7.27(m, 2H), 7.35-7.50(m, 2H), 7.69-7.78(m, 1H), 9.90(brs, 1H), 10.16(brs, 1H).

25 Example 4-70

[0832] MS ESI m/e: 652.0 (M+H), 650.0(M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 400MHz) δ 0.60-0.64(m, 2H), 0.89-0.94 (m, 2H), 1.19(s, 3H), 2.55-2.62 (m, 1H), 2.99 (s, 3H), 3.03 (s, 3H), 6.88(dd, J=8.0, 8.0Hz, 1H), 7.21(d, J=8.0Hz, 2H), 7.29 (d, J=8.0Hz, 2H), 7.51(d, J=8.0Hz, 1H), 7.75 (d, J=8.0Hz, 1H), 9.91(s, 1H), 11.02(s, 1H)

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Example 4-71

[0833] MS ESI m/e: 514.1 (M+H), 512.2 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.63-0.69 (m, 2H), 0.91-0.99 (m, 2H), 1.24 (s, 3H), 2.07 (s, 3H), 2.59-2.66 (m, 1H), 3.10 (s, 3H), 4.30 (s, 1H), 7.09(dd, J=8.7, 8.4Hz, 1H), 7.28(d, J=8.4Hz, 2H), 7.31(d, J=8.7Hz, 1H), 7.52 (d, J=8.4Hz, 1H), 7.64 (d, J=8.4Hz, 2H), 10.10(s, 1H), 11.08 (s, 1H)

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Example 4-72

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[0834] MS ESI m/e: 559 (M+H), 557 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.62-0.72 (m, 2H), 0.90-1.01 (m, 2H), 1.18 (s, 3H), 2.57-2.67 (m, 1H), 3.07 (s, 3H), 6.93 (t, J=8.5Hz, 1H), 7.34-7.50 (m, 5H), 7.52-7.58 (m, 1H), 7.79 (dd, J=1.5, 10.2Hz, 1H), 11.06 (brs, 1H).

45 Example 4-73

[0835] MS ESI m/e: 668 (M+H), 666 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.62-0.72 (m, 2H), 0.92-1.01 (m, 2H), 1.30 (s, 3H), 2.60-2.69 (m, 1H), 3.10 (s, 3H), 6.91-6.99 (m, 1H), 7.06-7.11 (m, 1H), 7.38-7.42(m, 1H), 7.52-7.60(m, 1H), 7.75-7.95 (m, 5H), 9.98 (brs, 1H), 11.09 (brs, 1H), 12.68 (brs, 1H).

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MS ESI m/e: 681 (M+H), 679 M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.64-0.72 (m, 2H), 0.90-1.02 (m, 2H), 1.31 (s, 3H), 2.60-2.69 (m, 1H), 3.09 (s, 3H), 3.89 (s, 3H), 6.09-6.11 (m, 1H), 6.90-6.97 (m, 1H), 7.01-7.11 (m, 3H), 7.37-7.42 (m, 1H), 7.52-7.60 (m, 1H), 7.73-7.84 (m, 3H), 9.90 (brs, 1H), 11.10 (brs, 1H).

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Example 4-74

[0836] MS ESI m/e: 647 (M+H), 645 (M-H).

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$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.64-0.69 (m, 2H), 0.92-0.99 (m, 2H), 1.27 (s, 3H), 2.58-2.66(m, 1H), 3.08 (s, 3H), 3.62 (s, 3H), 6.92(t, J=8.6Hz, 1H), 6.99-7.02 (m, 1H), 7.33 (t, J=8.1Hz, 1H), 7.54-7.57 (m, 1H), 7.61-7.66(m, 2H), 7.79(dd, J=1.8, 10.2Hz, 1H), 9.05(s, 1H), 9.58 (s, 1H), 11.08 (s, 1H).

5 Example 4-75

[0837] MS ESI m/e: 518.0 (M+H), 516.0(M-H).

10 $^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.64-0.70 (m, 2H), 0.92-1.00 (m, 2H), 1.19 (t, J=7.8Hz, 3H), 1.23 (s, 3H), 2.07 (s, 3H), 2.57-2.65 (m, 1H), 2.63 (q, J=7.8Hz, 2H), 3.02(s, 3H), 7.07-7.09 (m, 2H), 7.21-7.25 (m, 1H), 7.28 (d, J=9.0Hz, 2H) 7.63 (d, J=8.7Hz, 2H), 10.10 (s, 1H), 11.22(s, 1H)

Example 4-76

[0838] MS ESI m/e: 550.1 (M+H), 548.1 (M-H)

15 $^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.63-0.69 (m, 2H), 0.91-0.99 (m, 2H), 1.24 (s, 3H), 2.07 (s, 3H), 2.59-2.66 (m, 1H), 3.10 (s, 3H), 4.30 (s, 1H), 7.09 (dd, J=8.7, 8.4Hz, 1H), 7.28 (d, J=8.4Hz, 2H), 7.31 (d, J=8.7Hz, 1H), 7.52 (d, J=8.4Hz, 1H), 7.64 (d, J=8.4Hz, 2H), 10.10 (s, 1H), 11.08 (s, 1H)

Example 4-77

20 **[0839]** MS ESI m/e: 666.0 (M+H), 664.0 (M-H).
 $^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.63-0.69 (m, 2H), 0.92-0.99 (m, 2H), 1.21 (t, J=7.4Hz, 3H), 1.23 (s, 3H), 2.58-2.65 (m, 1H), 3.14 (q, J=7.4Hz, 2H), 6.92 (dd, J=7.5, 10.5Hz, 1H), 7.26 (d, J=9.0Hz, 2H), 7.32 (d, J=9.0Hz, 2H), 7.55 (d, J=7.5Hz, 1H), 7.79 (d, J=10.5Hz, 1H), 9.98 (s, 1H), 11.06 (s, 1H)

25 Example 4-78

[0840] MS ESI m/e: 554.2 (M+H), 552.1 (M-H)

30 $^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.64-0.70 (m, 2H), 0.92-0.99 (m, 2H), 1.19 (t, J=7.5Hz, 3H), 1.22 (s, 3H), 2.55-2.63 (m, 1H), 2.63 (q, J=7.5Hz, 2H), 3.02 (s, 3H), 3.04 (s, 3H), 7.07-7.09 (m, 2H), 7.21-7.25 (m, 1H), 7.25 (d, J=9.3Hz, 2H), 7.34 (d, J=9.3Hz, 2H), 9.95 (s, 1H), 11.22 (s, 1H)

Example 4-79

35 **[0841]** MS ESI m/e: 664 (M+H), 662 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 400MHz) δ 0.28-0.34 (m, 2H), 0.69-0.77 (m, 2H), 1.06 (brs, 3H), 2.30-2.37 (m, 1H), 2.99 (s, 3H), 4.21 (t, J=9.2Hz, 2H), 4.72 (t, J=8.6Hz, 2H), 6.50-6.57 (m, 1H), 7.06-7.11 (m, 1H), 7.14-7.24 (m, 3H), 7.29-7.35 (m, 1H), 7.35-7.41 (m, 1H), 9.91 (brs, 1H).

40 Example 4-80

[0842] MS ESI m/e: 661 (M+H), 659 (M-H).

45 $^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.65-0.69 (m, 2H), 0.93-0.98 (m, 2H), 1.27 (s, 3H), 2.60-2.65 (m, 1H), 3.05 (s, 3H), 3.08 (s, 3H), 3.67 (s, 3H), 6.92 (t, J=8.5Hz, 1H), 7.00-7.03 (m, 1H), 7.34 (t, J=7.9Hz, 1H), 7.54-7.57 (m, 1H), 7.61-7.67 (m, 2H), 7.77-7.81 (m, 1H), 9.24 (s, 1H), 11.08 (s, 1H).

Example 4-81

[0843] MS ESI m/e: 617 (M+H), 615 (M-H).

50 $^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.63-0.70 (m, 2H), 0.92-0.98 (m, 2H), 1.28 (s, 3H), 2.59-2.66 (m, 1H), 3.08 (s, 3H), 5.89 (s, 2H), 6.87-6.94 (m, 2H), 7.28 (t, J=7.9Hz, 1H), 7.35-7.45 (m, 2H), 7.53-7.56 (m, 1H), 7.75-7.81 (m, 1H), 8.71 (s, 1H), 11.09 (s, 1H).

Example 4-82

55 **[0844]** MS ESI m/e: 632 (M+H), 630 (M-H).
 $^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.64-0.69 (m, 2H), 0.92-0.98 (m, 2H), 1.25 (s, 3H), 2.60-2.64 (m, 1H), 3.08 (s, 3H), 3.99 (d, J=6.0Hz, 2H), 5.64 (t, J=6.0Hz, 1H), 6.92 (t, J=8.5Hz, 1H), 7.05-7.08 (m, 1H), 7.37(t, J=7.9Hz, 1H), 7.53-7.56 (m,

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1H), 7.71-7.81(m, 3H), 9.83 (s, 1H), 11.07 (s, 1H).

Example 4-83

5 **[0845]** MS ESI m/e: 511, 513 (M+H), 509, 511 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 1.20 (s, 3H), 3.08 (s, 3H), 3.22 (s, 3H), 3.50(t, J=6.2Hz, 2H), 4.04(t, J=6.2Hz, 2H), 7.07 (d, J=8.7Hz, 2H), 7.35-7.51(m, 5H), 7.55 (d, J=8.7Hz, 2H), 11.06 (s, 1H).

Example 4-84

10 **[0846]** MS ESI m/e: 511, 513 (M+H), 509, 511 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 1.22 (s, 3H), 3.08 (s, 3H), 4.50 (s, 2H), 7.08 (d, J=8.7Hz, 2H), 7.38-7.52 (m, 5H), 7.55 (d, J=8.7Hz, 2H), 10.89 (s, 1H).

Example 4-85

15 **[0847]** MS ESI m/e: 497, 499 (M+H), 495, 497 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 1.20 (s, 3H), 3.08 (s, 3H), 3.53 (q, J=6.3Hz, 2H), 3.94 (t, J=6.4Hz, 2H), 4.77 (t, J=5.8Hz, 1H), 7.06 (d, J=9.0Hz, 2H), 7.37-7.51 (m, 5H), 7.55(d, J=9.0Hz, 2H), 11.10 (s, 1H).

Example 4-86

20 **[0848]** MS ESI m/e: 524, 526 (M+H), 522, 524 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 1.20 (s, 3H), 2.16 (s, 6H), 2.42 (t, J=6.8Hz, 2H), 3.08 (s, 3H), 3.94 (t, J=7.2Hz, 2H), 7.07 (d, J=9.0Hz, 2H), 7.37-7.51 (m, 5H), 7.56 (d, J=8.7Hz, 2H), 11.07 (s, 1H).

Example 4-87

30 **[0849]** MS ESI m/e : 681 (M+H), 679 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.64-0.72 (m, 2H), 0.90-1.02 (m, 2H), 1.31 (s, 3H), 2.60-2.69 (m, 1H), 3.09 (s, 3H), 3.89 (s, 3H), 6.09-6.11 (m, 1H), 6.90-6.97 (m, 1H), 7.01-7.11 (m, 3H), 7.37-7.42 (m, 1H), 7.52-7.60 (m, 1H), 7.73-7.84 (m, 3H), 9.90 (brs, 1H), 11.10 (brs, 1H).

Example 4-88

35 **[0850]** MS ESI m/e: 614 (M+H), 612 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.72 (m, 2H), 0.91-1.01 (m, 2H), 1.31 (s, 3H), 2.55-2.68 (m, 1H), 3.09 (s, 3H), 3.57 (s, 2H), 6.87-6.96 (m, 3H), 7.25-7.28 (m, 1H), 7.55-7.58 (m, 1H), 7.78-7.81 (m, 1H), 10.49 (brs, 1H), 11.08 (brs, 1H).

Example 4-89

40 **[0851]** MS ESI m/e: 668 (M+H), 666 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.71 (m, 2H), 0.91-1.01 (m, 2H), 1.29 (s, 3H), 2.60-2.70 (m, 1H), 3.08 (s, 3H), 6.93 (dd, J=9.0, 9.0Hz, 1H), 7.08 (d, J=9.0Hz, 1H), 7.40 (dd, J=9.0, 9.0Hz, 1H), 7.56 (d, J=9.0Hz, 1H), 7.70 (s, 1H), 7.80 (d, J=9.0Hz, 2H), 8.05 (s, 1H), 8.38 (s, 1H), 9.96 (brs, 1H), 11.08 (brs, 1H), 13.27 (brs, 1H).

Example 4-90

50 **[0852]** MS ESI m/e: 603 (M+H), 601 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 0.64-0.71 (m, 2H), 0.93-1.00 (m, 2H), 1.19 (s, 3H), 2.58-2.66 (m, 1H), 3.08 (s, 3H), 6.95 (t, J=8.5Hz, 1H), 7.46-7.58 (m, 3H), 7.79 (dd, J=1.5, 10.2Hz, 1H), 8.01 (d, J=8.7Hz, 2H), 11.01 (s, 1H), 13.14 (br, 1H).

Example 4-91

55 **[0853]** MS ESI m/e: 602 (M+H), 600 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.64-0.71 (m, 2H), 0.92-1.00 (m, 2H), 1.19 (s, 3H), 2.59-2.65 (m, 1H), 3.08 (s, 3H), 6.94 (t, J=8.7Hz, 1H), 7.42-7.49 (m, 3H), 7.53-7.58 (m, 1H), 7.76-7.81 (m, 1H), 7.94 (d, J=8.7Hz, 2H), 8.07 (brs, 1H), 11.02 (s, 1H).

Example 4-92

[0854] MS ESI m/e: 616 (M+H) 614 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.64-0.70 (m, 2H), 0.92-1.00 (m, 2H), 1.18 (s, 3H), 2.58-2.66 (m, 1H), 2.81 (d, J=4.5Hz, 3H), 3.08 (s, 3H), 6.94 (t, J=8.7Hz, 1H), 7.47 (d, J=8.6Hz, 2H), 7.52-7.58 (m, 1H), 7.76-7.82 (m, 1H), 7.90 (d, J=8.6Hz, 2H), 8.51-8.56 (m, 1H), 11.02 (brs, 1H).

Example 4-93

[0855] MS ESI m/e: 630 (M+H), 628 (M-H) .

¹H-NMR (DMSO-d₆, 300MHz) δ 0.64-0.70 (m, 2H), 0.92-1.00 (m, 2H), 1.22 (s, 3H), 2.59-2.66 (m, 1H), 2.93 (brs, 3H), 3.00 (brs, 3H), 3.08 (s, 3H), 6.94 (t, J=8.5Hz, 1H), 7.42-7.49 (m, 4H), 7.53-7.57 (m, 1H), 7.77-7.81 (m, 1H), 11.04 (s, 1H).

Example 4-94

[0856] MS ESI m/e: 617 (M+H), 615 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.64-0.69 (m, 2H), 0.92-0.99 (m, 2H), 1.19 (s, 3H), 2.58-2.65 (m, 1H), 3.07 (s, 3H), 3.63 (s, 2H), 6.92 (t, J=8.7Hz, 1H), 7.28-7.36 (m, 4H), 7.53-7.57 (m, 1H), 7.75-7.81 (m, 1H), 11.07 (br, 1H), 12.39 (br, 1H).

Example 4-95

[0857] MS ESI m/e: 661 (M+H), 659 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.61-0.71 (m, 2H), 0.90-1.00 (m, 2H), 1.28 (s, 3H), 2.55-2.68 (m, 1H), 3.08 (s, 3H), 3.14 (q, J=5.6Hz, 2H), 3.43 (q, J=5.6Hz, 2H), 4.74 (t, J=5.6Hz, 1H), 6.20 (t, J=5.6Hz, 1H), 6.83-6.97 (m, 2H), 7.22-7.38 (m, 2H), 7.48 (s, 1H), 7.54 (d, J=9.0Hz, 1H), 7.78 (d, J=10.5Hz, 1H), 8.75 (s, 1H), 11.08 (s, 1H).

Example 4-96

[0858] MS ESI m/e: 784 (M+H), 782 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.71 (m, 2H), 0.90-1.02 (m, 2H), 1.24 (s, 3H), 2.57-2.69 (m, 1H), 3.00 (q, J=6.7Hz, 4H), 3.07 (s, 3H), 3.35 (q, J=6.7Hz, 2H), 3.89 (t, J=6.7Hz, 2H), 4.60 (t, J=5.7Hz, 1H), 6.86-7.05 (m, 3H), 7.10-7.21 (m, 2H), 7.35 (t, J=7.8Hz, 1H), 7.55 (d, J=7.8Hz, 1H), 7.71 (t, J=5.7Hz, 1H), 7.79 (dd, J=1.8, 9.6Hz, 1H), 9.88 (s, 1H), 11.09 (s, 1H).

Example 4-97

[0859] MS ESI m/e: 530 (M+H), 528 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.63-0.71 (m, 2H), 0.91-1.00 (m, 2H), 1.25 (s, 3H), 2.04(s, 3H), 2.10 (s, 3H), 2.58-2.68 (m, 1H), 3.07 (s, 3H), 5.16 (s, 1H), 5.52 (s, 1H), 7.04 (d, J=6.9Hz, 1H), 7.11 (t, J=8.6Hz, 1H), 7.32-7.40 (m, 2H), 7.51 (dd, J=1.8, 12.6Hz, 1H), 7.56-7.63 (m, 2H), 10.10 (s, 1H), 11.22 (s, 1H).

Example 4-98

[0860] MS ESI m/e: 532 (M+H), 530 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.60-0.73 (m, 2H), 0.89-1.00 (m, 2H), 1.20 (d, J=6.4Hz, 6H), 1.24 (s, 3H), 2.04 (s, 3H), 2.56-2.68 (m, 1H), 2.84-2.97 (m, 1H), 3.03 (s, 3H), 6.97-7.16 (m, 3H), 7.19-7.29 (m, 1H), 7.35 (t, J=8.0Hz, 1H), 7.53-7.66 (m, 2H), 10.10 (s, 1H), 11.22 (s, 1H).

Example 4-99

[0861] MS ESI m/e: 634. 0 (M+H), 632.1 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.63-0.69 (m, 2H), 0.91-0.98 (m, 2H), 1.28 (s, 3H), 2.09 (s, 3H), 2.57-2.66 (m, 1H), 3.07 (s, 3H), 6.92 (dd, J=9.0, 8.7Hz, 1H), 7.14-7.19 (m, 1H), 7.33 (dd, J=8.7, 10.5Hz, 1H), 7.55(d, J=8.7Hz, 1H), 7.79(d, J=12.0Hz, 1H), 7.88-7.92(m, 1H), 9.87 (s, 1H), 11.09 (s, 1H)

Example 4-100

[0862] MS ESI m/e: 646 (M+H), 644 (M-H).

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$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.52-0.62 (m, 2H), 0.82-0.96 (m, 2H), 1.28 (s, 3H), 2.04 (s, 3H), 2.44-2.59 (m, 1H), 3.58-3.65 (m, 2H), 4.01-4.08 (m, 2H), 5.58 (t, J=4.5Hz, 1H), 6.91 (t, J=8.6Hz, 1H), 6.99-7.08 (m, 1H), 7.30-7.45 (m, 2H), 7.57-7.65 (m, 2H), 7.66-7.75 (m, 1H), 10.09 (brs, 1H), 10.12 (brs, 1H).

5 Example 4-101

[0863] MS ESI m/e: 670.0 (M+H), 668.0 (M-H)

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.60-0.67 (m, 2H), 0.89-0.96 (m, 2H), 1.35 (s, 3H), 2.56-2.62 (m, 1H), 2.60 (s, 3H), 3.09 (s, 3H), 6.49-6.56 (m, 1H), 6.84-6.99 (m, 3H), 7.22 (dd, J=2.4, 7.5Hz, 1H), 7.46-7.52(m, 1H)

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Example 4-102

[0864] MS ESI m/e: 532.1 (M+H), 530.2 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.65-0.69 (m, 2H), 0.92-0.94 (m, 2H), 1.29 (s, 3H), 2.09 (s, 3H), 2.59-2.63 (m, 1H), 3.10 (s, 3H), 4.29 (s, 1H), 7.06-7.54 (m, 5H), 7.90 (d, 1H, J = 6.6 Hz), 9.86 (s, 1H), 11.11 (s, 1H).

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Example 4-103

[0865] MS ESI m/e: 615.1 (M+H), 613.1 (M-H)

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.63-0.71 (m, 2H), 0.91-0.98(m, 2H), 1.23 (s, 3H), 2.57-2.65 (m, 1H), 3.07 (s, 3H), 6.88-6.96 (m, 4H), 7.55 (d, J=8.7Hz, 1H), 7.78 (d, J=10.5Hz, 1H), 10.76 (s, 1H), 10.79 (s, 1H), 11.10 (s, 1H)

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Example 4-104

[0866] MS ESI m/e: 638 (M+H), 636 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.64-0.70 (m, 2H), 0.93-0.99 (m, 2H), 1.19 (s, 3H), 2.57-2.65 (m, 1H), 3.08 (s, 3H), 6.90-6.98(m, 1H), 7.48 (s, 2H), 7.52-7.61(m, 3H), 7.75-7.82 (m, 1H), 7.89 (d, J=8.6Hz, 2H), 11.00 (s, 1H).

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Example 4-105

[0867] MS ESI m/e: 536 (M+H), 534 (M-H). $^1\text{H-NMR}$ DMSO- d_6 , 300MHz) δ 0.63-0.71 (m, 2H), 0.91-1.00 (m, 2H), 1.24 (s, 3H), 2.04 (s, 3H), 2.51 (s, 3H), 2.59-2.65 (m, 1H), 3.04 (s, 3H), 7.00-7.14 (m, 3H), 7.27-7.40 (m, 2H), 7.56-7.62 (m, 2H), 10.09 (brs, 1H), 11.22 (brs, 1H).

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Example 4-106

[0868] MS ESI m/e: 572 (M+H), 570 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.62-0.72(m, 2H), 0.91-1.0 (m, 2H), 1.24 (s, 3H), 2.51 (s, 3H), 2.60-2.67 (m, 1H), 3.01(s, 3H), 3.04 (s, 3H), 7.05-7.15 (m, 3H), 7.20-7.34 (m, 3H), 7.40 (t, J=4.1Hz, 1H), 9.88(s, 1H), 11.22(s, 1H).

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Example 4-107

[0869] MS ESI m/e: 599 (M+H), 597 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.66-0.72(m, 2H), 0.93-0.98(m, 2H), 1.12(d, J=3.0Hz, 3H), 2.60-2.67(m, 1H), 3.08(s, 3H), 6.90-6.97 (m, 1H), 7.15-7.25(m, 1H), 7.54-7.57(m, 2H), 7.64-7.69(m, 1H), 7.77-7.81(m, 1H), 8.31(d, J=3.8Ez, 1H), 11.12(d, J=3.4Hz, 1H), 12.60(d, J=14.3Hz, 1H).

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Example 4-108

[0870] MS ESI m/e: 657 (M+H), 655 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.62-0.74 (m, 2H), 0.90-1.01(m, 2H), 1.26 (s, 3H), 2.58-2.70 (m, 1H), 3.08(s, 3H), 4.06 (s, 2H), 6.92(t, J=8.6Hz, 1H), 7.36-7.47(m, 3H), 7.51-7.60(m, 2H), 7.78(dd, J=1.8, 10.2Hz, 1H), 8.31(s, 1H), 11.04(s, 1H).

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Example 4-109

[0871] MS ESI m/e: 657 (M+H), 655 (M-H).

$^1\text{H-NMR}$ (DMSO- d_6 , 300MHz) δ 0.62-0.71 (m, 2H), 0.90-0.99(m, 2H), 1.26 (s, 3H), 2.56-2.67(m, 1H), 3.08(s, 3H), 4.44 (s, 2H), 6.93(t, J=8.7Hz, 1H), 7.13(d, J=7.5Hz, 1H), 7.45 (t, J=8.1Hz, 1H), 7.50-7.58 (m, 2H), 7.71-7.82 (m, 2H), 11.10

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(s, 1H), 11.23(s, 1H).

Example 4-110

5 **[0872]** MS ESI m/e : 643 (M+H), 641 (M-H).
¹H-NMR (DMSO-d₆, 300MHz) δ 0.62-0.72(m, 2H), 0.90-1.00(m, 2H), 1.27 (s, 3H), 2.58-2.67 (m, 1H) 3.08(s, 3H), 3.60-3.86 (m, 2H), 4.16-4.32(m, 2H), 6.84-6.97(m, 2H), 7.28(t, J=7.8Hz, 1H), 7.40-7.73(m, 2H), 7.55(d, J=8.4Hz, 1H), 7.78(dd, J=1.5, 10.2Hz, 1H), 9.15-9.51(brs, 1H), 11.09(s, 1H).

10 Example 4-111

[0873] MS ESI m/e: 613 (M+H), 611 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) 0.65-0.74(m, 2H), 0.91-1.01(m, 2H), 1.11 (s, 3H), 2.58-2.69 (m, 1H), 3.08(s, 3H), 3.89 (s, 3H), 6.94 (t, J=8.4Hz, 1H), 7.26-7.34(m, 1H), 7.51-7.58(m, 1H), 7.59-7.67(m, 2H), 7.74-7.84(m, 1H), 8.27(s, 1H), 11.10(brs, 1H).

Example 4-112

20 **[0874]** MS ESI m/e: 613 (M+H), 611 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 0.63-0.74(m, 2H), 0.91-1.02 (m, 2H), 1.13 (s, 3H), 2.57-2.69(m, 1H), 3.08(s, 3H), 4.09 (s, 3H), 6.94(t, J=8.5Hz, 1H), 7.39-7.47(m, 1H), 7.51-7.60(m, 1H), 7.66-7.74 (m, 2H), 7.75-7.83(m, 1H), 8.09(s, 1H), 11.10(brs, 1H).

Example 4-113

25 **[0875]** MS ESI m/e: 602 (M+H), 600 (M-H)
¹H-NMR(DMSO-d₆, 300MHz, 120°C) δ 0.72 (m,2H), 0.95(m, 2H), 1.30(s, 3H), 2.67(m, 1H), 3.12(s, 3H), 6.88(t, J=8.4Hz, 1H), 7.07(dd, J=1.8, 8.8Hz, 1H), 7.36(t, J=7.9Hz, 1H), 7.40-7.55(m, 3H), 7.67 (dd, J=1.8, 10.3Hz, 1H), 8.39(brs,1H), 9.84(brs,1H), 10.90(s,1H).

Example 4-114

30 **[0876]** MS ESI m/e: 679 (M+H), 677 (M-H).
¹H-NMR(DMSO-d₆, 400MHz)δ 0.62-0.72(m, 2H), 0.91-1.01(m, 2H), 1.25(s, 3H), 2.59-2.66(m, 1H), 3.08(s,3H), 3.48-3.56 (m, 2H), 3.84(t, J=6.4Hz, 2H), 6.92(t, J=8.6Hz, 1H), 7.09(d, J=8.0Hz, 1H), 7.16-7.26(m, 2H), 7.44 (t, J=8.2Hz, 1H), 7.55 (d, J=8.0Hz, 1H), 7.74-7.83 (m, 2H), 11.10(s, 1H).

Examples 4-115

40 **[0877]** MS ESI m/e: 599 (M+H), 597 (M-H).
¹H-NMR(DMSO-d₆, 300MHz)δ 0.65-0.73 (m, 2H), 0.91-1.00 (m, 2H), 1.14(s, 3H), 2.59-2.67(m, 1H), 3.09(s, 3H), 6.92 (t, J=4.1Hz, 1H), 7.11-7.16(m, 1H), 7.53-7.59(m, 2H), 7.76-7.83(m, 2H); 8.14(s, 1H), 11.10(s, 1H), 13.20(s,1H).

Example 4-116

45 **[0878]** MS ESI m/e: 685.9 (M+H), 684.0 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 0.62-0.70(m, 2H), 0.92-0.98 (m, 2H), 1.26 (s, 3H), 2.57-2.65 (m, 1H), 3.08 (s, 3H), 3.09(s, 3H), 6.94(dd, J=9.0, 8.7Hz, 1H), 7.38 (dd, J=2.3, 8.6Hz, 1H), 7.51-7.57(m, 3H), 7.63 (d, J=2.3Hz, 1H), 7.78(dd, J=1.5, 10.2Hz, 1H), 9.59 (s, 1H), 11.01(s, 1H)

Example 4-117

50 **[0879]** MS ESI m/e: 666.0 (M+H), 664.1 (M-H).
¹H-NMR(DMSO-d₆, 300MHz) δ 0.61-0.68 (m, 2H), 0.90-0.97 (m, 2H), 1.23(s, 3H), 2.30(s, 3H), 2.55-2.63 (m, 1H) 3.09 (s, 3H), 6.88-6.95(m, 1H), 7.15-7.34(m, 3H), 7.47-7.57(m, 2H), 7.70-7.80 (m, 2H).

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Example 4-118

[0880] MS ESI m/e: 630 (M+H), 628 (M-H).

5 $^1\text{H-NMR}(\text{CDCl}_3, 300\text{MHz}) \delta$ 0.75-0.81(m, 2H), 1.09-1.15(m, 2H), 1.47(s, 3H), 2.70-2.77 (m, 1H), 3.20(s, 3H), 4.66(s, 2H), 6.70 (t, J=8.5Hz, 1H), 6.81-6.88(m, 2H), 7.00(d, J=8.3Hz, 1H), 7.43-7.55(m, 2H), 8.12 (s, 1H), 11.31(s, 1H).

Example 4-119

[0881] MS ESI m/e: 612 (M+H), 610. (M-H).

10 $^1\text{H-NMR}(\text{DMSO-d}_6, 300\text{MHz}) \delta$ 1.21(s, 3H), 3.09(s, 3H), 3.21(s, 3H), 6.96(t, J=8.5Hz, 1H), 7.48(s, 2H), 7.53-7.64(m, 3H), 7.76-7.81(m, 1H), 7.90(d, J=8.3Hz, 2H), 11.13(s, 1H).

Example 4-120

15 **[0882]** MS ESI m/e: 573 (M+H), 571 (M-H).

$^1\text{H-NMR}(\text{DMSO-d}_6, 300\text{MHz}) \delta$ 0.66-0.69 (m, 2H), 0.94-0.98 (m, 2H), 1.26 (s, 3H), 2.50 (s, 3H), 2.61-2.66 (m, 1H), 3.04 (s, 3H), 6.98 (d, J = 7.3 Hz, 1H), 7.10-7.19 (m, 6H), 7.31-7.33 (m, 2H), 9.66 (s, 1H), 11.23 (s, 1H).

Example 4-121

20 **[0883]** MS ESI m/e: 600 (M+H), 598 (M-H).
 $^1\text{H-NMR}(\text{CDCl}_3, 300\text{MHz}) \delta$ 0.80-0.90(m, 2H), 1.11-1.20(m, 2H), 1.27(s, 3H), 2.74-2.83(m, 1H), 3.24 (s, 3H), 6.75(t, J=8.3Hz, 1H), 7.37(dd, J=1.9, 8.7Hz, 1H), 7.45-7.57 (m, 2H), 7.80(brs, 3H), 11.37 (s, 1H).

Example 4-122

[0884] MS ESI m/e: 671 (M+H), 669 (M-H).

30 $^1\text{H-NMR}(\text{DMSO-d}_6, 400\text{MHz}) \delta$ 0.60-0.67(m, 2H), 0.87-0.95(m, 2H), 1.21(s, 3H), 2.24(brs, 3H), 2.54-2.61(m, 1H), 2.69 (brs, 2H), 3.04(s, 3H), 3.07(brs, 2H), 3.62(brs, 2H), 6.89(t, J=8.7Hz, 1H), 7.24-7.29(m, 1H), 7.30-7.35(m, 2H), 7.40-7.46 (m, 1H), 7.48-7.53(m, 1H), -7.72-7.77 (m, 1H), 11.01(s, 1H).

Example 4-123

[0885] MS ESI m/e: 628 (M+H), 626(M-H).

35 $^1\text{H-NMR}(\text{DMSO-d}_6, 300\text{MHz}) \delta$ 0.61-0.71(m, 2H), 0.90-1.00(m, 2H), 1.30 (s, 3H), 2.50(t, J=7.5Hz, 2H), 2.55-2.67(m, 1H), 2.95(t, J=7.5Hz, 2H), 3.09(s, 3H), 6.87-6.95(m, 3H), 7.24(d, J=9.0Hz, 1H), 7.57(d, J=9.0Hz, 1H), 7.80(d, J=9.0Hz, 1H), 10.11(brs, 1H), 11.07(brs, 1H).

Example 4-124

40 **[0886]** MS ESI m/e: 643 (M+H), 641 (M-H).

$^1\text{X-NMR}(\text{DMSO-d}_6, 300\text{MHz}) \delta$ 0.63-0.72(m, 2H), 0.90-1.00(m, 2H), 1.27(s, 3H), 2.58-2.67(m, 1H), 3.08(s, 3H), 3.41(t, J=8.3Hz, 2H), 3.85(t, J=8.3Hz, 2H), 6.92(t, J=8.5Hz, 1H), 6.98(d, J=7.8Hz, 1H), 7.05(s, 1H), 7.37(t, J=8.1Hz, 1H), 7.49 (d, J=8.1Hz, 1H), 7.55(d, J=8.4Hz, 1H), 7.67-7.71(m, 1H), 7.79(dd, J=1.8, 10.5Hz, 1H), 11.11(s, 1H).

Example 4-125.

[0887] MS ESI m/e: 644 (M+H), 642 (M-H).

50 $^1\text{H-NMR}(\text{DMSO-d}_6, 300\text{MHz}) \delta$ 0.62-0.72 (m, 2H), 0.89-1.0 (m, 2H), 1.25 (s, 3H), 2.56-2.68 (m, 1H) 3.08 (s, 3H), 4.07 (t, J=8.4Hz, 2H), 4.45(t, J=8.4Hz, 2H); 6.92(t, J=8.3Hz, 1H), 7.14(d, J=8.1Hz, 1H), 7.46(t, J=8.1Hz, 1H), 7.51-7.60(m, 2H), 7.65-7.69(m, 1H), 7.78(d, J=9.3Hz, 1H), 11.10(s, 1H).

Example 4-126

55 **[0888]** MS ESI m/e: 616 (M+H), 614 (M-H).

$^1\text{H-NMR}(\text{DMSO-d}_6, 300\text{MHz}) \delta$ 0.62-0.73(m, 2H), 0.90-1.00 (m, 2H), 1.24(s, 3H), 2.57-2.67 (m; 1H), 3.08(s, 3H), 6.93 (t, J=8.6Hz, 1H), 7.08(dd, J=2.4, 8.7Hz, 1H), 7.18(d, J=2.1Hz, 1H), 7.34(d, J=8.1Hz, 1H), 7.55(d, J=8.7Hz, 1H), 7:79 (dd, J=1.5, 10.5Hz, 1H), 11.08(s, 1H), 11.80(s, 1H).

Example 4-127

[0889] MS ESI m/e: 638 (M+H), 636 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.64-0.72(m, 2H), 0.90-1.01(m, 2H), 1.19(s, 3H), 2.57-2.66(m, 1H), 3.09(s, 3H), 6.94(t, J=8.7Hz, 1H), 7.51(bris, 2H), 7.53-7.5(m, 1H), 7.61-7.70 (m, 2H), 7.76-7.88(m, 3H), 11.05(bris, 1H).

Example 4-128

[0890] MS ESI m/e: 642 (M+H), 640 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.59-0.72(m, 2H), 0.88-1.01(m, 2H), 1.27(s, 3H), 1.29(s, 6H), 2.55-2.67(m, 1H), 3.07 (s, 3H), 6.86-6.97(m, 2H), 7.34(d, J=7.9Hz, 1H), 7.55(dd, J=1.1, 7.9Hz, 1H), 7.78(dd, J=1.1, 10.6Hz, 1H), 10.44(bris, 1H), 11.07(s, 1H).

Example 4-129

[0891] MS ESI m/e: 574(M+H), 572(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.59-0.69(m, 2H), 0.89-0.99 (m, 2H), 1.35(s, 3H), 2.52-2.66(m, 1H), 3.07(s, 3H), 5.25 (bris, 2H), 6.46(d, J=6.0Hz, 1H), 6.53(s, 1H), 6.55(d, J=9.0Hz, 1H), 6.90(dd, J=9.0, 9.0Hz, 1H), 7.06(dd, J=9.0, 9.0Hz, 1H), 7.55(d, J=9.0Hz, 1H), 7.78(d, J=9.0Hz, 1H), 11.06(bris, 1H).

Example 4-130

[0892] MS ESI m/e: 640 (M+H), 638 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.60-0.71(m, 2H), 0.89-1.00(m, 2H), 1.29 (s,3H),1.47-1.55(m, 2H), 1.58-1.68 (m, 2H), 2.55-2.68 (m, 1H), 3.07(s, 3H), 6.87-6.96(m, 3H), 7.02(d, J=7.9Hz, 1H), 7.52-7.58(m, 1H), 7.78(dd, J=1.9, 10.2Hz, 1H), 10.66(bris, 1H), 11.07(bris, 1H).

Example 4-131.

[0893] MS ESI m/e: 472 (M+H), 470 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 0.59-0.70 (m, 2H), 0.89-1.01 (m, 2H), 1.36 (s, 3H), 2.56-2.67(m, 1H), 3.10(s, 3H), 4.28 (s; 1H), 5.24(s, 2H), 6.42-6.62 (m, 3H), 6.99-7.14(m, 2H), 7.26-7.36 (m, 1H), 7.46-7.57(m, 1H), 11.08(s, 1H).

Example 4-132

[0894] MS ESI m/e: 716 (M+H), 714 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.62-0.74 (m, 2H), 0.91-1.04(m, 2H), 1.28(s, 3H), 1.36(s, 9H), 2.48 (s, 3H), 2.59-2.69 (m, 1H), 3.08(s, 3H), 6.94 (t, J=8.6Hz, 1H), 7.17-7.24 (m, 2H), 7.38-7.57 (m, 3H), 7.79(d, J=10.3Hz, 1H), 11.0 (bris, 1H).

Example 4-133

[0895] MS ESI m/e: 694 (M+H), 692 (M-H).

¹H-NNLR(DMSO-d₆, 400MHz) δ 0.62-0.71 (m, 2H), 0.92-1.01(m, 2H), 1.17(s, 3H), 1.95(s, 3H), 2.59-2.69(m, 1H), 3.08 (s, 3H), 3.54(s, 3H), 6.94(d, J=9.0Hz, 1H), 7.52-7.60(m, 5H), 7.79(d, J=10.4Hz, 1H), 11.0(bris, 1H).

Example 4-134

[0896] MS ESI m/e: 620 (M+H), 618 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.27(s, 3H), 2.06 (s, 3H), 3.10 (s, 3H), 3.49-3.60 (m, 2H), 3.89-4.01(m, 2H), 4.78(bris, 1H),6.95(t, J=8.7Hz, 1H), 7.03-7.10(m, 1H), 7.41(t, J=8.0Hz, 1H), 7.51-7.60.(m, 2H), 7.68(s, 1H); 7.78-7.82(m, 1H), 10.1 (bris,1H); 11.3(bris, 1H).

Example 4-135

[0897] MS ESI m/e: 634 (M+H), 632(M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.27(s, 3H), 2.65-2.79.(m, 2H), 2.06(s, 3H), 3.09(s, 3H), 3.39-3.50 (m, 2H), 3.82-3.94 (m, 2H), 4.46(bris, 1H), 6.95(t, J=8.7Hz, 1H), 7.07-7.10(m, 1H), 7.38(t, J=8.0Hz, 1H), 7.55-7.58(m, 2H), 7.68(s, 1H), 7.78-7.81(m, 1H), 10.1(bris, 1H), 11.3(bris, 1H).

Example 4-136

[0898] MS ESI m/e: 650 (M+H), 648 (M-1).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.27(s,3H), 2.05(s,3H), 3.09(s,3H), 3.70-3.90(m, 2H), 4.02(q, J=7.8Hz 1H), 4.55(t, J=5.7Hz, 1H), 4.77(d, J=5.4Hz, 1H), 6.94(t, J=8.7Hz, 1H), 7.05(d, J=7.5Hz, 1H), 7.37(t, J=8.1Hz, 1H) 7.56(d, J=8.7Hz, 2H), 7.68(s, 1H), 7.79(dd, J=1.5, 10.2Hz, 1H), 10.10(s, 1H), 11.30(s, 1H).

Example 4-137

[0899] MS ESI m/e: 650 (M+H), 648 (M-1).

¹H-NMR (DMSO-d₆ 300MHz)δ 1.27(s, 3H), 2.05 (s, 3H), 3.09 (s,3H), 3.70-3.90(m, 2H), 4.02 (q, J=7.1Hz, 1H), 4.55 (brs, 1H), 4.77(d, J=3.9Hz, 1H), 6.944(t, J=8.5Hz, 1H), 7.04 (d, J=8.7Hz, 1H), 7.37 (t, J=8.1Hz, 1H), 7.56(d, J=8.7Hz, 2H), 7.68(s, 1H), 7.79(dd, J=2.4, 10.8Hz, 1H), 10.10(s, 1H), 11.30(s, 1H).

Example 4-138

[0900] MS ESI m/e: 723 (M+H), 721 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 0.65-0.72 (m, 2H), 0.91-1.01 (m, 2H), 1.27.(s , 3H), 1.91(s , 3H), 2.59-2.69(m, 1H), 2.93 (s, 6H), 3.10(s, 3H), 6.98 (t, J=8.6Hz, 1H), 7.43-7.60(m, 5H), 7.80(d, J=10.3Hz, 1H), 11.0(brs, 1H).

Example 4-139

[0901] MS ESI m/e: 630 (M+H), 628 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.63-0.71 (m, 2H), 0.92-1.00 (m, 2H), 1.26 (s, 3H), 1.82 (brs, 3H), 2.58-2.67 (m, 1H), 3.08 (s, 3H), 3.16 (brs, 3H), 6.94(t, J=8.7Hz, 1H), 7.30-7.46 (m, 3H), 7.47-7.60(m, 2H), 7.76-7.82(m, 1H), 11.02(s, 1H).

Example 4-140

[0902] MS ESI m/e: 658 (M+H), 656 (M-H).

¹H-NMR(DMSO-d₆, 400MHz) δ 0.61-0.72(m, 2H), 0.92-1.01 (m, 2H), 1.28 (s, 3H), 2.20 (s, 6H), 2.58-2.66(m, 1H), 3.08 (s, 3H), 6.94(t, J=8.6Hz, 1H), 7.29-7.35(m, 1H), 7.36-7.40(m, 1H), 7.42-7.48(m, 1H), 7.51-7.58 (m, 2H), 7.75-7.82 (m, 1H), 11.00(s, 1H).

Example 4-141

[0903] MS ESI m/e: 633 (M+H), 631 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.27 (s, 3H), 1.81-1.93 (m, 2H), 2.05(s, 3H), 2.75-2.87 (m, 2H), 3.09 (s, 3H), 3.91(t, 2H, J=6.2Hz), 6.93(t, 1H, J=8.5Hz), 7.04-7.10 (m, 1H), 7.38 (t, 1H, J=8.1Hz), 7.48-7.59(m, 2H), 7.69-7.86 (m, 5H), 10.18(s, 1H), 11.21(s, 1H).

Example 4-142

[0904] MS ESI m/e: 664 (M+H), 662 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.26 (s, 3H), 1.46-1.57(m, 1H), 1.65-1.80(m, 1H), 2.05(s, 3H), 3.08(s, 3H), 3.15-3.36 (m, 2H), 3.40-3.51(m, 1H), 3.78-3.91 (m, 1H), 3.98-4.11(m, 1H), 4.46-4.56(m, 2H), 6.94(t, 1H, J=8.7Hz), 7.04-7.10(m, 1H), 7.37(t, 1H, J=8.1Hz), 7.52-7.59(m, 2H), 7.65-7.69(m, 1H), 7.79(dd, 1H, J=1.9, 10.5Hz), 10.10(s, 1H), 11.28(s, 1H).

Example 4-143

[0905] MS ESI m/e: 664 (M+H), 662 (M-H).

¹H-NMR (DMSO-d₆, 300MHz)δ 1.26 (s, 3H), 1.43-1.59(m, 1H), 1.67-1.79(m, 1H), 2.04(s, 3H), 3.08 (s, 3H), 3.15-3.32 (m, 2H), 3.40-3.50 (m, 1H), 3.78-3.91 (m, 1H), 3.97-4.10 (m, 1H), 4.45-4.54 (m, 2H), 6.94 (t, 1H, J=8.7Hz), 7.04-7.09 (m, 1H), 7.37(t, 1H, J=8.1Hz), 7.53-7.59(m, 2H), 7.65-7.69(m, 1H), 7.79 (dd, 1H, J= 1.9, 10.2Hz), 10.10(s, 1H), 11.27 (s, 1H).

Example 4-144

[0906] MS ESI m/e: 648 (M+H), 646 (M-H).

EP 2 298 768 B9

¹H-NMR(CDC₃, 300MHz) δ 1.42(s, 3H), 1.53-1.82(m, 4H), 2.17(s, 3H), 3.21(s, 3H), 3.68(t, 2H, J=6.2Hz), 3.96-4.04 (m, 2H), 6.70(t, 1H, J=8.3Hz), 7.05-7.12 (m, 1H), 7.22-7.56 (m, 6H), 7.70 (s, 1H), 11.47(s, 1H).

Example 4-145

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[0907] MS ESI m/e: 670 (M+H), 668 (M-H).

¹H-NMR (DMSO-d₆, 300MHz) δ 1.26 (s, 3H), 1.66-1.75 (m, 2H), 3.02 (s, 3H), 3.08 (s, 3H), 3.42 (q, 2H, J = 5.9 Hz), 3.88-3.91 (m, 2H), 4.45 (t, 1H, J = 5.1 Hz), 6.94 (t, 1H, J = 8.6 Hz), 7.12-7.15 (m, 1H), 7.23-7.29 (m, 2H), 7.42 (t, 1H, J = 7.9 Hz), 7.54-7.57 (m, 1H), 7.78 (dd, 1H, J = 10.5, 1.7 Hz), 9.92 (s, 1H), 11.26 (s, 1H).

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Example 4-146

[0908] MS ESI m/e: 634 (M+H), 632 (M-H).

¹H-NMR (DMSO-d₆, 400MHz) δ 1.25 (s, 3H), 1.66-1.75 (m, 2H), 3.08(s, 3H), 3.42(q, 2H, J=4.5Hz), 3.86-3.93(m, 2H), 4.46 (t, 1H, J=3.8Hz), 6.95 (t, 1H, J=6.4Hz), 7.11 (dd, 1H, J=1.7, 6.4Hz), 7.22(d, 1H, J=1.6Hz), 7.35 (d, 1H, J=6.4Hz), 7.53-7.58 (m, 1H), 7.79 (dd, 1H, J=1.4, 7.8Hz), 11.27 (s, 1H), 11.84 (s, 1H).

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Example 4-147

[0909] MS ESI m/e: 577 (M+H), 575 (M-H).

¹H-NMR(DMSO-d₆, 300MHz) δ 1.19 (s, 3H), 1.65-1.76(m, 2H), 3.08(s, 3H), 3.43(q, 2H, J=5.9Hz), 3.86-3.94 (m, 2H), 4.46(t, 1H, J=5.3Hz), 6.95 (t, 1H, J=8.7Hz), 7.38-7.51(m, 5H), 7.52-7.58 (m, 1H), 7.79(dd, 1H, J=1.9, 10.2Hz), 11.25 (s, 1H).

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Example 4-148

[0910] MS ESI m/e: 650 (M+H), 648 (M-H).

¹H-MMR (DMSO-d₆, 300MHz) δ 1.26 (s, 3H), 1.70-1.72 (m, 2H), 3.08 (s, 3H), 3.42 (q, 2H, J = 5.7 Hz), 3.89-3.91 (m, 2H), 3.99 (d, 2H, J = 5.9 Hz), 4.44 (t, 1H, J = 5.3 Hz), 5.64 (t, 1H, J = 6.1 Hz), 6.94 (t, 1H, J = 8.6 Hz), 7.11 (d, 1H, J = 7.0 Hz), 7.39 (t, 1H, J = 8.3 Hz), 7.55 (d, 1H, J = 8.1 Hz), 7.70-7.81 (m, 3H), 9.83 (s, 1H), (s, 1H).

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[0911] The compound of the present invention shows superior p15 protein inducing action and/or p27 protein inducing action and/or MEK inhibitory action.

[0912] In addition, the compound of the present invention shows superior antitumor activity, and anti-rheumatism activity.

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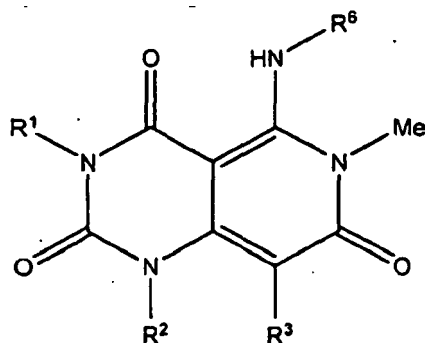
[0913] Therefore, the compound can be a pharmaceutical agent effective for the prophylaxis or treatment of a disease caused by undesirable cell proliferation, particularly, tumor or rheumatism.

Claims

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1. A method of preparing a compound of formula [I-3-2]

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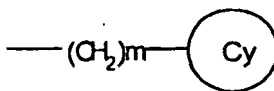
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[I-3-2]

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wherein

R¹, R², and R⁶ are the same or different and each is
 a C₁₋₆ alkyl group,
 a C₂₋₆ alkenyl group,
 wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally substituted by 1 to 3 substituents selected
 from the following group A, or



wherein m is 0 or an integer of 1 to 4,
 ring Cy is a C₃₋₁₂ carbon ring group or a heterocyclic group, wherein the heterocyclic group is a saturated or
 unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen
 atom and a sulfur atom, the C₃₋₁₂ carbon ring group and the heterocyclic group are optionally substituted by 1 to 5
 substituents selected from the following group B,

R³ is

a hydrogen atom,
 a hydroxyl group,
 a C₁₋₆ alkyl group,
 a C₂₋₆ alkenyl group,
 wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally
 substituted by 1 to 3 substituents selected from the following group A,

a C₃₋₁₂ carbon ring group or

a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero
 atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and the C₃₋₁₂ carbon ring group and the
 heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B;

wherein group A is a group consisting of

- 1) a halogen atom,
- 2) a nitro group,
- 3) a cyano group,
- 4) a C₁₋₄ alkyl group,
- 5) -OR^{A1} wherein R^{A1} is a hydrogen atom or a C₁₋₄ alkyl group,
- 6) -SR^{A2} wherein R^{A2} is a hydrogen atom or a C₁₋₄ alkyl group,
- 7) -NR^{A3}R^{A4} wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
- 8) -COOR^{A5} wherein R^{A5} is a hydrogen atom or a C₁₋₄ alkyl group,
- 9) -NR^{A6}COR^{A7} wherein R^{A6} is a hydrogen atom or a C₁₋₄ alkyl group, R^{A7} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon
 ring group or a heterocyclic group,
- 10) -NR^{A8}COOR^{A9} wherein R^{A8} and R^{A9} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl
 group,
- 11) a C₃₋₁₂ carbon ring group and
- 12) a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4
 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,

each of the C₁₋₄ alkyl groups of the above-mentioned 4), R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A6}, R^{A6}, R^{A7}, R^{A8} and R^{A9} is
 optionally substituted by the same or different 1 to 3 substituents selected from the following group C, and

each of the C₃₋₁₂ carbon ring groups of the above-mentioned 11) and R^{A7}, and the heterocyclic groups of 12)
 and R^{A7} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C,

group B is a group consisting of

- 1) a halogen atom,
- 2) a nitro group,
- 3) a cyano group,
- 4) a C₁₋₈ alkyl group,
- 5) a C₂₋₄ alkenyl group,

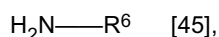
- 6) a C₂₋₄ alkenyl group,
 7) -OR^{B1} wherein R^{B1} is a hydrogen atom or a C₁₋₄ alkyl group,
 8) -SR^{B2} wherein R^{B2} is a hydrogen atom or a C₁₋₄ alkyl group,
 9) -NR^{B3}R^{B4} wherein R^{B3} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group, and R^{B4} is a hydrogen atom or a C₁₋₄ alkyl group,
 10) -NR^{B5}COR^{B6} wherein R^{B5} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B6} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,
 11) -NR^{B7}COOR^{B8} wherein R^{B7} and R^{B8} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 12) -NR^{B9}CONR^{B10}R^{B11} wherein R^{B9}, R^{B10} and R^{B11} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 13) -NR^{B12}CONR^{B13}OR^{B14} wherein R^{B12}, R^{B13} and R^{B14} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 14) -NR^{B15}SO₂R^{B16} wherein R^{B15} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B16} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,
 15) -SO₂-R^{B17} wherein R^{B17} is a C₁₋₄ alkyl group or a heterocyclic group,
 16) -SO₂NR^{B18}R^{B19} wherein R^{B18} and R^{B19} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 17) -P(=O)(R^{B20})(R^{B21}) wherein R^{B20} and R^{B21} are the same or different and each is a C₁₋₄ alkyl group,
 18) -COOR^{B22} wherein R^{B22} is a hydrogen atom or a C₁₋₄ alkyl group,
 19) -CONR^{B23}R^{B24} wherein R^{B23} and R^{B24} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 20) -NR^{B25}SO₂NR^{B26}R^{B27} wherein R^{B25}, R^{B26} and R^{B27} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31} wherein R^{B28}, R^{B29}, R^{B30} and R^{B31} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 22) a C₃₋₁₂ carbon ring group and
 23) a heterocyclic group
 wherein each of the "C₁₋₈ alkyl group" of the above-mentioned 4), and the C₁₋₄ alkyl groups for R^{B1} to R^{B31} is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A, each of the C₂₋₄ alkenyl group of 5) and the C₂₋₄ alkenyl group of 6) is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A, the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and
 each of the C₃₋₁₂ carbon ring group of the above-mentioned 22), R^{B3}, R^{B6} and R^{B16}, and the heterocyclic group of the above-mentioned 23), R^{B3}, R^{B6}, R^{B16} and R^{B17} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C, and

group C is a group consisting of

- 1) a halogen atom,
- 2) a cyano group,
- 3) a C₁₋₄ alkyl group,
- 4) -OR^{C1} wherein R^{C1} is a hydrogen atom or a C₁₋₄ alkyl group,
- 5) -NRC²RC³ wherein R^{C2} and R^{C3} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
- 6) -COOR^{C4} wherein R^{C4} is a hydrogen atom or a C₁₋₄ alkyl group and
- 7) an oxo group,

wherein the method comprises

(a) reacting a compound of formula [45]

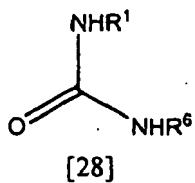


wherein R⁶ is defined above,
 with a compound of formula [1]



wherein R¹ is defined above, to form a compound of formula [28]

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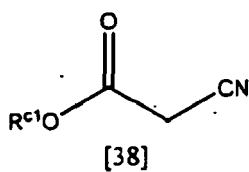


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wherein R¹ and R⁶ are defined above;

(b) reacting a compound of formula [28] with a compound of formula [38]

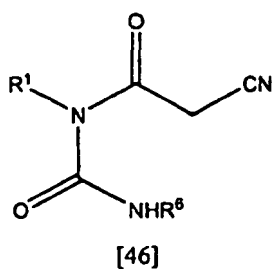
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wherein R⁶ is a hydrogen atom or C₁₋₆ alkyl group,
to form a compound of formula [46]

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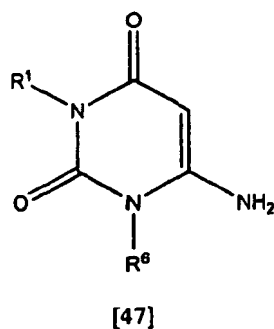
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wherein R¹ and R⁶ are defined above;

(c) converting a compound of formula [46] to a compound of formula [47]

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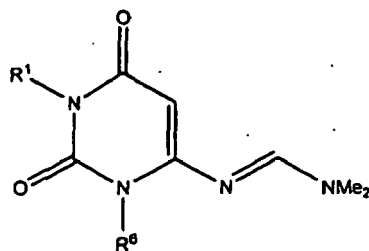
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wherein R¹ and R⁶ are defined above;

(d) converting a compound of formula [47] to a compound of formula [48]

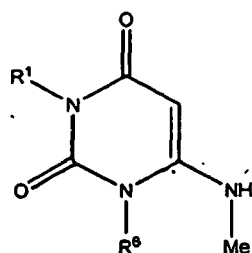
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[48]

wherein R¹ and R⁶ are defined above;

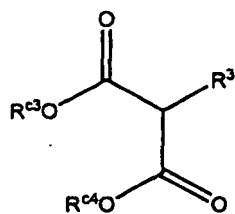
(e) converting a compound of formula [48] to a compound of formula [49]



[49]

wherein R¹ and R⁶ are defined above;

(f) reacting a compound of formula [49] with a compound of formula [33]

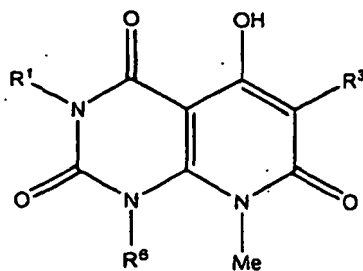


[33]

wherein

R³ is defined above; and

R³ and R⁴ are the same or different and each is a hydrogen atom or C₁₋₆ alkyl, to form a compound of formula [50]



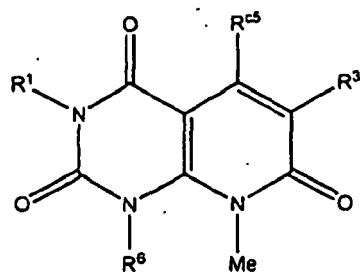
[50]

wherein R¹, R³, and R⁶ are defined above;

(g) converting a compound of formula [50] to a compound of formula [51];

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[51]

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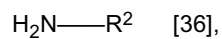
wherein

R¹, R³, and R⁶ are defined above, and

R⁵ is a leaving group;

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(h) reacting a compound of formula [51] with a compound of formula [36]



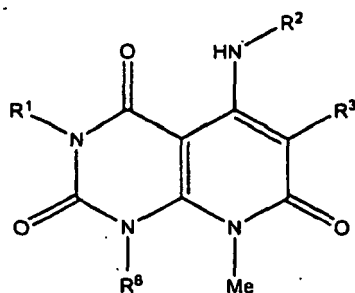
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wherein R² is defined above;

to form a compound of formula [52]

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[52]

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wherein R¹, R², R³, and R⁶ are defined above;

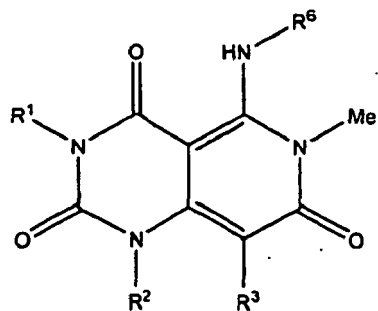
and

(i) converting a compound of formula [52] to a compound of formula [1-3-2]

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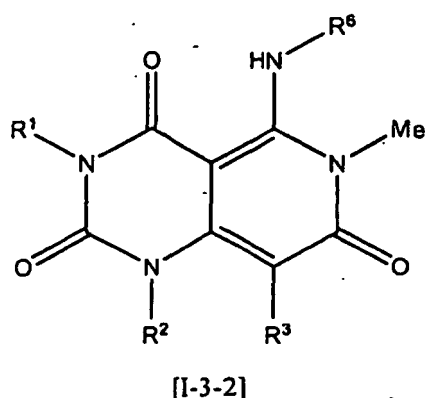
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[1-3-2]

2. A method of preparing a compound of formula [I-3-2]



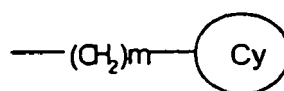
wherein

R¹, R², and R⁶ are the same or different and each is

a C₁₋₆ alkyl group,

a C₂₋₆ alkynyl group,

wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally substituted by 1 to 3 substituents selected from the following group A, or



wherein m is 0 or an integer of 1 to 4,

ring Cy is a C₃₋₁₂ carbon ring group or a heterocyclic group, wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, the C₃₋₁₂ carbon ring group and the heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B,

R³ is

a hydrogen atom,

a hydroxyl group,

a C₁₋₆ alkyl group,

a C₂₋₆ alkenyl, group,

wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally substituted by 1 to 3 substituents selected from the following group A,

a C₃₋₁₂ carbon ring group or

a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and the C₃₋₁₂ carbon ring group and the heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B;

wherein group A is a group consisting of

1) a halogen atom,

2) a nitro group,

3) a cyano group,

4) a C₁₋₄ alkyl group,

5) -OR^{A1} wherein R^{A1} is a hydrogen atom or a C₁₋₄ alkyl group,

6) -SR^{A2} wherein R^{A2} is a hydrogen atom or a C₁₋₄ alkyl group,

7) -NR^{A3}R^{A4} wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

8) -COOR^{A5} wherein R^{A5} is a hydrogen atom or a C₁₋₄ alkyl group,

9) -NR^{A6}COR^{A7} wherein R^{A6} is a hydrogen atom or a C₁₋₄alkyl group, R^{A7} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,

10) $-NR^{A8}COOR^{A9}$ wherein R^{A8} and R^{A9} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

11) a C_{3-12} carbon ring group and

12) a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,

each of the C_{1-4} alkyl groups of the above-mentioned 4), R^{A1} , R^{A2} , R^{A3} , R^{A4} , R^{A5} , R^{A6} , R^{A7} , R^{A8} and R^{A9} is optionally substituted by the same or different 1 to 3 substituents selected from the following group C, and

each of the C_{3-12} carbon ring groups of the above-mentioned 11) and R^{A7} and the heterocyclic groups of 12) and R^{A7} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C,

group B is a group consisting of

1) a halogen atom,

2) a nitro group,

3) a cyano group,

4) a C_{1-8} alkyl group,

5) a C_{2-4} alkenyl group,

6) a C_{2-4} alkynyl group,

7) $-OR^{B1}$ wherein R^{B1} is a hydrogen atom or a C_{1-4} alkyl group,

8) $-SR^{B2}$ wherein R^{B2} is a hydrogen atom or a C_{1-4} alkyl group,

9) $-NR^{B3}R^{B4}$ wherein R^{B3} is a hydrogen atom, a C_{1-4} alkyl group, a C_{3-12} carbon ring group or a heterocyclic group, and R^{B4} is a hydrogen atom or a C_{1-4} alkyl group,

10) $-NR^{B5}COR^{B6}$ wherein R^{B5} is a hydrogen atom or a C_{1-4} alkyl group, and R^{B6} is a hydrogen atom, a C_{1-4} alkyl group, a C_{3-12} carbon ring group or a heterocyclic group,

11) $-NR^{B7}COOR^{B8}$ wherein R^{B7} and R^{B8} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

12) $-NR^{B9}CONR^{B10}R^{B11}$ wherein R^{B9} , R^{B10} and R^{B11} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

13) $-NR^{B12}CONR^{B13}OR^{B14}$ wherein R^{B12} , R^{B13} and R^{B14} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

14) $-NR^{B15}SO_2R^{B16}$ wherein R^{B15} is a hydrogen atom or a C_{1-4} alkyl group, and R^{B16} is a C_{1-4} alkyl group, a C_{3-12} carbon ring group or a heterocyclic group,

15) $-SO_2R^{B17}$ wherein R^{B17} is a C_{1-4} alkyl group or a heterocyclic group,

16) $-SO_2NR^{B18}R^{B19}$ wherein R^{B18} and R^{B19} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

17) $-P(=O)(R^{B20})(R^{B21})$ wherein R^{B20} and R^{B21} are the same or different and each is a C_{1-4} alkyl group,

18) $-COOR^{B22}$ wherein R^{B22} is a hydrogen atom or a C_{1-4} alkyl group,

19) $-CONR^{B23}R^{B24}$ wherein R^{B23} and R^{B24} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

20) $-NR^{B25}SO_2NR^{B26}R^{B27}$ wherein R^{B25} , R^{B26} and R^{B27} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

21) $-NR^{B28}SO_2NR^{B29}CONR^{B30}R^{B31}$ wherein R^{B28} , R^{B29} , R^{B30} and R^{B31} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

22) a C_{3-12} carbon ring group and

23) a heterocyclic group

wherein each of the " C_{1-8} alkyl group" of the above-mentioned 4), and the C_{1-4} alkyl groups for R^{B1} to R^{B31} is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A,

each of the C_{2-4} alkenyl group of 5) and the C_{2-4} alkynyl group of 6) is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A,

the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and

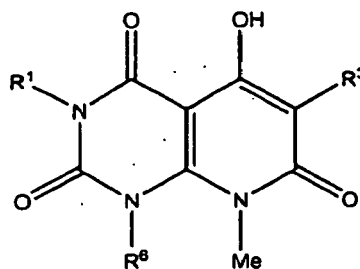
each of the C_{3-12} carbon ring group of the above-mentioned 22), R^{B3} , R^{B6} and R^{B16} , and the heterocyclic group of the above-mentioned 23), R^{B3} , R^{B6} , R^{B16} and R^{B17} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C, and

group C is a group consisting of

- 1) a halogen atom,
- 2) a cyano group,
- 3) a C₁₋₄ alkyl group,
- 4) -OR^{C1} wherein R^{C1} is a hydrogen atom or a C₁₋₄ alkyl group,
- 5) -NR^{C2}R^{C3} wherein R^{C2} and R^{C3} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
- 6) -COOR^{C4} wherein R^{C4} is a hydrogen atom or a C₁₋₄ alkyl group and
- 7) an oxo group,

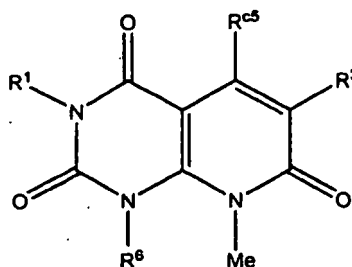
wherein the method comprises

(a) converting a compound of formula [50]



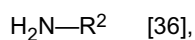
[50]

wherein R¹, R³, and R⁶ are defined above;
to a compound of formula [51];

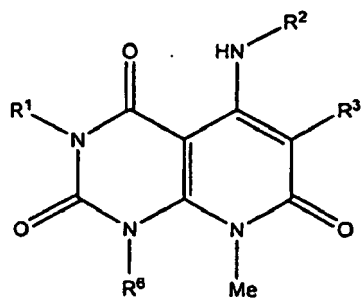


[51]

wherein R¹, R³, and R⁶ are defined above and R^{c5} is a leaving group;
(b) reacting a compound of formula [51] with a compound of formula [36]



wherein R² is defined above,
to form a compound of formula [52]

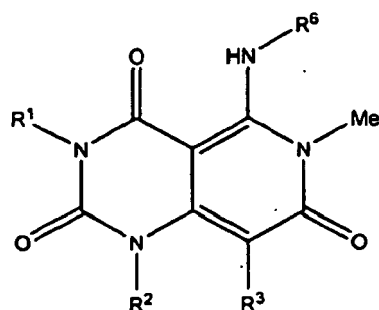


[52]

15 wherein R¹, R², R³, and R⁶ are defined above;

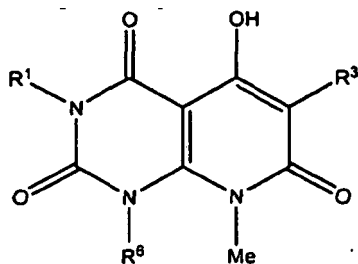
and

(c) converting a compound of formula [52] to a compound of formula [1-3-2]



[1-3-2]

3. A method of preparing a compound of formula [50]



[50]

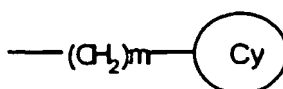
wherein

R¹ and R⁶ are the same or different and each is

a C₁₋₆ alkyl group,

a C₂₋₆ alkenyl group,

wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally substituted by 1 to 3 substituents selected from the following group A, or



wherein m is 0 or an integer of 1 to 4,

ring Cy is a C₃₋₁₂ carbon ring group or a heterocyclic group, wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, the C₃₋₁₂ carbon ring group and the heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B,

R³ is

a hydrogen atom,

a hydroxyl group,

a C₁₋₆ alkyl group,

a C₂₋₆ alkenyl group,

wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally substituted by 1 to 3 substituents selected from the following group A,

a C₃₋₁₂ carbon ring group or

a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and the C₃₋₁₂ carbon ring group and the heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B;

wherein group A is a group consisting of

1) a halogen atom,

2) a nitro group,

3) a cyano group,

4) a C₁₋₄ alkyl group,

5) -OR^{A1} wherein R^{A1} is a hydrogen atom or a C₁₋₄ alkyl group,

6) -SR^{A2} wherein R^{A2} is a hydrogen atom or a C₁₋₄ alkyl group,

7) -NR^{A3}R^{A4} wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

8) -COOR^{A5} wherein R^{A5} is a hydrogen atom or a C₁₋₄ alkyl group,

9) -NR^{A6}COR^{A7} wherein R^{A6} is a hydrogen atom or a C₁₋₄ alkyl group, R^{A7} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,

10) -NR^{A8}COOR^{A9} wherein R^{A8} and R^{A9} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

11) a C₃₋₁₂ carbon ring group and

12) a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,

each of the C₁₋₄ alkyl groups of the above-mentioned 4), R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} and R^{A9} is optionally substituted by the same or different 1 to 3 substituents

selected from the following group C, and

each of the C₃₋₁₂ carbon ring groups of the above-mentioned 11) and R^{A7}, and the heterocyclic groups of 12) and R^{A7} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C,

group B is a group consisting of

1) a halogen atom,

2) a nitro group,

3) a cyano group,

4) a C₁₋₈ alkyl group,

5) a C₂₋₄ alkenyl group,

6) a C₂₋₄ alkynyl group,

7) -OR^{B1} wherein R^{B1} is a hydrogen atom or a C₁₋₄ alkyl group,

8) -SR^{B2} wherein R^{B2} is a hydrogen atom or a C₁₋₄ alkyl group,

9) -NR^{B3}R^{B4} wherein R^{B3} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group, and R^{B4} is a hydrogen atom or a C₁₋₄ alkyl group,

10) -NR^{B5}COR^{B6} wherein R^{B5} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B6} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,

11) -NR^{B7}COOR^{B8} wherein R^{B7} and R^{B8} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

12) -NR^{B9}CONR^{B10}R^{B11} wherein R^{B9}, R^{B10} and R^{B11} are the same or different and each is a hydrogen atom

or a C₁₋₄ alkyl group,

13) -NR^{B12}CONR^{B13}OR^{B14} wherein R^{B12}, R^{B13} and R^{B14} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

14) -NR^{B15}SO₂R^{B16} wherein R^{B15} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B16} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,

15) -SO₂-R^{B17} wherein R^{B17} is a C₁₋₄ alkyl group or a heterocyclic group,

16) -SO₂NR^{B18}R^{B19} wherein R^{B18} and R^{B19} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

17) -P(=O)(R^{B20})(R^{B21}) wherein R^{B20} and R^{B21} are the same or different and each is a C₁₋₄ alkyl group,

18) -COOR^{B22} wherein R^{B22} is a hydrogen atom or a C₁₋₄ alkyl group,

19) -CONR^{B23}R^{B24} wherein R^{B23} and R^{B24} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

20) -NR^{B25}SO₂NR^{B26}R^{B27} wherein R^{B25}, R^{B26} and R^{B27} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31} wherein R^{B28}, R^{B29}, R^{B30} and R^{B31} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

22) a C₃₋₁₂ carbon ring group and

23) a heterocyclic group

wherein each of the "C₁₋₈ alkyl group" of the above-mentioned 4), and the C₁₋₄ alkyl groups for R^{B1} to R^{B31} is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A, each of the C₂₋₄ alkenyl group of 5) and the C₂₋₄ alkynyl group of 6) is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A,

the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and

each of the C₃₋₁₂ carbon ring group of the above-mentioned 22), R^{B3}, R^{B6} and R^{B16}, and the heterocyclic group of the above-mentioned 23), R^{B3}, R^{B6}, R^{B16} and R^{B17} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C, and

group C is a group consisting of

1) a halogen atom,

2) a cyano group,

3) a C₁₋₄ alkyl group,

4) -OR^{C1} wherein R^{C1} is a hydrogen atom or a C₁₋₄ alkyl group,

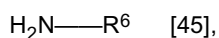
5) -NR^{C2}R^{C3} wherein R^{C2} and R^{C3} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

6) -COOR^{C4} wherein R^{C4} is a hydrogen atom or a C₁₋₄ alkyl group and

7) an oxo group,

wherein the method comprises

(a) reacting a compound of formula [45]

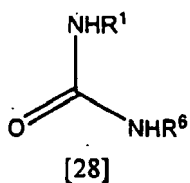


wherein R⁶ is defined above,

with a compound of formula [1]



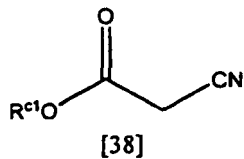
wherein R¹ is defined above, to form a compound of formula [28]



wherein R¹ and R⁶ are defined above;

(b) reacting a compound of formula [28] with a compound of formula [38]

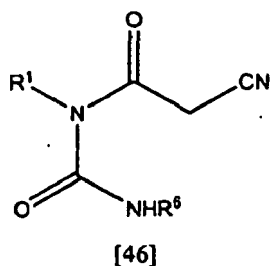
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wherein R^{c1} is a hydrogen atom or C₁₋₆ alkyl group,
to form a compound of formula [46]

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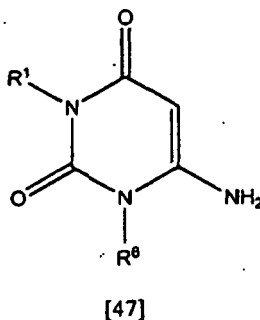
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wherein R¹ and R⁶ are defined above;

(c) converting a compound of formula [46] to a compound of formula [47]

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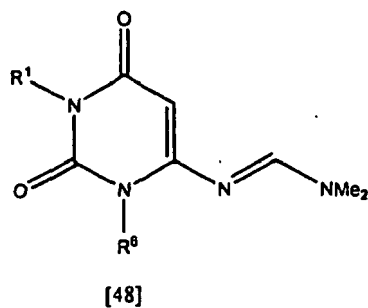
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wherein R¹ and R⁶ are defined above;

(d) converting a compound of formula [47] to a compound of formula [48]

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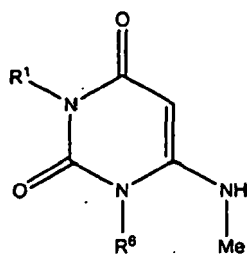
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wherein R¹ and R⁶ are defined above;

(e) converting a compound of formula [48] to a compound of formula [49]

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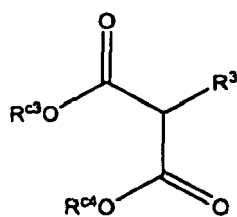
[49]

wherein R¹ and R⁶ are defined above;

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(f) reacting a compound of formula [49] with a compound of formula [33]

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[33]

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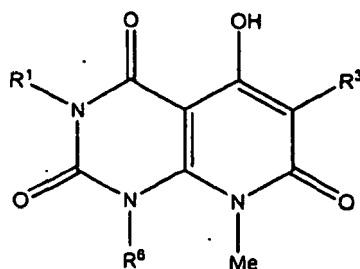
wherein

R³ is defined above; and

R^{3'} and R³ are the same or different and each is a hydrogen atom or C₁₋₆ alkyl, to form a compound of formula [50]

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[50]

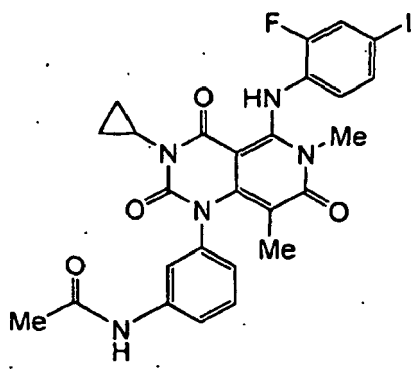
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4. A method of preparing a compound, salt, or solvate of the formula:

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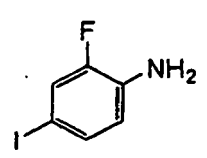
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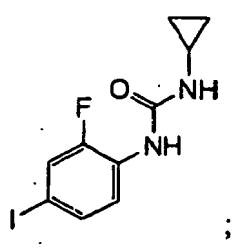


comprising

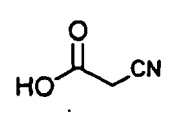
(a) reacting



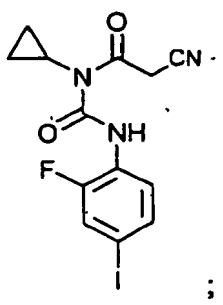
with cyclopropylamine to form



(b) reacting the product of step (a) with

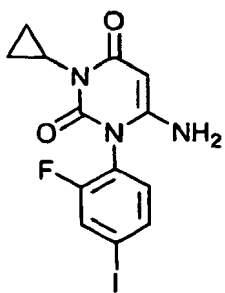


to form



(c) converting the product of step (b) to

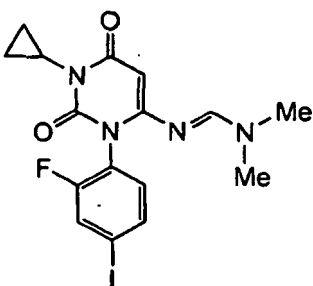
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(d) converting the product of step (c) to

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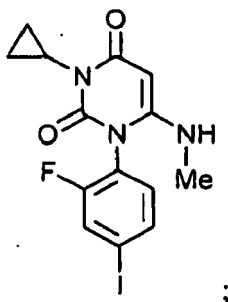


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(e) converting the product of step (d) to

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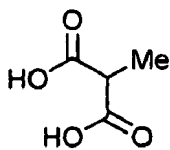


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(f) reacting the product of step (e) with

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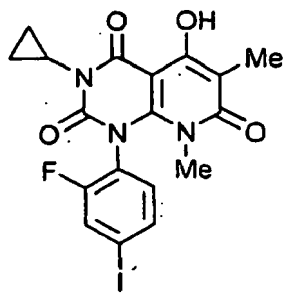


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to form

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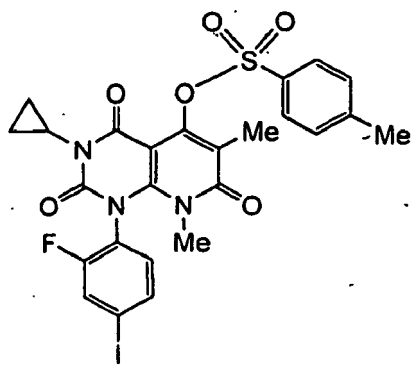
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(g) converting the product of step (f) to

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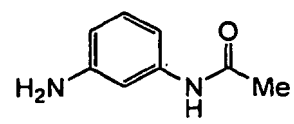


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(h) reacting the product of step (g) with

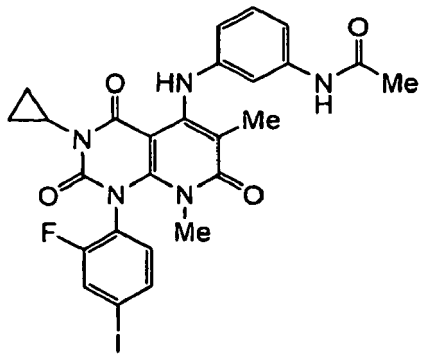
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to form

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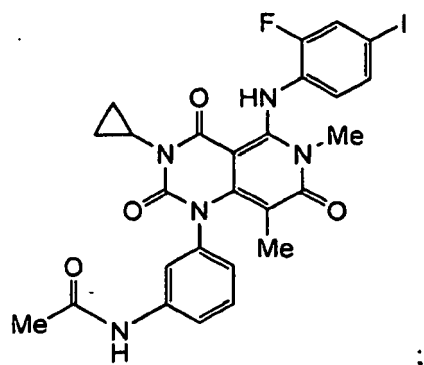
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(i) converting the product of step (h) to

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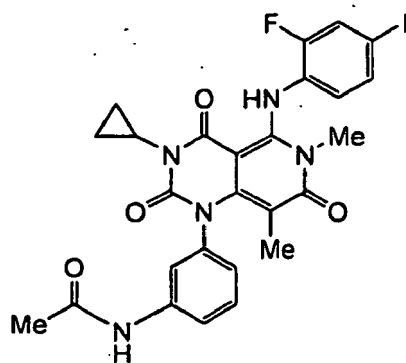
and
(j) optionally converting the product of step (i) to a salt or solvate.

5. A method of preparing a compound, salt, or solvate of the formula:

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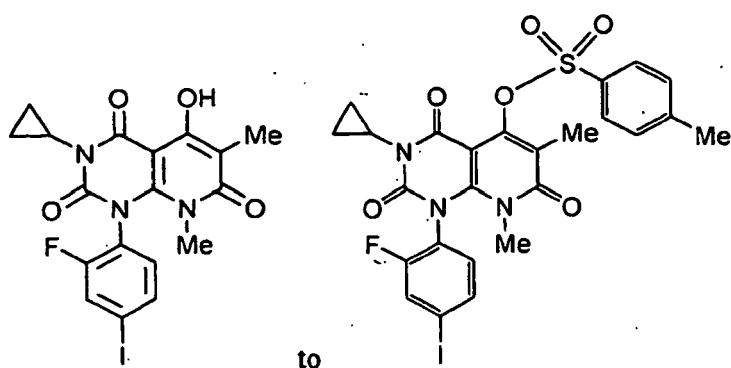
comprising

(a) converting

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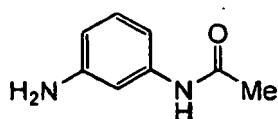
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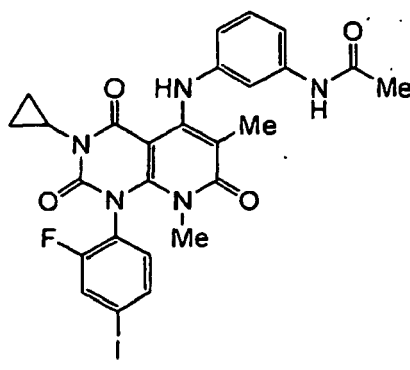
(b) reacting the product of step (a) with

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to form

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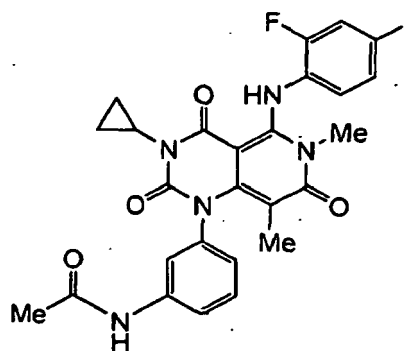


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(c) converting the product of step (b) to

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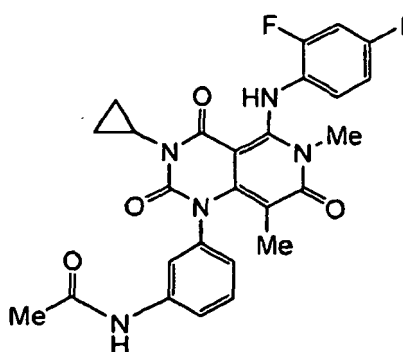
and

(d) optionally converting the product of step (c) to a salt or solvate.

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6. The method of claim 4 or 5, further comprising converting

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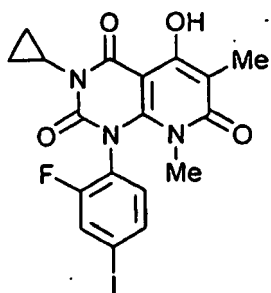
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to a solvate.

7. A method of preparing a compound of the formula:

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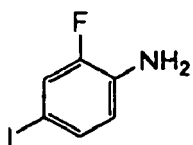
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comprising

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(a) reacting

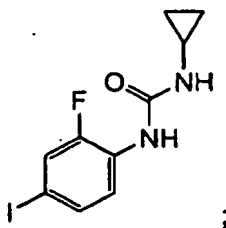
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with cyclopropylamine to form

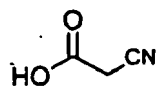
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(b) reacting the product of step (a) with

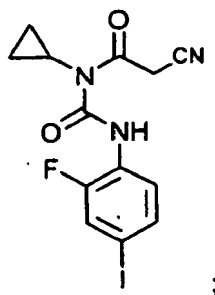
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to form

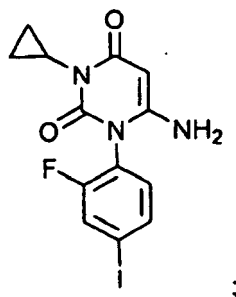
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(c) converting the product of step (b) to

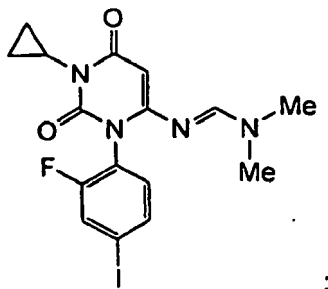
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(d) converting the product of step (c) to

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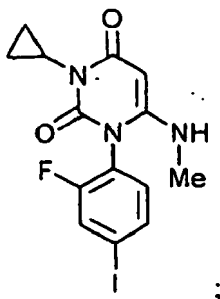


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(e) converting the product of step (d) to

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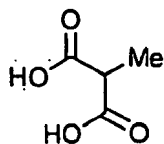


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and
(f) reacting the product of step (e) with

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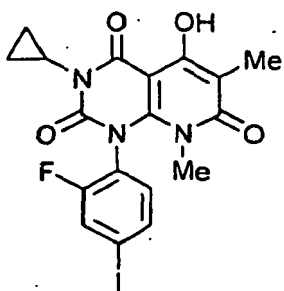


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to form

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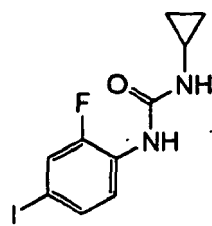
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8. A compound of the formula:

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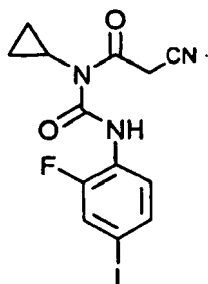
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or a salt or solvate thereof.

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9. A compound of the formula:

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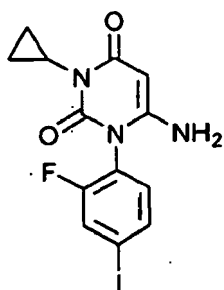
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or a salt or solvate thereof.

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10. A compound of the formula:

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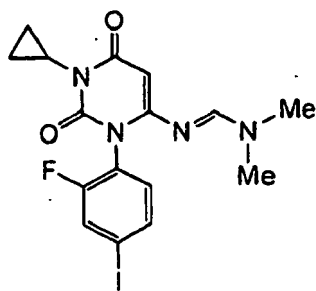
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or a salt or solvate thereof.

11. A compound of the formula:

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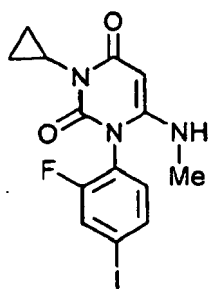


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or a salt or solvate thereof.

12. A compound of the formula:

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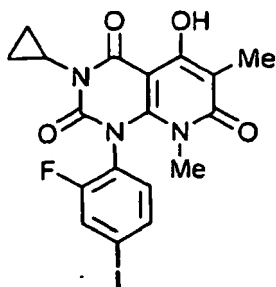
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or a salt or solvate thereof.

13. A compound of the formula:

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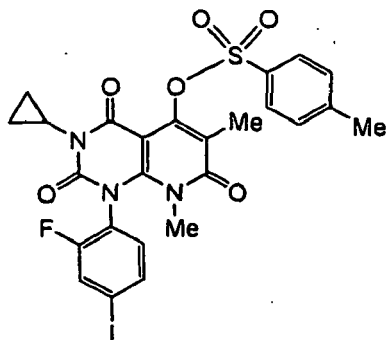
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or a salt or solvate thereof.

14. A compound of the formula:

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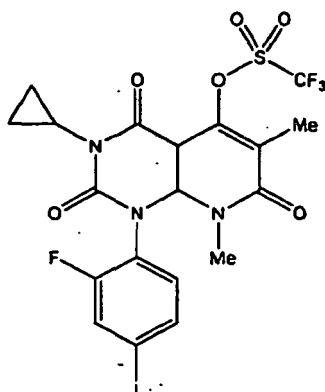
or a salt or solvate thereof.

15. A compound of the formula:

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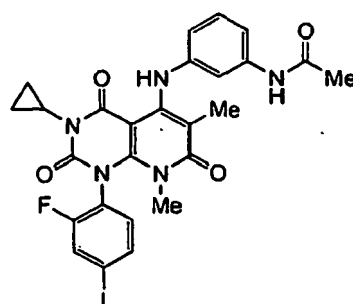
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or a salt or solvate thereof.

16. A compound of the formula:

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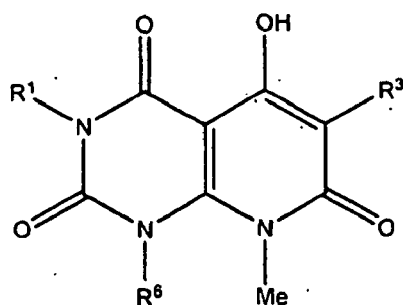
or a salt or solvate thereof.

17. A compound of the formula [50] or a salt or solvate thereof:

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[50]

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wherein

R³ is a methyl group, and

R¹ and R⁶ are the same or different and each is a C₃₋₁₂ carbon ring group or a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero

atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, the C₃₋₁₂ carbon ring group and the heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B, wherein group B is a group consisting of

- 5 1) a halogen atom,
 - 2) a nitro group,
 - 3) a cyano group,
 - 4) a C₁₋₈ alkyl group,
 - 10 5) a C₂₋₄ alkenyl group,
 - 6) a C₂₋₄ alkynyl group,
 - 7) -OR^{B1} wherein R^{B1} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 8) -SR^{B2} wherein R^{B2} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 9) -NR^{B3}R^{B4} wherein R^{B3} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group, and R^{B4} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 15 10) -NR^{B5}COR^{B6} wherein R^{B5} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B6} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,
 - 11) -NR^{B7}COOR^{B8} wherein R^{B7} and R^{B8} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 12) -NR^{B9}CONR^{B10}R^{B11} wherein R^{B9}, R^{B10} and R^{B11} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 20 13) -NR^{B12}CONR^{B13}OR^{B14} wherein R^{B12}, R^{B13} and R^{B14} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 14) -NR^{B15}SO₂R^{B16} wherein R^{B15} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B16} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,
 - 25 15) -SO₂-R^{B17} wherein R^{B17} is a C₁₋₄ alkyl group or a heterocyclic group,
 - 16) -SO₂NR^{B18}R^{B19} wherein R^{B18} and R^{B19} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 17) -P(=O)(R^{B20})(R^{B21}) wherein R^{B20} and R^{B21} are the same or different and each is a C₁₋₄ alkyl group,
 - 18) -COOR^{B22} wherein R^{B22} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 30 19) -CONR^{B23}R^{B24} wherein R^{B23} and R^{B24} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 20) -NR^{B25}SO₂NR^{B26}R^{B27} wherein R^{B25}, R^{B26} and R^{B27} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31} wherein R^{B28}, R^{B29}, R^{B30} and R^{B31} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 35 22) a C₃₋₁₂ carbon ring group and
 - 23) a heterocyclic group
- wherein each of the "C₁₋₈ alkyl group" of the above-mentioned 4), and the C₁₋₄ alkyl groups for R^{B1} to R^{B31} is optionally substituted by the same or different 1 to 3 substituents selected from the following group A, each of the C₂₋₄ alkenyl group of 5) and the C₂₋₄ alkynyl group of 6) is optionally substituted by the same or different 1 to 3 substituents selected from the following group A, the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and
- each of the C₃₋₁₂ carbon ring group of the above-mentioned 22), R^{B3}, R^{B6} and R^{B16}, and the heterocyclic group of the above-mentioned 23), R^{B3}, R^{B6}, R^{B16} and R^{B17} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C,

group A is a group consisting of

- 50 1) a halogen atom,
- 2) a nitro group,
- 3) a cyano group,
- 4) a C₁₋₄ alkyl group,
- 5) -OR^{A1} wherein R^{A1} is a hydrogen atom or a C₁₋₄ alkyl group,
- 55 6) -SR^{A2} wherein R^{A2} is a hydrogen atom or a C₁₋₄ alkyl group,
- 7) -NR^{A3}R^{A4} wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
- 8) -COOR^{A5} wherein R^{A5} is a hydrogen atom or a C₁₋₄ alkyl group,
- 9) -NR^{A6}COR^{A7} wherein R^{A6} is a hydrogen atom or a C₁₋₄ alkyl group, R^{A7} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon

ring group or a heterocyclic group,

10) $-NR^{A8}COOR^{A9}$ wherein R^{A8} and R^{A9} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

11) a C_{3-12} carbon ring group and

12) a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,

each of the C_{1-4} alkyl groups of the above-mentioned 4), R^{A1} , R^{A2} , R^{A3} , R^{A4} , R^{A5} , R^{A6} , R^{A7} , R^{A8} and R^{A9} is optionally substituted by the same or different 1 to 3 substituents selected from the following group C, and

each of the C_{3-12} carbon ring groups of the above-mentioned 11) and R^{A7} , and the heterocyclic groups of 12) and R^{A7} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C, and group C is a group consisting of

1) a halogen atom,

2) a cyano group,

3) a C_{1-4} alkyl group,

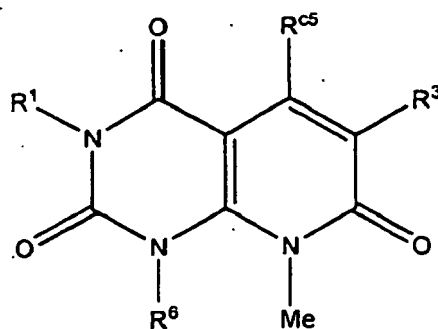
4) $-OR^{C1}$ wherein R^{C1} is a hydrogen atom or a C_{1-4} alkyl group,

5) $-NR^{C2}R^{C3}$ wherein R^{C2} and R^{C3} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

6) $-COOR^{C4}$ wherein R^{C4} is a hydrogen atom or a C_{1-4} alkyl group and

7) an oxo group.

18. A compound of the formula [51] or a salt or solvate thereof:



[51]

wherein

R^3 is a methyl group,

R^1 and R^6 are the same or different and each is a C_{3-12} carbon ring group or a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, the C_{3-12} carbon ring group and the

heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B, and

R^{C5} is a leaving group;

wherein group B is a group consisting of

1) a halogen atom,

2) a nitro group,

3) a cyano group,

4) a C_{1-8} alkyl group,

5) a C_{2-4} alkenyl group,

6) a C_{2-4} alkynyl group,

7) $-OR^{B1}$ wherein R^{B1} is a hydrogen atom or a C_{1-4} alkyl group,

8) $-SR^{B2}$ wherein R^{B2} is a hydrogen atom or a C_{1-4} alkyl group,

9) $-NR^{B3}R^{B4}$ wherein R^{B3} is a hydrogen atom, a C_{1-4} alkyl group, a C_{3-12} carbon ring group or a heterocyclic group, and R^{B4} is a hydrogen atom or a C_{1-4} alkyl group,

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10) $-NR^{B5}COR^{B6}$ wherein R^{B5} is a hydrogen atom or a C_{1-4} alkyl group, and R^{B6} is a hydrogen atom, a C_{1-4} alkyl group, a C_{3-12} carbon ring group or a heterocyclic group,

11) $-NR^{B7}COOR^{B8}$ wherein R^{B7} and R^{B8} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

12) $-NR^{B9}CONR^{B10}R^{B11}$ wherein R^{B9} , R^{B10} and R^{B11} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

13) $-NR^{B12}CONR^{B13}OR^{B14}$ wherein R^{B12} , R^{B13} and R^{B14} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

14) $-NR^{B15}SO_2R^{B16}$ wherein R^{B15} is a hydrogen atom or a C_{1-4} alkyl group, and R^{B16} is a C_{1-4} alkyl group, a C_{3-12} carbon ring group or a heterocyclic group,

15) $-SO_2-R^{B17}$ wherein R^{B17} is a C_{1-4} alkyl group or a heterocyclic group,

16) $-SO_2NR^{B18}R^{B19}$ wherein R^{B18} and R^{B19} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

17) $-P(=O)(R^{B20})(R^{B21})$ wherein R^{B20} and R^{B21} are the same or different and each is a C_{1-4} alkyl group,

18) $-COOR^{B22}$ wherein R^{B22} is a hydrogen atom or a C_{1-4} alkyl group,

19) $-CONR^{B23}R^{B24}$ wherein R^{B23} and R^{B24} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

20) $-NR^{B25}SO_2NR^{B26}R^{B27}$ wherein R^{B25} , R^{B26} and R^{B27} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

21) $-NR^{B28}SO_2NR^{B29}CONR^{B30}R^{B31}$ wherein R^{B28} , R^{B29} , R^{B30} and R^{B31} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

22) a C_{3-12} carbon ring group and

23) a heterocyclic group

wherein each of the " C_{1-8} alkyl group" of the above-mentioned 4), and the C_{1-4} alkyl groups for R^{B1} to R^{B31} is optionally substituted by the same or different 1 to 3 substituents selected from the following group A,

each of the C_{2-4} alkenyl group of 5) and the C_{2-4} alkynyl group of 6) is optionally substituted by the same or different 1 to 3 substituents selected from the following group A,

the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and

each of the C_{3-12} carbon ring group of the above-mentioned 22), R^{B3} , R^{B6} and R^{B16} , and the heterocyclic group of the above-mentioned 23), R^{B3} , R^{B6} , R^{B16} and R^{B17} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C,

group A is a group consisting of

1) a halogen atom,

2) a nitro group,

3) a cyano group,

4) a C_{1-4} alkyl group,

5) $-OR^{A1}$ wherein R^{A1} is a hydrogen atom or a C_{1-4} alkyl group,

6) $-SRA^2$ wherein R^{A2} is a hydrogen atom or a C_{1-4} alkyl group,

7) $-NRA^3RA^4$ wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

8) $-COOR^{A5}$ wherein R^{A5} is a hydrogen atom or a C_{1-4} alkyl group,

9) $-NRA^6COR^{A7}$ wherein R^{A6} is a hydrogen atom or a C_{1-4} alkyl group, R^{A7} is a C_{1-4} alkyl group, a C_{3-12} carbon ring group or a heterocyclic group,

10) $-NRA^8COOR^{A9}$ wherein R^{A8} and R^{A9} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

11) a C_{3-12} carbon ring group and

12) a heterocyclic group,

wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,

each of the C_{1-4} alkyl groups of the above-mentioned 4), R^{A1} , R^{A2} , R^{A3} , R^{A4} , R^{A5} , R^{A6} , R^{A7} , R^{A8} and R^{A9} is optionally substituted by the same or different 1 to 3 substituents selected from the following group C, and

each of the C_{3-12} carbon ring groups of the above-mentioned 11) and R^{A7} , and the heterocyclic groups of 12) and R^{A7} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C, and group C is a group consisting of

- 1) a halogen atom,
- 2) a cyano group,
- 3) a C₁₋₄ alkyl group,
- 4) -OR^{C1} wherein R^{C1} is a hydrogen atom or a C₁₋₄ alkyl group,
- 5) -NR^{C2}R^{C3} wherein R^{C2} and R^{C3} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
- 6) -COOR^{C4} wherein R^{C4} is a hydrogen atom or a C₁₋₄ alkyl group and
- 7) an oxo group.

19. The compound of claim 17 or 18, wherein R¹ is a C₃₋₁₂ carbon ring group, wherein the C₃₋₁₂ carbon ring group is optionally substituted by 1 to 5 substituents selected from group B.

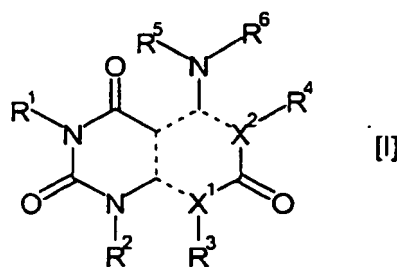
20. The compound of claim 19, wherein R¹ is cyclopropyl.

21. The compound of claim 17 or 18, wherein R⁶ is a phenyl group that is optionally substituted by 1 to 5 substituents selected from group B.

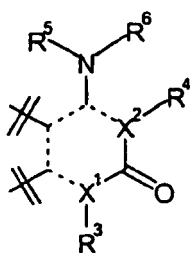
22. The compound of claim 21, wherein R⁶ is a phenyl group that is di-substituted at the 2,4-position.

23. The compound of claim 18, wherein R^{c5} is a leaving group selected from the group consisting of a halogen, p-toluenesulfonyloxy, methanesulfonyloxy, and trifluoromethanesulfonyloxy.

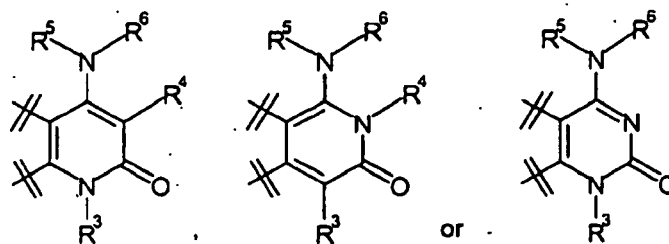
24. Use of a compound represented by the following formula [I] or a pharmaceutically acceptable salt thereof as an active ingredient for the production of a pharmaceutical agent for treating a tumor:



wherein
X¹ and X² are the same or different and each is a carbon atom or a nitrogen atom, a

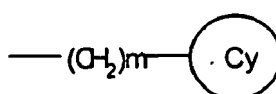


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R¹, R², and R⁶ are the same or different and each is
 a C₁₋₆ alkyl group,
 a C₂₋₆ alkenyl group,
 wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally substituted by 1 to 3 substituents selected
 from the following group A, or



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wherein m is 0 or an integer of 1 to 4,
 ring Cy is a C₃₋₁₂ carbon ring group or a heterocyclic group,
 wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero
 atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, the C₃₋₁₂ carbon ring group and the
 heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B,
 R³, R⁴, and R⁵ are the same or different and each is
 a hydrogen atom,
 a hydroxyl group,
 a C₁₋₆ alkyl group,
 a C₂₋₆ alkenyl group,
 wherein the C₁₋₆ alkyl group and the C₂₋₆ alkenyl group are optionally substituted by 1 to 3 substituents selected
 from the following group A,
 a C₃₋₁₂ carbon ring group or
 a heterocyclic group,
 wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero
 atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and the C₃₋₁₂ carbon ring group and the
 heterocyclic group are optionally substituted by 1 to 5 substituents selected from the following group B, or
 R² and R³ are optionally linked to form a C₁₋₄ alkylene group, or R⁴ and R⁵ are optionally linked to form a C₁₋₄
 alkylene group,
 wherein group A is a group consisting of

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- 1) a halogen atom,
 - 2) a nitro group,
 - 3) a cyano group,
 - 4) a C₁₋₄ alkyl group,
 - 5) -OR^{A1} wherein R^{A1} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 6) -SR^{A2} wherein R^{A2} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 7) -NR^{A3}R^{A4} wherein R^{A3} and R^{A4} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 8) -COOR^{A5} wherein R^{A5} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 9) -NR^{A6}COR^{A7} wherein R^{A6} is a hydrogen atom or a C₁₋₄ alkyl group, R^{A7} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon
 ring group or a heterocyclic group,
 - 10) -NR^{A8}COOR^{A9} wherein R^{A8} and R^{A9} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl
 group,
 - 11) a C₃₋₁₂ carbon ring group and
 - 12) a heterocyclic group,
 wherein the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4

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hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,
each of the C₁₋₄ alkyl groups of the above-mentioned 4), R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} and R^{A9} is
optionally substituted by the same or different 1 to 3 substituents selected from the following group C, and
each of the C₃₋₁₂ carbon ring groups of the above-mentioned 11) and R^{A7}, and the heterocyclic groups of 12)
and R^{A7} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C,

group B is a group consisting of

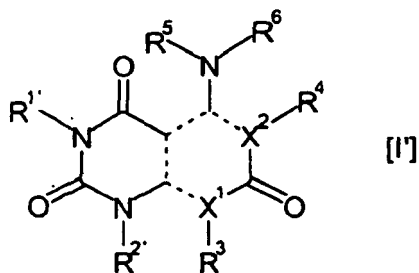
- 1) a halogen atom,
 - 2) a nitro group,
 - 3) a cyano group,
 - 4) a C₁₋₈ alkyl group,
 - 5) a C₂₋₄ alkenyl group,
 - 6) a C₂₋₄ alkynyl group,
 - 7) -OR^{B1} wherein R^{B1} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 8) -SR^{B2} wherein R^{B2} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 9) -NR^{B3}R^{B4} wherein R^{B3} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group, and R^{B4} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 10) -NR^{B5}COR^{B6} wherein R^{B5} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B6} is a hydrogen atom, a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,
 - 11) -NR^{B7}COOR^{B8} wherein R^{B7} and R^{B8} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 12) -NR^{B9}CONR^{B10}R^{B11} wherein R^{B9}, R^{B10} and R^{B11} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 13) -NR^{B12}CONR^{B13}OR^{B14} wherein R^{B12}, R^{B13} and R^{B14} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 14) -NR^{B15}SO₂R^{B16} wherein R^{B15} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{B16} is a C₁₋₄ alkyl group, a C₃₋₁₂ carbon ring group or a heterocyclic group,
 - 15) -SO₂-R^{B17} wherein R^{B17} is a C₁₋₄ alkyl group or a heterocyclic group,
 - 16) -SO₂NR^{B18}R^{B19} wherein R^{B18} and R^{B19} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 17) -P(=O)(R^{B20})(R^{B21}) wherein R^{B20} and R^{B21} are the same or different and each is a C₁₋₄ alkyl group,
 - 18) -COOR^{B22} wherein R^{B22} is a hydrogen atom or a C₁₋₄ alkyl group,
 - 19) -CONR^{B23}R^{B24} wherein R^{B23} and R^{B24} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 20) -NR^{B25}SO₂NR^{B26}R^{B27} wherein R^{B25}, R^{B26} and R^{B27} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31} wherein R^{B28}, R^{B29}, R^{B30} and R^{B31} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,
 - 22) a C₃₋₁₂ carbon ring group and
 - 23) a heterocyclic group
- wherein each of the "C₁₋₈ alkyl group" of the above-mentioned 4), and the C₁₋₄ alkyl groups for R^{B1} to R^{B31} is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A, each of the C₂₋₄ alkenyl group of 5) and the C₂₋₄ alkynyl group of 6) is optionally substituted by the same or different 1 to 3 substituents selected from the above-mentioned group A, the heterocyclic group is a saturated or unsaturated ring group having, besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and each of the C₃₋₁₂ carbon ring group of the above-mentioned 22), R^{B3}, R^{B6} and R^{B16}, and the heterocyclic group of the above-mentioned 23), R^{B3}, R^{B6}, R^{B16} and R^{B17} is optionally substituted by the same or different 1 to 5 substituents selected from the following group C, and

group C is a group consisting of

- 1) a halogen atom,
- 2) a cyano group,
- 3) a C₁₋₄ alkyl group,
- 4) -OR^{C1} wherein R^{C1} is a hydrogen atom or a C₁₋₄ alkyl group,
- 5) -NRC²RC³ wherein R^{C2} and R^{C3} are the same or different and each is a hydrogen atom or a C₁₋₄ alkyl group,

- 6) $-\text{COOR}^{\text{C4}}$ wherein R^{C4} is a hydrogen atom or a C_{1-4} alkyl group and
 7) an oxo group.

25. A compound represented by the following formula [I'] or a pharmaceutically acceptable salt thereof:

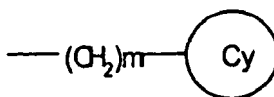


wherein

R^1 , R^2 and R^6 are the same or different and each is
 a C_{1-6} alkyl group,

a C_{2-6} alkenyl group,

wherein the C_{1-6} alkyl group and the C_{2-6} alkenyl group are optionally substituted by 1 to 3 substituents selected
 from group A of claim 1, or

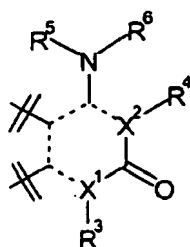


m is an integer of 0 or 1 to 4,

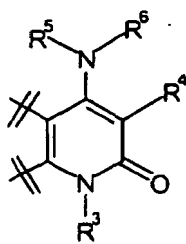
ring Cy is a C_{3-12} carbon ring group or a heterocyclic group

wherein the heterocyclic group is a saturated or unsaturated ring having, besides carbon atom, 1 to 4 hetero atoms
 selected from an oxygen atom, a nitrogen atom and a sulfur atom, and the C_{3-12} carbon ring group and the heterocyclic
 group are optionally substituted by 1 to 5 substituents selected from group B of claim 1,

provided that, when the



moiety is



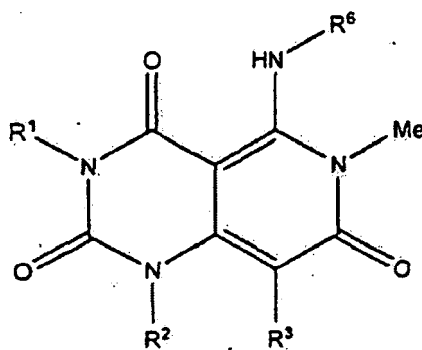
then R^2 is not a methyl group, and

when R² is a phenyl group, then R¹ is not a phenyl group,
and other symbols are as defined in claim 1.

- 5 26. Use of a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient for the production of an antitumor agent.
- 10 27. Use of a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient for the production of a pharmaceutical agent capable of inhibiting MEK.
- 15 28. Use of a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient for the production of a pharmaceutical agent capable of inducing p15 protein.
- 20 29. Use of a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient for the production of a pharmaceutical agent for treating a disease causing by an undesirable cell proliferation.
- 25 30. Use of a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient for the production of a pharmaceutical agent capable of inhibiting undesirable cell proliferation.
- 30 31. Use of a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient for the production of a pharmaceutical agent capable of regulating cell cycle.
- 35 32. A pharmaceutical composition which comprises a compound of the formula [I] of claim 25 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
- 40 33. Use of (a) a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient, which is used in combination with (b) at least one other antitumor compound, for the production of an antitumor agent.
- 45 34. Use of (a) compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof as an active ingredient and (b) at least one other antitumor compound, in combination, for the production of an antitumor agent.
- 50 35. A pharmaceutical composition comprising, as an active ingredient, (a) a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof and (b) at least one other antitumor compound, and a pharmaceutical acceptable carrier, in combination.
- 55 36. A kit for treating a tumor comprising (a) a pharmaceutical composition comprising, as an active ingredient, a compound of the formula [I] of claim 24 or a pharmaceutically acceptable salt thereof and (b) a pharmaceutical composition comprising, as an active ingredient, at least one other antitumor agent, in combination.

Patentansprüche

1. Ein Verfahren zur Herstellung einer Verbindung der Formel [I-3-2]



[I-3-2]

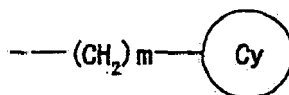
wobei

R^1 , R^2 und R^6 gleich oder verschieden sind und jeweils

einen C_{1-6} -Alkylrest,

einen C_{2-6} -Alkenylrest,

wobei der C_{1-6} -Alkylrest und der C_{2-6} -Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert sind, oder



bedeuten,

wobei m 0 oder eine ganze Zahl von 1 bis 4 ist,

der Ring Cy ein C_{3-12} -Kohlenstoffringrest oder ein heterocyclischer Rest ist, wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, der C_{3-12} -Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind,

R^3

ein Wasserstoffatom,

ein Hydroxylrest,

ein C_{1-6} -Alkylrest,

ein C_{2-6} -Alkenylrest,

wobei der C_{1-6} -Alkylrest und der C_{2-6} -Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert sind,

ein C_{3-12} -Kohlenstoffringrest oder

ein heterocyclischer Rest ist,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, und der C_{3-12} -Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind;

wobei Gruppe A eine Gruppe ist, die aus folgenden besteht

1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C_{1-4} -Alkylrest,

5) $-OR^{A1}$, wobei R^{A1} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

6) $-SRA^2$, wobei R^{A2} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

7) $-NRA^3RA^4$, wobei R^{A3} und R^{A4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

8) $-COOR^{A5}$, wobei R^{A5} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

9) $-NR^{A6}COR^{A7}$, wobei R^{A6} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist, R^{A7} ein C_{1-4} -Alkylrest, ein C_{3-12} -Kohlenstoffringrest oder ein heterocyclischer Rest ist,

10) $-NRA^8COOR^{A9}$, wobei R^{A8} und R^{A9} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

11) einem C_{3-12} -Kohlenstoffringrest und

12) einem heterocyclischen Rest,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

jeder der C_{1-4} -Alkylreste des vorstehenden Punktes 4), R^{A1} , R^{A2} , R^{A3} , R^{A4} , R^{A5} , R^{A6} ,

R^{A7} , R^{A8} und R^{A9} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

jeder der C_{3-12} -Kohlenstoffringreste des vorstehenden Punktes 11) und R^{A7} , und der heterocyclischen Reste von Punkt 12) und R^{A7} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist,

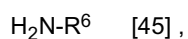
wobei Gruppe B eine Gruppe ist, die aus folgenden besteht

- 1) einem Halogenatom,
 - 2) einer Nitrogruppe,
 - 3) einer Cyanogruppe,
 - 4) einem C₁₋₈-Alkylrest,
 - 5) einem C₂₋₄-Alkenylrest,
 - 6) einem C₂₋₄-Alkinylrest,
 - 7) -OR^{B1}, wobei R^{B1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 8) -SR^{B2}, wobei R^{B2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 9) -NR^{B3}R^{B4}, wobei R^{B3} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist, und R^{B4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 10) -NR^{B5}COR^{B6}, wobei R^{B5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und R^{B6} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,
 - 11) -NR^{B7}COOR^{B8}, wobei R^{B7} und R^{B8} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 12) -NR^{B9}CONR^{B10}R^{B11}, wobei R^{B9}, R^{B10} und R^{B11} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 13) -NR^{B12}CONR^{B13}OR^{B14}, wobei R^{B12}, R^{B13} und R^{B14} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 14) -NR^{B15}SO₂R^{B16}, wobei R^{B15} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, und R^{B16} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,
 - 15) -SO₂-R^{B17}, wobei R^{B17} ein C₁₋₄-Alkylrest oder ein heterocyclischer Rest ist,
 - 16) -SO₂NR^{B18}R^{B19}, wobei R^{B18} und R^{B19} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 17) -P(=O)(R^{B20})(R^{B21}), wobei R^{B20} und R^{B21} gleich oder verschieden sind und jeweils ein C₁₋₄-Alkylrest sind,
 - 18) -COOR^{B22}, wobei R^{B22} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 19) -CONR^{B23}R^{B24}, wobei R^{B23} und R^{B24} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 20) -NR^{B25}SO₂NR^{B26}R^{B27}, wobei R^{B25}, R^{B26} und R^{B27} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31}, wobei R^{B28}, R^{B29}, R^{B30} und R^{B31} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 22) einem C₃₋₁₂-Kohlenstoffringrest und
 - 23) einem heterocyclischen Rest
- wobei jeder des "C₁₋₈-Alkylrests" des vorstehenden Punktes 4), und der C₁₋₄-Alkylreste für R^{B1} bis R^{B31} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,
- jeder des C₂₋₄-Alkenylrests von Punkt 5) und des C₂₋₄-Alkinylrests von Punkt 6) gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,
- der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, und
- jeder des C₃₋₁₂-Kohlenstoffringrests des vorstehenden Punktes 22), R^{B3}, R^{B6} und R^{B16} und des heterocyclischen Rests des vorstehenden Punktes 23), R^{B3}, R^{B6}, R^{B16} und R^{B17} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

Gruppe C eine Gruppe ist, die aus folgenden besteht:

- 1) einem Halogenatom,
 - 2) einer Cyanogruppe,
 - 3) einem C₁₋₄-Alkylrest,
 - 4) -OR^{C1}, wobei R^{C1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 5) -NR^{C2}RC³, wobei R^{C2} und R^{C3} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 6) -COOR^{C4}, wobei R^{C4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und
 - 7) einer Oxogruppe,
- wobei das Verfahren umfasst

(a) Umsetzen einer Verbindung der Formel [45]

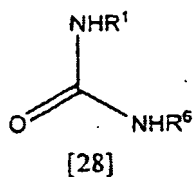


5 wobei R^6 wie vorstehend definiert ist,
mit einer Verbindung der Formel [1]



10 wobei R^1 wie vorstehend definiert ist,
um eine Verbindung der Formel [28] zu bilden

15

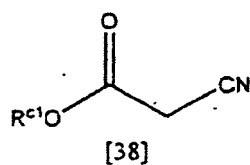


20

wobei R^1 und R^6 wie vorstehend definiert sind;

(b) Umsetzen einer Verbindung der Formel [28] mit einer Verbindung der Formel [38]

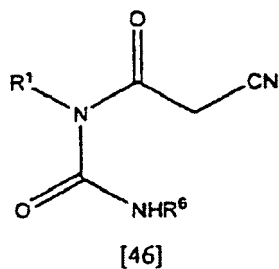
25



30

wobei R^1 ein Wasserstoffatom oder ein C_{1-6} -Alkylrest ist,
um eine Verbindung der Formel [46] zu bilden

35



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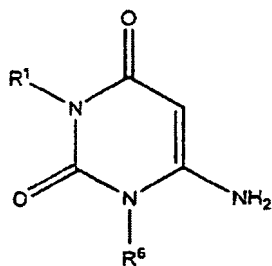
wobei R^1 und R^6 wie vorstehend definiert sind;

(c) Umwandeln einer Verbindung der Formel [46] in eine Verbindung der Formel [47]

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10

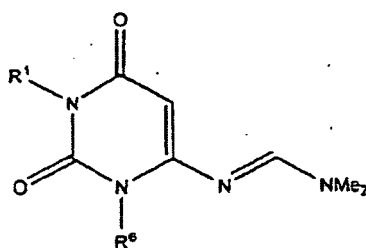
[47]

wobei R¹ und R⁶ wie vorstehend definiert sind;

15

(d) Umwandeln einer Verbindung der Formel [47] in eine Verbindung der Formel [48]

20



25

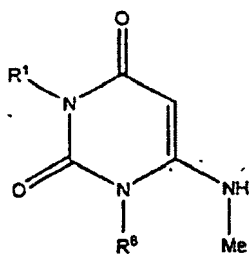
[48]

wobei R¹ und R⁶ wie vorstehend definiert sind;

30

(e) Umwandeln einer Verbindung der Formel [48] in eine Verbindung der Formel [49]

35



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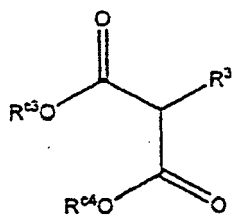
[49]

wobei R¹ und R⁶ wie vorstehend definiert sind;

45

(f) Umsetzen einer Verbindung der Formel [49] mit einer Verbindung der Formel [33]

50



55

[33]

wobei

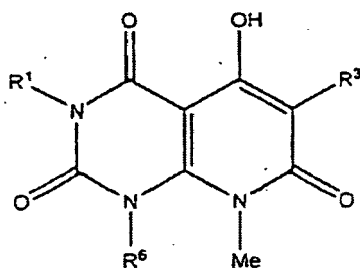
R^3 wie vorstehend definiert ist; und

R^{c3} und R^{c4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder C_{1-6} -Alkyl sind, um eine Verbindung der Formel [50] zu bilden

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10

15



[50]

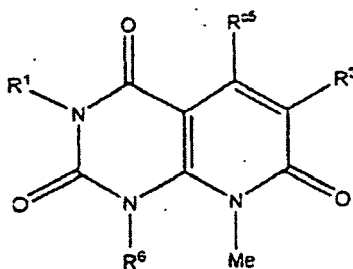
wobei R^1 , R^3 und R^6 wie vorstehend definiert sind;

20

(g) Umwandeln einer Verbindung der Formel [50] in eine Verbindung der Formel [51];

25

30



[51]

35

wobei

R^1 , R^3 und R^6 wie vorstehend definiert sind; und

R^{c5} eine Abgangsgruppe ist;

(h) Umsetzen einer Verbindung der Formel [51] mit einer Verbindung der Formel [36]

40



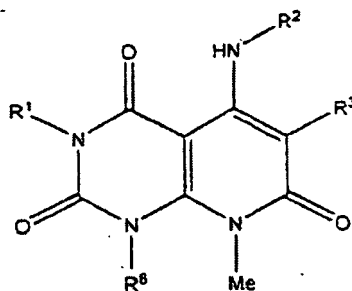
wobei R^2 wie vorstehend definiert ist;

um eine Verbindung der Formel [52] zu bilden

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[52]

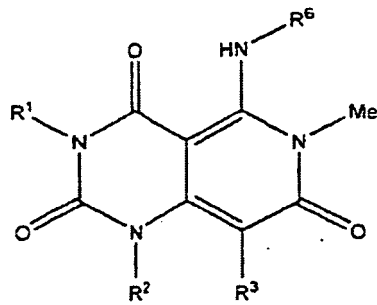
wobei R¹, R², R³ und R⁶ wie vorstehend definiert sind;
und

(i) Umwandeln einer Verbindung der Formel [52] in eine Verbindung der Formel [I-3-2]

5

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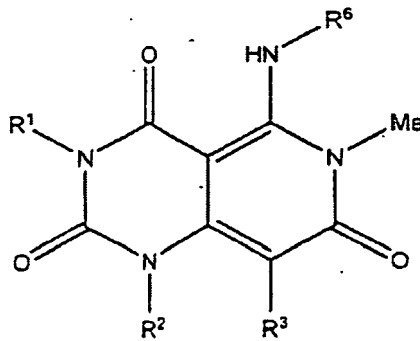
[I-3-2]

2. Ein Verfahren zur Herstellung einer Verbindung der Formel [I-3-2]

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[I-3-2]

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wobei

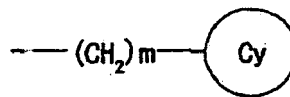
R¹, R² und R⁶ gleich oder verschieden sind und jeweils
einen C₁₋₆-Alkylrest,

einen C₂₋₆-Alkenylrest,

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wobei der C₁₋₆-Alkylrest und der C₂₋₆-Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der
folgenden Gruppe A, substituiert sind, oder

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bedeuten,

wobei m 0 oder eine ganze Zahl von 1 bis 4 ist,

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der Ring Cy ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist, wobei der heterocyclische Rest ein
gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausge-
wählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, der C₃₋₁₂-Kohlenstoffringrest und
der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, sub-
stituiert sind,

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R³

ein Wasserstoffatom,

ein Hydroxylrest,

ein C₁₋₆-Alkylrest,

ein C₂₋₆-Alkenylrest,

wobei der C₁₋₆-Alkylrest und der C₂₋₆-Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert sind,

ein C₃₋₁₂-Kohlenstoffringrest oder

ein heterocyclischer Rest ist,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, und der C₃₋₁₂-Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind;

wobei Gruppe A eine Gruppe ist, die aus folgenden besteht

1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C₁₋₄-Alkylrest,

5) -OR^{A1}, wobei R^{A1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

6) -SRA^{A2}, wobei R^{A2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

7) -NR^{A3}R^{A4}, wobei R^{A3} und R^{A4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

8) -COOR^{A5}, wobei R^{A5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

9) -NR^{A6}COR^{A7}, wobei R^{A6} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, R^{A7} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

10) NR^{A8}COOR^{A9}, wobei R^{A8} und R^{A9} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

11) einem C₃₋₁₂-Kohlenstoffringrest und

12) einem heterocyclischen Rest,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

jeder der C₁₋₄-Alkylreste des vorstehenden Punktes 4), R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} und R^{A9} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

jeder der C₃₋₁₂-Kohlenstoffringreste des vorstehenden Punktes 11) und R^{A7}, und der heterocyclischen Reste von Punkt 12) und R^{A7} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist,

wobei Gruppe B eine Gruppe ist, die aus folgenden besteht

1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C₁₋₈-Alkylrest,

5) einem C₂₋₄-Alkenylrest,

6) einem C₂₋₄-Alkylrest,

7) -OR^{B1}, wobei R^{B1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

8) -SR^{B2}, wobei R^{B2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

9) -NR^{B3}R^{B4}, wobei R^{B3} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist, und R^{B4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

10) -NR^{B5}COR^{B6}, wobei R^{B5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und R^{B6} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

11) -NR^{B7}COOR^{B8}, wobei R^{B7} und R^{B8} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

12) -NR^{B9}CONR^{B10}R^{B11}, wobei R^{B9}, R^{B10} und R^{B11} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

13) -NR^{B12}CONR^{B13}OR^{B14}, wobei R^{B12}, R^{B13} und R^{B14} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

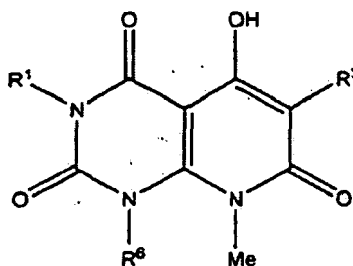
14) NR^{B15}SO₂R^{B16}, wobei R^{B15} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, und R^{B16} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

- 15)-SO₂-R^{B17}, wobei R^{B17} ein C₁₋₄-Alkylrest oder ein heterocyclischer Rest ist,
 16)-SO₂NR^{B18}R^{B19}, wobei R^{B18} und R^{B19} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 17)-P(=O)(R^{B20})(R^{B21}), wobei R^{B20} und R^{B21} gleich oder verschieden sind und jeweils ein C₁₋₄-Alkylrest sind,
 18)-COOR^{B22}, wobei R^{B22} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 19)-CONR^{B21}R^{B24}, wobei R^{B23} und R^{B24} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 20) NR^{B25}SO₂NR^{B26}R^{B27}, wobei R^{B25}, R^{B26} und R^{B27} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 21)-NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31}, wobei R^{B28}, R^{B29}, R^{B30} und R^{B31} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 22) einem C₃₋₁₂-Kohlenstoffringrest und
 23) einem heterocyclischen Rest
 wobei jeder des "C₁₋₈-Alkylrests" des vorstehenden Punktes 4), und der C₁₋₄-Alkylreste für R^{B1} bis R^{B31} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,
 jeder des C₂₋₄-Alkenylrests von Punkt 5) und des C₂₋₄-Alkylrests von Punkt 6) gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,
 der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, und
 jeder des C₃₋₁₂-Kohlenstoffringrests des vorstehenden Punktes 22), R^{B3}, R^{B6} und R^{B16} und des heterocyclischen Rests des vorstehenden Punktes 23), R^{B3}, R^{B6}, R^{B16} und R^{B17} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

Gruppe C eine Gruppe ist, die aus folgenden besteht

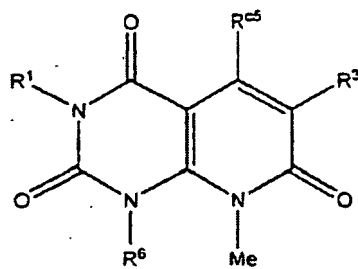
- 1) einem Halogenatom,
 - 2) einer Cyanogruppe,
 - 3) einem C₁₋₄-Alkylrest,
 - 4) -OR^{C1}, wobei R^{C1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 5) NR^{C2}R^{C3}, wobei R^{C2} und R^{C3} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 6) -COOR^{C4}, wobei R^{C4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und
 - 7) einer Oxogruppe,
- wobei das Verfahren umfasst

(a) Umwandeln einer Verbindung der Formel [50]



[50]

wobei R¹, R³ und R⁶ wie vorstehend definiert sind;
 in eine Verbindung der Formel [51];

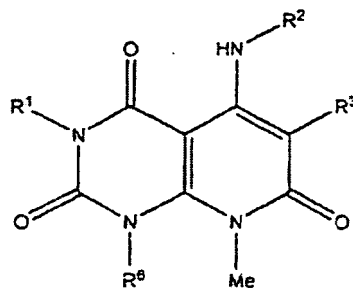


[51]

15 wobei R¹, R³ und R⁶ wie vorstehend definiert sind und R^{c5} eine Abgangsgruppe ist;
 (b) Umsetzen einer Verbindung der Formel [51] mit einer Verbindung der Formel [36]

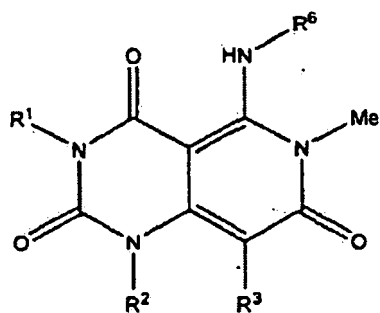


20 wobei R² wie vorstehend definiert ist;
 um eine Verbindung der Formel [52] zu bilden



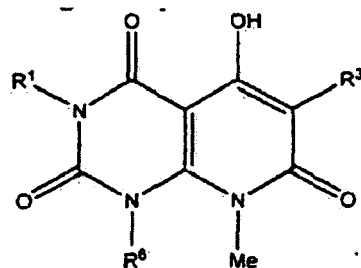
[52]

35 wobei R¹, R², R³ und R⁶ wie vorstehend definiert sind;
 und
 (c) Umwandeln einer Verbindung der Formel [52] in eine Verbindung der Formel [1-3-2]



[1-3-2]

3. Ein Verfahren zur Herstellung einer Verbindung der Formel [50]



[50]

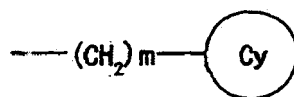
wobei

R¹ und R⁶ gleich oder verschieden sind und jeweils

einen C₁₋₆-Alkylrest,

einen C₂₋₆-Alkenylrest,

wobei der C₁₋₆-Alkylrest und der C₂₋₆-Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert sind, oder



bedeuten,

wobei m 0 oder eine ganze Zahl von 1 bis 4 ist,

der Ring Cy ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist, wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, der C₃₋₁₂-Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind,

R³

ein Wasserstoffatom,

ein Hydroxylrest,

ein C₁₋₆-Alkylrest,

ein C₂₋₆-Alkenylrest,

wobei der C₁₋₆-Alkylrest und der C₂₋₆-Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert sind,

ein C₃₋₁₂-Kohlenstoffringrest oder

ein heterocyclischer Rest ist,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

und der C₃₋₁₂-Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind;

wobei Gruppe A eine Gruppe ist, die aus folgenden besteht

1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C₁₋₄-Alkylrest,

5) -OR^{A1}, wobei R^{A1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

6) -SR^{A2}, wobei R^{A2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

7) -NR^{A3}R^{A4}, wobei R^{A3} und R^{A4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

8) -COOR^{A5}, wobei R^{A5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

9) -NR^{A6}COR^{A7}, wobei R^{A6} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, R^{A7} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

10)-NR^{A8}COOR^{A9}, wobei R^{A8} und R^{A9} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

11) einem C₃₋₁₂-Kohlenstoffringrest und

12) einem heterocyclischen Rest,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

jeder der C₁₋₄-Alkylreste des vorstehenden Punktes 4), R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} und R^{A9} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

jeder der C₃₋₁₂-Kohlenstoffringreste des vorstehenden Punktes 11) und R^{A7}, und der heterocyclischen Reste von Punkt 12) und R^{A7} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist,

wobei Gruppe B eine Gruppe ist, die aus folgenden besteht

1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C₁₋₈-Alkylrest,

5) einem C₂₋₄-Alkenylrest,

6) einem C₂₋₄-Alkynylrest,

7) -OR^{B1}, wobei R^{B1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

8) -SR^{B2}, wobei R^{B2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

9) -NR^{B3}R^{B4}, wobei R^{B3} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist, und R^{B4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

10) NR^{B5}COR^{B6}, wobei R^{B5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und R^{B6} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

11)-NR^{B7}COOR^{B8}, wobei R^{B7} und R^{B8} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

12)-NR^{B9}CONR^{B10}R^{B11}, wobei R^{B9}, R^{B10} und R^{B11} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

13) NR^{B12}CONR^{B13}OR^{B14}, wobei R^{B12}, R^{B13} und R^{B14} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

14)-NR^{B15}SO₂R^{B16}, wobei R^{B15} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, und R^{B16} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

15) -SO₂-R^{B17}, wobei R^{B17} ein C₁₋₄-Alkylrest oder ein heterocyclischer Rest ist,

16) -SO₂NR^{B18}R^{B19}, wobei R^{B18} und R^{B19} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

17)-P(=O)(R^{B20})(R^{B21}), wobei R^{B20} und R^{B21} gleich oder verschieden sind und jeweils ein C₁₋₄-Alkylrest sind,

18)-COOR^{B22}, wobei R^{B22} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

19)-CONR^{B23}R^{B24}, wobei R^{B23} und R^{B24} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

20) NR^{B25}SO₂NR^{B26}R^{B27}, wobei R^{B25}, R^{B26} und R^{B27} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31}, wobei R^{B28}, R^{B29}, R^{B30} und R^{B31} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,

22) einem C₃₋₁₂-Kohlenstoffringrest und

23) einem heterocyclischen Rest

wobei jeder des "C₁₋₈-Alkylrests" des vorstehenden Punktes 4), und der C₁₋₄-Alkylreste für R^{B1} bis R^{B31} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,

jeder des C₂₋₄-Alkenylrests von Punkt 5) und des C₂₋₄-Alkynylrests von Punkt 6) gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,

der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, und

jeder des C₃₋₁₂-Kohlenstoffringrests des vorstehenden Punktes 22), R^{B3}, R^{B6} und R^{B16} und des heterocyclischen

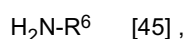
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Rests des vorstehenden Punktes 23), R^{B3}, R^{B6}, R^{B16} und R^{B17} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

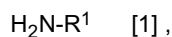
Gruppe C eine Gruppe ist, die aus folgenden besteht

- 1) einem Halogenatom,
 - 2) einer Cyanogruppe,
 - 3) einem C₁₋₄-Alkylrest,
 - 4) -OR^{C1}, wobei R^{C1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 5) -NR^{C2}R^{C3}, wobei R^{C2} und R^{C3} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 6) -COOR^{C4}, wobei R^{C4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und
 - 7) einer Oxogruppe,
- wobei das Verfahren umfasst

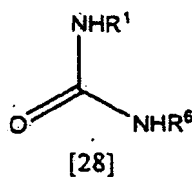
(a) Umsetzen einer Verbindung der Formel [45]



wobei R⁶ wie vorstehend definiert ist, mit einer Verbindung der Formel [1]

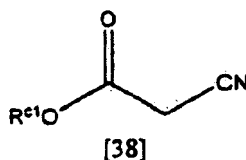


wobei R¹ wie vorstehend definiert ist, um eine Verbindung der Formel [28] zu bilden

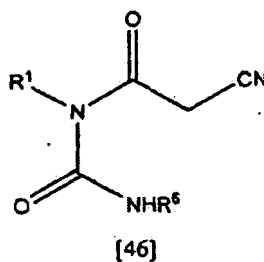


wobei R¹ und R⁶ wie vorstehend definiert sind;

(b) Umsetzen einer Verbindung der Formel [28] mit einer Verbindung der Formel [38]



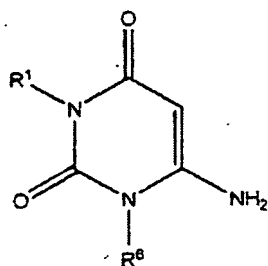
wobei R⁶ ein Wasserstoffatom oder C₁₋₆-Alkylrest ist, um eine Verbindung der Formel [46] zu bilden



wobei R¹ und R⁶ wie vorstehend definiert sind;

(c) Umwandeln einer Verbindung der Formel [46] in eine Verbindung der Formel [47]

5



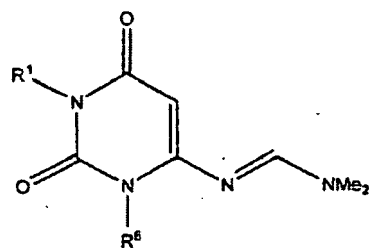
[47]

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wobei R¹ und R⁶ wie vorstehend definiert sind;

(d) Umwandeln einer Verbindung der Formel [47] in eine Verbindung der Formel [48]

15



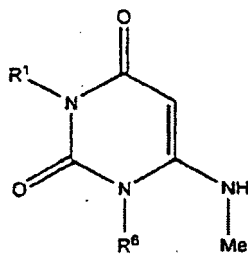
[48]

25

wobei R¹ und R⁶ wie vorstehend definiert sind;

(e) Umwandeln einer Verbindung der Formel [48] in eine Verbindung der Formel [49]

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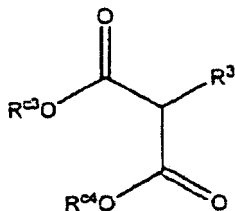
[49]

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wobei R¹ und R⁶ wie vorstehend definiert sind;

(f) Umsetzen einer Verbindung der Formel [49] mit einer Verbindung der Formel [33]

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[33]

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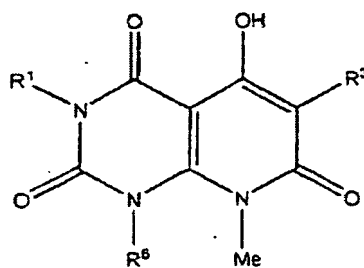
wobei

R³ wie vorstehend definiert ist; und

R^{c3} und R^{c4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder C₁₋₆-Alkyl sind, um eine Verbindung der Formel [50] zu bilden

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[50]

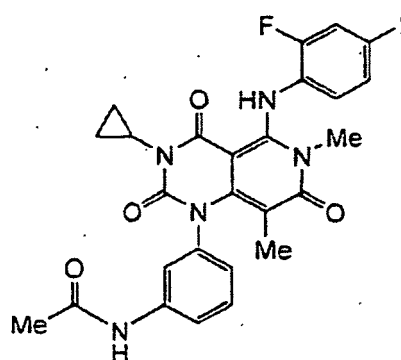
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4. Ein Verfahren zur Herstellung einer Verbindung, eines Salzes oder Solvats der Formel:

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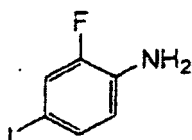


umfassend

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(a) Umsetzen von

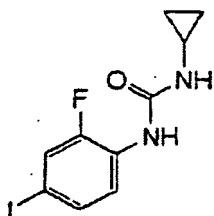
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mit Cyclopropylamin, um

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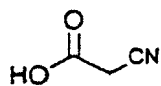


zu

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bilden;

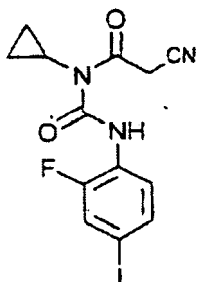
(b) Umsetzen des Produkts von Schritt (a) mit



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um

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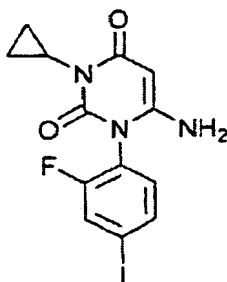
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zu bilden;

(c) Umwandeln des Produkts von Schritt (b) in

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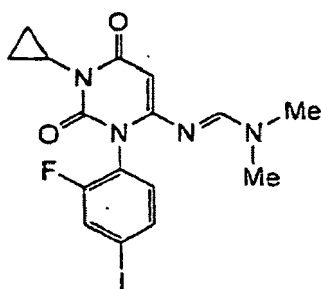


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(d) Umwandeln des Produkts von Schritt (c) in

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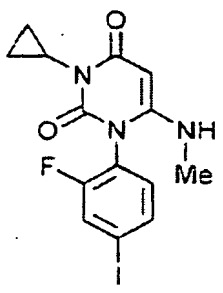
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(e) Umwandeln des Produkts von Schritt (d) in

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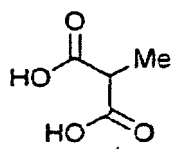


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(f) Umsetzen des Produkts von Schritt (e) mit

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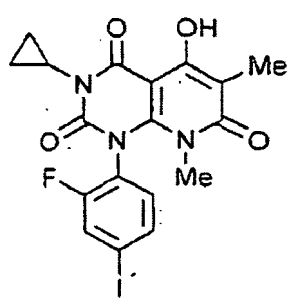


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um

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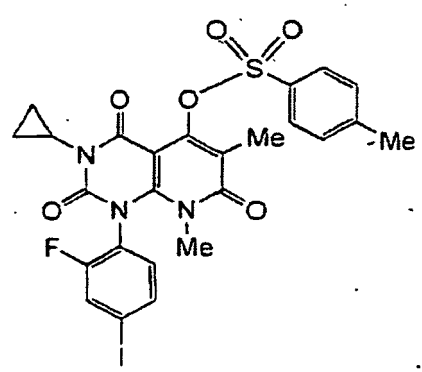
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zu bilden;

(g) Umwandeln des Produkts von Schritt (f) in

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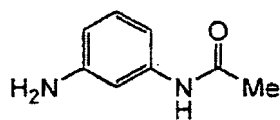
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(h) Umsetzen des Produkts von Schritt (g) mit

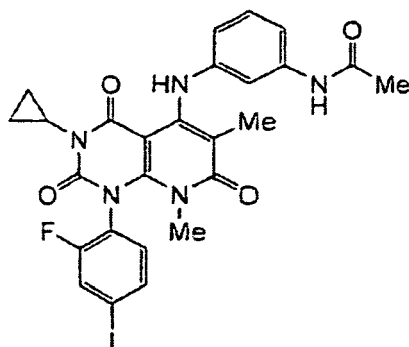
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um

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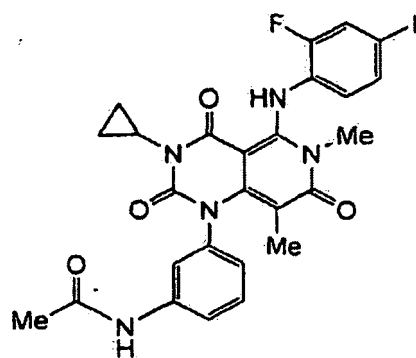
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zu bilden;

(i) Umwandeln des Produkts von Schritt (h) in

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und

(j) gegebenenfalls Umwandeln des Produkts von Schritt (i) in ein Salz oder Solvat.

5. Ein Verfahren zur Herstellung einer Verbindung, eines Salzes oder Solvats der Formel:
umfassend

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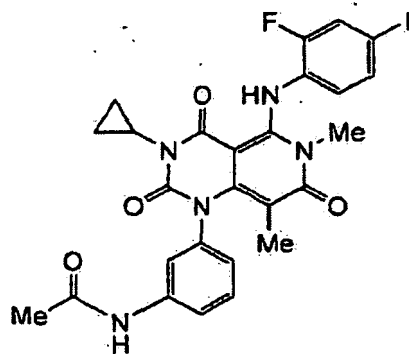
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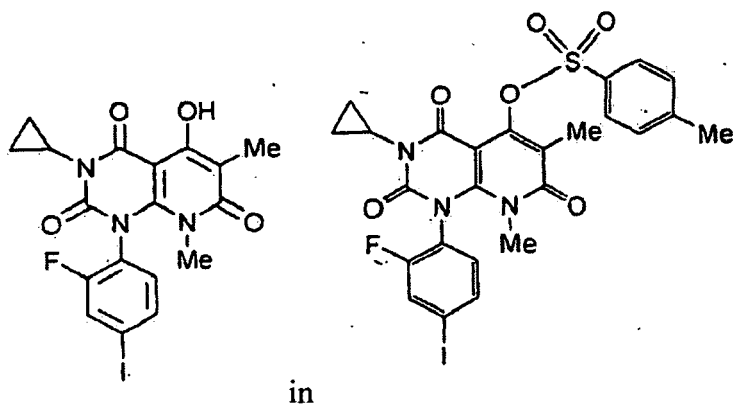


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(a) Umwandeln von

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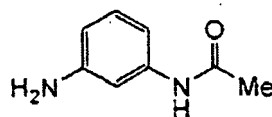
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(b) Umsetzen des Produkts von Schritt (a) mit

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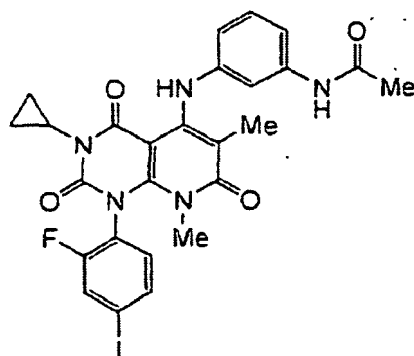


um

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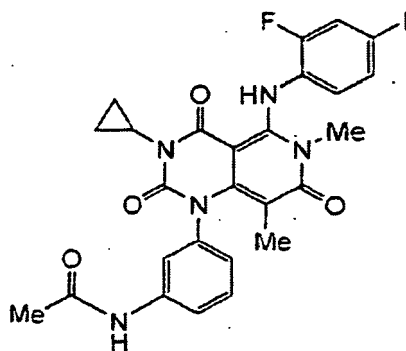
zu bilden;

(c) Umwandeln des Produkts von Schritt (b) in

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und

(d) gegebenenfalls Umwandeln des Produkts von Schritt (c) in ein Salz oder Solvat.

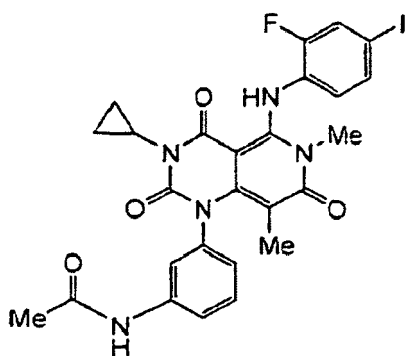
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6. Das Verfahren nach Anspruch 4 oder 5, weiter umfassend Umwandeln von

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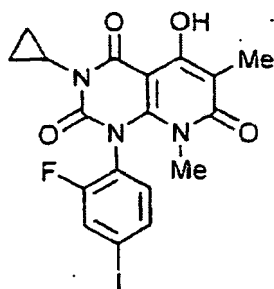
in ein Solvat.

7. Ein Verfahren zur Herstellung einer Verbindung der Formel:

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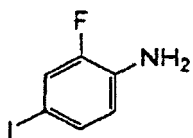


umfassend

(a) Umsetzen von

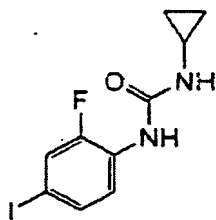
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mit Cyclopropylamin, um

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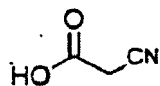


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zu bilden;

(b) Umsetzen des Produkts von Schritt (a) mit

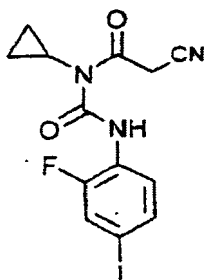
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um

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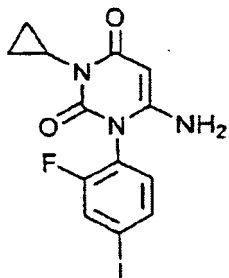
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zu

(c) Umwandeln des Produkts von Schritt (b) in

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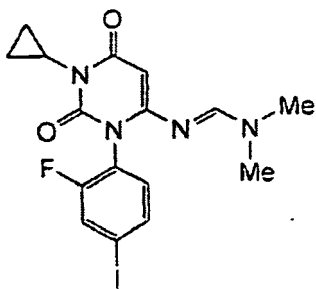


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(d) Umwandeln des Produkts von Schritt (c) in

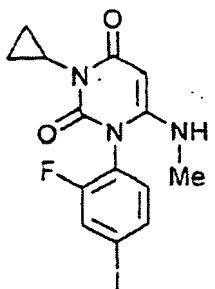
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(e) Umwandeln des Produkts von Schritt (d) in

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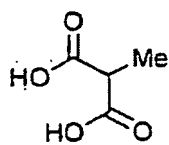
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und

(f) Umsetzen des Produkts von Schritt (e) mit

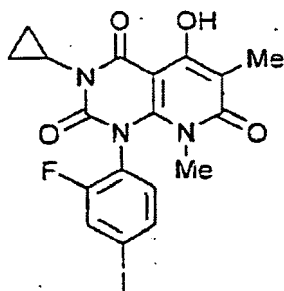
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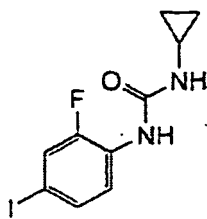
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zu bilden.

8. Eine Verbindung der Formel:

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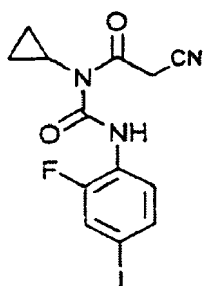


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oder ein Salz oder Solvat davon.

9. Eine Verbindung der Formel:

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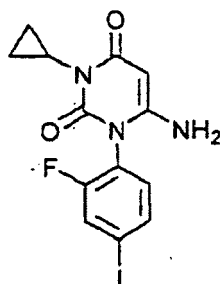


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oder ein Salz oder Solvat davon.

10. Eine Verbindung der Formel:

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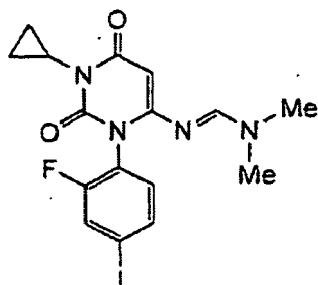


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oder ein Salz oder Solvat davon.

11. Eine Verbindung der Formel:

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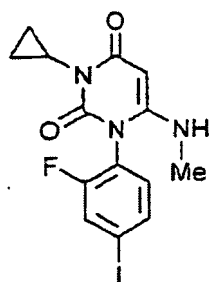
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oder ein Salz oder Solvat davon.

12. Eine Verbindung der Formel:

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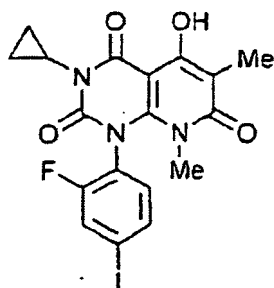


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oder ein Salz oder Solvat davon.

13. Eine Verbindung der Formel:

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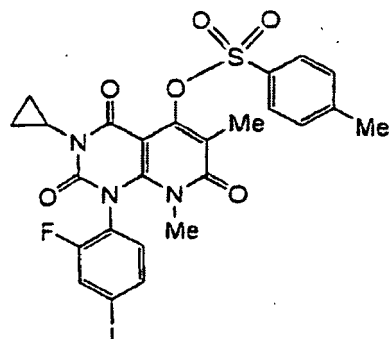
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oder ein Salz oder Solvat davon.

14. Eine Verbindung der Formel:

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oder ein Salz oder Solvat davon.

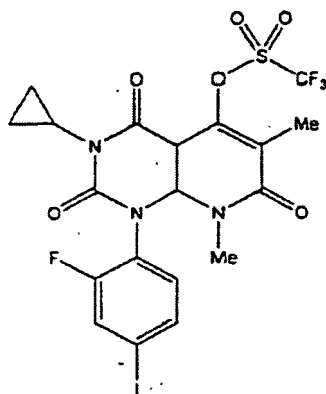
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15. Eine Verbindung der Formel:

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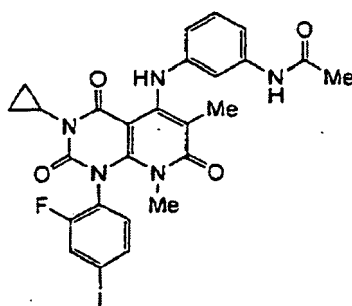
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oder ein Salz oder Solvat davon.

16. Eine Verbindung der Formel:

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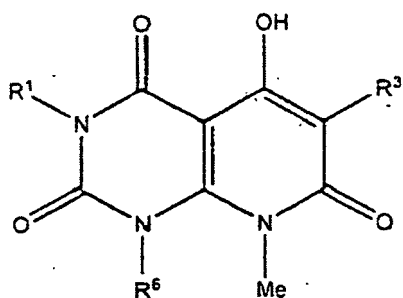
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oder ein Salz oder Solvat davon.

17. Eine Verbindung der Formel [50] oder ein Salz oder Solvat davon:

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[50]

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wobei

R³ eine Methylgruppe ist und

R¹ und R⁶ gleich oder verschieden sind und jeweils ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest sind, wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, der C₃₋₁₂-Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind,

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wobei Gruppe B eine Gruppe ist, die aus folgenden besteht

- 1) einem Halogenatom,
 - 2) einer Nitrogruppe,
 - 3) einer Cyanogruppe,
 - 4) einem C₁₋₈-Alkylrest,
 - 5) einem C₂₋₄-Alkenylrest,
 - 6) einem C₂₋₄-Alkinylrest,
 - 7) -OR^{B1}, wobei R^{B1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 8) -SR^{B2}, wobei R^{B2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 9) NR^{B3}R^{B4}, wobei R^{B3} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist, und R^{B4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 10) -NR^{B5}COR^{B6}, wobei R^{B5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und R^{B6} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,
 - 11) -NR^{B7}COOR^{B8}, wobei R^{B7} und R^{B8} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 12) -NR^{B9}CONR^{B10}R^{B11}, wobei R^{B9}, R^{B10} und R^{B11} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 13) -NR^{B12}CONR^{B13}OR^{B14}, wobei R^{B12}, R^{B13} und R^{B14} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 14) -NR^{B15}SO₂R^{B16}, wobei R^{B15} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, und R^{B16} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,
 - 15) -SO₂-R^{B17}, wobei R^{B17} ein C₁₋₄-Alkylrest oder ein heterocyclischer Rest ist,
 - 16) -SO₂NR^{B18}R^{B19}, wobei R^{B18} und R^{B19} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 17) -P(=O)(R^{B20})(R^{B21}), wobei R^{B20} und R^{B21} gleich oder verschieden sind und jeweils ein C₁₋₄-Alkylrest sind,
 - 18) -COOR^{B22}, wobei R^{B22} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 19) -CONR^{B23}R^{B24}, wobei R^{B23} und R^{B24} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 20) -NR^{B25}SO₂NR^{B26}R^{B27}, wobei R^{B25}, R^{B26} und R^{B27} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31}, wobei R^{B28}, R^{B29}, R^{B30} und R^{B31} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 22) einem C₃₋₁₂-Kohlenstoffringrest und
 - 23) einem heterocyclischen Rest
- wobei jeder des "C₁₋₈-Alkylrests" des vorstehenden Punktes 4), und der C₁₋₄-Alkylreste für R^{B1} bis R^{B31} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert ist,
- jeder des C₂₋₄-Alkenylrests von Punkt 5) und des C₂₋₄-Alkinylrests von Punkt 6) gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert ist,
- der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, und
- jeder des C₃₋₁₂-Kohlenstoffringrests des vorstehenden Punktes 22), R^{B3}, R^{B6} und R^{B16} und des heterocyclischen Rests des vorstehenden Punktes 23), R^{B3}, R^{B6}, R^{B16} und R^{B17} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist

wobei Gruppe A eine Gruppe ist, die aus folgenden besteht

- 1) einem Halogenatom,
- 2) einer Nitrogruppe,
- 3) einer Cyanogruppe,
- 4) einem C₁₋₄-Alkylrest,
- 5) -OR^{A1}, wobei R^{A1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
- 6) -SR^{A2}, wobei R^{A2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
- 7) -NR^{A3}R^{A4}, wobei R^{A3} und R^{A4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
- 8) -COOR^{A5}, wobei R^{A5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
- 9) -NR^{A6}COR^{A7}, wobei R^{A6} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, R^{A7} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Koh-

lenstoffringrest oder ein heterocyclischer Rest ist,

10) $-NR^{A8}COOR^{A9}$, wobei R^{A8} und R^{A9} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

11) einem C_{3-12} -Kohlenstoffringrest und

12) einem heterocyclischen Rest,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

jeder der C_{1-4} -Alkylreste des vorstehenden Punktes 4), R^{A1} , R^{A2} , R^{A3} , R^{A4} , R^{A5} , R^{A6} , R^{A7} , R^{A8} und R^{A9} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und jeder der C_{3-12} -Kohlenstoffringreste des vorstehenden Punktes 11) und R^{A7} , und der heterocyclischen Reste von Punkt 12) und R^{A7} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist, und

Gruppe C eine Gruppe ist, die aus folgenden besteht:

1) einem Halogenatom,

2) einer Cyanogruppe,

3) einem C_{1-4} -Alkylrest,

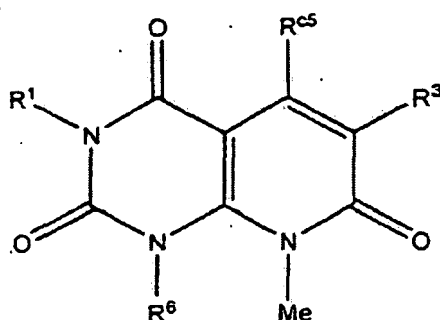
4) $-OR^{C1}$, wobei R^{C1} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

5) $-NR^{C2}R^{C3}$, wobei R^{C2} und R^{C3} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

6) $-COOR^{C4}$, wobei R^{C4} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist und

7) einer Oxogruppe.

18. Eine Verbindung der Formel [51] oder ein Salz oder Solvat davon:



[51]

wobei

R^3 eine Methylgruppe ist,

R^1 und R^6 gleich oder verschieden sind und jeweils ein C_{3-12} -Kohlenstoffringrest oder ein heterocyclischer Rest sind, wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, der C_{3-12} -Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind, und

R^{65} eine Abgangsgruppe ist;

wobei Gruppe B eine Gruppe ist, die aus folgenden besteht

1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C_{1-8} -Alkylrest,

5) einem C_{2-4} -Alkenylrest,

6) einem C_{2-4} -Alkinylrest,

- 7) -OR^{B1}, wobei R^{B1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 8) -SR^{B2}, wobei R^{B2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 9) -NR^{B3}R^{B4}, wobei R^{B3} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist, und R^{B4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 10) -NR^{B5}COR^{B6}, wobei R^{B5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und R^{B6} ein Wasserstoffatom, ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,
 11) -NR^{B7}COOR^{B8}, wobei R^{B7} und R^{B8} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 12) -NR^{B9}CONR^{B10}R^{B11}, wobei R^{B9}, R^{B10} und R^{B11} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 13) -NR^{B12}CONR^{B13}OR^{B14}, wobei R^{B12}, R^{B13} und R^{B14} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 14) -NR^{B15}SO₂R^{B16}, wobei R^{B15} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, und R^{B16} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,
 15) -SO₂-R^{B17}, wobei R^{B17} ein C₁₋₄-Alkylrest oder ein heterocyclischer Rest ist,
 16) -SO₂NR^{B18}R^{B19}, wobei R^{B18} und R^{B19} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 17) -P(=O)(R^{B20})(R^{B21}), wobei R^{B20} und R^{B21} gleich oder verschieden sind und jeweils ein C₁₋₄-Alkylrest sind,
 18) -COOR^{B22}, wobei R^{B22} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 19) -CONR^{B23}R^{B24}, wobei R^{B23} und R^{B24} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 20) NR^{B25}SO₂NR^{B26}R^{B27}, wobei R^{B25}, R^{B26} und R^{B27} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31}, wobei R^{B28}, R^{B29}, R^{B30} und R^{B31} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 22) einem C₃₋₁₂-Kohlenstoffringrest und
 23) einem heterocyclischen Rest
 wobei jeder des "C₁₋₈-Alkylrests" des vorstehenden Punktes 4), und der C₁₋₄-Alkylreste für R^{B1} bis R^{B31} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert ist,
 jeder des C₂₋₄-Alkenylrests von Punkt 5) und des C₂₋₄-Alkylrests von Punkt 6) gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert ist,
 der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,
 und
 jeder des C₃₋₁₂-Kohlenstoffringrests des vorstehenden Punktes 22), R^{B3}, R^{B6} und R^{B16} und des heterocyclischen Rests des vorstehenden Punktes 23), R^{B3}, R^{B6}, R^{B16} und R^{B17} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist,

Gruppe A eine Gruppe ist, die aus folgenden besteht

- 1) einem Halogenatom,
 - 2) einer Nitrogruppe,
 - 3) einer Cyanogruppe,
 - 4) einem C₁₋₄-Alkylrest,
 - 5) -OR^{A1}, wobei R^{A1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 6) -SRA², wobei R^{A2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 7) -NRA³RA⁴, wobei R^{A3} und R^{A4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 8) -COOR^{A5}, wobei R^{A5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
 - 9) -NRA⁶COR^{A7}, wobei R^{A6} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist, R^{A7} ein C₁₋₄-Alkylrest, ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,
 - 10) -NRA⁸COOR^{A9}, wobei R^{A8} und R^{A9} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
 - 11) einem C₃₋₁₂-Kohlenstoffringrest und
 - 12) einem heterocyclischen Rest,
- wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwe-

felatom,

jeder der C₁₋₄-Alkylreste des vorstehenden Punktes 4), R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} und R^{A9} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

jeder der C₃₋₁₂-Kohlenstoffringreste des vorstehenden Punktes 11) und R^{A7}, und der heterocyclischen Reste von Punkt 12) und R^{A7} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist, und

Gruppe C eine Gruppe ist, die aus folgenden besteht:

- 1) einem Halogenatom,
- 2) einer Cyanogruppe,
- 3) einem C₁₋₄-Alkylrest,
- 4) -OR^{C1}, wobei R^{C1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
- 5) -NR^{C2}R^{C3}, wobei R^{C2} und R^{C3} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
- 6) -COOR^{C4}, wobei R^{C4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und
- 7) einer Oxogruppe.

19. Die Verbindung nach Anspruch 17 oder 18, wobei R¹ ein C₃₋₁₂-Kohlenstoffringrest ist, wobei der C₃₋₁₂-Kohlenstoffringrest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus Gruppe B, substituiert ist.

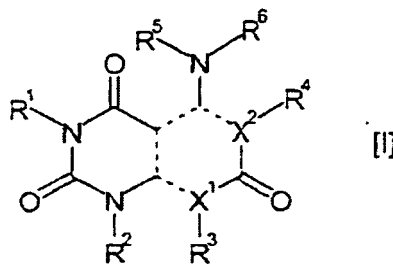
20. Die Verbindung nach Anspruch 19, wobei R¹ Cyclopropyl ist.

21. Die Verbindung nach Anspruch 17 oder 18, wobei R⁶ eine Phenylgruppe ist, die gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus Gruppe B, substituiert ist.

22. Die Verbindung nach Anspruch 21, wobei R⁶ eine Phenylgruppe ist, die an der 2,4-Position zweifach substituiert ist.

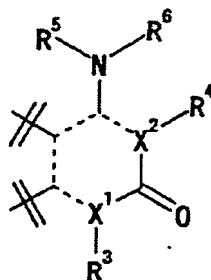
23. Die Verbindung nach Anspruch 18, wobei R^{C5} eine Abgangsgruppe ist, ausgewählt aus der Gruppe bestehend aus einem Halogen, p-Toluolsulfonyloxy, Methansulfonyloxy und Trifluormethansulfonyloxy.

24. Verwendung einer Verbindung, dargestellt durch die folgende Formel [I], oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff zur Herstellung eines Arzneimittels zur Behandlung eines Tumors:



wobei

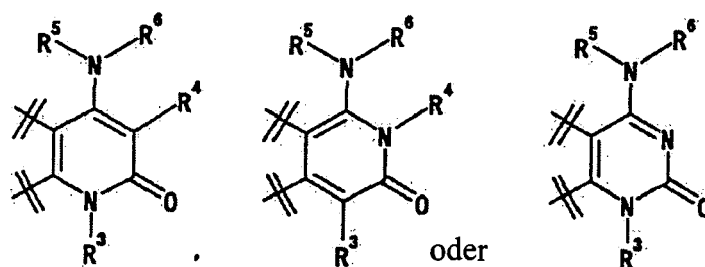
X¹ und X² gleich oder verschieden sind und jeweils ein Kohlenstoffatom oder ein Stickstoffatom bedeuten, eine



-Einheit

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bedeutet,

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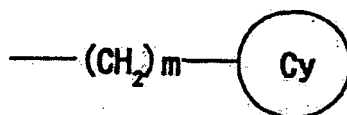
R¹, R² und R⁶ gleich oder verschieden sind und jeweils

einen C₁₋₆-Alkylrest,

einen C₂₋₆-Alkenylrest,

wobei der C₁₋₆-Alkylrest und der C₂₋₆-Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe A, substituiert sind, oder

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bedeuten,

wobei m 0 oder eine ganze Zahl von 1 bis 4 ist,

der Ring Cy ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

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wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben Kohlenstoffatomen, 1 bis

4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

der C₃₋₁₂-Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt

aus der folgenden Gruppe B, substituiert sind,

R³, R⁴ und R⁵ gleich oder verschieden sind und jeweils

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ein Wasserstoffatom,

eine Hydroxylgruppe,

ein C₁₋₆-Alkylrest,

ein C₂₋₆-Alkenylrest,

wobei der C₁₋₆-Alkylrest und der C₂₋₆-Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus der

folgenden Gruppe A, substituiert sind,

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ein C₃₋₁₂-Kohlenstoffringrest oder

ein heterocyclischer Rest sind,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der,

neben Kohlenstoffatomen, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffa-

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tom und einem Schwefelatom, und der C₃₋₁₂-Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit

1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe B, substituiert sind oder

R² und R³ gegebenenfalls verbunden sind, um einen C₁₋₄-Alkylrest zu bilden oder R⁴ und R⁵ gegebenenfalls

verbunden sind, um einen C₁₋₄-Alkylrest zu bilden,

wobei Gruppe A eine Gruppe ist, die aus folgenden besteht:

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1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C₁₋₄-Alkylrest,

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5) -OR^{A1}, wobei R^{A1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

6) -SR^{A2}, wobei R^{A2} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

7) -NR^{A3}R^{A4}, wobei R^{A3} und R^{A4} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Al-

kylrest sind,

8) -COOR^{A5}, wobei R^{A5} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,

9) $\text{-NR}^{\text{A6}}\text{COR}^{\text{A7}}$, wobei R^{A6} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist, R^{A7} ein C_{1-4} -Alkylrest, ein C_{3-12} -Kohlenstoffringrest oder ein heterocyclischer Rest ist,

10) $\text{NR}^{\text{A8}}\text{COOR}^{\text{A9}}$, wobei R^{A8} und R^{A9} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

11) einem C_{3-12} -Kohlenstoffringrest und

12) einem heterocyclischen Rest,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben Kohlenstoffatomen, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

jeder der C_{1-4} -Alkylreste des vorstehenden Punktes 4), R^{A1} , R^{A2} , R^{A3} , R^{A4} , R^{A5} , R^{A6} , R^{A7} , R^{A8} und R^{A9} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

jeder der C_{3-12} -Kohlenstoffringreste des vorstehenden Punktes 11) und R^{A7} , und der heterocyclischen Reste von Punkt 12) und R^{A7} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist,

Gruppe B eine Gruppe ist, die aus folgenden besteht

1) einem Halogenatom,

2) einer Nitrogruppe,

3) einer Cyanogruppe,

4) einem C_{1-8} -Alkylrest,

5) einem C_{2-4} -Alkenylrest,

6) einem C_{2-4} -Alkynylrest,

7) -OR^{B1} , wobei R^{B1} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

8) -SR^{B2} , wobei R^{B2} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

9) $\text{NR}^{\text{B3}}\text{R}^{\text{B4}}$, wobei R^{B3} ein Wasserstoffatom, ein C_{1-4} -Alkylrest, ein C_{3-12} -Kohlenstoffringrest oder ein heterocyclischer Rest ist, und R^{B4} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

10) $\text{-NR}^{\text{B5}}\text{COR}^{\text{B6}}$, wobei R^{B5} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist und R^{B6} ein Wasserstoffatom, ein C_{1-4} -Alkylrest, ein C_{3-12} -Kohlenstoffringrest oder ein heterocyclischer Rest ist,

11) $\text{-NR}^{\text{B7}}\text{COOR}^{\text{B8}}$, wobei R^{B7} und R^{B8} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

12) $\text{NR}^{\text{B9}}\text{CONR}^{\text{B10}}\text{R}^{\text{B11}}$, wobei R^{B9} , R^{B10} und R^{B11} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

13) $\text{NR}^{\text{B12}}\text{CONR}^{\text{B13}}\text{OR}^{\text{B14}}$, wobei R^{B12} , R^{B13} und R^{B14} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

14) $\text{-NR}^{\text{B15}}\text{SO}_2\text{R}^{\text{B16}}$, wobei R^{B15} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist, und R^{B16} ein C_{1-4} -Alkylrest, ein C_{3-12} -Kohlenstoffringrest oder ein heterocyclischer Rest ist,

15) $\text{-SO}_2\text{-R}^{\text{B17}}$, wobei R^{B17} ein C_{1-4} -Alkylrest oder ein heterocyclischer Rest ist,

16) $\text{-SO}_2\text{NR}^{\text{B18}}\text{R}^{\text{B19}}$, wobei R^{B18} und R^{B19} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

17) $\text{-P(=O)(R}^{\text{B20}}\text{)(R}^{\text{B21}}\text{)}$, wobei R^{B20} und R^{B21} gleich oder verschieden sind und jeweils ein C_{1-4} -Alkylrest sind,

18) $\text{-COOR}^{\text{B22}}$, wobei R^{B22} ein Wasserstoffatom oder ein C_{1-4} -Alkylrest ist,

19) $\text{-CONR}^{\text{B23}}\text{R}^{\text{B24}}$, wobei R^{B23} und R^{B24} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

20) $\text{-NR}^{\text{B21}}\text{SO}_2\text{NR}^{\text{B26}}\text{R}^{\text{B27}}$, wobei R^{B25} , R^{B26} und R^{B27} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

21) $\text{NR}^{\text{B28}}\text{SO}_2\text{NR}^{\text{B29}}\text{CONR}^{\text{B30}}\text{R}^{\text{B31}}$, wobei R^{B28} , R^{B29} , R^{B30} und R^{B31} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C_{1-4} -Alkylrest sind,

22) einem C_{3-12} -Kohlenstoffringrest und

23) einem heterocyclischen Rest

wobei jeder des " C_{1-8} -Alkylrests" des vorstehenden Punktes 4), und der C_{1-4} -Alkylreste für R^{B1} bis R^{B31} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,

jeder des C_{2-4} -Alkenylrests von Punkt 5) und des C_{2-4} -Alkynylrests von Punkt 6) gegebenenfalls mit den gleichen oder verschiedenen 1 bis 3 Substituenten, ausgewählt aus der vorstehenden Gruppe A, substituiert ist,

der heterocyclische Rest ein gesättigter oder ungesättigter Ringrest ist, der, neben dem Kohlenstoffatom, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom,

und

jeder des C₃₋₁₂-Kohlenstoffringrests des vorstehenden Punktes 22), R^{B3}, R^{B6} und R^{B16} und des heterocyclischen Rests des vorstehenden Punktes 23), R^{B3}, R^{B6}, R^{B16} und R^{B17} gegebenenfalls mit den gleichen oder verschiedenen 1 bis 5 Substituenten, ausgewählt aus der folgenden Gruppe C, substituiert ist und

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Gruppe C eine Gruppe ist, die aus folgenden besteht:

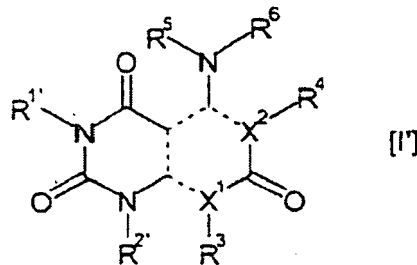
- 1) einem Halogenatom,
- 2) einer Cyanogruppe,
- 3) einem C₁₋₄-Alkylrest,
- 4) -OR^{C1}, wobei R^{C1} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist,
- 5) -NR^{C2}R^{C3}, wobei R^{C2} und R^{C3} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder ein C₁₋₄-Alkylrest sind,
- 6) -COOR^{C4}, wobei R^{C4} ein Wasserstoffatom oder ein C₁₋₄-Alkylrest ist und
- 7) einer Oxogruppe.

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25. Eine Verbindung, dargestellt durch die folgende Formel [I'], oder ein pharmazeutisch verträgliches Salz davon:

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wobei

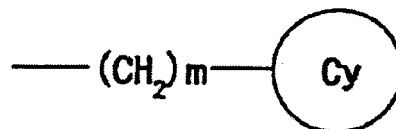
R^{1'}, R^{2'} und R⁶ gleich oder verschieden sind und jeweils

ein C₁₋₆-Alkylrest,

ein C₂₋₆-Alkenylrest,

wobei der C₁₋₆-Alkylrest und der C₂₋₆-Alkenylrest gegebenenfalls mit 1 bis 3 Substituenten, ausgewählt aus Gruppe A nach Anspruch 1, substituiert sind, oder

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sind,

m eine ganze Zahl von 0 oder 1 bis 4 ist,

der Ring Cy ein C₃₋₁₂-Kohlenstoffringrest oder ein heterocyclischer Rest ist,

wobei der heterocyclische Rest ein gesättigter oder ungesättigter Ring ist, der, neben Kohlenstoffatomen, 1 bis 4 Heteroatome aufweist, ausgewählt aus einem Sauerstoffatom, einem Stickstoffatom und einem Schwefelatom, und

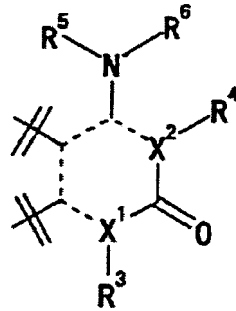
der C₃₋₁₂-Kohlenstoffringrest und der heterocyclische Rest gegebenenfalls mit 1 bis 5 Substituenten, ausgewählt aus Gruppe B nach Anspruch 1, substituiert sind,

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mit der Maßgabe, dass wenn die

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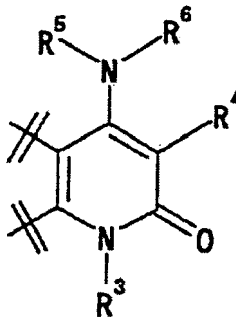
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-Einheit für

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steht,

dann R² keine Methylgruppe ist, und

wenn R² eine Phenylgruppe ist, dann R¹ keine Phenylgruppe ist,

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und andere Symbole wie in Anspruch 1 definiert sind.

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26. Verwendung einer Verbindung der Formel [I] nach Anspruch 24 oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff zur Herstellung eines Antitumormittels.

27. Verwendung einer Verbindung der Formel [I] nach Anspruch 24 oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff zur Herstellung eines Arzneimittels, das zur Hemmung von MEK in der Lage ist.

28. Verwendung einer Verbindung der Formel [I] nach Anspruch 24 oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff zur Herstellung eines Arzneimittels, das zum Induzieren von p15 Protein in der Lage ist.

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29. Verwendung einer Verbindung der Formel [I] nach Anspruch 24 oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff zur Herstellung eines Arzneimittels zur Behandlung einer Krankheit, die durch eine unerwünschte Zellproliferation verursacht wird.

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30. Verwendung einer Verbindung der Formel [I] nach Anspruch 24 oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff zur Herstellung eines Arzneimittels, das zur Hemmung unerwünschter Zellproliferation in der Lage ist.

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31. Verwendung einer Verbindung der Formel [I] nach Anspruch 24 oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff zur Herstellung eines Arzneimittels, das zur Regulation des Zellzyklus in der Lage ist.

32. Ein Arzneimittel, umfassend eine Verbindung der Formel [I] nach Anspruch 25 oder ein pharmazeutisch verträgliches Salz davon und einen pharmazeutisch verträglichen Träger.

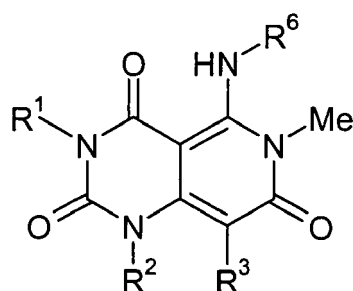
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33. Verwendung von (a) einer Verbindung der Formel [I] nach Anspruch 24 oder eines pharmazeutisch verträglichen Salzes davon als Wirkstoff, der in Kombination mit (b) mindestens einer anderen Antitumorverbindung zur Herstellung eines Antitumormittels verwendet wird.

34. Utilisation de (a) d'un composé de la formule [I] selon la revendication 24 ou d'un sel pharmaceutiquement acceptable de celui-ci comme agent actif et (b) d'au moins d'une autre molécule antitumorale en combinaison pour la fabrication d'un médicament antitumoral.
35. Un médicament, comprenant comme agent actif (a) d'un composé de la formule [I] selon la revendication 24 ou un sel pharmaceutiquement acceptable de celui-ci et (b) d'au moins d'une autre molécule antitumorale et d'un support pharmaceutiquement acceptable en combinaison.
36. Un kit pour le traitement d'un tumeur, comprenant (a) un médicament, comprenant comme agent actif d'un composé de la formule [I] selon la revendication 24 ou un sel pharmaceutiquement acceptable de celui-ci et (b) un médicament, comprenant comme agent actif d'au moins d'une autre molécule antitumorale en combinaison.

Revendications

1. Procédé pour préparer un composé de formule [I-3-2]



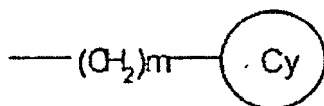
dans laquelle

R¹, R² et R⁶ sont identiques ou différents et sont chacun

un groupe alkyle en C₁ à C₆,

un groupe alcényle en C₂ à C₆,

le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant, ou



où m vaut 0 ou est un entier de 1 à 4,

le cycle Cy est un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant,

R³ est

un atome d'hydrogène,

un groupe hydroxyle,

un groupe alkyle en C₁ à C₆,

un groupe alcényle en C₂ à C₆,

le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant,

un groupe cyclique carboné en C₃ à C₁₂ ou

un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé comportant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et le groupe cyclique

carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant ;

le groupe A étant un groupe consistant en

- 5
- 1) un atome d'halogène,
 - 2) un groupe nitro,
 - 3) un groupe cyano,
 - 4) un groupe alkyle en C₁ à C₄,
 - 5) -OR^{A1} où R^{A1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 10 6) -SRA^{A2} où R^{A2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 7) -NRA^{A3}R^{A4} où R^{A3} et R^{A4} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 8) -COORA^{A5} où R^{A5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 9) -NRA^{A6}CORA^{A7} où R^{A6} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, R^{A7} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
 - 15 10) -NRA^BCOORA^{A9} où R^{A8} et R^{A9} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 11) un groupe cyclique carboné en C₃ à C₁₂ et
 - 12) un groupe hétérocyclique,
- 20 le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, chacun des groupes alkyle en C₁ à C₄ du 4) mentionné ci-dessus, R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} et R^{A9} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe C suivant, et chacun des groupes cycliques carbonés en C₃ à C₁₂ du 11) mentionné ci-dessus et R^{A7}, et des
- 25 groupes hétérocycliques de 12) et R^{A7} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant,

le groupe B étant un groupe consistant en

- 30
- 1) un atome d'halogène,
 - 2) un groupe nitro,
 - 3) un groupe cyano,
 - 4) un groupe alkyle en C₁ à C₈,
 - 5) un groupe alcényle en C₂ à C₄,
 - 35 6) un groupe alcynyle en C₂ à C₄,
 - 7) -ORB^{B1} où R^{B1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 8) -SRB^{B2} où R^{B2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 9) -NRB^{B3}RB^{B4} où R^{B3} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique, et R^{B4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 40 10) -NRB^{B5}CORB^{B6} où R^{B5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B6} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
 - 11) -NRB^{B7}COORB^{B8} où R^{B7} et R^{B8} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 12) -NRB^{B9}CONRB^{B10}RB^{B11} où R^{B9}, R^{B10} et R^{B11} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 45 13) -NRB^{B12}CONRB^{B13}ORB^{B14} où R^{B12}, R^{B13} et R^{B14} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 14) -NRB^{B15}SO₂RB^{B16} où R^{B15} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B16} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
 - 50 15) -SO₂-RB^{B17} où R^{B17} est un groupe alkyle en C₁ à C₄ ou un groupe hétérocyclique,
 - 16) -SO₂NRB^{B18}RB^{B19} où R^{B18} et R^{B19} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 17) -P(=O)(R^{B20})(R^{B21}) où R^{B20} et R^{B21} sont identiques ou différents et sont chacun un groupe alkyle en C₁ à C₄,
 - 18) -COORB^{B22} où R^{B22} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 55 19) -CONRB^{B23}RB^{B24} où R^{B23} et R^{B24} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 20) -NRB^{B25}SO₂NRB^{B26}RB^{B27} où R^{B25}, R^{B26} et R^{B27} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

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21) $-NR^{B28}SO_2NR^{B29}CONR^{B30}R^{B31}$ où R^{B28} , R^{B29} , R^{B30} et R^{B31} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

22) un groupe cyclique carboné en C_3 à C_{12} et

23) un groupe hétérocyclique,

chacun du "groupe alkyle en C_1 à C_8 " du 4) mentionné ci-dessus et des groupes alkyle en C_1 à C_4 pour R^{B1} à R^{B31} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,

chacun du groupe alcényle en C_2 à C_4 de 5) et du groupe alcynyle en C_2 à C_4 de 6) étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et

chacun du groupe cyclique carboné en C_3 à C_{12} du 22) mentionné ci-dessus, R^{B3} , R^{B6} et R^{B16} , et du groupe hétérocyclique du 23) mentionné ci-dessus, R^{B3} , R^{B6} , R^{B16} et R^{B17} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant, et

le groupe C étant un groupe consistant en

1) un atome d'halogène,

2) un groupe cyano,

3) un groupe alkyle en C_1 à C_4 ,

4) $-OR^{C1}$ où R^{C1} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

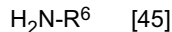
5) $-NR^{C2}R^{C3}$ où R^{C2} et R^{C3} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

6) $-COOR^{C4}$ où R^{C4} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 et

7) un groupe oxo,

lequel procédé comprend

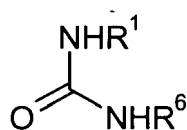
(a) la réaction d'un composé de formule [45]



dans laquelle R^6 est tel que défini ci-dessus, avec un composé de formule [1]



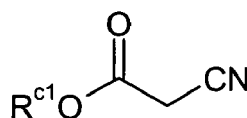
dans laquelle R^1 est tel que défini ci-dessus, pour former un composé de formule [28]



[28]

dans laquelle R^1 et R^6 sont tels que définis ci-dessus ;

(b) la réaction d'un composé de formule [28] avec un composé de formule [38]

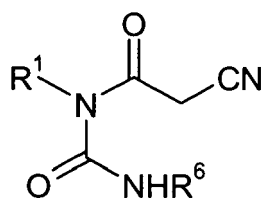


[38]

dans laquelle R^{C1} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 , pour former un composé de

formule [46]

5



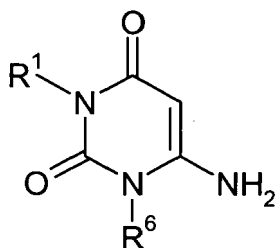
10

[46]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(c) la conversion d'un composé de formule [46] en un composé de formule [47]

15



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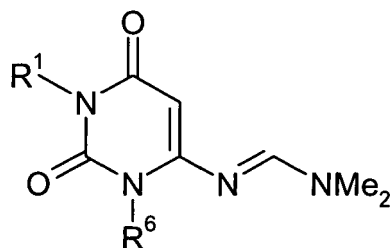
25

[47]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(d) la conversion d'un composé de formule [47] en un composé de formule [48]

30



35

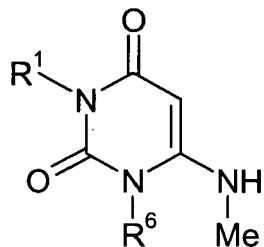
40

[48]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(e) la conversion d'un composé de formule [48] en un composé de formule [49]

45



50

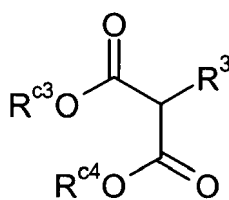
55

[49]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(f) la réaction d'un composé de formule [49] avec un composé de formule [33]

5



10

[33]

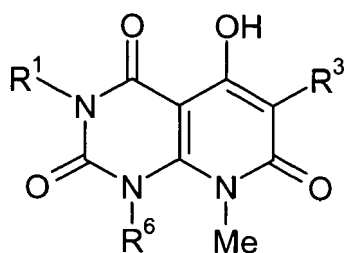
dans laquelle

R³ est tel que défini ci-dessus ; et

15

R^{C3} et R^{C4} sont identiques ou différents et représentent chacun un atome d'hydrogène ou un alkyle en C₁ à C₆, pour former un composé de formule [50]

20



25

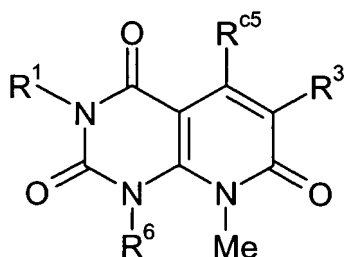
[50]

dans laquelle R¹, R³ et R⁶ sont tels que définis ci-dessus ;

30

(g) la conversion d'un composé de formule [50] en un composé de formule [51]

35



40

[51]

dans laquelle

R¹, R³ et R⁶ sont tels que définis ci-dessus, et

45

R^{C5} est un groupe partant ;

(h) la réaction d'un composé de formule [51] avec un composé de formule [36]

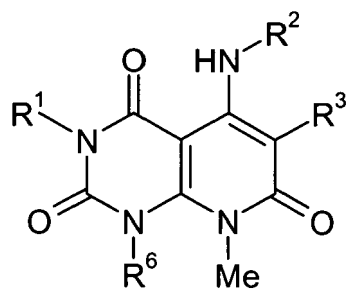
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dans laquelle R² est tel que défini ci-dessus ;

pour former un composé de formule [52]

55

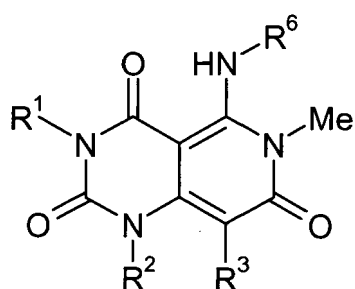


[52]

15 dans laquelle R^1 , R^2 , R^3 et R^6 sont tels que définis ci-dessus ;

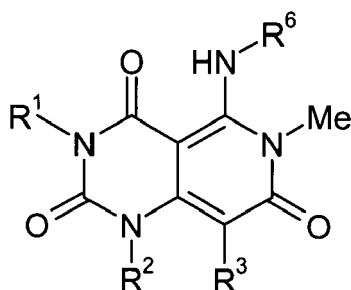
et

(i) la conversion d'un composé de formule [52] en un composé de formule [I-3-2]



[I-3-2]

30 2. Procédé pour préparer un composé de formule [I-3-2]



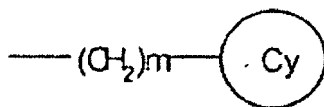
45 dans laquelle

R^1 , R^2 et R^6 sont identiques ou différents et sont chacun

un groupe alkyle en C_1 à C_6 ,

un groupe alcényle en C_2 à C_6 ,

le groupe alkyle en C_1 à C_6 et le groupe alcényle en C_2 à C_6 étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant, ou



où m vaut 0 ou est un entier de 1 à 4,

le cycle Cy est un groupe cyclique carboné en C_3 à C_{12} ou un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant,

5 R³ est
 un atome d'hydrogène,
 un groupe hydroxyle,
 un groupe alkyle en C₁ à C₆,
 un groupe alcényle en C₂ à C₆,
 10 le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant,
 un groupe cyclique carboné en C₃ à C₁₂ ou
 un groupe hétérocyclique,
 15 le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé comportant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant;
 le groupe A étant un groupe consistant en

20 1) un atome d'halogène,
 2) un groupe nitro,
 3) un groupe cyano,
 4) un groupe alkyle en C₁ à C₄,
 5) -OR^{A1} où R^{A1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 25 6) -SR^{A2} où R^{A2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 7) -NR^{A3}R^{A4} où R³ et R^{A4} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 8) -COOR^{A5} où R^{A5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 9) -NR^{A6}COR^{A7} où R^{A6} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, R^{A7} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
 30 10) -NR^{A8}COOR^{A9} où R^{A8} et R^{A9} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 11) un groupe cyclique carboné en C₃ à C₁₂ et
 12) un groupe hétérocyclique,
 35 le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre,
 chacun des groupes alkyle en C₁ à C₄ du 4) mentionné ci-dessus, R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} et R^{A9} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe C suivant, et chacun des groupes cycliques carbonés en C₃ à C₁₂ du 11) mentionné ci-dessus et R^{A7}, et des
 40 groupes hétérocycliques de 12) et R^{A7} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant,

le groupe B étant un groupe consistant en

45 1) un atome d'halogène,
 2) un groupe nitro,
 3) un groupe cyano,
 4) un groupe alkyle en C₁ à C₈,
 5) un groupe alcényle en C₂ à C₄,
 50 6) un groupe alcynyle en C₂ à C₄,
 7) -OR^{B1} où R^{B1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 8) -SR^{B2} où R^{B2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 9) -NR^{B3}R^{B4} où R^{B3} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique, et R^{B4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 55 10) -NR^{B5}COR^{B6} où R^{B5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B6} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
 11) -NR^{B7}COOR^{B8} où R^{B7} et R^{B8} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

12) $-NR^{B9}CONR^{B10}R^{B11}$ où R^{B9} , R^{B10} et R^{B11} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

13) $-NR^{B12}CONR^{B13}OR^{B14}$ où R^{B12} , R^{B13} et R^{B14} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

14) $-NR^{B15}SO_2R^{B16}$ où R^{B15} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 , et R^{B16} est un groupe alkyle en C_1 à C_4 , un groupe cyclique carboné en C_3 à C_{12} ou un groupe hétérocyclique,

15) $-SO_2-R^{B17}$ où R^{B17} est un groupe alkyle en C_1 à C_4 ou un groupe hétérocyclique,

16) $-SO_2NR^{B18}R^{B19}$ où R^{B18} et R^{B19} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

17) $-P(=O)(R^{B20})(R^{B21})$ où R^{B20} et R^{B21} sont identiques ou différents et sont chacun un groupe alkyle en C_1 à C_4 ,

18) $-COOR^{B22}$ où R^{B22} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

19) $-CONR^{B23}R^{B24}$ où R^{B23} et R^{B24} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

20) $-NR^{B25}SO_2NR^{B26}R^{B27}$ où R^{B25} , R^{B26} et R^{B27} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

21) $-NR^{B28}SO_2NR^{B29}CONR^{B30}R^{B31}$ où R^{B28} , R^{B29} , R^{B30} et R^{B31} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

22) un groupe cyclique carboné en C_3 à C_{12} et

23) un groupe hétérocyclique,

chacun du "groupe alkyle en C_1 à C_8 " du 4) mentionné ci-dessus et des groupes alkyle en C_1 à C_4 pour R^{B1} à R^{B31} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,

chacun du groupe alcényle en C_2 à C_4 de 5) et du groupe alcynyle en C_2 à C_4 de 6) étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et

chacun du groupe cyclique carboné en C_3 à C_{12} du 22) mentionné ci-dessus, R^{B3} , R^{B6} et R^{B16} , et du groupe hétérocyclique du 23) mentionné ci-dessus, R^{B3} , R^{B6} , R^{B16} et R^{B17} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant, et

le groupe C étant un groupe consistant en

1) un atome d'halogène,

2) un groupe cyano,

3) un groupe alkyle en C_1 à C_4 ,

4) $-OR^{C1}$ où R^{C1} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

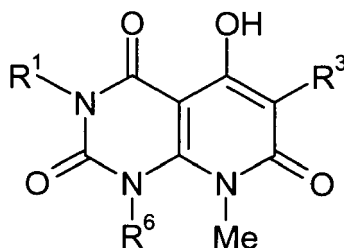
5) $-NR^{C2}R^{C3}$ où R^{C2} et R^{C3} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

6) $-COOR^{C4}$ où R^{C4} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 et

7) un groupe oxo,

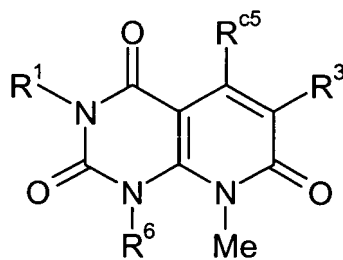
lequel procédé comprend

(a) la conversion d'un composé de formule [50]



[50]

dans laquelle R^1 , R^3 et R^6 sont tels que définis ci-dessus ; en un composé de formule [51]

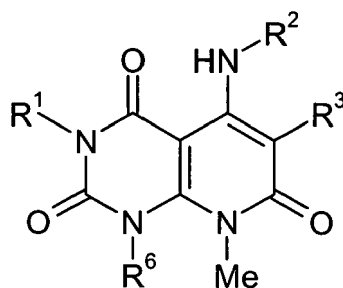


[51]

10
15 dans laquelle R¹, R³ et R⁶ sont tels que définis ci-dessus et R^{C5} est un groupe partant ;
(b) la réaction d'un composé de formule [51] avec un composé de formule [36]



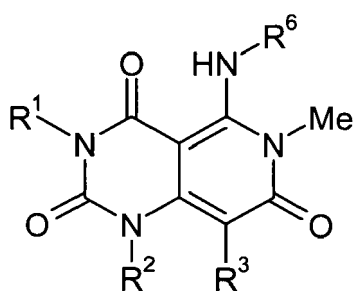
20 dans laquelle R² est tel que défini ci-dessus ;
pour former un composé de formule [52]



[52]

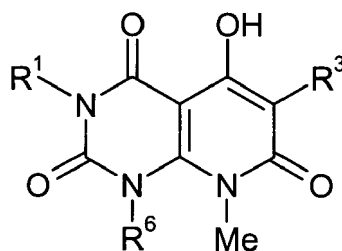
30
35 dans laquelle R¹, R², R³ et R⁶ sont tels que définis ci-dessus ;
et

(c) la conversion d'un composé de formule [52] en un composé de formule [I-3-2]



[I-3-2]

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55 3. Procédé pour préparer un composé de formule [50]



[50]

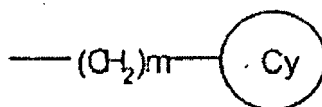
dans laquelle

R¹ et R⁶ sont identiques ou différents et sont chacun

un groupe alkyle en C₁ à C₆,

un groupe alcényle en C₂ à C₆,

le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant, ou



où m vaut 0 ou est un entier de 1 à 4,

le cycle Cy est un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant, R³ est

un atome d'hydrogène,

un groupe hydroxyle,

un groupe alkyle en C₁ à C₆,

un groupe alcényle en C₂ à C₆,

le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant,

un groupe cyclique carboné en C₃ à C₁₂ ou

un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé comportant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant ;

le groupe A étant un groupe consistant en

1) un atome d'halogène,

2) un groupe nitro,

3) un groupe cyano,

4) un groupe alkyle en C₁ à C₄,

5) -OR^{A1} où R^{A1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

6) -SR^{A2} où R^{A2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

7) -NR^{A3}R^{A4} où R^{A3} et R^{A4} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

8) -COOR^{A5} où R^{A5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

9) -NR^{A6}COR^{A7} où R^{A6} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, R^{A7} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

10) -NR^{A8}COOR^{A9} où R^{A8} et R^{A9} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

11) un groupe cyclique carboné en C₃ à C₁₂ et

12) un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre,

chacun des groupes alkyle en C₁ à C₄ du 4) mentionné ci-dessus, R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} et R^{A9} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe C suivant, et chacun des groupes cycliques carbonés en C₃ à C₁₂ du 11) mentionné ci-dessus et R^{A7}, et des groupes hétérocycliques de 12) et R^{A7} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant,

le groupe B étant un groupe consistant en

1) un atome d'halogène,

2) un groupe nitro,

3) un groupe cyano,

4) un groupe alkyle en C₁ à C₈,

5) un groupe alcényle en C₂ à C₄,

6) un groupe alcynyle en C₂ à C₄,

7) -OR^{B1} où R^{B1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

8) -SR^{B2} où R^{B2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

9) -NR^{B3}R^{B4} où R^{B3} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique, et R^{B4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

10) -NR^{B5}COR^{B6} où R^{B5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B6} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

11) -NR^{B7}COOR^{B8} où R^{B7} et R^{B8} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

12) -NR^{B9}CONR^{B10}R^{B11} où R^{B9}, R^{B10} et R^{B11} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

13) -NR^{B12}CONR^{B13}OR^{B14} où R^{B12}, R^{B13} et R^{B14} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

14) -NR^{B15}SO₂R^{B16} où R^{B15} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B16} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

15) -SO₂-R^{B17} où R^{B17} est un groupe alkyle en C₁ à C₄ ou un groupe hétérocyclique,

16) -SO₂NR^{B18}R^{B19} où R^{B18} et R^{B19} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

17) -P(=O)(R^{B20})(R^{B21}) où R^{B20} et R^{B21} sont identiques ou différents et sont chacun un groupe alkyle en C₁ à C₄,

18) -COOR^{B22} où R^{B22} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

19) -CONR^{B23}R^{B24} où R^{B23} et R^{B24} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

20) -NR^{B25}SO₂NR^{B26}R^{B27} où R^{B25}, R^{B26} et R^{B27} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31} où R^{B28}, R^{B29}, R^{B30} et R^{B31} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

22) un groupe cyclique carboné en C₃ à C₁₂ et

23) un groupe hétérocyclique,

chacun du "groupe alkyle en C₁ à C₈" du 4) mentionné ci-dessus et des groupes alkyle en C₁ à C₄ pour R^{B1} à R^{B31} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,

chacun du groupe alcényle en C₂ à C₄ de 5) et du groupe alcynyle en C₂ à C₄ de 6) étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et

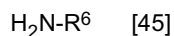
chacun du groupe cyclique carboné en C₃ à C₁₂ du 22) mentionné ci-dessus, R^{B3}, R^{B6} et R^{B16}, et du groupe hétérocyclique du 23) mentionné ci-dessus, R^{B3}, R^{B6}, R^{B16} et R^{B17} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant, et

le groupe C étant un groupe consistant en

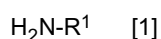
EP 2 298 768 B9

- 1) un atome d'halogène,
 2) un groupe cyano,
 3) un groupe alkyle en C₁ à C₄,
 4) -OR^{C1} où R^{C1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 5) -NR^{C2}R^{C3} où R^{C2} et R^{C3} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe
 alkyle en C₁ à C₄,
 6) -COOR^{C4} où R^{C4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄ et
 7) un groupe oxo,
 lequel procédé comprend

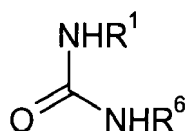
(a) la réaction d'un composé de formule [45]



dans laquelle R⁶ est tel que défini ci-dessus,
 avec un composé de formule [1]



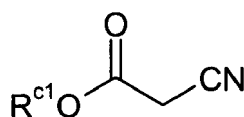
dans laquelle R¹ est tel que défini ci-dessus,
 pour former un composé de formule [28]



[28]

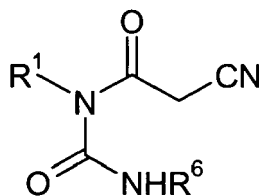
dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(b) la réaction d'un composé de formule [28] avec un composé de formule [38]



[38]

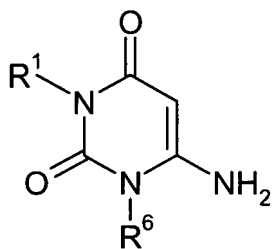
dans laquelle R^{c1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, pour former un composé de
 formule [46]



[46]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(c) la conversion d'un composé de formule [46] en un composé de formule [47]

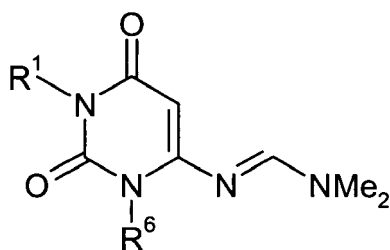


[47]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(d) la conversion d'un composé de formule [47] en un composé de formule [48]

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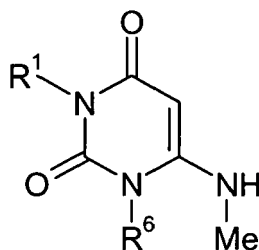


[48]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(e) la conversion d'un composé de formule [48] en un composé de formule [49]

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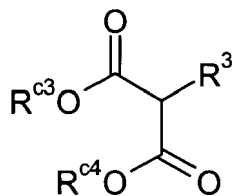


[49]

dans laquelle R¹ et R⁶ sont tels que définis ci-dessus ;

(f) la réaction d'un composé de formule [49] avec un composé de formule [33]

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[33]

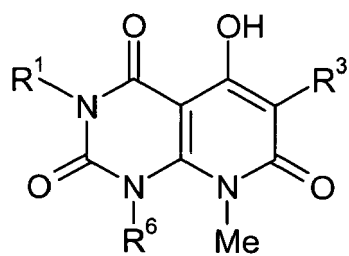
dans laquelle

R³ est tel que défini ci-dessus ; et

R^{c3} et R^{c4} sont identiques ou différents et représentent chacun un atome d'hydrogène ou un alkyle en C₁ à C₆.

pour former un composé de formule [50]

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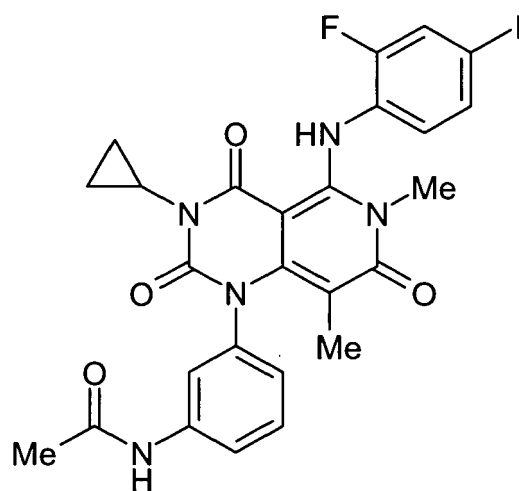


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[50]

15 4. Procédé pour préparer un composé, sel ou solvate de formule :
comprenant

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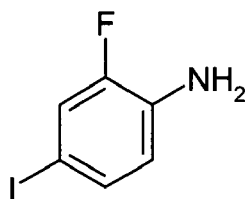


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35 (a) la réaction de

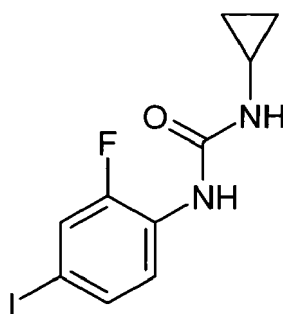
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avec de la cyclopropylamine pour former

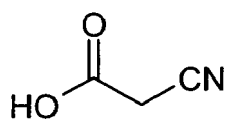
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(b) la réaction du produit de l'étape (a) avec

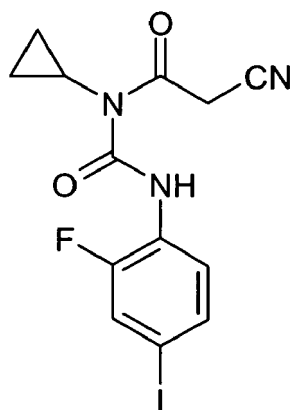
5



pour former

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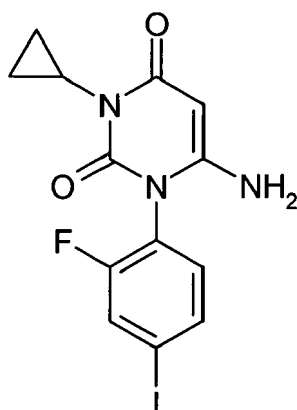


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(c) la conversion du produit de l'étape (b) en

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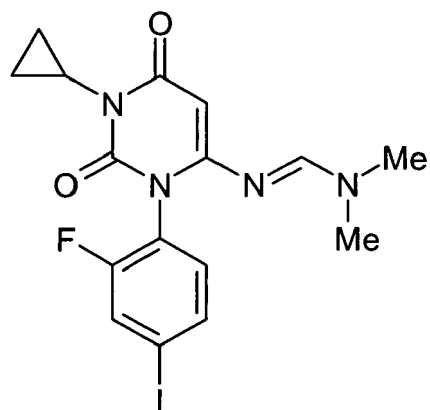
35

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(d) la conversion du produit de l'étape (c) en

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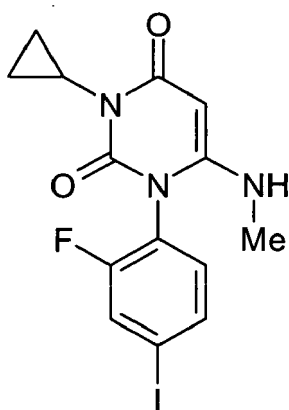
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(e) la conversion du produit de l'étape (d) en

5

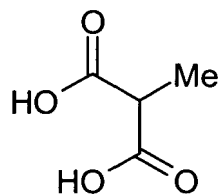


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(f) la réaction du produit de l'étape (e) avec

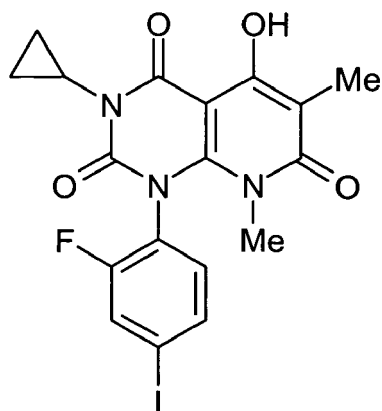
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pour former

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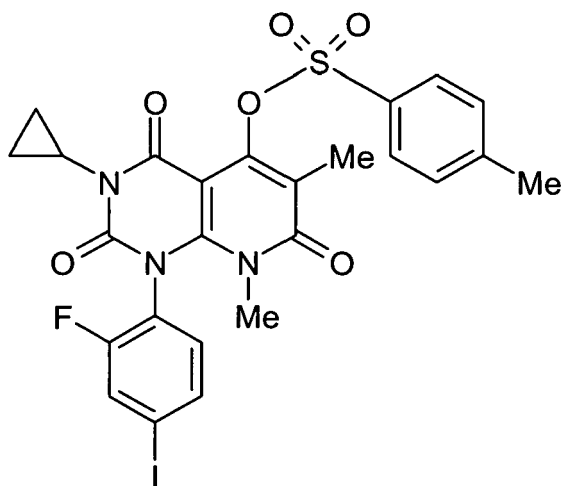
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(g) la conversion du produit de l'étape (f) en

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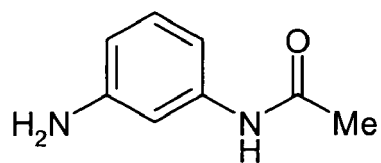


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(h) la réaction du produit de l'étape (g) avec

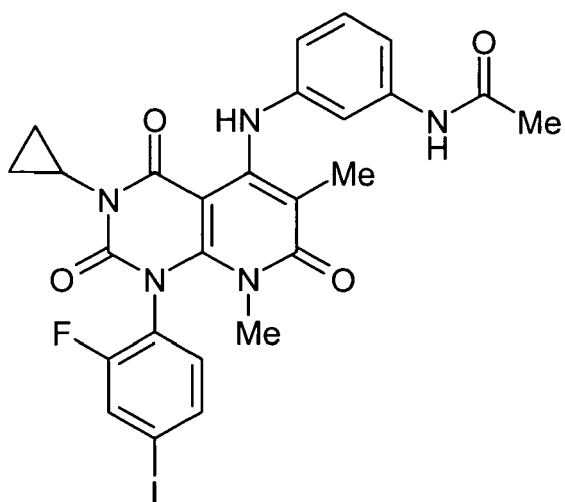
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pour former

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(i) la conversion du produit de l'étape (h) en

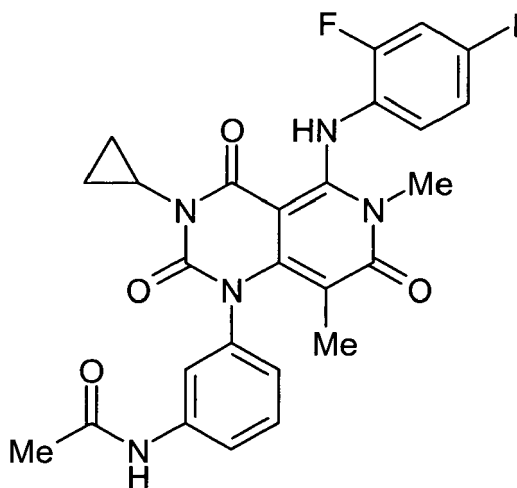
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et

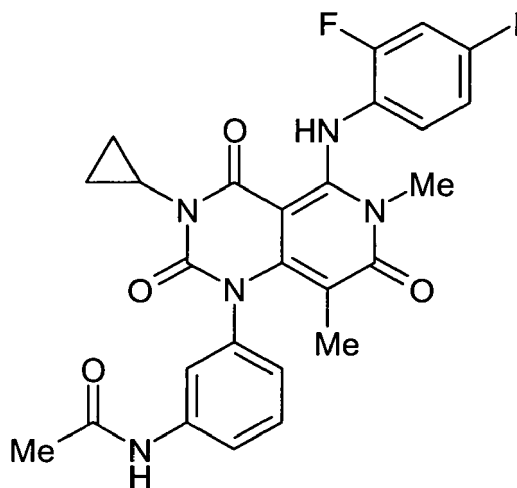
(j) éventuellement la conversion du produit de l'étape (i) en un sel ou solvate.

5. Procédé pour préparer un composé, sel ou solvate de formule :

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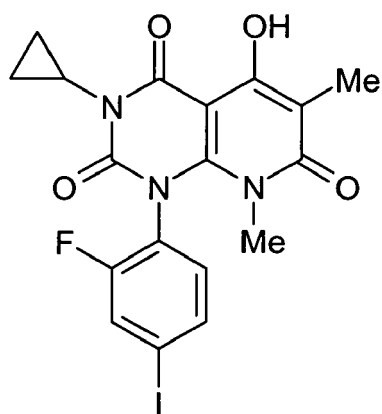
comprenant

(a) la conversion de

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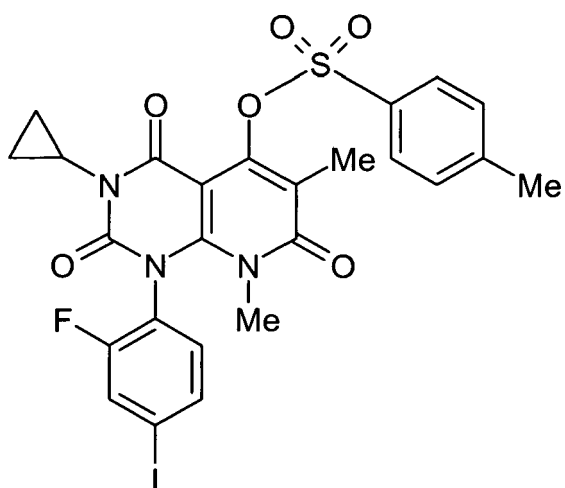


en

5

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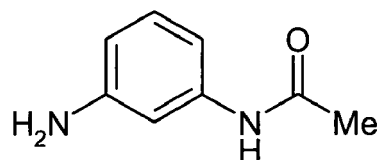
15



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(b) la réaction du produit de l'étape (a) avec

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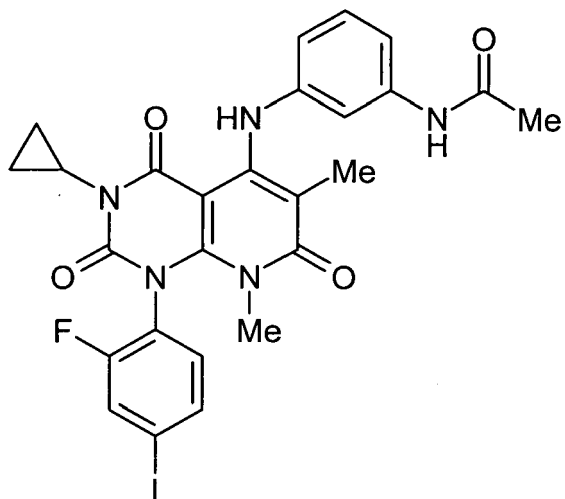
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pour former

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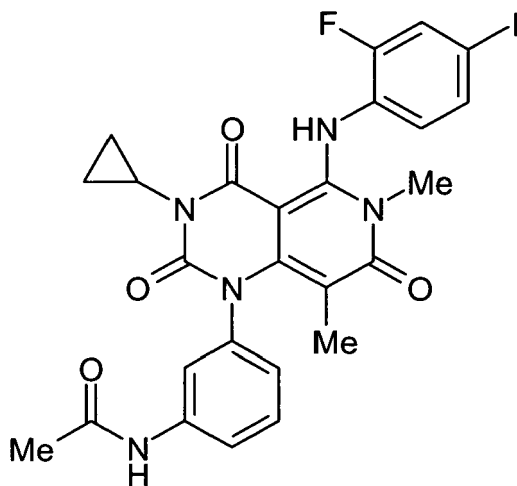
(c) la conversion du produit de l'étape (b) en et

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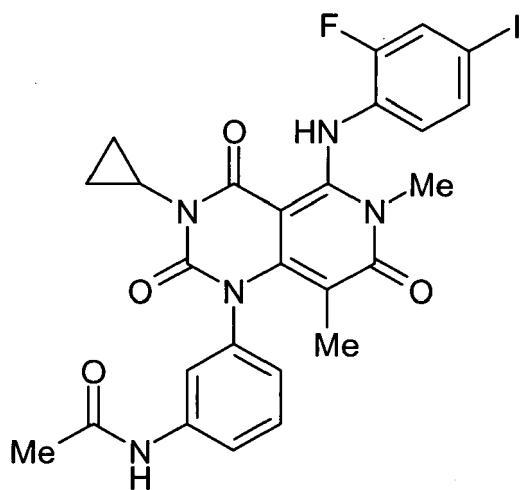
(d) éventuellement la conversion du produit de l'étape (c) en un sel ou solvate.

6. Procédé selon la revendication 4 ou 5, comprenant en outre la conversion de

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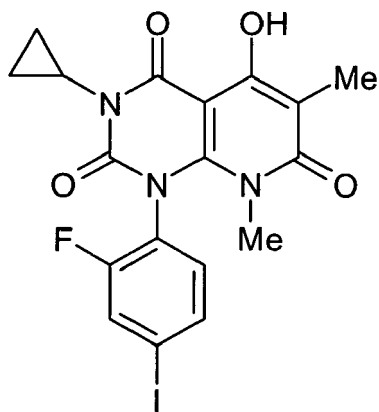
en un solvate.

7. Procédé pour préparer un composé de formule

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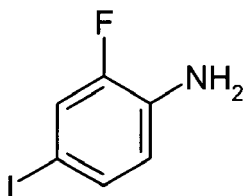
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comprenant

(a) la réaction de

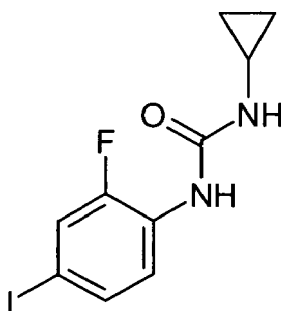
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avec de la cyclopropylamine pour former

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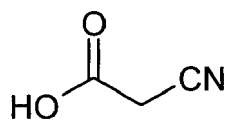


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(b) la réaction du produit de l'étape (a) avec

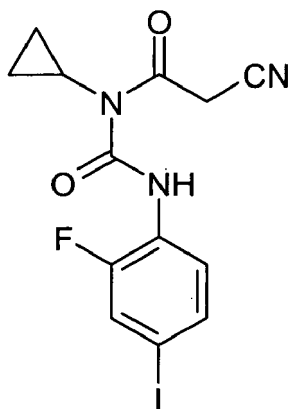
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pour former

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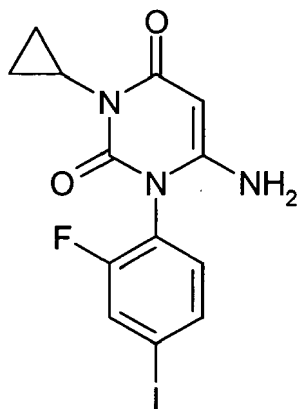
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(c) la conversion du produit de l'étape (b) en

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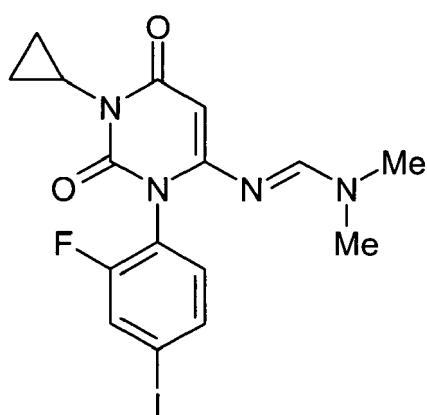


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(d) la conversion du produit de l'étape (c) en

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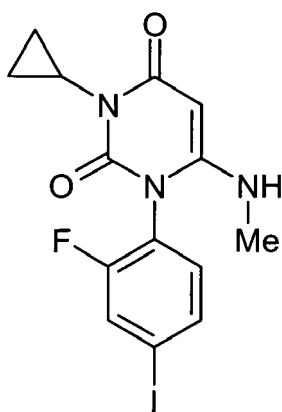


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(e) la conversion du produit de l'étape (d) en et

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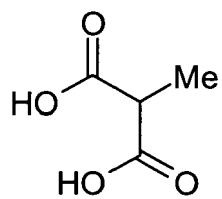
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et
(f) la réaction du produit de l'étape (e) avec

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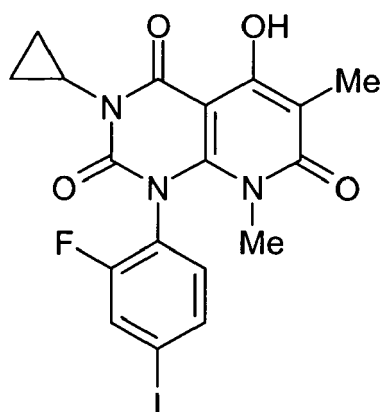
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pour former

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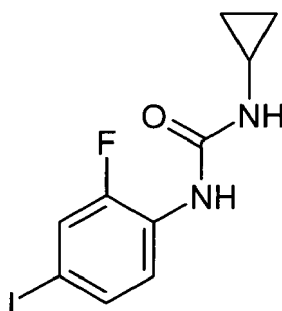


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8. Composé de formule :

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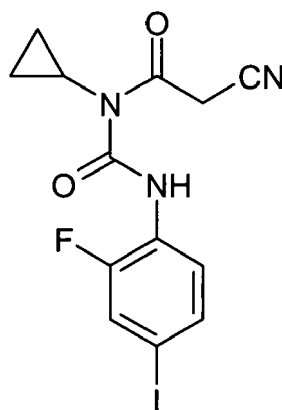
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ou un sel ou solvate de celui-ci.

9. Composé de formule :

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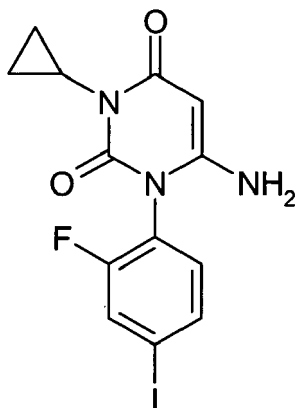
ou un sel ou solvate de celui-ci.

10. Composé de formule :

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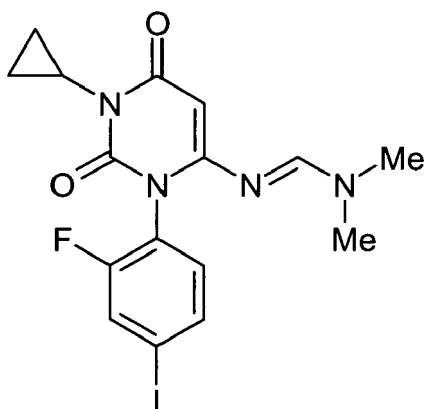
ou un sel ou solvate de celui-ci.

11. Composé de formule :

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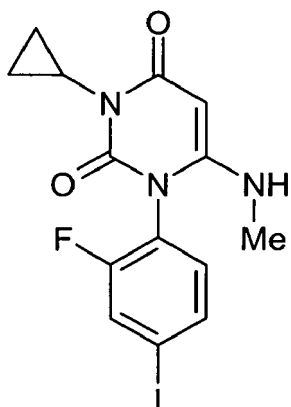
ou un sel ou solvate de celui-ci.

12. Composé de formule :

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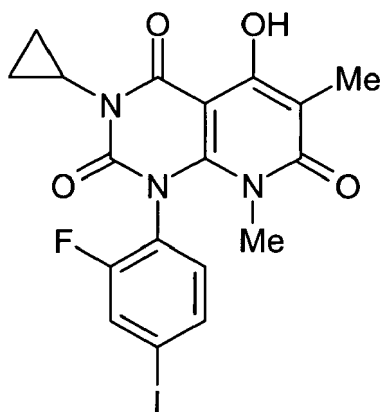
ou un sel ou solvate de celui-ci.

13. Composé de formule :

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ou un sel ou solvate de celui-ci.

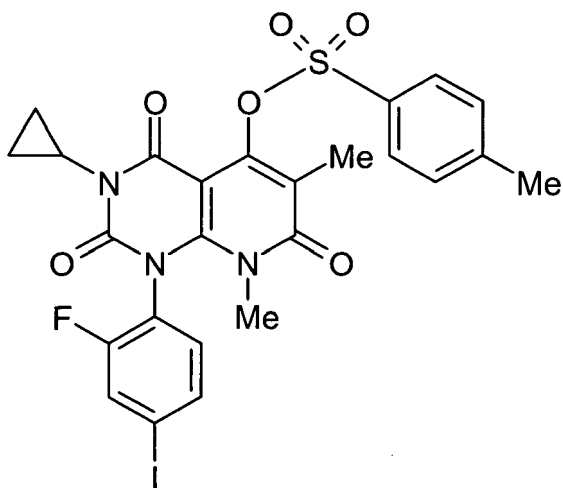
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14. Composé de formule :

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ou un sel ou solvate de celui-ci.

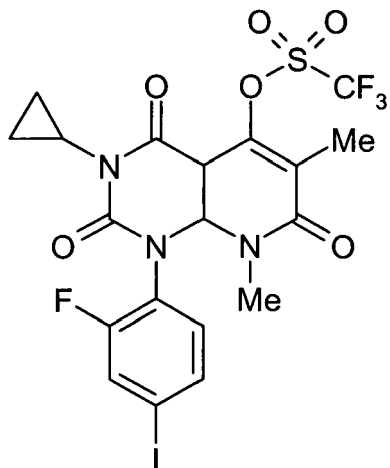
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15. Composé de formule :

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ou un sel ou solvate de celui-ci.

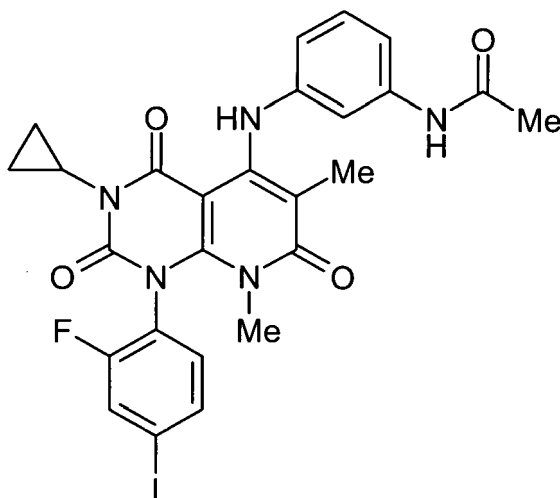
16. Composé de formule :

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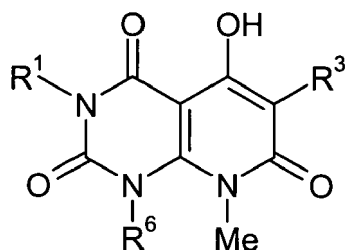


ou un sel ou solvate de celui-ci.

25 17. Composé de formule [50] ou un sel ou solvate de celui-ci :

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[50]

dans laquelle

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R³ est un groupe méthyle, et

R¹ et R⁶ sont identiques ou différents et sont chacun un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant,

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le groupe B étant un groupe consistant en

1) un atome d'halogène,

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2) un groupe nitro,

3) un groupe cyano,

4) un groupe alkyle en C₁ à C₈,

5) un groupe alcényle en C₂ à C₄,

6) un groupe alcynyle en C₂ à C₄,

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7) -OR^{B1} où R^{B1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

8) -SR^{B2} où R^{B2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

9) -NR^{B3}R^{B4} où R^{B3} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique, et R^{B4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

10) $-NR^{B5}COR^{B6}$ où R^{B5} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 , et R^{B6} est un atome d'hydrogène, un groupe alkyle en C_1 à C_4 , un groupe cyclique carboné en C_3 à C_{12} ou un groupe hétérocyclique,

11) $-NR^{B7}COOR^{B8}$ où R^{B7} et R^{B8} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

12) $-NR^{B9}CONR^{B10}R^{B11}$ où R^{B9} , R^{B10} et R^{B11} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

13) $-NR^{B12}CONR^{B13}OR^{B14}$ où R^{B12} , R^{B13} et R^{B14} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

14) $-NR^{B15}SO_2R^{B16}$ où R^{B15} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 , et R^{B16} est un groupe alkyle en C_1 à C_4 , un groupe cyclique carboné en C_3 à C_{12} ou un groupe hétérocyclique,

15) $-SO_2R^{B17}$ où R^{B17} est un groupe alkyle en C_1 à C_4 ou un groupe hétérocyclique,

16) $-SO_2NR^{B18}R^{B19}$ où R^{B18} et R^{B19} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

17) $-P(=O)(R^{B20})(R^{B21})$ où R^{B20} et R^{B21} sont identiques ou différents et sont chacun un groupe alkyle en C_1 à C_4 ,

18) $-COOR^{B22}$ où R^{B22} est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

19) $-CONR^{B23}R^{B24}$ où R^{B23} et R^{B24} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

20) $-NR^{B25}SO_2NR^{B26}R^{B27}$ où R^{B25} , R^{B26} et R^{B27} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

21) $-NR^{B28}SO_2NR^{B29}CONR^{B30}R^{B31}$ où R^{B28} , R^{B29} , R^{B30} et R^{B31} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

22) un groupe cyclique carboné en C_3 à C_{12} et

23) un groupe hétérocyclique,

chacun du "groupe alkyle en C_1 à C_8 " du 4) mentionné ci-dessus et des groupes alkyle en C_1 à C_4 pour R^{B1} à R^{B31} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A suivant, chacun du groupe alcényle en C_2 à C_4 de 5) et du groupe alcynyle en C_2 à C_4 de 6) étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A suivant, le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et

chacun du groupe cyclique carboné en C_3 à C_{12} du 22) mentionné ci-dessus, R^{B3} , R^{B6} et R^{B16} , et du groupe hétérocyclique du 23) mentionné ci-dessus, R^{B3} , R^{B6} , R^{B16} et R^{B17} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant,

le groupe A étant un groupe consistant en

1) un atome d'halogène,

2) un groupe nitro,

3) un groupe cyano,

4) un groupe alkyle en C_1 à C_4 ,

5) $-ORA^1$ où RA^1 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

6) $-SRA^2$ où RA^2 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

7) $-NRA^3RA^4$ où RA^3 et RA^4 sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

8) $-COORA^5$ où RA^5 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

9) $-NRA^6COR^{A7}$ où RA^6 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 , RA^7 est un groupe alkyle en C_1 à C_4 , un groupe cyclique carboné en C_3 à C_{12} ou un groupe hétérocyclique,

10) $-NRA^8COORA^9$ où RA^8 et RA^9 sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C_1 à C_4 ,

11) un groupe cyclique carboné en C_3 à C_{12} et

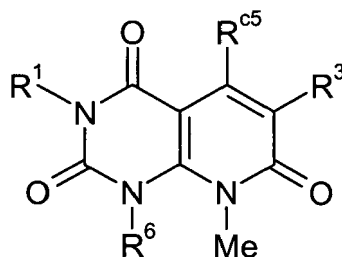
12) un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, chacun des groupes alkyle en C_1 à C_4 du 4) mentionné ci-dessus, RA^1 , RA^2 , RA^3 , RA^4 , RA^5 , RA^6 , RA^7 , RA^8 et RA^9 étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe C suivant, et chacun des groupes cycliques carbonés en C_3 à C_{12} du 11) mentionné ci-dessus et RA^7 , et des groupes hétérocycliques de 12) et RA^7 étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant, et

le groupe C étant un groupe consistant en

- 1) un atome d'halogène,
- 2) un groupe cyano,
- 3) un groupe alkyle en C₁ à C₄,
- 4) -OR^{C1} où R^{C1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 5) -NR^{C2}R^{C3} où R^{C2} et R^{C3} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 6) -COOR^{C4} où R^{C4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄ et
- 7) un groupe oxo.

18. Composé de formule [51] ou un sel ou solvate de celui-ci :



[51]

dans laquelle

R³ est un groupe méthyle,

R¹ et R⁶ sont identiques ou différents et sont chacun un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant, et

R^{C5} est un groupe partant ;

le groupe B étant un groupe consistant en

- 1) un atome d'halogène,
- 2) un groupe nitro,
- 3) un groupe cyano,
- 4) un groupe alkyle en C₁ à C₈,
- 5) un groupe alcényle en C₂ à C₄,
- 6) un groupe alcynyle en C₂ à C₄,
- 7) -OR^{B1} où R^{B1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 8) -SR^{B2} où R^{B2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 9) -NR^{B3}R^{B4} où R^{B3} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique, et R^{B4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 10) -NR^{B5}COR^{B6} où R^{B5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B6} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
- 11) -NR^{B7}COOR^{B8} où R^{B7} et R^{B8} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 12) -NR^{B9}CONR^{B10}R^{B11} où R^{B9}, R^{B10} et R^{B11} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 13) -NR^{B12}CONR^{B13}OR^{B14} où R^{B12}, R^{B13} et R^{B14} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 14) -NR^{B15}SO₂R^{B16} où R^{B15} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B16} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
- 15) -SO₂-R^{B17} où R^{B17} est un groupe alkyle en C₁ à C₄ ou un groupe hétérocyclique,
- 16) -SO₂NR^{B18}R^{B19} où R^{B18} et R^{B19} sont identiques ou différents et sont chacun un atome d'hydrogène ou un

groupe alkyle en C₁ à C₄,

17) -P(=O)(R^{B20})(R^{B21}) où R^{B20} et R^{B21} sont identiques ou différents et sont chacun un groupe alkyle en C₁ à C₄,

18) -COOR^{B22} où R^{B22} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

19) -CONR^{B23}R^{B24} où R^{B23} et R^{B24} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

20) -NR^{B25}SO₂NR^{B26}R^{B27} où R^{B25}, R^{B26} et R^{B27} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31} où R^{B28}, R^{B29}, R^{B30} et R^{B31} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

22) un groupe cyclique carboné en C₃ à C₁₂ et

23) un groupe hétérocyclique,

chacun du "groupe alkyle en C₁ à C₈" du 4) mentionné ci-dessus et des groupes alkyle en C₁ à C₄ pour R^{B1} à R^{B31} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A

suivant, chacun du groupe alcényle en C₂ à C₄ de 5) et du groupe alcynyle en C₂ à C₄ de 6) étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A suivant,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant,

outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et

chacun du groupe cyclique carboné en C₃ à C₁₂ du 22) mentionné ci-dessus, R^{B3}, R^{B6} et R^{B16}, et du groupe hétérocyclique du 23) mentionné ci-dessus, R^{B3}, R^{B6}, R^{B16} et R^{B17} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant,

le groupe A étant un groupe consistant en

1) un atome d'halogène,

2) un groupe nitro,

3) un groupe cyano,

4) un groupe alkyle en C₁ à C₄,

5) -OR^{A1} où R^{A1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

6) -SRA^{A2} où R^{A2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

7) -NR^{A3}R^{A4} où R^{A3} et R^{A4} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

8) -COOR^{A5} où R^{A5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

9) -NR^{A6}COR^{A7} où R^{A6} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, R^{A7} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

10) -NR^{A8}COOR^{A9} où R^{A8} et R^{A9} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

11) un groupe cyclique carboné en C₃ à C₁₂ et

12) un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre,

chacun des groupes alkyle en C₁ à C₄ du 4) mentionné ci-dessus, R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} et R^{A9} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe C

suivant, et chacun des groupes cycliques carbonés en C₃ à C₁₂ du 11) mentionné ci-dessus et R^{A7}, et des groupes hétérocycliques de 12) et R^{A7} étant éventuellement substitué par 1 à 5 substituants identiques ou

différents choisis dans le groupe C suivant, et

le groupe C étant un groupe consistant en

1) un atome d'halogène,

2) un groupe cyano,

3) un groupe alkyle en C₁ à C₄,

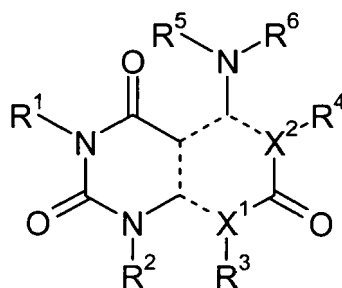
4) -OR^{C1} où R^{C1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

5) -NR^{C2}R^{C3} où R^{C2} et R^{C3} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

6) -COOR^{C4} où R^{C4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄ et

7) un groupe oxo.

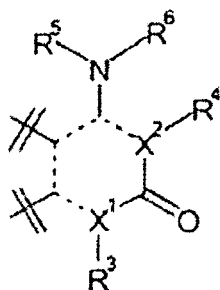
19. Composé selon la revendication 17 ou 18, dans lequel R¹ est un groupe cyclique carboné en C₃ à C₁₂, lequel groupe cyclique carboné en C₃ à C₁₂ est éventuellement substitué par 1 à 5 substituants choisis dans le groupe B.
20. Composé selon la revendication 19, dans lequel R¹ est cyclopropyle.
21. Composé selon la revendication 17 ou 18, dans lequel R⁶ est un groupe phényle qui est éventuellement substitué par 1 à 5 substituants choisis dans le groupe B.
22. Composé selon la revendication 21, dans lequel R⁶ est un groupe phényle qui est disubstitué en position 2,4.
23. Composé selon la revendication 18, dans lequel R^{C5} est un groupe partant choisi dans l'ensemble constitué par un halogène, p-toluènesulfonyloxy, méthanesulfonyloxy, et trifluorométhanesulfonyloxy.
24. Utilisation d'un composé représenté par la formule [I] suivante ou d'un sel pharmaceutiquement acceptable de celui-ci en tant qu'ingrédient actif pour la production d'un agent pharmaceutique destiné au traitement d'une tumeur :



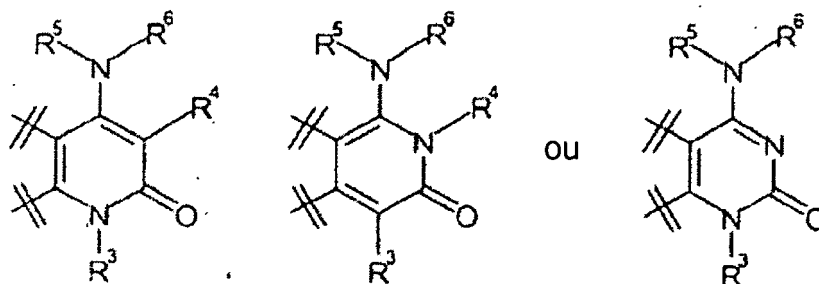
[I]

dans laquelle

X¹ et X² sont identiques ou différents et sont chacun un atome de carbone ou un atome d'azote, le fragment



est

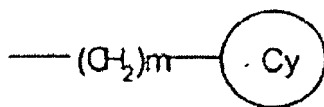


R¹, R² et R⁶ sont identiques ou différents et sont chacun un groupe alkyle en C₁ à C₆,

un groupe alcényle en C₂ à C₆,

le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant, ou

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où m vaut 0 ou est un entier de 1 à 4,

le cycle Cy est un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant,

15

R³, R⁴ et R⁵ sont identiques ou différents et sont chacun

un atome d'hydrogène,

un groupe hydroxyle,

20

un groupe alkyle en C₁ à C₆,

un groupe alcényle en C₂ à C₆,

le groupe le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A suivant,

un groupe cyclique carboné en C₃ à C₁₂ ou

25

un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé comportant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B suivant, ou bien

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R² et R³ sont éventuellement liés pour former un groupe alkylène en C₁ à C₄, ou bien R⁴ et R⁵ sont éventuellement liés pour former un groupe alkylène en C₁ à C₄,

le groupe A étant un groupe consistant en

35

1) un atome d'halogène,

2) un groupe nitro,

3) un groupe cyano,

4) un groupe alkyle en C₁ à C₄,

5) -OR^{A1} où R^{A1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

6) -SR^{A2} où R^{A2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

40

7) -NR^{A3}R^{A4} où R^{A3} et R^{A4} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

8) -COOR^{A5} où R^{A5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

9) -NR^{A6}COR^{A7} où R^{A6} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, R^{A7} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

45

10) -NR^{A8}COOR^{A9} où R^{A8} et R^{A9} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,

11) un groupe cyclique carboné en C₃ à C₁₂ et

12) un groupe hétérocyclique,

le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre,

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chacun des groupes alkyle en C₁ à C₄ du 4) mentionné ci-dessus, R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, R^{A8} et R^{A9} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe C suivant, et chacun des groupes cycliques carbonés en C₃ à C₁₂ du 11) mentionné ci-dessus et R^{A7}, et des groupes hétérocycliques de 12) et R^{A7} étant éventuellement substitué par 1 à 5 substituants identiques ou

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différents choisis dans le groupe C suivant,

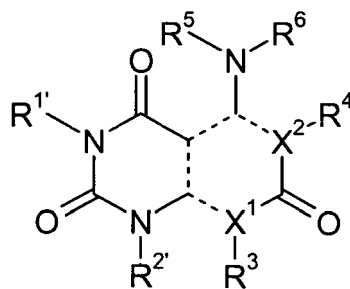
le groupe B étant un groupe consistant en

- 1) un atome d'halogène,
 - 2) un groupe nitro,
 - 3) un groupe cyano,
 - 4) un groupe alkyle en C₁ à C₈,
 - 5) un groupe alcényle en C₂ à C₄,
 - 6) un groupe alcynyle en C₂ à C₄,
 - 7) -OR^{B1} où R^{B1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 8) -SR^{B2} où R^{B2} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 9) -NR^{B3}R^{B4} où R^{B3} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique, et R^{B4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 10) -NR^{B5}COR^{B6} où R^{B5} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B6} est un atome d'hydrogène, un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
 - 11) -NR^{B7}COOR^{B8} où R^{B7} et R^{B8} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 12) -NR^{B9}CONR^{B10}R^{B11} où R^{B9}, R^{B10} et R^{B11} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 13) -NR^{B12}CONR^{B13}OR^{B14} où R^{B12}, R^{B13} et R^{B14} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 14) -NR^{B15}SO₂R^{B16} où R^{B15} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄, et R^{B16} est un groupe alkyle en C₁ à C₄, un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,
 - 15) -SO₂-R^{B17} où R^{B17} est un groupe alkyle en C₁ à C₄ ou un groupe hétérocyclique,
 - 16) -SO₂NR^{B18}R^{B19} où R^{B18} et R^{B19} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 17) -P(=O)(R^{B20})(R^{B21}) où R^{B20} et R^{B21} sont identiques ou différents et sont chacun un groupe alkyle en C₁ à C₄,
 - 18) -COOR^{B22} où R^{B22} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 19) -CONR^{B23}R^{B24} où R^{B23} et R^{B24} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 20) -NR^{B25}SO₂NR^{B26}R^{B27} où R^{B25}, R^{B26} et R^{B27} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 21) -NR^{B28}SO₂NR^{B29}CONR^{B30}R^{B31} où R^{B28}, R^{B29}, R^{B30} et R^{B31} sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
 - 22) un groupe cyclique carboné en C₃ à C₁₂ et
 - 23) un groupe hétérocyclique,
- chacun du "groupe alkyle en C₁ à C₈" du 4) mentionné ci-dessus et des groupes alkyle en C₁ à C₄ pour R^{B1} à R^{B31} étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,
- chacun du groupe alcényle en C₂ à C₄ de 5) et du groupe alcynyle en C₂ à C₄ de 6) étant éventuellement substitué par 1 à 3 substituants identiques ou différents choisis dans le groupe A mentionné ci-dessus,
- le groupe hétérocyclique étant un groupe cyclique saturé ou insaturé ayant,
- outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, et
- chacun du groupe cyclique carboné en C₃ à C₁₂ du 22) mentionné ci-dessus, R^{B3}, R^{B6} et R^{B16}, et du groupe hétérocyclique du 23) mentionné ci-dessus, R^{B3}, R^{B6}, R^{B16} et R^{B17} étant éventuellement substitué par 1 à 5 substituants identiques ou différents choisis dans le groupe C suivant, et

le groupe C étant un groupe consistant en

- 1) un atome d'halogène,
- 2) un groupe cyano,
- 3) un groupe alkyle en C₁ à C₄,
- 4) -OR^{C1} où R^{C1} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 5) -NRC²RC³ où RC² et RC³ sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe alkyle en C₁ à C₄,
- 6) -COOR^{C4} où R^{C4} est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄ et
- 7) un groupe oxo.

25. Composé représenté par la formule [I'] suivante ou un sel pharmaceutiquement acceptable de celui-ci :



[I']

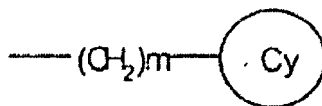
dans laquelle

15 R^{1'}, R^{2'} et R⁶ sont identiques ou différents et sont chacun

un groupe alkyle en C₁ à C₆,

un groupe alcényle en C₂ à C₆,

le groupe alkyle en C₁ à C₆ et le groupe alcényle en C₂ à C₆ étant éventuellement substitués par 1 à 3 substituants choisis dans le groupe A de la revendication 1, ou



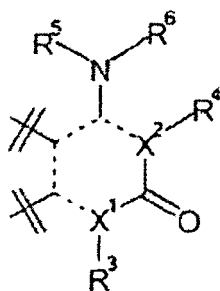
m vaut 0 ou est un entier de 1 à 4,

le cycle Cy est un groupe cyclique carboné en C₃ à C₁₂ ou un groupe hétérocyclique,

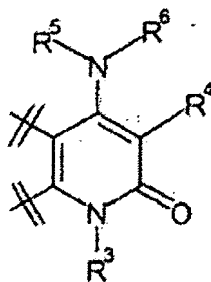
30 le groupe hétérocyclique étant un cycle saturé ou insaturé ayant, outre les atomes de carbone, 1 à 4 hétéroatomes choisis parmi un atome d'oxygène, un atome d'azote et un atome de soufre, le groupe cyclique carboné en C₃ à C₁₂ et le groupe hétérocyclique étant éventuellement substitués par 1 à 5 substituants choisis dans le groupe B de la revendication 1,

avec les conditions suivantes :

35 quand le fragment



est



alors R^{2'} n'est pas un groupe méthyle, et
 quand R^{2'} est un groupe phényle, alors R^{1'} n'est pas un groupe phényle,
 et les autres symboles sont tels que définis dans la revendication 1.

- 5 **26.** Utilisation d'un composé de formule [I] selon la revendication 24 ou d'un sel pharmaceutiquement acceptable de celui-ci en tant qu'ingrédient actif pour la production d'un agent antitumoral.
- 10 **27.** Utilisation d'un composé de formule [I] selon la revendication 24 ou d'un sel pharmaceutiquement acceptable de celui-ci en tant qu'ingrédient actif pour la production d'un agent pharmaceutique capable d'inhiber la MEK.
- 15 **28.** Utilisation d'un composé de formule [I] selon la revendication 24 ou d'un sel pharmaceutiquement acceptable de celui-ci en tant qu'ingrédient actif pour la production d'un agent pharmaceutique capable d'induire la protéine p15.
- 20 **29.** Utilisation d'un composé de formule [I] selon la revendication 24 ou d'un sel pharmaceutiquement acceptable de celui-ci en tant qu'ingrédient actif pour la production d'un agent pharmaceutique destiné à traiter une maladie provoquée par une prolifération cellulaire indésirable.
- 25 **30.** Utilisation d'un composé de formule [I] selon la revendication 24 ou d'un sel pharmaceutiquement acceptable de celui-ci en tant qu'ingrédient actif pour la production d'un agent pharmaceutique capable d'inhiber une prolifération cellulaire indésirable.
- 30 **31.** Utilisation d'un composé de formule [I] selon la revendication 24 ou d'un sel pharmaceutiquement acceptable de celui-ci en tant qu'ingrédient actif pour la production d'un agent pharmaceutique capable de réguler le cycle cellulaire.
- 35 **32.** Composition pharmaceutique qui comprend un composé de formule [I'] selon la revendication 25 ou un sel pharmaceutiquement acceptable de celui-ci, et un véhicule pharmaceutiquement acceptable.
- 40 **33.** Utilisation de (a) un composé de formule [I] selon la revendication 24 ou un sel pharmaceutiquement acceptable de celui-ci, en tant qu'ingrédient actif, qui est utilisé en combinaison avec (b) au moins un autre composé antitumoral, pour la production d'un agent antitumoral.
- 45 **34.** Utilisation de (a) un composé de formule [I] selon la revendication 24 ou un sel pharmaceutiquement acceptable de celui-ci, en tant qu'ingrédient actif, et de (b) au moins un autre composé antitumoral, en combinaison, pour la production d'un agent antitumoral.
- 50 **35.** Composition pharmaceutique comprenant, en tant qu'ingrédient actif, (a) un composé de formule [I] selon la revendication 24 ou un sel pharmaceutiquement acceptable de celui-ci et (b) au moins un autre composé antitumoral, et un véhicule pharmaceutiquement acceptable, en combinaison.
- 55 **36.** Trousse pour traiter une tumeur comprenant (a) une composition pharmaceutique comprenant, en tant qu'ingrédient actif, un composé de formule [I] selon la revendication 24 ou un sel pharmaceutiquement acceptable de celui-ci et (b) une composition pharmaceutique comprenant, en tant qu'ingrédient actif, au moins un autre agent antitumoral, en combinaison.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 0203997 A1 [0015]
- WO 03062236 A1 [0016]
- WO 02094824 A1 [0017]
- JP 2003504401 A [0019]
- WO 01005393 A [0019]
- JP 2002332247 A [0019]
- CA 2385412 [0019]
- JP 2002532414 A [0019]
- WO 0035435 A [0019]
- JP 2002532415 B [0019]
- WO 0035436 A [0019]
- JP 2002534380 A [0019]
- WO 0040235 A [0019]
- JP 2002534381 A [0019]
- WO 0040237 A [0019]
- WO 2002087620 A [0019]
- US 2004138285 A [0019]
- WO 02006520 A [0019]
- JP 2004504294 A [0022]
- WO 2002006213 A [0022]
- WO 2002094824 A [0027]

Non-patent literature cited in the description

- *Letters to Nature*, 15 September 1994, vol. 371, 257-261 [0008]
- *FEBS Letters*, 2003, vol. 554, 347-350 [0009]
- *The Journal of Biological Chemistry*, 2001, vol. 276 (4), 2686-2692 [0014]
- *Journal für Praktische Chemie-Chemiker Zeitung*, 1996, vol. 338 (2), 151-156 [0018]
- *Khimiia geterotsiklicheskikh soedinenii*, 1991, 674-680 [0024]
- *Chem. Pharm. Bull.*, 1973, vol. 9 (21), 2014-2018 [0025]
- *Journal für Praktische Chemie*, 1996, vol. 338, 151-156 [0028]
- *Journal of Medicinal Chemistry*, 1986, vol. 29 (5), 709-715 [0029]