DESCRIPTION

FUSED HETEROCYCLIC RING DERIVATIVE AND USE THEREOF

Technical Field

[0001]

The present invention relates to a fused heterocycle derivative and use thereof. More particularly, the present invention relates to a compound having a strong Smo inhibitory activity and useful for the prophylaxis or treatment of cancer and the like, and use thereof.

[0002]

(Background of the Invention)

The study of morphogenesis during the developmental stage has been conducted based on the screening of variant using Drosophila. Hedgehog gene (hh) was found as one of the genes that cause morphological abnormality of Drosophila embryo due to mutation thereof. Hedgehog gene product (Hh) is a secretory protein, which is produced as an about 45 kDa precursor and then divided, due to autolysis, into a 20 kDa N-terminal side domain, which is a main active principle, and a 25 kDa C-terminal side domain. The 20 kDa N-terminal side domain, which is a main active principle, is modified by fatty acid on the N-terminal and cholesterol on the C-terminal thereof. The Hedgehog signal transduction system is formed by the protein group described below. Hh receptor is Patched (Ptch), which is a twelve-transmembrane-type protein. Ptch acts on Smoothened (Smo), which is a seven-transmembrane-type protein, and suppresses the function of Smo in the absence of Hh. When Hh is bound to the receptor Ptch, suppression of Smo is released and Smo is activated. The signal produced by the activation of Smo activates transcription factor Ci, which regulates the expression of the gene group involved in the morphogenesis (Curr. Opin. Genet. Dev., vol.12, pages 503-511, 2002).

A pathway corresponding to the Drosophila Hedgehog signal transduction system has been confirmed also in mammals. In

human, for example, three types of gene products, sonic hedgehog (Shh), indian hedgehog (Ihh) and desert hedgehog (Dhh), are known to correspond to Drosophila Hh, and undergo post-translational modification as in Drosophila Hh (Cell, vol.103, pages 371-374, 2000). In human Shh, a 19 kDa active principle is cleaved out from a 45 kDa precursor protein by autolysis, and fatty acid is added to the N-terminal thereof, and cholesterol is added to the C-terminal thereof (J. Biol. Chem., vol.273, pages 14037-14045, 1998). Such modification is considered to be essential for the maintenance of Shh activity and, for example, 40 times enhanced activity was achieved by the addition of palmitic acid to Escherichia coli recombinant human Shh free of N-terminal modification with fatty acid, and 160 times enhanced activity was achieved by the addition of myristic acid thereto (Biochemistry, vol.40, pages 4359-4371, 2001). On the other hand, as a human gene corresponding to Drosophila Smo, human Smo is known, and as a human gene corresponding to Drosophila Ptch, 2 types of Ptch1 and Ptch2 are known. In addition, a transcription factor corresponding to Drosophila Ci is considered to be Gli in human, and 3 types of Gli1, Gli2 and Gli3 are known (Nature Rev. Cancer, vol.2, pages 361-372, 2002). Shh/Ihh/Dhh are each bound to Ptch1 and activate Smo by inhibiting the bond between Ptch1 and Smo. Shh/Ihh/Dhh are also bound to Ptch2, Hip1, Gas1 and Cdo/Boc, besides Ptch1, and regulate the activation of Smo. A signal transduction from Smo induces nuclear localization of Gli1 and Gli2, and activate transcription of Gli1 (Curr. Opin. Cell Biol., vol.19, pages 159-165, 2007).

The Hedgehog signal is involved in the morphogenesis in the developmental stages also in mammals. In human, for example, patients with Holoprosencephaly, which is a congenital developmental abnormality, showed mutation in Shh (Nat. Genet., vol.14, pages 357-360, 1996). Moreover, a natural compound Cyclopamine derived from white hellebore known as a compound inducing Cyclopus in sheep (Am. J. Vet.

Res., vol.24, pages 1164-1175, 1963) was confirmed to inhibit Smo as action mechanism thereof (Development, vol.125, pages 3553-3562, 1998). Furthermore, an Shh knockout mouse was prepared, and its phenotype was found to include Cyclopus, malformation of extremities (Nature, vol.383, pages 407-413, 1996), and neural plate malformation (Cell, vol.111, pages 63-75, 2002).

Hedgehog signal is inherently a developmental signal, which is promoted in tumor tissues and functions as a cancer cell proliferation and survival signal. Hedgehog signal is considered to function for the growth and survival of cancer cells in an autocrine mode, or function between cancer cells and cancer interstitial cells in a paracrine mode, in tumor tissues (Nat. Rev. Drug Discov., vol.5, pages 1026-1033, 2006). In an autocrine mode, it works for the growth and maintenance of cancer cells, via transcription activation by Gli-1, by abnormal cell cycle control due to increased expression of Cyclin D and decreased expression of p21, promotion of proliferation signal by activation of EGFR pathway and the like. On the other hand, since Shh expressed in cancer cells acts on Smo in cancer interstitial cells, growth factors such as insulin-like growth factor-1, fibroblast growth factor, platelet-derived growth factor and the like are transmitted from cancer interstitial cells to cancer cells, and function for the growth and survival of cancer cells. It is also considered that promotion of VEGF, PDGF pathway and the like by Gli-1 promotes tumor angiogenesis (Clin Cancer Res., vol.12, pages 5924-5928, 2006). As to the mechanism of promotion of Hedgehog signal, a cancer in which Hedgehog signal is promoted due to mutation of Ptch1 and a cancer which is promoted by overexpression of Shh, which is one of the ligands, have been reported (Nature Rev. Cancer, vol.3, pages 903-911, 2003). As a cancer in which Hedgehog signal is promoted due to mutation, basal cell cancer and medulloblastoma are known, and mutation of Ptch1 observed in these cancers activates Hedgehog signal

in a ligand independent manner (Am. J. Med. Gen., vol.123A, pages 5-28, 2003). As a cancer in which Hedgehog signal is promoted by overexpression of Shh, pancreatic cancer (Nature, vol.425, pages 846-851, 2003) and the like have been reported. In a transgenic mouse in which Shh is forcedly expressed in the pancreas, Hedgehog signal is suggested to be involved not only in the growth and maintenance of cancer, but also carcinogenic process, since a PanIN-like lesion in the initial stages of cancer progress was found in the pancreas (Nature, vol.425, pages 851-856, 2003). Furthermore, Hedgehog signal is considered to function for the growth and survival of cancer stem cells, and play a key role in the metastasis or postoperative recurrence of tumor and the like (Trends Cell Biol., vol.17, pages 438-447, 2007).

As the Hedgehog signal inhibitor, the following are known. Cyclopamine, which is a naturally occurring Smo inhibitory compound, has been reported to show a tumor growth suppressive effect on glioma (Development, vol.128, pages 5201-5212, 2001) and the like. As a synthetic low-molecular-weight compound inhibiting Smo, CUR-61414 (Proc. Natl. Acad. Sci. U.S.A., vol.100, pages 4616-4621, 2003) and SANT-1, 2, 3, 4 (Proc. Natl. Acad. Sci. U.S.A., vol.99, pages 14071-14076, 2002) have been reported. As for the Hedgohog signal inhibitory antibody, it has been reported that administration of an anti-Shh antibody to a cancer-carrying nude mouse transplanted with colorectal cancer cell line HT-29 caused regression of cancer (WO 2004/020599).

[0003]

Patent documents 1 to 5 disclose fused heterocycle compounds.

Document List

Patent Documents

[0004]

Patent Document 1: WO 01/64639

Patent Document 2: WO 02/12189

Patent Document 3: WO 03/059884

Patent Document 4: WO 2005/081960

Patent Document 5: WO 2006/030032

Summary of the Invention

Problems to be Solved by the Invention

[0005]

An object of the present invention is to provide a compound having a superior Smo inhibitory activity, low toxicity and sufficiently satisfactory as a pharmaceutical product.

Means of Solving the Problems

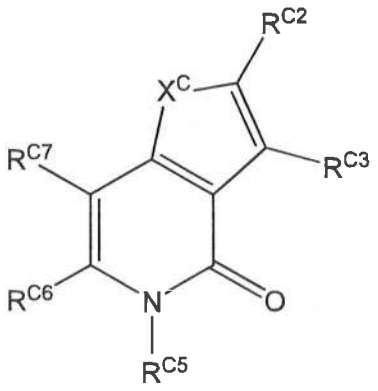
[0006]

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a compound represented by the following formula and a salt thereof have a superior Smo inhibitory activity, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

[1] a compound represented by the formula

[0007]



(CI)

[0008]

wherein

X^C is NR^{C1}, a sulfur atom or an oxygen atom;

R^{C1} is a hydrogen atom or a C_{1-6} alkyl group;

R^{C2} is a carbamoyl group optionally having substituent(s);

R^{C3} is a hydroxy group optionally having a substituent;

R^{C5} is a cyclic group optionally having substituent(s);

R^{C6} is a C_{1-6} alkyl group optionally having substituent(s);

R^{C7} is a hydrogen atom, a halogen atom or a C_{1-6} alkyl group, or a salt thereof (in the present specification, sometimes to be abbreviated as "compound (CI)");

[2] the compound or salt of the above-mentioned [1], wherein X^C is NR^{C1} wherein R^{C1} is a hydrogen atom or a C_{1-6} alkyl group; R^{C2} is a carbamoyl group optionally having 1 or 2 substituents selected from

(1) a C_{1-6} alkyl group optionally having substituent(s),

(2) a C_{2-6} alkynyl group optionally having substituent(s),

(3) a C_{3-8} cycloalkyl group optionally having substituent(s),

(4) a C_{6-10} aryl group optionally having substituent(s), and

(5) a heterocyclic group optionally having substituent(s);

R^{C3} is an optionally halogenated C_{1-6} alkoxy group;

R^{C5} is

(1) a C_{6-10} aryl group optionally having substituent(s), or

(2) a heterocyclic group optionally having substituent(s);

R^{C6} is a C_{1-6} alkyl group; and

R^{C7} is a hydrogen atom;

[3] the compound or salt of the above-mentioned [2], wherein X^C is NR^{C1} wherein R^{C1} is methyl;

[4] 6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof;

[5] 6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof;

[6] 3-ethoxy-6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof;

[7] a prodrug of the compound or salt of any of the above-mentioned [1] to [6];

[8] a medicament comprising the compound or salt of any of the above-mentioned [1] to [6] or a prodrug thereof;

[9] the medicament of the above-mentioned [8], which is an Smo inhibitor;

[10] the medicament of the above-mentioned [8], which is an agent for the prophylaxis or treatment of cancer;

[11] a method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound or salt of any of the above-mentioned [1] to [6] or a prodrug thereof to the mammal; and

[12] use of the compound or salt of any of the above-mentioned [1] to [6] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer.

Effect of the Invention

[0009]

Since the compound of the present invention has a strong Smo inhibitory action, it can provide a clinically useful agent for the prophylaxis or treatment of cancer, a cancer growth inhibitor and a cancer metastasis suppressive agent.

[0010]

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

In the present specification, the "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

In the present specification, the "C_{1-6} alkyl group" means, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl or the like.

In the present specification, the "C_{2-6} alkenyl group" means, for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl or the like.

In the present specification, the "C_{2-6} alkynyl group" means, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-

pentynyl, 1,1-dimethylprop-2-yn-1-yl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl or the like.

In the present specification, the "C_{1-6} alkoxy group" means, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, hexoxy or the like.

[0011]

In the present specification, the "an optionally halogenated C_{1-6} alkoxy group" means, for example, a C_{1-6} alkoxy group optionally having halogen atom(s) (preferably 1 to 5 halogen atoms, more preferably 1 to 3 halogen atoms s) at substitutable position(s).

[0012]

In the present specification, the "C_{1-6} alkyl-carbonyl group" means, for example, acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, pentylcarbonyl, hexylcarbonyl or the like.

[0013]

In the present specification, the "C_{1-6} alkoxy-carbonyl group" means, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl or the like.

[0014]

In the present specification, the "C_{3-8} cycloalkyl group" means, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or the like.

In the present specification, the "C_{3-8} cycloalkane" means, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane or the like.

In the present specification, the "C_{3-6} cycloalkane" means, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane or the like.

In the present specification, the "C_{3-8} cycloalkenyl group" means, for example, cyclopropenyl (e.g., 2-cyclopropen-

1-yl), cyclobutenyl (e.g., 2-cyclobuten-1-yl), cyclopentenyl (e.g., 2-cyclopenten-1-yl, 3-cyclopenten-1-yl), cyclohexenyl (e.g., 2-cyclohexen-1-yl, 3-cyclohexen-1-yl) or the like.

In the present specification, the "C_{6-10} aryl group" means, for example, phenyl, 1-naphthyl, 2-naphthyl or the like.

In the present specification, the "C_{6-10} arene" means, for example, benzene, naphthalene or the like.

In the present specification, the "C_{7-13} aralkyl group" means, for example, benzyl, phenethyl, naphthylmethyl or the like.

In the present specification, the "C_{6-10} aryl-carbonyl group" means, for example, benzoyl, 1-naphthoyl, 2-naphthoyl or the like.

[0015]

In the present specification, the "heterocyclic group" means an aromatic heterocyclic group (e.g., a 5- to 12-membered aromatic heterocyclic group) or a non-aromatic heterocyclic group (e.g., a 4- to 12-membered non-aromatic heterocyclic group).

In the present specification, the "aromatic heterocyclic group" means a monocyclic aromatic heterocyclic group and a fused aromatic heterocyclic group.

Examples of the monocyclic aromatic heterocyclic group include a 5- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom (optionally oxidized). Examples thereof include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-

pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-3-yl, 1,2,4-triazin-6-yl) and the like.

Examples of the fused aromatic heterocyclic group include a 8- to 12-membered fused aromatic heterocyclic group, specifically, a group derived from a fused ring wherein a ring corresponding to the above-mentioned 5- to 7-membered monocyclic aromatic heterocyclic group and a C_{6-10} arene are condensed; and a group derived from a fused ring wherein rings corresponding to the above-mentioned 5- to 7-membered monocyclic aromatic heterocyclic groups are condensed. Specific examples thereof include quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuranyl (e.g., 2-benzofuranyl, 3-benzofuranyl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 3-benzisoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzoisothiazolyl (e.g., 3-benzoisothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), isoindolyl (e.g., isoindol-1-yl, isoindol-2-yl, isoindol-3-yl, isoindol-5-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-

imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), thienopyridinyl (e.g., thieno[2,3-b]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like.

[0016]

In the present specification, the "non-aromatic heterocyclic group" means a monocyclic non-aromatic heterocyclic group and a fused non-aromatic heterocyclic group.

Examples of the monocyclic non-aromatic heterocyclic group include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom. Examples thereof include azetidinyl (e.g., 1-azetidinyl, 2-azetidinyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidyl (e.g., piperidino, 2-piperidyl, 3-piperidyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), oxazolidinyl (e.g., oxazolidin-2-yl), thiazolidinyl (e.g., thiazolidin-2-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), pyranyl (e.g., 2-pyranyl, 4-pyranyl), dihydropyranyl (e.g., 2,3-dihydropyran-2-yl, 2,3-dihydropyran-3-yl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), dihydrothiopyranyl (e.g., dihydrothiopyran-3-yl, dihydrothiopyran-4-yl), tetrahydrothiopyranyl (e.g., 2-

tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxidotetrahydrothiopyranyl (e.g., 1-oxidotetrahydrothiopyran-4-yl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-dioxidotetrahydrothiopyran-4-yl), tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydropyrimidinyl (e.g., tetrahydropyrimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl), azepanyl (e.g., 1-azepanyl, 2-azepanyl, 3-azepanyl, 4-azepanyl), dihydropyridyl (e.g., dihydropyridin-1-yl, dihydropyridin-2-yl, dihydropyridin-3-yl, dihydropyridin-4-yl), tetrahydropyridyl (e.g., tetrahydropyridin-1-yl, tetrahydropyridin-2-yl, tetrahydropyridin-3-yl, tetrahydropyridin-4-yl) and the like.

Examples of the fused non-aromatic heterocyclic group include a 8- to 12-membered fused non-aromatic heterocyclic group, specifically, a group derived from a fused ring wherein a ring corresponding to the above-mentioned 4- to 7-membered monocyclic non-aromatic heterocyclic group and a C_{6-10} arene are condensed; a group derived from a fused ring wherein rings corresponding to the above-mentioned 4- to 7-membered monocyclic non-aromatic heterocyclic groups are condensed; a group derived from a fused ring wherein a ring corresponding to the above-mentioned 4- to 7-membered monocyclic non-aromatic heterocyclic group and a ring corresponding to the above-mentioned 5- to 7-membered monocyclic aromatic heterocyclic group are condensed; and a group wherein the above-mentioned group is partially saturated. Specific examples thereof include dihydroindolyl (e.g., 2,3-dihydro-1H-indol-1-yl), dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-dihydro-1-benzofuran-5-yl), tetrahydrobenzofuranyl (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), dihydrobenzodioxinyl (e.g., 2,3-dihydro-1,4-

benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-dihydro-2H-1,5-benzodioxepinyl), chromenyl (e.g., 4H-chromen-2-yl, 2H-chromen-3-yl), dihydrochromenyl (e.g., 3,4-dihydro-2H-chromen-2-yl), dihydroquinolinyl (e.g., 1,2-dihydroquinolin-4-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydroisoquinolin-4-yl), dihydrophthalazinyl (e.g., 1,4-dihydrophthalazin-4-yl), azabicyclohexyl (e.g., 2-azabicyclo[3.1.0]hexan-3-yl) and the like.

[0017]

In the present specification, the "heterocycle" means an aromatic heterocycle (e.g., a 5- to 12-membered aromatic heterocycle) or a non-aromatic heterocycle (e.g., a 4- to 12-membered non-aromatic heterocycle).

In the present specification, the "aromatic heterocycle" means a monocyclic aromatic heterocycle and a fused aromatic heterocycle.

Examples of the monocyclic aromatic heterocycle include a 5- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocycle containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom (optionally oxidized). Examples thereof include furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, oxadiazole, thiadiazole, triazole, tetrazole, triazine and the like.

Examples of the fused aromatic heterocycle include a 8- to 12-membered fused aromatic heterocycle, specifically, a fused ring wherein the above-mentioned 5- to 7-membered monocyclic aromatic heterocycle and a C_{6-10} arene are condensed; and a fused ring wherein the above-mentioned 5- to 7-membered monocyclic aromatic heterocycles are condensed. Specific examples thereof include quinoline, isoquinoline, quinazoline,

quinoxaline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzoisothiazole, benzimidazole, benzotriazole, indole, isoindole, indazole, pyrrolopyrazine (e.g., 1H-pyrrolo[2,3-b]pyrazine), imidazopyridine (e.g., 2H-imidazo[1,2-a]pyridine, 1H-imidazo[4,5-b]pyridine, 1H-imidazo[4,5-c]pyridine), thienopyridine (e.g., thieno[2,3-b]pyridine), imidazopyrazine (e.g., 1H-imidazo[4,5-b]pyrazine), pyrazolopyridine (e.g., 1H-pyrazolo[4,3-c]pyridine), pyrazolothiophene (e.g., 2H-pyrazolo[3,4-b]thiophene), pyrazolotriazine (e.g., pyrazolo[5,1-c][1,2,4]triazine) and the like.

[0018]

In the present specification, the "non-aromatic heterocycle" means a monocyclic non-aromatic heterocycle and a fused non-aromatic heterocycle.

Examples of the monocyclic non-aromatic heterocycle include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom (optionally oxidized) and a nitrogen atom. Examples thereof include azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxazolidine, thiazolidine, imidazolidine, oxazoline, thiazoline, imidazoline, dioxole, dioxolane, dihydrooxadiazole, pyran, dihydropyran, tetrahydropyran, thiopyran, dihydrothiopyran, tetrahydrothiopyran, 1-oxidotetrahydrothiopyran, 1,1-dioxidotetrahydrothiopyran, tetrahydrofuran, pyrazolidine, pyrazoline, tetrahydropyrimidine, dihydrotriazole, tetrahydrotriazole, azepane, dihydropyridine, tetrahydropyridine and the like.

Examples of the fused non-aromatic heterocycle include a 8- to 12-membered fused non-aromatic heterocycle, specifically, a fused ring wherein the above-mentioned 4- to 7-membered monocyclic non-aromatic heterocycle and a C_{6-10} arene are condensed; a fused ring wherein the above-mentioned 4- to 7-

membered monocyclic non-aromatic heterocycles are condensed; a fused ring wherein the above-mentioned 4- to 7-membered monocyclic non-aromatic heterocycle and the above-mentioned 5- to 7-membered monocyclic aromatic heterocycle are condensed; and a ring wherein the above-mentioned ring is partially saturated. Specific examples thereof include dihydroindole (e.g., 2,3-dihydro-1H-indole), dihydroisoindole (e.g., 1,3-dihydro-2H-isoindole), dihydrobenzofuran (e.g., 2,3-dihydro-1-benzofuran), tetrahydrobenzofuran (e.g., 4,5,6,7-tetrahydro-1-benzofuran), dihydrobenzodioxine (e.g., 2,3-dihydro-1,4-benzodioxine), dihydrobenzodioxepine (e.g., 3,4-dihydro-2H-1,5-benzodioxepine), chromene, dihydrochromene (e.g., 3,4-dihydro-2H-chromene), dihydroquinoline (e.g., 1,2-dihydroquinoline), tetrahydroquinoline (e.g., 1,2,3,4-tetrahydroquinoline), dihydroisoquinoline (e.g., 1,2-dihydroisoquinoline), tetrahydroisoquinoline (e.g., 1,2,3,4-tetrahydroisoquinoline), dihydrophthalazine (e.g., 1,4-dihydrophthalazine), azabicyclohexane (e.g., 2-azabicyclo[3.1.0]hexane) and the like.

[0019]

In the present specification, the "nitrogen-containing heterocycle" means, for example, a 5- to 7-membered nitrogen-containing heterocycle containing, as a ring constituting atom besides carbon atom, at least one nitrogen atom, and optionally further containing 1 or 2 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom. Preferable examples of the nitrogen-containing heterocycle include pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, thiazolidine, oxazolidine and the like.

[0020]

In the present specification, the "heterocyclyl-carbonyl group" means a carbonyl group substituted by the aforementioned "heterocyclic group". Specific examples of the heterocyclyl-carbonyl group include pyrrolylcarbonyl, pyrazolylcarbonyl,

pyridylcarbonyl, pyrrolidinylcarbonyl, thienylcarbonyl, furylcarbonyl, thiazolylcarbonyl, oxazolylcarbonyl, piperidinocarbonyl, piperazinylcarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, tetrahydrobenzo[c]azepinylcarbonyl, tetrahydroisoquinolinylcarbonyl and the like.

[0021]

In the present specification, the "C_{3-8} cycloalkyl-carbonyl group" means, for example, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclooctylcarbonyl or the like.

[0022]

In the present specification, examples of the substituent that the C_{1-6} alkyl group of the "C_{1-6} alkyl group optionally having substituent(s)" optionally has include substituents selected from the following Substituent A Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0023]

Substituent A Group:

(1) a halogen atom;

(2) a cyano group;

(3) a nitro group;

(4) a hydroxy group;

(5) a carboxy group;

(6) a C_{3-8} cycloalkyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, and

(e) an oxo group;

(7) a C_{6-10} aryl group optionally having 1 to 3 substituents

selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, and

(d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms;

(8) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, and

(d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms;

(9) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(d) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms,

(e) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 hydroxy, and

(f) an oxo group;

(10) an amino group optionally having 1 or 2 substituents selected from

(a) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(b) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 substituents selected from

(i) a halogen atom,

(ii) a hydroxy group, and

(iii) a C_{6-10} aryl group,

(c) a C_{1-6} alkoxy-carbonyl group optionally having 1 to 3 substituents selected from

(i) a halogen atom, and

(ii) a C_{6-10} aryl group,

(d) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl) optionally having 1 to 3 substituents selected from

(i) a halogen atom, and

(ii) a C_{6-10} aryl group,

(e) a C_{6-10} arylsulfonyl group (e.g., phenylsulfonyl),

(f) a carbamoyl group optionally having 1 or 2 C_{1-6} alkyl groups optionally having 1 to 3 halogen atoms,

(g) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(i) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(ii) a hydroxy group,

(iii) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, and

(iv) a halogen atom, and

(h) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(i) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(ii) a hydroxy group,

(iii) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms,

(iv) a halogen atom, and

(v) an oxo group;

(11) an imino group;

(12) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 halogen atoms;

(13) a C_{1-6} alkoxy-carbonyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a C_{1-6} alkoxy group,

(c) a C_{6-10} aryl group,

(d) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(i) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(ii) a hydroxy group,

(iii) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, and

(iv) a halogen atom, and

(e) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(i) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(ii) a hydroxy group,

(iii) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms,

(iv) a halogen atom, and

(v) an oxo group;

(14) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom, and

(b) a C_{1-6} alkoxy group;

(15) a C_{6-10} arylsulfonyl group (e.g., phenylsulfonyl);

(16) a carbamoyl group optionally having 1 or 2 substituents selected from

(a) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, and

(b) a C_{6-10} aryl group;

(17) a thiocarbamoyl group optionally having 1 or 2 C_{1-6} alkyl groups optionally having 1 to 3 halogen atoms;

(18) a sulfamoyl group optionally having 1 or 2 C_{1-6} alkyl groups optionally having 1 to 3 halogen atoms;

(19) a C_{1-6} alkoxy group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a carboxy group,

(c) a C_{1-6} alkoxy group,

(d) a C_{1-6} alkoxy-carbonyl group optionally having 1 to 3 C_{6-10} aryl groups,

(e) an amino group optionally having 1 or 2 substituents selected from a C_{1-6} alkyl group and a C_{1-6} alkoxy-carbonyl group,

(f) a C_{3-8} cycloalkyl group,

(g) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(i) a halogen atom,

(ii) a hydroxy group,

(iii) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, and

(iv) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, and

(h) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group optionally having 1 to 3 substituents selected from

(i) a halogen atom,

(ii) a hydroxy group,

(iii) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(iv) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms, and

(v) an oxo group;

(20) a C_{2-6} alkenyloxy group (e.g., ethenyloxy) optionally having 1 to 3 halogen atoms;

(21) a C_{3-8} cycloalkyloxy group (e.g., cyclopropoxy,

cyclopentyloxy) optionally having 1 to 3 substituents selected from

(a) a halogen atom, and

(b) a C_{1-6} alkoxy group;

(22) a C_{6-10} aryloxy group (e.g., phenyloxy, naphthyloxy);

(23) a C_{7-13} aralkyloxy group (e.g., benzyloxy);

(24) a C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, tert-butylcarbonyloxy);

(25) a C_{6-10} aryl-carbonyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom, and

(b) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms;

(26) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclyl-carbonyl group (e.g., thienylcarbonyl, pyrazolylcarbonyl, pyrazinylcarbonyl, isoxazolylcarbonyl, pyridylcarbonyl, thiazolylcarbonyl) optionally having 1 to 3 substituents selected from a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms;

(27) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclyl-carbonyl group (e.g., pyrrolidinylcarbonyl, morpholinylcarbonyl) optionally having 1 to 3 substituents selected from a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms;

(28) a C_{3-8} cycloalkyl-carbonyl group;

(29) a C_{7-13} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl);

(30) a mercapto group;

(31) a C_{1-6} alkylthio group (e.g., methylthio, ethylthio) optionally having 1 to 3 substituents selected from

(a) a halogen atom, and

(b) a C_{1-6} alkoxy-carbonyl group;

(32) a C_{7-13} aralkylthio group (e.g., benzylthio);

(33) a C_{6-10} arylthio group (e.g., phenylthio, naphthylthio);

(34) a C_{1-3} alkyleneoxy group (e.g., methyleneoxy, ethyleneoxy);

and

(35) a C_{1-3} alkylenedioxy group (e.g., methylenedioxy, ethylenedioxy).

[0024]

In the present specification, examples of the substituent that the C_{2-6} alkenyl group of the "C_{2-6} alkenyl group optionally having substituent(s)" optionally has include substituents selected from the aforementioned Substituent A Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0025]

In the present specification, examples of the substituent that the C_{2-6} alkynyl group of the "C_{2-6} alkynyl group optionally having substituent(s)" optionally has include substituents selected the aforementioned Substituent A Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0026]

In the present specification, examples of the substituent that the C_{1-6} alkoxy group of the "C_{1-6} alkoxy group optionally having substituent(s)" optionally has include substituents selected from the aforementioned Substituent A Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0027]

In the present specification, examples of the substituent that the C_{1-6} alkyl-carbonyl group of the "C_{1-6} alkyl-carbonyl group optionally having substituent(s)" optionally has include substituents selected from the aforementioned Substituent A

Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0028]

In the present specification, examples of the substituent that the C_{6-10} aryl group of the "C_{6-10} aryl group optionally having substituent(s)" optionally has include substituents selected from the following Substituent B Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0029]

Substituent B Group:

(1) the substituent selected from the aforementioned Substituent A Group;

(2) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a carboxy group,

(d) a C_{1-6} alkoxy group,

(e) a C_{1-6} alkoxy-carbonyl group,

(f) an amino group optionally having 1 or 2 C_{1-6} alkyl groups, and

(g) a C_{6-10} aryl-carbonyl group;

(3) a C_{2-6} alkenyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a carboxy group,

(d) a C_{1-6} alkoxy group,

(e) a C_{1-6} alkoxy-carbonyl group, and

(f) an amino group optionally having 1 or 2 C_{1-6} alkyl groups; and

(4) a C_{7-13} aralkyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms, and

(d) a C_{1-6} alkoxy group.

[0030]

In the present specification, examples of the substituent that the C_{3-8} cycloalkyl group of the "C_{3-8} cycloalkyl group optionally having substituent(s)" optionally has include substituents selected from the following Substituent C Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0031]

Substituent C Group:

(1) the substituent selected from the aforementioned Substituent A Group;

(2) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a carboxy group,

(d) a C_{1-6} alkoxy group,

(e) a C_{1-6} alkoxy-carbonyl group,

(f) an amino group optionally having 1 or 2 C_{1-6} alkyl groups, and

(g) a C_{6-10} aryl-carbonyl group;

(3) a C_{2-6} alkenyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a carboxy group,

(d) a C_{1-6} alkoxy group,

(e) a C_{1-6} alkoxy-carbonyl group, and

(f) an amino group optionally having 1 or 2 C_{1-6} alkyl groups;

(4) a C_{7-13} aralkyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group optionally having 1 to 3 halogen atoms,

(d) a C_{1-6} alkoxy group; and

(5) an oxo group.

[0032]

In the present specification, examples of the substituent that the C_{6-10} aryl-carbonyl group of the "C_{6-10} aryl-carbonyl group optionally having substituent(s)" optionally has include substituents selected from the aforementioned Substituent B Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0033]

In the present specification, when the heterocyclic group of the "heterocyclic group optionally having substituent(s)" is an "aromatic heterocyclic group", examples of the substituent that the aromatic heterocyclic group optionally has include substituents selected from the aforementioned Substituent B Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0034]

In the present specification, when the heterocyclic group of the "heterocyclic group optionally having substituent(s)" is a "non-aromatic heterocyclic group", examples of the substituent that the non-aromatic heterocyclic group optionally has include substituents selected from the aforementioned Substituent C Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0035]

In the present specification, when the heterocyclyl-carbonyl group of the "heterocyclyl-carbonyl group optionally having substituent(s)" is an "aromatic heterocyclyl-carbonyl group", examples of the substituent that the aromatic heterocyclyl-carbonyl group optionally has include substituents selected from the aforementioned Substituent B Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0036]

In the present specification, when the heterocyclyl-carbonyl group of the "heterocyclyl-carbonyl group optionally having substituent(s)" is a "non-aromatic heterocyclyl-carbonyl group", examples of the substituent that the non-aromatic heterocyclyl-carbonyl group optionally has include substituents selected from the aforementioned Substituent C Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0037]

In the present specification, the "amino group optionally having substituent(s)" means, for example, an "amino group" optionally having 1 or 2 substituents selected from

(1) a C_{1-6} alkyl group optionally having substituent(s);

(2) a C_{2-6} alkenyl group optionally having substituent(s);

(3) a C_{2-6} alkynyl group optionally having substituent(s);

(4) a C_{1-6} alkoxy group optionally having substituent(s);

(5) a C_{1-6} alkyl-carbonyl group optionally having substituent(s);

(6) a C_{3-8} cycloalkyl group optionally having substituent(s);

(7) a C_{6-10} aryl group optionally having substituent(s);

(8) a C_{6-10} aryl-carbonyl group optionally having substituent(s);

(9) a heterocyclic group optionally having substituent(s);

(10) a heterocyclyl-carbonyl group optionally having substituent(s);

and the like.

When the "amino group optionally having substituent(s)" is an amino group having 2 substituents, these substituents optionally form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle. Specific examples of the nitrogen-containing heterocycle include a 5- to 7-membered nitrogen-containing heterocycle. The nitrogen-containing heterocycle optionally further has substituent(s). Examples of the substituent include substituents selected from the aforementioned Substituent C Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0038]

In the present specification, the "carbamoyl group optionally having substituent(s)" means, for example, a "carbamoyl group" optionally having 1 or 2 substituents

selected from

(1) a C_{1-6} alkyl group optionally having substituent(s);

(2) a C_{2-6} alkenyl group optionally having substituent(s);

(3) a C_{2-6} alkynyl group optionally having substituent(s);

(4) a C_{1-6} alkoxy group optionally having substituent(s);

(5) a C_{1-6} alkyl-carbonyl group optionally having substituent(s);

(6) a C_{3-8} cycloalkyl group optionally having substituent(s);

(7) a C_{6-10} aryl group optionally having substituent(s);

(8) a C_{6-10} aryl-carbonyl group optionally having substituent(s);

(9) a heterocyclic group optionally having substituent(s);

(10) a heterocyclyl-carbonyl group optionally having substituent(s);

and the like.

When the "carbamoyl group optionally having substituent(s)" is a carbamoyl group having 2 substituents, these substituents optionally form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle. Specific examples of the nitrogen-containing heterocycle include a 5- to 7-membered nitrogen-containing heterocycle. The nitrogen-containing heterocycle optionally further has substituent(s). Examples of the substituent include substituents selected from the aforementioned Substituent C Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0039]

In the present specification, the "optionally substituted hydroxy group" means, for example, a hydroxy group optionally substituted by a substituent selected from

(1) a C_{1-6} alkyl group optionally having substituent(s);

(2) a C_{2-6} alkenyl group optionally having substituent(s);

(3) a C_{2-6} alkynyl group optionally having substituent(s);

(4) a C_{1-6} alkyl-carbonyl group optionally having substituent(s);
(5) a C_{3-8} cycloalkyl group optionally having substituent(s);
(6) a C_{6-10} aryl group optionally having substituent(s);
(7) a C_{6-10} aryl-carbonyl group optionally having substituent(s);
(8) a heterocyclic group optionally having substituent(s);
(9) a heterocyclyl-carbonyl group optionally having substituent(s);
and the like.

[0040]

In the present specification, the "optionally substituted mercapto group" means, for example, a mercapto group optionally substituted by a substituent selected from
(1) a C_{1-6} alkyl group optionally having substituent(s);
(2) a C_{2-6} alkenyl group optionally having substituent(s);
(3) a C_{2-6} alkynyl group optionally having substituent(s);
(4) a C_{1-6} alkoxy group optionally having substituent(s);
(5) a C_{1-6} alkyl-carbonyl group optionally having substituent(s);
(6) a C_{3-8} cycloalkyl group optionally having substituent(s);
(7) a C_{6-10} aryl group optionally having substituent(s);
(8) a C_{6-10} aryl-carbonyl group optionally having substituent(s);
(9) a heterocyclic group optionally having substituent(s);
(10) a heterocyclyl-carbonyl group optionally having substituent(s);
and the like.

[0041]

In the present specification, the "cyclic group" of the "cyclic group optionally having substituent(s)" means, for example, a C_{3-8} cycloalkyl group, a group derived from a fused ring wherein a C_{3-8} cycloalkane and a benzene ring are condensed (e.g., indanyl, 1,2,3,4-tetrahydronaphthyl), a C_{6-10} aryl group, an aromatic heterocyclic group, a non-aromatic heterocyclic

group or the like.

[0042]

When the "cyclic group optionally having substituent(s)" is a C_{3-8} cycloalkyl group optionally having substituent(s), examples of the substituent that the C_{3-8} cycloalkyl group optionally has include substituents selected from the aforementioned Substituent C Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0043]

When the "cyclic group optionally having substituent(s)" is a group derived from a fused ring wherein a C_{3-8} cycloalkane and a benzene ring are condensed, which optionally has substituent(s), examples of the substituent that the fused ring group optionally has include substituents selected from the aforementioned Substituent C Group. The position of the substituent is not particularly limited as long as it is a substitutable position, and may be on the benzene ring moiety or C_{3-8} cycloalkane moiety. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0044]

When the "cyclic group optionally having substituent(s)" is a C_{6-10} aryl group optionally having substituent(s), examples of the substituent that the C_{6-10} aryl group optionally has include substituents selected from the aforementioned Substituent B Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0045]

When the "cyclic group optionally having substituent(s)" is an aromatic heterocyclic group optionally having substituent(s), Examples of the substituent that the aromatic heterocyclic group optionally has include substituents selected from the aforementioned Substituent B Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0046]

When the "cyclic group optionally having substituent(s)" is a non-aromatic heterocyclic group optionally having substituent(s), examples of the substituent that the non-aromatic heterocyclic group optionally has include substituents selected from the aforementioned Substituent C Group. While the number of the substituents is not particularly limited as long as it is a substitutable number, preferably 1 to 5, more preferably 1 to 3. When plural substituents are present, the respective substituents may be the same or different.

[0047]

In the formula (CI), X^C is NR^{C1}, a sulfur atom or an oxygen atom. R^{C1} is a hydrogen atom or a C_{1-6} alkyl group.

X^C is preferably NR^{C1} or a sulfur atom, more preferably NR^{C1}. R^{C1} is preferably a C_{1-6} alkyl group (e.g., methyl), more preferably methyl.

[0048]

In the formula (CI), R^{C2} is a carbamoyl group optionally having substituent(s).

R^{C2} is preferably a carbamoyl group optionally having 1 or 2 substituents selected from

(1) a C_{1-6} alkyl group optionally having substituent(s),

(2) a C_{2-6} alkynyl group optionally having substituent(s),

(3) a C_{3-8} cycloalkyl group optionally having substituent(s),

(4) a C_{6-10} aryl group optionally having substituent(s), and
(5) a heterocyclic group optionally having substituent(s).
[0049]

In one embodiment, R^{C2} is more preferably a carbamoyl group having one substituent selected from
(1) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group (e.g., piperidyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally having 1 to 3 substituents selected from
(a) a C_{1-6} alkyl group optionally having 1 to 3 hydroxy groups, and
(b) a C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups;
(2) a C_{3-8} cycloalkyl group (e.g., cyclohexyl) optionally having 1 to 3 hydroxy groups; and
(3) a C_{1-6} alkyl group (e.g., ethyl, propyl) having one substituent selected from
(a) a C_{1-6} alkylsulfonyl group (e.g., ethylsulfonyl) optionally having 1 to 3 C_{1-6} alkoxy groups (e.g., methoxy), and
(b) an amino group having one C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups.
[0050]

In another embodiment, R^{C2} is more preferably a carbamoyl group having 1 or 2 substituents selected from
(1) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group (e.g., morpholinyl, piperidyl, azepanyl) optionally having 1 to 3 substituents selected from
(a) a C_{1-6} alkyl group optionally having 1 to 3 hydroxy groups,
(b) a C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups, and
(c) an oxo group;
(2) a C_{3-8} cycloalkyl group (e.g., cyclopropyl, cyclopentyl,

cyclohexyl) optionally having 1 to 3 substituents selected from

(a) a hydroxy group,

(b) a C_{1-6} alkyl group (e.g., methyl) optionally having 1 to 3 hydroxy groups,

(c) a carbamoyl group,

(d) a cyano group,

(e) a C_{2-6} alkynyl group (e.g., ethynyl), and

(f) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group (e.g., thienyl);

(3) a C_{1-6} alkyl group (e.g., ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl) having one substituent selected from

(a) a C_{1-6} alkylsulfonyl group (e.g., ethylsulfonyl) optionally having 1 to 3 C_{1-6} alkoxy groups (e.g., methoxy),

(b) an amino group having one C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups,

(c) an amino group having 1 or 2 C_{1-6} alkyl groups (e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups,

(d) a C_{6-10} aryl group (e.g., phenyl) optionally having 1 to 3 C_{1-6} alkylsulfonyl groups (e.g., methylsulfonyl),

(e) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group (e.g., pyrrolidinyl, tetrahydrofuryl) optionally having 1 to 3 oxo groups,

(f) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group (e.g., furyl),

(g) a hydroxy group, and

(h) a C_{1-6} alkoxy group (e.g., methoxy);

(4) a C_{6-10} aryl group (e.g., phenyl) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom);

(5) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group (e.g., pyridyl); and

(6) a C_{2-6} alkynyl group (e.g., 2-propynyl).

[0051]

In the formula (CI), R^{C3} is a hydroxy group optionally

having a substituent.

R^{C3} is preferably an optionally halogenated C_{1-6} alkoxy group, more preferably a C_{1-6} alkoxy group (e.g., ethoxy, isopropoxy) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom).

[0052]

In the formula (CI), R^{C5} is a cyclic group optionally having substituent(s).

R^{C5} is preferably

(1) a C_{6-10} aryl group optionally having substituent(s), or

(2) a heterocyclic group optionally having substituent(s).

R^{C5} is more preferably

(1) a C_{6-10} aryl group (e.g., phenyl, naphthyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom), and

(c) a C_{1-6} alkoxy group (e.g., methoxy, isopropoxy); or

(2) a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl), and

(c) a C_{1-6} alkoxy group (e.g., methoxy).

R^{C5} is more preferably

(1) phenyl optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom), and

(c) a C_{1-6} alkoxy group (e.g., methoxy, isopropoxy).

[0053]

In the formula (CI), R^{C6} is a C_{1-6} alkyl group optionally having substituent(s).

R^{C6} is preferably a C_{1-6} alkyl group (e.g., methyl, ethyl).

[0054]

In the formula (CI), R^{C7} is a hydrogen atom, a halogen atom or a C_{1-6} alkyl group.

R^{C7} is preferably a hydrogen atom.

[0055]

Preferable specific examples of compound (CI) include the following compounds.

Compound (CI-1)

In the formula (CI), a compound wherein

X^C is NR^{C1} wherein R^{C1} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl), a sulfur atom or an oxygen atom (preferably X^C is NR^{C1}, and R^{C1} is methyl);

R^{C2} is a carbamoyl group optionally having 1 or 2 substituents selected from

(1) a C_{1-6} alkyl group optionally having substituent(s),

(2) a C_{2-6} alkynyl group optionally having substituent(s),

(3) a C_{3-8} cycloalkyl group optionally having substituent(s),

(4) a C_{6-10} aryl group optionally having substituent(s), and

(5) a heterocyclic group optionally having substituent(s);

R^{C3} is an optionally halogenated C_{1-6} alkoxy group;

R^{C5} is

(1) a C_{6-10} aryl group optionally having substituent(s), or

(2) a heterocyclic group optionally having substituent(s);

R^{C6} is a C_{1-6} alkyl group; and

R^{C7} is a hydrogen atom;

or a salt thereof.

[0056]

Compound (CI-2)

In the formula (CI), a compound wherein

X^C is NR^{C1}, a sulfur atom or an oxygen atom (preferably NR^{C1} or a sulfur atom);

R^{C1} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl) (preferably a C_{1-6} alkyl group (e.g., methyl));

R^{C2} is a carbamoyl group having one substituent selected from

(1) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group (e.g., piperidyl,

tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxidotetrahydrothiopyranyl, 1,1-dioxidotetrahydrothiopyranyl) optionally having 1 to 3 substituents selected from

(a) a C_{1-6} alkyl group optionally having 1 to 3 hydroxy groups, and

(b) a C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups;

(2) a C_{3-8} cycloalkyl group (e.g., cyclohexyl) optionally having 1 to 3 hydroxy groups; and

(3) a C_{1-6} alkyl group (e.g., ethyl, propyl) having one substituent selected from

(a) a C_{1-6} alkylsulfonyl group (e.g., ethylsulfonyl) optionally having 1 to 3 C_{1-6} alkoxy groups (e.g., methoxy), and

(b) an amino group having one C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups;

R^{C3} is a C_{1-6} alkoxy group (e.g., ethoxy, isopropoxy) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom);

R^{C5} is

(1) a C_{6-10} aryl group (e.g., phenyl, naphthyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom), and

(c) a C_{1-6} alkoxy group (e.g., methoxy, isopropoxy); or

(2) a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl), and

(c) a C_{1-6} alkoxy group (e.g., methoxy);

R^{C6} is a C_{1-6} alkyl group (e.g., methyl, ethyl); and

R^{C7} is a hydrogen atom;

or a salt thereof.

[0057]

Compound (CI-3)

In the formula (CI), a compound wherein

X^C is NR^{C1} wherein R^{C1} is methyl;

R^{C2} is a carbamoyl group having 1 or 2 substituents selected from

(1) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group (e.g., morpholinyl, piperidyl, azepanyl) optionally having 1 to 3 substituents selected from

(a) a C_{1-6} alkyl group optionally having 1 to 3 hydroxy groups,

(b) a C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups, and

(c) an oxo group;

(2) a C_{3-8} cycloalkyl group (e.g., cyclopropyl, cyclopentyl, cyclohexyl) optionally having 1 to 3 substituents selected from

(a) a hydroxy group,

(b) a C_{1-6} alkyl group (e.g., methyl) optionally having 1 to 3 hydroxy groups,

(c) a carbamoyl group,

(d) a cyano group,

(e) a C_{2-6} alkynyl group (e.g., ethynyl), and

(f) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group (e.g., thienyl);

(3) a C_{1-6} alkyl group (e.g., ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl) having one substituent selected from

(a) a C_{1-6} alkylsulfonyl group (e.g., ethylsulfonyl) optionally having 1 to 3 C_{1-6} alkoxy groups (e.g., methoxy),

(b) an amino group having one C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally having 1 to 3 hydroxy groups,

(c) an amino group having 1 or 2 C_{1-6} alkyl groups (e.g., methyl, ethyl) optionally having 1 to 3 hydroxy groups,

(d) a C_{6-10} aryl group (e.g., phenyl) optionally having 1 to 3 C_{1-6} alkylsulfonyl groups (e.g., methylsulfonyl),

(e) a 4- to 12-membered (preferably 4- to 7-membered) non-aromatic heterocyclic group (e.g., pyrrolidinyl, tetrahydrofuryl) optionally having 1 to 3 oxo groups,

(f) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group (e.g., furyl),

(g) a hydroxy group, and

(h) a C_{1-6} alkoxy group (e.g., methoxy);

(4) a C_{6-10} aryl group (e.g., phenyl) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom);

(5) a 5- to 12-membered (preferably 5- or 6-membered) aromatic heterocyclic group (e.g., pyridyl); and

(6) a C_{2-6} alkynyl group (e.g., 2-propynyl);

R^{C3} is a C_{1-6} alkoxy group (e.g., ethoxy, isopropoxy) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom);

R^{C5} is

(1) a C_{6-10} aryl group (e.g., phenyl, naphthyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom), and

(c) a C_{1-6} alkoxy group (e.g., methoxy, isopropoxy); or

(2) a 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl), and

(c) a C_{1-6} alkoxy group (e.g., methoxy)

(preferably

(1) phenyl optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(b) a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., a fluorine atom), and

(c) a C_{1-6} alkoxy group (e.g., methoxy, isopropoxy));

R^{C6} is a C_{1-6} alkyl group (e.g., methyl, ethyl); and

R^{C7} is a hydrogen atom;

or a salt thereof.

[0058]

Compound (CI-4)

6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide; or

3-ethoxy-6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

or a salt thereof.

[0059]

Examples of the salt in compound (CI) include metal salts, ammonium salts, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the like. Preferable examples of the metal salt include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; an aluminum salt and the like. Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include salts with arginine, lysine,

ornithine and the like, and preferable examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid and the like.

Of these, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, examples thereof include inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt etc., and when a compound has a basic functional group, examples thereof include salts with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or salts with organic acids such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

[0060]

The production method of the compound of the present invention is described in the following.

In each of the following production methods, when alkylation reaction, amidation reaction (condensation reaction), esterification reaction, reduction reaction, reductive amination reaction, amination reaction, halogenation reaction, oxidation reaction and the like are performed, these reactions are performed according to methods known per se. Examples of such methods include the methods described in Organic Functional Group Preparations, 2nd edition, Academic Press, Inc. (1989), Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like, and the like.

[0061]

In the following reaction, the starting compound or the intermediate may be in the form of a salt. Examples of the salt include those similar to the aforementioned salt of compound (CI).

The obtained compound in each step may be used in the

form of the reaction mixture or as a crude product for the next step, or may be isolated from the reaction mixture according to a conventional method (e.g., separation means such as recrystallization, distillation, chromatography etc.).

[0062]

In each of the above-mentioned reactions, when the starting compound has an amino group, a carboxyl group or a hydroxy group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained. The protection and deprotection are performed according to a method known per se, for example, the method described in Protective Groups in Organic Synthesis, 3rd edition, John Wiley and Sons, Inc. (1999).

Examples of the amino-protecting group include a formyl group, a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group, a benzoyl group, a C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), a C_{7-14} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), a trityl group, a phthaloyl group, an N,N-dimethylaminomethylene group, a substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a C_{2-6} alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkoxy group and a nitro group.

Examples of the carboxy-protecting group include a C_{1-6} alkyl group, a C_{7-11} aralkyl group (e.g., benzyl), a phenyl group, a trityl group, a substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a C_{2-6} alkenyl group (e.g., 1-allyl) and the like.

Examples of the hydroxy-protecting group include a C_{1-6} alkyl group, a phenyl group, a trityl group, a C_{7-10} aralkyl

group (e.g., benzyl), a formyl group, a C_{1-6} alkyl-carbonyl group, a benzoyl group, a C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), a 2-tetrahydropyranyl group, a 2-tetrahydrofuranyl group, a substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a C_{2-6} alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group and a nitro group.

[0063]

The solvents indicated in generic terms, which are used in the following reactions are explained in the following.

Examples of the "alcohols" include methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like.

Examples of the "ethers" include diethyl ether, diisopropyl ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like.

Examples of the "esters" include ethyl acetate, methyl acetate, tert-butyl acetate and the like.

Examples of the "hydrocarbons" include benzene, toluene, xylene, cyclohexane, hexane, pentane and the like.

Examples of the "amides" include N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like.

Examples of the "halogenated hydrocarbons" include dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethylene, chlorobenzene and the like.

Examples of the "nitriles" include acetonitrile, propionitrile and the like.

Examples of the "ketones" include acetone, 2-butanone and the like.

Examples of the "organic acids" include formic acid, acetic acid, propionic acid, trifluoroacetic acid,

methanesulfonic acid and the like.

Examples of the "aromatic amines" include pyridine, 2,6-lutidine, quinoline and the like.

Examples of the "sulfoxides" include dimethyl sulfoxide and the like.

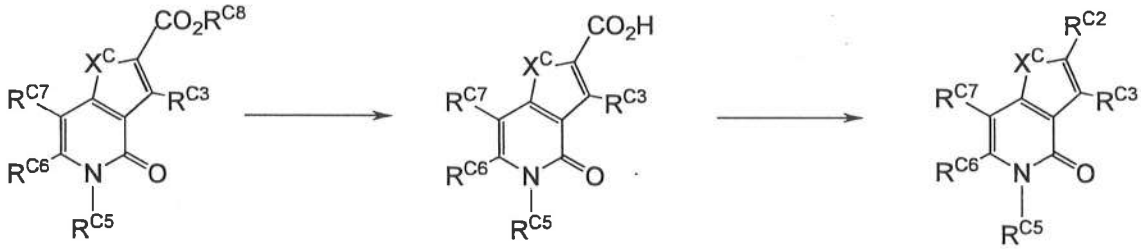
[0064]

Compound (CI) can be produced, for example, according to the following [Method CA] or a method analogous thereto.

[Method CA]

Compound (CI) can be produced by subjecting compound (CIII) to hydrolysis, and then condensing the obtained compound (CII) with an amine.

[0065]



(CIII) (CII) (CI)

[0066]

wherein R^{C8} is a C_{1-6} alkyl group or a C_{7-13} aralkyl group, and other symbols are as defined above.

R^{C8} is preferably ethyl.

[0067]

The reaction from compound (CIII) to compound (CII) can be carried out by subjecting compound (CIII) to hydrolysis in the presence of an acid or a base, in a solvent that does not adversely influence the reaction.

Particularly, when R^{C8} is benzyl, the reaction can also be carried out by subjecting compound (CIII) to a catalytic hydrogenation reaction in a solvent that does not adversely influence the reaction.

Examples of the acid include hydrochloric acid, sulfuric acid and the like.

Examples of the base include sodium hydroxide, potassium

hydroxide, lithium hydroxide and the like.

The amount of the acid or base to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (CIII).

Examples of the catalyst used for the catalytic hydrogenation reaction include Raney-nickel; platinum oxide; palladium, ruthenium, rhodium or iridium, which is supported on activated carbon, barium sulfate, calcium carbonate or the like; and the like.

The amount of the catalyst to be used is generally 0.01 to 1 mol, preferably 0.05 to 0.5 mol, per 1 mol of compound (CIII).

Examples of the hydrogen source include hydrogen, cyclohexene, hydrazine, ammonium formate and the like.

Examples of the solvent that does not adversely influence the reaction include ethers, alcohols, hydrocarbons, ketones, nitriles, amides, esters, organic acids, water and the like, and alcohols, ethers and water are particularly preferable. These solvents may be used in a mixture of two or more kinds thereof in an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0068]

The reaction from compound (CII) to compound (CI) can be carried out by condensing compound (CII) with an amine compound corresponding to R^{C2} using a condensing agent in a solvent that does not adversely influence the reaction. Where necessary, a base such as a tertiary amine and the like may be added.

Examples of the condensing agent include carbodiimides (e.g., dicyclohexylcarbodiimide (DCCD), water-soluble carbodiimide (WSCD)), phosphates (e.g., diethyl cyanophosphonate, diethyl chlorophosphonate,

diphenylphosphoryl azide), BOP reagents (e.g., 1H-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP)), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), carbonyldiimidazole and the like, and WSCD and HATU are particularly preferable.

The amount of the amine corresponding to R^{C2} to be used is generally 1 to 10 mol, preferably 1 to 2 mol, per 1 mol of compound (CII).

The amount of the condensing agent to be used is generally 1 to 10 mol, preferably 1 to 2 mol, per 1 mol of compound (CII).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, ketones, nitriles, amides, esters and the like, and ethers and amides are particularly preferable. These solvents may be used in a mixture of two or more kinds thereof in an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

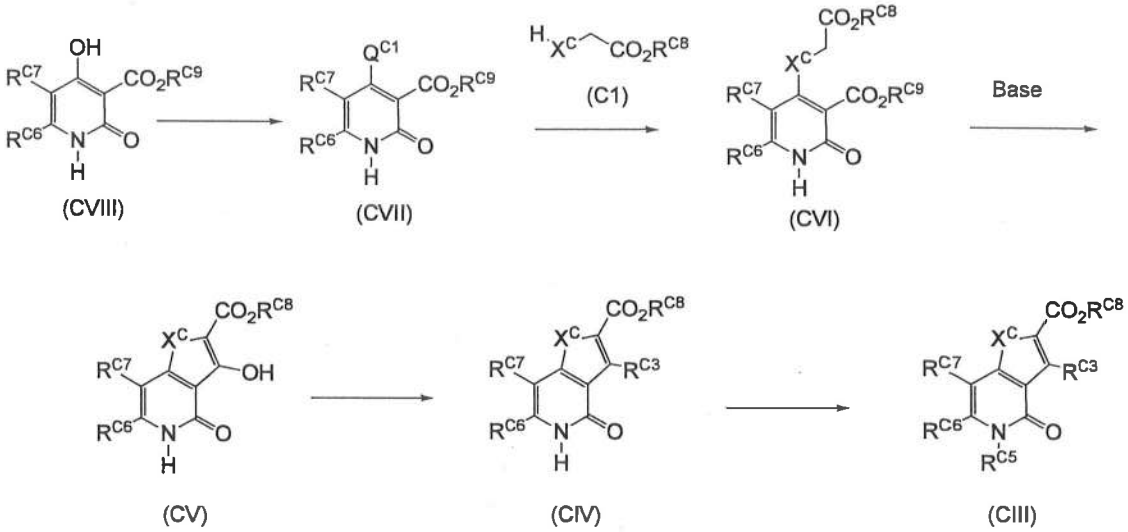
The amine corresponding to R^{C2} may be commercially available product, or can be produced from the corresponding starting compound according to a method known per se.

[0069]

Compound (CIII) can be produced, for example, according to the following [Method CB] or a method analogous thereto.

[Method CB]

[0070]



[0071]

wherein Q^{C1} is a leaving group, R^{C9} is a C_{1-6} alkyl group, and other symbols are as defined above.

Examples of the leaving group for Q^{C1} include a halogen atom, a C_{1-6} alkylsulfonyloxy group optionally having 1 to 3 halogen atoms (e.g., methylsulfonyloxy, ethylsulfonyloxy, trifluoromethylsulfonyloxy), a C_{6-10} arylsulfonyloxy group optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., benzenesulfonyloxy, 4-toluenesulfonyloxy), a methylmercapto group, a methanesulfonyl group and the like, and a halogen atom is particularly preferable.

[0072]

The conversion of the hydroxy group of compound (CVIII) to the leaving group Q^{C1} can be carried out using a halogenating reagent in a solvent that does not adversely influence the reaction or without solvent, in the presence of a base, as necessary.

Examples of the halogenating reagent include thionyl chloride, phosphoryl chloride, phosphorus pentachloride, phosphorus tribromide and the like.

The amount of the halogenating reagent to be used is generally 1 to 20 mol, preferably 2 to 10 mol, per 1 mol of compound (CVIII).

Examples of the base include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and

the like.

The amount of the base to be used is generally 1 to 20 mol, preferably 2 to 10 mol, per 1 mol of compound (CVIII).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used. This reaction is preferably carried out without solvent.

The reaction temperature is generally 0 to 130°C, preferably 20 to 130°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0073]

Alternatively, the conversion of the hydroxy group of compound (CVIII) to the leaving group Q^{C1} can be carried out using a sulfonylating reagent in a solvent that does not adversely influence the reaction or without solvent, in the presence of a base, as necessary.

Examples of the sulfonylating reagent include trifluoromethanesulfonic anhydride, methanesulfonyl halides optionally having 1 to 3 halogen atoms, benzenesulfonyl halides optionally having 1 to 3 C_{1-6} alkyl groups, and the like.

The amount of the sulfonylating reagent to be used is generally 1 to 2 mol, preferably 1 to 1.5 mol, per 1 mol of compound (CVIII).

Examples of the base include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like.

The amount of the base to be used is generally 2 to 5 mol, preferably 2 to 3 mol, per 1 mol of compound (CVIII).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, and ethers and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally -10 to 100°C, preferably 0 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0074]

The reaction of compound (CVII) with compound (C1) can be carried out in a solvent that does not adversely influence the reaction, in the presence of a base, as necessary.

The amount of compound (C1) to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (CVII).

Examples of the base include sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like.

The amount of the base to be used is generally 2 to 20 mol, preferably 2 to 15 mol, per 1 mol of compound (CVII).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, and ethers and amides are particularly preferable. These solvents may be used in a mixture of two or more kinds thereof in an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

Compound (C1) can be synthesized according to a method known per se, or can be directly used commercially available product.

[0075]

The reaction from compound (CVI) to compound (CV) can be carried out by reacting compound (CVI) with a base in a solvent that does not adversely influence the reaction.

Examples of the base include sodium methoxide, sodium ethoxide, sodium hydroxide, triethylamine and the like.

The amount of the base to be used is generally 2 to 5 mol, preferably 2 to 3 mol, per 1 mol of compound (CVI).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, and ethers and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

Compound (CV) can also be obtained directly from compound (CVII) without isolation of compound (CVI).

[0076]

The reaction from compound (CV) to compound (CIV) can be carried out by reacting compound (CV) with a halide, sulfate, sulfonate or the like, which corresponds to the "substituent" of the "optionally substituted hydroxy group" for R^{C3}, in the presence of a base, in a solvent that does not adversely influence the reaction. The hydroxy group of compound (CV) is converted to R^{C3} by the reaction.

The above-mentioned halide, sulfate, sulfonate or the like may be commercially available product, or can be produced from the corresponding starting material compound according to a method known per se.

The amount of the above-mentioned halide, sulfate, sulfonate or the like to be used is generally 1 to 3 mol, preferably 1 to 2 mol, per 1 mol of compound (CV).

Examples of the base include sodium methoxide, sodium ethoxide, cesium carbonate, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like.

The amount of the base to be used is generally 2 to 5 mol,

preferably 2 to 3 mol, per 1 mol of compound (CV).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, esters and the like, and ethers, amides and ketones are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0077]

The reaction from compound (CIV) to compound (CIII) can be carried out by reacting compound (CIV) with a halide, boronic acid or borate corresponding to R^{C5}, in a solvent that does not adversely influence the reaction.

Specifically, compound (CIV) is reacted with a halide, boronic acid or borate corresponding to R^{C5}, a copper compound (e.g., copper powder, copper(I) iodide, copper(I) chloride, copper oxide, copper(II) acetate and the like) and a base (e.g., potassium carbonate, potassium phosphate, triethylamine, pyridine).

Alternatively, compound (CIV) is reacted with a halide corresponding to R^{C5}, a palladium compound (e.g., tris(dibenzylideneacetone)dipalladium(0), palladium(II) acetate), a ligand (e.g., 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene) and a base (e.g., cesium carbonate, sodium t-butoxide).

The amount of the halide, boronic acid or borate corresponding to R^{C5} to be used is generally 1 to 5 mol, preferably 1 to 3 mol, per 1 mol of compound (CIV).

The amount of the copper compound to be used is generally 0.01 to 1 mol, preferably 0.1 to 0.5 mol, per 1 mol of compound (CIV).

The amount of the palladium compound to be used is

generally 0.01 to 1 mol, preferably 0.1 to 0.5 mol, per 1 mol of compound (CIV).

The amount of the ligand to be used is generally 0.01 to 1 mol, preferably 0.1 to 0.5 mol, per 1 mol of compound (CIV).

The amount of the base to be used is generally 1 to 5 mol, preferably 1 to 3 mol, per 1 mol of compound (CIV).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, and ethers and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0078]

The halide, boronic acid or borate corresponding to R^{C5} may be commercially available product, or can be produced from the corresponding starting material compound according to a method known per se.

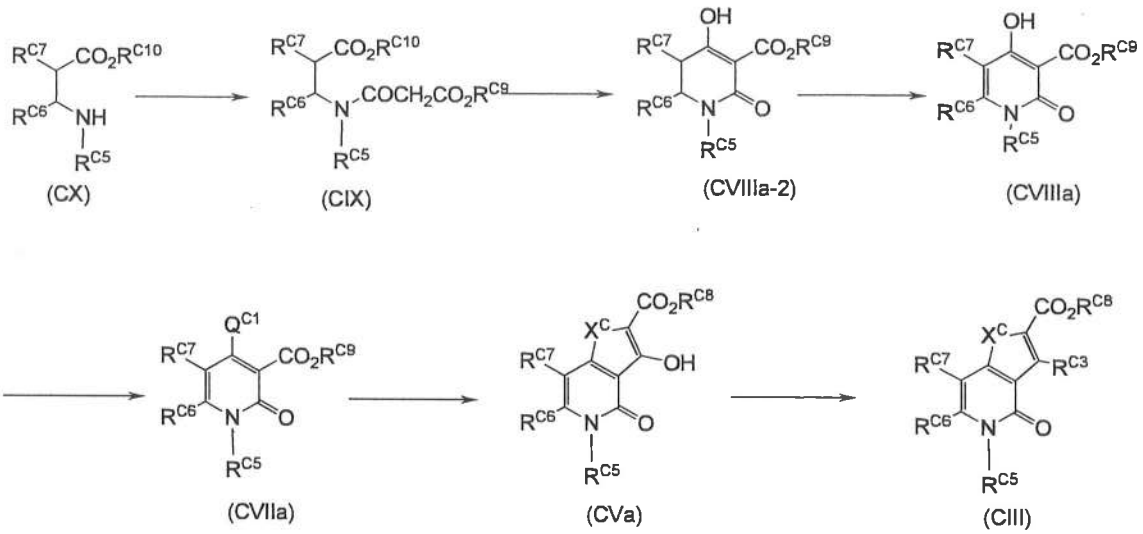
Compound (CVIII) can be synthesized according to a method known per se (e.g., the method described in Journal of Organic Chemistry, vol. 46, pages 3040-3048, 1981).

[0079]

Compound (CIII) can also be produced, for example, according to the following [Method CC] or a method analogous thereto.

[Method CC]

[0080]



[0081]

wherein R^{C10} is a C_{1-6} alkyl group, and other symbols are as defined above.

[0082]

The reaction from compound (CX) to compound (CIX) can be carried out using a malonic acid monoester corresponding to R^{C9} and a condensing agent, or using an acid halide corresponding to R^{C9} such as ethyl (chloroformyl)acetate and the like, in a solvent that does not influence the reaction, in the presence of a base, as necessary.

Examples of the condensing agent include those exemplified in [Method CA].

The amount of the condensing agent to be used is generally 1 to 10 mol, preferably 1 to 2 mol, per 1 mol of compound (CX).

The amount of the malonic acid monoester corresponding to R^{C9} to be used is generally 1 to 10 mol, preferably 1 to 2 mol , per 1 mol of compound (CX).

The amount of the acid halide corresponding to R^{C9} to be used is generally 1 to 10 mol, preferably 1 to 2 mol, per 1 mol of compound (CX).

Examples of the base include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like.

The amount of the base to be used is generally 1 to 10

mol, preferably 1 to 2 mol, per 1 mol of compound (CX).

Examples of the solvent that does not influence the reaction include ethers, hydrocarbons, amides, esters and the like, and ethers and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 100°C, preferably 0 to 50°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

The malonic acid monoester corresponding to R^{C9} may be commercially available product, or can be produced from the corresponding starting material compound according to a method known per se.

The acid halide corresponding to R^{C9} may be commercially available product, or can be produced from the corresponding starting material compound according to a method known per se.

[0083]

The reaction from compound (CIX) to compound (CVIIIa-2) can be carried out by reacting compound (CIX) with a base in a solvent that does not influence the reaction.

Examples of the base include sodium methoxide, sodium ethoxide, cesium carbonate, sodium carbonate, sodium hydroxide, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like.

The amount of the base to be used is generally 1 to 5 mol, preferably 1 to 3 mol, per 1 mol of compound (CIX).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, esters and the like, and ethers, alcohols and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably

1 to 48 hr.

[0084]

The reaction from compound (CVIIIa-2) to compound (CVIIIa) can be carried out by reacting compound (CVIIIa-2) with an oxidant in a solvent that does not influence the reaction.

Examples of the oxidant include ceric ammonium nitrate (CAN), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), bromine and the like.

The amount of the oxidant to be used is generally 1 to 5 mol, preferably 1 to 3 mol, per 1 mol of compound (CVIIIa-2).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, esters and the like, and hydrocarbons, nitriles and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 120°C, preferably 20 to 100°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0085]

The reaction from compound (CVIIIa) to compound (CVIIa) can be carried out according to the reaction from compound (CVIII) to compound (CVII) shown in [Method CB].

The reaction from compound (CVIIa) to compound (CVa) can be carried out according to the reaction from compound (CVII) to compound (CV) shown in [Method CB].

The reaction from compound (CVa) to compound (CIII) can be carried out according to the reaction from compound (CV) to compound (CIV) shown in [Method CB].

[0086]

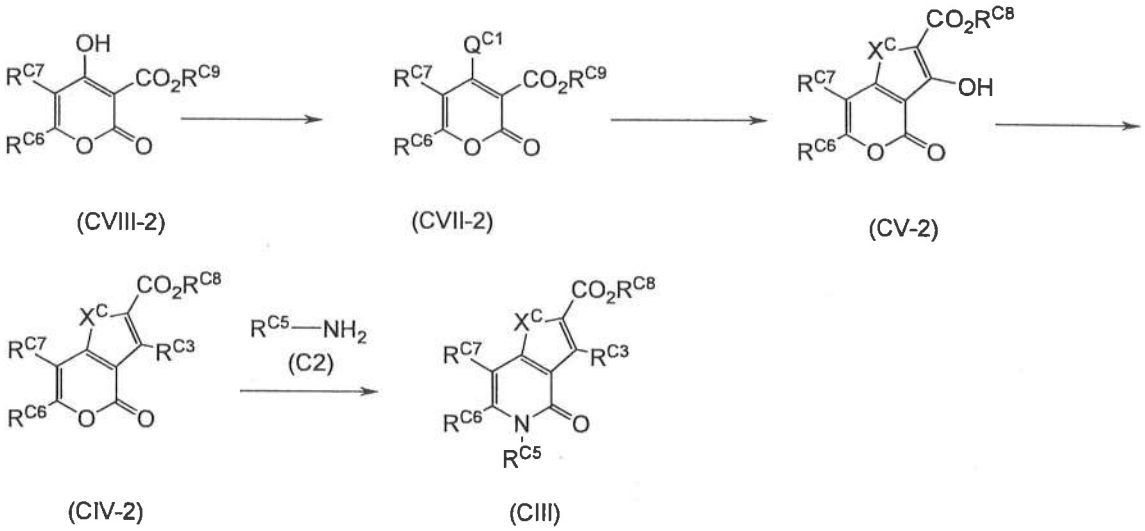
Compound (CX) can be synthesized according to a method known per se (e.g., the method described in Journal of Organic Chemistry, vol. 59, pages 5328-5335, 1994) and the like.

[0087]

Compound (CIII) can also be produced, for example, according to the following [Method CD] or a method analogous thereto.

[Method CD]

[0088]



[0089]

wherein each symbol is as defined above.

[0090]

The reaction from compound (CVIII-2) to compound (CVII-2) can be carried out according to the reaction from compound (CVIII) to compound (CVII) shown in [Method CB].

The reaction from compound (CVII-2) to compound (CV-2) can be carried out according to the reaction from compound (CVII) to compound (CV) shown in [Method CB].

The reaction from compound (CV-2) to compound (CIV-2) can be carried out according to the reaction from compound (CV) to compound (CIV) shown in [Method CB].

[0091]

The reaction from compound (CIV-2) to compound (CIII) can be carried out by reacting compound (CIV-2) with compound (C2) in a solvent that does not influence the reaction, in the presence of an acid, as necessary.

The amount of compound (C2) to be used is generally 1 to 30 mol, preferably 1 to 20 mol, per 1 mol of compound (CIV-2).

Examples of the acid include p-toluenesulfonic acid, acetic acid, trifluoroacetic acid and the like.

The amount of the acid to be used is generally 1 to 40 mol, preferably 1 to 30 mol, per 1 mol of compound (CIV-2).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, esters and the like, and hydrocarbons, nitriles and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 200°C, preferably 20 to 160°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0092]

Compound (CVIII-2) can be synthesized according to a method known per se (e.g., the method described in Journal of Organic Chemistry, vol. 52, pages 5275-5276, 1987, or the method described in Synthesis, pages 652-653, 1975) and the like.

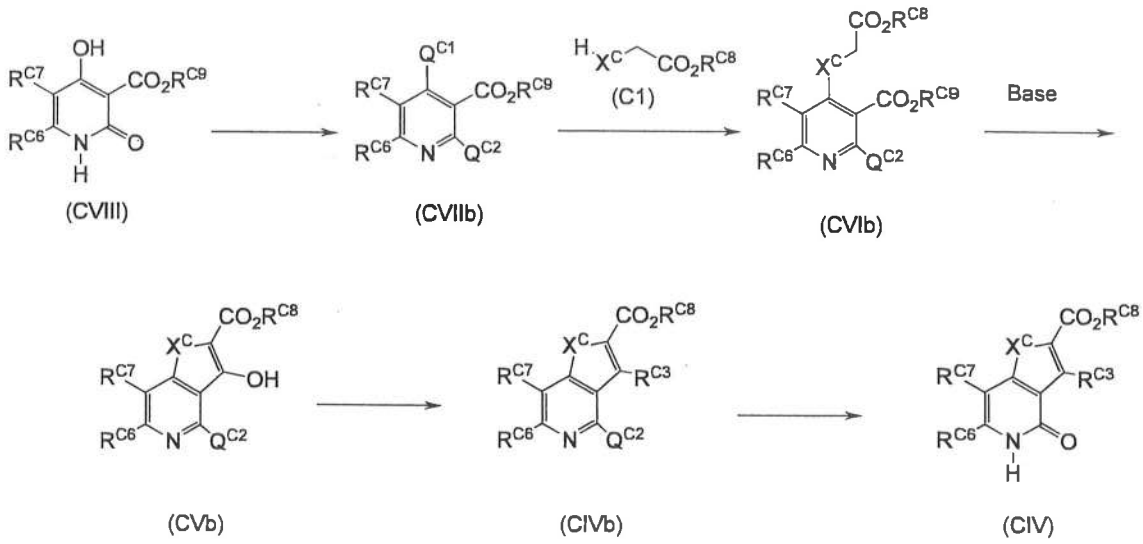
Compound (C2) may be commercially available product, or can be synthesized according to a method known per se (e.g., the method described in Organic Functional Group Preparations 2nd edition, Academic Press, Inc. 1989, Comprehensive Organic Transformations, VCH Publishers Inc., 1989, or the like).

[0093]

Compound (CIV) can also be produced, for example, according to the following [Method CE] or a method analogous thereto.

[Method CE]

[0094]



[0095]

wherein Q^{C2} is a leaving group, and other symbols are as defined above.

Examples of the "leaving group" for Q^{C2} include those similar to the "leaving group" for Q^{C1}, and a halogen atom is particularly preferable.

[0096]

The reaction from compound (CVIII) to compound (CVIIb) can be carried out using a halogenating reagent in a solvent that does not adversely influence the reaction or without solvent, in the presence of a base, as necessary.

Examples of the halogenating reagent include thionyl chloride, phosphoryl chloride, phosphorus pentachloride, phosphorus tribromide and the like.

The amount of the halogenating reagent to be used is generally 2 to 40 mol, preferably 3 to 20 mol, per 1 mol of compound (CVIII).

Examples of the base include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like.

The amount of the base to be used is generally 1 to 40 mol, preferably 2 to 20 mol, per 1 mol of compound (CVIII).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides,

esters and the like. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used. This reaction is preferably carried out without solvent.

The reaction temperature is generally 0 to 130°C, preferably 20 to 130°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0097]

Alternatively, the reaction from compound (CVIII) to compound (CVIIb) can be carried out using a sulfonylating reagent, in a solvent that does not adversely influence the reaction or without solvent, in the presence of a base, as necessary.

Examples of the sulfonylating reagent include trifluoromethanesulfonic anhydride, methanesulfonyl halides optionally having 1 to 3 halogen atoms, benzenesulfonyl halides optionally having 1 to 3 C_{1-6} alkyl groups, and the like.

The amount of the sulfonylating reagent to be used is generally 2 to 40 mol, preferably 3 to 20 mol, per 1 mol of compound (CVIII).

Examples of the base include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like.

The amount of the base to be used is generally 2 to 5 mol, preferably 2 to 3 mol, per 1 mol of compound (CVIII).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, and ethers and amides are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally -10 to 100°C, preferably 0 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0098]

The reaction from compound (CVIIb) to compound (CVIb) can be carried out according to the reaction from compound (CVII) to compound (CVI) shown in [Method CB].

The reaction from compound (CVIb) to compound (CVb) can be carried out according to the reaction from compound (CVI) to compound (CV) shown in [Method CB].

The reaction from compound (CVb) to compound (CIVb) can be carried out according to the reaction from compound (CV) to compound (CIV) shown in [Method CB].

[0099]

The reaction from compound (CIVb) to compound (CIV) can be carried out by subjecting compound (CIVb) to hydrolysis in a solvent that does not adversely influence the reaction.

The hydrolysis can be carried out in the presence of an acid or a base. From among, an acid is preferable.

Examples of the acid include hydrochloric acid, sulfuric acid and the like.

Examples of the base include sodium hydroxide, potassium hydroxide, lithium hydroxide and the like.

The amount of the acid or base to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (CIVb).

The hydrolysis can also be carried out using a combination of an organic acid salt and an organic acid, such as a combination of sodium acetate and acetic acid.

The amount of the organic acid salt to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (CIVb).

Examples of the solvent that does not adversely influence the reaction include ethers, alcohols, hydrocarbons, ketones, nitriles, amides, esters, organic acids, water and the like, and organic acids, alcohols, ethers and water are particularly preferable. Two or more kinds of the above-mentioned solvents may mixed in an appropriate ratio and used.

The reaction temperature is generally 0 to 130°C,

preferably 20 to 100°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0100]

Compound (CI) can also be produced, when desired, by a combination of the above-mentioned reaction and each or two more of known hydrolysis, deprotection, acylation reaction, alkylation reaction, oxidation reaction, cyclization reaction, carbon chain extension reaction and substituent exchange reaction.

[0101]

Compound (CI) can be isolated and purified by a means known *per se*, such as phase transfer, concentration, solvent extraction, fractionation, liquid conversion, crystallization, recrystallization, chromatography and the like. When compound (CI) is obtained as a free compound, it can be converted to a desired salt by a method known *per se* or a method analogous thereto. Conversely, when the compound is obtained as a salt, it can be converted to a free form or other desired salt by a method known *per se* or a method analogous thereto.

[0102]

A compound within the scope of the present invention can also be produced by applying a means known *per se* to compound (CI) for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to amino by hydrolysis of amide, conversion to carboxy by hydrolysis of ester, conversion to carbamoyl by amidation of carboxy, conversion to hydroxymethyl by reduction of carboxy, conversion to alcohol compound by reduction or alkylation of carbonyl, reductive amination of carbonyl, oximation of carbonyl, acylation, ureation, sulfonylation or alkylation of amino, substitution and amination of active halogen by amine, amination by reduction of nitro, alkylation of hydroxy, substitution and amination of hydroxy and the like. When a reactive substituent

that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can also be produced.

[0103]

Compound (CI) may be used as a prodrug. A prodrug of compound (CI) means a compound converted to compound (CI) by a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound converted to compound (CI) by oxidation, reduction, hydrolysis, etc. due to an enzyme, a compound converted to compound (CI) by hydrolysis etc. due to gastric acid, and the like.

[0104]

Examples of the prodrug of compound (CI) include a compound obtained by subjecting amino in compound (CI) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting amino in compound (CI) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting hydroxy in compound (CI) to acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting hydroxy in the compound (CI) to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminoacethylation); a compound obtained by subjecting carboxy in compound (CI) to esterification or amidation (e.g., a compound obtained by subjecting carboxy in compound (CI) to ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification,

pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation) and the like. Any one of these compounds can be produced from compound (CI) by a method known *per se*.

[0105]

A prodrug of compound (CI) may also be a compound converted into compound (CI) under physiological conditions, such as those described in IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

[0106]

When compound (CI) has an isomer such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, any isomer and a mixture thereof are encompassed in compound (CI). For example, when compound (CI) has an optical isomer, an optical isomer resolved from a racemate is also encompassed in compound (CI). Such isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

[0107]

Compound (CI) may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (CI). Crystals can be produced by crystallization according to crystallization methods known *per se*.

Compound (CI) may also be a cocrystal.

Compound (CI) may be a hydrate, a non-hydrate, a solvate or a non-solvate.

A compound labeled with an isotope (e.g., ^{2}H, ^{3}H, ^{14}C, ^{35}S, ^{125}I etc.) is also encompassed in compound (CI).

Compound (CI) may be a deuterium conversion.

[0108]

Compound (CI) or a prodrug thereof (sometimes to be

abbreviated as "the compound of the present invention" in the present specification) interacts, for example, with human Smo protein and changes the steric structure thereof, whereby formation of a complex with a protein involved in the signal transduction in the cytoplasm is inhibited and the Hedgehog signal transduction system is inhibited. Alternatively, the compound of the present invention interacts with human Smo protein and directly inhibits formation of a complex of human Smo protein with a protein involved in the Hedgehog signal transduction system in the cytoplasm, whereby the Hedgehog signal transduction system is inhibited. Alternatively, the compound of the present invention interacts with a site of an Smo protein, for example, phosphorylation site and the like, which is modified by a protein involved in the Hedgehog signal transduction system, whereby modification such as phosphorylation of Smo and the like is inhibited and the Hedgehog signal transduction system is inhibited.

Inhibition of the Hedgehog signal transduction system can be measured, for example, by quantifying a decrease in the expression level of a reporter gene connected to the downstream of the Gli binding site based on the fluorescence intensity according to the following Experimental Example 1. Alternatively, it can be measured by quantifying the expression of Gli-1 mRNA in a cell extract by quantitative PCR method and the like. A compound that inhibits Hedgehog signal targets Smo, which can be confirmed, for example, by binding fluorescence-labeled Cyclopamine and a test compound to cells expressing Smo, measuring the fluorescence level of the cell, and comparing the value with that without addition of a test compound to find a decrease.

[0109]

Accordingly, the compound of the present invention is useful as an Smo inhibitor for mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human). The compound of the present invention is used as a medicament of

diseases possibly influenced by Smo, for example, cancer [e.g., colorectal cancer (e.g., colorectal cancer, rectal cancer, anal cancer, familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor), pharyngeal cancer, laryngeal cancer, esophageal cancer, esophagus cancer, gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous cancer), duodenal cancer, small intestinal cancer, breast cancer (e.g., invasive ductal breast carcinoma, ductal cancer in situ, inflammatory breast cancer), ovarian cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor), testicular tumor, prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer), liver cancer (e.g., hepatocellular carcinoma, primary liver cancer, bile duct cancer, extrahepatic bile duct cancer), thyroid cancer (e.g., medullary thyroid cancer), kidney cancer (e.g., renal cell carcinoma, renal pelvis and ureter transitional cell cancer), uterine cancer (e.g., cervical cancer, cancer of uterine body, uterine sarcoma), brain tumor (e.g., medulloblastoma, glioma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, pituitary adenoma), retinoblastoma, skin cancer (e.g., basal cell carcinoma, malignant melanoma), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma), malignant bone tumor, urinary bladder cancer, hematologic cancer (e.g., multiple myeloma, leukemia, malignant lymphoma, Hodgkin's disease, chronic myeloproliferative disorder), cancer unknown primary], a cancer growth inhibitor, a cancer metastasis inhibitor, an apoptosis promoter and the like.

Among these, the compound of the present invention is effective, for example, for brain tumor, skin cancer, lung cancer, pancreatic cancer, biliary tract cancer, prostate

cancer, esophagus cancer, gastric cancer, colorectal cancer, sarcoma and breast cancer.

Especially, the compound of the present invention is effective for glioma, medulloblastoma, basal cell tumor, small cell lung cancer, pancreatic cancer, biliary tract cancer, prostate cancer, esophagus cancer, gastric cancer, colorectal cancer, rhabdomyosarcoma and breast cancer.

[0110]

The compound of the present invention can be administered orally or parenterally as it is or in a mixture with a pharmacologically acceptable carrier.

The dosage form of the compound of the present invention for oral administration is, for example, tablet (including sugar-coated tablet, film-coated tablet), pill, granule, powder, capsule (including soft capsule, microcapsule), syrup, emulsion, suspension and the like, and the dosage form for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to make a sustained release preparation by combining the compound with a suitable base (e.g., polymer of butyric acid, polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of a polymer of butyric acid and a polymer of glycolic acid, polyglycerol fatty acid ester etc.).

[0111]

As a method for producing the compound of the present invention in the above-mentioned dosage form, a known production method generally used in the pertinent field can be employed. When the above-mentioned dosage form is produced, suitable amounts of additives such as excipient, binder, disintegrant, lubricant, sweetening agent, surfactant, suspending agent, emulsifier and the like, generally used in the pharmaceutical field, are appropriately added as necessary for production.

[0112]

When the compound of the present invention is prepared into a tablet, for example, it can be produced by adding an

excipient, a binder, a disintegrant, a lubricant and the like, and when a pill or a granule is to be prepared, it can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder or a capsule is to be prepared, it can be produced by adding an excipient and the like, when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

[0113]

Examples of the excipient include lactose, sucrose, glucose, starch, sucrose, crystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binder include 5 to 10 wt% starch liquid paste, 10 to 20 wt% gum arabic solution or gelatin solution, 1 to 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate, stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, bentonite and the like.

Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

[0114]

Furthermore, when the compound of the present invention is

produced in the above-mentioned dosage form, a suitable amount of a colorant, a preservative, an aromatic, a corrigent, a stabilizer, a thickening agent and the like typically used in the field of preparation can be added on demand.

[0115]

As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection, intramuscular injection, instillation and the like are mentioned, and as the sustained release preparation, an iontophoresis transdermal agent and the like are mentioned.

[0116]

Such injections are prepared by methods known *per se*, or by dissolving, suspending or emulsifying the compound of the present invention in a sterilized aqueous or oily liquid. As an aqueous liquid for injection, physiological saline, isotonic solutions containing glucose or other auxiliary drugs (e.g., D-sorbitol, D-mannitol, sodium chloride) and the like, and they can be used in combination with suitable solubilizing agents, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol), nonionic surfactants (e.g., polysorbate 80, HCO-50) and the like. As an oily liquid, sesame oil, soybean oil and the like, which may be used in combination with solubilizing agents such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate buffer), soothing agents (e.g., benzalkonium chloride, procaine hydrochloride), stabilizers (e.g., human serum albumin, polyethylene glycol), preservatives (e.g., benzyl alcohol, phenol) and the like can be blended. A prepared injection is generally filled in an ampoule.

[0117]

While the content of the compound of the present invention in the medicament of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 0.01 to 100 wt%, preferably about 2 to 85 wt%, more preferably about 5 to 70 wt%, relative to the entire preparation.

[0118]

While the content of the additive in the medicament of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 1 to 99.9 wt%, preferably about 10 to 90 wt%, relative to the entire preparation.

[0119]

The compound of the present invention is stable and low toxic, and can be used safely. While the daily dose varies depending on the condition and body weight of patients, the kind of compound, administration route and the like, in the case of, for example, oral administration to patients for the treatment of cancer, the daily dose to an adult (body weight about 60 kg) is about 1 to 1000 mg, preferably about 3 to 300 mg, more preferably about 10 to 200 mg, as an active ingredient (the compound of the present invention), which can be given in a single administration or administered in 2 or 3 portions a day.

[0120]

When the compound of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). While the dose varies depending on the subject of administration, target organ, symptom, administration method and the like, it is, for example, about 0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg, in the form of an injection, relative to 1 kg body weight, which is preferably given by intravenous injection.

[0121]

The compound of the present invention can be used concurrently with other drugs. To be specific, the compound of the present invention can be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, medicaments inhibiting the action of cell growth factors or cell growth factor receptors and the like. In the following, the drugs that can be used in combination with

the compound of the present invention are abbreviated as concomitant drugs.

[0122]

Examples of the "hormonal therapeutic agents" include fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate), pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane), anti-androgens (e.g., flutamide, bicartamide, nilutamide), 5α-reductase inhibitors (e.g., finasteride, epristeride), aderenal cortex hormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone), androgen synthesis inhibitors (e.g., abiraterone), retinoid and drugs that retard retinoid metabolism (e.g., liarozole), thyroid hormone, and DDS (Drug Delivery System) preparations thereof, and the like.

[0123]

Examples of the "chemotherapeutic agents" include alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

[0124]

Examples of the "alkylating agents" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, sodium estramustine phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine,

ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, DDS preparations thereof, and the like.

[0125]

Examples of the "antimetabolites" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emitefur, capecitabine), aminopterine, nelzarabine, leucovorin calcium, tabloid, butocine, calcium folinate, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, bendamustine, DDS preparations thereof, and the like.

[0126]

Examples of the "anticancer antibiotics" include actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, DDS preparations thereof, and the like.

[0127]

Examples of the "plant-derived anticancer agents" include etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, DDS preparations thereof, and the like.

[0128]

Examples of the "immunotherapeutic agents (BRM)" include picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor,

granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, *Corynebacterium parvum*, levamisole, polysaccharide K, procodazole, anti-CTLA4 antibody, and the like.

[0129]

Example of the "cell growth factors" in the "medicaments inhibiting the action of cell growth factors or cell growth factor receptors" include any substances that promote cell proliferation, which are normally peptides having not more than 20,000 molecular weight that are capable of exhibiting their activity at low concentrations by binding to a receptor, including (1) EGF (epidermal growth factor) or substances possessing substantially the same activity as EGF [e.g., TGFα], (2) insulin or substances possessing substantially the same activity as insulin [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as FGF [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10], and (4) other cell growth factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGFβ (transforming growth factor β), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), heregulin, angiopoietin].

[0130]

Examples of the "cell growth factor receptors" include any receptors capable of binding to the aforementioned cell growth factors, including EGF receptor, heregulin receptor (HER3, etc.), insulin receptor inhibitor, IGF receptor-1, IGF receptor-2, FGF receptor-1 or FGF receptor-2, VEGF receptor, angiopoietin receptor (Tie2 etc.), PDGF receptor, c-MET, c-Kit, Trk and the like.

[0131]

Examples of the "medicaments inhibiting the action of cell growth factors or cell growth factor receptors" include

EGF inhibitor, TGFα inhibitor, heregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGFβ inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 inhibitor, c-Kit inhibitor, Src inhibitor, PKC inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, MEK(MEK1/2) inhibitor, MET inhibitor, Akt inhibitor, ERK inhibitor and the like. More specifically, anti-VEGF antibody (Bevacizumab etc.), anti-HER2 antibody (Trastuzumab, Pertuzumab etc.), anti-EGFR antibody (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anti-VEGFR antibody, Imatinib mesylate, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Silorimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide (VX-680), 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl phosphate (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt

(ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (CI-2536), 2-hydroxyethyl 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamate (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901) and the like are used.

[0132]

In addition to the aforementioned drugs, cell cycle inhibitors (e.g., Aurora A inhibitors, Aurora B inhibitors, PLK inhibitors, CDK inhibitors), pro-apoptotic agents (e.g., Bcl-2 inhibitors, IAP inhibitors, Nedd-8 inhibitors), proteasome inhibitors (e.g., bortezomib), (Hedgehog signal inhibitors (e.g., Vismodegib, LDE225, IPI-926), Wnt signal inhibitors (e.g., β-catenin/TCF inhibitors, anti-Wnt antibody), Notch signal inhibitors (e.g., antti-Notch antibody, γ-secretase inhibitors), L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan), topoisomerase II inhibitors (e.g., sobuzoxane), differentiation inducers (e.g., retinoid, vitamin D), other angiogenesis inhibitors (e.g., humagillin, shark extract, COX-2 inhibitor), α-blockers (e.g., tamsulosin hydrochloride), bisphosphonic acids (e.g., pamidronate, zoledronate), thalidomide, 5-azacytidine, decitabine, antitumor antibody such as anti-CD20 antibody and the like, toxin labeled antibody and the like can also be used.

[0133]

By combining the compound of the present invention and a concomitant drug, a superior effect such as

(1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,

(2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),

(3) the period of treatment can be set longer,

(4) a sustained treatment effect can be designed,

(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

[0134]

In the present specification, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

For use of the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention and the concomitant drug can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically set, and can be appropriately selected depending on the administration subject, administration route, disease, combination and the like.

[0135]

Examples of the administration mode of the combined use of the compound of the present invention and the concomitant drug include the following methods: (1) The compound of the present invention and the concomitant drug are simultaneously produced to give a single preparation, which is then administered. (2) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by the same administration route at different times. (4) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by different administration routes. (5) The compound of the present

invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by different administration routes at different times (e.g., the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order). The dose of the concomitant drug is appropriately determined in accordance with its clinical dose, and the ratio of the compound of the present invention and the concomitant drug is appropriately determined depending on the administration subject, administration route, target disease, symptom, combination, and the like. For example, when the administration subject is human, the concomitant drug is used in 0.01 to 100 (parts by weight), relative to 1 part by weight of the compound of the present invention.

[0136]

The combination agent of the present invention has low toxicity and, for example, the compound of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, such as tablets (including sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsule), solutions, injections, suppositories, sustained release agents and the like, which can be safely administered orally or parenterally (e.g., local, rectum, venous). An injection can be administered by intravenous, intramuscular, subcutaneous or intra-organ administration, or directly to the lesion.

[0137]

As a pharmacologically acceptable carrier which may be used for preparing the combination agent of the present invention, those similar to the aforementioned pharmacologically acceptable carriers, that can be used for the production of the pharmaceutical agent of the present invention, can be mentioned. Where necessary, the aforementioned additives that can be used for the production of the pharmaceutical agent of the present

invention, such as preservatives, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can also be appropriately used in appropriate amounts.

[0138]

The compounding ratio of the compound of the present invention to the concomitant drug in the combination agent of the present invention can be appropriately set depending on the administration subject, administration route, diseases and the like.

For example, the content of the compound of the present invention in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the entire preparation.

The content of the concomitant drug in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 90% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the entire preparation.

The content of additives in the combination agent of the present invention varies depending on the dosage form, and is usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the entire preparation.

When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

[0139]

These preparations can be produced by a method known *per se*, which is generally employed in the preparation process.

For example, the compound of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (manufactured by Atlas Powder, US), HCO 60 (manufactured by Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate,

hydroxypropylmethylcellulose, dextrin), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite), a surfactant (e.g., Polysorbate 80, macrogol), a solubilizer (e.g., glycerin, ethanol), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose), a pH adjuster (e.g., hydrochloric acid, sodium hydroxide), a preservative (e.g., ethyl paraoxybenzoate, benzoic acid, methylparaben, propylparaben, benzyl alcohol), a dissolving agent (e.g., conc. glycerin, meglumine), a solubilizing agent (e.g., propylene glycol, sucrose), a soothing agent (e.g., glucose, benzyl alcohol), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a solubilizing agent such as propylene glycol and the like and prepared into an oily injection, whereby an injection is afforded.

[0140]

In addition, an excipient (e.g., lactose, sucrose, starch), a disintegrating agent (e.g., starch, calcium carbonate), a binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000) and the like may be added to the compound of the present invention or the concomitant drug, and the mixture can be compression-molded, according to a method known *per se* then if desirable, the molded product can be coated by a method known *per se* for the purpose of masking of taste, enteric property or durability, to give a preparation for oral administration. As the coating agent, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudoragit (methacrylic acid·acrylic acid copolymer, manufactured by Rohm, DE), pigment (e.g., iron oxide

red, titanium dioxide) and the like can be used. The preparation for oral administration may be any of an immediate-release preparation and a sustained release preparation.

[0141]

Moreover, the compound of the present invention and the concomitant drug can be made into an oily or aqueous solid, semisolid or liquid suppository according to a method known *per se*, by mixing them with an oily substrate, aqueous substrate or aqueous gel substrate. As the above-mentioned oily substrate, for example, glycerides of higher fatty acid [e.g., cacao butter, Witepsols (manufactured by Dynamit Nobel, Germany)], glycerides of medium chain fatty acid [e.g., Miglyols (manufactured by Dynamit Nobel, Germany)], or vegetable oils (e.g., sesame oil, soybean oil, cotton seed oil), and the like are mentioned. Furthermore, as the aqueous substrate, for example, polyethylene glycol, propylene glycol and the like are mentioned, and as the aqueous gel substrate, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are mentioned.

[0142]

As the above-mentioned sustained release preparation, sustained release microcapsules and the like are mentioned. The sustained release microcapsule can be produced by a method known *per se*, for example, a method shown in the following [2].

[0143]

The compound of the present invention is preferably molded into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a preparation for rectal administration such as a suppository and the like. Particularly, a preparation for oral administration is preferable.

The concomitant drug can be made into the above-mentioned drug form depending on the kind of the drug.

[0144]

[1] An injection of the compound of the present invention

or the concomitant drug, and preparation thereof, [2] a sustained release preparation or immediate-release preparation of the compound of the present invention or the concomitant drug, and preparation thereof, [3] a sublingual, buccal or intraoral quick integrating agent of the compound of the present invention or the concomitant drug, and preparation thereof, will be described below specifically.

[0145]

[1] Injection and preparation thereof

An injection prepared by dissolving the compound of the present invention or the concomitant drug into water is preferable. This injection may be allowed to contain a benzoate and/or salicylate.

The injection is obtained by dissolving the compound of the present invention or the concomitant drug, and if desirable, a benzoate and/or salicylate, into water.

[0146]

As the above-mentioned salts of benzoic acid and salicylic acid, for example, salts of alkali metals such as sodium, potassium and the like, salts of alkaline earth metals such as calcium, magnesium and the like, ammonium salts, meglumine salts, salts with organic bases such as tromethamol and the like, etc. are listed.

[0147]

The concentration of the compound of the present invention or the concomitant drug in an injection is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%. The concentration of a benzoate or/and salicylate is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%.

[0148]

The injection of the present invention appropriately contains additives usually used in an injection, for example, a stabilizer (e.g., ascorbic acid, sodium pyrosulfite), a surfactant (e.g., Polysorbate 80, macrogol), a solubilizer (e.g., glycerin, ethanol), a buffer (e.g., phosphoric acid and

alkali metal salt thereof, citric acid and alkali metal salt thereof), an isotonizing agent (e.g., sodium chloride, potassium chloride), a dispersing agent (e.g., hydroxypropylmethylcellulose, dextrin), a pH regulator (e.g., hydrochloric acid, sodium hydroxide), a preservative (e.g., ethyl parahydroxybenzoate, benzoic acid), a dissolving agent (e.g., conc. glycerin, meglumine), a solubilizing agent (e.g., propylene glycol, sucrose), a soothing agent (e.g., glucose, benzyl alcohol), and the like. These additives are generally blended in a proportion usually used in an injection.

[0149]

It is advantageous that pH of an injection be controlled from pH 2 to 12, preferably from pH 2.5 to 8.0, by addition of a pH regulator.

An injection is obtained by dissolving the compound of the present invention or the concomitant drug and if desirable, a benzoate and/or a salicylate, and if necessary, the above-mentioned additives into water. These may be dissolved in any order, and can be appropriately dissolved in the same manner as in a conventional method of producing an injection.

[0150]

An aqueous solution for injection may be advantageously heated, alternatively, for example, filter sterilization, high pressure heat sterilization and the like can be conducted in the same manner as for a usual injection, to provide an injection.

It may be advantageous that an aqueous solution for injection is subjected to high pressure heat sterilization at 100 to 121°C for 5 to 30 min.

Further, a preparation endowed with an antibacterial property of a solution may also be produced so that it can be used as a preparation which is divided and administered multiple-times.

[0151]

[2] Sustained release preparation or immediate-release

preparation, and preparation thereof

A sustained release preparation is preferable which is obtained, if desirable, by coating a nucleus containing the compound of the present invention or the concomitant drug with a film agent such as a water-insoluble substance, swellable polymer and the like. For example, a sustained release preparation for oral administration of once administration per day type is preferable.

[0152]

As the water-insoluble substance used in a film agent, there are listed, for example, cellulose ethers such as ethylcellulose, butylcellulose and the like, cellulose esters such as cellulose acetate, cellulose propionate and the like, polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate and the like, acrylic acid/methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamide copolymers, poly(methyl methacrylate), polymethacrylate, polymethacrylamide, aminoalkyl methacrylate copolymers, poly(methacrylic anhydride), glycidyl methacrylate copolymer, particularly, acrylic acid-based polymers such as Eudoragit (Rohm Pharma) such as Eudoragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate/methyl methacrylate/trimethylchloride methacrylate/ethyl ammonium copolymer), Eudoragit NE-30D (methyl methacrylate/ethyl acrylate copolymer), and the like, hydrogenated oils such as hydrogenated castor oil (e.g., LUBRI WAX; Freund Corporation)), waxes such as carnauba wax, fatty acid glycerin ester, paraffin and the like, polyglycerin fatty acid esters, and the like.

[0153]

As the swellable polymer, polymers having an acidic dissociating group and showing pH dependent swell are preferable, and polymers having an acidic dissociating group,

which manifest small swelling in acidic regions such as in stomach and large swelling in neutral regions such as in small intestine and large intestine, are preferable.

As such a polymer having an acidic dissociating group and showing pH dependent swell, cross-linkable polyacrylic acid polymers such as, for example, Carbomer 934P, 940, 941, 974P, 980, 1342 and the like, polycarbophil, calcium polycarbophil (all of which are manufactured by BF Goodrich), Hiviswako 103, 104, 105, 304 (all are manufactured by Wako Pure Chemical Industries, Ltd.), and the like, are listed.

[0154]

The film agent used in a sustained release preparation may further contain a hydrophilic substance.

As the hydrophilic substance, for example, polysaccharides which may contain a sulfate group such as pullulan, dextrin, alkali metal alginate and the like, polysaccharides having a hydroxyalkyl or carboxyalkyl such as hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium and the like, methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol and the like.

[0155]

The content of a water-insoluble substance in the film agent of a sustained release preparation is from about 30 to about 90% (w/w), preferably from about 35 to about 80% (w/w), further preferably from about 40 to about 75% (w/w), the content of a swellable polymer is from about 3 to about 30% (w/w), preferably from about 3 to about 15% (w/w). The film agent may further contain a hydrophilic substance, and in which case, the content of a hydrophilic substance in the film agent is about 50% (w/w) or less, preferably about 5 to about 40% (w/w), further preferably from about 5 to about 35% (w/w). This % (w/w) indicates % by weight based on a film agent composition which is obtained by removing a solvent (e.g., water, lower alcohols such as methanol, ethanol and the like)

from a film agent solution.

[0156]

The sustained release preparation is produced by preparing a nucleus containing a drugs as exemplified below, then, coating the resulted nucleus with a film agent solution prepared by heat-solving a water-insoluble substance, swellable polymer and the like or by dissolving or dispersing it in a solvent.

[0157]

I. Preparation of nucleus containing drug

The form of nucleus containing a drug to be coated with a film agent (hereinafter, sometimes simply referred to as nucleus) is not particularly restricted, and preferably the nucleus is formed into particles such as a granule or fine particle.

When the nucleus is composed of granules or fine particles, the average particle size thereof is preferably from about 150 to about 2000 μm, further preferably from about 500 to about 1400 μm.

Preparation of the nucleus can be effected by a usual production method. For example, a suitable excipient, binding agent, disintegrating agent, lubricant, stabilizer and the like are mixed with a drug, and the mixture is subjected to a wet extrusion granulating method, fluidized bed granulating method or the like, to prepare a nucleus.

The content of drugs in a nucleus is from about 0.5 to about 95% (w/w), preferably from about 5.0 to about 80% (w/w), further preferably from about 30 to about 70% (w/w).

[0158]

As the excipient contained in the nucleus, for example, saccharides such as sucrose, lactose, mannitol, glucose and the like, starch, crystalline cellulose, calcium phosphate, corn starch and the like are used. Among them, crystalline cellulose, corn starch are preferable.

[0159]

As the binding agent, for example, polyvinyl alcohol, hydroxypropylcellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum Arabic, gelatin, starch and the like are used. As the disintegrating agent, for example, carboxymethylcellulose calcium (ECG505), croscarmelose sodium (Ac-Di-Sol), crosslinked polyvinylpyrrolidone (Crospovidone), low substituted hydroxypropylcellulose (L-HPC) and the like are used. Among them, hydroxypropylcellulose, polyvinylpyrrolidone, lower substituted hydroxypropylcellulose are preferable. As the lubricant and coagulation inhibitor, for example, talc, magnesium stearate and inorganic salts thereof are used, and as the lubricant, polyethylene glycol and the like are used. As the stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, are used.

[0160]

A nucleus can also be prepared by, in addition to the above-mentioned productions method, for example, a rolling granulation method in which a drug or a mixture of a drug with an excipient, lubricant and the like is added portionwise onto an inert carrier particle which is the core of the nucleus while spraying a binder dissolved in a suitable solvent such as water, lower alcohol (e.g., methanol, ethanol and the like) and the like, a pan coating method, a fluidized bed coating method or a melt granulating method. As the inert carrier particle, for example, those made of sucrose, lactose, starch, crystalline cellulose or waxes can be used, and the average particle size thereof is preferably from about 100 μm to about 1500 μm.

[0161]

For separating a drug contained in a nucleus and a film agent, the surface of the nucleus may be coated with a protective agent. As the protective agent, for example, the above-mentioned hydrophilic substances, water-insoluble substances and the like are used. As the protective agent,

preferably polyethylene glycol, and polysaccharides having a hydroxyalkyl or carboxyalkyl are used, more preferably hydroxypropylmethylcellulose and hydroxypropylcellulose are used. The protective agent may contain, as stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, and lubricants such as talc and the like. When the protective agent is used, the coating amount is from about 1 to about 15% (w/w), preferably from about 1 to about 10% (w/w), further preferably from about 2 to about 8% (w/w), based on the nucleus.

[0162]

The protective agent can be coated by a usual coating method, and specifically, the protective agent can be coated by spray-coating the nucleus, for example, by a fluidized bed coating method, pan coating method and the like.

[0163]

II. Coating of nucleus with film agent

A nucleus obtained in the above-mentioned step I is coated with a film agent solution obtained by heat-solving the above-mentioned water-insoluble substance and pH-dependent swellable polymer, and a hydrophilic substance, or by dissolving or dispersing them in a solvent, to give a sustained release preparation.

As the method for coating a nucleus with a film agent solution, for example, a spray coating method and the like are listed.

The composition ratio of a water-insoluble substance, swellable polymer or hydrophilic substance in a film agent solution is appropriately selected so that the contents of these components in a coated film are the above-mentioned contents, respectively.

The coating amount of a film agent is from about 1 to about 90% (w/w), preferably from about 5 to about 50% (w/w), further preferably from about 5 to about 35% (w/w), based on a nucleus (not including coating amount of protective agent).

[0164]

As the solvent in a film agent solution, water or an organic solvent can be used alone or in admixture thereof. In the case of use in admixture, the mixing ratio of water to an organic solvent (water/organic solvent: by weight) can be varied in the range from 1 to 100%, and preferably from 1 to about 30%. The organic solvent is not particularly restricted providing it dissolves a water-insoluble substance, and for example, lower alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol and the like, lower alkanone such as acetone and the like, acetonitrile, chloroform, methylene chloride and the like are used. Among them, lower alcohols are preferable, and ethyl alcohol and isopropyl alcohol are particularly preferable. Water, and a mixture of water with an organic solvent are preferably used as a solvent for a film agent. In this case, if necessary, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like may also be added into a film agent solution for stabilizing the film agent solution.

[0165]

An operation of coating by spray coating can be effected by a usual coating method, and specifically, it can be effected by spray-coating a film agent solution onto a nucleus by a fluidized bed coating method, pan coating method and the like. In this case, if necessary, talc, titanium oxide, magnesium stearate, calcium stearate, light anhydrous silicic acid and the like may also be added as a lubricant, and glycerin fatty acid ester, hydrogenated castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol and the like may also be added as a plasticizer.

[0166]

After coating with a film agent, if necessary, an antistatic agent such as talc and the like may be mixed.

The immediate-release preparation may be liquid (solution, suspension, emulsion and the like) or solid (particle, pill,

tablet and the like). As the immediate-release preparation, oral administration agents and parenteral administration agents such as an injection and the like are used, and oral administration agents are preferable.

[0167]

The immediate-release preparation, usually, may contain, in addition to an active component drug, also carriers, additives and excipients conventionally used in the pharmaceutical field (hereinafter, sometimes abbreviated as excipient). The excipient used is not particularly restricted providing it is an excipient ordinarily used as a preparation excipient. For example, as the excipient for an oral solid preparation, lactose, starch, corn starch, crystalline cellulose (Avicel PH101, manufactured by Asahi Kasei Corporation, and the like), powder sugar, granulated sugar, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine and the like are listed, and preferably corn starch and mannitol and the like are listed. These excipients can be used alone or in combination of two or more. The content of the excipient is, for example, from about 4.5 to about 99.4 w/w%, preferably from about 20 to about 98.5 w/w%, further preferably from about 30 to about 97 w/w%, based on the total amount of the immediate-release preparation.

[0168]

The content of a drug in the immediate-release preparation can be appropriately selected in the range from about 0.5 to about 95w/w%, preferably from about 1 to about 60w/w% based on the total amount of the immediate-release preparation.

[0169]

When the immediate-release preparation is an oral solid preparation, it usually contains, in addition to the above-mentioned components, also an integrating agent. As this integrating agent, for example, carboxymethylcellulose calcium (ECG-505, manufactured by Gotoku Yakuhin), croscarmelose

sodium (e.g., Actisol, manufactured by Asahi Kasei Corporation), crospovidone (e.g., Kollidon CL, manufactured by BASF), low substituted hydroxypropylcellulose (Shin-Etsu Chemical Co., Ltd.), carboxymethylstarch (Matsutani Kagaku K.K.), carboxymethylstarch sodium (Exprotab, manufactured by Kimura Sangyo), partially pregelatinized starch (PCS, manufactured by Asahi Kasei Corporation), and the like are used, and for example, those which disintegrate a granule by absorbing water in contact with water, causing swelling, or making a channel between an effective ingredient and an excipient constituting the nucleus, can be used. These disintegrating agents can be used alone or in combination of two or more. The amount of the disintegrating agent used is appropriately selected depending on the kind and blending amount of a drug used, design of releasing property, and the like, and for example, from about 0.05 to about 30 w/w%, preferably from about 0.5 to about 15 w/w%, based on the total amount of the immediate-release preparation.

[0170]

When the immediate-release preparation is an oral solid preparation, it may further contain, in addition to the above-mentioned composition, if desired, additives conventional in solid preparations. As such an additive, there are used, for example, a binder (e.g., sucrose, gelatin, gum Arabic powder, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin and the like), a lubricant (e.g., polyethylene glycol, magnesium stearate, talc, light anhydrous silicic acid (e.g., Aerosil (Nippon Aerosil))), a surfactant (e.g., anionic surfactants such as sodium alkylsulfate and the like, nonionic surfactants such as polyoxyethylene fatty acid ester and polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivatives and the like), a colorant (e.g., tar coloring matter, caramel, iron oxide red, titanium oxide, riboflavins), if necessary, an

appetizing agent (e.g., sweetening agent, flavoring agent and the like), an adsorbent, preservative, wetting agent, antistatic agent, and the like. Further, as the stabilizer, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid and the like may also be added.

[0171]

As the above-mentioned binder, hydroxypropylcellulose, polyethylene glycol and polyvinylpyrrolidone and the like are preferably used.

[0172]

The immediate-release preparation can be prepared by, based on a usual technology of producing preparations, mixing the above-mentioned components, and if necessary, further kneading the mixture, and molding it. The above-mentioned mixing is conducted by generally used methods, for example, mixing, kneading and the like. Specifically, when a immediate-release preparation is formed, for example, into a particle, it can be prepared, according to the same means as in the above-mentioned method for preparing a nucleus of a sustained release preparation, by mixing the components using a vertical granulator, universal kneader (manufactured by Hata Tekkosho), fluidized bed granulator FD-5S (manufactured by Powrex Corporation), and the like, and then, granulating the mixture by a wet extrusion granulation method, fluidized bed granulation method and the like.

[0173]

Thus obtained immediate-release preparation and sustained release preparation may be themselves made into products or made into products appropriately together with preparation excipients and the like, separately, by an ordinary method, then, may be administered simultaneously or may be administered in combination at any administration interval, or they may be themselves made into one preparation for oral administration (e.g., granule, fine particle, tablet, capsule) or made into one preparation for oral administration

appropriately together with preparation excipients and the like. It may also be permissible that they are made into granules or fine particles, and filled in the same capsule to be used as a preparation for oral administration.

[0174]

[3] Sublingual, buccal or intraoral quick disintegrating agent and preparation thereof

Sublingual, buccal or intraoral quick disintegrating agents may be a solid preparation such as tablet and the like, or may be an oral mucosa membrane patch (film).

As the sublingual, buccal or intraoral quick disintegrating agent, a preparation containing the compound of the present invention or the concomitant drug and an excipient is preferable. It may contain also auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer and the like. Further, for easy absorption and increased *in vivo* use efficiency, β-cyclodextrin or β-cyclodextrin derivatives (e.g., hydroxypropyl-β-cyclodextrin) and the like may also be contained.

[0175]

As the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like are listed. As the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like are listed, and particularly, magnesium stearate and colloidal silica are preferable. As the isotonizing agent, sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin, urea and the like are listed, and particularly, mannitol is preferable. As the hydrophilic carrier, swellable hydrophilic carriers such as crystalline cellulose, ethylcellulose, crosslinkable polyvinylpyrrolidone, light anhydrous silicic acid, silicic acid, dicalcium phosphate, calcium carbonate and the like are listed, and particularly, crystalline cellulose (e.g., microcrystalline

cellulose) is preferable. As the water-dispersible polymer, gums (e.g., gum tragacanth, acacia gum, cyamoposis gum), alginates (e.g., sodium alginate), cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), gelatin, water-soluble starch, polyacrylic acids (e.g., Carbomer), polymethacylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbophil, ascorbic acid, palmitates and the like are listed, and hydroxypropylmethylcellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose, polyvinylpyrrolidone, polyethylene glycol and the like are preferable. Particularly, hydroxypropylmethylcellulose is preferable. As the stabilizer, cysteine, thiosorbitol, tartaric acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like are listed, and particularly, citric acid and ascorbic acid are preferable.

[0176]

The sublingual, buccal or intraoral quick disintegrating agent can be produced by mixing the compound of the present invention or the concomitant drug and an excipient by a method known per se. Further, if desired, the above-mentioned auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, colorant, sweetening agent, preservative and the like may be mixed. The sublingual, buccal or intraoral quick disintegrating agent is obtained by mixing the above-mentioned components simultaneously or at a time interval, then subjecting the mixture to tablet-making molding under pressure. For obtaining suitable hardness, it may also be permissible that the materials are moistened by using a solvent such as water, alcohol and the like if desired before and after the tablet making process, and after the molding, the materials are dried, to obtain a product.

[0177]

In the case of molding into a mucosa membrane patch (film), the compound of the present invention or the concomitant drug and the above-mentioned water-dispersible polymer (preferably hydroxypropylcellulose, hydroxypropylmethylcellulose), excipient and the like are dissolved in a solvent such as water and the like, and the resulted solution is cast to give a film. Further, additives such as a plasticizer, stabilizer, antioxidant, preservative, colorant, buffer, sweetening agent and the like may also be added. For imparting suitable elasticity to the film, glycols such as polyethylene glycol, propylene glycol and the like may be contained, or for enhancing adhesion of the film to an intraoral mucosa membrane lining, a bio-adhesive polymer (e.g., polycarbophil, carbopol) may also be contained. In the casting, a solution is poured on the non-adhesive surface, spread to uniform thickness (preferably about 10 to 1000 micron) by an application tool such as a doctor blade and the like, then, the solution is dried to form a film. It may be advantageous that thus formed film is dried at room temperature or under heat, and cut into a desired area.

[0178]

As the preferable intraoral quick disintegrating agent, there are listed solid quick scattering dose agents composed of a network body comprising the compound of the present invention or the concomitant drug, and a water-soluble or water-diffusible carrier which is inert to the compound of the present invention or concomitant drug, are listed. This network body is obtained by sublimating a solvent from the solid composition constituted of a solution prepared by dissolving the compound of the present invention or the concomitant drug in a suitable solvent.

[0179]

It is preferable that the composition of an intraoral quick disintegrating agent contains a matrix forming agent and a secondary component, in addition to the compound of the

present invention or the concomitant drug.

[0180]

Examples of the matrix forming agent include gelatins, dextrins, animal proteins or vegetable proteins such as soybean, wheat and psyllium seed protein and the like; rubber substances such as gum Arabic, guar gum, agar, xanthan and the like; polysaccharides; alginic acids; carboxymethylcelluloses; carageenans; dextrans; pectines; synthetic polymers such as polyvinylpyrrolidone and the like; substances derived from a gelatin-gum Arabic complex, and the like. Further, saccharides such as mannitol, dextrose, lactose, galactose, trehalose and the like; cyclic saccharides such as cyclodextrin and the like; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicate and the like; amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine and the like, are contained.

[0181]

One or more of the matrix forming agents can be introduced in a solution or suspension before solidification. Such as matrix forming agent may be present in addition to a surfactant, or may be present while a surfactant being excluded. The matrix forming agents aid to maintain the compound of the present invention or the concomitant drug in the solution or suspension in diffused condition, in addition to formation of the matrix.

[0182]

The composition may contain secondary components such as a preservative, antioxidant, surfactant, thickening agent, colorant, pH controlling agent, flavoring agent, sweetening agent, food taste masking agent and the like. As the suitable colorant, there are listed red, black and yellow iron oxides, and FD & C dyes such as FD & C Blue 2, FD & C Red 40 and the like manufactured by Ellis and Everard. Examples of the suitable flavoring agent include mint, raspberry, licorice,

orange, lemon, grapefruit, caramel, vanilla, cherry, grape flavor and combinations thereof. Examples of the suitable pH controlling agent include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the suitable sweetening agent include aspartame, acesulfame K and thaumatin and the like. Examples of the suitable food taste masking agent include sodium bicarbonate, ion exchange resin, cyclodextrin-inclusion compounds, adsorbent substances and microcapsulated apomorphine.

[0183]

The preparation contains the compound of the present invention or the concomitant drug in an amount usually from about 0.1 to about 50% by weight, preferably from about 0.1 to about 30% by weight, and preferable are preparations (such as the above-mentioned sublingual agent, buccal and the like) which can dissolve 90% or more of the compound of the present invention or the concomitant drug (into water) within the time range of about 1 to about 60 min, preferably of about 1 to about 15 min, more preferably of about 2 to about 5 min, and intraoral quick disintegrating preparations which are disintegrated within the range of 1 to 60 sec, preferably of 1 to 30 sec, further preferably of 1 to 10 sec, after placed in an oral cavity.

[0184]

The content of the above-mentioned excipient in the whole preparation is from about 10 to about 99% by weight, preferably from about 30 to about 90% by weight. The content of β-cyclodextrin or β-cyclodextrin derivative in the whole preparation is from 0 to about 30% by weight. The content of the lubricant in the whole preparation is from about 0.01 to about 10% by weight, preferably from about 1 to about 5% by weight. The content of the isotonizing agent in the whole preparation is from about 0.1 to about 90% by weight, preferably from about 10 to about 70% by weight. The content of the hydrophilic carrier in the whole preparation is from

about 0.1 to about 50% by weight, preferably from about 10 to about 30% by weight. The content of the water-dispersible polymer in the whole preparation is from about 0.1 to about 30% by weight, preferably from about 10 to about 25% by weight. The content of the stabilizer in the whole preparation is from about 0.1 to about 10% by weight, preferably from about 1 to 5% by weight. The above-mentioned preparation may further contain additives such as a colorant, sweetening agent, preservative and the like, if necessary.

[0185]

The dosage of a combination agent of the present invention differs depending on the kind of a compound of the present invention, age, body weight, condition, drug form, administration method, administration period and the like, and for example, for one cancer patient (adult, body weight: about 60 kg), the combination agent is administered intravenously, at a dose of about 0.01 to about 1000 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, more preferably about 0.1 to about 100 mg/kg/day, particularly about 0.1 to about 50 mg/kg/day, especially about 1.5 to about 30 mg/kg/day, in terms of the compound of the present invention or the concomitant drug, respectively, once or several times in division a day. Of course, since the dose as described above varies depending on various conditions, amounts smaller than the above-mentioned dosage may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

[0186]

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity of the symptom, age, sex, body weight, sensitivity difference of the administration subject, administration period, interval, and nature, pharmacy, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral

administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg body weight of a mammal, which is usually administered once to 4-times in division a day.

[0187]

In administration of a combination agent of the present invention, the compound of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the compound of the present invention, though they may be administered simultaneously. When administered at a time interval, the interval differs depending on the effective ingredient to be administered, drug form and administration method, and for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 min to 3 days, preferably from 10 min to 1 day, more preferably from 15 min to 1 hr after administration of the concomitant drug is exemplified. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 min to 1 day, preferably from 10 min to 6 hrs, more preferably from 15 min to 1 hr after administration of the compound of the present invention is exemplified.

[0188]

In a preferable administration method, for example, the concomitant drug which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.001 to 200 mg/kg, and about 15 min later, the compound of the present invention which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.005 to 100 mg/kg.

[0189]

Furthermore, the compound of the present invention or the combination agent of the present invention can be used

concurrently with a non-drug therapy. To be precise, the compound of the present invention or the combination agent of the present invention can be combined with a non-drug therapy such as (1) surgery, (2) hypertensive chemotherapy using angiotensin II etc., (3) gene therapy, (4) thermotherapy, (5) cryotherapy, (6) laser cauterization, (7) radiotherapy, and the like.

[0190]

For example, by using the compound of the present invention or the combination agent of the present invention before or after an surgery and the like, or before or after a combined treatment of two or three kinds thereof, effects such as prevention of emergence of resistance, prolongation of Disease-Free Survival, suppression of cancer metastasis or recurrence, prolongation of life and the like can be afforded.

[0191]

In addition, it is possible to combine a treatment with the compound of the present invention or the combination agent of the present invention with a supportive therapy [(i) administration of antibiotic (e.g., β-lactam type such as pansporin and the like, macrolide type such as clarithromycin and the like) for the complication with various infectious diseases, (ii) administration of high-calorie transfusion, amino acid preparation or general vitamin preparation for the improvement of malnutrition, (iii) administration of morphine for pain mitigation, (iv) administration of a pharmaceutical agent for ameliorating side effects such as nausea, vomiting, anorexia, diarrhea, leucopenia, thrombocytopenia, decreased hemoglobin concentration, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of a pharmaceutical agent for suppressing multiple drug resistance of cancer and the like].

[0192]

Preferably, the compound of the present invention or the combination agent of the present invention is administered

orally (including sustained-release preparations), intravenously (including boluses, infusions and clathrates), subcutaneously and intramuscularly (including boluses, infusions and sustained-release preparations), transdermally, intratumorally or proximally before or after the above-described treatment is conducted.

[0193]

As a period for administering the compound of the present invention or the combination agent of the present invention before the surgery, etc., for example, it can be administrated 1-time about 30 min to 24 hrs before the surgery, etc., or in 1 to 3 cycles about 3 months to 6 months before the surgery, etc. In this way, the surgery, etc. can be conducted easily because, for example, a cancer tissue would be reduced by administering the compound of the present invention or the combination agent of the present invention before the surgery, and the like.

[0194]

As a period for administering the compound of the present invention or the combination agent of the present invention after the surgery, etc., for example, it can be administrated repeatedly per a few weeks to 3 months, about 30 min to 24 hrs after the surgery, and the like. In this way, it enhances the effect of the surgery, etc. by administering the compound of the present invention or the combination agent of the present invention after the surgery, and the like.

Examples

[0195]

The present invention is explained in detail in the following by referring to Reference Examples, Examples, Formulation Examples and Experimental Examples, which are not to be construed as limitative.

[0196]

In the Reference Examples and Examples, the purity of the compounds was measured under the following HPLC conditions.

measurement device: SHIMADZU Corporation LC-10 Avp system

column: CAPSEL PAK C18UG120 S-3 μm, 2.0 X 50 mm
solvent: Solution A; 0.1% trifluoroacetic acid-containing water,

Solution B; 0.1% trifluoroacetic acid-containing acetonitrile

gradient cycle: 0.00 min (Solution A/Solution B=90/10), 4.00 min (Solution A/Solution B=5/95), 5.50 min (Solution A/Solution B=5/95), 5.51 min (Solution A/Solution B=90/10), 8.00 min (Solution A/Solution B=90/10)

injection volume: 2 μl
flow rate: 0.5 ml/min
detection method: UV 220 nm

In the Reference Examples and Examples, the purification of the compounds by preparative HPLC was performed under the following conditions.

measurement device: Gilson Company Inc., High Throughput Purification System

column: YMC CombiPrep ODS-A, S-5 μm, 50 X 20 mm
detection method: UV 220 nm

solvent: Solution A; 0.1% trifluoroacetic acid-containing water,

Solution B; 0.1% trifluoroacetic acid-containing acetonitrile

gradient cycle: representative example 0.00 min (SOLUTION A/SOLUTION B=98/2), 1.00 min (SOLUTION A/SOLUTION B=98/2), 5.20 min (SOLUTION A/SOLUTION B=0/100), 6.40 min (SOLUTION A/SOLUTION B=0/100), 6.50 min (SOLUTION A/SOLUTION B=98/2), 6.60 min (SOLUTION A/SOLUTION B=98/2), flow rate: 25 mL/min, or,

0.00 min (SOLUTION A/SOLUTION B=90/10), 1.00 min (SOLUTION A/SOLUTION B=90/10), 4.00 min (SOLUTION A/SOLUTION B=10/95), 8.50 min (SOLUTION A/SOLUTION B=10/95), 8.60 min (SOLUTION A/SOLUTION B=90/10), 8.70 min (SOLUTION A/SOLUTION B=90/10), flow rate: 20 mL/min

In the Reference Examples and Examples, mass spectrum

(MS) was measured under the following conditions.
measurement device: Micromass platform II or Waters ZMD
ionization method: Atmospheric Pressure Chemical Ionization (APCI) or electron impact ionization method (Electron Spray Ionization: ESI)

In Reference Example and Example, HPLC-mass spectrum (LC-MS) was measured under the following conditions.
measurement device: Micromass ZMD, Agilent Technologies HP1100 and 1200 LC/MSD
column: CAPCELL PAK C18UG120, S-3 μm, 1.5 X 35 mm
solvent: SOLUTION A; 0.05% trifluoroacetic acid-containing water,

SOLUTION B; 0.04% trifluoroacetic acid-containing acetonitrile
gradient cycle: 0.00 min (SOLUTION A/SOLUTION B=90/10), 2.00 min (SOLUTION A/SOLUTION B=5/95), 2.75 min (SOLUTION A/SOLUTION B=5/95), 2.76 min (SOLUTION A/SOLUTION B=90/10), 3.45 min (SOLUTION A/SOLUTION B=90/10)
injection volume: 2 μL, flow rate: 0.5 mL/min, detection method: UV 220 nm
ionization method: electron impact ionization method (Electron Spray Ionization: ESI)

^{1}H NMR spectrum was measured using tetramethylsilane as the internal standard by AVANCE DPX-300 (300MHz) manufactured by Bruker, AV-300M (300MHz) manufactured by Bruker and VARIAN Mercury-300 (300MHz), and all δ values were shown by ppm.

As the Microwave reaction apparatus, Emrys Optimizer, Biotage Japan Ltd. was used.

Unless otherwise specified, the numerical value of mixed solvent shows a volume mixing ratio of each solvent. Unless otherwise specified, % means weight %. While the room temperature (ambient temperature) in the present specification means a temperature of from about 10°C to about 35°C, it is not particularly strictly limited.

Other abbreviations used in the specification mean the

following:

s: singlet

d: doublet

t: triplet

q: quartet

spt: septet

m: multiplet

br: broad

J: coupling constant

Hz: hertz

$CDCl_3$: deuterated chloroform

DMSO-d_6: dimethyl sulfoxide-d_6

CD_3OD: deuterated methanol

^1H-NMR: proton nuclear magnetic resonance

DMF: N,N-dimethylformamide

THF: tetrahydrofuran

WSCD: water-soluble carbodiimide (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) hydrochloride

HOBt: 1-hydroxybenzotriazole

mCPBA: m-chloroperbenzoic acid

CDI: N,N'-carbonyldiimidazole

DMT-MM: 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride

DPPA: diphenylphosphoryl azide

MeCN: acetonitrile

TFA: trifluoroacetic acid

Me: methyl

Et: ethyl

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

DIPEA: diisopropylethylamine

[0197]

Reference Example 1

Production of methyl (2Z)-3-(phenylamino)pent-2-enoate

A mixture of methyl 3-oxovalerate (5.21 g, 40.0 mmol),

aniline (3.66 mL, 40.0 mmol), p-toluenesulfonic acid monohydrate (533 mg, 2.80 mmol) and cyclohexane (25 mL) was stirred with heating under reflux for 2 hr. The mixture was concentrated under reduced pressure, the insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=98:2→94:6) to give the title compound (5.93 g, 72%) as a colorless oil.
^{1}H NMR (300 MHz, DMSO-d_6) δ:0.95 (3 H, t, J = 7.5 Hz), 2.35 (2 H, q, J = 7.5 Hz), 3.59 (3 H, s), 4.73 (1 H, s), 7.09-7.29 (3 H, m), 7.31-7.47 (2 H, m), 10.29 (1 H, s).

[0198]

Reference Example 2

Production of methyl 3-(phenylamino)pentanoate

A mixture of the compound of Reference Example 1 (5.00 g, 24.4 mmol), 10% palladium carbon (2.50 g) and THF (100 mL) was stirred at room temperature for 7 hr under a hydrogen atmosphere. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=99:1→93:7) to give the title compound (4.15 g, 82%) as a colorless oil.
^{1}H NMR (300 MHz, DMSO-d_6) δ:0.88 (3 H, t, J = 7.4 Hz), 1.44-1.59 (2 H, m), 2.39-2.48 (2 H, m), 3.56 (3 H, s), 3.59-3.71 (1 H, m), 5.39 (1 H, d, J = 9.1 Hz), 6.42-6.63 (3 H, m), 6.98-7.12 (2 H, m).

[0199]

Reference Example 3

Production of ethyl 6-ethyl-4-hydroxy-2-oxo-1-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate

A mixture of the compound of Reference Example 2 (4.05 g, 19.5 mmol), ethyl (chloroformyl)acetate (3.71 mL, 29.3 mmol), triethylamine (5.40 mL, 39.0 mmol) and THF (41 mL) was stirred at room temperature for 4 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution

(100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added ethanol (188 mL) and 20% ethanol solution (13.3 mL, 39.0 mmol) of sodium ethoxide, and the mixture was stirred at 50°C for 3 hr. The reaction mixture was concentrated under reduced pressure, and to the residue was added 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=98:2→70:30) to give the title compound (3.15 g, 56%) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.77 (3 H, t, J = 7.5 Hz), 1.23 (3 H, t, J = 7.1 Hz), 1.53-1.68 (2 H, m), 3.16-3.30 (2 H, m), 3.78-3.90 (1 H, m), 4.20 (2 H, q, J = 7.1 Hz), 7.15-7.54 (5 H, m), 12.64 (1 H, br s).

[0200]

Reference Example 4

Production of ethyl 6-ethyl-4-hydroxy-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate

A mixture of the compound of Reference Example 3 (3.15 g, 10.9 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.97 g, 13.1 mmol) and toluene (63 mL) was stirred with heating under reflux for 1 hr. To the reaction mixture was added water (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by amino silica gel column chromatography (eluate, ethyl acetate:ethanol=100:0→95:5) to give the title compound (2.66 g, 85%) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.96 (3 H, t, J = 7.5 Hz), 1.22 (3 H, t, J = 7.1 Hz), 2.13 (2 H, q, J = 7.5 Hz), 4.22 (2 H, q, J = 7.1 Hz), 6.01 (1 H, s), 7.15-7.34 (2 H, m), 7.36-7.71 (3 H, m), 12.43 (1 H, br s).

[0201]

Reference Example 5

Production of ethyl 4-chloro-6-ethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate

A mixture of the compound of Reference Example 4 (2.66 g, 9.26 mmol), phosphorus oxychloride (2.59 mL, 27.8 mmol) and MeCN (53 mL) was stirred with heating under reflux for 2 hr. The mixture was concentrated under reduced pressure, and to the residue was added ice-water. The precipitated solid was collected by filtration, and washed with water and diisopropyl ether to give the title compound (2.11 g, 75%) as a yellow powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.98 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 2.20 (2 H, q, J = 7.4 Hz), 4.26 (2 H, q, J = 7.1 Hz), 6.46 (1 H, s), 7.28-7.40 (2 H, m), 7.45-7.66 (3 H, m).

[0202]

Reference Example 6

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

A mixture of the compound of Reference Example 5 (2.11 g, 6.90 mmol), ethyl sarcosinate hydrochloride (2.12 g, 13.8 mmol), triethylamine (10.6 mL) and ethanol (63 mL) was stirred with heating under reflux for 40 hr. The reaction mixture was concentrated under reduced pressure, and to the residue was added water (50 mL), and the mixture was acidified with 5N hydrochloric acid. The precipitate was collected by filtration, and washed with water to give the title compound (1.72 g, 73%) as a beige powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.4 Hz), 1.32 (3 H, t, J = 7.1 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.82 (3 H, s),

4.31 (2 H, q, J = 7.1 Hz), 6.46 (1 H, s), 7.16-7.30 (2 H, m), 7.40-7.58 (3 H, m), 8.89 (1 H, s).

[0203]

Reference Example 7

Production of ethyl 6-ethyl-1-methyl-4-oxo-5-phenyl-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

A mixture of the compound of Reference Example 6 (1.28 g, 3.76 mmol), cesium carbonate (1.47 g, 4.51 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.597 mL, 4.14 mmol) and DMF (12.8 mL) was stirred at room temperature for 2 hr. To the mixture was added water (50 mL), and the precipitate was collected by filtration, and washed successively with water and diisopropyl ether to give the title compound (1.55 g, 97%) as a beige powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.29 (3 H, t, J = 7.1 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.88 (3 H, s), 4.26 (2 H, q, J = 7.1 Hz), 4.83 (2 H, q, J = 9.3 Hz), 6.62 (1 H, s), 7.23-7.33 (2 H, m), 7.43-7.60 (3 H, m).

[0204]

Reference Example 8

Production of 6-ethyl-1-methyl-4-oxo-5-phenyl-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

A mixture of the compound of Reference Example 7 (1.40 g, 3.31 mmol), 8N aqueous sodium hydroxide solution (2.80 mL) and ethanol (42 mL) was stirred at 60°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and to the residue was added water (30 mL), and the mixture was acidified with 5N hydrochloric acid. The precipitate was collected by filtration, and washed with water to give the title compound (1.08 g, 82%) as a beige powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 2.20 (2 H, q, J = 7.4 Hz), 3.88 (3 H, s), 4.81 (2 H, q, J = 9.3 Hz), 6.60 (1 H, s), 7.16-7.38 (2 H, m), 7.39-7.66 (3 H, m), 12.72

(1 H, br s).

[0205]

Reference Example 9

Production of methyl (2Z)-3-[(2,6-difluorophenyl)amino]pent-2-enoate

By a method similar to that in Reference Example 1, from the title compound (8.31 g, 86%) was obtained as a colorless oil from methyl 3-oxovalerate (5.21 g, 40.0 mmol), 2,6-difluoroaniline (4.03 mL, 40.0 mmol), p-toluenesulfonic acid monohydrate (533 mg, 2.80 mmol) and cyclohexane (25 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.95 (3 H, t, J = 7.5 Hz), 2.04 (2 H, q, J = 7.5 Hz), 3.60 (3 H, s), 4.81 (1 H, s), 7.17-7.29 (2 H, m), 7.34-7.51 (1 H, m), 9.56 (1 H, s).

[0206]

Reference Example 10

Production of methyl 3-[(2,6-difluorophenyl)amino]pentanoate

A mixture of the compound of Reference Example 9 (7.90 g, 32.7 mmol), 5% platinum-activated carbon (2.37 g), acetic acid (26 mL) and ethanol (53 mL) was stirred at room temperature for 7 hr under a hydrogen atmosphere. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue was added saturated aqueous sodium hydrogen carbonate solution (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=99:1→93:7) to give the title compound (4.29 g, 54%) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.88 (3 H, t, J = 7.4 Hz), 1.41-1.61 (2 H, m), 2.52-2.55 (2 H, m), 3.50 (3 H, s), 3.86 (1 H, s), 4.62-4.77 (1 H, m), 6.59-6.77 (1 H, m), 6.84-7.01 (2 H, m).

[0207]

Reference Example 11

Production of ethyl 1-(2,6-difluorophenyl)-6-ethyl-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate

A mixture of the compound of Reference Example 10 (3.70 g, 15.2 mmol), ethyl (chloroformyl)acetate (2.89 mL, 22.8 mmol) and THF (37 mL) was stirred at room temperature for 2 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added ethanol (109 mL) and 20% ethanol solution (6.72 mL, 19.8 mmol) of sodium ethoxide, and the mixture was stirred at 50°C for 2 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=95:5→70:30) to give the title compound (4.75 g, 96%) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.78 (3 H, t, J = 7.4 Hz), 1.22 (3 H, t, J = 6.99 Hz), 1.45-1.60 (2 H, m), 2.66 (1 H, dd, J = 17.4, 5.1 Hz), 3.08 (1 H, dd, J = 17.4, 6.0 Hz), 3.61-3.81 (1 H, m), 4.14-4.29 (2 H, m), 7.10-7.32 (2 H, m), 7.37-7.56 (1 H, m), 12.86 (1 H, br s).

[0208]

Reference Example 12

Production of ethyl 1-(2,6-difluorophenyl)-6-ethyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 4, the title compound (3.47 g, 74%) was obtained as a white solid from the compound of Reference Example 11 (4.75 g, 14.6 mmol),

2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.65 g, 16.1 mmol) and toluene (95 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.00 (3 H, t, J = 7.4 Hz), 1.23 (3 H, t, J = 7.1 Hz), 2.21 (2 H, q, J = 7.4 Hz), 4.23 (2 H, q, J = 7.1 Hz), 6.13 (1 H, s), 7.32-7.44 (2 H, m), 7.58-7.72 (1 H, m), 12.55 (1 H, br s).

[0209]

Reference Example 13

Production of ethyl 4-chloro-1-(2,6-difluorophenyl)-6-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 5, the title compound (4.05 g, 98%) was obtained as a yellow oil from the compound of Reference Example 12 (3.47 g, 12.1 mmol), phosphorus oxychloride (3.38 mL, 36.2 mmol) and MeCN (69 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.26 (3 H, t, J = 7.1 Hz), 2.30 (2 H, q, J = 7.4 Hz), 4.29 (2 H, q, J = 7.1 Hz), 6.63 (1 H, s), 7.37-7.52 (2 H, m), 7.63-7.83 (1 H, m).

[0210]

Reference Example 14

Production of ethyl 5-(2,6-difluorophenyl)-6-ethyl-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 6, the title compound (2.90 g, 88%) was obtained as a beige powder from the compound of Reference Example 13 (3.00 g, 8.78 mmol), ethyl sarcosinate hydrochloride (2.70 g, 17.6 mmol), triethylamine (15 mL) and ethanol (60 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.32 (3 H, t, J = 7.1 Hz), 2.23 (2 H, q, J = 7.4 Hz), 3.83 (3 H, s), 4.32 (2 H, q, J = 7.1 Hz), 6.62 (1 H, s), 7.31-7.44 (2 H, m), 7.56-7.73 (1 H, m), 9.04 (1 H, br s).

[0211]

Reference Example 15

Production of ethyl 5-(2,6-difluorophenyl)-6-ethyl-1-methyl-4-

oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 7, the title compound (1.56 g, 78%) was obtained as a yellow solid from the compound of Reference Example 14 (1.64 g, 4.36 mmol), cesium carbonate (1.70 g, 5.23 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.691 mL, 4.79 mmol) and DMF (16.4 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.06 (3 H, t, J = 7.4 Hz), 1.29 (3 H, t, J = 7.1 Hz), 2.27 (2 H, q, J = 7.4 Hz), 3.90 (3 H, s), 4.27 (2 H, q, J = 7.1 Hz), 4.81 (2 H, q, J = 9.3 Hz), 6.75 (1 H, s), 7.32-7.44 (2 H, m), 7.60-7.73 (1 H, m).

[0212]

Reference Example 16

Production of 5-(2,6-difluorophenyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (1.07 g, 84%) was obtained as a yellow powder from the compound of Reference Example 15 (1.36 g, 2.97 mmol), 8N aqueous sodium hydroxide solution (1.36 mL) and ethanol (27 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.05 (3 H, t, J = 7.5 Hz), 2.27 (2 H, q, J = 7.5 Hz), 3.90 (3 H, s), 4.79 (2 H, q, J = 9.3 Hz), 6.73 (1 H, s), 7.30-7.48 (2 H, m), 7.56-7.76 (1 H, m), 12.85 (1 H, br s).

[0213]

Reference Example 17

Production of ethyl 3-ethoxy-6-ethyl-1-methyl-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

To a solution of the compound of Reference Example 6 (150 mg, 0.441 mmol) in acetone (3.0 mL) were added potassium carbonate (122 mg, 0.882 mmol) and diethyl sulfate (86.4 µL, 0.662 mmol), and the mixture was stirred with heating under reflux for 3 hr. The reaction mixture was cooled to 0°C, water

(20 mL) was added thereto, and the mixture was extracted with ethyl acetate (50 mL). The extract was washed with brine (20 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, ethyl acetate:ethanol=90:10→60:40) to give the title compound (141 mg, 87%) as a white powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.4 Hz), 1.23 (3 H, t, J = 7.1 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.19 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.15 (2 H, q, J = 7.1 Hz), 4.26 (2 H, q, J = 7.1 Hz), 6.55 (1 H, s), 7.20-7.29 (2 H, m), 7.40-7.57 (3 H, m).

[0214]

Reference Example 18

Production of 3-ethoxy-6-ethyl-1-methyl-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (115 mg, 88%) was obtained as a white powder from the compound of Reference Example 17 (141 mg, 0.383 mmol), 8N aqueous sodium hydroxide solution (0.282 mL) and ethanol (2.8 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.5 Hz), 1.21 (3 H, t, J = 7.1 Hz), 2.18 (2 H, q, J = 7.5 Hz), 3.85 (3 H, s), 4.16 (2 H, q, J = 7.1 Hz), 6.53 (1 H, s), 7.18-7.31 (2 H, m), 7.40-7.60 (3 H, m), 12.43 (1 H, br s).

[0215]

Reference Example 19

Production of ethyl 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

To a solution of the compound of Reference Example 6 (150 mg, 0.441 mmol) in acetone (3.0 mL) were added potassium carbonate (122 mg, 0.882 mmol) and diisopropyl sulfate (110 µL, 0.662 mmol), and the mixture was stirred with heating under reflux for 7 hr. The reaction mixture was cooled to 0°C, water

(20 mL) was added thereto, and the mixture was extracted with ethyl acetate (50 mL). The extract was washed with brine (20 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, ethyl acetate:ethanol=90:10→60:40) to give the title compound (105 mg, 62%) as a pale-yellow powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.0 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 4.75 (1 H, spt, J = 6.0 Hz), 6.54 (1 H, s), 7.18-7.34 (2 H, m), 7.40-7.61 (3 H, m).

[0216]

Reference Example 20

Production of 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (98.0 mg, 100%) was obtained as a white powder from the compound of Reference Example 19 (105 mg, 0.275 mmol), 8N aqueous sodium hydroxide solution (0.210 mL) and ethanol (2.1 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.0 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.72 (1 H, spt, J = 6.0 Hz), 6.53 (1 H, s), 7.20-7.29 (2 H, m), 7.41-7.58 (3 H, m), 12.31 (1 H, br s).

[0217]

Reference Example 21

Production of methyl (2Z)-3-[(4-fluorophenyl)amino]pent-2-enoate

By a method similar to that in Reference Example 1, the title compound (11.4 g, 67%) was obtained as a yellow oil from methyl 3-oxovalerate (10.0 g, 76.8 mmol), 4-fluoroaniline (7.36 mL, 76.8 mmol), p-toluenesulfonic acid monohydrate (730 mg, 3.84 mmol), cyclohexane (40 mL) and toluene (10 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.92 (3 H, t, J = 7.5 Hz), 2.27 (2 H, q, J = 7.4 Hz), 3.58 (3 H, s), 4.70 (1 H, s), 7.14-7.31 (4 H, m), 10.12 (1 H, s).

[0218]

Reference Example 22

Production of methyl 3-[(4-fluorophenyl)amino]pentanoate

By a method similar to that in Reference Example 10, the title compound (7.71 g, 68%) was obtained as a pale-yellow oil from the compound of Reference Example 21 (11.2 g, 50.2 mmol), 5% platinum-activated carbon (2.24 g), acetic acid (56 mL) and ethanol (56 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.87 (3 H, t, J = 7.5 Hz), 1.40-1.59 (2 H, m), 2.43 (2 H, dd, J = 6.5, 2.7 Hz), 3.52-3.65 (4 H, m), 5.53 (1 H, d, J = 9.4 Hz), 6.50-6.61 (2 H, m), 6.84-6.95 (2 H, m).

[0219]

Reference Example 23

Production of ethyl 6-ethyl-1-(4-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate

A mixture of the compound of Reference Example 22 (7.70 g, 34.2 mmol), ethyl (chloroformyl)acetate (6.50 mL, 51.3 mmol) and THF (77 mL) was stirred at room temperature for 12 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added ethanol (232 mL) and 20% ethanol solution (17.5 mL, 51.3 mmol) of sodium ethoxide, and the mixture was stirred at 70°C for 24 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The

insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=98:2→70:30). To the toluene solution (210 mL) of the obtained yellow oil was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (8.54 g, 37.6 mmol), and the mixture was stirred with heating under reflux for 1 hr. To the reaction mixture was added water (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was passed through amino silica gel (eluate, ethyl acetate:ethanol=1:1), and the eluate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=95:5→50:50) to give the title compound (5.04 g, 48%) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.97 (3 H, t, J = 7.4 Hz), 1.22 (3 H, t, J = 7.1 Hz), 2.14 (2 H, q, J = 7.4 Hz), 4.22 (2 H, q, J = 7.1 Hz), 6.01 (1 H, s), 7.25-7.42 (4 H, m), 12.43 (1 H, s).

[0220]

Reference Example 24

Production of ethyl 4-chloro-6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 5, the title compound (4.36 g, 82%) was obtained as a yellow powder from the compound of Reference Example 23 (5.04 g, 16.5 mmol), phosphorus oxychloride (4.62 mL, 49.5 mmol) and MeCN (100 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.99 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 2.20 (2 H, q, J = 7.4 Hz), 4.26 (2 H, q, J = 7.1 Hz), 6.46 (1 H, s), 7.34-7.48 (4 H, m).

[0221]

Reference Example 25

Production of ethyl 6-ethyl-5-(4-fluorophenyl)-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-

carboxylate

A mixture of the compound of Reference Example 24 (3.70 g, 11.4 mmol), ethyl sarcosinate hydrochloride (3.51 g, 22.9 mmol), diisopropylethylamine (9.93 mL, 57.0 mmol) and ethanol (37 mL) was stirred with heating under reflux for 3 hr. After cooling, to the reaction mixture was added 20% ethanol solution (15 mL) of sodium ethoxide, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and to the residue was added water (50 mL), and the mixture was acidified with 2N hydrochloric acid. The precipitate was collected by filtration, and washed successively with water and diisopropyl ether to give the title compound (3.92 g, 96%) as a yellow powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.32 (3 H, t, J = 7.1 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.81 (3 H, s), 4.31 (2 H, q, J = 7.1 Hz), 6.49 (1 H, s), 7.28-7.40 (4 H, m), 8.87 (1 H, br s).

[0222]

Reference Example 26

Production of ethyl 6-ethyl-5-(4-fluorophenyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 7, the title compound (146 mg, 66%) was obtained as a yellow powder from the compound of Reference Example 25 (180 mg, 0.502 mmol), cesium carbonate (196 mg, 0.602 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (79.7 µL, 0.553 mmol) and DMF (1.8 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.29 (3 H, t, J = 7.1 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.88 (3 H, s), 4.26 (2 H, q, J = 7.1 Hz), 4.82 (2 H, q, J = 9.3 Hz), 6.62 (1 H, s), 7.27-7.45 (4 H, m).

[0223]

Reference Example 27

Production of 6-ethyl-5-(4-fluorophenyl)-1-methyl-4-oxo-3-

(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (120 mg, 88%) was obtained as a pale-yellow solid from the compound of Reference Example 26 (145 mg, 0.329 mmol), 8N aqueous sodium hydroxide solution (0.290 mL) and ethanol (2.9 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.3 Hz), 2.21 (2 H, q, J = 7.3 Hz), 3.87 (3 H, s), 4.80 (2 H, q, J = 9.3 Hz), 6.59 (1 H, s), 7.29-7.41 (4 H, m), 12.74 (1 H, br s).

[0224]

Reference Example 28

Production of ethyl 3-ethoxy-6-ethyl-5-(4-fluorophenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 17, the title compound (149 mg, 67%) was obtained as a pale-yellow powder from the compound of Reference Example 25 (200 mg, 0.558 mmol), potassium carbonate (154 mg, 1.12 mmol), diethyl sulfate (94.8 μL, 0.726 mmol) and acetone (4.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.23 (3 H, t, J = 7.1 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.19 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.15 (2 H, q, J = 7.1 Hz), 4.26 (2 H, q, J = 7.1 Hz), 6.55 (1 H, s), 7.25-7.44 (4 H, m).

[0225]

Reference Example 29

Production of 3-ethoxy-6-ethyl-5-(4-fluorophenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (119 mg, 86%) was obtained as a white powder from the compound of Reference Example 28 (149 mg, 0.386 mmol), 8N aqueous sodium hydroxide solution (0.298 mL) and ethanol (3.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.21 (3 H, t, J = 7.0 Hz), 2.19 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s),

4.15 (2 H, q, J = 7.0 Hz), 6.54 (1 H, s), 7.26-7.40 (4 H, m), 12.44 (1 H, br s).

[0226]

Reference Example 30

Production of ethyl 6-ethyl-5-(4-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 19, the title compound (120 mg, 54%) was obtained as a pale-yellow solid from the compound of Reference Example 25 (200 mg, 0.558 mmol), potassium carbonate (154 mg, 1.12 mmol), diisopropyl sulfate (120 µL, 0.726 mmol) and acetone (4.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.0 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.19 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 4.74 (1 H, spt, J = 6.0 Hz), 6.55 (1 H, s), 7.28-7.41 (4 H, m).

[0227]

Reference Example 31

Production of 6-ethyl-5-(4-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (90.9 mg, 81%) was obtained as a pale-yellow solid from the compound of Reference Example 30 (120 mg, 0.300 mmol), 8N aqueous sodium hydroxide solution (0.240 mL) and ethanol (2.4 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.0 Hz), 2.19 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.63-4.79 (1 H, m), 6.53 (1 H, s), 7.26-7.40 (4 H, m), 12.32 (1 H, br s).

[0228]

Reference Example 32

Production of methyl (2Z)-3-{[4-(trifluoromethyl)phenyl]amino}pent-2-enoate

By a method similar to that in Reference Example 1, the

title compound (11.5 g, 55%) was obtained as a colorless oil from methyl 3-oxovalerate (10.0 g, 76.8 mmol), 4-trifluoromethylaniline (9.54 mL, 76.8 mmol), p-toluenesulfonic acid monohydrate (730 mg, 3.84 mmol) and cyclohexane (50 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.98 (3 H, t, J = 7.5 Hz), 2.43-2.50 (2 H, m), 3.61 (3 H, s), 4.86 (1 H, s), 7.36 (2 H, d, J = 8.4 Hz), 7.69 (2 H, d, J = 8.4 Hz), 10.42 (1 H, s).

[0229]

Reference Example 33

Production of methyl 3-{[4-(trifluoromethyl)phenyl]amino}pentanoate

By a method similar to that in Reference Example 10, the title compound (5.88 g, 89%) was obtained as a yellow oil from the compound of Reference Example 32 (6.54 g, 23.9 mmol), 5% platinum-activated carbon (654 mg), acetic acid (33 mL) and ethanol (33 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.87 (3 H, t, J = 7.4 Hz), 1.40-1.66 (2 H, m), 2.46-2.50 (2 H, m), 3.56 (3 H, s), 3.65-3.82 (1 H, m), 6.23 (1 H, d, J = 8.9 Hz), 6.67 (2 H, d, J = 8.7 Hz), 7.35 (2 H, d, J = 8.7 Hz).

[0230]

Reference Example 34

Production of ethyl 6-ethyl-4-hydroxy-2-oxo-1-[4-(trifluoromethyl)phenyl]-1,2,5,6-tetrahydropyridine-3-carboxylate

By a method similar to that in Reference Example 11, the title compound (3.28 g, 47%) was obtained as a yellow oil from the compound of Reference Example 33 (5.88 g, 21.4 mmol), ethyl (chloroformyl)acetate (3.51 mL, 27.8 mmol), THF (59 mL) and 20% ethanol solution (13.4 mL, 39.4 mmol) of sodium ethoxide and ethanol (77 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.79 (3 H, t, J = 7.5 Hz), 1.23 (3 H, t, J = 7.1 Hz), 1.56-1.70 (2 H, m), 2.58 (1 H, dd, J = 17.4, 2.5 Hz), 3.22-3.31 (1 H, m),3.91-4.03 (1 H, m), 4.20 (2 H, q, J = 7.1 Hz), 7.56 (2 H, d, J = 8.6 Hz), 7.74 (2 H, d, J = 8.6

Hz), 12.74 (1 H, br s).

[0231]

Reference Example 35

Production of ethyl 6-ethyl-4-hydroxy-2-oxo-1-[4-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 4, the title compound (1.95 g, 63%) was obtained as a yellow oil from the compound of Reference Example 34 (3.28 g, 8.74 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.20 g, 9.61 mmol) and toluene (66 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.97 (3 H, t, J = 7.4 Hz), 1.22 (3 H, t, J = 7.1 Hz), 2.13 (2 H, q, J = 7.4 Hz), 4.22 (2 H, q, J = 7.1 Hz), 6.04 (1 H, s), 7.55 (2 H, d, J = 8.3 Hz), 7.90 (2 H, d, J = 8.3 Hz), 12.48 (1 H, s).

[0232]

Reference Example 36

Production of ethyl 4-chloro-6-ethyl-2-oxo-1-[4-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 5, the title compound (1.79 g, 87%) as a white solid from the compound of Reference Example 35 (1.95 g, 5.49 mmol), phosphorus oxychloride (1.53 mL, 16.5 mmol) and MeCN (39 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.99 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 2.19 (2 H, q, J = 7.4 Hz), 4.27 (2 H, q, J = 7.1 Hz), 6.50 (1 H, s), 7.66 (2 H, d, J = 8.3 Hz), 7.94 (2 H, d, J = 8.3 Hz).

[0233]

Reference Example 37

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 25, the title compound (1.78 g, 91%) was obtained as a beige powder from the compound of Reference Example 36 (1.79 g, 4.79 mmol), ethyl sarcosinate hydrochloride (1.47 g, 9.58 mmol),

triethylamine (8.95 mL), ethanol (36 mL) and 20% ethanol solution (8.95 mL) of sodium ethoxide.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.32 (3 H, t, J = 7.1 Hz), 2.17 (2 H, q, J = 7.4 Hz), 3.83 (3 H, s), 4.31 (2 H, q, J = 7.1 Hz), 6.54 (1 H, s), 7.54 (2 H, d, J = 8.4 Hz), 7.90 (2 H, d, J = 8.4 Hz), 8.93 (1 H, br s).

[0234]

Reference Example 38

Production of ethyl 6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 7, the title compound (270 mg, 90%) was obtained as a yellow powder from the compound of Reference Example 37 (250 mg, 0.612 mmol), cesium carbonate (239 mg, 0.734 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (97.1 µL, 0.673 mmol) and DMF (2.5 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.3 Hz), 1.29 (3 H, t, J = 7.1 Hz), 2.20 (2 H, q, J = 7.3 Hz), 3.89 (3 H, s), 4.27 (2 H, q, J = 7.1 Hz), 4.81 (2 H, q, J = 9.1 Hz), 6.67 (1 H, s), 7.58 (2 H, d, J = 8.4 Hz), 7.91 (2 H, d, J = 8.4 Hz).

[0235]

Reference Example 39

Production of 6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (115 mg, 45%) was obtained as a yellow solid from the compound of Reference Example 38 (270 mg, 0.551 mmol), 8N aqueous sodium hydroxide solution (0.540 mL) and ethanol (5.4 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.3 Hz), 2.20 (2 H, q, J = 7.3 Hz), 3.89 (3 H, s), 4.79 (2 H, q, J = 9.3 Hz), 6.65 (1 H, s), 7.57 (2 H, d, J = 8.3 Hz), 7.91 (2 H, d, J = 8.3 Hz), 12.77 (1 H, br s).

[0236]

Reference Example 40

Production of ethyl 3-ethoxy-6-ethyl-1-methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 17, the title compound (139 mg, 52%) was obtained as a pale-yellow powder from the compound of Reference Example 37 (250 mg, 0.612 mmol), potassium carbonate (169 mg, 1.12 mmol), diethyl sulfate (104 μL, 0.796 mmol) and acetone (5.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.23 (3 H, t, J = 7.0 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.87 (3 H, s), 4.14 (2 H, q, J = 7.0 Hz), 4.27 (2 H, q, J = 7.1 Hz), 6.60 (1 H, s), 7.55 (2 H, d, J = 8.4 Hz), 7.90 (2 H, d, J = 8.4 Hz).

[0237]

Reference Example 41

Production of 3-ethoxy-6-ethyl-1-methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (101 mg, 78%) was obtained as a white solid from the compound of Reference Example 40 (139 mg, 0.319 mmol), 8N aqueous sodium hydroxide solution (0.278 mL) and ethanol (2.8 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.21 (3 H, t, J = 7.0 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.87 (3 H, s), 4.15 (2 H, q, J = 7.0 Hz), 6.58 (1 H, s), 7.54 (2 H, d, J = 8.2 Hz), 7.90 (2 H, d, J = 8.2 Hz), 12.46 (1 H, br s).

[0238]

Reference Example 42

Production of ethyl 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 19, the

title compound (130 mg, 47%) was obtained as a pale-yellow solid from the compound of Reference Example 37 (250 mg, 0.612 mmol), potassium carbonate (169 mg, 1.12 mmol), diisopropyl sulfate (132 μL, 0.796 mmol) and acetone (5.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.0 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.87 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 4.65-4.81 (1 H, m), 6.59 (1 H, s), 7.55 (2 H, d, J = 8.4 Hz), 7.90 (2 H, d, J = 8.4 Hz).

[0239]

Reference Example 43

Production of 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (122 mg, 100%) was obtained as a pale-yellow solid from the compound of Reference Example 42 (130 mg, 0.289 mmol), 8N aqueous sodium hydroxide solution (0.260 mL) and ethanol (2.6 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.3 Hz), 1.17 (6 H, d, J = 6.0 Hz), 2.18 (2 H, q, J = 7.3 Hz), 3.87 (3 H, s), 4.60-4.77 (1 H, m), 6.57 (1 H, s), 7.54 (2 H, d, J = 8.4 Hz), 7.89 (2 H, d, J = 8.4 Hz), 12.35 (1 H, br s).

[0240]

Reference Example 44

Production of methyl (2Z)-3-[(4-methoxyphenyl)amino]pent-2-enoate

By a method similar to that in Reference Example 1, the title compound (10.5 g, 67%) was obtained as a yellow oil from methyl 3-oxovalerate (8.67 g, 66.6 mmol), 4-methoxyaniline (8.20 g, 66.6 mmol), p-toluenesulfonic acid monohydrate (633 mg, 3.33 mmol), cyclohexane (30 mL) and toluene (30 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.91 (3 H, t, J = 7.6 Hz), 2.22 (2 H, q, J = 7.6 Hz), 3.57 (3 H, s), 3.76 (3 H, s), 4.64 (1 H, s), 6.90-6.97 (2 H, m), 7.09-7.19 (2 H, m), 10.05 (1 H, s).

[0241]

Reference Example 45

Production of methyl 3-[(3-ethoxy-3-oxopropanoyl)(4-methoxyphenyl)amino]pentanoate

A mixture of the compound of Reference Example 44 (10.5 g, 44.6 mmol), 5% platinum-activated carbon (1.05 g), acetic acid (50 mL) and ethanol (50 mL) was stirred at room temperature under a hydrogen atmosphere for 2 hr. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue was added saturated aqueous sodium hydrogen carbonate solution (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added THF (97 mL) and ethyl (chloroformyl)acetate (6.17 mL, 48.8 mmol), and the mixture was stirred at room temperature for 4 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=99:1→50:50) to give the title compound (4.22 g, 27%) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.93 (3 H, t, J = 7.3 Hz), 1.11 (3 H, t, J = 7.1 Hz), 1.31-1.45 (2 H, m), 2.32-2.39 (2 H, m), 3.01 (2 H, s), 3.59 (3 H, s), 3.78 (3 H, s), 3.97 (2 H, q, J = 7.1 Hz), 4.77-4.95 (1 H, m), 6.96-7.06 (2 H, m), 7.07-7.22 (2 H, m).

[0242]

Reference Example 46

Production of ethyl 6-ethyl-4-hydroxy-1-(4-methoxyphenyl)-2-

oxo-1,2,5,6-tetrahydropyridine-3-carboxylate

A mixture of the compound of Reference Example 45 (4.22 g, 12.0 mmol), 20% ethanol solution (8.17 mL, 24.0 mmol) of sodium ethoxide and ethanol (42 mL) was stirred at 60°C for 2 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=99:1→50:50) to give the title compound (2.47 g, 64%) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.76 (3 H, t, J = 7.5 Hz), 1.22 (3 H, t, J = 7.2 Hz), 1.47-1.66 (2 H, m), 2.52-2.62 (1 H, dm), 3.13-3.29 (1 H, m), 3.70-3.80 (4 H, m), 4.20 (2 H, q, J = 7.2 Hz), 6.84-7.02 (2 H, m), 7.11-7.32 (2 H, m), 12.61 (1 H, br s).

[0243]

Reference Example 47

Production of ethyl 6-ethyl-4-hydroxy-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 4, the title compound (2.35 g, 96%) was obtained as a white powder from the compound of Reference Example 46 (2.47 g, 7.73 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.93 g, 8.51 mmol) and toluene (49 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.90 (3 H, t, J = 7.4 Hz), 1.18 (3 H, t, J = 7.1 Hz), 2.03 (2 H, q, J = 7.4 Hz), 3.79 (3 H, s), 4.07 (2 H, q, J = 7.1 Hz), 5.61 (1 H, s), 6.94-7.02 (2 H, m), 7.02-7.10 (2 H, m), 12.24 (1 H, br s).

[0244]

Reference Example 48

Production of ethyl 4-chloro-6-ethyl-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 5, the

title compound (2.01 g, 80%) was obtained as a yellow oil from the compound of Reference Example 47 (2.35 g, 7.41 mmol), phosphorus oxychloride (2.06 mL, 22.2 mmol) and MeCN (47 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.98 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 2.22 (2 H, q, J = 7.4 Hz), 3.81 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 6.43 (1 H, s), 6.98-7.15 (2 H, m), 7.18-7.32 (2 H, m).

[0245]

Reference Example 49

Production of ethyl 6-ethyl-3-hydroxy-5-(4-methoxyphenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 25, the title compound (2.02 g, 91%) was obtained as a beige powder from the compound of Reference Example 48 (2.01 g, 5.99 mmol), ethyl sarcosinate hydrochloride (1.84 g, 12.0 mmol), triethylamine (10 mL), ethanol (40 mL) and 20% ethanol solution (10 mL) of sodium ethoxide.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.4 Hz), 1.32 (3 H, t, J = 7.1 Hz), 2.20 (2 H, q, J = 7.4 Hz), 3.81 (3 H, s), 3.82 (3 H, s), 4.30 (2 H, q, J = 7.1 Hz), 6.47 (1 H, s), 6.97-7.10 (2 H, m), 7.10-7.25 (2 H, m), 8.88 (1 H, br s).

[0246]

Reference Example 50

Production of ethyl 6-ethyl-5-(4-methoxyphenyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 7, the title compound (295 mg, 81%) was obtained as a beige powder from the compound of Reference Example 49 (300 mg, 0.810 mmol), cesium carbonate (317 mg, 0.972 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (128 μL, 0.891 mmol) and DMF (3.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.29 (3 H, t, J = 7.1 Hz), 2.23 (2 H, q, J = 7.4 Hz), 3.82 (3 H, s),

3.87 (3 H, s), 4.26 (2 H, q, J = 7.1 Hz), 4.83 (2 H, q, J = 9.2 Hz), 6.59 (1 H, s), 6.98-7.10 (2 H, m), 7.12-7.24 (2 H, m).

[0247]

Reference Example 51

Production of 6-ethyl-5-(4-methoxyphenyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (171 mg, 63%) was obtained as a yellow powder from the compound of Reference Example 50 (290 mg, 0.641 mmol), 8N aqueous sodium hydroxide solution (0.580 mL) and ethanol (5.8 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 2.22 (2 H, q, J = 7.4 Hz), 3.82 (3 H, s), 3.87 (3 H, s), 4.81 (2 H, q, J = 9.3 Hz), 6.57 (1 H, s), 7.00-7.11 (2 H, m), 7.13-7.23 (2 H, m), 12.70 (1 H, br s).

[0248]

Reference Example 52

Production of ethyl 3-ethoxy-6-ethyl-5-(4-methoxyphenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 17, the title compound (163 mg, 50%) was obtained as a yellow powder from the compound of Reference Example 49 (300 mg, 0.810 mmol), potassium carbonate (224 mg, 1.62 mmol), diethyl sulfate (138 µL, 1.05 mmol) and acetone (6.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.23 (3 H, t, J = 7.0 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.82 (3 H, s), 3.84 (3 H, s), 4.15 (2 H, q, J = 7.0 Hz), 4.26 (2 H, q, J = 7.1 Hz), 6.52 (1 H, s), 6.98-7.09 (2 H, m), 7.10-7.22 (2 H, m).

[0249]

Reference Example 53

Production of 3-ethoxy-6-ethyl-5-(4-methoxyphenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (139 mg, 92%) was obtained as a pale-yellow powder from the compound of Reference Example 52 (163 mg, 0.409 mmol), 8N aqueous sodium hydroxide solution (0.326 mL) and ethanol (3.3 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.21 (3 H, t, J = 7.1 Hz), 2.20 (2 H, q, J = 7.4 Hz), 3.82 (3 H, s), 3.84 (3 H, s), 4.15 (2 H, q, J = 7.1 Hz), 6.50 (1 H, s), 6.99-7.09 (2 H, m), 7.10-7.20 (2 H, m), 12.41 (1 H, br s).

[0250]

Reference Example 54

Production of ethyl 6-ethyl-5-(4-methoxyphenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 19, the title compound (141 mg, 42%) was obtained as a yellow solid from the compound of Reference Example 49 (300 mg, 0.810 mmol), potassium carbonate (224 mg, 1.62 mmol), diisopropyl sulfate (174 μL, 1.05 mmol) and acetone (6.0 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.2 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.82 (3 H, s), 3.84 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 4.66-4.84 (1 H, m), 6.51 (1 H, s), 6.99-7.09 (2 H, m), 7.11-7.20 (2 H, m).

[0251]

Reference Example 55

Production of 6-ethyl-5-(4-methoxyphenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (123 mg, 94%) was obtained as a pale-yellow powder from the compound of Reference Example 54 (141 mg, 0.342 mmol), 8N aqueous sodium hydroxide solution (0.282 mL) and ethanol (2.8 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.17 (6

H, d, J = 6.0 Hz), 2.20 (2 H, q, J = 7.4 Hz), 3.82 (3 H, s), 3.84 (3 H, s), 4.63-4.81 (1 H, m), 6.50 (1 H, s), 6.98-7.09 (2 H, m), 7.10-7.21 (2 H, m), 12.29 (1 H, br s).

[0252]

Reference Example 56

Production of methyl (2Z)-3-[(3-fluorophenyl)amino]pent-2-enoate

By a method similar to that in Reference Example 1, the title compound (5.00 g, 45%) was obtained as a colorless oil from methyl 3-oxovalerate (6.42 g, 49.3 mmol), 3-fluoroaniline (5.48 g, 49.3 mmol), p-toluenesulfonic acid monohydrate (281 mg, 1.48 mmol), cyclohexane (23 mL) and toluene (23 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.95 (3 H, t, J = 7.4 Hz), 2.41 (2 H, q, J = 7.4 Hz), 3.59 (3 H, s), 4.77 (1 H, s), 6.96-7.15 (3 H, m), 7.34-7.45 (1 H, m), 10.27 (1 H, s).

[0253]

Reference Example 57

Production of methyl 3-[(3-ethoxy-3-oxopropanoyl)(3-fluorophenyl)amino]pentanoate

By a method similar to that in Reference Example 45, the title compound (4.41 g, 58%) was obtained as a yellow oil from the compound of Reference Example 56 (5.00 g, 22.4 mmol), 5% platinum-activated carbon (1.00 g), acetic acid (25 mL), ethanol (25 mL), ethyl (chloroformyl)acetate (5.17 mL, 40.9 mmol) and THF (46 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.93 (3 H, t, J = 7.4 Hz), 1.11 (3 H, t, J = 7.1 Hz), 1.36-1.52 (2 H, m), 2.41-2.48 (2 H, m), 3.08 (2 H, s), 3.60 (3 H, s), 3.97 (2 H, q, J = 7.1 Hz), 4.70-4.89 (1 H, m), 7.06-7.21 (2 H, m), 7.28-7.38 (1 H, m), 7.48-7.60 (1 H, m).

[0254]

Reference Example 58

Production of ethyl 6-ethyl-1-(3-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate

A mixture of the compound of Reference Example 57 (4.41 g,

13.0 mmol), 20% ethanol solution (8.85 mL, 26.0 mmol) of sodium ethoxide and ethanol (44 mL) was stirred at 60°C for 2 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=95:5→50:50). To the toluene solution (56 mL) of the obtained yellow oil was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.28 g, 10.1 mmol), and the mixture was stirred with heating under reflux for 1 hr. To the reaction mixture was added water (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, and the residue was purified by amino silica gel column chromatography (eluate, ethyl acetate:ethanol=1:1) to give the title compound (2.11 g, 53%) as a yellow oil.
^{1}H NMR (300 MHz, DMSO-d_6) δ:0.98 (3 H, t, J = 7.4 Hz), 1.22 (3 H, t, J = 7.0 Hz), 2.16 (2 H, q, J = 7.4 Hz), 4.22 (2 H, q, J = 7.0 Hz), 6.00 (1 H, s), 7.07-7.17 (1 H, m), 7.23-7.41 (2 H, m), 7.50-7.62 (1 H, m), 12.44 (1 H, br s).

[0255]

Reference Example 59

Production of ethyl 4-chloro-6-ethyl-1-(3-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

By a method similar to that in Reference Example 5, the title compound (1.71 g, 76%) was obtained as a yellow oil from the compound of Reference Example 58 (2.11 g, 6.91 mmol), phosphorus oxychloride (2.57 mL, 27.6 mmol) and MeCN (42 mL).
^{1}H NMR (300 MHz, DMSO-d_6) δ:1.00 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 2.22 (2 H, q, J = 7.4 Hz), 4.26 (2 H, q, J = 7.1 Hz), 6.47 (1 H, s), 7.20-7.27 (1 H, m), 7.32-7.45 (2 H,

m), 7.54-7.66 (1 H, m).

[0256]

Reference Example 60

Production of ethyl 6-ethyl-5-(3-fluorophenyl)-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 25, the title compound (1.75 g, 93%) was obtained as a yellow solid from the compound of Reference Example 59 (1.71 g, 5.28 mmol), ethyl sarcosinate hydrochloride (1.62 g, 10.6 mmol), triethylamine (8.6 mL), ethanol (34 mL) and 20% ethanol solution (8.6 mL) of sodium ethoxide.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.30 (3 H, t, J = 7.1 Hz), 2.20 (2 H, q, J = 7.4 Hz), 3.75 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 6.45 (1 H, s), 7.08-7.17 (1 H, m), 7.20-7.39 (2 H, m), 7.48-7.62 (1 H, m), 8.65 (1 H, br s).

[0257]

Reference Example 61

Production of ethyl 6-ethyl-5-(3-fluorophenyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 7, the title compound (240 mg, 89%) was obtained as a yellow solid from the compound of Reference Example 60 (220 mg, 0.614 mmol), cesium carbonate (240 mg, 0.737 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (97.4 µL, 0.675 mmol) and DMF (2.2 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.05 (3 H, t, J = 7.4 Hz), 1.29 (3 H, t, J = 7.1 Hz), 2.23 (2 H, q, J = 7.4 Hz), 3.88 (3 H, s), 4.26 (2 H, q, J = 7.1 Hz), 4.82 (2 H, q, J = 9.3 Hz), 6.63 (1 H, s), 7.13-7.20 (1 H, m), 7.26-7.41 (2 H, m), 7.50-7.67 (1 H, m).

[0258]

Reference Example 62

Production of 6-ethyl-5-(3-fluorophenyl)-1-methyl-4-oxo-3-

(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (220 mg, 98%) was obtained as a yellow powder from the compound of Reference Example 61 (240 mg, 0.545 mmol), 8N aqueous sodium hydroxide solution (0.480 mL) and ethanol (4.8 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.05 (3 H, t, J = 7.3 Hz), 2.23 (2 H, q, J = 7.3 Hz), 3.88 (3 H, s), 4.80 (2 H, q, J = 9.1 Hz), 6.61 (1 H, s), 7.12-7.20 (1 H, m), 7.25-7.40 (2 H, m), 7.50-7.66 (1 H, m), 12.75 (1 H, br s).

[0259]

Reference Example 63

Production of ethyl 3-ethoxy-6-ethyl-5-(3-fluorophenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 17, the title compound (223 mg, 94%) was obtained as a yellow solid from the compound of Reference Example 60 (220 mg, 0.614 mmol), potassium carbonate (170 mg, 1.23 mmol), diethyl sulfate (104 µL, 0.798 mmol) and acetone (4.4 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.24 (3 H, t, J = 7.0 Hz), 1.31 (3 H, t, J = 7.0 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.86 (3 H, s), 4.15 (2 H, q, J = 7.0 Hz), 4.26 (2 H, q, J = 7.0 Hz), 6.56 (1 H, s), 7.08-7.18 (1 H, m), 7.22-7.40 (2 H, m), 7.50-7.65 (1 H, m).

[0260]

Reference Example 64

Production of 3-ethoxy-6-ethyl-5-(3-fluorophenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (160 mg, 77%) was obtained as a white powder from the compound of Reference Example 63 (223 mg, 0.577 mmol), 8N aqueous sodium hydroxide solution (0.446 mL) and ethanol (4.5 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.21 (3 H, t, J = 7.0 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.86 (3 H, s), 4.15 (2 H, q, J = 7.0 Hz), 6.54 (1 H, s), 7.07-7.17 (1 H, m), 7.21-7.39 (2 H, m), 7.49-7.66 (1 H, m), 12.45 (1 H, br s).

[0261]

Reference Example 65

Production of ethyl 6-ethyl-5-(3-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

By a method similar to that in Reference Example 19, the title compound (195 mg, 79%) was obtained as a pale-yellow solid from the compound of Reference Example 60 (220 mg, 0.614 mmol), potassium carbonate (170 mg, 1.23 mmol), diisopropyl sulfate (132 μL, 0.798 mmol), acetone (4.4 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.18 (6 H, d, J = 6.0 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.86 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 4.65-4.84 (1 H, m), 6.55 (1 H, s), 7.07-7.20 (1 H, m), 7.22-7.40 (2 H, m), 7.49-7.66 (1 H, m).

[0262]

Reference Example 66

Production of 6-ethyl-5-(3-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (163 mg, 90%) was obtained as a white powder from the compound of Reference Example 65 (195 mg, 0.487 mmol), 8N aqueous sodium hydroxide solution (0.390 mL) and ethanol (3.9 mL).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.2 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.86 (3 H, s), 4.63-4.80 (1 H, m), 6.54 (1 H, s), 7.07-7.17 (1 H, m), 7.22-7.39 (2 H, m), 7.50-7.63 (1 H, m), 12.33 (1 H, br s).

[0263]

Reference Example 67

Production of ethyl 4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carboxylate

To a solution of diethyl malonate (10.0 g, 62.43 mmol) in THF (50 mL) was added sodium hydride (oil about 60%; 2.50 g, 62.43 mmol) under ice-cooling, and the mixture was stirred for 30 min. To this mixture was added a solution of diketene (2.62 g, 31.22 mmol) in THF (15 mL) under ice-cooling, and the mixture was stirred at 0°C for 1 hr, and then at room temperature for 3 days. The reaction mixture was acidified with 1 N hydrochloric acid (70 mL) under ice-cooling, and extracted three times with ethyl acetate. The extracts were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=1:1) to give the title compound (1.79 g, 29%) as a pale-yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.27 (3 H, t, J = 7.1 Hz), 2.23 (3 H, s), 4.26 (2 H, q, J = 7.1 Hz), 6.20 (1 H, s), 12.80-13.40 (1 H, br).

[0264]

Reference Example 68

Production of ethyl 4-chloro-6-methyl-2-oxo-2H-pyran-3-carboxylate

A mixture of the compound of Reference Example 67 (1.65 g, 8.33 mmol), N,N-diisopropylethylamine (1.08 g,8.33 mmol) and phosphorus oxychloride (6.20 g, 40.4 mmol) was stirred at 110°C for 1 hr. The reaction mixture was allowed to cool, and concentrated under reduced pressure. The residue was added to ice water, and the precipitate was collected by filtration, and washed with water. The obtained solid was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=1:1) to give the title compound (1.20 g, 67%) as an orange solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.27 (3 H, t, J = 7.1 Hz), 2.28 (3 H, d, J = 0.9 Hz), 4.30 (2 H, q, J = 7.1 Hz), 6.64 (1 H, d, J

= 0.9 Hz).

[0265]

Reference Example 69

Production of ethyl 4-[(2-ethoxy-2-oxoethyl)(methyl)amino]-6-methyl-2-oxo-2H-pyran-3-carboxylate

A solution of the compound of Reference Example 68 (1.0 g, 4.62 mmol), ethyl sarcosinate hydrochloride (0.85 g, 5.54 mmol) and triethylamine (1.03 g, 10.16 mmol) in THF (20 mL) was stirred at room temperature for 16 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate, and extracted twice with ethyl acetate. The extracts were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give the title compound (1.34 g, 98%) as a dark red oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.20-1.25 (6 H, m), 2.14 (3 H, s), 2.97 (3 H, s), 4.07-4.19 (4 H, m), 4.27 (2 H, s), 6.17 (1 H, d, J = 0.9 Hz).

[0266]

Reference Example 70

Production of ethyl 3-hydroxy-1,6-dimethyl-4-oxo-1,4-dihydropyrano[4,3-b]pyrrole-2-carboxylate

To a solution of the compound of Reference Example 69 (1.34 g, 4.51 mmol) in ethanol (10 mL) was added 20% ethanol solution (1.50 g, 4.51 mmol) of sodium ethoxide, and the mixture was stirred at room temperature for 30 min. The reaction mixture was acidified with 1 N hydrochloric acid (5 mL), diluted with water (15 mL), and stirred at room temperature for 30 min. The precipitate was collected by filtration, washed with water, and dried under reduced pressure to give the title compound (0.91 g, 80%) as a beige powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.31 (3 H, t, J =7.1 Hz), 2.24 (3 H, s), 3.75 (3 H, s), 4.30 (2 H, q, J = 7.1 Hz), 6.70 (1 H, s), 9.24 (1 H, s).

[0267]

Reference Example 71

Production of ethyl 1,6-dimethyl-4-oxo-3-(2,2,2-trifluoroethoxy)-1,4-dihydropyrano[4,3-b]pyrrole-2-carboxylate

By a method similar to that in Reference Example 7, the title compound (933 mg, 83%) was obtained as a beige solid from the compound of Reference Example 70 (850 mg, 3.38 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.28 (3 H, t, J = 7.1 Hz), 2.27 (3 H, d, J = 0.9 Hz), 3.81 (3 H, s), 4.26 (2 H, q, J=7.1 Hz), 4.82 (2 H, q, J = 9.1 Hz), 6.82 (1 H, d, J = 0.9 Hz).

[0268]

Reference Example 72

Production of ethyl 1,6-dimethyl-5-(4-methylphenyl)-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

A suspension of the compound of Reference Example 71 (50 mg, 0.15 mmol) and p-toluidine (322 mg, 3.00 mmol) in acetic acid (1 mL) was heated under microwave irradiation at 180°C for 1 hr. The reaction mixture was diluted with 1 N hydrochloric acid (10 mL), and the precipitate was collected by filtration. The obtained solid was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=2:1) to give the title compound (20 mg, 32%) as a pale-brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.29 (3 H, t, J = 7.1 Hz), 1.95 (3 H, s), 2.38 (3 H, s), 3.84 (3 H, s), 4.26 (2 H, q, J=7.1 Hz), 4.82 (2 H, q, J = 9.3 Hz), 6.69 (1 H, s), 7.13 (2 H, d, J = 8.1 Hz), 7.32 (2 H, d, J = 8.1 Hz).

[0269]

Reference Example 73

Production of 1,6-dimethyl-5-(4-methylphenyl)-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

By a method similar to that in Reference Example 8, the title compound (23 mg, 53%) was obtained as a pale-beige powder from the compound of Reference Example 72 (45 mg, 0.11 mmol).

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.94 (3 H, s), 2.38 (3 H, s), 3.83 (3 H, s), 4.80 (2 H, q, J = 9.3 Hz), 6.66 (1 H, s), 7.12 (2 H, d, J = 8.4 Hz), 7.31 (2 H, d, J =8.4 Hz), 12.60-12.80 (1 H, br).

[0270]

Reference Example 74

Production of methyl (2Z)-3-[(4-fluorophenyl)amino]pent-2-enoate

A mixture of methyl 3-oxovalerate (10.0 g, 76.8 mmol), 4-fluoroaniline (7.36 mL, 76.8 mmol), p-toluenesulfonic acid monohydrate (730 mg, 3.84 mmol), cyclohexane (40 mL) and toluene (10 mL) was stirred with heating under reflux for 15 hr. The mixture was concentrated under reduced pressure, the insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=99:1→92:8) to give the title compound (11.4 g, 67%) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.92 (3 H, t, J = 7.5 Hz), 2.27 (2 H, q, J = 7.4 Hz), 3.58 (3 H, s), 4.70 (1 H, s), 7.14-7.31 (4 H, m), 10.12 (1 H, s).

[0271]

Reference Example 75

Production of methyl 3-[(4-fluorophenyl)amino]pentanoate

A mixture of the compound of Reference Example 74 (11.2 g, 50.2 mmol), 5% platinum-activated carbon (2.24 g), acetic acid (56 mL) and ethanol (56 mL) was stirred under a hydrogen atmosphere at room temperature for 7 hr. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue was added saturated aqueous sodium hydrogen carbonate solution (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced

pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=99:1→93:7) to give the title compound (7.71 g, 68%) as a pale-yellow oil.
^{1}H NMR (300 MHz, DMSO-d_6) δ:0.87 (3 H, t, J = 7.5 Hz), 1.40-1.59 (2 H, m), 2.43 (2 H, dd, J = 6.5, 2.7 Hz), 3.52-3.65 (4 H, m), 5.53 (1 H, d, J = 9.4 Hz), 6.50-6.61 (2 H, m), 6.84-6.95 (2 H, m).

[0272]

Reference Example 76

Production of ethyl 6-ethyl-1-(4-fluorophenyl)-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate

A mixture of the compound of Reference Example 75 (7.70 g, 34.2 mmol), ethyl (chloroformyl)acetate (6.50 mL, 51.3 mmol) and THF (77 mL) was stirred at room temperature for 12 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added ethanol (232 mL) and 20% ethanol solution (17.5 mL, 51.3 mmol) of sodium ethoxide, and the mixture was stirred at 70°C for 24 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added 1N hydrochloric acid (100 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=98:2→70:30). To a toluene solution (210 mL) of the obtained yellow oil was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (8.54 g, 37.6 mmol), and the mixture was stirred with heating under reflux for 1 hr. To the reaction mixture was added water (100 mL), and the mixture was

extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was passed through amino silica gel (eluate, ethyl acetate:ethanol=1:1), and the eluate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate, hexane:ethyl acetate=95:5→50:50) to give the title compound (5.04 g, 48%) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.97 (3 H, t, J = 7.4 Hz), 1.22 (3 H, t, J = 7.1 Hz), 2.14 (2 H, q, J = 7.4 Hz), 4.22 (2 H, q, J = 7.1 Hz), 6.01 (1 H, s), 7.25-7.42 (4 H, m), 12.43 (1 H, s).

[0273]

Reference Example 77

Production of ethyl 4-chloro-6-ethyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

A mixture of the compound of Reference Example 76 (5.04 g, 16.5 mmol), phosphorus oxychloride (4.62 mL, 49.5 mmol) and MeCN (100 mL) was stirred with heating under reflux for 1 hr. The mixture was concentrated under reduced pressure, to the residue was added ice-water, and the precipitated solid was collected by filtration, and washed with water and diisopropyl ether to give the title compound (4.36 g, 82%) as a yellow powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:0.99 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 2.20 (2 H, q, J = 7.4 Hz), 4.26 (2 H, q, J = 7.1 Hz), 6.46 (1 H, s), 7.34-7.48 (4 H, m).

[0274]

Reference Example 78

Production of ethyl 6-ethyl-5-(4-fluorophenyl)-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

A mixture of the compound of Reference Example 77 (3.70 g, 11.4 mmol), ethyl sarcosinate hydrochloride (3.51 g, 22.9 mmol), diisopropylethylamine (9.93 mL, 57.0 mmol) and ethanol

(37 mL) was stirred with heating under reflux for 3 hr. After cooling, to the reaction mixture was added 20% ethanol solution (15 mL) of sodium ethoxide, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added water (50 mL), and the mixture was acidified with 2N hydrochloric acid. The precipitate was collected by filtration, and washed successively with water and diisopropyl ether to give the title compound (3.92 g, 96%) as a yellow powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.32 (3 H, t, J = 7.1 Hz), 2.18 (2 H, q, J = 7.4 Hz), 3.81 (3 H, s), 4.31 (2 H, q, J = 7.1 Hz), 6.49 (1 H, s), 7.28-7.40 (4 H, m), 8.87 (1 H, br s).

[0275]

Reference Example 79

Production of ethyl 6-ethyl-5-(4-fluorophenyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

A mixture of the compound of Reference Example 78 (180 mg, 0.502 mmol), cesium carbonate (196 mg, 0.602 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (79.7μL, 0.553 mmol) and DMF (1.8 mL) was stirred at room temperature for 1 hr. To the mixture was added water (7.0 mL), and the precipitate was collected by filtration, and washed successively with water and diisopropyl ether to give the title compound (146 mg, 66%) as a yellow powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.29 (3 H, t, J = 7.1 Hz), 2.21 (2 H, q, J = 7.4 Hz), 3.88 (3 H, s), 4.26 (2 H, q, J = 7.1 Hz), 4.82 (2 H, q, J = 9.3 Hz), 6.62 (1 H, s), 7.27-7.45 (4 H, m).

[0276]

Reference Example 80

Production of 6-ethyl-5-(4-fluorophenyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

A mixture of the compound of Reference Example 79 (145 mg, 0.329 mmol), 8N aqueous sodium hydroxide solution (0.290 mL) and ethanol (2.9 mL) was stirred at 50°C for 1 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added water (5.0 mL), and the mixture was acidified with 5N hydrochloric acid. The precipitate was collected by filtration, and washed with water to give the title compound (120 mg, 88%) as a pale-yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.3 Hz), 2.21 (2 H, q, J = 7.3 Hz), 3.87 (3 H, s), 4.80 (2 H, q, J = 9.3 Hz), 6.59 (1 H, s), 7.29-7.41 (4 H, m), 12.74 (1 H, br s).

[0277]

Reference Example 81

Production of ethyl 6-ethyl-5-(4-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

To a solution of the compound of Reference Example 78 (200 mg, 0.558 mmol) in acetone (4.0 mL) were added potassium carbonate (154 mg, 1.12 mmol) and diisopropyl sulfate (120 µL, 0.726 mmol), and the mixture was stirred with heating under reflux for 7 hr. The reaction mixture was cool to 0°C, water (20 mL) was added thereto, and the mixture was extracted with ethyl acetate (50 mL). The extract was washed with brine (20 mL), and dried over anhydrous sodium sulfate. The insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate, ethyl acetate:ethanol=90:10→60:40) to give the title compound (120 mg, 54%) as a pale-yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.0 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.19 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.25 (2 H, q, J = 7.1 Hz), 4.74 (1 H, spt, J = 6.0 Hz), 6.55 (1 H, s), 7.28-7.41 (4 H, m).

[0278]

Reference Example 82

Production of 6-ethyl-5-(4-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

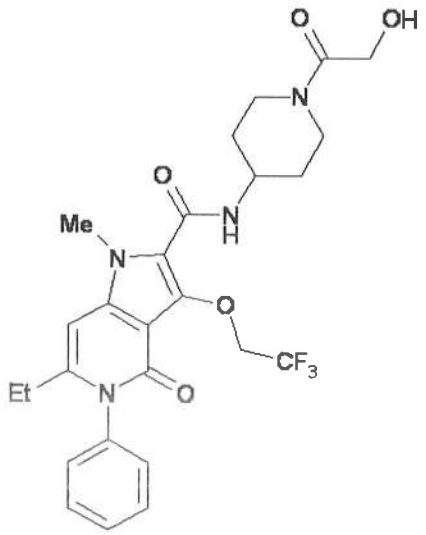
A mixture of the compound of Reference Example 81 (120 mg, 0.300 mmol), 8N aqueous sodium hydroxide solution (0.240 mL) and ethanol (2.4 mL) was stirred at 40°C for 10 hr. The reaction mixture was concentrated under reduced pressure, to the residue was added water (5.0 mL), and the mixture was acidified with 5N hydrochloric acid. The precipitate was collected by filtration, and washed with water to give the title compound (90.9 mg, 81%) as a pale-yellow solid.
^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.17 (6 H, d, J = 6.0 Hz), 2.19 (2 H, q, J = 7.4 Hz), 3.85 (3 H, s), 4.63-4.79 (1 H, m), 6.53 (1 H, s), 7.26-7.40 (4 H, m), 12.32 (1 H, br s).

[0279]

Example 1

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-phenyl-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0280]



[0281]

A mixture of the compound of Reference Example 8 (200 mg, 0.635 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (148 mg, 0.761 mmol), HOBt (171 mg, 1.27 mmol),

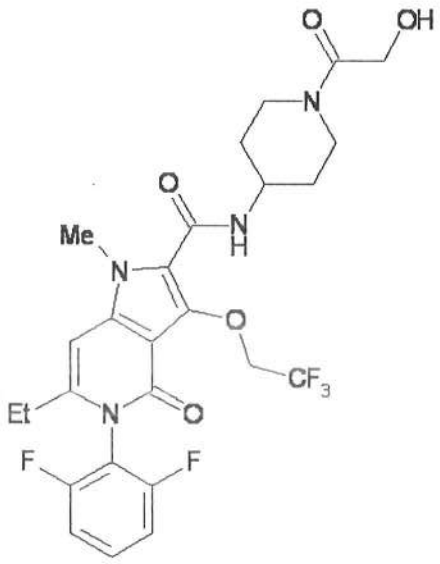
WSCD (243 mg, 1.27 mmol), triethylamine (0.352 mL, 2.54 mmol) and DMF (4.0 mL) was stirred at room temperature for 2 days. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extracts were combined, washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate to give the title compound (39.2 mg, 47%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.27-1.50 (2 H, m), 1.81-1.96 (2 H, m), 2.21 (2 H, q, J = 7.4 Hz), 2.77-2.87 (1 H, m), 3.02-3.17 (1 H, m), 3.64-3.75 (1 H, m), 3.88 (3 H, s), 3.97-4.16 (3 H, m), 4.19-4.35 (1 H, m), 4.53 (1 H, t, J = 5.4 Hz), 5.04 (2 H, q, J = 9.3 Hz), 6.60 (1 H, s), 7.21-7.32 (2 H, m), 7.43-7.60 (4 H, m).

[0282]

Example 2

Production of 5-(2,6-difluorophenyl)-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0283]



[0284]

By a method similar to that in Example 1, the title

compound (130 mg, 49%) was obtained as a white powder from the compound of Reference Example 16 (200 mg, 0.465 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (109 mg, 0.558 mmol), HOBt (96.7 mg, 0.698 mmol), WSCD (134 mg, 0.698 mmol), triethylamine (0.193 mL, 1.40 mmol) and DMF (4.0 mL).

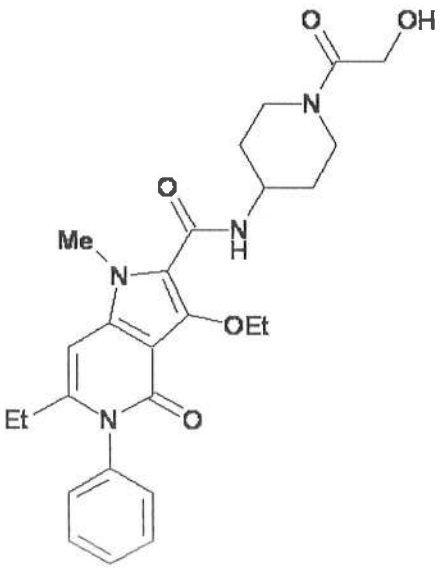
^{1}H NMR (300 MHz, DMSO-d_6) δ:1.05 (3 H, t, J = 7.4 Hz), 1.22-1.51 (2 H, m), 1.80-1.96 (2 H, m), 2.27 (2 H, q, J = 7.4 Hz), 2.75-2.93 (1 H, m), 3.02-3.19 (1 H, m), 3.62-3.77 (1 H, m), 3.88 (3 H, s), 3.96-4.17 (3 H, m), 4.19-4.34 (1 H, m), 4.53 (1 H, t, J = 5.5 Hz), 5.01 (2 H, q, J = 9.3 Hz), 6.73 (1 H, s), 7.32-7.44 (2 H, m), 7.57 (1 H, d, J = 7.6 Hz), 7.60-7.73 (1 H, m).

[0285]

Example 3

Production of 3-ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0286]



[0287]

By a method similar to that in Example 1, the title compound (123 mg, 76%) was obtained as a white powder from the compound of Reference Example 18 (115 mg, 0.338 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (79.0 mg, 0.406 mmol), HOBt (68.5 mg, 0.507 mmol), WSCD (97.2 mg, 0.507

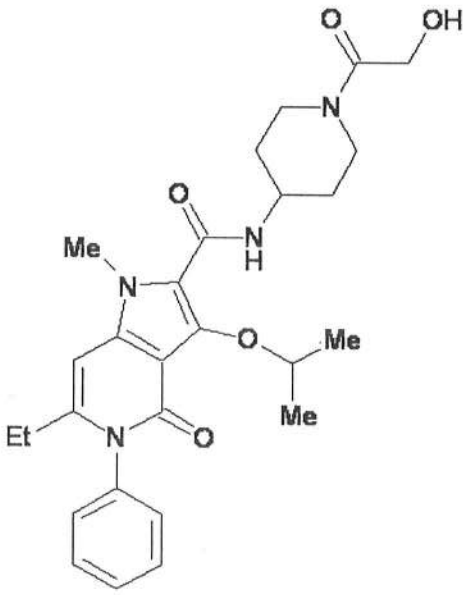
mmol), triethylamine (0.140 mL, 1.01 mmol) and DMF (2.3 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.0 Hz), 1.32-1.56 (2 H, m), 1.84-1.96 (2 H, m), 2.19 (2 H, q, J = 7.4 Hz), 2.81-2.95 (1 H, m), 3.05-3.19 (1 H, m), 3.59-3.74 (1 H, m), 3.91 (3 H, s), 3.97-4.14 (3 H, m), 4.18-4.28 (1 H, m), 4.33 (2 H, q, J = 7.0 Hz), 4.51 (1 H, t, J = 5.4 Hz), 6.54 (1 H, s), 7.20-7.29 (2 H, m), 7.42-7.57 (3 H, m), 7.68 (1 H, d, J = 7.7 Hz).

[0288]

Example 4

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0289]



[0290]

By a method similar to that in Example 1, the title compound (111 mg, 93%) was obtained as a white powder from the compound of Reference Example 20 (95.3 mg, 0.269 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (62.9 mg, 0.323 mmol), HOBt (54.6 mg, 0.404 mmol), WSCD (77.4 mg, 0.404 mmol), triethylamine (0.112 mL, 0.807 mmol) and DMF (1.9 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.4 Hz), 1.21 (6 H, d, J = 6.2 Hz), 1.26-1.56 (2 H, m), 1.84-1.97 (2 H, m), 2.19 (2 H, q, J = 7.4 Hz), 2.77-2.93 (1 H, m), 3.03-3.19 (1 H,

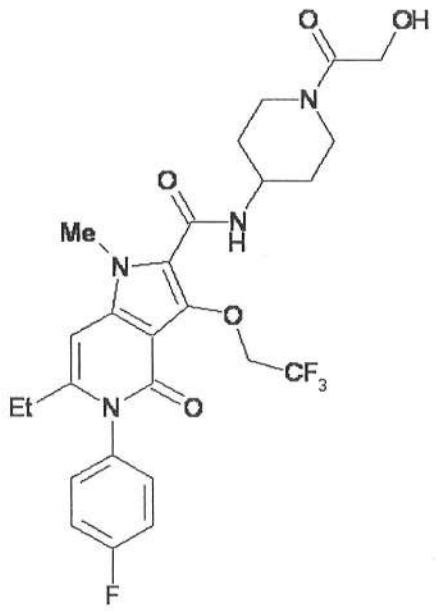
m), 3.60-3.75 (1 H, m), 3.92 (3 H, s), 3.97-4.17 (3 H, m), 4.21-4.34 (1 H, m), 4.51 (1 H, t, J = 5.3 Hz), 4.99 (1 H, spt, J = 6.2 Hz), 6.54 (1 H, s), 7.19-7.32 (2 H, m), 7.38-7.58 (3 H, m), 7.65 (1 H, d, J = 7.7 Hz).

[0291]

Example 5

Production of 6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0292]



[0293]

By a method similar to that in Example 1, the title compound (122 mg, 76%) was obtained as a white powder from the compound of Reference Example 27 (120 mg, 0.291 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (68.0 mg, 0.349 mmol), HOBt (59.1 mg, 0.437 mmol), WSCD (83.7 mg, 0.437 mmol), triethylamine (0.121 mL, 0.873 mmol) and DMF (2.4 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.22-1.50 (2 H, m), 1.82-1.95 (2 H, m), 2.21 (2 H, q, J = 7.4 Hz), 2.75-2.88 (1 H, m), 3.02-3.16 (1 H, m), 3.62-3.75 (1 H, m), 3.88 (3 H, s), 3.95-4.13 (3 H, m), 4.21-4.33 (1 H, m), 4.53 (1 H, t, J = 5.4 Hz), 5.04 (2 H, q, J = 9.3 Hz), 6.60 (1 H, s),

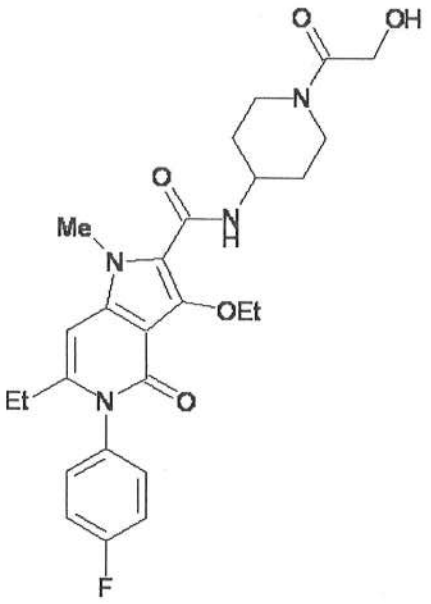
7.30-7.39 (4 H, m), 7.49 (1 H, d, J = 7.6 Hz).

[0294]

Example 6

Production of 3-ethoxy-6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0295]



[0296]

By a method similar to that in Example 1, the title compound (119 mg, 72%) was obtained as a white powder from the compound of Reference Example 29 (119 mg, 0.332 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (77.6 mg, 0.398 mmol), HOBt (67.3 mg, 0.498 mmol), WSCD (95.5 mg, 0.498 mmol), triethylamine (0.138 mL, 0.996 mmol) and DMF (2.4 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 1.32-1.56 (2 H, m), 1.83-1.96 (2 H, m), 2.20 (2 H, q, J = 7.4 Hz), 2.80-2.95 (1 H, m), 3.03-3.19 (1 H, m), 3.60-3.74 (1 H, m), 3.91 (3 H, s), 3.97-4.15 (3 H, m), 4.17-4.29 (1 H, m), 4.33 (2 H, q, J = 7.1 Hz), 4.51 (1 H, t, J = 5.5 Hz), 6.55 (1 H, s), 7.27-7.39 (4 H, m), 7.68 (1 H, d, J = 7.6 Hz).

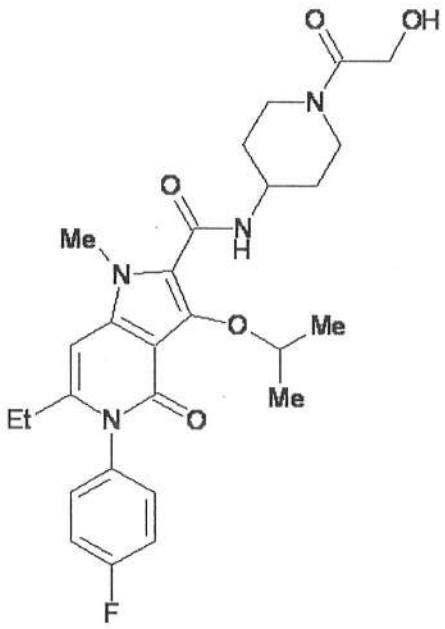
[0297]

Example 7

Production of 6-ethyl-5-(4-fluorophenyl)-N-[1-

(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0298]



[0299]

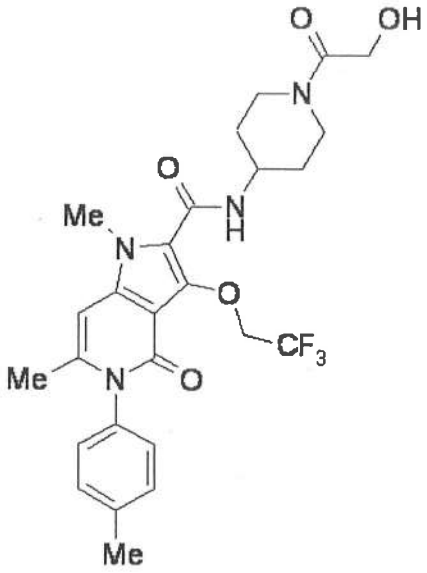
By a method similar to that in Example 1, the title compound (105 mg, 84%) was obtained as a white powder from the compound of Reference Example 31 (90.9 mg, 0.244 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (57.0 mg, 0.293 mmol), HOBt (49.5 mg, 0.366 mmol), WSCD (70.2 mg, 0.366 mmol), triethylamine (0.101 mL, 0.732 mmol) and DMF (1.8 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.21 (6 H, d, J = 6.2 Hz), 1.28-1.55 (2 H, m), 1.84-1.97 (2 H, m), 2.19 (2 H, q, J = 7.4 Hz), 2.77-2.91 (1 H, m), 3.03-3.19 (1 H, m), 3.61-3.74 (1 H, m), 3.92 (3 H, s), 3.96-4.16 (3 H, m), 4.21-4.33 (1 H, m), 4.51 (1 H, t, J = 5.3 Hz), 4.92-5.05 (1 H, m), 6.55 (1 H, s), 7.27-7.38 (4 H, m), 7.65 (1 H, d, J = 7.9 Hz).

[0300]

Example 8

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-5-(4-methylphenyl)-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0301]



[0302]

By a method similar to that in Example 1, the title compound (12 mg, 44%) was obtained as beige crystals from the compound of Reference Example 73 (20 mg, 0.051 mmol).

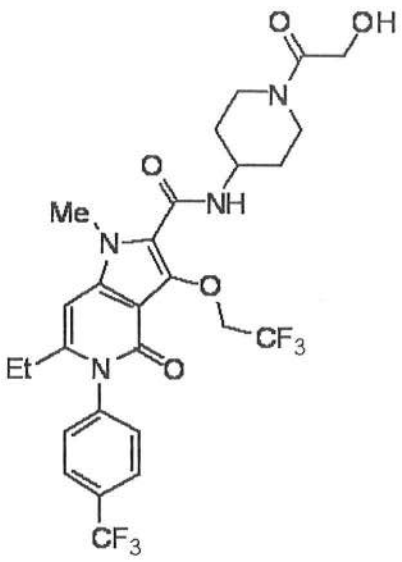
^{1}H NMR (300MHz, DMSO-d_6) δ 1.20-1.50 (2H, m), 1.80-2.00 (5H, m), 2.38 (3H, s), 2.83 (1H, t, J = 12.0 Hz), 3.09 (1H, t, J = 12.0 Hz), 3.69 (1H, d, J = 10.2 Hz), 3.84 (3H, s), 4.00-4.20 (3H, m), 4.26 (1H, d, J = 12.0 Hz), 4.49 (1H, t, J = 5.4 Hz), 5.05 (2H, q, J = 9.2 Hz), 6.67 (1H, s), 7.12 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.44 (1H, d, J = 7.5 Hz).

[0303]

Example 9

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0304]



[0305]

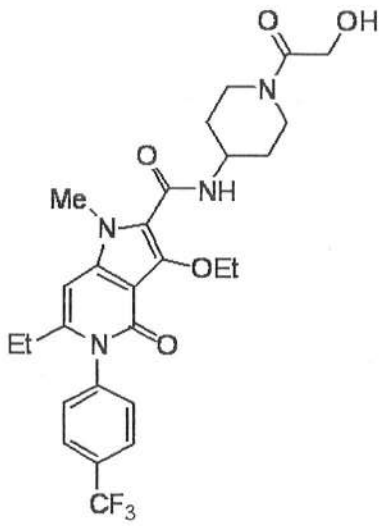
By a method similar to that in Example 1, the title compound (110 mg, 73%) was obtained as a white powder from the compound of Reference Example 39 (115 mg, 0.249 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (58.2 mg, 0.299 mmol), HOBt (50.5 mg, 0.374 mmol), WSCD (71.6 mg, 0.374 mmol), triethylamine (0.103 mL, 0.747 mmol) and DMF (2.3 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.3 Hz), 1.22-1.52 (2 H, m), 1.82-1.95 (2 H, m), 2.20 (2 H, q, J = 7.3 Hz), 2.75-2.91 (1 H, m), 3.02-3.17 (1 H, m), 3.63-3.75 (1 H, m), 3.89 (3 H, s), 3.96-4.15 (3 H, m), 4.21-4.34 (1 H, m), 4.53 (1 H, t, J = 5.5 Hz), 5.02 (2 H, q, J = 9.2 Hz), 6.65 (1 H, s), 7.48-7.61 (3 H, m), 7.91 (2 H, d, J = 8.3 Hz).

[0306]

Example 10

Production of 3-ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0307]



[0308]

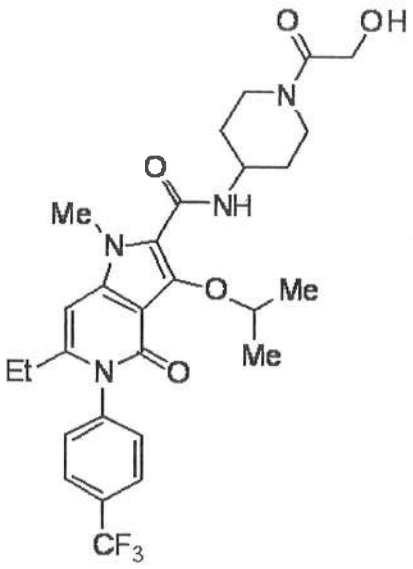
By a method similar to that in Example 1, the title compound (94.8 mg, 70%) was obtained as a white powder from the compound of Reference Example 41 (101 mg, 0.247 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (57.8 mg, 0.297 mmol), HOBt (50.1 mg, 0.371 mmol), WSCD (71.0 mg, 0.371 mmol), triethylamine (0.102 mL, 0.741 mmol) and DMF (2.0 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 1.30-1.57 (2 H, m), 1.84-1.95 (2 H, m), 2.19 (2 H, q, J = 7.4 Hz), 2.80-2.95 (1 H, m), 3.03-3.19 (1 H, m), 3.60-3.72 (1 H, m), 3.93 (3 H, s), 3.98-4.14 (3 H, m), 4.18-4.28 (1 H, m), 4.33 (2 H, q, J = 7.1 Hz), 4.51 (1 H, t, J = 5.4 Hz), 6.59 (1 H, s), 7.54 (2 H, d, J = 8.3 Hz), 7.69 (1 H, d, J = 7.9 Hz), 7.90 (2 H, d, J = 8.3 Hz).

[0309]

Example 11

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0310]



[0311]

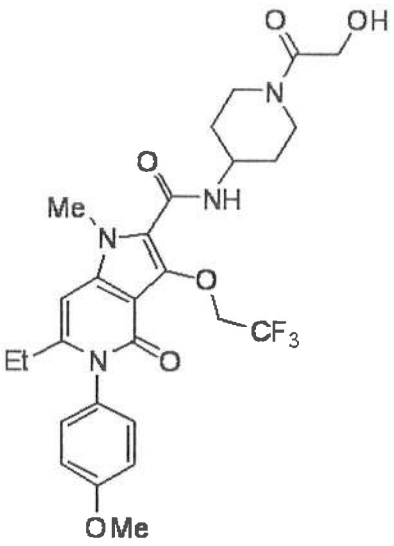
By a method similar to that in Example 1, the title compound (126 mg, 78%) was obtained as a white powder from the compound of Reference Example 43 (122 mg, 0.289 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (67.5 mg, 0.347 mmol), HOBt (58.6 mg, 0.434 mmol), WSCD (83.1 mg, 0.434 mmol), triethylamine (0.120 mL, 0.867 mmol) and DMF (2.4 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.3 Hz), 1.21 (6 H, d, J = 6.2 Hz), 1.27-1.56 (2 H, m), 1.84-1.97 (2 H, m), 2.18 (2 H, q, J = 7.3 Hz), 2.76-2.94 (1 H, m), 3.02-3.19 (1 H, m), 3.61-3.75 (1 H, m), 3.94 (3 H, s), 4.00-4.19 (3 H, m), 4.20-4.34 (1 H, m), 4.51 (1 H, t, J = 5.4 Hz), 4.87-5.04 (1 H, m), 6.59 (1 H, s), 7.54 (2 H, d, J = 8.2 Hz), 7.65 (1 H, d, J = 7.7 Hz), 7.90 (2 H, d, J = 8.2 Hz).

[0312]

Example 12

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-5-(4-methoxyphenyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0313]



[0314]

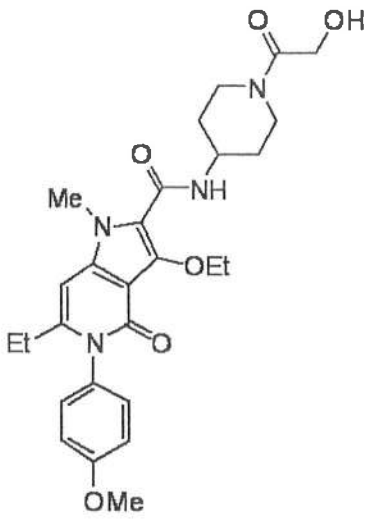
By a method similar to that in Example 1, the title compound (186 mg, 82%) was obtained as a white powder from the compound of Reference Example 51 (171 mg, 0.403 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (94.1 mg, 0.484 mmol), HOBt (81.7 mg, 0.605 mmol), WSCD (116 mg, 0.605 mmol), triethylamine (0.168 mL, 1.21 mmol) and DMF (3.4 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.3 Hz), 1.21-1.50 (2 H, m), 1.80-1.96 (2 H, m), 2.23 (2 H, q, J = 7.3 Hz), 2.75-2.91 (1 H, m), 3.01-3.17 (1 H, m), 3.60-3.76 (1 H, m), 3.82 (3 H, s), 3.87 (3 H, s), 3.95-4.16 (3 H, m), 4.20-4.36 (1 H, m), 4.53 (1 H, t, J = 5.4 Hz), 5.05 (2 H, q, J = 9.3 Hz), 6.57 (1 H, s), 6.99-7.10 (2 H, m), 7.13-7.23 (2 H, m), 7.48 (1 H, d, J = 7.6 Hz).

[0315]

Example 13

Production of 3-ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-5-(4-methoxyphenyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0316]



[0317]

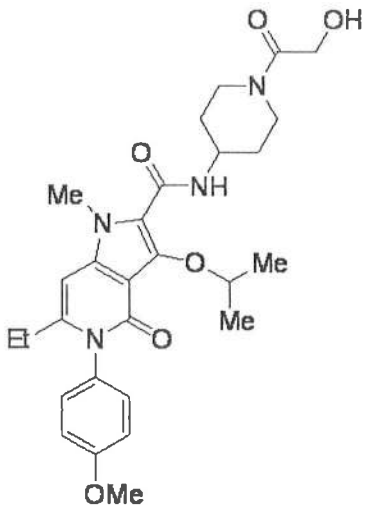
By a method similar to that in Example 1, the title compound (149 mg, 78%) was obtained as a white powder from the compound of Reference Example 53 (139 mg, 0.375 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (87.7 mg, 0.450 mmol), HOBt (76.1 mg, 0.563 mmol), WSCD (108 mg, 0.563 mmol), triethylamine (0.156 mL, 1.13 mmol) and DMF (2.8 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.25 (3 H, t, J = 7.1 Hz), 1.30-1.56 (2 H, m), 1.82-1.96 (2 H, m), 2.21 (2 H, q, J = 7.4 Hz), 2.80-2.96 (1 H, m), 3.03-3.21 (1 H, m), 3.59-3.74 (1 H, m), 3.82 (3 H, s), 3.91 (3 H, s), 3.97-4.17 (3 H, m), 4.17-4.29 (1 H, m), 4.34 (2 H, q, J = 7.1 Hz), 4.51 (1 H, t, J = 5.4 Hz), 6.51 (1 H, s), 6.98-7.09 (2 H, m), 7.10-7.20 (2 H, m), 7.68 (1 H, d, J = 7.9 Hz).

[0318]

Example 14

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-5-(4-methoxyphenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0319]



[0320]

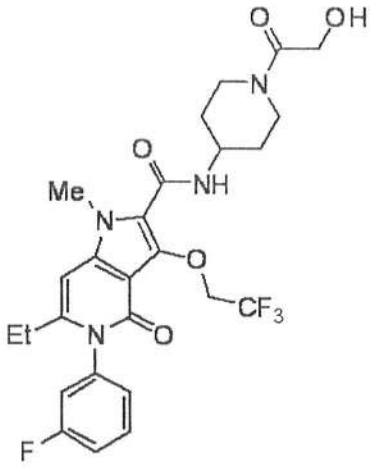
By a method similar to that in Example 1, the title compound (144 mg, 86%) was obtained as a white powder from the compound of Reference Example 55 (123 mg, 0.320 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (74.7 mg, 0.384 mmol), HOBt (64.9 mg, 0.480 mmol), WSCD (92.0 mg, 0.480 mmol), triethylamine (0.133 mL, 0.960 mmol) and DMF (2.5 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.21 (6 H, d, J = 6.2 Hz), 1.25-1.56 (2 H, m), 1.84-1.97 (2 H, m), 2.21 (2 H, q, J = 7.4 Hz), 2.77-2.90 (1 H, m), 3.02-3.19 (1 H, m), 3.61-3.74 (1 H, m), 3.81 (3 H, s), 3.92 (3 H, s), 3.98-4.17 (3 H, m), 4.21-4.34 (1 H, m), 4.51 (1 H, t, J = 5.1 Hz), 4.92-5.07 (1 H, m), 6.51 (1 H, s), 6.96-7.09 (2 H, m), 7.10-7.23 (2 H, m), 7.64 (1 H, d, J = 7.6 Hz).

[0321]

Example 15

Production of 6-ethyl-5-(3-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0322]



[0323]

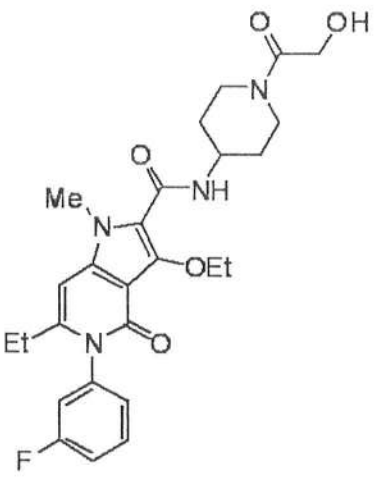
By a method similar to that in Example 1, the title compound (76.3 mg, 26%) was obtained as a white powder from the compound of Reference Example 62 (220 mg, 0.534 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (125 mg, 0.641 mmol), HOBt (108 mg, 0.801 mmol), WSCD (154 mg, 0.801 mmol), triethylamine (0.222 mL, 1.60 mmol) and DMF (4.4 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.21-1.51 (2 H, m), 1.81-1.95 (2 H, m), 2.23 (2 H, q, J = 7.4 Hz), 2.75-2.91 (1 H, m), 2.99-3.17 (1 H, m), 3.63-3.76 (1 H, m), 3.88 (3 H, s), 3.96-4.16 (3 H, m), 4.20-4.35 (1 H, m), 4.53 (1 H, t, J = 5.3 Hz), 5.03 (2 H, q, J = 9.3 Hz), 6.61 (1 H, s), 7.10-7.19 (1 H, m), 7.24-7.40 (2 H, m), 7.46-7.63 (2 H, m).

[0324]

Example 16

Production of 3-ethoxy-6-ethyl-5-(3-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0325]



[0326]

By a method similar to that in Example 1, the title compound (188 mg, 91%) was obtained as a white powder from the compound of Reference Example 64 (160 mg, 0.414 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (96.7 mg, 0.497 mmol), HOBt (83.9 mg, 0.621 mmol), WSCD (119 mg, 0.621 mmol), triethylamine (0.172 mL, 1.24 mmol) and DMF (3.2 mL).

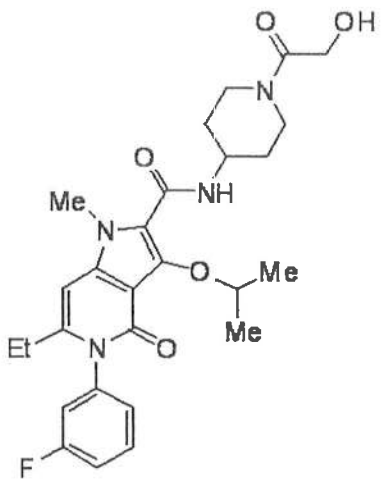
^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.26 (3 H, t, J = 7.0 Hz), 1.30-1.59 (2 H, m), 1.83-1.96 (2 H, m), 2.22 (2 H, q, J = 7.4 Hz), 2.79-2.95 (1 H, m), 3.03-3.19 (1 H, m), 3.59-3.73 (1 H, m), 3.92 (3 H, s), 3.96-4.14 (3 H, m), 4.18-4.29 (1 H, m), 4.33 (2 H, q, J = 7.0 Hz), 4.51 (1 H, t, J = 5.5 Hz), 6.56 (1 H, s), 7.09-7.17 (1 H, m), 7.21-7.39 (2 H, m), 7.50-7.62 (1 H, m), 7.68 (1 H, d, J = 7.6 Hz).

[0327]

Example 17

Production of 6-ethyl-5-(3-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0328]



[0329]

By a method similar to that in Example 1, the title compound (127 mg, 57%) was obtained as a white powder from the compound of Reference Example 66 (163 mg, 0.438 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (102 mg, 0.526 mmol), HOBt (88.8 mg, 0.657 mmol), WSCD (126 mg, 0.657 mmol), triethylamine (0.182 mL, 1.31 mmol) and DMF (3.3 mL).

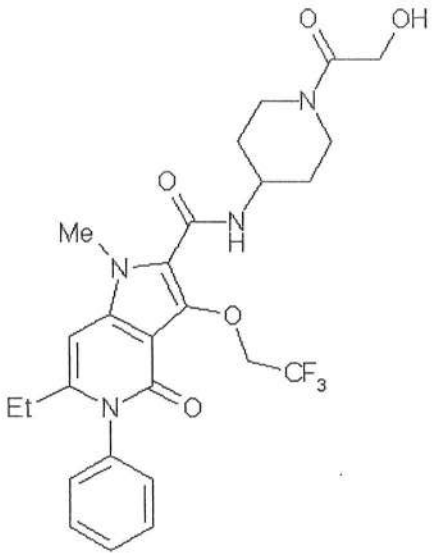
^{1}H NMR (300 MHz, DMSO-d_6) δ:1.04 (3 H, t, J = 7.4 Hz), 1.21 (6 H, d, J = 6.0 Hz), 1.26-1.56 (2 H, m), 1.84-1.97 (2 H, m), 2.21 (2 H, q, J = 7.4 Hz), 2.77-2.89 (1 H, m), 3.03-3.19 (1 H, m), 3.60-3.75 (1 H, m), 3.93 (3 H, s), 3.97-4.15 (3 H, m), 4.20-4.35 (1 H, m), 4.51 (1 H, t, J = 5.5 Hz), 4.91-5.07 (1 H, m), 6.56 (1 H, s), 7.09-7.17 (1 H, m), 7.22-7.39 (2 H, m), 7.51-7.62 (1 H, m), 7.65 (1 H, d, J = 7.7 Hz).

[0330]

Example 18

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-phenyl-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0331]



[0332]

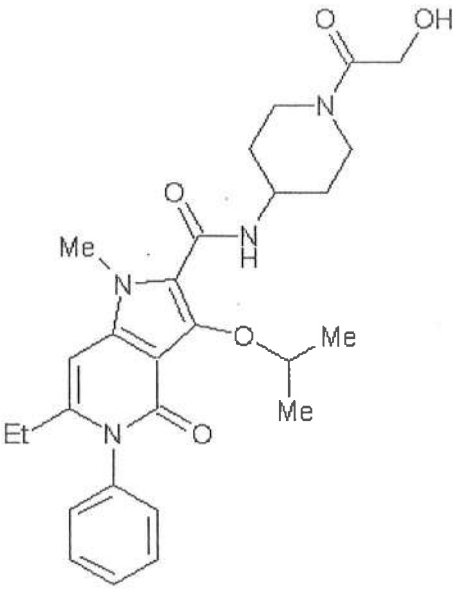
A mixture of the compound of Reference Example 8 (200 mg, 0.635 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (148 mg, 0.761 mmol), HOBt (171 mg, 1.27 mmol), WSCD (243 mg, 1.27 mmol), triethylamine (0.352 mL, 2.54 mmol) and DMF (4.0 mL) was stirred at room temperature for 2 days. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extracts were combined, washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate to give the title compound (240 mg, 71%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.27-1.50 (2 H, m), 1.81-1.96 (2 H, m), 2.21 (2 H, q, J = 7.4 Hz), 2.77-2.87 (1 H, m), 3.02-3.17 (1 H, m), 3.64-3.75 (1 H, m), 3.88 (3 H, s), 3.97-4.16 (3 H, m), 4.19-4.35 (1 H, m), 4.53 (1 H, t, J = 5.4 Hz), 5.04 (2 H, q, J = 9.3 Hz), 6.60 (1 H, s), 7.21-7.32 (2 H, m), 7.43-7.60 (4 H, m).

[0333]

Example 19

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0334]



[0335]

A mixture of the compound of Reference Example 20 (95.3 mg, 0.269 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (62.9 mg, 0.323 mmol), HOBt (54.6 mg, 0.404 mmol), WSCD (77.4 mg, 0.404 mmol), triethylamine (0.112 mL, 0.807 mmol) and DMF (1.9 mL) was stirred at room temperature for 5 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extracts were combined, washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel chromatography (eluate; hexane:ethyl acetate=10:90→0:100), and the obtained solid was recrystallized from ethyl acetate to give the title compound (111 mg, 83%) as a white powder.

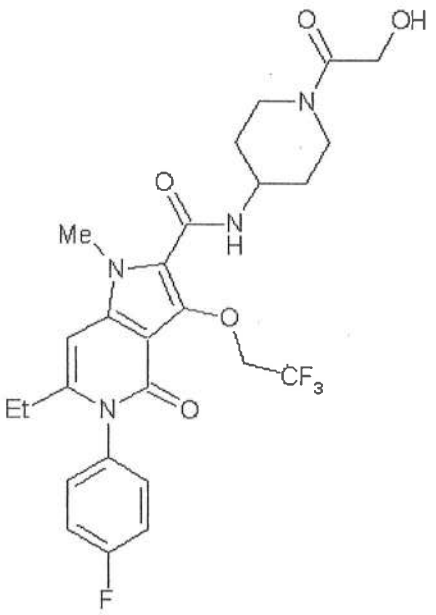
^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (3 H, t, J = 7.4 Hz), 1.21 (6 H, d, J = 6.2 Hz), 1.26-1.56 (2 H, m), 1.84-1.97 (2 H, m), 2.19 (2 H, q, J = 7.4 Hz), 2.77-2.93 (1 H, m), 3.03-3.19 (1 H, m), 3.60-3.75 (1 H, m), 3.92 (3 H, s), 3.97-4.17 (3 H, m), 4.21-4.34 (1 H, m), 4.51 (1 H, t, J = 5.3 Hz), 4.99 (1 H, spt, J = 6.2 Hz), 6.54 (1 H, s), 7.19-7.32 (2 H, m), 7.38-7.58 (3 H, m), 7.65 (1 H, d, J = 7.7 Hz).

[0336]

Example 20

Production of 6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0337]



[0338]

A mixture of the compound of Reference Example 80 (120 mg, 0.323 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (68.0 mg, 0.349 mmol), HOBt (59.1 mg, 0.437 mmol), WSCD (83.7 mg, 0.437 mmol), triethylamine (0.121 mL, 0.873 mmol) and DMF (2.4 mL) was stirred at room temperature for 4 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extracts were combined, washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel chromatography (eluate; hexane:ethyl acetate=10:90→0:100), and the obtained solid was recrystallized from ethyl acetate to give the title compound (122 mg, 76%) as a white powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.03 (3 H, t, J = 7.4 Hz), 1.22-1.50 (2 H, m), 1.82-1.95 (2 H, m), 2.21 (2 H, q, J = 7.4 Hz), 2.75-2.88 (1 H, m), 3.02-3.16 (1 H, m), 3.62-3.75 (1 H, m), 3.88 (3 H, s), 3.95-4.13 (3 H, m), 4.21-4.33 (1 H, m), 4.53 (1

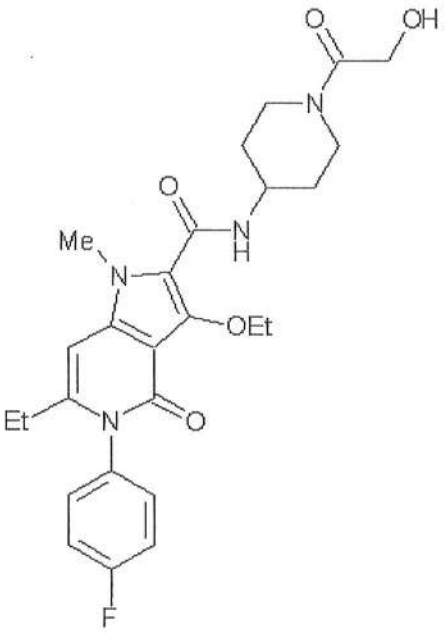
H, t, J = 5.4 Hz), 5.04 (2 H, q, J = 9.3 Hz), 6.60 (1 H, s), 7.30-7.39 (4 H, m), 7.49 (1 H, d, J = 7.6 Hz).

[0339]

Example 21

Production of 3-ethoxy-6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0340]



[0341]

A mixture of the compound of Reference Example 29 (119 mg, 0.332 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (77.6 mg, 0.398 mmol), HOBt (67.3 mg, 0.498 mmol), WSCD (95.5 mg, 0.498 mmol), triethylamine (0.138 mL, 0.996 mmol) and DMF (2.4 mL) was stirred at room temperature for 5 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extracts were combined, washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel chromatography (eluate; hexane:ethyl acetate=10:90→0:100), and the obtained solid was recrystallized from ethyl acetate to give the title compound (119 mg, 72%) as a white powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.25 (3

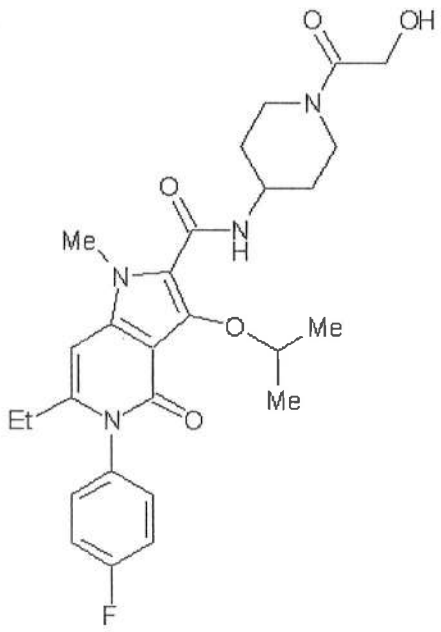
H, t, J = 7.1 Hz), 1.32-1.56 (2 H, m), 1.83-1.96 (2 H, m), 2.20 (2 H, q, J = 7.4 Hz), 2.80-2.95 (1 H, m), 3.03-3.19 (1 H, m), 3.60-3.74 (1 H, m), 3.91 (3 H, s), 3.97-4.15 (3 H, m), 4.17-4.29 (1 H, m), 4.33 (2 H, q, J = 7.1 Hz), 4.51 (1 H, t, J = 5.5 Hz), 6.55 (1 H, s), 7.27-7.39 (4 H, m), 7.68 (1 H, d, J = 7.6 Hz).

[0342]

Example 22

Production of 6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0343]



[0344]

A mixture of the compound of Reference Example 82 (90.9 mg, 0.244 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (57.0 mg, 0.293 mmol), HOBt (49.5 mg, 0.366 mmol), WSCD (70.2 mg, 0.366 mmol), triethylamine (0.101 mL, 0.732 mmol) and DMF (1.8 mL) was stirred at room temperature for 5 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extracts were combined, washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel chromatography (eluate; hexane:ethyl

acetate=10:90→0:100), and the obtained solid was recrystallized from ethyl acetate to give the title compound (105 mg, 84%) as a white powder.

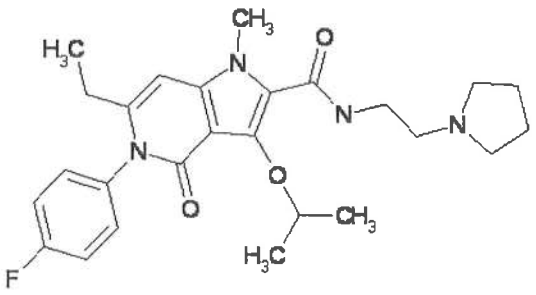
^{1}H NMR (300 MHz, DMSO-d_6) δ:1.02 (3 H, t, J = 7.4 Hz), 1.21 (6 H, d, J = 6.2 Hz), 1.28-1.55 (2 H, m), 1.84-1.97 (2 H, m), 2.19 (2 H, q, J = 7.4 Hz), 2.77-2.91 (1 H, m), 3.03-3.19 (1 H, m), 3.61-3.74 (1 H, m), 3.92 (3 H, s), 3.96-4.16 (3 H, m), 4.21-4.33 (1 H, m), 4.51 (1 H, t, J = 5.3 Hz), 4.92-5.05 (1 H, m), 6.55 (1 H, s), 7.27-7.38 (4 H, m), 7.65 (1 H, d, J = 7.9 Hz).

[0345]

Example 23

Production of 6-ethyl-5-(4-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-N-(2-(pyrrolidin-1-yl)ethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0346]



[0347]

To a 0.19M-DMF solution (500 µL, 96 µmol) of 2-(pyrrolidin-1-yl)ethanamine was added a 0.16M-DMF solution (500 µL, 80 µmol) of the compound of Reference Example 31, and a DMF solution (500µL) of HOBt (120 µmol) and WSCD (120 µmol) was added thereto. The reaction mixture was stirred overnight at room temperature. The mixture was extracted with ethyl acetate (3 mL) and 2% aqueous sodium hydrogen carbonate solution (2 mL), and the organic layer was collected upper layer Phase Septube (manufactured by Wako Pure Chemical Industries, Ltd.). The ethyl acetate was evaporated by blowing nitrogen, the residue was dissolved in DMSO:acetonitrile (1:4) (1000µL), and the solution was purified by preparative HPLC

(acetonitrile-10 mM ammonium carbonate-containing water) to give the title compound.

yield: 22.5mg

LC-MS analysis: purity 98%

MS(ESI+): 469.3(M+H)

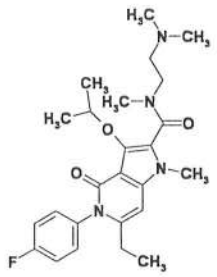
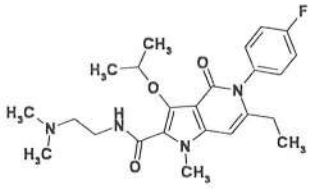
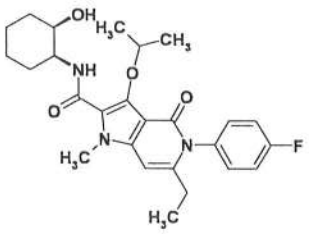
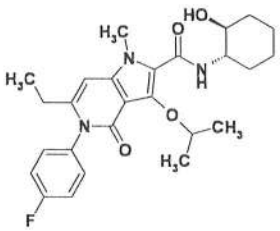
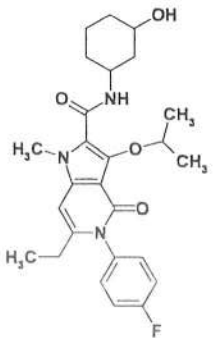
[0348]

Example 24-Example 50

By a method similar to that in Example 23, the compounds shown in Table 1 were obtained from the compound of Reference Example 31 and the corresponding amine.

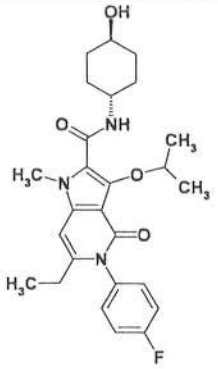
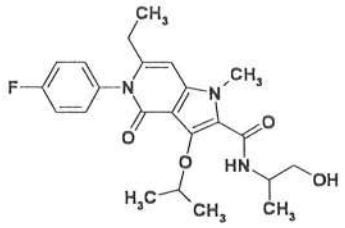
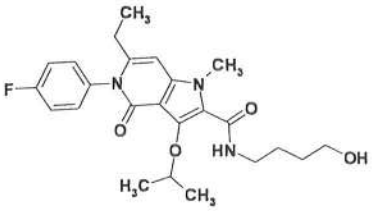
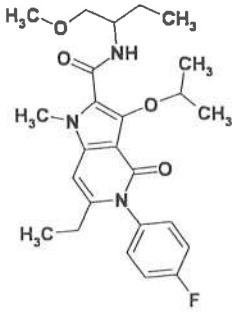
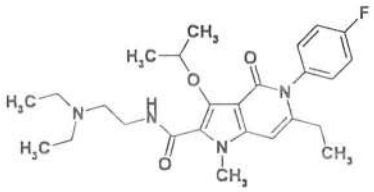
[0349]

Table 1-1

Ex. No.	structure	yield (mg)	purity (%)	MS (ESI+)
24		25.7	99	457.2
25		21.3	96	443.3
26		24.3	100	470.2
27		21.4	100	470.2
28		25.4	100	470.2

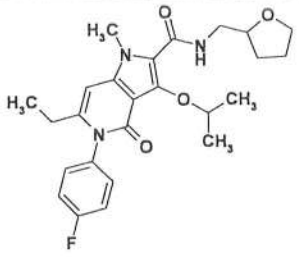
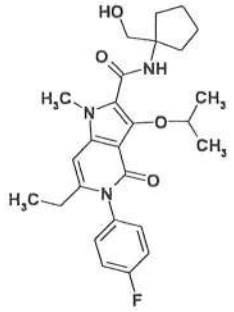
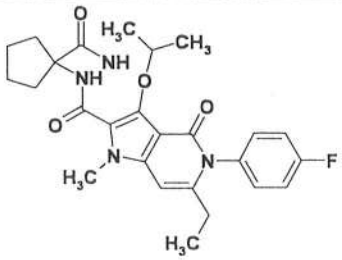
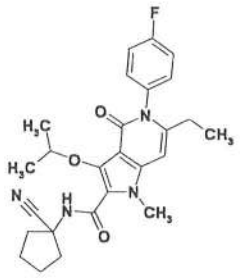
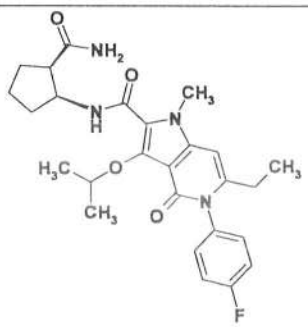
[0350]

Table 1-2

Ex. No.	structure	yield (mg)	purity (%)	MS (ESI+)
29		29.7	100	470.2
30		26.4	100	430.2
31		24.9	100	444.3
32		28.1	100	458.2
33		25.7	86	471.3

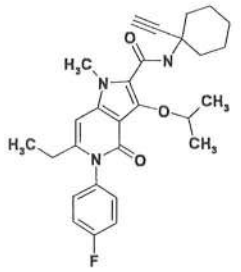
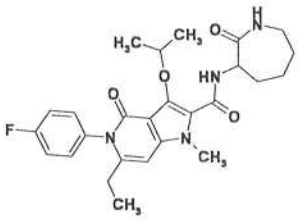
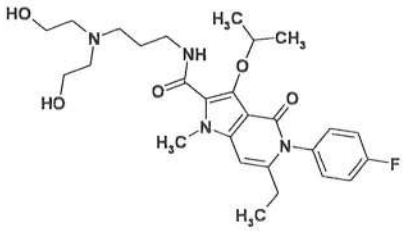
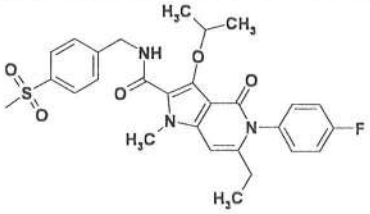
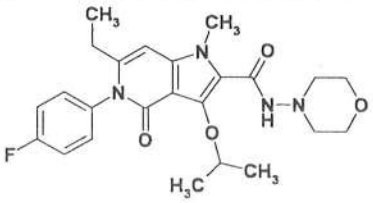
[0351]

Table 1-3

Ex. No.	structure	yield (mg)	purity (%)	MS (ESI+)
34		25.5	88	456.3
35		25.4	100	470.2
36		30.2	99	483.2
37		4.4	100	465.2
38		27.0	100	483.2

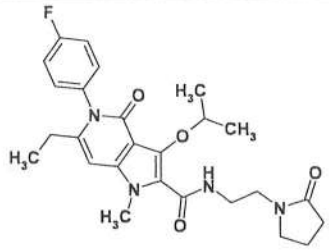
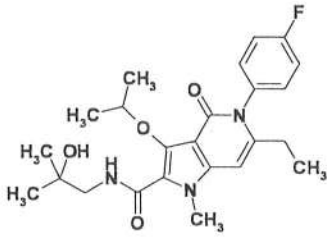
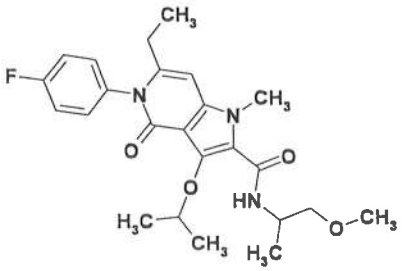
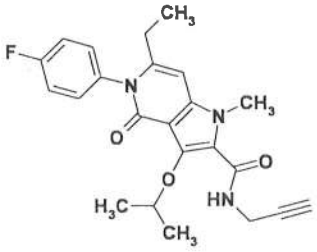
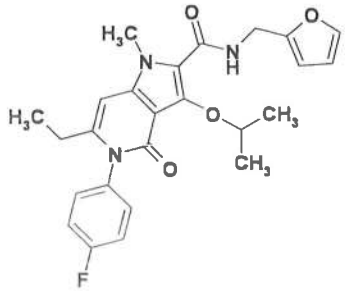
[0352]

Table 1-4

Ex. No.	structure	yield (mg)	purity (%)	MS (ESI+)
39		28.8	100	478.2
40		7.9	100	483.2
41		18.6	100	517.3
42		3.5	100	540.2
43		22.6	100	457.2

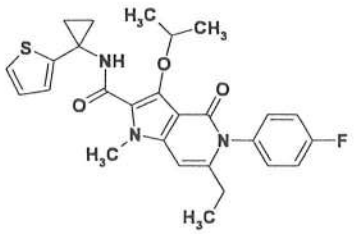
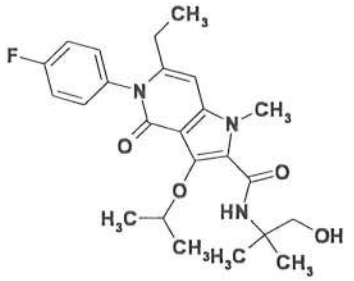
[0353]

Table 1-5

Ex. No.	structure	yield (mg)	purity (%)	MS (ESI+)
44		25.5	100	483.2
45		22.0	100	444.2
46		28.9	100	444.2
47		16.2	100	410.2
48		26.3	100	452.2

[0354]

Table 1-6

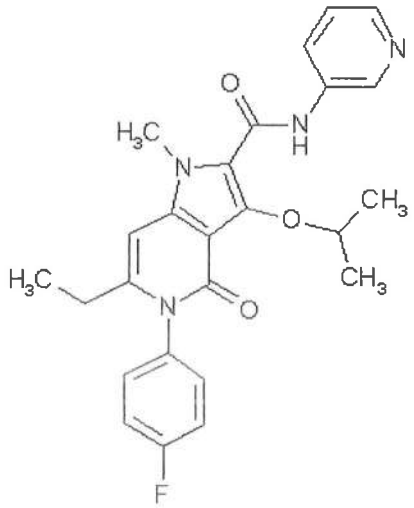
Ex. No.	structure	yield (mg)	purity (%)	MS (ESI+)
49		15.1	100	494.2
50		25.6	100	444.2

[0355]

Example 51

Production of 6-ethyl-5-(4-fluorophenyl)-1-methyl-3-(1-methylethoxy)-4-oxo-N-(pyridin-3-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0356]



[0357]

To a 0.19M-DMF solution (500 μL, 96 μmol) of pyridin-3-amine was added a 0.16M-DMF solution (500μL, 80 μmol) of the

compound of Reference Example 31, and a DMF solution (500μL) of HATU (160 μmol) and DIPEA (160 μmol) was added thereto. The reaction mixture was stirred overnight at 70°C. The mixture was extracted with ethyl acetate (3 mL) and 2% aqueous sodium hydrogen carbonate solution (2 mL), and the organic layer was collected by upper layer Phase Septube (manufactured by Wako Pure Chemical Industries, Ltd.). Ethyl acetate was evaporated by blowing nitrogen, the residue was dissolved DMSO:acetonitrile(1:4)(1000μL), and the solution was purified by preparative HPLC (acetonitrile-10mM ammonium carbonate-containing water) to give the title compound.

yield: 7.2mg

LC-MS analysis: purity 100%

MS(ESI+):449.2(M+H)

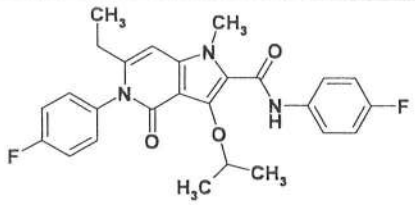
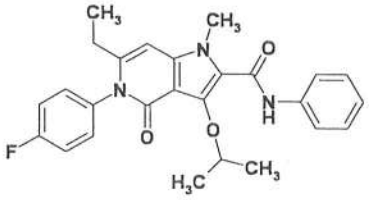
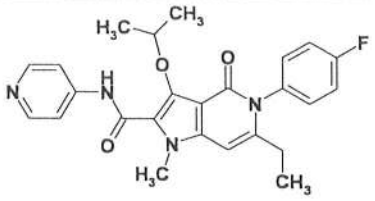
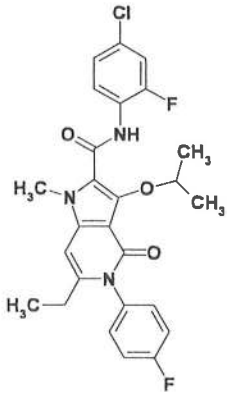
[0358]

Example 52-Example 55

By a method similar to that in Example 51, the compounds shown in Table 2 were obtained from the compound of Reference Example 31 and the corresponding amine.

[0359]

Table 2

Ex. No.	structure	yield (mg)	purity (%)	MS (ESI+)
52		3.2	100	466.2
53		1.9	100	448.2
54		4.6	100	449.2
55		1.7	100	500.1

[0360]

Formulation Example 1

A medicament containing the compound of the present invention as an active ingredient can be produced, for example, based on the following composition.

1. capsule

(1) the compound obtained in Example 1	40 mg
(2) lactose	70 mg
(3) crystalline cellulose	9 mg
(4) magnesium stearate	1 mg

1 capsule 120 mg

(1), (2), (3) and 1/2 of (4) are blended and granulated. Thereto is added the rest of (4) and the total amount is filled in a gelatin capsule.

[0361]

2. tablet

(1) the compound obtained in Example 1	40 mg
(2) lactose	58 mg
(3) cornstarch	18 mg
(4) crystalline cellulose	3.5 mg
(5) magnesium stearate	0.5 mg
1 tablet	120 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are blended and granulated. Thereto is added the rest of (4) and (5) and the mixture is compression formed to give a tablet.

[0362]

Formulation Example 2

The compound obtained in Example 1 (50 mg) is dissolved in the Japanese Pharmacopoeia distilled water for injection (50 ml), and the Japanese Pharmacopoeia distilled water for injection is added to 100 ml. The solution is filtered under sterile conditions, and 1 ml of the solution is filled in an injection vial under sterile conditions, and freeze-dried and sealed.

[0363]

Genetic operation methods described in Experimental Examples below are based on the methods described in a book (Maniatis et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989), and the appended protocol of the reagent.

[0364]

Experimental Example 1

1. Construction of Gli reporter plasmid

Gli reporter plasmid was constructed by inserting 8 x Gli-binding site and chicken δ-crystalline promoter into the upstream of luc+ of pGL3 (Promega).

δ-Crystalline promoter was cloned by PCR method using, as a primer set, synthetic DNAs

5′-GAAGATCTGCCAGCCCAGGCTCCGGGGC-3′ (SEQ ID NO: 1)

5′-CCCAAGCTTCTGCCCGCACAGCCCTGCTC-3′ (SEQ ID NO: 2)

prepared in reference to the base sequence described in GenBank accession No.; X02187, and chicken genome DNA (Clontech) as a template. PCR reaction was performed using Pfu Turbo (Stratagene) and following the attached protocol. The obtained 108 bp fragment was digested with restriction enzymes BglII and HindIII, and inserted into BglII-HindIII site of pGL3 to give plasmid pGL3/δ-cry promoter.

As 8 x Gli-binding site, a sequence containing eight 9-bp Gli bound consensus sequences (GACCACCCA) described in Yoon et al., J. Biol. Chem., vol. 273, pages 3496-3501 (1998) was prepared from synthetic DNA. That is, two synthetic DNAs,

5′-

GGGGTACCGACCACCCAGACCACCCAGACCACCCAGACCACCCAGACCACCCAGACCACCCA

GACCACCCAGACCACCCAAGATCTTC-3′ (SEQ ID NO: 3)

5′-

GAAGATCTTGGGTGGTCTGGGTGGTCTGGGTGGTCTGGGTGGTCTGGGTGGTCTGGGTGGTC

TGGGTGGTCTGGGTGGTCGGTACCCC-3′ (SEQ ID NO: 4)

were heat treated at 95°C for 2 minutes, and incubated at 37°C for 1 hr for annealing to give a double stranded DNA of the above-mentioned two synthetic DNAs. The obtained double stranded DNA was digested with restriction enzymes BglII and KpnI, and the obtained DNA fragment was inserted into BglII-KpnI site of pGL3/δ-cry promoter to construct plasmid pGL3/δ-cry promoter, 8 x Gli binding site, i.e., Gli reporter plasmid.

[0365]

2. Construction of plasmid for expression of mouse Shh-N end fragment

As a material for construction of plasmid for Shh-N end fragment expression, mouse Shh cDNA was cloned at first.

The mouse Shh cDNA was cloned by Nested PCR method using mouse 11-day fetus cDNA (Clontech) as a template. The primer

sequence was prepared in reference to the base sequence described in GenBank accession No.; NM_009170.

As the primer set for 1st PCR,

5'-CTGGGTGGGGATCGGAGACA-3' (SEQ ID NO: 5)

5'-GCGCTTTCCCATCAGTTCCTTATT-3' (SEQ ID NO: 6) were used, and as the primer set for 2nd PCR,

5'-GGGGTACCATGCTGCTGCTGCTGGCCA-3' (SEQ ID NO: 7)

5'-GCTCTAGATCAGCTGGACTTGACCGCCA-3' (SEQ ID NO: 8)

were used. PCR reaction was performed using Pfu Turbo (Stratagene) and following the attached protocol. The resulting PCR product was cloned by pcDNA3.1 (+) (Invitrogen), and the inserted base sequence was confirmed.

Using the mouse Shh cDNA sequence obtained as mentioned above as a template, a partial cDNA sequence wherein stop codon (TGA) was added to 3'-terminal of cDNA sequence encoding 1st to 198th amino acid sequence of mouse Shh was obtained by PCR method. As the primer set,

5'-ATGCTGCTGCTGCTGGCCAG-3' (SEQ ID NO: 9)

5'-TCAGCCGCCGGATTTGGCCG-3' (SEQ ID NO: 10)

were used.

PCR reaction was performed using Pfu Turbo (Stratagene) and following the attached protocol. The obtained PCR product was cloned by pcDNA3.1 (+) (Invitrogen), and the inserted base sequence was confirmed.

In the manner mentioned above, a plasmid for mouse Shh-N end fragment expression, pcDNA3.1/mShh-N, was constructed.

[0366]

3. Production of recombinant type mouse Shh-N end fragment

HEK293 cells were grown in D-MEM medium (Invitrogen) containing 10% fetal bovine serum in a 10 cm dish and pcDNA3.1/mShh-N was introduced into the cells using FuGENE6 (Roche Applied Science). Thereafter, the HEK293 cells were cultured in a carbon dioxide gas incubator at 37°C for 24 hours, and the medium was exchanged with D-MEM medium (Invitrogen) containing 2% fetal bovine serum. After culturing for 48 hr, a

culture supernatant containing recombinant type mouse Shh-N end fragment was obtained by filtration using a filter (0.22 μM).

[0367]

4. Introduction of plasmid for Gli-1 expression and reporter plasmid into NIH-3T3 cells and production of expressing cells

Using D-MEM (Invitrogen) containing 10% fetal bovine serum, expression plasmid pcDNA3.1 and Gli reporter plasmid (pGL3/δ-cry promoter, 8 x Gli binding site) produced by the method of Experimental Example 1 were introduced into NIH-3T3 cells grown in a 10 cm dish by the use of FuGENE6 (Roche Applied Science).

After culture for 24 hr, the cells were recovered, suspended in D-MEM medium containing 10% fetal bovine serum and supplemented with Geneticin (Life Technologies Oriental, Inc.) to a final concentration of 500 μg/ml, diluted to 10^4 cells/ml, plated on a 96 well plate, and cultured in a carbon dioxide gas incubator at 37°C to give Geneticin resistant transformed cell line.

The obtained transformed cell line was cultured in a 96 well plate, mouse Shh-N end fragment obtained in Experimental Example 3 was added, and NIH-3T3/Gli reporter cell, which is a cell line capable of induction of luciferase expression, was selected.

[0368]

5. Evaluation of compound

NIH-3T3/Gli reporter cells cultured in D-MEM (Invitrogen) containing 10% fetal bovine serum were plated in a 96 well white plate at $1x10^4$ cells/well, and cultured overnight in a carbon dioxide gas incubator at 37°C. The medium was removed, a compound (50 μl) and culture supernatant of mouse Shh-N end fragment-expressing HEK293 (D-MEM medium containing 2% fetal bovine serum, 50 μl) were added, and the cells were cultured for 48 hr in a carbon dioxide gas incubator at 37°C. Bright-Glo (Promega, 50 μl) was added, and the mixture was stirred,

after which luciferase activity was measured by EnVision (PerkinElmer). The inhibition rate was calculated based on the luciferase activity of the control without addition of the compound as 100. The results are shown in Table 3 below.

[0369]

Table 3

Example	inhibition rate (%) at 1 μM
1	98
3	97
4	97
5	96
6	96
7	97
8	97
9	97
10	96
11	96
12	97
13	97
14	96
15	99
16	96
17	95
20	96
21	96
22	97

[0370]

Experimental Example 2 In vivo anti-tumor test

According to the description in Sasaki, K. et al., (2006) Cancer Res. 66: 4215-4222, an anti-tumor effect of a compound was evaluated using a mouse medulloblastoma allogeneic transplantation model. To be precise, Patched 1 gene mutant mouse (lineage name: Ptch1tm1Mps/J) was purchased from The Jackson Laboratory and p53 gene mutant mouse (lineage name: P53N4-M, Nomenclature: B6.129-Trp53tm/BrdN4) was purchased from Taconic, and a mouse of Patched 1(+/-), p53(-/-) phenotype was prepared by mating. The tumor tissue of

medulloblastoma spontaneously occurred in the cerebellum of 7- to 9-week-old Patched 1(+/-), p53(-/-) mouse was taken and subcutaneously transplanted into a nude mouse (lineage name: CAnN.Cg-Foxn1<nu>/CrlCrlj).

An anti-tumor test was performed using a tumor passaged by subcutaneous transplantation. A tumor mass was isolated by a 40 μm cell strainer (BD Biosciences, Cat. No. 352340), a tumor suspension was prepared with Leibovitz's L-15 medium (GIBCO, Cat. No. 11415-114) in a 2-fold amount relative to the tumor mass weight, mixed with the same amount of matrigel (BD Biosciences, Cat. No. 356237), and subcutaneously transplanted to a mouse at 100 μl per transplantation site. The tumor diameter after transplantation was measured and, when the tumor size reached 150 - 250 mm^3, the anti-tumor test was started using 5 mice per group.

The test compound was prepared to achieve a dose of 1 mg/kg with a 0.5 % methylcellulose (Shin-Etsu Chemical Co., Ltd., Cat. No. SM-100) suspension, and orally administered twice a day for 2 weeks. The tumor size was calculated based on the longer diameter and shorter diameter of the tumor measured with an electron vernier caliper. After the start of the test, the tumor size was measured every 2 or 3 days and the growth rate of the tumor size was calculated. The growth rate of the tumor size by each test compound at the end of the test is shown in the following Table 4.

The tumor growth rate and the results of a significant difference test by the administration of each test compound are shown in the Table. The growth rate of the tumor size (T/C) was calculated according to:

growth rate (T/C) = ((tumor size of compound administration group at the end of administration)-(tumor size of compound administration group at the start of administration))/((tumor size of control group at the end of administration)-(tumor size of control group at the start of administration))X100.

[0371]

Table 4

Example	T/C (%)	P value (Dunnett's test)
5	42	p<0.025
7	40	p<0.025

[0372]

From the above-mentioned results, the compound of the present invention was shown to have a superior Smo inhibitory action.

Industrial Applicability

[0373]

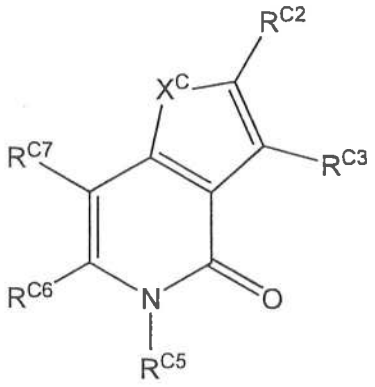
Since the compound of the present invention shows a superior Smo inhibitory action, a clinically useful agent for the prophylaxis or treatment of diseases related to Smo (e.g., cancer etc.) can be provided. In addition, since the compound of the present invention is also superior in the efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability, it is useful as a medicament.

[0374]

This application is based on patent application Nos. 2009-195770 and 2010-015644 filed in Japan, the contents of which are encompassed in full herein.

CLAIMS

1. A compound represented by the formula



(CI)

wherein

X^C is NR^{C1}, a sulfur atom or an oxygen atom;

R^{C1} is a hydrogen atom or a C_{1-6} alkyl group;

R^{C2} is a carbamoyl group optionally having substituent(s);

R^{C3} is a hydroxy group optionally having a substituent;

R^{C5} is a cyclic group optionally having substituent(s);

R^{C6} is a C_{1-6} alkyl group optionally having substituent(s);

R^{C7} is a hydrogen atom, a halogen atom or a C_{1-6} alkyl group,

or a salt thereof.

2. The compound or salt of claim 1, wherein

X^C is NR^{C1} wherein R^{C1} is a hydrogen atom or a C_{1-6} alkyl group;

R^{C2} is a carbamoyl group optionally having 1 or 2 substituents selected from

(1) a C_{1-6} alkyl group optionally having substituent(s),

(2) a C_{2-6} alkynyl group optionally having substituent(s),

(3) a C_{3-8} cycloalkyl group optionally having substituent(s),

(4) a C_{6-10} aryl group optionally having substituent(s), and

(5) a heterocyclic group optionally having substituent(s);

R^{C3} is an optionally halogenated C_{1-6} alkoxy group;

R^{C5} is

(1) a C_{6-10} aryl group optionally having substituent(s), or

(2) a heterocyclic group optionally having substituent(s);

R^{C6} is a C_{1-6} alkyl group; and

R^{C7} is a hydrogen atom.

3. The compound or salt of claim 2, wherein X^C is NR^{C1} wherein R^{C1} is methyl.

4. 6-Ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

5. 6-Ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

6. 3-Ethoxy-6-ethyl-5-(4-fluorophenyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

7. A prodrug of the compound or salt of any of claims 1 to 6.

8. A medicament comprising the compound or salt of any of claims 1 to 6 or a prodrug thereof.

9. The medicament of claim 8, which is an Smo inhibitor.

10. The medicament of claim 8, which is an agent for the prophylaxis or treatment of cancer.

11. A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound or salt of any of claims 1 to 6 or a prodrug thereof to the mammal.

12. Use of the compound or salt of any of claims 1 to 6 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer.

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