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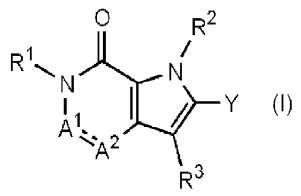
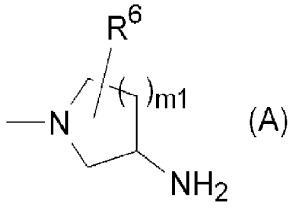
(54) Title: BICYCLIC PYRROLE DERIVATIVES

(54) 発明の名称: 二環性ピロール誘導体



(I)



(A)

(57) Abstract: Compounds represented by the general formula (I), prodrugs thereof, or pharmaceutically acceptable salts of both are provided as compounds which have high DPP-IV inhibiting activity and are improved in safety, toxicity and so on: (I) wherein the solid or broken line between A^1 and A^2 represents a double bond (A^1=A^2) or the like; A^1 is C(R^4) or the like; A^2 is nitrogen or the like; R^1 is hydrogen, optionally substituted alkyl, or the like; R^2 is hydrogen, optionally substituted alkyl, or the like; R^3 is hydrogen, halogeno, or the like; R^4 is hydrogen, hydroxyl, halogeno, or the like; and Y is a group represented by the general formula (A) or the like: (A) [wherein m1 is 0, 1, 2 or 3; and the group (A) may be freed from R^6 or substituted with one or two R^6's which are each independently halogeno or the like].

(57) 要約: DPP-IV阻害活性が高く、または安全性、毒性等で改善された化合物として、下記式（Ｉ）で表される化合物もしくはそのプロドラッグ、またはそれらの薬学上許容される塩を提供する。[式中、A^1とA^2間の実線および点線は、二重結合（A^1＝A^2）等を表す。A^1は、式Ｃ（R^4）で表される基等を表す。A^2は、窒素原子等を表す。R^1は、水素原子、置換されてもよいアルキル基等を表す。R^2は、水素原子、置換されてもよいアルキル基等を表す。R^3は、水素原子、ハロゲン原子等を表す。R^4は、水素原子、水酸基、ハロゲン原子等を表す。Ｙは、下記式（Ａ）で表される基等を表す（ｍ１は０、１、２または３を表し、R^6は、存在しないか、１つまたは２つ存在し、各々独立して、ハロゲン原子等を表す。）。]

WO 2006/068163 A1

添付公開書類:
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DESCRIPTION

BICYCLIC PYRROLE DERIVATIVES

TECHNICAL FIELD

[0001]

The present invention relates to bicyclic pyrrole derivatives useful as drugs. More particularly, it relates to novel bicyclic pyrrole derivatives effective as a dipeptidyl peptidase IV (DPP-IV) inhibitor. Furthermore, it relates to a pharmaceutical composition for the treatment of diabetes containing a bicyclic pyrrole derivative effective as a dipeptidyl peptidase IV (DPP-IV) inhibitor, as an active ingredient.

BACKGROUND ART

[0002]

DPP-IV is a serine protease widely present in the body, is one of dipeptidyl aminopeptidases capable of hydrolyzing and releasing a N-terminal dipeptide and markedly acts on, in particular, peptides containing proline as the second amino acid from the N-terminal. Therefore, DPP-IV is referred to also as prolyl end peptidase. DPP-IV is known to accept, as substrates, various biological peptides concerned in the endocrine system, the neuroendocrine system, immunological functions and the like. It is known that many

physiologically active peptides such as the pancreatic polypeptide family represented by pancreatic polypeptides (PP), neuropeptide Y (NPY) and the like; the glucagon/VIP family represented by vasoactive intestinal polypeptides (VIP), glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptides (GIP), growth hormone-releasing factor (GRF) and the like; and the chemocaine family are substrates for DPP-IV and are subject to the influences of DPP-IV, such as activation/inactivation, metabolism acceleration and the like (non-patent document 1).

[0003]

DPP-IV severs two amino acids (His-Ala) from the N-terminal of GLP-1. It is known that although the severed peptide binds weekly to a GLP-1 receptor, it has no activating effect on the receptor and acts as an antagonist (non-patent document 2). The metabolism of GLP-1 by DPP-IV in blood is known to be very rapid, and the concentration of active GLP-1 in blood is increased by the inhibition of DPP-IV (non-patent document 3). GLP-1 is a peptide secreted from intestinal tract by the ingestion of sugars and is a main accelerating factor for the glucose-responsive secretion of insulin by pancreas. In addition, GLP-1 is known to have accelerating effect on insulin synthesis in pancreatic β cells and accelerating effect on β cell proliferation. Moreover, it is known that GLP-1 receptors appear also in digestive tracts, liver,

muscle, adipose tissue and the like, and it is also known that in these tissues, GLP-1 affects working of the digestive tracts, the secretion of acid in stomach, the synthesis and degradation of glycogen, insulin-dependent glucose uptake, and the like. Accordingly, there is expected the development of a DPP-IV inhibitor effective against type 2 diabetes (non-insulin-dependent diabetes) which brings about effects such as the acceleration of insulin secretion dependent on blood sugar level, the improvement of pancreas function, the improvement of a high postprandial blood sugar level, the improvement of glucose tolerance abnormality, the improvement of insulin resistance, and the like, by increasing the concentration of GLP-1 in blood (non-patent document 4).

[0004]

Various DPP-IV inhibitors have been reported. For example, patent documents 1 and 2 report that derivatives having an imidazole ring are effective as DPP-IV inhibitors.

Patent document 1: International Publication No. WO02/068420 pamphlet

Patent document 2: International Publication No. WO03/104229 pamphlet

Non-patent document 1: J. Langner and S. Ansorge, "Cellular Peptidases in Immune Functions and Disease 2", Advances in Experimental Medicine and Biology

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Non-patent document 2: L.B. Knudsen et al., European Journal of Pharmacology, Vol. 318, p429-435, 1996

Non-patent document 3: T.J. Kieffer et al., Endocrinology, Vol. 136, p3585-3596, 1995

Non-patent document 4: R.A. Pederson et al., Diabetes Vol. 47, p1253-1258, 1998

DISCLOSURE OF THE INVENTION

Problem to be Solved by the Invention

[0005]

An aim of the present invention is to provide a novel compound having an excellent DPP-IV inhibiting activity, or an intermediate compound useful in the preparation of the novel compound, or to at least provide the public with a useful alternative.

Means for Solving the Problem

[0006]

The present inventors earnestly investigated in order to achieve the above aim, and consequently found that the following compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug (if necessary, they are hereinafter abbreviated as the present inventive compounds in some cases) has an excellent DPP-IV inhibiting effect, whereby the present invention has been accomplished.

[0007]

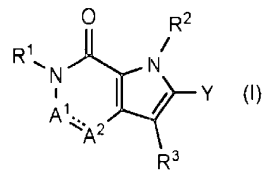
That is, the present invention relates to the

following:

[1] A compound represented by the formula (I):

[0008]

[Formula 1]



(I)

wherein R^1 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

the solid line and dotted line between A^1 and A^2 indicate a double bond (A^1=A^2) or a single bond (A^1-A^2);

A^1 is a group represented by the formula $C(R^4)$ and A^2 is a nitrogen atom, in the case of the solid line and dotted line between A^1 and A^2 being a double bond (A^1=A^2);

A^1 is a group represented by the formula C=O and A^2 is a group represented by the formula $N(R^5)$, in the case of the solid line and dotted line between A^1 and A^2 being a single bond (A^1-A^2);

R^2 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally

substituted heteroarylalkyl group, an optionally substituted alkenyl group or an optionally substituted alkynyl group;

R^3 is a hydrogen atom, a halogen atom, a cyano group, a formyl group, a carboxyl group, an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroarylalkyl group, an optionally substituted alkylcarbonyl group, an optionally substituted cycloalkylcarbonyl group, an optionally substituted aroyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted carbamoyl group, a hydroxyl group, an optionally substituted alkoxy group, or the formula: -Rd-C(O)O-Re wherein Rd is a single bond, an alkylene group or an alkenylene group and Re is tetrahydrofuranyl, cinnamyl, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-(tert-butyl)-2-oxo-1,3-dioxolen-4-ylmethyl or the formula: -$CH(R^{4a})OC(O)R^{4b}$ wherein R^{4a} is a hydrogen atom, an alkyl group, an alkenyl group, a cycloalkyl group or an alkoxy group and R^{4b} is an optionally substituted alkyl group, an optionally substituted alkenyl group, a

cycloalkyl group, a cycloalkyloxy group, an optionally substituted alkoxy group, an optionally substituted alkenyloxy group, a 2-indanyloxy group, a 5-indanyloxy group or an optionally substituted aryloxy group;

R^4 is a hydrogen atom, a hydroxyl group, a halogen atom, a cyano group, a formyl group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkyloxy group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, an optionally substituted arylthio group, an optionally substituted arylsulfinyl group, an optionally substituted arylsulfonyl group, an optionally substituted alkylthio group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, an optionally substituted alkylcarbonyl group, an optionally substituted nitrogen-containing saturated heterocyclic

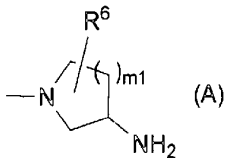
group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyloxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, or the formula: -Rd-C(O)O-Re wherein Rd and Re are as defined above;

R^5 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted vinyl group, an optionally substituted nitrogen-containing saturated heterocyclic group, or an optionally substituted heteroaryl group;

-Y is a group represented by any of the formula (A), formula (B), formula (C) and formula (D) shown below:

[0009]

[Formula 2]



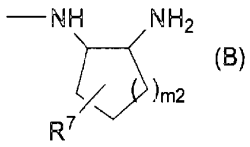
(A)

wherein m1 is 0, 1, 2 or 3, and R^6 is absent or one or two R^6s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally

substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group, or two R^6s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring;

[0010]

[Formula 3]

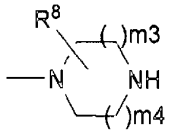


wherein m2 is 0, 1, 2 or 3, and R^7 is absent or one or two R^7s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group, or two R^7s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring;

[0011]

[Formula 4]

10

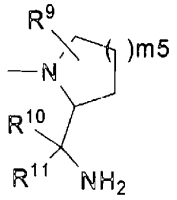


(C)

wherein m3 and m4 are independently 0 or 1, and R^6 is absent or one or two R^3s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group, or two R^5s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring; and

[0012]

[Formula 5]



(D)

wherein m5 is 1, 2 or 3, R^9 is absent or one or two R^9s are present and are independently a halogen atom, a

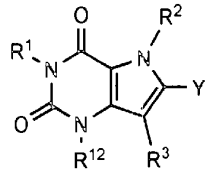
hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group, or two R^9s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring, and R^{10} and R^{11} are independently a hydrogen atom, methyl, ethyl, propyl or isopropyl, or R^{10} and R^{11}, when taken together, represent cyclopropyl, cyclobutyl or cyclopentyl,

a prodrug of said compound, or a pharmaceutically acceptable salt of said compound or prodrug.

[2] A compound according to [1], which is represented by the formula (II):

[0013]

[Formula 6]



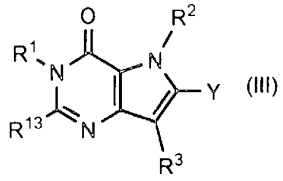
(II)

wherein R^1, R^2, R^3 and Y are as defined in [1] and R^{12} is a hydrogen atom, an optionally substituted alkyl group or an optionally substituted aryl group, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

[3] A compound according to [1], which is represented by the formula (III):

[0014]

[Formula 7]



(III)

wherein R^1, R^2, R^3 and Y are as defined in [1] and R^{13} is a hydrogen atom, a hydroxyl group, a cyano group, a carboxyl group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted alkoxy group, an optionally substituted cycloalkyloxy group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, an optionally substituted alkylcarbonyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyloxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, an optionally substituted

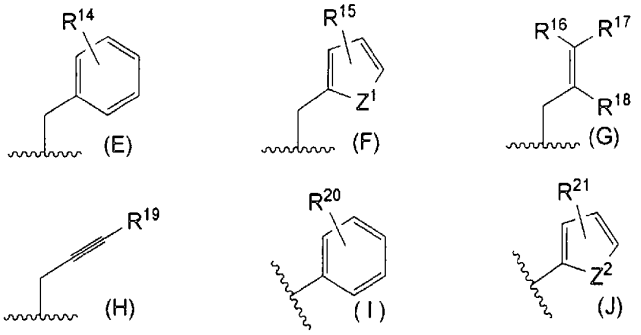
alkylsulfonyl group, or the formula: -Rd-C(O)O-Re wherein Rd and Re are as defined in [1], a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

[4] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to [3], wherein R^{13} is a hydrogen atom, a hydroxyl group, a cyano group, a carboxyl group, a trifluoromethyl group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aroyl group, an optionally substituted alkylcarbonyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyloxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, an optionally substituted alkylsulfonyl group, or the formula: -Rd-C(O)O-Re wherein Rd and Re are as defined in [1].

[5] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [4], wherein R^{2} is a group represented by any of the following formula (E), formula (F), formula (G), formula (H), formula (I) and formula (J):

[0015]

[Formula 8]



wherein each of Z^1 and Z^2 is an oxygen atom, the formula S(O)p or the formula $N(R^{22})$;

each of R^{14} and R^{20} is absent or one or two R^{14}s and/or one or two R^{20}s are present and are independently a halogen atom, a hydroxyl group, a formyl group, a carboxyl group, a cyano group, an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, a haloalkoxy group, an optionally substituted amino group, an optionally substituted carbamoyl group, an alkoxycarbonyl group, an optionally substituted alkylcarbonyl group, a cycloalkylcarbonyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted nitrogen-containing heteroaryl group, or two R^{14}s or two R^{20}s, when taken together, represent a C_{1-3} alkylenedioxy group;

each of R^{15} and R^{21} is absent or one or two

R^{15}s and/or one or two R^{21}s are present and are independently a halogen atom, a cyano group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group or a haloalkoxy group;

R^{16} is methyl, ethyl, a chlorine atom or a bromine atom;

R^{17} is a hydrogen atom, methyl, ethyl, a chlorine atom or a bromine atom;

R^{18} is a hydrogen atom, methyl or ethyl;

R^{19} is a hydrogen atom, methyl, ethyl, cyclopropyl or cyclobutyl;

p is 0, 1 or 2; and

R^{22} is a hydrogen atom or an alkyl group.

[6] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [5], wherein -Y is a group represented by the formula (A) in which m1 is 1 or 2, or -Y is a group represented by the formula (B) in which m2 is 1 or 2, or -Y is a group represented by the formula (C) in which each of m3 and m4 is 1.

[7] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [6], wherein R^2 is a group represented by any of the formula (E), formula (H) and formula (I).

[8] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [7], wherein R^1 is a

hydrogen atom, an optionally substituted C_1-C_3 alkyl group or an optionally substituted aryl group, and the substituent(s) of the optionally substituted alkyl group is selected from fluorine atom, optionally substituted aroyl groups, carboxyl group, optionally substituted alkoxycarbonyl groups, optionally substituted aryl groups and optionally substituted aryloxy groups.

[9] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [7], wherein R^1 is a group represented by the formula: -Ra-Rb-Rc in which

Ra is an alkylene group;

Rb is a single bond or a carbonyl group; and

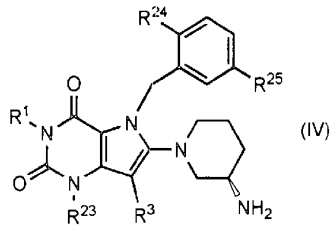
Rc is an optionally substituted alkyl group, an optionally substituted alkoxy group, an optionally substituted aryl group, an optionally substituted aryloxy group or an optionally substituted heteroarylamino group.

[10] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [7], wherein R^1 is a hydrogen atom, methyl or ethyl.

[11] A compound according to [1], which is represented by the formula (IV):

[0016]

[Formula 9]



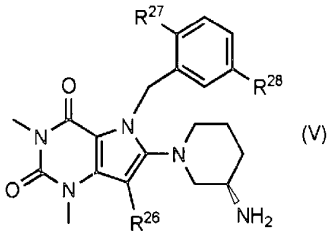
(IV)

wherein R^1 and R^3 are as defined in [1]; R^{23} is a hydrogen atom or an optionally substituted alkyl group; R^{24} is a halogen atom, a cyano group, a carbamoyl group, a methyl group, a trifluoromethyl group, a difluoromethyl group, a monofluoromethyl group, a methoxy group, a trifluoromethoxy group, difluoromethoxy group or a monofluoromethoxy group; and R^{25} is a hydrogen atom, a fluorine atom or a chlorine atom, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

[12] A compound according to [1], which is represented by the formula (V):

[0017]

[Formula 10]



(V)

wherein R^{26} is a hydrogen atom, a cyano group, an optionally substituted alkyl group, an optionally

substituted carbamoyl group, a hydroxyl group or an optionally substituted alkoxy group; R^{27} is a chlorine atom, a bromine atom, a cyano group, a carbamoyl group, a methyl group, a trifluoromethyl group, a difluoromethyl group, a monofluoromethyl group, a methoxy group, a trifluoromethoxy group, difluoromethoxy group or a monofluoromethoxy group; and R^{28} is a hydrogen atom or a fluorine atom, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

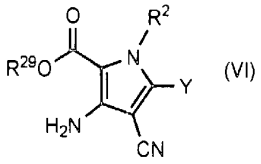
[13] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to [12], wherein R^{27} is a chlorine atom or a cyano group.

[14] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to either [12] or [13], wherein R^{26} is a hydrogen atom or an optionally substituted carbamoyl group.

[15] A compound represented by the formula (VI):

[0018]

[Formula 11]



(VI)

wherein R^2 and Y are as defined in [1] and R^{29} is a hydrogen atom, an optionally substituted alkyl group,

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an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group or an optionally substituted heteroarylalkyl group, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

[16] A pharmaceutical composition comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [14] as an active ingredient.

[17] A dipeptidyl peptidase IV inhibitor comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [14] as an active ingredient.

[18] A pharmaceutical composition for the treatment of diabetes comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [14] as an active ingredient.

[19] Use of a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [14] in the manufacture of a dipeptidyl peptidase IV inhibitor.

[20] Use of a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [14] in the manufacture of a pharmaceutical composition for the treatment of diabetes.

[21] A method for treating diabetes comprising administering an effective amount of a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [14] to a patient who needs the treatment.

[22] Use of a compound according to [15] in the manufacture of a dipeptyidyl peptidase IV inhibitor or in the manufacture of a compound according to any one of [1] to [14].

[23] A process for preparing a compound of formula (I):

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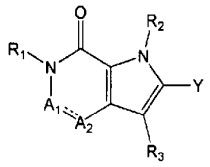
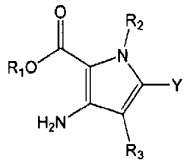


(I)

wherein R_1, R_2, R_3, A_1, A_2 and Y, for formula (I) are as defined in [1], and wherein the process comprises the steps of:

(i) reacting in an organic solvent an isocyanate or isothiocyanate compound with a compound of formula (VIa), wherein R_1, R_2, R_3 and Y, are as defined in [1]:



(VIa)

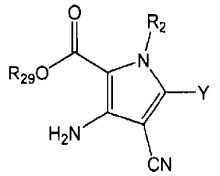
in the presence of a base to obtain a reaction product; and

(ii) reacting the product obtained from (i) with a base and a source of methyl anion in an organic solvent, and (iii) performing an aqueous work up of the product to form the compound of formula (I).

[24] The process of [23], wherein the source of methyl anion is methyl iodide.

[25] The process of [23] or [24], wherein the step (ii) is carried out a temperature between 50 and 160°C.

[26] A process for preparing a compound of formula (VI):



(VI)

wherein R_2, R_{29} and Y, for formula (VI) are as defined in [15], and wherein the process comprises the steps of:

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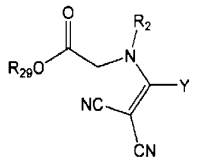
(i) reacting in an organic solvent a compound of formula (VIb), where R_1, R_2, R_3 and Y, are as defined in [1]:



(VIb)

with a strong base to obtain a reaction product; and

(ii) performing an aqueous work up of the product obtained from (i) to form the compound of formula (VI).

[27] The process of [26], wherein the strong base is a hydride.

[0019]

The compound represented by the formula (I), a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug is hereinafter generically named "the present inventive compound" if necessary.

Advantages of the Invention

[0020]

The present inventive compound has an excellent DPP-IV inhibiting activity and is useful as a therapeutic agent for diabetes.

BEST MODE FOR CARRYING OUT THE INVENTION

[0021]

The present invention is explained below in further detail.

In the present description, the number of substituents of each group defined by the term "optionally substituted" or "substituted" is not particularly limited as long as the substitution is

possible, and it is 1 or more. Unless otherwise specified, the explanation of each group applies also to the case where the group is a portion or the substituent of another group.

[0022]

The "halogen atom" includes, for example, fluorine atom, chlorine atom, bromine atom and iodine atom.

The "alkyl group" includes, for example, linear or branched alkyl groups of 1 to 6 carbon atoms. Specific examples thereof are 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, etc. Preferable examples thereof are linear or branched alkyl groups of 1 to 4 carbon atoms. Specific examples of such groups are methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.

The "alkenyl group" includes, for example, alkenyl groups of 2 to 6 carbon atoms. Specific examples thereof are vinyl, propenyl, methylpropenyl, butenyl, methylbutenyl, etc.

The "alkynyl group" includes, for example, alkynyl groups of 2 to 6 carbon atoms. Specific examples thereof are ethynyl, 1-propynyl, 2-propynyl, 2-butynyl, pentynyl, hexynyl, etc.

The "cycloalkyl group" includes, for example,

cycloalkyl groups of 3 to 10 carbon atoms. Specific examples thereof are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, etc. Preferable examples thereof are cycloalkyl groups of 3 to 6 carbon atoms. Specific examples of such groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "alkylene group" includes, for example, alkylene groups of 1 to 3 carbon atoms. Specific examples thereof are methylene, ethylene, trimethylene, etc.

The "alkenylene group" includes, for example, alkenylene groups of 2 to 4 carbon atoms. Specific examples thereof are vinylene, propenylene, butenylene, etc.

[0023]

The "aryl group" includes, for example, aryl groups of 6 to 10 carbon atoms. Specific examples thereof are phenyl, 1-naphthyl, 2-naphthyl, etc.

The "aralkyl group" includes, for example, groups formed by bonding of an aryl group to an alkylene group. Specific examples thereof are benzyl, 2-phenylethyl, 1-naphthylmethyl, etc.

The "heteroaryl group" includes, for example, 5- to 10-membered monocyclic or polycyclic groups containing one or more (for example, 1 to 4) heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom. Specific examples thereof are

pyrrolyl, thienyl, benzothienyl, benzofuranyl, benzoxazolyl, benzothiazolyl, furyl, oxazolyl, thiazolyl, isoxazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, triazolyl, triazinyl, tetrazolyl, indolyl, imidazo[1,2-a]pyridyl, dibenzofuranyl, benzimidazolyl, quinoxalyl, cinnolyl, quinazolyl, indazolyl, naphthyridyl, quinolinolyl, isoquinolinolyl, etc. Preferable examples thereof are 5- or 6-membered groups containing a heteroatom selected from nitrogen atom, sulfur atom and oxygen atom. Specific examples of such groups are pyridyl, thienyl, furyl, etc.

The heteroaryl portion of the "heteroarylalkyl group" includes the groups exemplified above as the heteroaryl group.

[0024]

The "alkylcarbonyl group" includes, for example, alkylcarbonyl groups of 2 to 4 carbon atoms. Specific examples thereof are acetyl, propionyl, butyryl, etc.

The "cycloalkylcarbonyl group" includes cycloalkylcarbonyl groups of 4 to 11 carbon atoms, and the like. Specific examples thereof are cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl, norbornylcarbonyl, etc. Preferable examples thereof are cycloalkylcarbonyl groups of 4 to 7 carbon atoms. Specific examples of such groups are

cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.

The "aroyl group" includes, for example, aroyl groups of 7 to 11 carbon atoms. Specific examples thereof are benzoyl, 1-naphthoyl, 2-naphthoyl, etc.

The heteroaryl portion of the "heteroarylcarbonyl group" includes the groups exemplified above as the heteroaryl group.

The "alkoxycarbonyl group" includes, for example, alkoxycarbonyl groups of 2 to 5 carbon atoms. Specific examples thereof are methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 2-propoxycarbonyl, tert-butoxycarbonyl, etc.

The "aryloxycarbonyl group" includes aryloxycarbonyl groups of 7 to 11 carbon atoms, and the like. Specific examples thereof are phenyloxycarbonyl, 2-naphthyloxycarbonyl, 1-naphthyloxycarbonyl, etc.

[0025]

The "alkoxy group" includes, for example, alkoxy groups of 1 to 4 carbon atoms. Specific examples thereof are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.

The "cycloalkyloxy group" includes, for example, cycloalkyloxy groups of 3 to 10 carbon atoms. Specific examples thereof are cyclopropyloxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy,

cycloheptyloxy, adamantyloxy, norbornyloxy, etc. Preferable examples thereof are cycloalkyloxy groups of 3 to 6 carbon atoms. Specific examples of such groups are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, etc.

The cycloalkyloxy portion of the "cycloalkyloxycarbonyl group" includes the groups exemplified above as the cycloalkyloxy group.

The "aryloxy group" includes, for example, aryloxy groups of 6 to 10 carbon atoms. Specific examples thereof are phenoxy, 1-naphthyloxy, 2-naphthyloxy, etc.

The aralkyl portion of the "aralkyloxy group" includes the groups exemplified above as the aralkyl group. Specific examples thereof are benzyloxy, 2-phenylethyloxy, etc.

The aralkyl portion of the "aralkyloxycarbonyl group" includes the groups exemplified above as the aralkyl group.

The heteroaryl portion of the "heteroaryloxy group" includes the groups exemplified above as the heteroaryl group.

[0026]

The "alkylthio group" includes, for example, alkylthio groups of 1 to 6 carbon atoms. Specific examples thereof are methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio, hexylthio, etc. Preferable

examples thereof are alkylthio groups of 1 to 4 carbon atoms. Specific examples of such groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.

The "alkylsulfinyl group" includes, for example, alkylsulfinyl groups of 1 to 6 carbon atoms. Specific examples thereof are methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, hexylsulfinyl, etc. Preferable examples thereof are alkylsulfinyl groups of 1 to 4 carbon atoms. Specific examples of such groups are methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, etc.

The "alkylsulfonyl group" includes, for example, alkylsulfonyl groups of 1 to 6 carbon atoms. Specific examples thereof are methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc. Preferable examples thereof are alkylsulfonyl groups of 1 to 4 carbon atoms. Specific examples of such groups are methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, etc.

The "arylthio group" includes, for example, arylthio groups of 6 to 10 carbon atoms. Specific examples thereof are phenylthio, 1-naphthylthio, 2-naphthylthio, etc.

The "arylsulfinyl group" includes, for example, arylsulfinyl groups of 6 to 10 carbon atoms.

Specific examples thereof are phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl, etc.

The "arylsulfonyl group" includes, for example, arylsulfonyl groups of 6 to 10 carbon atoms. Specific examples thereof are phenylsulfonyl, tosyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.

[0027]

The "nitrogen-containing saturated heterocyclic group" includes, for example, 5- or 6-membered saturated heterocyclic groups which have one or two nitrogen atoms and may further have an oxygen atom or a sulfur atom. Specific examples thereof are pyrrolidinyl, imidazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, hexamethyleneiminyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, oxoimidazolidinyl, dioxoimidazolidinyl, oxooxazolidinyl, dioxooxazolidinyl, dioxothiazolidinyl, tetrahydrofuranyl, tetrahydropyridinyl, etc.

[0028]

The substituent(s) of the "optionally substituted alkyl group" includes, for example, (1) halogen atoms, (2) hydroxyl group, (3) cyano group, (4) carboxyl group, (5) optionally substituted cycloalkyl groups, (6) optionally substituted aryl groups, (7) optionally substituted heteroaryl groups, (8) optionally substituted aroyl groups, (9) optionally substituted heteroarylcarbonyl groups, (10) optionally substituted arylaminocarbonyl groups, (11) optionally

substituted heteroarylaminocarbonyl groups, (12) optionally substituted aryloxy groups, (13) optionally substituted arylsulfonyl groups, (14) optionally substituted aralkylsulfonyl groups, (15) optionally substituted alkoxy groups, (16) optionally substituted cycloalkyloxy groups, (17) optionally substituted alkoxycarbonyl groups, (18) optionally substituted aryloxycarbonyl groups, (19) optionally substituted amino groups, (20) optionally substituted carbamoyl groups, (21) alkylsulfonyl groups, (22) optionally substituted alkylcarbonyl groups, (23) cycloalkyloxycarbonyl groups, (24) tetrahydrofuranyloxycarbonyl group, and (25) tetrahydrofuranyl group.

[0029]

The above items (1) to (25) are explained below.

The substituents of the "optionally substituted cycloalkyl groups" of the above item (5) include, for example, alkyl groups, aralkyl groups, alkoxy groups, alkoxycarbonyl groups and fluorine atom.

The substituents of the "optionally substituted aryl groups" of the above item (6) include those exemplified hereinafter as the substituent(s) of the "optionally substituted aryl group".

The substituents of the "optionally substituted heteroaryl groups" of the above item (7) include, for example,

(a) hydroxyl group,

(b) halogen atoms,

(c) alkyl groups,

(d) alkyl groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(e) alkoxy groups,

(f) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(g) cyano group,

(h) carboxyl group,

(i) alkoxycarbonyl groups,

(j) carbamoyl groups which may be substituted by an alkyl group(s) (for example, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl and diethylcarbamoyl),

(k) aryl groups,

and (l) amino group.

The substituents of the "optionally substituted aroyl groups" of the above item (8) include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

The substituents of the "optionally substituted heteroarylcarbonyl groups" of the above item (9) include those exemplified as the substituents of the "optionally substituted heteroaryl groups" of the above item (7).

The substituents of the "optionally substituted arylaminocarbonyl groups" of the above item (10) include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

The substituents of the "optionally substituted heteroarylaminocarbonyl groups" of the above item (11) include those exemplified as the substituents of the "optionally substituted heteroaryl groups" of the above item (7).

The substituents of the "optionally substituted aryloxy groups" of the above item (12) and the "optionally substituted arylsulfonyl groups" of the above item (13) include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

The aralkyl portion of the "optionally

substituted aralkylsulfonyl group" of the above item (14) includes the groups exemplified above as the aralkyl group.

The substituents of the "optionally substituted aralkylsulfonyl groups" include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

The substituents of the "optionally substituted alkoxy groups" of the above item (15) include, for example,

(a) hydroxyl group,

(b) carboxyl group,

(c) alkoxy groups,

(d) alkoxycarbonyl groups,

(e) amino groups which may be substituted by an alkyl group(s) (for example, amino, dimethylamino and diethylamino),

(f) carbamoyl groups substituted by an alkyl group(s),

(g) sulfamoyl groups substituted by an alkyl group(s),

(h) ureido groups substituted by an alkyl group(s),

(i) phenyl groups which may be substituted by a halogen atom or an alkoxy group (for example, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-isopropoxyphenyl and 3-isopropoxyphenyl),

(j) 5-oxo-2-tetrahydrofuranyl,

(k) 1,3-dihydro-3-oxo-1-isobenzofuranyl,

(l) tetrahydrofuranyl,

(m) nitrogen-containing saturated heterocyclic groups,

(n) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(o) cycloalkyl groups,

(p) cycloalkyl groups substituted by a halogen atom or an alkoxy group (for example, 2-fluorocyclopropyl, 2-methoxycyclopropyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl and 3-methoxycyclobutyl), and

(q) halogen atoms.

The substituents of the "optionally substituted cycloalkyloxy groups" of the above item (16) and the "optionally substituted alkoxycarbonyl groups" of the above item (17) include those exemplified as the substituents of the "optionally substituted alkoxy groups" of the above item (15).

The substituents of the "optionally substituted aryloxycarbonyl groups" of the above item (18) include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

The substituents of the "optionally substituted amino groups" of the above item (19) include, for example,

(a) alkyl groups,

(b) alkylcarbonyl groups,

(c) aroyl groups,

(d) alkylsulfonyl groups,

(e) arylsulfonyl groups,

(f) optionally substituted aryl groups (their substituents include, for example, halogen atoms, alkyl groups and alkoxy groups),

(g) alkoxycarbonylmethyl groups (the carbon atom of the methyl portion may be substituted by one or two alkyl groups, and the two alkyl groups on the carbon atom of the methyl portion may bind to each other to form cyclopropyl, cyclobutyl or cyclopentyl together with the carbon atom of the methyl portion),

and (h) aralkyl groups.

As the optionally substituted amino groups, (i) imides are also exemplified.

The substituents of the "optionally substituted carbamoyl groups" of the above item (20) include, for example, alkyl groups and cycloalkyl groups. The two substituents of the carbamoyl group may bind to each other to form an aliphatic heterocyclic ring which may contain carbon atoms, a nitrogen atom(s) and/or an oxygen atom(s), such as pyrrolidine (which may be substituted by a hydroxyl

group), piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine dioxide, piperazine (the nitrogen atom of this piperazine may be substituted by methyl or ethyl), or the like.

Specific examples of the "optionally substituted carbamoyl groups" are carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, methylpropylcarbamoyl, cyclopropylcarbamoyl, cyclopropylmethylcarbamoyl, pyrrolidinocarbonyl, piperidinocarbonyl, morpholinocarbonyl, etc.

The substituents of the "optionally substituted alkylcarbonyl groups" of the above item (22) include, for example,

(a) halogen atoms,

(b) alkoxy groups,

(c) cycloalkyl groups,

(d) alkoxycarbonyl groups,

(e) optionally substituted aryl groups (their substituents include, for example, halogen atoms, alkyl groups, alkoxy groups and alkoxycarbonyl groups), and (f) hydroxyl group.

[0030]

The substituent(s) of each of the "optionally substituted alkylthio group", "optionally substituted alkylsulfinyl group" and "optionally substituted alkylsulfonyl group" includes those exemplified as the substituent(s) of the above-mentioned "optionally

substituted alkyl group".

[0031]

The substituent(s) of each of the "optionally substituted alkenyl group" and the "optionally substituted alkynyl group" includes, for example,

(1) hydroxyl group,

(2) halogen atoms,

(3) alkyl groups,

(4) alkyl groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, methoxypropyl and ethoxypropyl),

(5) alkoxy groups,

(6) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(7) phenyl groups or aroyl groups, which may be substituted by the following (aa), (bb) or (cc):

(aa) an alkoxy group(s) which may be

substituted by a halogen atom(s) or an alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(bb) an alkyl group(s) which may be substituted by a halogen atom(s) (for example, methyl, ethyl, propyl, isopropyl, butyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl and 1-(difluoromethyl)-2,2-difluoroethyl),

(cc) a halogen atom(s),

(8) cyano group,

(9) carboxyl group,

(10) alkoxycarbonyl groups,

(11) carbamoyl groups which may be substituted by an alkyl group(s) (for example, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl and diethylcarbamoyl),

(12) alkylsulfonyl groups,

and (13) phenyloxy group.

[0032]

The substituent(s) of the "optionally

substituted vinyl group" includes, for example, halogen atoms and alkyl groups.

Specific examples of the substituted vinyl groups are 1-propylene, 2-methyl-1-propylene, 2-chloro-1-propylene, etc.

The substituent(s) of the "optionally substituted cycloalkyl group" includes those exemplified as the substituents of (5) the "optionally substituted cycloalkyl groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

[0033]

The substituent(s) of the "optionally substituted aryl group" includes, for example,

(1) hydroxyl group,

(2) halogen atoms,

(3) alkyl groups,

(4) alkyl groups substituted by a halogen atom(s), an alkoxy group or a cycloalkyl group (for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, methoxypropyl and ethoxypropyl),

(5) phenyl groups which may be substituted by the following (aa), (bb) or (cc):

(aa) an alkoxy group(s) which may be

substituted by a halogen atom(s) or an alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(bb) an alkyl group(s) which may be substituted by a halogen atom(s) (for example, methyl, ethyl, propyl, isopropyl, butyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl and 1-(difluoromethyl)-2,2-difluoroethyl),

(cc) a halogen atom(s),

(6) cyano group,

(7) carboxyl group,

(8) alkoxycarbonyl groups which may be substituted by a halogen atom(s) (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, fluoromethoxycarbonyl, difluoromethoxycarbonyl, 2,2-difluoroethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, methoxycarbonyl and ethoxycarbonyl),

(9) carbamoyl groups which may be substituted by an

alkyl group(s) (for example, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl and diethylcarbamoyl),

(10) alkylsulfonyl groups,

(11) C_{1-3} alkylenedioxy groups,

(12) formyl group,

(13) optionally substituted phenyloxy groups (their substituents include, for example, halogen atoms, alkyl groups and alkoxy groups),

(14) nitrogen-containing saturated heterocyclic groups (for example, pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl (the nitrogen atom of the piperazine may be substituted, for example, by methyl, ethyl or propyl)),

(15) cycloalkyloxy groups which may be substituted by a hydroxyl group, an oxo group, a carboxyl group, a carboxymethyl group, an alkoxycarbonyl group, an alkoxycarbonylalkyl group (e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl or isopropoxycarbonylmethyl), an alkyl group, a fluoroalkyl group (e.g. fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or perfluoroethyl), an alkoxyalkyl group (e.g. methoxymethyl, ethoxymethyl or isopropoxymethyl), a cycloalkyloxyalkyl group (e.g. cyclopropyloxymethyl, cyclopropyloxyethyl or cyclobutyloxy), an alkoxy group, a cycloalkyloxy group or a halogen atom(s) (for example, 3-carboxycyclobutyloxy, 3-methoxycarbonylcyclobutyloxy,

3-ethoxycarbonylbutyloxy, 2-methylcyclopropyloxy, 2-fluorocyclopropyloxy, 3-methoxycyclobutyloxy, 3-fluorocyclobutyloxy, 3,3-difluorocyclobutyloxy and 3-(2-fluoroethyl)cyclobutyloxy),

(16) alkoxy groups which may be substituted by a hydroxyl group, an oxo group, a carboxyl group, an alkoxycarbonyl group, a cycloalkyl group, an alkoxy group, a cycloalkyloxy group, an optionally substituted oxygen-containing heterocyclic group (e.g. a 5- or 6-membered saturated heterocyclic group having an oxygen atom(s), specific examples of which are tetrahydrofuranyl, tetrahydropyranyl, etc.; the substituent(s) includes, for example, halogen atoms, oxo group and alkoxy groups), or a halogen atom(s) (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, 2-hydroxyethoxy, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, cyclopropylmethoxy, cyclobutylmethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, isopropoxymethoxy, cyclopropyloxymethoxy, cyclobutoxymethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy and 1-(difluoromethyl)-2,2-difluoroethoxy),

(17) difluoromethylenedioxy,

(18) alkenyl groups which may be substituted by a halogen atom (for example, vinyl, propenyl,

methylpropenyl, butenyl and methylbutenyl),

(19) amino groups which may be substituted by an alkyl group(s) (for example, amino, methylamino, ethylamino, propylamino, dimethylamino, methylethylamino and diethylamino),

(20) optionally substituted alkylcarbonyl groups (their substituents include, for example, halogen atoms, alkoxy groups and cycloalkyl groups),

(21) alkylcarbonyloxy groups (for example, methylcarbonyloxy, ethylcarbonyloxy and isopropylcarbonyloxy),

(22) cycloalkyl groups which may be substituted by a fluorine atom (for example, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorocyclopropyl, 2-fluorocyclobutyl, 3-fluorocyclobutylcyclobutyl, adamantyl and norbornyl),

(23) cycloalkylcarbonyl groups which may be substituted by a fluorine atom (for example, cyclopropylcarbonyl, 2-fluorocyclopropylcarbonyl, cyclobutylcarbonyl and cyclopentylcarbonyl),

(24) alkylthio groups,

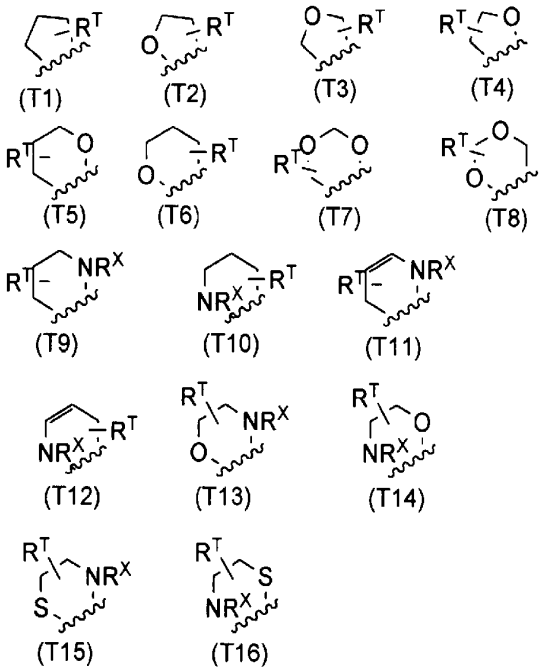
(25) alkylsulfinyl groups,

(26) optionally substituted heteroaryl groups (their substituents include, for example, halogen atoms, alkyl groups, alkoxy groups, haloalkyl groups and haloalkoxy groups),

(27) groups represented by the following formulas (T1) to (T16):

[0034]

[Formula 12]



wherein R^T is absent or one or more R^Ts are present and are independently a halogen atom, a hydroxyl group, an oxo group, a carboxyl group, an optionally substituted alkyl group (its substituent(s) includes, for example, halogen atoms and alkoxy groups), an optionally substituted alkoxycarbonyl group (its substituent(s) includes, for example, halogen atoms and alkoxy groups), an optionally substituted alkoxy group (its substituent(s) includes, for example, halogen atoms and

alkoxy groups), an optionally substituted carbamoyl group (its substituent(s) includes, for example, alkyl groups), or a saturated heterocyclic group oxycarbonyl group (the saturated heterocyclic group includes, for example, 5- or 6-membered saturated heterocyclic groups having an oxygen atom(s), a nitrogen atom(s) and/or a sulfur atom(s), each in a number of 1 or 2, specific examples of which are tetrahydrofuranyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrothiopyranyl, tetrahydrodioxothiopyranyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, oxazolidinyl and thiazolidinyl), or two R^Ts, when taken together, may represent methylene, ethylene, trimethylene, tetramethylenel or butenylene and may bind to one or more carbon atoms constituting the ring, to form a new ring; and R^X is a hydrogen atom or an alkyl group,

(28) aroyl groups, and

(29) groups represented by the formula: -Rd-CO(O)-Re

wherein Rd and Re are as defined above.

[0035]

The substituent(s) of each of the "optionally substituted heteroaryl group", "optionally substituted aralkyl group", "optionally substituted heteroarylalkyl group", "optionally substituted aroyl group", "optionally substituted heteroarylcarbonyl group", "optionally substituted aryloxycarbonyl group", "optionally substituted aryloxy group", "optionally

substituted aralkyloxy group", "optionally substituted aralkyloxycarbonyl group", "optionally substituted heteroaryloxy group", "optionally substituted arylthio group", "optionally substituted arylsulfinyl group" and "optionally substituted arylsulfonyl group" includes those exemplified as the substituent(s) of the above-mentioned "optionally substituted aryl group".

[0036]

The substituent(s) of the "optionally substituted alkylcarbonyl group" includes those exemplified as the substituents of (22) the "optionally substituted alkylcarbonyl groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

The substituent(s) of the "optionally substituted cycloalkylcarbonyl group" includes, for example, halogen atoms and alkoxy groups.

The substituent(s) of each of the "optionally substituted alkoxy group" and the "optionally substituted alkoxycarbonyl group" includes those exemplified as the substituents of (15) the "optionally substituted alkoxy groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

The substituent(s) of each of the "optionally substituted cycloalkyloxy group" and the "optionally substituted cycloalkyloxycarbonyl group" includes those exemplified as the substituents of (16) the "optionally substituted cycloalkyloxy groups" as the substituent(s)

of the above-mentioned "optionally substituted alkyl group".

[0037]

The substituent(s) of the "optionally substituted amino group" includes those exemplified as the substituents of (19) the "optionally substituted amino groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

The substituent(s) of the "optionally substituted carbamoyl group" includes, for example,

(1) optionally substituted alkyl groups (their substituents include, for example, hydroxyl group, halogen atoms, alkoxy groups optionally substituted by a halogen atom(s), cycloalkoxy groups optionally substituted by a halogen atom(s), and tetrahydrofuranyl),

(2) cycloalkyl groups which may be substituted by a halogen atom(s),

(3) aryl groups which may be substituted by the following (aa), (bb), (cc) or (dd):

(aa) a halogen atom(s),

(bb) an alkoxy group(s) which may be substituted by a halogen atom(s) (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy and 1-(difluoromethyl)-2,2-

difluoroethoxy),

(cc) an alkyl group(s) which may be substituted by a halogen atom(s) (for example, methyl, ethyl, propyl, isopropyl, butyl, methyl, ethyl, propyl, isopropyl, butyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl and 1-(difluoromethyl)-2,2-difluoroethyl),

(dd) a C_{1-3} alkylenedioxy group(s),

(4) alkylsulfonyl groups,

(5) cycloalkylsulfonyl groups,

(6) optionally substituted arylsulfonyl groups (their substituents include, for example, halogen atoms, alkyl groups, haloalkyl groups, alkoxy groups and haloalkoxy groups),

(7) alkylcarbonyl groups,

(8) alkoxycarbonyl groups,

(9) optionally substituted aroyl groups (their substituents include, for example, halogen atoms, alkyl groups, haloalkyl groups, alkoxy groups, haloalkoxy groups, alkoxycarbonyl groups and C_{1-3} alkylenedioxy groups),

(10) cycloalkylalkyl groups,

(11) isoxazolyl group,

and (12) optionally substituted adamantyl groups (their substituents include, for example, hydroxyl group).

Specific examples of the "optionally substituted carbamoyl group" are carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, phenylcarbamoyl, phenylmethylcarbamoyl, cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopropylmethylcarbamoyl, cyclohexylmethylcarbamoyl, 2,3-dihydroxypropylcarbamoyl, tetrahydrofuranylalkylcarbamoyl, methoxyethylcarbamoyl, trifluoroethylcarbamoyl, adamantylcarbamoyl, hydroxyadamantylcarbamoyl, etc.

The two substituents of the carbamoyl group may bind to each other to form a 4- to 6-membered aliphatic heterocyclic ring which may contain carbon, nitrogen, oxygen or sulfur, such as pyrrolidine, piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine dioxide, piperazine (the nitrogen atom of this piperazine may be substituted by methyl, ethyl or propyl), or the like, and the carbamoyl group may be further substituted by a hydroxyl group. Specific examples of such a substituted carbamoyl group are pyrrolidinocarbamoyl, piperidinocarbamoyl, morpholinocarbamoyl, 4-hydroxypiperidinocarbamoyl, etc.

[0038]

The substituent(s) of the "optionally substituted nitrogen-containing saturated heterocyclic group" includes, for example,

(1) halogen atoms,

(2) alkyl groups,

(3) alkyl groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, perfluoroethyl and methoxyethyl),

(4) alkoxy groups,

(5) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(6) cyano group,

and (7) oxo group.

[0039]

When two R^6s, R^7s, R^8s or R^9s are present, they may be present on one and the same carbon atom or may be present on different carbon atoms, respectively.

The phrase "two R^6s, R^7s, R^8s or R^9s, when taken together, represent methylene or ethylene and bind to one or more carbon atoms constituting the ring, to form a new ring" means that they form a spiro ring or a bicyclo ring through one and the same carbon atom or different carbon atoms, respectively.

The phrase "two R^Ts, when taken together, represent methylene, ethylene, trimethylene, tetramethylene or butenylene and bind to one or two carbon atoms constituting the ring, to form a new ring" means that they form a spiro ring or a bicyclo ring

through one and the same carbon atom or different carbon atoms, respectively.

[0040]

The "haloalkoxy group" includes, for example, alkoxy groups of 1 to 4 carbon atoms substituted by a halogen atom(s). Specific examples thereof are fluoromethoxy, difluoromethoxy, trifluoromethoxy, etc.

The "haloalkyl group" includes, for example, alkyl groups of 1 to 4 carbon atoms substituted by a halogen atom(s). Specific examples thereof are fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, perfluoroethyl, etc.

The "C_{1-3} alkylenedioxy group" includes, for example, methylenedioxy, ethylenedioxy and trimethylenedioxy.

[0041]

The "substituted alkyl group" for R^{4b} includes, for example, alkyl groups of 1 to 3 carbon atoms substituted by a cycloalkyl group of 3 to 7 carbon atoms (e.g. cyclopentyl, cyclohexyl or cycloheptyl) or an optionally substituted aryl group (e.g. phenyl group). Specific examples thereof are benzyl, p-chlorobenzyl, p-methoxybenzyl, p-fluorobenzyl, cyclopentylmethyl, cyclohexymethyl, etc.

The "substituted alkenyl group" for R^{4b} includes, for example, alkenyl groups of 2 or 3 carbon atoms substituted by a cycloalkyl group of 5 to 7 carbon atoms (e.g. cyclopentyl, cyclohexyl or

cycloheptyl) or an aryl group (e.g. phenyl group). Examples thereof are vinyl, propenyl, allyl, isopropenyl, etc., which are substituted by phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or the like.

The "alkenyloxy group" for R^{4b} includes, for example, linear or branched alkenyloxy groups of 2 to 8 carbon atoms. Specific examples thereof are allyloxy, isobutenyloxy, etc.

The "substituted alkoxy group" for R^{4b} includes, for example, alkoxy groups of 1 to 3 carbon atoms substituted by a cycloalkyl group of 3 to 7 carbon atoms (e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl) or an optionally substituted aryl group (e.g. phenyl group). Specific examples thereof are benzyloxy, phenethyloxy, cyclopropylmethyloxy, cyclopropylethyloxy, cyclopentylmethyloxy, etc.

The "substituted alkenyloxy group" for R^{4b} includes, for example, alkenyloxy groups of 2 or 3 carbon atoms substituted by a cycloalkyl group of 3 to 7 carbon atoms (e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl) or an optionally substituted aryl group (e.g. phenyl group). Examples thereof are vinyloxy, propenyloxy, allyloxy, isopropenyloxy, etc., which are substituted by phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or the like.

Specific examples of the "optionally substituted aryloxy group" for R^{4b} are phenoxy, p-

nitrophenoxy, p-methoxyphenoxy, p-fluorophenoxy, naphthoxy, etc.

[0042]

Specific examples of each of the "substituted alkoxycarbonyl group" and the group represented by the formula: -Rd-CO(O)-Re wherein Rd and Re are as defined above, are pivaloyloxymethoxycarbonyl, 1-(pivaloyloxy)ethoxycarbonyl, 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethoxycarbonyl, 5-(tert-butyl)-2-oxo-1,3-dioxolen-4-ylmethoxycarbonyl, acetoxymethyloxycarbonyl, propyloxymethoxycarbonyl, n-butoxymethoxycarbonyl, isobutoxymethoxycarbonyl, 1-(ethoxycarbonyloxy)ethoxycarbonyl, 1-(tert-butoxycarbonyloxy)ethoxycarbonyl, 1-(acetyloxy)ethoxycarbonyl, 1-(isobutoxy)ethoxycarbonyl, cyclohexylcarbonyloxymethoxycarbonyl, 1-(cyclohexylcarbonyloxy)ethoxycarbonyl, cyclopentylcarbonyloxymethoxycarbonyl, 1-(cyclopentylcarbonyloxy)ethoxycarbonyl, etc.

[0043]

The substituent(s) of each of the "optionally substituted alkyl group" and the "optionally substituted alkoxy group" for Rc includes, for example, halogen atoms, alkoxy groups and cycloalkyl groups.

The substituent(s) of the "optionally substituted heteroarylamino group" for Rc includes those exemplified as the substituents of (7) the

"optionally substituted heteroaryl groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

[0044]

As the "alkylene group" for Rd, there are exemplified the above-exemplified ones, preferably methylene.

As the "alkenylene group" for Rd, there are exemplified the above-exemplified ones, preferably vinylene.

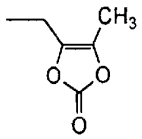
[0045]

As the "prodrug", there are exemplified those which can easily be hydrolyzed in a living body to regenerate the compound (I) of the present invention. Specific examples thereof are compounds obtained by converting the amino group of the compound represented by the formula (I) to $-NHQ^X$. Here, the following are exemplified as Q^X:

(1)

[0046]

[Formula 13]



(2) $-COR^{33}$

(3) $-COO-CR^{34}(R^{35})-OCOR^{36}$

(4) $-COOR^{37}$

wherein R^{33} is a hydrogen atom, an alkyl group or an optionally substituted aryl group; R^{34} and R^{35} are independently a hydrogen atom or an alkyl group; R^{36} is a hydrogen atom, an alkyl group, an aryl group or a benzyl group; and R^{37} is an alkyl group or a benzyl group.

Preferable examples of Q^X are the group of (1) and the groups of (3). Preferable examples of the groups of (3) are groups in which R^{34} is a hydrogen atom, R^{35} is a hydrogen atom, methyl or ethyl and R^{36} is methyl or ethyl. These compounds may be produced according to conventional processes (for example, J. Med. Chem. 35, 4727 (1992) and WO 01/40180). In addition, the prodrug may be one which is converted to the original compound under physiological conditions, such as those described in "Development of Medicines Vol.7, Molecular Design", pp. 163-198, Hirokawa Shoten, 1990.

[0047]

As the "pharmaceutically acceptable salt", there are exemplified inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate, nitrate, etc., and organic acid salts such as acetic acid salt, propionic acid salt, oxalic acid salt, succinic acid salt, lactic acid salt, malic acid salt, tartaric acid salt, citric acid salt, maleic acid salt, fumaric acid salt, methanesulfonic acid salt, benzenesulfonic acid salt, p-toluenesulfonic acid salt,

ascorbic acid salt, etc.

[0048]

In addition, the present invention includes compounds represented by the formula (I), prodrugs thereof and pharmaceutically acceptable salts of the compounds or prodrugs. The present invention also includes their hydrates or solvates (e.g. ethanol solvates). Furthermore, the present invention includes all tautomers, all existing stereoisomers and all crystal forms of the compound (I) of the present invention.

[0049]

Preferable examples of the compound of the present invention are the following compounds. In the compounds listed in the following tables, the following abbreviations are used in some cases for the simplification of description.

2-Py: 2-pyridyl group, 3-Py: 3-pyridyl group, 4-Py: 4-pyridyl group, Ph: phenyl group, Et: ethyl group, Me: methyl group, n-Pr: n-propyl group, i-Pr: isopropyl group, n-Bu: n-butyl group, t-Bu: tert-butyl group, Bn: benzyl group, Ac: acetyl group, cycpro: cyclopropyl group, cycbu: cyclobutyl group, cychex: cyclohexyl group, etoet: ethoxyethyl group, meoet: methoxyethyl group, f2etoet: 2,2-difluoroethoxyethyl group, f2meoet: difluoromethoxyethyl group, cycprooet: cyclopropyloxyethyl group, isoproet: isopropoxyethyl group, ms: methanesulfonyl group, etomet: ethoxymethyl

group, meomet: methoxymethyl group, f2meomet: difluoromethoxymethyl group, and f2etomet: 2,2-difluoroethoxymethyl group.

The following abbreviations for partial structures are used in some cases.

[0050]

[Formula 14]

Q1: 

Q2: 

Q3: 

Q4: 

Q5: 

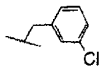
Q6: 

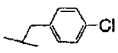
Q7: 

Q8: 

Q9: 

Q10: 

Q11: 

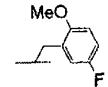
Q12: 

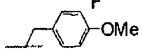
Q13: 

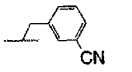
Q14: 

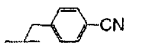
Q15: 

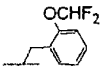
Q16: 

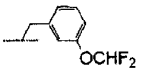
Q17: 

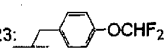
Q18: 

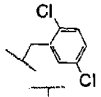
Q19: 

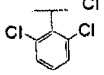
Q20: 

Q21: 

Q22: 

Q23: 

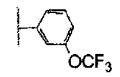
Q24: 

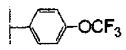
Q25: 

Q26: 

Q27: 

Q28: 

Q29: 

Q30: 

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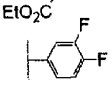
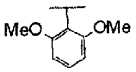
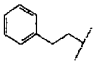
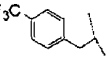
Q32: 

Q33: 

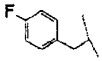
Q34: 

Q35: 

Q36: 

Q37: 

Q38: 

Q39: 

Q40: 

Q41:

Q42:

Q43:

Q44:

Q45:

Q46:

Q47:

Q48:

Q49:

Q50:

Q51:

Q52:

Q53:

Q54:

Q55:

Q56:

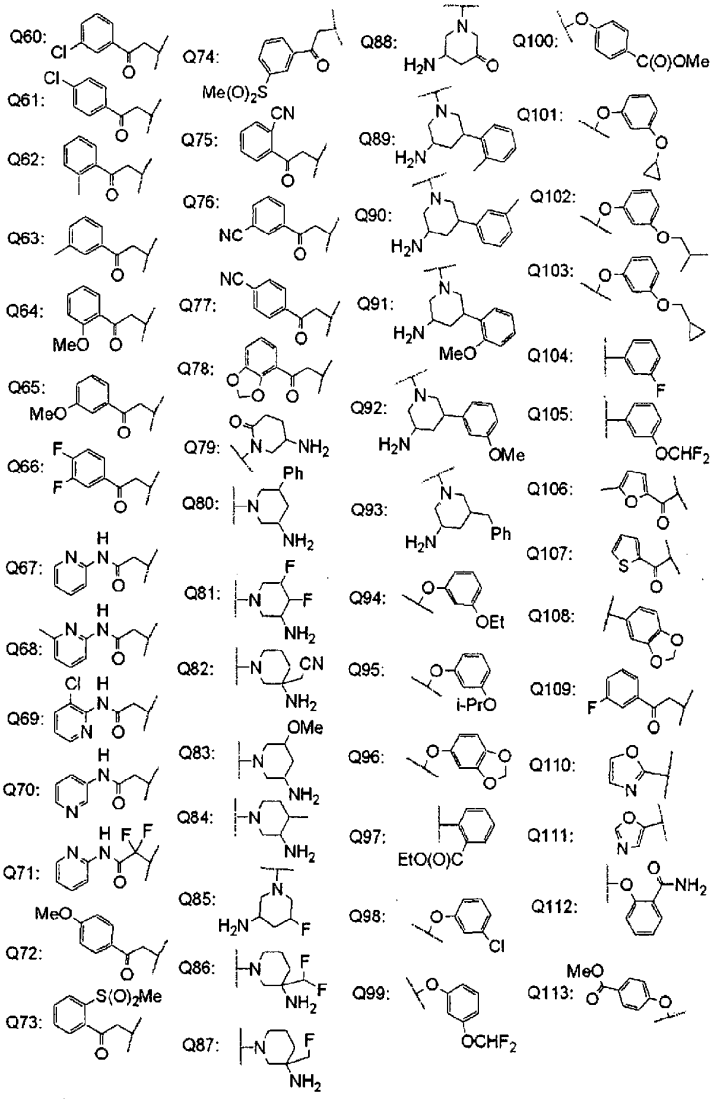
Q57:

Q58:

Q59:

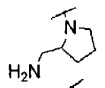
[0051]

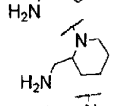
[Formula 15]

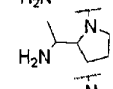


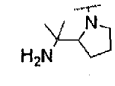
[0052]

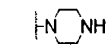
[Formula 16]

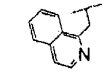
Q114: 

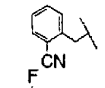
Q115: 

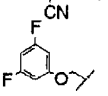
Q116: 

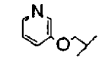
Q117: 

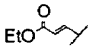
Q118: 

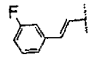
Q119: 

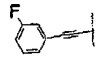
Q120: 

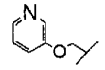
Q121: 

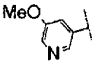
Q122: 

Q123: 

Q124: 

Q125: 

Q126: 

Q127: 

Q128: MeOC(O)

Q129: EtOC(O)

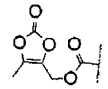
Q130: i-PrOC(O)

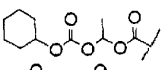
Q131: t-BuOC(O)

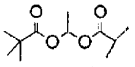
Q132: $H_2NC(O)$

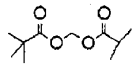
Q133: $Me_2NC(O)$

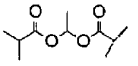
Q134: $Et_2NC(O)$

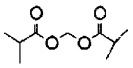
Q135: 

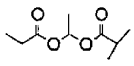
Q136: 

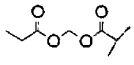
Q137: 

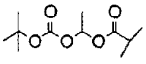
Q138: 

Q139: 

Q140: 

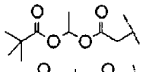
Q141: 

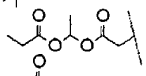
Q142: 

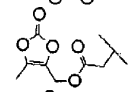
Q143: 

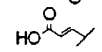
Q144: $CH_2C(O)OH$

Q145: $CH_2C(O)OEt$

Q146: 

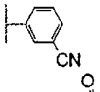
Q147: 

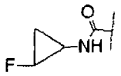
Q148: 

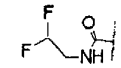
Q149: 

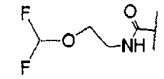
Q150: 

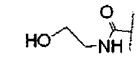
Q151: 

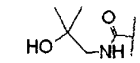
Q152: 

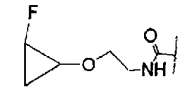
Q153: 

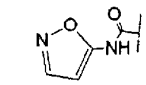
Q154: 

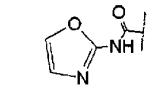
Q155: 

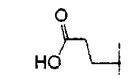
Q156: 

Q157: 

Q158: 

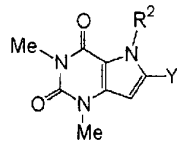
Q159: 

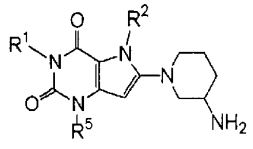
Q160: 

Q161: 

[0053]

[Formula 17]

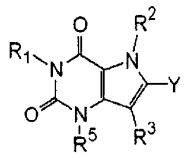




No.	Y	R^2	No.	Y	R^2	No.	R^1	R^2	R^5	No.	R^1	R^2	R^5
1	Q1	Q13	27	Q1	Q12	53	Q35	Q4	Me	79	Q73	Q4	Me
2	Q2	Q13	28	Q1	Q13	54	Q36	Q5	Me	80	Q74	Q5	Me
3	Q79	Q13	29	Q1	Q14	55	Q37	Q13	Me	81	Q75	Q13	Me
4	Q80	Q13	30	Q1	Q15	56	Q38	Q4	Me	82	Q76	Q4	Me
5	Q81	Q13	31	Q1	Q16	57	Q39	Q5	Me	83	Q77	Q5	Me
6	Q82	Q13	32	Q1	Q17	58	H	Q13	Me	84	Q78	Q13	Me
7	Q83	Q13	33	Q1	Q18	59	Q47	Q4	Me	85	Q119	Q4	Me
8	Q84	Q13	34	Q1	Q19	60	Q48	Q5	Me	86	Q120	Q5	Me
9	Q85	Q13	35	Q1	Q20	61	Q54	Q13	Me	87	Q121	Q13	Me
10	Q86	Q13	36	Q1	Q21	62	Q56	Q4	Me	88	Q122	Q4	Me
11	Q87	Q13	37	Q1	Q22	63	Q57	Q5	Me	89	Q77	Q5	Me
12	Q88	Q13	38	Q1	Q23	64	Q58	Q13	Me	90	Q78	Q13	Me
13	Q89	Q13	39	Q1	Q24	65	Q59	Q4	Me	91	Me	Q4	etoet
14	Q90	Q13	40	Q2	Q3	66	Q60	Q5	Me	92	Me	Q5	meoet
15	Q91	Q13	41	Q2	Q4	67	Q61	Q13	Me	93	Me	Q13	f2etoet
16	Q92	Q13	42	Q2	Q5	68	Q62	Q4	Me	94	Me	Q4	f2meoet
17	Q93	Q13	43	Q2	Q6	69	Q63	Q5	Me	95	Me	Q5	cycproet
18	Q1	Q3	44	Q2	Q7	70	Q64	Q13	Me	96	Me	Q13	isoproet
19	Q1	Q4	45	Q2	Q10	71	Q65	Q4	Me	97	Me	Q4	etomet
20	Q1	Q5	46	Q1	Q26	72	Q66	Q5	Me	98	Me	Q5	meomet
21	Q1	Q6	47	Q1	Q27	73	Q67	Q13	Me	99	Me	Q13	f2meomet
22	Q1	Q7	48	Q114	Q13	74	Q68	Q4	Me	100	Me	Q13	Q144
23	Q1	Q8	49	Q115	Q13	75	Q69	Q5	Me	101	Me	Q13	Q145
24	Q1	Q9	50	Q116	Q13	76	Q70	Q13	Me	102	Me	Q13	Q146
25	Q1	Q10	51	Q117	Q13	77	Q71	Q4	Me	103	Me	Q13	Q147
26	Q1	Q11	52	Q118	Q13	78	Q72	Q5	Me	104	Me	Q13	Q148

[0054]

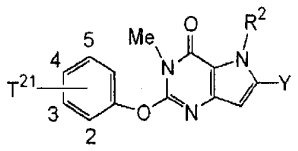
[Formul 18]

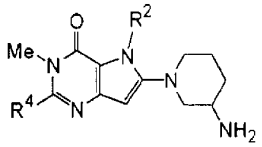


No.	R^1	R^2	R^3	R^5	Y
105	Me	Q13	Ac	Me	Q1
106	Me	Q13	Me	Me	Q1
107	Me	Q13	Et	Me	Q1
108	Me	Q5	etomet	Me	Q1
109	Me	Q5	meomet	Me	Q1
110	Me	Q5	f2meomet	Me	Q1
111	Me	Q13	Q149	Me	Q1
112	Me	Q13	Q123	Me	Q1
113	Me	Q13	CO_2H	Me	Q1
114	Me	Q13	Q135	Me	Q1
115	Me	Q13	Q136	Me	Q1
116	Me	Q13	Q137	Me	Q1
117	Me	Q13	Q138	Me	Q1
118	Me	Q13	Q139	Me	Q1
119	Me	Q13	Q140	Me	Q1
120	Me	Q13	Q141	Me	Q1
121	Me	Q13	Q142	Me	Q1
122	Me	Q13	Q143	Me	Q1
123	Me	Q13	Q124	Me	Q1
124	Me	Q5	Q125	Me	Q1
125	Me	Q13	Q126	Me	Q1
126	Me	Q4	Q127	Me	Q1
127	Me	Q13	etomet	Me	Q2
128	Me	Q13	meomet	Me	Q118
129	Me	Q4	Q103	Me	Q1
130	Me	Q13	Q49	Me	Q1
131	Me	Q4	Q49	Me	Q1
132	Me	Q5	Q50	Me	Q1
133	Me	Q13	Q51	Me	Q1
134	H	Q13	Q52	Me	Q1
135	Me	Q5	Q53	Me	Q1
136	Me	Q13	Q54	Me	Q1
137	Me	Q4	Q56	Me	Q1
138	Me	Q5	Q128	Me	Q1
139	Me	Q13	Q129	Me	Q1
140	Me	Q4	Q130	Me	Q1
141	Me	Q5	Q131	Me	Q1
142	Me	Q13	Q132	Me	Q1
143	Q66	Q13	etomet	Me	Q1
144	Q67	Q5	meomet	Me	Q1
145	Q68	Q13	etomet	Me	Q1
146	Q69	Q13	etomet	Me	Q1
147	Me	Q5	Ac	Me	Q2
148	Me	Q13	Me	Me	Q2
149	Q65	Q5	Et	Me	Q2
150	Me	Q5	CN	Me	Q2
151	Me	Q13	meomet	Me	Q2
152	Me	Q5	f2meomet	Me	Q2
153	Me	Q5	isoproet	Me	Q2
154	Me	Q13	cycproet	Me	Q2
155	H	Q5	Q50	Me	Q2
156	Me	Q5	Q27	Me	Q2

[0055]

[Formula 19]

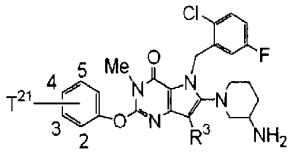




No.	T^{21}	R^2	Y	No.	R^2	R^4
157	3-$OCHF_2$	Q13	Q1	183	Q4	CN
158	3-OEt	Q13	Q1	184	Q5	CF_3
159	3-O(i-Pr)	Q13	Q1	185	Q13	Ph
160	3-Q150	Q5	Q1	186	Q13	Ac
161	3-Q151	Q5	Q1	187	Q13	CO_2H
162	3-OMe/5-OMe	Q5	Q1	188	Q13	Q135
163	4-$OCHF_2$	Q13	Q1	189	Q13	Q136
164	2-$OCHF_2$	Q13	Q1	190	Q13	Q137
165	2-Q132	Q13	Q1	191	Q13	Q138
166	3-$OCHF_2$	Q5	Q2	192	Q13	Q139
167	3-OEt	Q5	Q2	193	Q13	Q140
168	3-O(i-Pr)	Q5	Q2	194	Q13	Q141
169	3-Q150	Q13	Q2	195	Q13	Q142
170	3-Q151	Q5	Q2	196	Q13	Q143
171	3-OMe/5-OMe	Q13	Q2	197	Q13	Q129
172	CO_2H	Q5	Q2	198	Q13	Q130
173	2-Q132	Q14	Q118	199	Q5	Q132
174	2-OMe	Q13	Q118	200	Q13	i-Pr
175	3-$OCHF_2$	Q13	Q114	201	Q5	EtO
176	3-OEt	Q5	Q115	202	Q5	Q50
177	3-O(i-Pr)	Q13	Q83	203	Q13	Q46
178	3-Q150	Q4	Q84	204	Q5	Q152
179	3-Q151	Q13	Q85	205	Q5	Q111
180	4-Q135	Q13	Q1	206	Q13	Q110
181	4-$OCHF_2$	Q4	Q87	207	Q5	NMe_2
182	H	Q13	Q1	208	Q5	Q34

[0056]

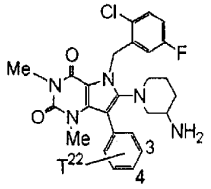
[Formula 20]

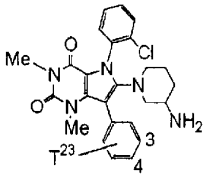


No.	T^{21}	R^3	No.	T^{21}	R^3
209	3-$OCHF_2$	Ac	225	2-Q132	f2meomet
210	3-OEt	Me	226	2-OMe	isoproet
211	3-O(i-Pr)	Et	227	3-$OCHF_2$	cycproet
212	3-Q150	CN	228	3-OEt	Q149
213	3-Q151	Q50	229	3-O(i-Pr)	Q123
214	3-OMe/5-OMe	Q52	230	3-OEt	CO_2H
215	4-$OCHF_2$	Q54	231	3-OEt	Q135
216	2-$OCHF_2$	Q128	232	3-OEt	Q136
217	2-Q132	Q129	233	3-OEt	Q137
218	3-$OCHF_2$	Q130	234	3-OEt	Q138
219	3-OEt	Q131	235	3-OEt	Q139
220	3-O(i-Pr)	Q132	236	3-OEt	Q140
221	3-Q150	etomet	237	3-OEt	Q141
222	3-Q151	meomet	238	3-OEt	Q142
223	3-OMe/5-OMe	etomet	239	3-OEt	Q143
224	4-$OCHF_2$	etomet			

[0057]

[Formula 21]

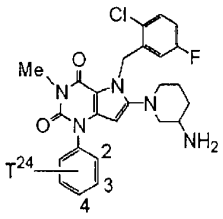




No.	T^{22}	No.	T^{22}	No.	T^{23}	No.	T^{23}
240	3-CO_2H	250	4-CO_2H	260	3-CO_2H	270	4-CO_2H
241	3-Q135	251	4-Q135	261	3-Q135	271	4-Q135
242	3-Q136	252	4-Q136	262	3-Q136	272	4-Q136
243	3-Q137	253	4-Q137	263	3-Q137	273	4-Q137
244	3-Q138	254	4-Q138	264	3-Q138	274	4-Q138
245	3-Q139	255	4-Q139	265	3-Q139	275	4-Q139
246	3-Q140	256	4-Q140	266	3-Q140	276	4-Q140
247	3-Q141	257	4-Q141	267	3-Q141	277	4-Q141
248	3-Q142	258	4-Q142	268	3-Q142	278	4-Q142
249	3-Q143	259	4-Q143	269	3-Q143	279	4-Q143

[0058]

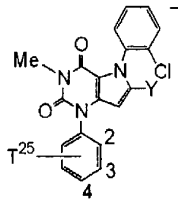
[Formula 22]



No.	T^{24}	No.	T^{24}	No.	T^{24}
280	2-CO_2H	290	3-CO_2H	300	4-CO_2H
281	2-Q135	291	3-Q135	301	4-Q135
282	2-Q136	292	3-Q136	302	4-Q136
283	2-Q137	293	3-Q137	303	4-Q137
284	2-Q138	294	3-Q138	304	4-Q138
285	2-Q139	295	3-Q139	305	4-Q139
286	2-Q140	296	3-Q140	306	4-Q140
287	2-Q141	297	3-Q141	307	4-Q141
288	2-Q142	298	3-Q142	308	4-Q142
289	2-Q143	299	3-Q143	309	4-Q143

[0059]

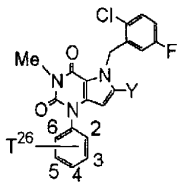
[Formula 23]



No.	T^{25}	Y	No.	T^{25}	Y
310	2-CO_2H	Q1	319	2-CO_2H	Q118
311	2-Q135	Q1	320	2-Q135	Q118
312	3-CO_2H	Q1	321	3-CO_2H	Q118
313	3-Q135	Q1	322	3-Q135	Q118
314	4-CO_2H	Q1	323	4-CO_2H	Q118
315	4-Q135	Q1	324	4-Q135	Q118
316	2-CN	Q1	325	2-CN	Q118
317	3-CN	Q1	326	3-CN	Q118
318	4-CN	Q1	327	4-CN	Q118

[0060]

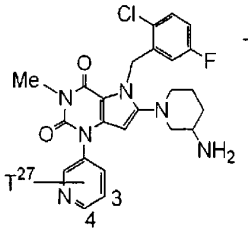
[Formula 24]



No.	T^{26}	Y	No.	T^{26}	Y
328	3-CN/5-CO_2H	Q1	337	2-CO_2H	Q118
329	3-CN/5-Q135	Q1	338	2-Q135	Q118
330	2-CN/5-CO_2H	Q1	339	3-CO_2H	Q118
331	2-CN/5-Q135	Q1	340	3-Q135	Q118
332	4-CN/5-CO_2H	Q1	341	4-CO_2H	Q118
333	4-CN/5-Q135	Q1	342	4-Q135	Q118
334	2-CN	Q1	343	2-CN	Q118
335	3-CN	Q1	344	3-CN	Q118
336	4-CN	Q1	345	4-CN	Q118

[0061]

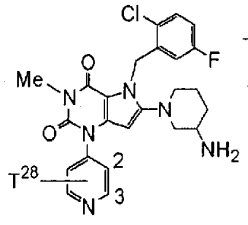
[Formula 25]



No.	T^{27}
346	4-CN
347	3-CN
348	4-CO_2H
349	4-Q135
350	3-CO_2H
351	3-Q135

[0062]

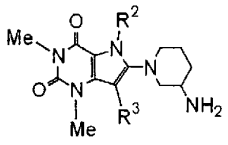
[Formula 26]



No.	T^{28}
352	2-CN
353	3-CN
354	2-CO_2H
355	2-Q135
356	3-CO_2H
357	3-Q135

[0063]

[Formula 27]



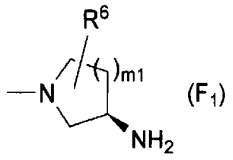
No.	R^2	R^3	No.	R^2	R^3
358	Q6	Q153	363	Q6	Q158
359	Q6	Q154	364	Q6	Q159
360	Q6	Q155	365	Q6	Q160
361	Q13	Q156	366	Q13	Q161
362	Q13	Q157			

[0064]

When the portion corresponding to Y described in the item [1] is an unsubstituted or substituted 3-aminopyrrolidin-1-yl group, an unsubstituted or substituted 3-aminopiperidin-1-yl group or an unsubstituted or substituted (3-amino)hexahydroazepin-1-yl group in the above compounds having compound numbers 1 to 366, bicyclic pyrrole derivatives are more preferable in which the amino group at the 3-position is in an absolute configuration represented by the following formula (F_1):

[0065]

[Formula 28]



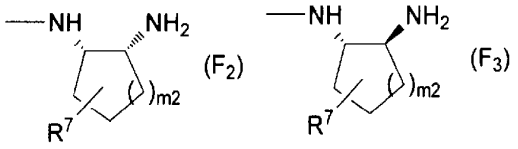
(F_1)

wherein m1 and R^6 are as defined in the item [1].

When the portion corresponding to Y described in the item [1] is an unsubstituted or substituted (2-aminocycloalkyl)amino group in the above compounds having compound numbers 1 to 366, compounds are more preferable in which the amino groups at the 1-position and 2-position are in an absolute configuration represented by the following formula (F_2) or (F_3):

[0066]

[Formula 29]

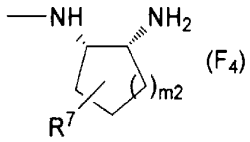


wherein m2 and R^7 are as defined in the item [1].

In addition, compounds are still more preferable in which the amino groups at the 1-position and 2-position are in an absolute configuration represented by the following formula (F_4):

[0067]

[Formula 30]



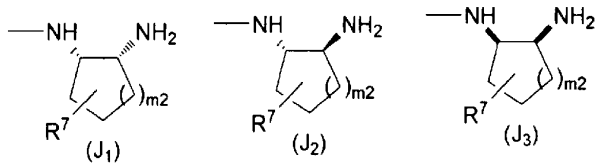
wherein m2 and R^7 are as defined in the item [1].

[0068]

In the following description, a bond shown by a wedge-shaped solid line or broken line as in the formula (J_1) and formula (J_2) indicates an absolute configuration relating to an amino group, and a bond shown by a thick line as in the formula (J_3) indicates a relative configuration relating to an amino group (for example, the formula (J_3) represents a (±)-cis form).

[0069]

[Formula 31]



wherein m2 and R^7 are as defined in the item [1].

[0070]

Of the above compounds having compound numbers 1 to 366 as the compound of the formula (I) described in the item [1], compounds containing in the formula "an alkoxycarbonyl group", "an optionally substituted alkoxycarbonyl group", "an optionally substituted cycloalkoxycarbonyl group", "an optionally substituted aryloxycarbonyl group", "an optionally substituted aralkyloxycarbonyl group" or the formula: -Rd-C(O)O-Re wherein Rd and Re are as defined above, are such that such a substituent is converted to "a carboxyl group" in some cases under physiological conditions in a living body by oxidation, reduction, hydrolysis or the like by an enzyme, or hydrolysis by acid in the stomach, or the like.

[0071]

A process for producing the compound represented by the formula (I) of the present invention is explained below with reference to examples, which should not be construed as limiting the scope of the invention. In the present description, the following abbreviations are used in some cases for the

simplification of description.

Boc: tert-butoxycarbonyl group

Cbz: benzyloxycarbonyl group

TMS: trimethylsilyl group

TBS: tert-butyldimethylsilyl group

SEM: 2-[(trimethylsilyl)ethoxy]methyl group

Ac: acetyl group

Me: methyl group

Et: ethyl group

Pr: propyl group

i-Pr: isopropyl group

Bu: butyl group

i-Bu: isobutyl group

t-Bu: tert-butyl group

Ph: phenyl group

Bn: benzyl group

Ms: methanesulfonyl group

TFA: trifluoroacetic acid

Alloc: allyloxycarbonyl group

[0072]

The compound represented by the formula (I) may be synthesized from a well-known compound by a combination of well-known synthesis processes. It may be synthesized, for example, by any of the following processes.

[0073]

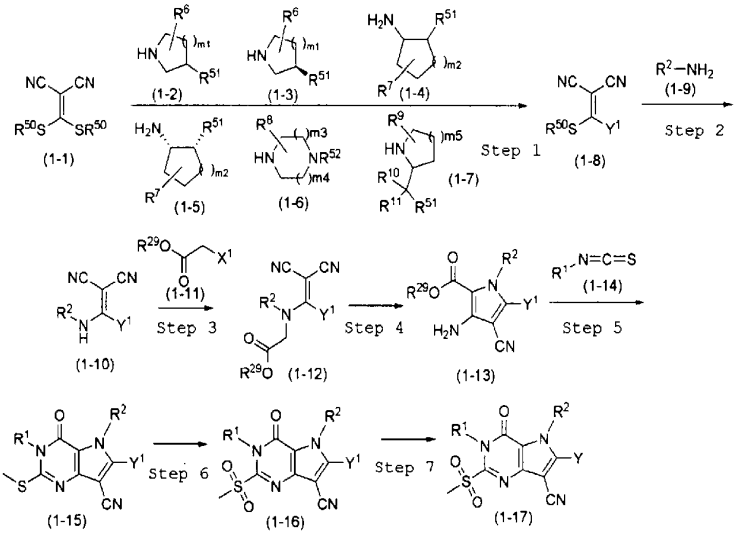
Production Process 1

A compound represented by the formula (1-17)

or a salt thereof is produced, for example, by the following process:

[0074]

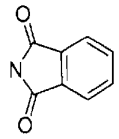
[Formula 32]



wherein R^1, R^2, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{29}, m^1, m^2, m^3, m^4 and m^5 are as defined above; X^1 is a leaving group (for example, an iodine atom, a bromine atom, a chlorine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy or p-toluenesulfonyloxy); R^{51} is Alloc, $N=C(Ph)_2$, NHBoc, NHCbz or the following formula (G1):

[0075]

[Formula 33]


(G1)

R^{52} is Alloc, Boc or Cbz; and Y^1 is the protected state of the primary or secondary amino group in Y described in the item [1].

1) Step 1

A compound (1-8) may be produced by reacting a compound (1-1) with a compound selected from a compound (1-2), a compound (1-3), a compound (1-4), a compound (1-5), a compound (1-6) and a compound (1-7) in an inert solvent in the presence or absence of a base. The base includes, for example, organic bases (e.g. 1-hydroxybenzotriazole, N-methylmorpholine, triethylamine, diisopropylethylamine, tributylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene, 1,5-diazabicyclo[4,3,0]nona-5-ene, 1,4-diazabicyclo[5,4,0]undec-7-ene, pyridine, dimethylaminopyridine and picoline), and inorganic bases (e.g. sodium ethoxide, sodium methoxide, potassium tert-butoxide and sodium hydride). The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (1-1). The amount of the compound (1-2), compound (1-3), compound (1-4), compound (1-5), compound (1-6) or compound (1-7) used is usually chosen in the range of 1 to 2 equivalents per equivalent of the compound (1-1).

The inert solvent includes, for example, alcohol solvents (e.g. methanol, ethanol and 2-propanol), ether solvents (tetrahydrofuran and 1,4-dioxane), and mixed solvents thereof. The reaction temperature may be chosen in the range of about 50°C to about 120°C.

The compound (1-2) may be produced by the process described in the production process 19 described hereinafter, the compound (1-3) by the process described in the production process 20 described hereinafter, and the compound (1-5) by the process described in the production process 21 described hereinafter. As the compound (1-6), a commercial reagent may be used, or the compound (1-6) may be produced by the process described in literature (for example, Synthesis 391 (1994), Org. Lett. 5, 1591 (2003), Synthesis 1065 (1992), Synlett 755 (2002), J. Org. Chem. 56, 3063 (1991), J. Org. Chem. 60, 4177 (1995) and J. Org. Chem. 57, 6653 (1992)). The compound (1-7) may be produced by the same process as that described in literature (for example, J. Org. Chem. 61, 6700 (1996)) or the like.

2) Step 2

A compound (1-10) is produced by reacting the compound (1-8) with a compound (1-9) in an inert solvent. The amount of the compound (1-9) used is usually chosen in the range of 1 equivalent to excess equivalents per equivalent of the compound (1-8). The inert solvent includes, for example, organic bases (e.g.

1-hydroxybenzotriazole, N-methylmorpholine, triethylamine, diisopropylethylamine, tributylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene, 1,5-diazabicyclo[4,3,0]nona-5-ene, 1,4-diazabicyclo[5,4,0]undec-7-ene, pyridine, dimethylaminopyridine and picoline), alcohol solvents (e.g. methanol, ethanol and 2-propanol), acetic acid, and mixed solvent thereof. The reaction temperature is chosen in the range of about 50°C to about 150°C and the reaction is usually carried out with refluxing.

3) Step 3

A compound (1-12) may be produced by reacting the compound (1-10) with a compound (1-11) in an inert solvent in the presence or absence of a base (see, for example, J. Heterocycl. Chem. 37, 1033 (2000), J. Chem. Soc., Perkin Trans. 1, 13, 1833 (1999) and J. Med. Chem. 38, 3838 (1995)). The amount of the compound (1-11) used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (1-10). The base includes, for example, alkali carbonates (e.g. potassium carbonate, sodium carbonate, potassium hydrogencarbonate and sodium hydrogencarbonate), alkali hydrides (e.g. sodium hydride and potassium hydride), and alkali hydroxides (e.g. potassium hydroxide and sodium hydroxide). A suitable example thereof is potassium carbonate. The amount of the base used is usually chosen in the range of 1 to 3 equivalents per equivalent of the compound (1-10). The inert solvent

includes, for example, aprotic solvents (e.g. N,N-dimethylformamide and dimethyl sulfoxide), ether solvents (e.g. diethyl ether, tetrahydrofuran and 1,4-dioxane), ketones (e.g. acetone), and mixed solvents thereof. Suitable examples thereof are N,N-dimethylformamide and dimethyl sulfoxide. The reaction temperature may be chosen in the range of about 10°C to about 180°C.

4) Step 4

A compound (1-13) may be produced by reacting the compound (1-12) with a base in an inert solvent (see, for example, WO02/068420). The base includes alkali hydrides (e.g. sodium hydride and potassium hydride) and the like. A suitable example thereof is sodium hydride. The amount of the base used is usually chosen in the range of 1 to 3 equivalents per equivalent of the compound (1-12). The inert solvent includes N,N-dimethylformamide, ether solvents (e.g. diethyl ether, tetrahydrofuran and 1,4-dioxane), and mixed solvents thereof. A suitable example thereof is tetrahydrofuran. The reaction temperature may be chosen in the range of about 10°C to about 100°C.

5) Step 5

A compound (1-15) may be produced from the compound (1-13) by carrying out the following reactions (1) to (3).

(1) The compound (1-13) is reacted with a compound (1-14) in pyridine in the presence of a base.

The reaction temperature may be chosen in the range of about 50°C to about 160°C. The amount of the compound (1-14) used is usually chosen in the range of 1 to 5 equivalents.

(2) A base is added to the reaction mixture obtained in the above item (1) and the reaction is carried out. The base includes cesium carbonate, potassium carbonate, sodium carbonate, etc. The amount of the base used is usually chosen in the range of 1 to 5 equivalents. The reaction temperature is chosen in the range of about 50°C to about 160°C.

(3) Methyl iodide is added to the reaction mixture obtained in the above item (2) and the reaction is carried out. The amount of methyl iodide used is usually chosen in the range of 1 to 5 equivalents. The reaction temperature is chosen in the range of about 10°C to about 40°C.

6) Step 6

In this step 6, the following production process (A) or production process (B) may be adopted.

Production process (A): A compound (1-16) may be produced by reacting the compound (1-15) with a mixture of sodium tungstate and an aqueous hydrogen peroxide solution in an inert solvent. The inert solvent includes alcohol solvents (e.g. ethanol, methanol and 2-propanol), organic acids (e.g. acetic acid and propionic acid), etc. A mixed solvent of the alcohol solvent and the organic acid is usually used as the

inert solvent. The amount of sodium tungstate used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (1-15). The amount of the aqueous hydrogen peroxide solution (usually a 30% aqueous solution) used is usually chosen in the range of 10 to 100 equivalents per equivalent of the compound (1-15). The reaction temperature may be chosen in the range of about -10°C to about 70°C.

Production process (B): A compound (1-16) may be produced by reacting the compound (1-15) with Oxon (a registered trade name; Aldrich) in an inert solvent. The inert solvent includes alcohol solvents (e.g. ethanol, methanol and 2-propanol), etc. The amount of Oxon (a registered trade name; Aldrich) used is usually chosen in the range of 1 to 20 equivalents per equivalent of the compound (1-15). The reaction temperature may be chosen in the range of about -10°C to about 70°C.

7) Step 7

The compound (1-17) may be produced from the compound (1-16) by the same process as in the step 2 described in production process 2.

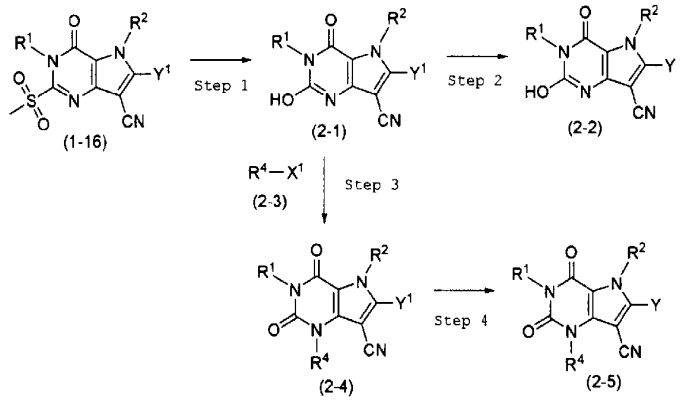
[0076]

Production Process 2

Each of compounds of the formula (2-2) and the formula (2-5) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0077]

[Formula 34]



wherein R^1, R^2, R^4, X^1, Y^1 and Y are as defined above.

1) Step 1

A compound (2-1) may be produced by reacting a compound (1-16) with a base in an inert solvent. The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium carbonate, etc. A suitable example thereof is sodium hydroxidec. The amount of the base used is usually chosen in the range of 1 equivalent to large-excess equivalents per equivalent of the compound (1-16). The inert solvent includes, for example, water, alcohol solvents (e.g. methanol, ethanol and 2-propanol), tetrahydrofuran, and mixed solvents thereof. The reaction temperature is chosen in the range of about 50°C to about 100°C.

In this step, a compound in which a protective group for the primary amino group or secondary amino group in Y has been removed is produced in some cases. The compound (2-1) in which the primary amino group or secondary amino group in Y has been protected again with a protective group (e.g. Boc or Cbz) may be produced by the same production process as described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

2) Step 2

The compound (2-2) may be produced from the compound (2-1) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

3) Step 3

A compound (2-4) may be produced by reacting the compound (2-1) with a compound (2-3) in an inert solvent in the presence of a base. The amount of the compound (2-3) used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (2-1). The base includes, for example, alkali carbonates (e.g. potassium carbonate, sodium carbonate, potassium hydrogencarbonate and sodium hydrogencarbonate), alkali hydrides (e.g. sodium hydride and potassium hydride), and alkali hydroxides (e.g. potassium hydroxide and sodium hydroxide). A suitable example thereof is

potassium carbonate. The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (2-1). The inert solvent includes, for example, aprotic solvents (e.g. N,N-dimethylformamide and dimethyl sulfoxide), ether solvents (e.g. diethyl ether, tetrahydrofuran and 1,4-dioxane), ketones (e.g. acetone), and mixed solvents thereof. A suitable example thereof is N,N-dimethylformamide. The reaction temperature may be chosen in the range of about 0°C to about 180°C.

4) Step 4

The compound (2-5) may be produced from the compound (2-4) by the same process as in the above step 2.

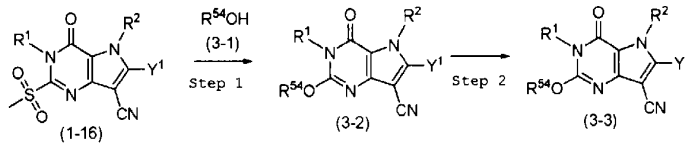
[0078]

Production Process 3

A compound of the formula (3-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0079]

[Formula 35]



wherein R^1, R^2, Y^1 and Y are as defined above, and $R^{54}O$ is "an optionally substituted alkoxy group", "an

optionally substituted aryloxy group", "an optionally substituted aralkyloxy group", "an optionally substituted heteroaryloxy group" or "an optionally substituted cycloalkyloxy group".

1) Step 1

A compound (3-2) may be produced by reacting a compound (1-16) with a compound (3-1) in an inert solvent in the presence of a base. The base includes potassium tert-butoxide, sodium tert-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, sodium phenoxide, potassium phenoxide, sodium hydride, etc. A suitable example thereof is sodium hydride. The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (3-1). The inert solvent includes tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, mixed solvents thereof, etc. The reaction temperature may be chosen in the range of about -10°C to about 50°C.

2) Step 2

The compound (3-3) may be produced from the compound (3-2) by the same process as in the step 2 described in production process 2.

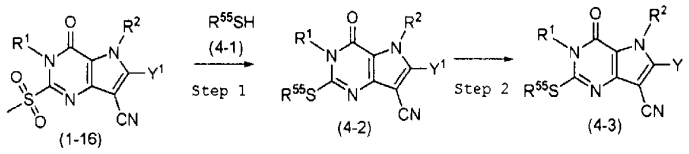
[0080]

Production Process 4

A compound of the formula (4-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0081]

[Formula 36]



wherein R^1, R^2, Y^1 and Y are as defined above, and $R^{55}S$ is "an optionally substituted alkylthio group" or "an optionally substituted arylthio group".

1) Step 1

A compound (4-2) may be produced from a compound (1-16) by the same process as in the step 1 described in production process 3.

2) Step 2

The compound (4-3) may be produced from the compound (4-2) by the same process as in the step 2 described in production process 2.

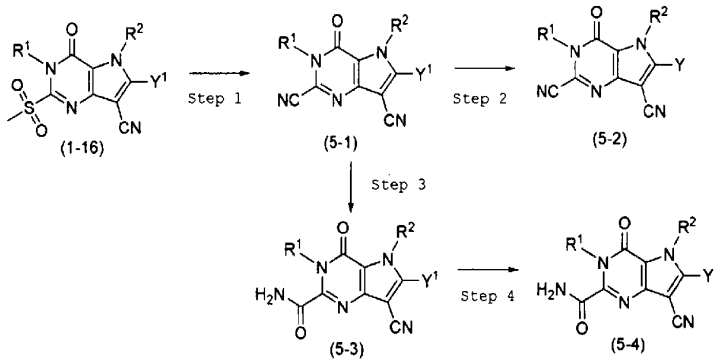
[0082]

Production Process 5

Each of compounds of the formula (5-2) and the formula (5-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0083]

[Formula 37]



wherein R^1, R^2, Y^1 and Y are as defined above.

1) Step 1

A compound (5-1) may be produced by reacting a compound (1-16) with sodium cyanide or potassium cyanide in an inert solvent. The amount of sodium cyanide or potassium cyanide used is usually chosen in the range of 0.8 to 5 equivalents per equivalent of the compound (1-16). The inert solvent includes tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, mixed solvents thereof, etc. The reaction temperature may be chosen in the range of about 10°C to about 100°C.

2) Step 2

The compound (5-2) may be produced from the compound (5-1) by the same process as in the step 2 described in production process 2.

3) Step 3

A compound (5-3) may be produced by reacting the compound (5-1) with an aqueous hydrogen peroxide

solution in an inert solvent in the presence of a base. The base includes, for example, inorganic bases such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, etc. The amount of the base used is usually chosen in the range of 0.5 to 10 equivalents per equivalent of the compound (5-1). The amount of the aqueous hydrogen peroxide solution used is usually chosen in the range of 1 to 20 equivalents per equivalent of the compound (5-1). The inert solvent includes dimethyl sulfoxide, acetone, etc. A suitable example thereof is dimethyl sulfoxide. The reaction temperature may be chosen in the range of about 10°C to about 100°C.

4) Step 4

The compound (5-4) may be produced from the compound (5-3) by the same process as in the step 2 described in production process 2.

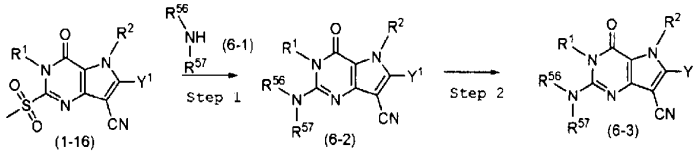
[0084]

Production Process 6

A compound of the formula (6-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0085]

[Formula 38]



wherein R^1, R^2, Y^1 and Y are as defined above, and $R^{56}R^{57}N$ is "an optionally substituted nitrogen-containing saturated heterocyclic group" or "an optionally substituted amino group".

1) Step 1

A compound (6-2) may be produced by reacting a compound (1-16) with a compound (6-1) in the presence or absence of an inert solvent. The amount of the compound (6-1) used is usually chosen in the range of 1 to 100 equivalents per equivalent of the compound (1-16). When the compound (6-1) is liquid, it may be used also as a solvent. The inert solvent includes alcohol solvents (e.g. ethanol, methanol and 2-propanol), etc. The reaction temperature may be chosen in the range of about 50°C to about 150°C.

2) Step 2

The compound (6-3) may be produced from the compound (6-2) by the same process as in the step 2 described in production process 2.

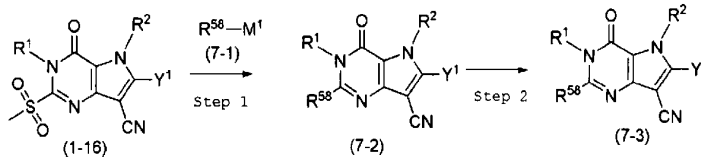
[0086]

Production Process 7

A compound of the formula (7-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0087]

[Formula 39]



wherein R^1, R^2, Y^1 and Y are as defined above; R^{58} is "an optionally substituted alkyl group", "an optionally substituted cycloalkyl group", "an optionally substituted alkenyl group", "an optionally substituted aryl group", "an optionally substituted heteroaryl group", "an optionally substituted heteroarylalkyl group" or "an optionally substituted aralkyl group"; and M^1 is lithium, magnesium chloride or magnesium bromide.

1) Step 1

A compound (7-2) may be produced by reacting a compound (1-16) with a compound (7-1) in an inert solvent. The amount of the compound (7-1) used is usually chosen in the range of 1 to 10 equivalents per equivalent of the compound (1-16). The inert solvent includes tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, mixed solvents thereof, etc. The reaction temperature may be chosen in the range of about -10°C to about 50°C.

2) Step 2

The compound (7-3) may be produced from the compound (7-2) by the same process as in the step 2

described in production process 2.

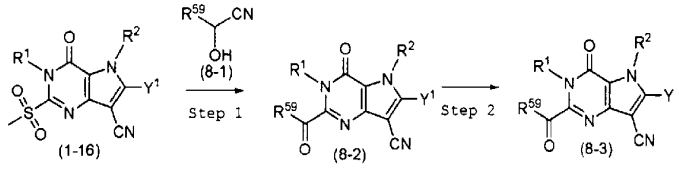
[0088]

Production Process 8

A compound of the formula (8-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0089]

[Formula 40]



wherein R^1, R^2, Y^1 and Y are as defined above, and $R^{59}C(O)$ is "an optionally substituted aroyl group", "an optionally substituted heteroarylcarbonyl group" or "an optionally substituted alkylcarbonyl group".

1) Step 1

A compound (8-2) may be produced by reacting a compound (1-16) with a compound (8-1) in an inert solvent in the presence of a base. The amount of the compound (8-1) used is usually chosen in the range of 1 to 10 equivalents per equivalent of the compound (1-16). The base includes sodium hydride, etc. The inert solvent includes tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, mixed solvents thereof, etc. The reaction temperature may be chosen in the range of about 50°C to about 150°C.

2) Step 2

The compound (8-3) may be produced from the compound (8-2) by the same process as in the step 2 described in production process 2.

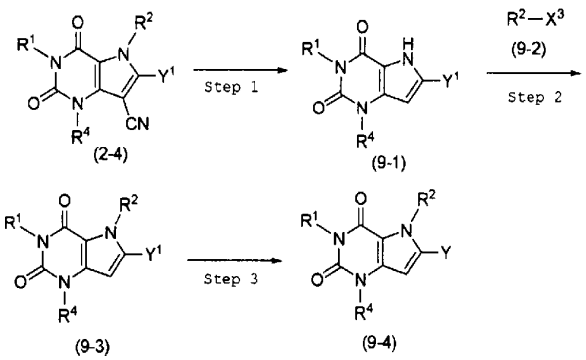
[0090]

Production Process 9

A compound of the formula (9-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0091]

[Formula 41]



wherein R^1, R^2, R^4, Y^1 and Y are as defined above, and X^3 is a leaving group (e.g. an iodine atom, a bromine atom, a chlorine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy or p-toluenesulfonyloxy).

1) Step 1

When R^2 in the item [4] is a group of any of the formula (E), formula (F), formula (G) and formula

(H), a compound (9-1) may be produced from a compound (2-4) by the following process 1.

Process 1

A compound (9-1) may be produced by reacting a compound (2-4) with an acid in an inert solvent. The acid includes inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, etc. A suitable example thereof is sulfuric acid. The amount of the acid used is usually chosen in the range of 1 equivalent to large-excess equivalents per equivalent of the compound (2-4). The inert solvent includes water and the like. The reaction temperature is chosen in the range of about 50°C to about 200°C.

In this step, a compound in which a protective group for the primary amino group or secondary amino group in Y has been removed is produced in some cases. The compound (9-1) in which the primary amino group or secondary amino group in Y has been protected again with a protective group (e.g. Boc or Cbz) may be produced by the same production process as described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

When R^2 in the item [4] is a group of either the formula (I) or the formula (J), a compound (9-1) may be produced from a compound (2-4) by the following process 2 [(1)~(2)].

Process 2

(1) R^2 of the compound (2-4) is removed by the same method as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.), Tetrahedron 27, 5523 (1971) and Aus. J. Chem. 22, 1321 (1969)) or the like.

(2) The same reaction as in the process 1 in the step 1 described in production process 9 is carried out.

2) Step 2

A compound (9-3) may be produced from the compound (9-1) by the same process as that described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989, Bioorg. Med. Chem. Lett. 11, 1993 (2001), Organic Letters 4, 4033 (2002), Organic Letters 5, 4987 (2003), Synlett 128 (2004), and J. Am. Chem. Soc. 124, 116847 (2002)) or the like.

When R^2 in the item [4] is a group of any of the formula (E), formula (F), formula (G) and formula (H), a compound (9-3) may be produced from the compound (9-1) by the same process as in the step 3 described in production process 1.

3) Step 3

The compound (9-4) may be produced from the compound (9-3) by the same process as in the step 2 described in production process 2.

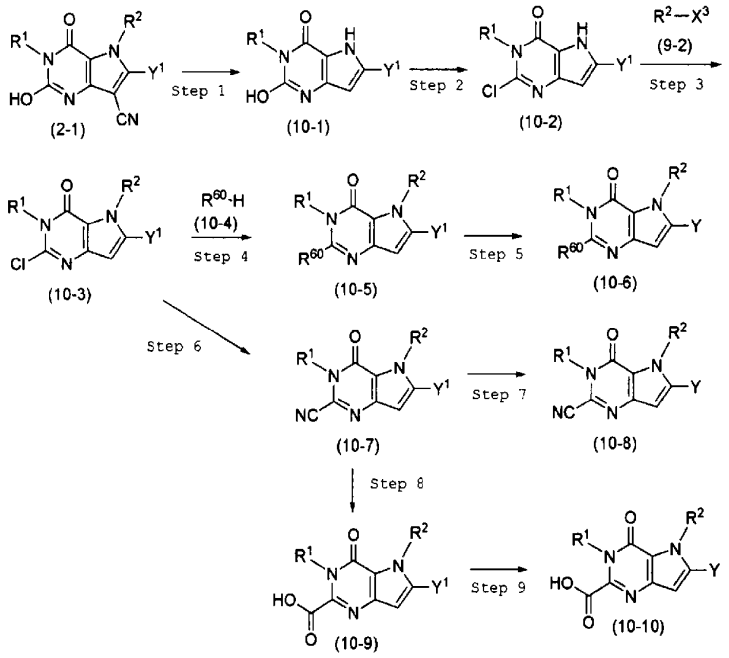
[0092]

Production Process 10

Each of compounds of the formula (10-6), formula (10-8) and formula (10-10) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0093]

[Formula 42]



wherein R^1, R^2, X^3, Y^1 and Y are as defined above, and R^{60} is the above-mentioned $R^{54}O$, $R^{55}S$ or $R^{56}R^{57}N$.

1) Step 1

A compound (10-1) may be produced from a compound (2-1) by the same process as in the step 1 described in production process 9.

2) Step 2

A compound (10-2) may be produced from the compound (10-1) by the same production process as described in literature (for example, WO03/104229 and Chem. Pharm. Bull. 50, 1163 (2002)).

3) Step 3

A compound (10-3) may be produced from the compound (10-2) by the same process as in the step 2 described in production process 9.

4) Step 4

A compound (10-5) may be produced from the compound (10-3) by the same process as in the step 1 described in production process 3, the step 1 described in production process 4 or the step 1 described in production process 6.

5) Step 5

The compound (10-6) may be produced from the compound (10-5) by the same process as in the step 2 described in production process 2.

6) Step 6

A compound (10-7) may be produced from the compound (10-3) by the same process as in the step 1 described in production process 5.

7) Step 7

The compound (10-8) may be produced from the compound (10-7) by the same process as in the step 2 described in production process 2.

8) Step 8

A compound (10-9) may be produced from the compound (10-7) by the same production process as described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989, WO03/104229 and WO03/104229).

In this step, a compound in which a protective group for the primary amino group or secondary amino group in Y has been removed is produced in some cases. The compound (10-9) in which the primary amino group or secondary amino group in Y has been protected again with a protective group (e.g. Boc or Cbz) may be produced by the same production process as described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

9) Step 9

The compound (10-10) may be produced from the compound (10-9) by the same process as in the step 2 described in production process 2.

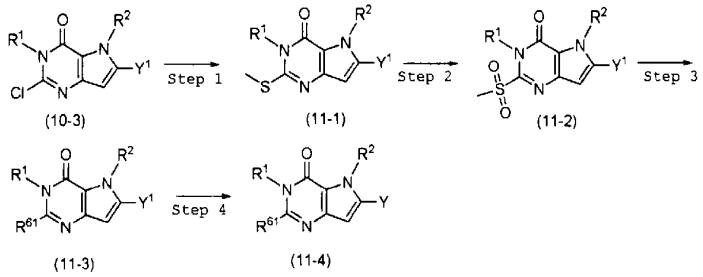
[0094]

Production Process 11

A compound of the formula (11-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0095]

[Formula 43]



wherein R^1, R^2, Y^1 and Y are as defined above, and R^{61} is "an optionally substituted alkoxy group", "an optionally substituted aryloxy group", "an optionally substituted aralkyloxy group", "an optionally substituted heteroaryloxy group", "an optionally substituted cycloalkyloxy group", "an optionally substituted alkylthio group", "an optionally substituted arylthio group", cyano, "an optionally substituted nitrogen-containing saturated heterocyclic group", "an optionally substituted amino group", "an optionally substituted alkyl group", "an optionally substituted cycloalkyl group", "an optionally substituted alkenyl group", "an optionally substituted aryl group", "an optionally substituted heteroaryl group", "an optionally substituted heteroarylalkyl group", "an optionally substituted aralkyl group", "an optionally substituted aroyl group", "an optionally substituted heteroarylcarbonyl group" or "an optionally

substituted alkylcarbonyl group".

1) Step 1

A compound (11-1) may be produced by reacting a compound (10-3) with sodium methanethiol in an inert solvent in the presence or absence of a base. The base includes, for example, inorganic bases such as sodium hydride, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, etc.; and organic bases such as 1-hydroxybenzotriazole, N-methylmorpholine, triethylamine, diisopropylethylamine, tributylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene, 1,5-diazabicyclo[4,3,0]nona-5-ene, 1,4-diazabicyclo[5,4,0]undec-7-ene, pyridine, dimethylaminopyridine, picoline, etc. The amount of the base used is usually chosen in the range of 1 equivalent to large-excess equivalents per equivalent of the compound (10-3). The amount of sodium methanethiol used is usually chosen in the range of 1 equivalent to large-excess equivalents per equivalent of the compound (10-3). The inert solvent includes, for example, aprotic solvents (e.g. N,N-dimethylformamide and dimethyl sulfoxide), ether solvents (e.g. diethyl ether, tetrahydrofuran and 1,4-dioxane), ketones (e.g. acetone), and mixed solvents thereof. The reaction temperature may be chosen in the range of about 10°C to about 120°C.

2) Step 2

A compound (11-2) may be produced from the compound (11-1) by the same process as in the step 6 described in production process 1.

3) Step 3

A compound (11-3) may be produced from the compound (11-2) by the same process as in the step 1 described in production process 3, the step 1 described in production process 4, the step 1 described in production process 5, the step 1 described in production process 6, the step 1 described in production process 7 or the step 1 described in production process 8.

4) Step 4

The compound (11-4) may be produced from the compound (11-3) by the same process as in the step 2 described in production process 2.

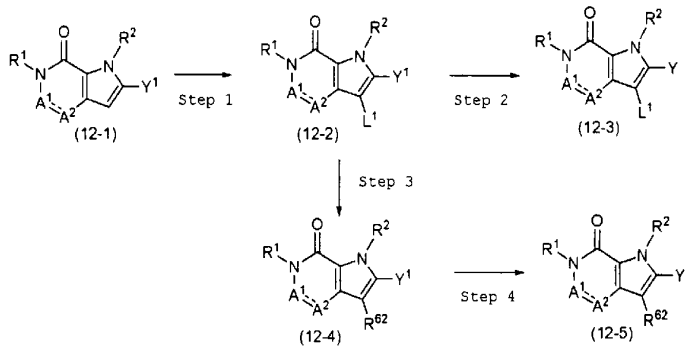
[0096]

Production Process 12

Each of compounds of the formula (12-3) and the formula (12-5) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0097]

[Formula 44]



wherein A^1, A^2, R^1, R^2, Y^1 and Y are as defined above; a compound of the formula (12-1) includes the compound (9-3) described in production process 9 and the compound (11-3) described in production process 11; L1 is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom; and R^{62} is "an optionally substituted alkyl group", "an optionally substituted alkenyl group", "an optionally substituted alkynyl group", "an optionally substituted cycloalkyl group", "an optionally substituted aryl group", "an optionally substituted heteroaryl group", "an optionally substituted aralkyl group" or "an optionally substituted heteroarylalkyl group".

1) Step 1

A compound (12-2) may be produced from a compound (12-1) by the same production process as described in literature (for example, Synth. Commun. 33, 2671 (2003), Tetrahedron Letters 42, 863 (2001), Synthesis 926 (1995), Tetrahedron Letters 37, 1095

(1996), J. Org. Chem. 64, 5366 (1999), Indian J. Chem., Sect B 35, 141 (1996) and J. Heterocycl. Chem. 24, 1313 (1987)).

2) Step 2

The compound (12-3) may be produced from the compound (12-2) by the same process as in the step 2 described in production process 2.

3) Step 3

A compound (12-4) may be produced from the compound (12-2) by the same production process as described in literature (for example, Chem. Rev. 95, 2457 (1995), Chem. Rev. 103, 1979 (2003), Chem. Rev. 100, 3009 (2000), Organic Process Research & Development 5, 254 (2001), J. Med. Chem. 45, 999 (2002), Synthesis 563 (1997), J. Org. Chem. 65, 9001 (2000), J. Org. Chem. 64, 4196 (1999), J. Org. Chem. 67, 3904 (2002), Adv. Synth. Catal. 345, 620 (2003) and J. Med. Chem. 43, 675 (2000)).

4) Step 4

The compound (12-5) may be produced from the compound (12-4) by the same process as in the step 2 described in production process 2.

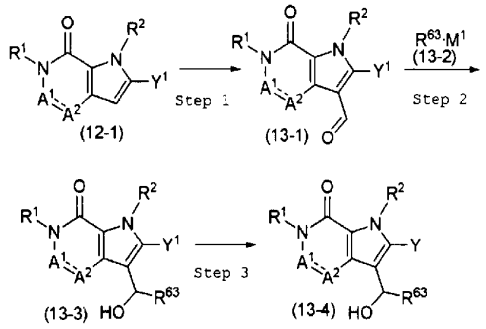
[0098]

Production Process 13

A compound of the formula (13-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0099]

[Formula 45]



wherein A^1, A^2, R^1, R^2, M^1, Y^1 and Y are as defined above; a compound of the formula (12-1) is as described above; and R^{63} is "an optionally substituted alkyl group", "an optionally substituted cycloalkyl group", "an optionally substituted aryl group" or "an optionally substituted heteroaryl group".

1) Step 1

A compound (13-1) may be produced from a compound (12-1) by the same production process as described in literature (for example, J. Heterocycl. Chem. 30, 957 (1993), Chem. Pharm. Bull. 42, 237 (1994), Aust. J. Chem. 47, 1009 (1994) and J. Heterocycl. Chem. 12, 517 (1975)).

2) Step 2

A compound (13-3) may be produced from the compound (13-1) by the same production process as described in literature (for example, R.C. Larock,

Comprehensive Organic transformation, VCH publisher Inc., 1989).

As a compound (13-2), a commercial one may be used, or the compound (13-2) may be produced by the process described, for example, in Japanese Chemical Association, Jikken Kagaku Koza (Experimental Chemistry) Vol. 25, Maruzen Co., Ltd.

3) Step 3

The compound (13-4) may be produced from the compound (13-3) by the same process as in the step 2 described in production process 2.

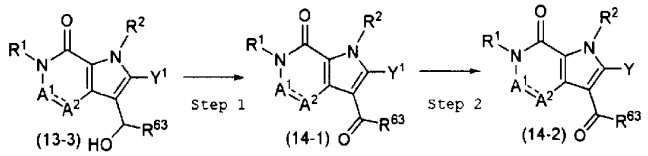
[0100]

Production Process 14

A compound of the formula (14-2) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0101]

[Formula 46]



wherein A^1, A^2, R^1, R^2, R^{63}, Y^1 and Y are as defined above.

1) Step 1

A compound (14-1) may be produced from a compound (13-3) by the same production process as described in literature (for example, R.C. Larock,

Comprehensive Organic transformation, VCH publisher Inc., 1989).

2) Step 2

The compound (14-2) may be produced from the compound (14-1) by the same process as in the step 2 described in production process 2.

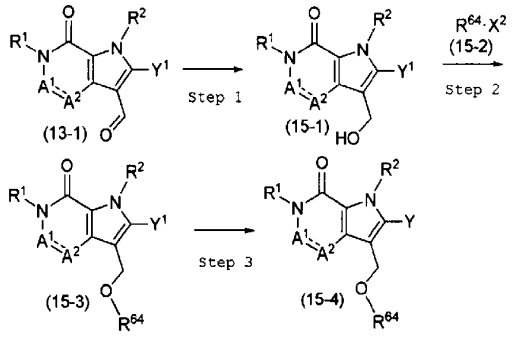
[0102]

Production Process 15

A compound of the formula (15-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0103]

[Formula 47]



wherein A^1, A^2, R^1, R^2, Y^1 and Y are as defined above; $R^{64}O$ is "an optionally substituted alkoxy group", "an optionally substituted aryloxy group", "an optionally substituted aralkyloxy group", "an optionally substituted heteroaryloxy group" or "an optionally substituted cycloalkyloxy group"; and X^2 is a hydroxyl

group or a leaving group (e.g. an iodine atom, a bromine atom, a chlorine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy or p-toluenesulfonyloxy).

1) Steps 1 to 2

A compound (15-3) may be produced from a compound (13-1) by the same production process as described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., (1989), Organic Reactions (New York) 42, 335-656 (1992), Tetrahedron Lett. 44, 4873 (2003) and J. Am. Chem. Soc. 125, 4978 (2003)).

2) Step 3

The compound (15-4) may be produced from the compound (15-3) by the same process as in the step 2 described in production process 2.

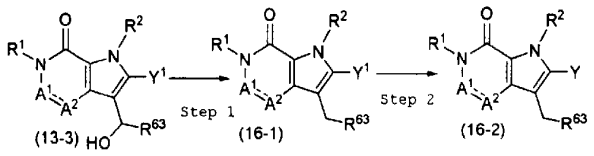
[0104]

Production Process 16

A compound of the formula (16-2) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0105]

[Formula 48]



wherein A^1, A^2, R^1, R^2, R^{63}, Y^1 and Y are as defined above.

1) Step 1

A compound (16-1) may be produced from a compound (13-3) by the same production process as described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., (1989), J. Org. Chem. 65, 6179 (2000), J. Org. Chem. 58, 6913 (1993), Bull. Chem. Soc. Jpn. 67, 1107 (1994) and J. Org. Chem. 60, 2430 (1995).

2) Step 2

The compound (16-2) may be produced from the compound (16-1) by the same process as in the step 2 described in production process 2.

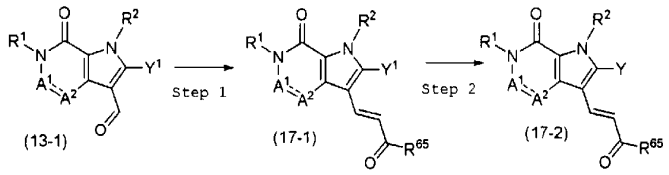
[0106]

Production Process 17

A compound of the formula (17-2) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0107]

[Formula 49]



wherein A^1, A^2, R^1, R^2, Y^1 and Y are as defined above, and $R^{65}C(O)$ is a carboxyl group, "an optionally substituted carbamoyl group", "an optionally substituted alkoxycarbonyl group", "an optionally

substituted aryloxycarbonyl group", "an optionally substituted aralkyloxycarbonyl group", "an optionally substituted cycloalkyloxycarbonyl group", "an optionally substituted alkylcarbonyl group", "an optionally substituted heterocarylcarbonyl group", "an optionally substituted aroyl group" or "an optionally substituted cycloalkylcarbonyl group".

1) Step 1

A compound (17-1) may be produced from a compound (13-1) by the same production process as described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., (1989) and A. Hassner et al., Organic Synthesis Based On Name Reactions And Unnamed Reactions, Elsevier Science Ltd., (1994)).

In the case of a compound (17-1) in which $R^{65}C(O)$ is "an optionally substituted alkoxycarbonyl group", "an optionally substituted aryloxycarbonyl group", "an optionally substituted aralkyloxycarbonyl group" or "an optionally substituted cycloalkyloxycarbonyl group", this compound may be converted to another compound (17-1) in which $R^{65}C(O)$ is a carboxyl group by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

2) Step 2

The compound (17-2) may be produced from the

compound (17-1) by the same process as in the step 2 described in production process 2.

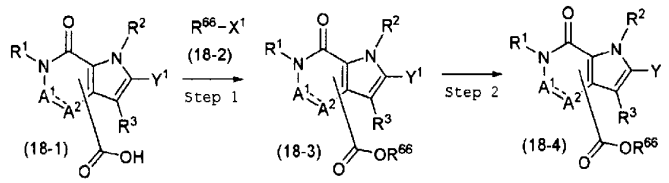
[0108]

Production Process 18

A compound of the formula (18-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0109]

[Formula 50]



wherein A^1, A^2, R^1, R^2, R^3, X^1, Y^1 and Y are as defined above; CO_2H shown in a compound (18-1) indicates that R^3 or R^4 shown in the formula (I) is a carboxyl group or that a carboxyl group is present in the partial structure of R^3, R^4 or R^5; and CO_2R^{66} shown in a compound (18-3) and the compound (18-4) indicates a state in which the CO_2H of the compound (18-1) has been converted to CO_2R^{66}, and specifically, CO_2R^{66} indicates, for example, the formula: C(O)O-Re wherein Re is as defined above.

1) Step 1

A compound (18-3) may be produced by reacting a compound (18-1) with a compound (18-2) in an inert solvent in the presence of a base. The amount of the

compound (18-2) used is usually chosen in the range of 1 to 3 equivalents per equivalent of the compound (18-1). The base includes, for example, alkali carbonates (e.g. potassium carbonate, sodium carbonate, potassium hydrogencarbonate and sodium hydrogencarbonate), alkali hydroxides (e.g. potassium hydroxide and sodium hydroxide), alkali hydrides (e.g. sodium hydride and potassium hydride), and alkoxyalkalis (e.g. potassium tert-butoxide). Suitable examples thereof are potassium carbonate and sodium hydride. The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (18-1). The inert solvent includes, for example, aprotic solvents (e.g. N,N-dimethylformamide and dimethyl sulfoxide), ether solvents (e.g. diethyl ether, tetrahydrofuran and 1,4-dioxane), ketones (e.g. acetone), and mixed solvents thereof. A suitable example thereof is N,N-dimethylformamide. The reaction temperature may be chosen in the range of about 10°C to about 100°C.

As the compound (18-2), a commercial reagent may be used, or the compound (18-2) may be produced by the same production process as described in literature (for example, WO03/027098, WO00/06581, and R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989).

2) Step 2

The compound (18-4) may be produced from the compound (18-3) by the same process as in the step 2

described in production process 2.

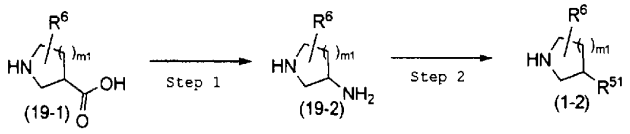
[0110]

Production Process 19

The compound (1-2) described in production process 1 may be produced, for example, by the following process:

[0111]

[Formula 51]



wherein m1, R^6 and R^{51} are as defined above.

1) Step 1

A compound (19-2) may be produced from a compound (19-1) by the same production process as described in literature (for example, J. Org. Chem. 58, 879 (1993)).

2) Step 2

The compound (1-2) may be produced from the compound (19-2) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

[0112]

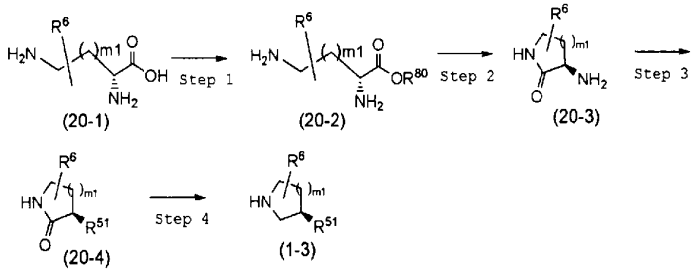
Production Process 20

The compound (1-3) described in production

process 1 may be produced, for example, by the following process:

[0113]

[Formula 52]



wherein m1, R^6 and R^{51} are as defined above, and R^{80} is an alkyl group.

1) Step 1

A compound (20-2) may be produced by reacting a compound (20-1) with thionyl chloride in an alcohol solvent. The alcohol solvent includes methanol, ethanol, etc. The amount of thionyl chloride used is usually chosen in the range of 2 to 10 equivalents per equivalent of the compound (20-1). The reaction temperature may be chosen in the range of about -90°C to about 30°C.

2) Step 2

A compound (20-3) may be produced by reacting the compound (20-2) with a base in water solvent. The base includes sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium

carbonate, etc. The reaction temperature may be chosen in the range of about 30°C to about 100°C.

3) Step 3

A compound (20-4) may be produced from the compound (20-3) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

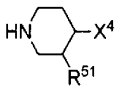
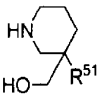
4) Step 4

The compound (1-3) may be produced by reacting the compound (20-4) with a reducing agent in an inert solvent. The reducing agent includes aluminum lithium hydride, borane complexes (e.g. borane-dimethyl sulfide complexes and borane-tetrahydrofuran complexes) and the like. The inert solvent includes tetrahydrofuran, 1,4-dioxane, mixed solvents thereof, and the like. The reaction temperature is chosen in the range of about -20°C to about 60°C.

Examples of the synthesis of compounds (1-2a) to (1-2j) as specific examples of the compound (1-2) are given below. The compounds (1-2a) to (1-2j) include pharmaceutically acceptable salts thereof.

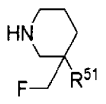
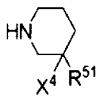
[0114]

[Formula 53]

Compound	Production process
	WO 02/48138 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
(1-2a): $X^4 = CH_3$ (1-2b): $X^4 = CH_2CH_3$ (1-2c): $X^4 = CH_2CH_2OH$ (1-2d): $X^4 = CH_2CH_2F$ (1-2e): $X^4 = H$	
 (1-2f)	J. Org. Chem. 44, 2732 (1979) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

[0115]

[Formula 54]

Compound	Production process
 (1-2g)	Synthesized from compound (1-2f) as a starting material according to, for example, the process described in J. Org. Chem. 44, 3872 (1979), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
	Arch. Pharm. 322, 499 (1989) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
(1-2h): $X^4 = CH_3$ (1-2i): $X^4 = CH_2CH_3$ (1-2j): $X^4 = CH_2CH_2CH_3$	

wherein R^{51} is as defined above.

[0116]

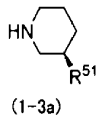
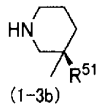
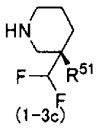
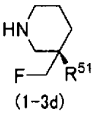
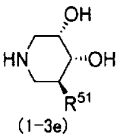
As hydrochloride of the compound (1-2e), a commercial one may also be used. It is also possible to synthesize the compound (1-2) from a substituted DL-ornithine by a well-known process. A specific example of the process is that described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

[0117]

Examples of the synthesis of compounds (1-3a) to (1-3i) as specific examples of the compound (1-3) are given below. The compounds (1-3a) to (1-3i) include pharmaceutically acceptable salts thereof.

[0118]

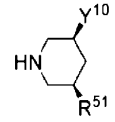
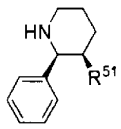
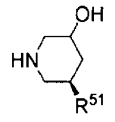
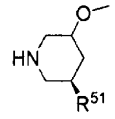
[Formula 55]

Compound	Production process
 (1-3a)	WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3b)	Int. J. Peptide Protein Res. 40, 119 (1992) WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3c)	US 4413141 WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3d)	Tetrahedron: Asymmetry 8, 327 (1997) WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3e)	Tetrahedron: Asymmetry 11, 567 (2000) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

wherein R^{51} is as defined above.

[0119]

[Formula 56]

Compound	Production process
 (1-3f)	Chem. Eur. J. 6, 2830 (2000) WO 00/26332 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3g)	JP-T-2002-525325 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3h)	Bull. Chem. Soc. Jpn. 53, 2605 (1980) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3i)	Synthesized from compound (1-3h) as a starting material according to, for example, the process described in J. Am. Chem. Soc. 80, 2584 (1958), J. Chem. Soc. PT1 499 (1972), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

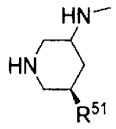
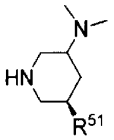
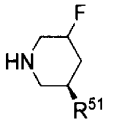
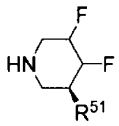
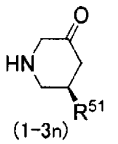
wherein R^{51} is as defined above, and Y^{10} is NH_2, Alloc, NHBoc or NHCbz.

[0120]

Examples of the synthesis of compounds (1-3j) to (1-3v) as specific examples of the compound (1-3) are given below. The compounds (1-3j) to (1-3v) include pharmaceutically acceptable salts thereof.

[0121]

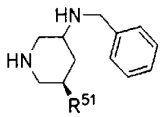
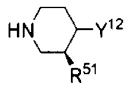
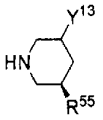
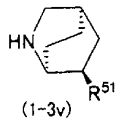
[Formula 57]

Compound	Production process
 (1-3j)	Synthesized from compound (1-3f in which Y^{10} is NH_2) as a starting material according to, for example, the process described in J. Chem. Soc. Chem. Commun. 611 (1981), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3k)	Synthesized from compound (1-3f in which Y^{10} is NH_2) as a starting material according to, for example, the process described in J. Chem. Soc. Chem. Commun. 611 (1981), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3l)	Synthesized from compound (1-3h) as a starting material according to, for example, the process described in J. Org. Chem. 44, 3872 (1979), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3m)	Synthesized from compound (1-3e) as a starting material according to, for example, the process described in J. Org. Chem. 44, 3872 (1979), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-3n)	Synthesized from compound (1-3h) as a starting material according to, for example, the process described in Bull. Chem. Soc. Jpn. 64, 2857 (1991), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

wherein R^{51} is as defined above.

[0122]

[Formula 58]

Compound	Production process
 (1-3o)	Synthesized from compound (1-3f in which Y^{10} is NH_2) as a starting material according to, for example, the process described in Tetrahedron Lett. 40, 5609(1999), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 ($1-3p$): Y^{12} = (R)-C_6H_5 ($1-3q$): Y^{12} = (S)-C_6H_5	J. Med. Chem. 35, 833 (1992), R.C. Larock, "Comprehensive Organic transformation", VCH publisher Inc., 1989, J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 ($1-3r$): Y^{13} = $NHS(O)_2CH_3$ ($1-3s$): Y^{13} = $NHC(O)CH_3$ ($1-3t$): Y^{13} = $NHC(O)C_6H_5$ ($1-3u$): Y^{13} = $N(CH_3)C(O)CH_3$	Synthesized from compound (1-3f in which Y^{10} is NH_2) as a starting material according to, for example, the process described in R.C. Larock "Comprehensive Organic transformation", VCH publisher Inc., 1989, J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 ($1-3v$)	WO 02/068420 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

wherein R^{51} is as defined above.

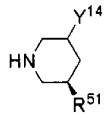
[0123]

Examples of the synthesis of compounds (1-3w) to (1-3dd) as specific examples of the compound (1-3)

are given below. The compounds (1-3w) to (1-3dd) include pharmaceutically acceptable salts thereof.

[0124]

[Formula 59]

Compound	Production process
 (1−3w): Y^{14} = 2-CH_3-C_6H_5 (1−3x): Y^{14} = 3-CH_3-C_6H_5 (1−3y): Y^{14} = 4-CH_3-C_6H_5 (1−3z): Y^{14} = 2-CH_3O-C_6H_5 (1−3aa): Y^{14} = 3-CH_3O-C_6H_5 (1−3bb): Y^{14} = 4-CH_3O-C_6H_5 (1−3cc): Y^{14} = C_6H_5 (1−3dd): Y^{14} = $CH_2C_6H_5$	Synthesized from compound (1−3f in which Y^{10} is NH_2) as a starting material according to, for example, the process described in R.C. Larock, "Comprehensive Organic transformation", VCH publisher Inc., 1989 , J. Org.. Chem. 66, 3593 (2001), J. Prakt. Chem. 342, 421 (2000), Tetrahedron Lett. 36, 5611 (1994), J. Org.. Chem. 53, 5143 (1988), Bioorg. Med. Chem. Lett. 11, 1281 (2001), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

wherein R^{51} is as defined above.

[0125]

The compound (1-3) may be synthesized from a substituted D-ornithine by a well-known process. A specific example of the process is that described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989).

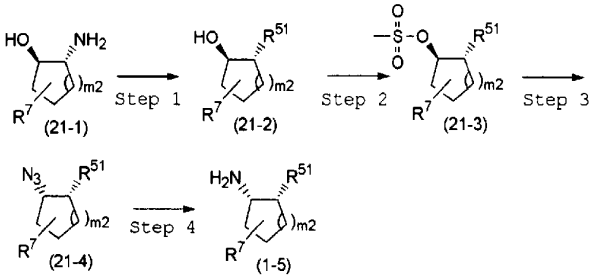
[0126]

Production Process 21

The compound (1-5) described in production process 1 may be produced, for example, by the following process:

[0127]

[Formula 60]



wherein m2, R^7 and R^{51} are as defined above.

1) Step 1

A compound (21-2) may be produced from a compound (21-1) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

2) Steps 2 to 4

The compound (1-5) may be produced from the compound (21-2) by the same process as described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989).

[0128]

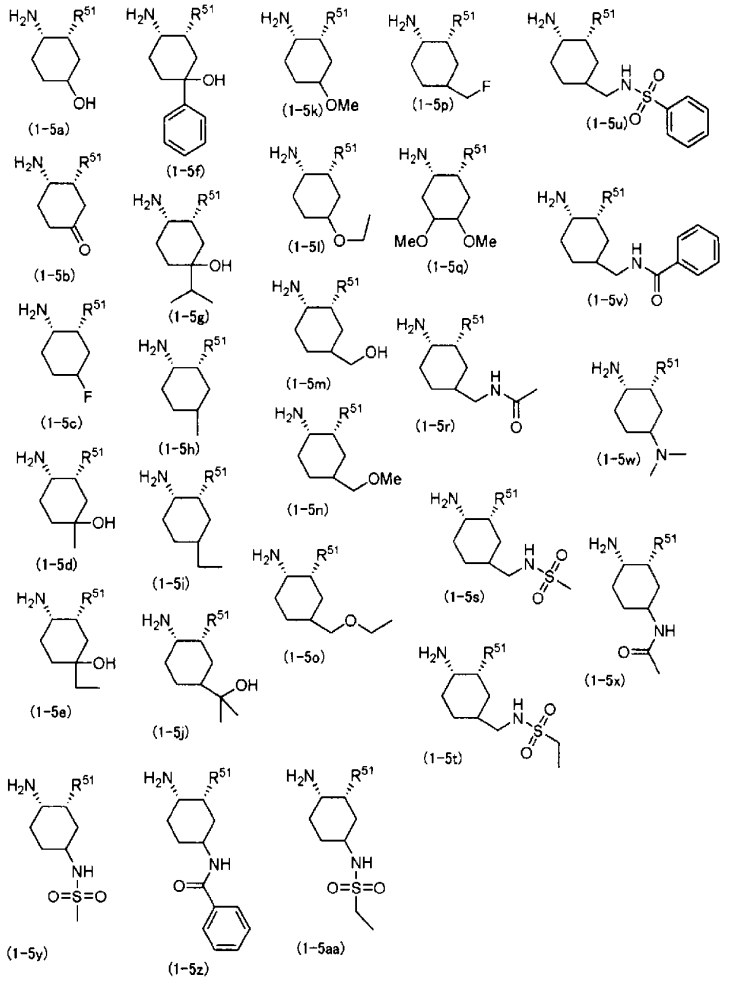
Examples of the synthesis of compounds (1-5a) to (1-5aa) as specific examples of the compound (1-5) are given below. The compounds (1-5a) to (1-5aa) include pharmaceutically acceptable salts thereof.

The compounds (1-5a) to (1-5aa) may be produced according to the processes described in

literature (for example, WO01/74774 and R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989).

[0129]

[Formula 61]



wherein R^{51} is as defined above.

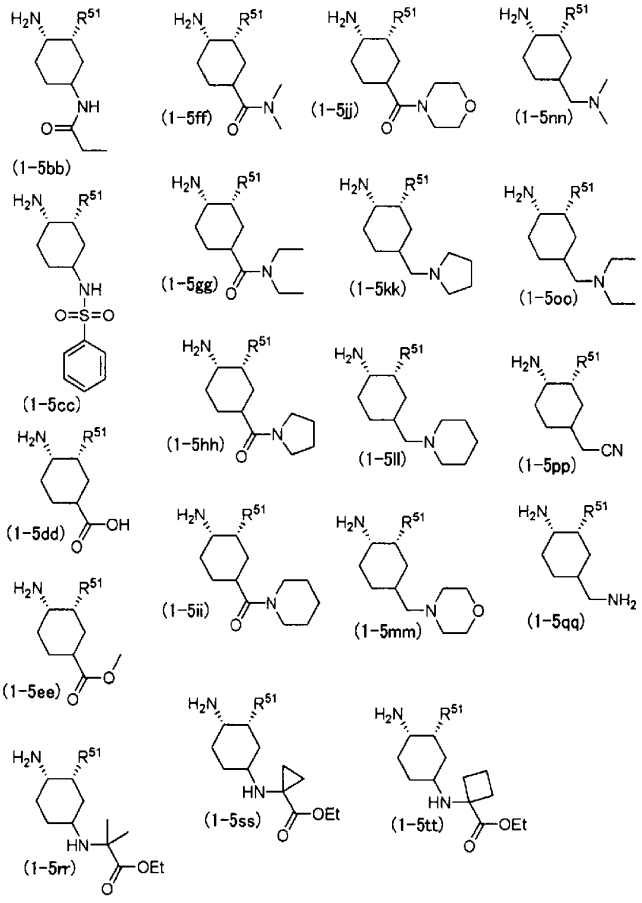
[0130]

Examples of the synthesis of compounds (1-5bb) to (1-5tt) as specific examples of the compound (1-5) are given below. The compounds (1-5bb) to (1-5tt) include pharmaceutically acceptable salts thereof.

The compounds (1-5bb) to (1-5tt) may be produced according to the processes described in literature (for example, WO01/74774, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989, and Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

[0131]

[Formula 62]



wherein R^{51} is as defined above.

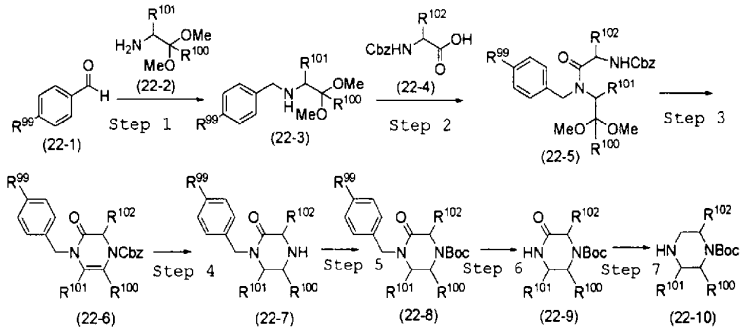
[0132]

Production Process 22

A compound (22-10) as a specific example of the compound (1-6) described in production process 1 may be produced, for example, by the following process:

[0133]

[Formula 63]



wherein R^{100}, R^{101} and R^{102} are independently a hydrogen atom, "an optionally substituted alkyl group", "an optionally substituted aryl group" or "an optionally substituted aralkyl group", and R99 is a hydrogen atom or methoxy.

1) Step 1

A compound (22-3) may be produced by carrying out reductive amination of a compound (22-1) with a compound (22-2) by the same method as described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989).

2) Steps 2 to 4

A compound (22-7) may be produced from the compound (22-3) by the same production process as described in literature (e.g. WO01/07436).

3) Step 5

A compound (22-8) may be produced from the

compound (22-7) by the same production process as described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

4) Step 6

A compound (22-9) may be produced from the compound (22-8) by the same production process as described in literature (for example, J. Chem. Soc. Perkin Trans. I 3281 (2001), Heterocycles 38, 17 (1994), Tetrahedron Lett. 34, 6673 (1993), J. Org. Chem. 60, 4602 (1995) and J. Med. Chem. 38, 2866 (1995)).

5) Step 7

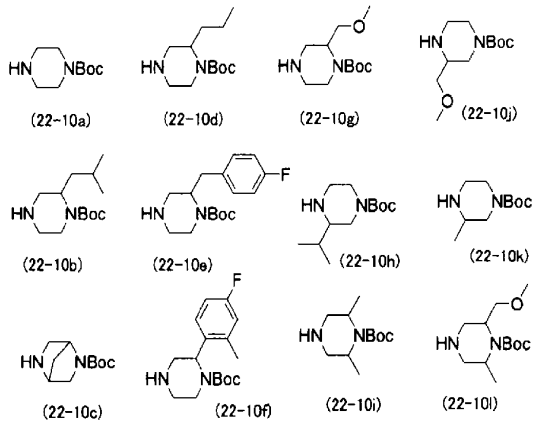
The compound (22-10) may be produced from the compound (22-9) by the same process as that described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989) or the like.

[0134]

Examples of the synthesis of compounds (22-10a) to (22-10l) as specific examples of the compound (22-10) are given below. The compounds (22-10a) to (22-10l) include pharmaceutically acceptable salts thereof.

[0135]

[Formula 64]



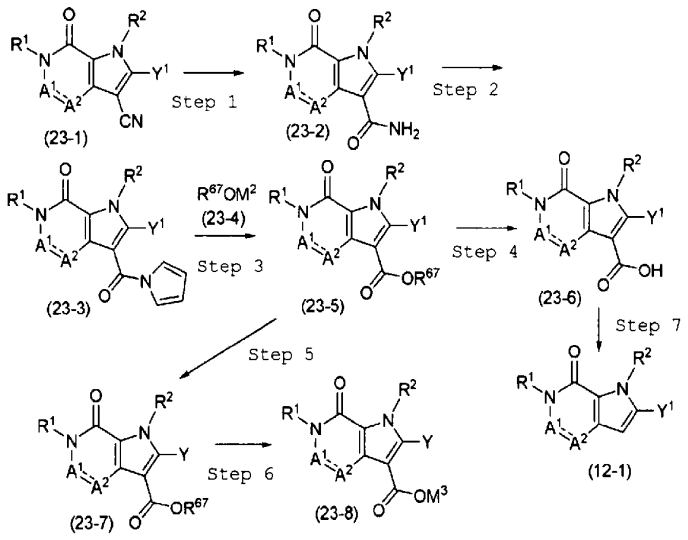
[0136]

Production Process 23

Each of compounds of the formula (23-2), formula (23-3), formula (23-5), formula (23-6), formula (23-7), formula (23-8) and formula (12-1) is produced, for example, by the following process:

[0137]

[Formula 65]



wherein A^1, A^2, R^1, R^2 and Y^1 are as defined above; $R^{67}O$ is "an optionally substituted alkoxy group"; and each of M^2 and M^3 is lithium, sodium or potassium.

1) Step 1

The compound (23-2) may be produced from a compound (23-1) by the same production process as described in literature (for example, Can. J. Chem. 78, 697 (2000)).

2) Step 2

The compound (23-3) may be produced by reacting the compound (23-2) with 2,5-dimethoxytetrahydrofuran in the presence of thionyl chloride and in the presence or absence of an inert solvent. The amount of thionyl chloride used is

usually chosen in the range of 0.1 to 3 equivalents per equivalent of the compound (23-2). The amount of 2,5-dimethoxytetrahydrofuran used is usually chosen in the range of 10 to 100 equivalents per equivalent of the compound (23-2), and 2,5-dimethoxytetrahydrofuran may be used also as a solvent. The inert solvent includes, for example, aprotic solvents (e.g. N,N-dimethylformamide and dimethyl sulfoxide), ether solvents (e.g. diethyl ether, tetrahydrofuran and 1,4-dioxane), ketones (e.g. acetone), aprotic solvents (e.g. acetonitrile, N,N-dimethylformamide and dimethyl sulfoxide), and mixed solvents thereof. Suitable examples thereof are N,N-dimethylformamide and dimethyl sulfoxide. The reaction temperature may be chosen in the range of about 10°C to about 80°C.

3) Step 3

The compound (23-5) may be produced by reacting the compound (23-3) with a compound (23-4) in an inert solvent. The amount of the compound (23-4) used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (23-3). The inert solvent includes alcohol solvents (e.g. methanol, ethanol and 2-propanol) and the like. The reaction temperature may be chosen in the range of about 30°C to about 100°C.

4) Step 4

The compound (23-6) may be produced by reacting the compound (23-5) with a base in an inert

solvent. As the base, alkali hydroxides (e.g. potassium hydroxide and sodium hydroxide) are exemplified, and an aqueous solution of the base may be used. The amount of the base used is usually chosen in the range of 1 to 30 equivalents per equivalent of the compound (23-5). The inert solvent includes alcohol solvents (e.g. methanol, ethanol and 2-propanol), water, mixed solvents thereof, and the like. The reaction temperature may be chosen in the range of about 30°C to about 130°C.

5) Step 5

The compound (23-7) may be produced from the compound (23-5) by the same process as in the step 2 described in production process 2.

6) Step 6

The compound (23-8) may be produced from the compound (23-7) by the same process as in the above step 4.

7) Step 7

The compound (12-1) may be produced by reacting the compound (23-6) in an inert solvent in the presence or absence of an organic acid. The organic acid includes, for example, acetic acid, propionic acid, oxalic acid, succinic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, methanesulfonic acid, p-toluenesulfonic acid and ascorbic acid. The inert solvent includes, for example, alcohol solvents (e.g. methanol, ethanol and 2-

propanol), ether solvents (e.g. tetrahydrofuran and 1,4-dioxane), ketones (e.g. acetone), aprotic solvents (e.g. acetonitrile, N,N-dimethylformamide and dimethyl sulfoxide), and mixed solvents thereof. The reaction temperature may be chosen in the range of about 0°C to about 100°C.

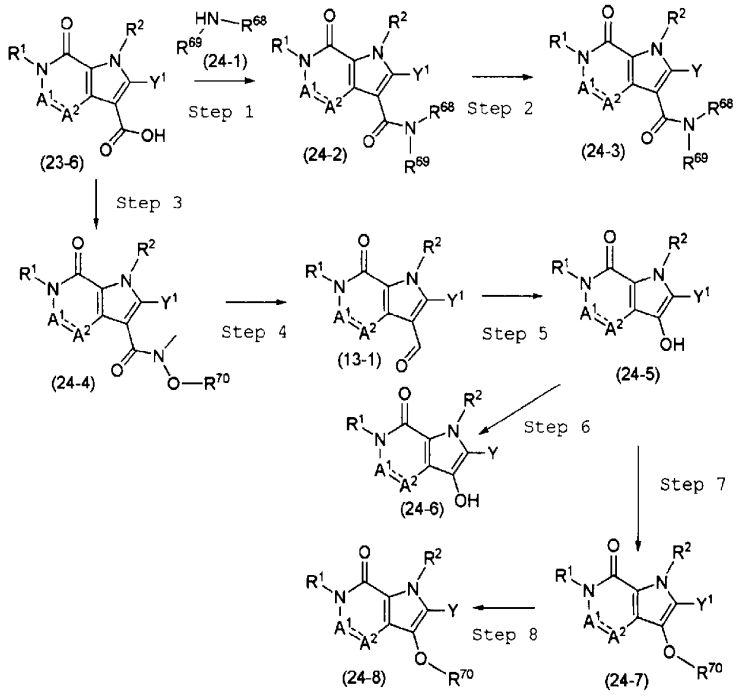
[0138]

Production Process 24

Each of compounds of the formula (24-3), formula (24-6) and formula (24-8) as the compound of the formula (I), or a salt thereof and a compound of the formula (13-1) are produced, for example, by the following processes:

[0139]

[Formula 66]



wherein A^1, A^2, R^1, R^2, Y^1 and Y are as defined above; $C(O)NR^{68}R^{69}$ is "an optionally substituted carbamoyl group"; and R^{70} is "an optionally substituted alkyl group", "an optionally substituted alkenyl group", "an optionally substituted alkynyl group", "an optionally substituted cycloalkyl group", "an optionally substituted aryl group", "an optionally substituted heteroaryl group", "an optionally substituted aralkyl group" or "an optionally substituted heteroarylalkyl group".

1) Step 1

A compound (24-2) may be produced from a compound (23-6) by the same production process as described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 972-976 (1989)).

2) Step 2, Step 6 and Step 8

By the same process as in the step 2 described in production process 2, the compound (24-3) may be produced from the compound (24-2), the compound (24-6) from a compound (24-5), and the compound (24-8) from a compound (24-7).

3) Step 3

A compound (24-4) may be produced from a compound (23-6) by the same production process as described in literature (for example, Bioorg. Med. Chem. Lett. 11, 2951 (2001), Tetrahedron Letters 42, 8955 (2001), Organic Letters 2, 4091 (2000), Synlett 5, 715 (2002), Bioorg. Med. Chem. Lett. 11, 287 (2001), Tetrahedron Letters 45, 7107 (2004) and Tetrahedron Letters 42, 3763 (2001)).

4) Step 4

The compound (13-1) may be produced from the compound (24-4) by the same production process as described in literature (for example, Tetrahedron Letters 45, 7107 (2004)).

5) Step 5

The compound (24-5) may be produced from the

compound (13-1) by the same production process as described in literature (for example, Indian J. Chem. 33B, 1103 (1994)).

6) Step 6 and Step 8

The compound (24-6) may be produced from the compound (24-5) by the same process as in the step 2 described in production process 2.

7) Step 7

The compound (24-7) may be produced from the compound (24-5) by the same process as that described in literature (for example, R.C. Larock, Comprehensive Organic transformation, VCH publisher Inc., 1989) or the like.

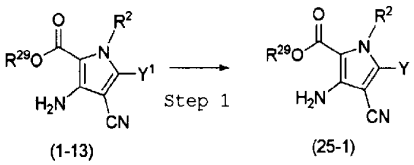
[0140]

Production Process 25

A compound of the formula (25-1) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0141]

[Formula 67]



(1-13) (25-1)

wherein R^2, R^{29}, Y and Y^1 are as defined above.

1) Step 1

The compound (25-1) may be produced from a

compound (1-13) by the same process as in the step 2 described in production process 2.

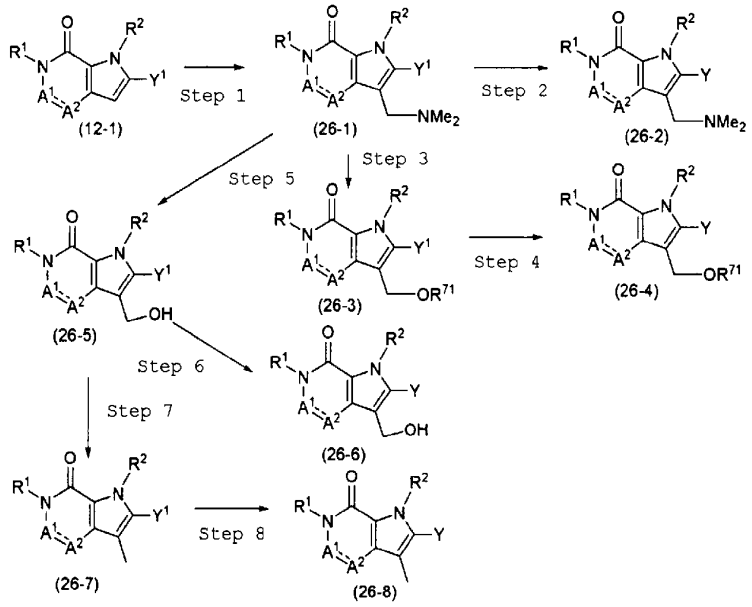
[0142]

Production Process 26

Each of compounds of the formula (26-2), formula (26-4), formula (26-6) and formula (26-8) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

[0143]

[Formula 68]



wherein A^1, A^2, R^1, R^2, Y^1 and Y are as defined above, and R^{71} is an alkyl group.

1) Step 1 and Step 3

A compound (26-3) may be produced from a compound (12-1) by the same production process as described in literature (for example, J. Am. Chem. Soc. 74, 3916 (1952)).

2) Step 2

The compound (26-2) may be produced from a compound (26-1) by the same process as in the step 2 described in production process 2.

3) Step 4

The compound (26-4) may be produced from the compound (26-3) by the same process as in the step 2 described in production process 2.

4) Step 5 and Step 7

A compound (26-7) may be produced from a compound (26-1) by the same production process as described in literature (for example, J. Org. Chem. 22, 355 (1957)).

6) Step 6

The compound (26-6) may be produced from a compound (26-5) by the same process as in the step 2 described in production process 2.

7) Step 8

The compound (26-8) may be produced from the compound (26-7) by the same process as in the step 2 described in production process 2.

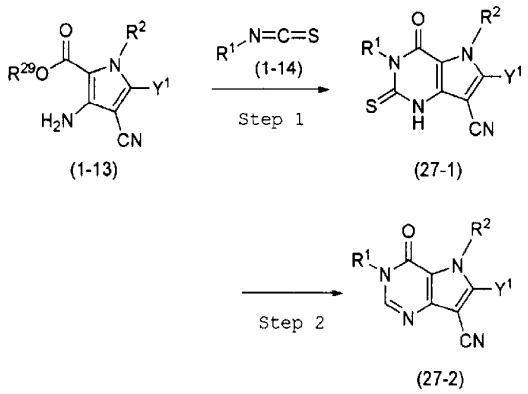
[0144]

Production Process 27

A compound of the formula (27-2) as the compound of the formula (23-1) described in production process 23 is produced, for example, by the following process:

[0145]

[Formula 69]



wherein R^1, R^2, R^{29} and Y^1 are as defined above.

1) Step 1

A compound (27-1) may be produced from a compound (1-13) by the same production process as described in literature (for example, Tetrahedron 50, 3259 (1994)).

2) Step 2

The compound (27-2) may be produced from the compound (27-1) by the same production process as described in literature (for example, Tetrahedron 50, 3259 (1994)).

[0146]

Unless otherwise specified, the starting materials, reagents and the like used above may be commercial compounds or may be produced from well-known compounds by well-known processes.

[0147]

In each of the production processes described above, when the starting compound in each reaction has a reactive group such as hydroxyl group, amino group or carboxyl group, the reactive group in a site other than a site where the reaction is desired is previously protected with a suitable protective group if necessary, and the protective group is removed after carrying out each reaction or after carrying out several reactions, whereby a desired compound may be obtained. As the protective group for protecting the hydroxyl group, amino group, carboxyl group or the like, conventional protective groups used in the field of organic synthetic chemistry may be used. The introduction and removal of such a protective group may be carried out according to a conventional method (for example, the method described in T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd Edition, John Wiley & Sons, Inc. (1991)).

For example, the protective group for the hydroxyl group includes tert-butyldimethylsilyl group, methoxymethyl group, tetrahydropyranyl group and the like. The protective group for the amino group

includes tert-butoxycarbonyl group, benzyloxycarbonyl group and the like. Such a protective group for the hydroxyl group may be removed by reaction in a solvent such as aqueous methanol, aqueous ethanol or aqueous tetrahydrofuran in the presence of an acid such as hydrochloric acid, sulfuric acid or acetic acid. In the case of tert-butyldimethylsilyl group, it is also possible to carry out the removal in a solvent such as tetrahydrofuran in the presence of, for example, tetrabutylammonium fluoride. When the protective group for the amino group is tert-butoxycarbonyl group, it may be removed, for example, by reaction in a solvent such as aqueous tetrahydrofuran, methylene chloride, chloroform or aqueous methanol in the presence of an acid such as hydrochloric acid or trifluoroacetic acid. In the case of benzyloxycarbonyl group, the removal may be carried out, for example, by reaction in a solvent such as acetic acid in the presence of an acid such as hydrobromic acid.

As a form in which the carboxyl group is protected, tert-butyl esters, orthoesters and acid amides are exemplified. The protective group used for this protection is removed as follows. In the case of the tert-butyl esters, the removal is carried out, for example, by reaction in an aqueous solvent in the presence of hydrochloric acid. In the case of the orthoesters, the removal is carried out, for example, by treatment with an acid and then an alkali such as

sodium hydroxide in a solvent such as aqueous methanol, aqueous tetrahydrofuran or aqueous 1,2-dimethoxyethane. In the case of the acid amides, the removal may be carried out, for example, by reaction in a solvent such as water, aqueous methanol or aqueous tetrahydrofuran in the presence of an acid such as hydrochloric acid or sulfuric acid.

[0148]

The compound of the formula (I) includes those having a center for optical activity. Such a compound having a center for optical activity may be obtained as a racemic modification, or it may be obtained as an optically active substance when an optically active starting material is used. If necessary, the racemic modification obtained may be physically or chemically resolved into optical antipodes by a well-known method. Preferably, diastereomers are formed from the racemic modification by a reaction using a reagent for optical resolution. The diastereomers different in form may be resolved by a well-known method such as fractional crystallization.

[0149]

The compound or prodrug thereof of the present invention may be converted to a salt, for example, by mixing with a pharmaceutically acceptable acid in a solvent such as water, methanol, ethanol or acetone. The pharmaceutically acceptable acid includes, for example, inorganic acids such as hydrochloric acid,

hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, etc.; and organic acids such as acetic acid, propionic acid, oxalic acid, succinic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, methanesulfonic acid, p-toluenesulfonic acid, ascorbic acid, etc.

[0150]

The present inventive compounds are expected to be usable for the treatment of various diseases because of their inhibitory effect on DPP-IV. The compounds described in the present description are useful for the suppression of postprandial hyperglycemia in prediabetes, the treatment of non-insulin-dependent diabetes, the treatment of autoimmune diseases such as arthritis and articular rheumatism, the treatment of intestinal mucosa diseases, growth acceleration, the inhibition of transplantation rejection, the treatment of obesity, the treatment of eating disorder, the treatment of HIV infection, the suppression of cancer metastasis, the treatment of prostatomegaly, the treatment of periodontitis, and the treatment of osteoporosis.

[0151]

When used for the treatment, the present inventive compounds may be administered as a pharmaceutical composition orally or parenterally (for example, by intravenous, subcutaneous or intramuscular injection, locally, intrarectally, percutaneously, or

through nose). Compositions for the oral administration include, for example, tablets, capsules, pills, granules, powders, solutions and suspensions. Compositions for the parenteral administration include, for example, aqueous or oily preparations for injection, ointments, creams, lotions, aerosols, suppositories and patches. These pharmaceutical compositions are prepared by conventional techniques and may contain non-toxic and inactive carriers or excipients conventionally used in the field of formulation.

[0152]

Although the dose is varied depending on the individual compounds, the disease, age, body weight and sex of a patient, symptom, administration route and the like, the bicyclic pyrrole derivative of the present invention, the prodrug thereof or the pharmaceutically acceptable salt of the derivative or prodrug is administered to an adult (body weight: 50 kg) usually in a dose of 0.1 to 1000 mg/day, preferably 1 to 300 mg/day in one portion or two or three portions a day. It is also possible to administer the derivative, prodrug or salt at intervals of several days to several weeks.

[0153]

The present inventive compounds may be used in combination with drugs such as remedies for diabetes, remedies for diabetic complications, hypolipidemic drugs, hypotensors, antiobesity drugs, diuretics, etc.

(these drugs are hereinafter abbreviated as concomitant drugs) in order to enhance the effects of the compounds. The timing of administration of the present inventive compound and the concomitant drug(s) is not limited. They may be administered to an object of administration either at the same time or at different times. It is also possible to prepare a mixture of the present inventive compound and the concomitant drug(s). The dose of the concomitant drug(s) may be properly chosen on the basis of a dose clinically employed. The proportions of the present inventive compound and the concomitant drug(s) may be properly chosen depending on an object of administration, an administration route, a disease to be treated, symptoms, a combination of the compound and the concomitant drug(s), and the like. For example, when the object of administration is a human being, the concomitant drug(s) is used in an amount of 0.01 to 100 parts by weight per part by weight of the present inventive compound.

[0154]

The remedies for diabetes include insulin products (e.g. animal insulin products extracted from bovine or porcine pancreas; and human insulin products synthesized by a genetic engineering technique by the use of Escherichia coli or yeast), insulin resistance improving agents (e.g. pioglitazone or its hydrochloride, troglitazone, rosiglitazone or its maleate, GI-262570, JTT-501, MCC-555, YM-440, KRP-297

and CS-011), α-glucosidase inhibitors (e.g. voglibose, acarbose, miglitol and emiglitate), biguanide preparations (e.g. metformin), insulin secretion accelerators (e.g. sulfonylurea preparations such as tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, etc.; repaglinide, senaglinide, nateglinide and mitiglinide), GLP-1, GLP-1 analogs (e.g. exenatide, liraglutide, SUN-E7001, AVE010, BIM-51077 and CJC1131), protein tyrosine phosphatase inhibitors (e.g. vanadates), and β3 agonists (e.g. GW-427353B and N-5984).

[0155]

The remedies for diabetic complications includes aldose reductase inhibitors (e.g. tolrestat, epalresat, zenarestat, zopolrestat, minarestat, fidarestat, SK-860 and CT-112), neurotrophic factors (e.g. NGF, NT-3 and BDNF), PKC inhibitors (e.g. LY-333531), AGE inhibitors (e.g. ALT946, pimagedine, pyratoxathine and N-phenacylthiazolium bromide (ALT766)), active-oxygen removers (e.g. thioctic acid), and cerebrovasodilators (e.g. tiapride and mexiletine). The hypolipidemic drugs include HMG-CoA reductase inhibitors (e.g. pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, itavastatin, and their sodium salts), squalene synthetase inhibitors, ACAT inhibitors, and the like. The hypotensors include angiotensin-converting-enzyme inhibitors (e.g.

captopril, enalapril, aracepril, delapril, lisinopril, imidapril, benazepril, cilazapril, temocapril and trandolapril), angiotensin II antagonists (e.g. ormesartan, medoxomill, candesartan, cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan and tasosartan), calcium antagonists (e.g. nicardipine hydrochloride, manidipine hydrochloride, nisoldipine, nitrendipine, nilvadipine and amlodipine), and the like.

[0156]

The antiobesity drugs include, for example, central antiobesity drugs (e.g. phentermine, sibutramine, amfepramone, dexamfetamine, mazindol and SR-141716A), pancreas lipase inhibitors (e.g. orlistat), peptidergic anorexiants (e.g. leptin and CNTF (ciliary nerve trophic factor)) and cholecystokinin agonists (e.g. lintitript and FPL-15849). The diuretics include, for example, xanthine derivatives (e.g. sodium salicylate theobromine and calcium salicylate theobromine), thiazide preparations (e.g. ethiazide, cyclopenthiazide, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, bentylhydrochlorothiazide, penflutizide, polythiazide and methyclothiazide), anti-aldosterone preparations (e.g. spironolactone and triamterene), carbonate dehydratase inhibitors (e.g. acetazolamide), chlorobenzenesulfoneamide preparations (e.g. chlorthalidone, mefruside and indapamide), azosemide,

isosorbide, ethacrynic acid, piretanide, bumetanide and furosemide.

[0157]

The concomitant drugs are preferably GLP-1, the GLP-1 analogs, the α-glucosidase inhibitors, the biguanide preparations, the insulin secretion accelerators, the insulin resistance improving agents, and the like. The above-exemplified concomitant drugs may be used in combination of two or more thereof in proper proportions.

[0158]

When the present inventive compound is used in combination with the concomitant drug(s), the amount of the drug(s) used may be reduced so as to be within a safe range in view of the side effects of the drug(s). In particular, the dose of the biguanide preparations may be reduced as compared with a conventional dose. Therefore, side effects causable by these drugs are safely preventable. In addition, the doses of the remedies for diabetic complications, the hypolipidemic drugs, the hypotensors and the like may be reduced. As a result, side effects causable by these drugs are effectively preventable.

[0159]

EXAMPLES

The present invention is more concretely illustrated below with reference examples, working examples and test examples, which should not be

construed as limiting the scope of the invention. The nomenclature of compounds shown in the reference examples and working examples mentioned below is not always based on IUPAC. Abbreviations are used in these examples for the simplification of description in some cases and they have the same meanings as defined above.

Example 1

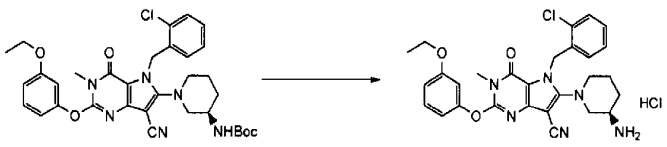
[0160]

Example 1

6-[(3R)-3-Aminopiperidin-1-yl]-5-(2-chlorobenzyl)-2-(3-ethoxyphenoxy)-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile hydrochloride

[0161]

[Formula 70]



A 4N hydrochloric acid/1,4-dioxane solution (5 ml) was added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-2-(3-ethoxyphenoxy)-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidine-3-yl}carbamate (185 mg) in 1,4-dioxane (3 ml), and the resulting mixture was stirred at 25°C for 2 hours and then concentrated under reduced pressure to obtain the title compound (170 mg).

^{1}H NMR (400 MHz, CD_3OD) δ 7.48-7.41 (m, 1H), 7.36-7.16 (m, 3H), 6.91-6.78 (m, 3H), 6.57-6.49 (m, 1H), 5.69 (s, 2H), 4.06 (q, J= 7.0 Hz, 2H), 3.73-3.60 (m, 2H), 3.50 (s, 3H), 3.49-3.42 (m, 1H), 3.10-2.92 (m, 2H), 2.10-1.98 (m, 1H), 1.80-1.70 (m, 1H), 1.65-1.45 (m, 2H), 1.40 (t, J= 7.0 Hz, 3H).

MS (ESI+) 533(M^++1, 100%).

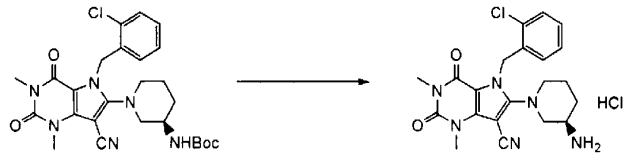
[0162]

Example 2

6-[(3R)-3-Aminopiperidin-1-yl]-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile hydrochloride

[0163]

[Formula 71]



The title compound was synthesized from a corresponding compound by the same process as in Example 1.

^{1}H NMR (400 MHz, CD_3OD) δ 7.47-7.44 (m, 1H), 7.30-7.16 (m, 2H), 6.65-6.58 (m, 1H), 5.72-5.62 (m, 2H), 3.73 (s, 3H), 3.70-3.61 (m, 1H), 3.51-3.41 (m, 1H), 3.27 (s, 3H), 3.23-3.10 (m, 1H), 3.05-2.97 (m, 2H), 2.13-2.03 (m, 1H), 1.82-1.72 (m, 1H), 1.63-1.41 (m, 2H).

MS (ESI+) 427 (M^++1, 88%).

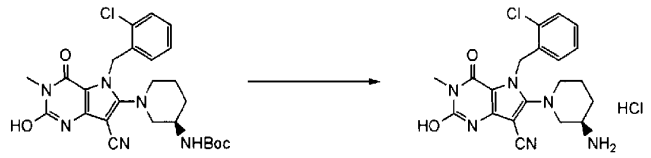
[0164]

Example 3

6-[(3R)-3-Aminopiperidin-1-yl]-5-(2-chlorobenzyl)-2-hydroxy-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile hydrochloride

[0165]

[Formula 72]



The title compound was synthesized from a corresponding compound by the same process as in Example 1.

^{1}H NMR (400 MHz, CD_3OD) δ 7.47-7.44 (m, 1H), 7.32-7.20 (m, 2H), 6.65-6.60 (m, 1H), 5.67-5.57 (m, 2H), 3.52-3.45 (m, 1H), 3.27-3.15 (m, 2H), 3.26 (s, 3H), 3.09-2.94 (m, 2H), 2.12-2.04 (m, 1H), 1.83-1.75 (m, 1H), 1.66-1.43 (m, 2H).

MS (ESI+) 413 (M^++1, 93%).

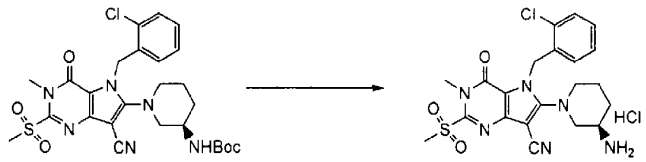
[0166]

Example 4

6-[(3R)-3-Aminopiperidin-1-yl]-5-(2-chlorobenzyl)-3-methyl-2-(methylsulfonyl)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile hydrochloride

[0167]

[Formula 73]



The title compound was synthesized from a corresponding compound by the same process as in Example 1.

^{1}H NMR (400 MHz, CD_3OD) δ 7.49-7.44 (m, 1H), 7.31-7.17 (m, 2H), 6.63-6.57 (m, 1H), 5.78-5.63 (m, 2H), 3.81 (s, 3H), 3.79-3.68 (m, 1H), 3.58 (s, 3H), 3.37-3.17 (m, 2H), 3.15-3.05 (m, 1H), 3.03-2.92 (m, 1H), 2.15-2.03 (m, 1H), 1.84-1.76 (m, 1H), 1.67-1.43 (m, 2H).

MS (ESI+) 475 (M^++1, 100%).

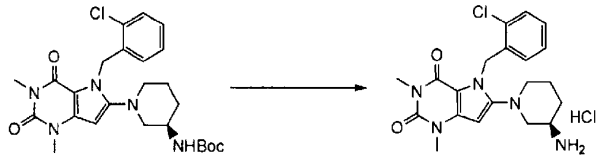
[0168]

Example 5

6-(3-Aminopiperidin-1-yl)-5-(2-chlorobenzyl)-1,3-dimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione hydrochloride

[0169]

[Formula 74]



The title compound was synthesized from a

corresponding compound by the same process as in Example 1.

^{1}H NMR (400 MHz, CD_3OD) δ 7.43-7.40 (m, 1H), 7.25-7.11 (m, 2H), 6.47-6.42 (m, 1H), 6.04 (s, 1H), 5.66-5.53 (m, 2H), 3.48 (s, 3H), 3.38-3.28 (m, 2H), 3.25 (s, 3H), 2.95-2.85 (m, 2H), 2.81-2.71 (m, 1H), 2.07-1.98 (m, 1H), 1.84-1.73 (m, 1H), 1.67-1.49 (m, 2H).

MS (ESI+) 402 (M^++1, 100%).

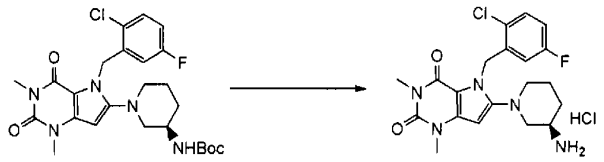
[0170]

Example 6

6-(3-Aminopiperidin-1-yl)-5-(2-chloro-5-fluorobenzyl)-1,3-dimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione hydrochloride

[0171]

[Formula 75]



The title compound was synthesized from a corresponding compound by the same process as in Example 1.

^{1}H NMR (400 MHz, CD_3OD) δ 7.47-7.43 (m, 1H), 7.04-6.98 (m, 1H), 6.17-6.14 (m, 1H), 6.05 (s, 1H), 5.56 (s, 2H), 3.49 (s, 3H), 3.40-3.21 (m, 2H), 3.27 (s, 3H), 2.97-2.70 (m, 3H), 2.08-1.98 (m, 1H), 1.86-1.73 (m, 1H), 1.68-1.46 (m, 2H).

MS (ESI+) 420 (M^++1, 100%).

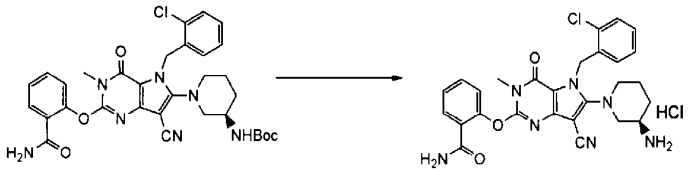
[0172]

Example 7

2-{[6-(3-Aminopiperidin-1-yl)-5-(2-chlorobenzyl)-7-cyano-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl]oxy}benzamide hydrochloride

[0173]

[Formula 76]



The title compound was synthesized from a corresponding compound by the same process as in Example 1.

^{1}H NMR (400 MHz, CD_3OD) δ 8.04-7.97 (m, 1H), 7.50-7.41 (m, 2H), 7.32-7.17 (m, 2H), 7.00-6.91 (m, 2H), 6.67-6.59 (m, 1H), 5.71 (s, 2H), 3.57 (s, 3H), 3.72-3.20 (m, 3H), 3.15-2.97 (m, 2H), 2.15-2.03 (m, 1H), 1.87-1.75 (m, 1H), 1.70-1.42 (m, 2H).

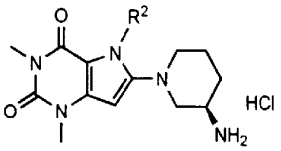
MS (ESI+) 532 (M^++1, 100%).

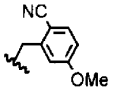
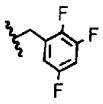
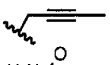
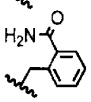
[0174]

Each of the compounds of Examples 8 to 70 was synthesized according to the processes described in a corresponding reference example and Example 1.

[0175]

[Formula 77]



Example No.	R^2	Example No.	R^2
Example 8		Example 12	
Example 9		Example 13	
Example 10		Example 14	
Example 11		Example 15	

[0176]

Example 8

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (brs, 3H), 7.86 (d, J = 6.6 Hz, 1H), 7.57 (m, 1H), 7.43 (t, J = 7.6 Hz, 1H), 6.62 (d, J = 7.9 Hz, 1H), 6.12 (s, 1H), 5.64 (d, J = 16.2 Hz, 1H), 5.56 (d, J = 16.2 Hz, 1H), 3.39 (s, 3H), 3.36-3.23 (m, 2H), 3.11 (s, 3H), 2.92-2.75 (m, 3H), 1.91-1.80 (m, 2H), 1.55-1.51 (m, 2H).

MS (ESI+) 393(M^++1, 100%).

Example 9

^{1}H NMR (400 MHz, CD_3OD) δ 7.10-7.03 (m, 1H), 6.28-6.25

(m, 1H), 6.02 (s, 1H), 5.58 (s, 2H), 3.47 (s, 3H), 3.41-2.79 (m, 5H), 3.27 (s, 3H), 2.10-1.52 (m, 4H).

MS (ESI+) 422 (M^++1, 100%).

Example 10

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (brs, 3H), 7.23-7.18 (m, 1H), 6.95-6.90 (m, 1H), 6.05 (s, 1H), 5.98-5.94 (m, 1H), 5.40 (d, J = 16.5 Hz, 1H), 5.32 (d, J = 16.5 Hz, 1H), 3.38 (s, 3H), 3.35-3.23 (m, 2H), 3.11 (s, 3H), 2.86-2.81 (m, 2H), 2.68-2.64 (m, 1H), 2.32 (s, 3H), 1.88-1.74 (m, 2H), 1.49-1.44 (m, 2H).

MS (ESI+) 400(M^++1, 100%).

Example 11

^{1}H NMR (300 MHz, CD_3OD) δ 7.09-6.88 (m, 3H), 6.19 (d, J = 7.5Hz, 1H), 5.93 (s, 1H), 5.43 (d, J = 16.3 Hz, 1H), 5.36 (d, J = 16.3 Hz, 1H), 3.38 (s, 3H), 3.27-3.21 (m, 2H), 3.14 (s, 3H), 2.89-2.73 (m, 3H), 2.31 (s, 3H), 1.94-1.91 (m, 1H), 1.70-1.49 (m, 3H).

MS (ESI+) 382(M^++1, 100%).

Example 12

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.59 (m, 1H), 6.83-6.79 (m, 1H), 6.32 (d, J = 2.4Hz, 1H), 5.67 (s, 1H), 5.66 (s, 1H), 5.60 (s, 1H), 3.74 (s, 3H), 3.47 (s, 3H), 3.36 (s, 3H), 3.03-2.93 (m, 2H), 2.86-2.82 (m, 1H), 2.69-2.61 (m, 1H), 2.52-2.46 (m, 1H), 1.88-1.61 (m, 4H).

MS (ESI+) 423(M^++1, 100%).

Example 13

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (brs, 3H), 7.71-7.65 (m, 1H), 7.07-7.00 (m, 1H), 6.57-6.53 (m, 1H), 5.84 (d, J =

16.7 Hz, 1H), 5.73 (s, 1H), 5.64 (d, J = 16.7 Hz, 1H), 3.59-3.57 (m, 1H), 3.45 (s, 3H), 3.39-3.37 (m, 1H), 3.33 (s, 3H), 3.16-3.09 (m, 1H), 2.70-2.68 (m, 2H), 2.08-2.06 (m, 1H), 1.80-1.78 (m, 2H), 1.60-1.58 (m, 1H).

MS (ESI+) 411(M^++1, 100%).

Example 14

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (brs, 3H), 5.91 (s, 1H), 5.08-4.89 (m, 2H), 3.35 (s, 3H), 3.35-3.28 (m, 2H), 3.21 (s, 3H), 2.99-2.89 (m, 3H), 1.95-1.91 (m, 2H), 1.76 (s, 3H), 1.67-1.63 (m, 2H).

MS (ESI+) 330(M^++1, 100%).

Example 15

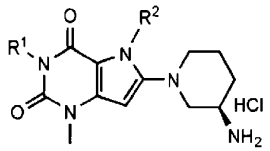
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (brs, 3H), 7.53-7.49 (m, 1H), 7.32-7.24 (m, 2H), 6.41-6.38 (m, 1H), 6.05 (s, 1H), 5.63 (s, 2H), 3.37 (s, 3H), 3.30-3.19 (m, 2H), 3.14 (s, 3H), 2.82-2.78 (m, 2H), 2.62-2.60 (m, 1H), 1.91-1.87 (m, 1H), 1.71-1.69 (m, 1H), 1.47-1.45 (m, 2H).

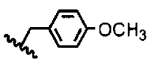
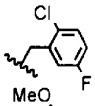
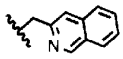
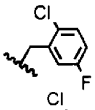
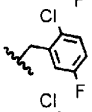
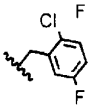
MS (ESI+) 411(M^++1, 100%).

[0177]

[Formula 78]

150



Example No.	R^1	R^2
Example 16		
Example 17	CH_3	
Example 18		
Example 19	$PhC(O)CH_2$	
Example 20	H	

[018]

Example 16

^{1}H NMR (400 MHz, CD_3OD) δ 7.47-7.43 (m, 1H), 7.22-7.19 (m, 2H), 7.04-7.01 (m, 1H), 6.79-6.75 (m, 2H), 6.18-6.15 (m, 1H), 6.03 (s, 1H), 5.56 (s, 2H), 5.01 (s, 2H), 3.73 (s, 3H), 3.47 (s, 3H), 3.40-2.73 (m, 5H), 2.12-1.52 (m, 4H).

MS (ESI+) 526 (M^++1, 100%).

Example 17

^{1}H NMR (400 MHz, CD_3OD) δ 7.49-7.43 (m, 1H), 7.32-7.27 (m, 1H), 7.18-7.15 (m, 1H), 7.08-7.03 (m, 1H), 5.91 (s, 1H), 3.50 (s, 3H), 3.40-3.30 (m, 1H), 3.12 (s, 3H), 3.11-3.00 (m, 2H), 2.80-2.66 (m, 2H), 2.01-1.92 (m, 1H),

1.68-1.59 (m, 1H), 1.50-1.30 (m, 2H).

MS (ESI+) 384 (M^++1, 100%).

Example 18

^{1}H NMR (400 MHz, CD_3OD) δ 8.58-8.56 (m, 1H), 8.36-8.33 (m, 1H), 8.25-8.17 (m, 2H), 8.12-8.07 (m, 1H), 7.90-7.84 (m, 1H), 7.46-7.42 (m, 1H), 7.05-6.99 (m, 1H), 6.27-6.23 (m, 1H), 6.13 (s, 1H), 5.93 (s, 2H), 5.56 (s, 2H), 3.50 (s, 3H), 3.40-3.30 (m, 2H), 3.01-2.92 (m, 2H), 2.89-2.77 (m, 1H), 2.10-2.03 (m, 1H), 1.92-1.81 (m, 1H), 1.75-1.53 (m, 2H).

MS (ESI+) 547 (M^++1, 100%).

Example 19

^{1}H NMR (400 MHz, CD_3OD) δ 8.04-8.01 (m, 2H), 7.67-7.63 (m, 1H), 7.54-7.50 (m, 2H), 7.44-7.40 (m, 1H), 7.03-6.98 (m, 1H), 6.24-6.20 (m, 1H), 6.11 (s, 1H), 5.56 (s, 2H), 5.39 (s, 2H), 3.51 (s, 3H), 3.40-3.30 (m, 2H), 3.00-2.91 (m, 2H), 2.85-2.79 (m, 1H), 2.10-2.02 (m, 1H), 1.90-1.80 (m, 1H), 1.72-1.53 (m, 2H).

MS (ESI+) 524 (M^++1, 100%).

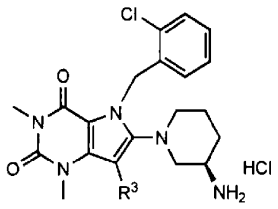
Example 20

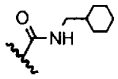
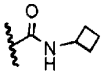
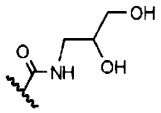
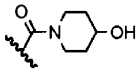
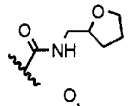
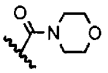
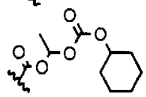
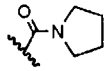
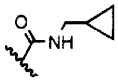
^{1}H NMR (400 MHz, CD_3OD) δ 7.48-7.44 (m, 1H), 7.06-7.01 (m, 1H), 6.22-6.19 (m, 1H), 6.07 (s, 1H), 5.55 (s, 2H), 3.45 (s, 3H), 3.40-3.28 (m, 2H), 3.00-2.92 (m, 2H), 2.85-2.77 (m, 1H), 2.11-2.01 (m, 1H), 1.90-1.81 (m, 1H), 1.82-1.53 (m, 2H).

MS (ESI+) 406 (M^++1, 100%).

[0179]

[Formula 79]



Example No.	R^3	Example No.	R^3
Example 21	$C(O)NH_2$	Example 30	
Example 22		Example 31	
Example 23	$C(O)OCH_3$	Example 32	
Example 24	$C(O)OCH_2CH_3$	Example 33	
Example 25	$C(O)N(CH_3)_2$	Example 34	
Example 26		Example 35	
Example 27			
Example 28			
Example 29			

[0180]

Example 21

^1H NMR (400 MHz, CD_3OD) δ 7.47-7.43 (m, 1H), 7.30-7.17 (m, 2H), 6.49-6.44 (m, 1H), 5.69 (s, 2H), 3.57 (s, 3H), 3.30 (s, 3H), 3.18-2.90 (m, 5H), 2.08-1.99 (m, 1H), 1.77-1.68 (m, 1H), 1.55-1.35 (m, 2H).

MS (ESI+) 445 (M^++1, 59%).

Example 22

^{1}H NMR (400 MHz, CD_3OD) δ 7.49-7.42 (m, 1H), 7.30-7.21 (m, 2H), 6.58-6.54 (m, 1H), 5.76 (s, 2H), 3.29 (s, 3H), 3.10-2.75 (m, 3H), 3.05 (s, 3H), 2.53-2.32 (m, 2H), 1.98-1.85 (m, 1H), 1.62-1.49 (m, 1H), 1.40-1.16 (m, 2H).

MS (ESI+) 470 (M^++1, 100%).

Example 23

^{1}H NMR (400 MHz, CD_3OD) δ 7.47-7.43 (m, 1H), 7.29-7.21 (m, 2H), 6.47-6.43 (m, 1H), 5.75 (s, 2H), 3.94 (s, 3H), 3.54 (s, 3H), 3.32 (s, 3H), 3.10-2.81 (m, 4H), 2.72-2.62 (m, 1H), 1.96-1.89 (m, 1H), 1.61-1.54 (m, 1H), 1.40-1.25 (m, 2H).

MS (ESI+) 460 (M^++1, 100%).

Example 24

^{1}H NMR (400 MHz, CD_3OD) δ 7.47-7.44 (m, 1H), 7.29-7.17 (m, 2H), 6.47-6.43 (m, 1H), 5.79-5.69 (m, 2H), 4.43-4.34 (m, 2H), 3.56 (s, 3H), 3.35 (s, 3H), 3.17-2.72 (m, 5H), 2.07-1.97 (m, 1H), 1.72-1.63 (m, 1H), 1.48-1.30 (m, 2H), 1.43-1.38 (m, 3H).

MS (ESI+) 474 (M^++1, 100%).

Example 25

^{1}H NMR (400 MHz, CD_3OD) δ 7.47-7.44 (m, 1H), 7.30-7.20 (m, 2H), 6.56-6.52 (m, 1H), 5.72-5.68 (m, 2H), 3.42 (s, 3H), 3.27 (s, 3H), 3.27-3.20 (m, 1H), 3.16-3.11 (m, 6H), 2.95-2.85 (m, 3H), 2.08-1.99 (m, 1H), 1.76-1.68 (m, 1H), 1.50-1.30 (m, 3H).

MS (ESI+) 473 (M^++1, 100%).

Example 26

^{1}H NMR (400 MHz, CD_3OD) δ 7.46-7.43 (m, 1H), 7.30-7.20 (m, 2H), 6.55-6.50 (m, 1H), 5.79-5.60 (m, 2H), 3.91-3.62 (m, 8H), 3.40 (s, 3H), 3.27 (s, 3H), 3.27-3.10 (m, 1H), 2.97-2.75 (m, 3H), 2.05-1.95 (m, 1H), 1.78-1.63 (m, 1H), 1.54-1.25 (m, 3H).

MS (ESI+) 515 (M^++1, 100%).

Example 27

^{1}H NMR (400 MHz, CD_3OD) δ 7.46-7.43 (m, 1H), 7.29-7.20 (m, 2H), 6.53-6.48 (m, 1H), 5.69 (s, 2H), 3.71-3.59 (m, 4H), 3.50-2.78 (m, 5H), 3.44 (s, 3H), 3.34-3.26 (m, 3H), 2.09-1.93 (m, 5H), 1.78-1.68 (m, 1H), 1.65-1.38 (m, 2H).

MS (ESI+) 499 (M^++1, 100%).

Example 28

^{1}H NMR (400 MHz, CD_3OD) δ 7.39-7.34 (m, 1H), 7.22-7.11 (m, 2H), 6.50-6.43 (m, 1H), 5.67-5.52 (m, 2H), 4.48-3.80 (m, 4H), 3.55-3.47 (m, 3H), 3.35 (s, 3H), 3.30-3.10 (m, 2H), 2.85-2.11 (m, 5H), 1.69-1.41 (m, 4H).

MS (ESI+) 485 (M^++1, 100%).

Example 29

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.36 (m, 1H), 7.21-7.10 (m, 2H), 6.46-6.42 (m, 1H), 5.69 (d, J= 17 Hz, 1H), 5.61 (d, J= 17 Hz, 1H), 3.58 (s, 3H), 3.35 (s, 3H), 3.32-3.27 (m, 2H), 3.08-3.03 (m, 1H), 2.91-2.83 (m, 2H), 2.78-2.60 (m, 2H), 1.85-1.16 (m, 4H), 1.10-1.02 (m, 1H), 0.61-0.56 (m, 2H), 0.31-0.27 (m, 2H).

MS (ESI+) 499 (M^++1, 100%).

Example 30

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (brs, 3H), 7.37-7.33 (m, 1H), 7.25-7.10 (m, 2H), 6.60 (brs, 1H), 6.52-6.42 (m, 1H), 5.72-5.50 (m, 2H), 3.56-3.42 (m, 1H), 3.49 (s, 3H), 3.40-3.13 (m, 4H), 3.32 (s, 3H), 2.88-2.72 (m, 2H), 2.12-1.98 (m, 1H), 1.96-0.99 (m, 15H).

MS (ESI+) 541 (M^++1, 100%).

Example 31

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70-8.33 (brs, 3H), 7.38-7.34 (m, 1H), 7.22-7.10 (m, 2H), 6.91-6.77 (brs, 1H), 6.43-6.36 (m, 1H), 5.74 (d, J= 16 Hz, 1H), 5.50 (d, J= 16 Hz, 1H), 4.51 (m, 1H), 3.49 (s, 3H), 3.32 (s, 3H), 3.28-3.18 (m, 2H), 2.83-2.74 (m, 2H), 2.53-2.30 (m, 2H), 2.09-1.90 (m, 3H), 1.81-1.60 (m, 6H).

MS (ESI+) 499 (M^++1, 100%).

Example 32

MS (ESI+) 519 (M^++1, 100%).

Example 33

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (brs, 3H), 7.39-7.33 (m, 1H), 7.23-7.13 (m, 2H), 6.60-6.53 (m, 1H), 5.74-5.52 (m, 2H), 4.47-2.53 (m, 11H), 3.50-3.31 (m, 6H), 2.20-1.22 (m, 8H).

MS (ESI+) 529 (M^++1, 100%).

Example 34

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 1H), 7.21-7.13 (m, 2H), 6.50-6.45 (m, 1H), 5.78-5.52 (m, 2H), 4.27-4.15 (m, 1H), 3.98-3.14 (m, 7H), 3.53-3.49 (m, 3H), 3.35-3.33 (m, 3H), 2.94-2.82 (m, 1H), 2.75-2.65 (m, 1H),

2.13-1.38 (m, 8H).

MS (ESI+) 529 (M^++1, 100%).

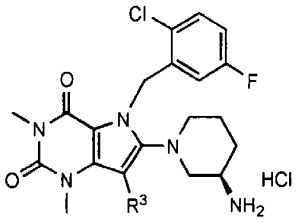
Example 35

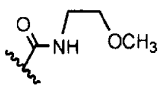
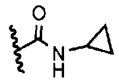
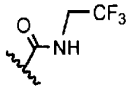
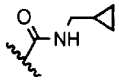
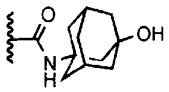
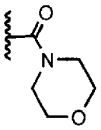
^{1}H NMR (400 MHz, CD_3OD) δ 7.51-7.45 (m, 1H), 7.31-7.18 (m, 2H), 7.03 (q, J= 5.4 Hz, 1H), 6.53-6.45 (m, 1H), 5.81-5.65 (m, 2H), 4.69-4.56 (m, 1H), 3.57 (s, 3H), 3.32 (s, 3H), 3.21-2.67 (m, 5H), 2.13-1.82 (m, 3H), 1.80-1.69 (m, 1H), 1.67 (d, J= 5.4 Hz, 3H), 1.66-1.22 (m, 10H).

MS (ESI+) 616 (M^++1, 45%).

[0181]

[Formula 80]



Example No.	R^3	Example No.	R^3
Example 36	$C(O)N(CH_3)_2$	Example 41	
Example 37	$C(O)NHCH_3$		
Example 38		Example 42	
Example 39		Example 43	
Example 40		Example 44	

[0182]

Example 36

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 1H), 7.00-6.90 (m, 1H), 6.32-6.25 (m, 1H), 5.63-5.50 (m, 2H), 3.53-3.28 (m, 3H), 3.45-3.33 (m, 6H), 3.28-3.03 (m, 6H), 2.82-2.65 (m, 2H), 2.21-2.10 (m, 1H), 1.81-1.40 (m, 3H).

MS (ESI+) 491 (M^++1, 100%).

Example 37

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (brs, 3H), 7.37-7.31 (m, 1H), 6.95-6.85 (m, 2H), 6.25-6.18 (m, 1H), 5.62 (d, J= 17 Hz, 1H), 5.46 (d, J= 17 Hz, 1H), 3.58-3.40 (m, 1H), 3.47 (s, 3H), 3.38-3.20 (m, 2H), 3.32 (s, 3H), 3.01 (s, 3H), 2.82-2.72 (m, 2H), 2.20-1.41 (m, 4H).

MS (ESI+) 477(M^++1, 100%).

Example 38

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (brs, 3H), 7.38-7.31 (m, 1H), 7.02 (brs, 1H), 6.93-6.87 (m, 1H), 6.25-6.13 (m, 1H), 5.63 (d, J= 17 Hz, 1H), 5.44 (d, J= 17 Hz, 1H), 3.61-3.53 (m, 1H), 3.45 (s, 3H), 3.31 (s, 3H), 3.38-3.20 (m, 2H), 3.03-2.95 (m, 1H), 2.83-2.73 (m, 2H), 2.23-1.62 (m, 4H), 0.93-0.83 (m, 2H), 0.74-0.58 (m, 2H).

MS (ESI+) 503 (M^++1, 100%).

Example 39

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (brs, 3H), 7.41-7.35 (m, 1H), 7.00-6.89 (m, 1H), 6.78 (brs, 1H), 6.30-6.16 (m, 1H), 5.78-5.62 (m, 1H), 5.49-5.38 (m, 1H), 3.59-3.21 (m, 5H), 3.52 (s, 3H), 3.33 (s, 3H), 2.88-2.71 (m, 2H), 2.21-1.45 (m, 4H), 1.16-1.04 (m, 1H), 0.65-0.49 (m, 2H),

0.38-0.25 (m, 2H).

MS (ESI+) 517 (M^++1, 100%).

Example 40

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (brs, 3H), 7.41-7.30 (m, 1H), 6.96-6.83 (m, 1H), 6.77 (brs, 1H), 6.28-6.10 (m, 1H), 5.75-5.33 (m, 2H), 4.59-4.42 (m, 1H), 3.49 (s, 3H), 3.40-3.19 (m, 2H), 3.33 (s, 3H), 2.84-2.66 (m, 2H), 2.54-2.33 (m, 2H), 2.22-1.91 (m, 3H), 1.87-1.50 (m, 6H).

MS (ESI+) 517 (M^++1, 100%).

Example 41

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (brs, 3H), 7.37-7.33 (m, 1H), 6.93-6.89 (m, 2H), 6.30-6.23 (m, 1H), 5.64 (d, J= 17 Hz, 1H), 5.45 (d, J= 17 Hz, 1H), 3.79-3.58 (m, 4H), 3.55-3.22 (m, 3H), 3.51 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H), 2.89-2.69 (m, 2H), 2.18-1.43 (m, 4H).

MS (ESI+) 521 (M^++1, 100%).

Example 42

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (brs, 3H), 7.51 (brs, 1H), 7.41-7.29 (m, 1H), 6.95-6.83 (m, 1H), 6.21-6.11 (m, 1H), 5.67 (d, J= 17 Hz, 1H), 5.44 (d, J= 17 Hz, 1H), 4.31-3.97 (m, 2H), 3.51-3.12 (m, 3H), 3.45 (s, 3H), 3.29 (s, 3H), 2.82-2.69 (m, 2H), 2.11-1.35 (m, 4H).

MS (ESI+) 545 (M^++1, 100%).

Example 43

^{1}H NMR (400 MHz, CD_3OD) δ 7.49-7.44 (m, 1H), 7.08-7.00 (m, 1H), 6.29-6.24 (m, 1H), 5.64 (d, J= 17 Hz, 1H), 5.58 (d, J= 17Hz, 1H), 3.57 (s, 3H), 3.30 (s, 3H), 2.30-1.25 (m, 23H).

MS (ESI+) 613 (M^++1, 100%).

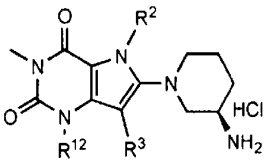
Example 44

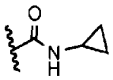
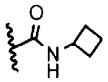
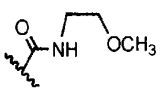
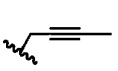
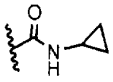
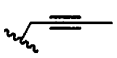
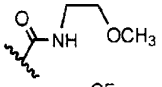
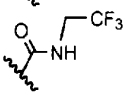
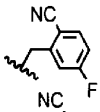
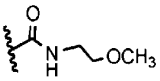
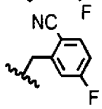
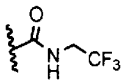
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.33 (m, 1H), 6.97-6.89 (m, 1H), 6.33-6.24 (m, 1H), 5.72-5.49 (m, 2H), 4.00-3.62 (m, 8H), 3.50-3.34 (m, 6H), 3.45-2.62 (m, 5H), 2.19-1.49 (m, 4H).

MS (ESI+) 533 (M^++1, 100%).

[0183]

[Formula 81]



Examole No.	R^{12}	R^2	R^3
Example 45	CH_3		
Example 46	CH_3		
Example 47	CH_3		
Example 48	CH_3		
Example 49	CH_3		
Example 50	CH_3		
Example 51	CH_3		
Example 52	CH_3		

[0184]

Example 45

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (d, J = 4.0 Hz, 1H), 8.04 (brs, 3H), 7.88 (d, J = 7.5 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 6.62 (d, J = 7.5

Hz, 1H), 5.69 (d, J = 16.3 Hz, 1H), 5.59 (d, J = 16.3 Hz, 1H), 3.36 (s, 3H), 3.24-3.19 (m, 1H), 3.15 (s, 3H), 2.94-2.73 (m, 4H), 1.92-1.90 (m, 1H), 1.70-1.67 (m, 1H), 1.46-1.23 (m, 3H), 0.74-0.68 (m, 2H), 0.58-0.53 (m, 2H).

MS (ESI+) 476(M^++1, 100%).

Example 46

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.96 (d, J = 7.5 Hz, 1H), 7.99 (brs, 3H), 7.90-7.87 (m, 1H), 7.61 (m, 1H), 7.45 (t, J = 7.4 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 5.70 (d, J = 16.5 Hz, 1H), 5.59 (d, J = 16.5 Hz, 1H), 4.39-4.31 (m, 1H), 3.37 (s, 3H), 3.26-3.19 (m, 1H), 3.15 (s, 3H), 2.92-2.83 (m, 3H), 2.26-2.23 (m, 2H), 2.03-1.87 (m, 3H), 1.74-1.62 (m, 3H), 1.42-1.23 (m, 3H).

MS (ESI+) 490(M^++1, 100%).

Example 47

^{1}H NMR (400 MHz, CD_3OD) δ 7.76-7.73 (m, 1H), 7.57-7.52 (m, 1H), 7.44-7.38 (m, 1H), 6.76-6.72 (m, 1H), 5.81 (d, J= 17 Hz, 1H), 5.73 (d, J= 17 Hz, 1H), 3.60-3.53 (m, 4H), 3.53 (s, 3H), 3.38 (s, 3H), 3.28 (s, 3H), 3.14-3.11 (m, 1H), 2.92-2.85 (m, 2H), 2.76-2.68 (m, 2H), 1.99-1.84 (m, 1H), 1.78-1.59 (m, 1H), 1.51-1.13 (m, 2H).

MS (ESI+) 494 (M^++1, 100%).

Example 48

^{1}H NMR (400 MHz, CD_3OD) δ 5.16-5.01 (m, 2H), 3.47-3.41 (m, 2H), 3.44 (s, 3H), 3.34 (s, 3H), 3.29-3.22 (m, 1H), 3.12-3.03 (m, 2H), 2.94-2.87 (m, 1H), 2.17-1.77 (m, 3H), 1.77-1.73 (m, 3H), 1.64-1.50 (m, 1H), 0.87-0.79 (m, 2H), 0.64-0.58 (m, 2H).

MS (ESI+) 413 (M^++1, 100%).

Example 49

^{1}H NMR (400 MHz, CD_3OD) δ 5.15-5.02 (m, 2H), 3.60-3.52 (m, 4H), 3.48-3.06 (m, 5H), 3.47 (s, 3H), 3.37 (s, 3H), 3.34 (s, 3H), 2.14-2.05 (m, 1H), 1.96-1.78 (m, 3H), 1.76-1.73 (m, 3H), 1.66-1.55 (m, 1H).

MS (ESI+) 431 (M^++1, 100%).

Example 50

^{1}H NMR (400 MHz, CD_3OD) δ 7.80-7.75 (m, 1H), 7.60-7.53 (m, 1H), 7.47-7.41 (m, 1H), 6.83-6.78 (m, 1H), 5.87 (d, J= 17 Hz, 1H), 5.73 (d, J= 17 Hz, 1H), 4.21-4.07 (m, 2H), 3.47 (s, 3H), 3.30 (s, 3H), 3.25-2.76 (m, 5H), 2.11-1.98 (m, 1H), 1.78-1.35 (m, 3H).

MS (ESI+) 518 (M^++1, 100%).

Example 51

^{1}H NMR (400 MHz, CD_3OD) δ 7.90-7.86 (m, 1H), 7.26-7.19 (m, 1H), 6.59-6.55 (m, 1H), 5.84 (d, J= 17 Hz, 1H), 5.73 (d, J= 17 Hz, 1H), 3.65-3.55 (m, 4H), 3.53 (s, 3H), 3.41 (s, 3H), 3.37 (s, 3H), 3.14-2.76 (m, 5H), 2.11-2.01 (m, 1H), 1.81-1.71 (m, 1H), 1.61-1.38 (m, 2H).

MS (ESI+) 512 (M^++1, 100%).

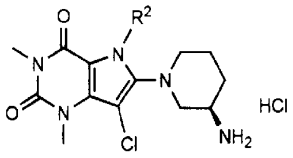
Example 52

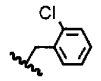
^{1}H NMR (400 MHz, CD_3OD) δ 7.92-7.85 (m, 1H), 7.27-7.20 (m, 1H), 6.60-6.53 (m, 1H), 5.87 (d, J= 17 Hz, 1H), 5.74 (d, J= 17 Hz, 1H), 4.23-4.10 (m, 2H), 3.49 (s, 3H), 3.40-2.82 (m, 5H), 3.30 (s, 3H), 2.12-2.02 (m, 1H), 1.71-1.37 (m, 3H).

MS (ESI+) 536 (M^++1, 100%).

[0185]

[Formula 82]



Example No.	R^2
Example 53	
Example 54	

[0186]

Example 53

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (bs, 3H), 7.51-7.48 (m, 1H), 7.32-7.21 (m, 2H), 6.43 (d, J = 6.8 Hz, 1H), 5.63 (d, J = 16.6 Hz, 1H), 5.55 (d, J = 16.6 Hz, 1H), 3.66 (s, 3H), 3.36-3.16 (m, 2H), 3.16 (s, 3H), 2.96-2.72 (m, 3H), 1.92-1.90 (m, 1H), 1.62-1.60 (m, 1H), 1.25-1.22 (m, 2H).

MS (ESI+) 436(M^++1, 100%).

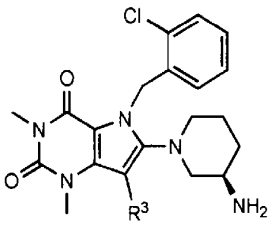
Example 54

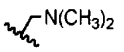
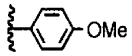
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (bs, 3H), 7.87 (d, J = 6.8 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 6.78-6.76 (m, 1H), 5.74 (d, J = 16.4 Hz, 1H), 5.63 (d, J = 16.4 Hz, 1H), 3.64 (s, 3H), 3.22-3.18 (m, 2H), 3.15 (s, 3H), 3.01-2.95 (m, 2H), 2.68-2.66 (m, 1H), 1.96-1.92 (m, 1H), 1.63-1.61 (m, 1H), 1.41-1.32 (m, 2H).

MS (ESI+) 427(M^++1, 100%).

[0187]

[Formula 83]



Example No.	R^3	Salt
Example 55		2 HCl
Example 56	CH_2OCH_3	HCl
Example 57	Br	CF_3CO_2H
Example 58	F	CF_3CO_2H
Example 59	CH_3	HCl
Example 60	CHO	CF_3CO_2H
Example 61	$CH_3C(O)$	CF_3CO_2H
Example 62		CF_3CO_2H

[0188]

Example 55

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01-9.87 (m, 1H), 8.35-8.17 (m, 3H), 7.51 (d, J = 7.7 Hz, 1H), 7.32-7.18 (m, 2H), 6.34-6.21 (m, 1H), 5.65-5.56 (m, 2H), 4.42-4.26 (m, 2H), 3.67 (s, 3H), 3.55-3.36 (m, 2H), 3.15 (s, 3H), 2.91-2.60 (m, 3H), 2.79 (s, 6H), 2.01-1.49 (m, 4H).

MS (ESI+) 458(M^++1, 56%).

Example 56

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 (brs, 3H), 7.49 (d, J = 7.5 Hz, 1H), 7.31-7.22 (m, 2H), 6.31-6.28 (m, 1H), 5.63-5.53 (m, 2H), 4.55-4.51 (m, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 3.50-3.47 (m, 1H), 3.17 (s, 3H), 3.08-3.05 (m, 1H), 2.79-2.75 (m, 3H), 1.94-1.91 (m, 1H), 1.56-1.35 (m, 3H).

MS (ESI+) 446(M^++1, 10%).

Example 57

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (brs, 3H), 7.44-7.36 (m, 1H), 7.18-7.04 (m, 2H), 6.44-6.39 (m, 1H), 5.68 (s, 2H), 3.83 (s, 3H), 3.46-3.60 (m, 1H), 3.37 (s, 3H), 3.22-3.04 (m, 3H), 2.70-2.64 (m, 1H), 2.12-1.94 (m, 1H), 1.68-1.42 (m, 3H).

MS (ESI+) 482(M^++1, 48%).

Example 58

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.37 (m, 1H), 7.20-7.16 (m, 2H), 6.51-6.48 (m, 1H), 5.79 (d, J = 16.5 Hz, 1H), 5.57 (d, J = 16.5 Hz, 1H), 3.62 (s, 3H), 3.46-3.44 (m, 1H), 3.37 (s, 3H), 3.34-3.32 (m, 1H), 3.14-3.09 (m, 1H), 2.87-2.85 (m, 2H), 1.86-1.62 (m, 4H).

MS (ESI+) 420(M^++1, 61%).

Example 59

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (brs, 3H), 7.50-7.47 (m, 1H), 7.29-7.19 (m, 2H), 6.30-6.28 (m, 1H), 5.58 (d, J = 16.1 Hz, 1H), 5.49 (d, J = 16.1 Hz, 1H), 3.61 (s, 3H), 3.16 (s, 3H), 3.07-3.04 (m, 2H), 2.91-2.65 (m, 3H), 2.31 (s, 3H), 1.93-1.90 (m, 1H), 1.57-1.54 (m, 1H),

1.25-1.15 (m, 2H).

MS (ESI+) 416(M^++1, 100%).

Example 60

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.51 (brs, 3H), 7.38-7.35 (m, 1H), 7.24-7.11 (m, 2H), 6.44 (d, J = 6.2 Hz, 1H), 5.73-5.69 (m, 2H), 3.79 (s, 3H), 3.49-3.44 (m, 1H), 3.39 (s, 3H), 3.23-3.20 (m, 1H), 3.03-2.78 (m, 3H), 1.90-1.55 (m, 4H).

MS (ESI+) 430(M^++1, 85%).

Example 61

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (brs, 3H), 7.39-7.36 (m, 1H), 7.21-7.13 (m, 2H), 6.38 (d, J = 7.5 Hz, 1H), 5.70 (s, 2H), 3.44 (s, 3H), 3.37 (s, 3H), 3.31-3.27 (m, 1H), 3.20-3.17 (m, 2H), 3.06-2.94 (m, 2H), 2.53 (s, 3H), 2.15-1.85 (m, 2H), 1.65-1.54 (m, 2H).

MS (ESI+) 444(M^++1, 100%).

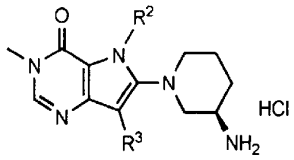
Example 62

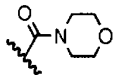
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.36 (m, 1H), 7.26-7.19 (m, 4H), 6.96-6.89 (m, 2H), 6.52-6.49 (m, 1H), 6.66-5.52 (m, 2H), 3.84 (s, 3H), 3.39 (s, 3H), 3.19-3.15 (m, 1H), 3.09 (s, 3H), 3.04-2.46 (m, 4H), 1.80-1.40 (m, 4H).

MS (ESI+) 508(M^++1, 100%).

[0189]

[Formula 84]



Example No.	R^2	R^3
Example 63		CN
Example 64		H
Example 65		$C(O)N(CH_3)_2$
Example 66		

[0190]

Example 63

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.31 (brs, 3H), 7.50 (d, J = 6.6 Hz, 1H), 7.33-7.21 (m, 2H), 6.49 (d, J = 6.6 Hz, 1H), 5.64 (d, J = 17.0 Hz, 1H), 5.56 (d, J = 17.0 Hz, 1H), 3.56-3.54 (m, 1H), 3.42 (s, 3H), 3.26-3.19 (m, 1H), 3.08-2.87 (m, 3H), 1.96-1.93 (m, 1H), 1.75-1.72 (m, 1H), 1.52-1.43 (m, 2H).

MS (ESI+) 397(M^++1, 100%).

Example 64

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.21 (brs, 3H), 7.58-7.53 (m, 1H), 7.20-7.13 (m, 1H), 6.19 (s, 1H), 6.05-6.01 (m, 1H), 5.60 (d, J = 16.8 Hz, 1H), 5.52 (d, J = 16.8 Hz, 1H), 3.42 (s, 3H), 3.31-3.16 (m, 2H),

2.91-2.84 (m, 2H), 2.73-2.67 (m, 1H), 1.92-1.79 (m, 2H), 1.55-1.47 (m, 2H).

MS (ESI+) 390(M^++1, 100%).

Example 65

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (brs, 4H), 7.57-7.52 (m, 1H), 7.19-7.12 (m, 1H), 6.14-6.09 (m, 1H), 5.60 (d, J = 17.0 Hz, 1H), 5.53 (d, J = 17.0 Hz, 1H), 3.42 (s, 3H), 3.23-3.21 (m, 1H), 3.01 (s, 3H), 3.00 (s, 3H), 2.96-2.94 (m, 2H), 2.79-2.76 (m, 2H), 1.90-1.88 (m, 1H), 1.70-1.67 (m, 1H), 1.35-1.30 (m, 2H).

MS (ESI+) 461(M^++1, 100%).

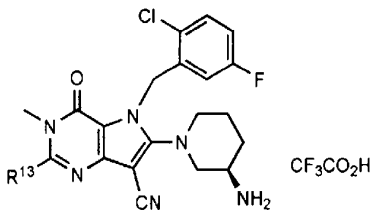
Example 66

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.19 (brs, 3H), 7.58-7.53 (m, 1H), 7.20-7.13 (m, 1H), 6.19-6.15 (m, 1H), 5.56 (s, 2H), 3.69-3.55 (m, 6H), 3.48-3.41 (m, 2H), 3.41 (s, 3H), 3.22-3.17 (m, 1H), 3.00-2.96 (m, 2H), 2.81-2.79 (m, 2H), 1.90-1.88 (m, 1H), 1.69-1.67 (m, 1H), 1.35-1.33 (m, 2H).

MS (ESI+) 503(M^++1, 100%).

[0191]

[Formula 85]



Example No.	R^{13}
Example 67	SO_2Me
Example 68	$C(O)NH_2$
Example 69	CN

[0192]

Example 67

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (brs, 3H), 7.61-7.56 (m, 1H), 7.24-7.18 (m, 1H), 6.65-6.61 (m, 1H), 5.55 (s, 2H), 3.69 (s, 3H), 3.64 (s, 3H), 3.53-3.50 (m, 1H), 3.27-3.17 (m, 2H), 3.08-3.03 (m, 1H), 2.96-2.93 (m, 1H), 1.97-1.95 (m, 1H), 1.78-1.75 (m, 1H), 1.49-1.45 (m, 2H).

MS (ESI+) 493(M^++1, 100%).

Example 68

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.21 (s, 1H), 7.99 (brs, 3H), 7.61-7.56 (m, 1H), 7.25-7.17 (m, 1H), 6.48-6.44 (m, 1H), 5.54 (s, 2H), 3.54-3.51 (m, 1H), 3.42 (s, 3H), 3.27-3.21 (m, 2H), 3.11-3.07 (m, 1H), 2.97-2.94 (m, 1H), 1.97-1.95 (m, 1H), 1.79-1.77 (m, 1H), 1.51-1.47 (m, 2H).

MS (ESI+) 458(M^++1, 100%).

Example 69

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03 (brs, 3H), 7.61-7.55 (m,

1H), 7.24-7.17 (m, 1H), 6.54-6.50 (m, 1H), 5.54 (s, 2H), 3.59 (s, 3H), 3.55-3.53 (m, 1H), 3.29-3.22 (m, 2H), 3.12-3.08 (m, 1H), 2.95-2.93 (m, 1H), 1.96-1.94 (m, 1H), 1.79-1.77 (m, 1H), 1.49-1.47 (m, 2H).

MS (ESI+) 440(M^++1, 100%).

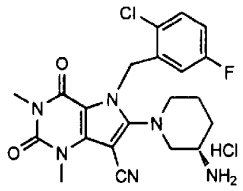
[0193]

Example 70

6-[(3S)-3-Aminopiperidin-1-yl]-5-(2-chloro-5-fluorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile hydrochloride

[0194]

[Formula 86]



MS (ESI+) 445 (M^++1, 100%).

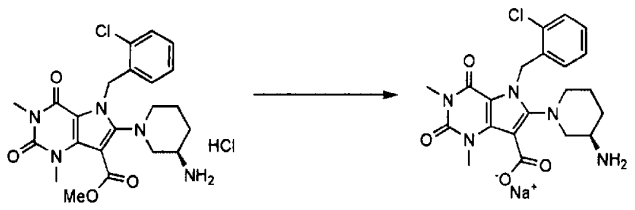
[0195]

Example 71

Sodium 6-[(3R)-3-aminopiperidin-1-yl]-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

[0196]

[Formula 87]



A 1N aqueous sodium hydroxide solution (1 ml), ethanol (1 ml) and tetrahydrofuran (1 ml) were added to methyl 6-[(3R)-3-aminopiperidin-1-yl]-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate hydrochloride (53 mg), and the resulting mixture was stirred at 80°C for 3 hours. After the reaction solution was cooled to 25°C, water was added thereto, followed by washing with ethyl acetate, and the aqueous layer was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered and the filtrate was concentrated under reduced pressure to obtain the title compound (41 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δppm 7.41-7.38 (m, 1H), 7.22-7.13 (m, 2H), 6.42-6.38 (m, 1H), 5.67 (d, J= 17 Hz, 1H), 5.58 (d, J= 17 Hz, 1H), 3.65 (s, 3H), 3.27 (s, 3H), 3.20-3.13 (m, 1H), 3.05-2.95 (m, 1H), 2.93-2.85 (m, 1H), 2.83-2.75 (m, 1H), 2.64-2.54 (m, 1H), 1.83-1.73 (m, 1H), 1.64-1.52 (m, 1H), 1.40-1.25 (m, 2H).

MS (ESI+) 445 (M^++1, 100%).

[0197]

The compound of Example 72 was synthesized from a corresponding compound according to the process described in Example 1.

[0198]

Example 72

Ethyl 3-amino-5-[(3R)-3-aminopiperidin-1-yl]-1-(2-chlorobenzyl)-4-cyano-1H-pyrrole-2-carboxylate hydrochloride

[0199]

[Formula 88]

MS (ESI+) 402 (M^++1, 100%).

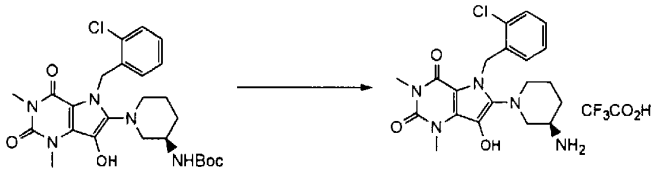
[0200]

Example 73

6-[(3R)-3-Aminopiperidin-1-yl]-5-(2-chlorobenzyl)-7-hydroxy-1,3-dimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H, 5H)dione trifluoroacetate

[0201]

[Formula 89]



Trifluoroacetic acid (1.5 ml) was added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-hydroxy-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (54 g) in chloroform (1 ml), and the resulting mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure to obtain the title compound (45 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δppm 8.27 (s, 1H), 7.90 (brs, 3H), 7.49-7.45 (m, 1H), 7.28-7.18 (m, 2H), 6.29-6.26 (m, 1H), 5.48 (s, 2H), 3.60 (s, 3H), 3.18-3.08 (m, 2H), 3.14 (s, 3H), 2.98-2.72 (m, 3H), 1.87-1.85 (m, 1H), 1.66-1.64 (m, 1H), 1.33-1.31 (m, 2H).

MS (ESI+) 418(M^++1, 100%).

[0202]

Example 74

Methyl 6-[(3R)-3-aminopiperidin-1-yl]-5-(2-chloro-5-fluorobenzyl)-7-cyano-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-2-carboxylate

[0203]

[Formula 90]

Methyl cyanoformate (170 µl) was added to a solution of ethyl 3-amino-5-{(3R)-3-[(tert-

butoxycarbonyl}amino]piperidin-1-yl}-1-(2-chloro-5-fluorobenzyl)-4-cyano-1H-pyrrole-2-carboxylate (104 mg) in hydrochloric acid-methanol reagent 10 (4 ml), and the resulting mixture was stirred with heating at 90°C in a sealed tube for 15 hours. The reaction solution was concentrated under reduced pressure and chloroform was added to the residue. The solid precipitated was removed by filtration and the filtrate was concentrated under reduced pressure. To the resulting residue was added diethyl ether, and the solid precipitated was collected by filtration to obtain a crude product of the title compound (107 mg).

MS (ESI+) 459 (M^++1, 13%).

[0204]

Each of the compounds of Examples 75 and 76 was synthesized from a corresponding compound according to the process described in Example 1.

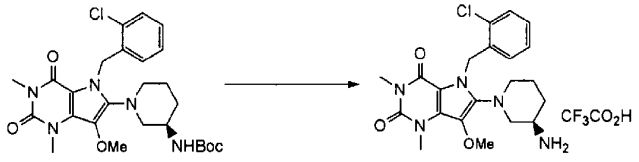
[0205]

Example 75

6-[(3R)-3-Aminopiperidin-1-yl]-5-(2-chlorobenzyl)-7-methoxy-1,3-dimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione trifluoroacetate

[0206]

[Formula 91]



^{1}H NMR (300 MHz, $CDCl_3$) δppm 7.40-7.37 (m, 1H), 7.22-7.12 (m, 2H), 6.39-6.36 (m, 1H), 5.84 (d, J = 17.4 Hz, 1H), 5.49 (d, J = 17.4 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.42-3.33 (m, 2H), 3.37 (s, 3H), 3.13-3.10 (m, 1H), 2.96-2.88 (m, 2H), 1.87-1.64 (m, 4H).

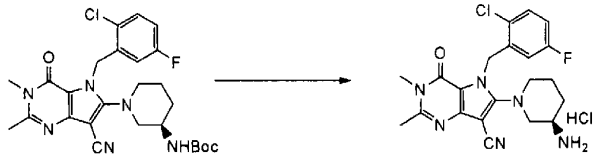
MS (ESI+) 432(M^++1, 100%).

Example 76

6-[(3R)-3-Aminopiperidin-1-yl]-5-(2-chloro-5-fluorobenzyl)-2,3-dimethyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

[0207]

[Formula 92]



^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (brs, 3H), 7.57-7.53 (m, 1H), 7.21-7.14 (m, 1H), 6.39-6.34 (m, 1H), 5.54 (d, J = 17.4 Hz, 1H), 5.48 (d, J = 17.4 Hz, 1H), 3.47-3.44 (m, 1H), 3.40 (s, 3H), 3.25-3.15 (m, 2H), 3.05-3.01 (m, 1H), 2.94-2.87 (m, 1H), 2.53 (s, 3H), 1.94-1.92 (m, 1H), 1.79-1.77 (m, 1H), 1.52-1.48 (m, 2H).

MS (ESI+) 429(M^++1, 100%).

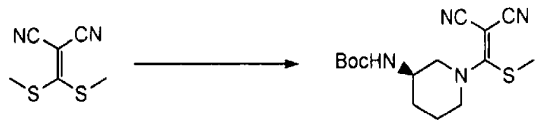
[0208]

Reference Example 1

tert-Butyl {(3R)-1-[2,2-dicyano-1-(methylthio)vinyl]piperidin-3-yl}carbamate

[0209]

[Formula 93]



A solution of [bis(methylthio)methylene]-propanedinitrile (10 g) and (R)-tert-3-butyl piperidin-3-ylcarbamate (11.8 g) in ethanol (350 ml) was stirred at 80°C for 3 hours, and the reaction solution was cooled to 25°C and then concentrated under reduced pressure to obtain the title compound (19 g) as a light-yellow amorphous substance.

^{1}H NMR (400 MHz, $CDCl_3$) δppm 4.60-4.48 (m, 1H), 4.18-4.03 (m, 1H), 3.94-3.80 (m,1H), 3.77-3.61 (m, 1H), 3.59-3.35 (m, 2H), 2.61 (s, 3H), 2.12-2.00 (m, 1H), 1.98-1.86 (m, 1H), 1.82-1.68 (m, 1H), 1.68-1.50 (m, 1H), 1.46 (s, 9H).

MS (ESI+) 323 (M^++1, 40%).

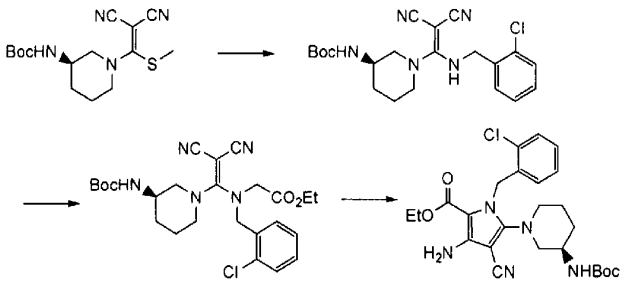
[0210]

Reference Example 2

Ethyl 3-amino-5-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-4-cyano-1H-pyrrole-2-carboxylate

[0211]

[Formula 94]



2-Chlorobenzylamine (1.7 ml) was added to a solution of tert-butyl {(3R)-1-[2,2-dicyano-1-(methylthio)vinyl]piperidin-3-yl}carbamate (15 g) in isopropanol (28 ml), and the resulting mixture was heated under reflux. After 5 hours, 2-chlorobenzylamine (2.8 ml) was added thereto, followed by heating under reflux for another 10 hours. The reaction solution was cooled to 25°C and then concentrated under reduced pressure, and the resulting residue was roughly purified by a silica gel column chromatography (hexane / ethyl acetate = 5/1 to 1/1). The reaction mixture (9.82 g) thus obtained was dissolved in acetone (90 ml), followed by adding thereto potassium carbonate (6.2 g) and ethyl bromoacetate (1.5 ml), and the resulting mixture was stirred at 60°C for 3 hours. The reaction solution was cooled to 25°C and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered

and the filtrate was concentrated under reduced pressure. The resulting residue (7.53 g) was dissolved in tetrahydrofuran (150 ml) and the resulting solution was cooled to 0°C. Then, sodium hydride (60%, 780 mg) was added thereto and the resulting mixture was stirred for 1 hour while being slowly warmed to 25°C. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and concentrated under reduced pressure, and the resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 2/1 to 1/1) to obtain the title compound (2.7 g) as a white amorphous substance.

MS (ESI+) 502 (M^++1, 100%).

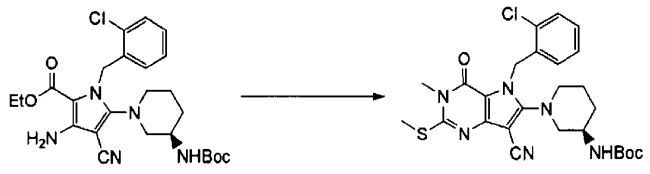
[0212]

Reference Example 3

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-3-methyl-2-(methylthio)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0213]

[Formula 95]



Under a nitrogen atmosphere, methyl isothiocyanate (71 µl) and potassium carbonate (143 mg) were added to a solution (2.5 ml) of ethyl 3-amino-5-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-4-cyano-1H-pyrrole-2-carboxylate (260 mg) in pyridine, and the resulting mixture was stirred with heating at 130°C for 3 hours. After the reaction solution was cooled to 25°C and then concentrated under reduced pressure, toluene (5 ml) was added thereto and the resulting mixture was concentrated under reduced pressure. This procedure was repeated three times. To the resulting residue was added acetone (2.5 ml), and the resulting mixture was cooled to 0°C. Methyl iodide (65 µl) was added dropwise thereto and the resulting mixture was warmed to 25°C and stirred for 4 hours. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 5/1 to 1/1) to obtain the title compound (250 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 1H), 7.23-7.08 (m, 2H), 6.49-6.40 (m, 1H), 5.71 (d, J= 17.0 Hz, 1H), 5.61 (d, J= 17.0 Hz, 1H), 3.80-3.69 (m, 1H), 3.52 (s, 3H), 3.50-3.42 (m, 1H), 3.04-2.91 (m, 3H), 2.68 (s, 3H), 1.88-1.76 (m, 1H), 1.74-1.50 (m, 3H), 1.42 (s, 9H).

MS (ESI+) 543 (M^++1, 100%).

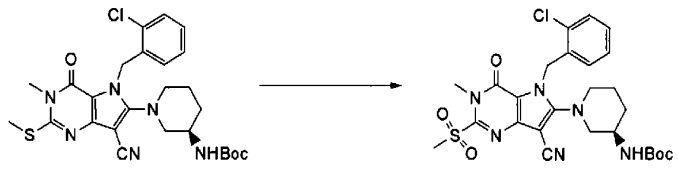
[0214]

Reference Example 4

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-3-methyl-2-(methylsulfonyl)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0215]

[Formula 96]



Sodium tungstate dihydrate (139 mg) was added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-3-methyl-2-(methylthio)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (230 mg) in a mixture of methanol (2 ml), acetic acid (0.7 ml) and water (0.25 ml), and the resulting mixture was heated to 50°C. A 30% aqueous hydrogen peroxide solution (0.29 ml) was added dropwise thereto, followed by stirring at 60°C for 4 hours. After the reaction mixture was allowed to cool, the precipitate formed was collected by filtration, washed with water and then dried under reduced pressure to obtain the title compound (230 mg) as a white solid.

MS (ESI+) 575 (M^++1, 46%).

[0216]

Reference Example 5

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-2-hydroxy-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0217]

[Formula 97]

To a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-3-methyl-2-(methylsulfonyl)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (100 mg) in ethanol (1 ml) was added 1N sodium hydroxide (1 ml), and the resulting mixture was stirred at 80°C for 5 hours. After the reaction solution was allowed to cool, a saturated aqueous ammonium chloride solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (81 mg) as a white solid.

MS (ESI+) 513 (M^++1, 40%).

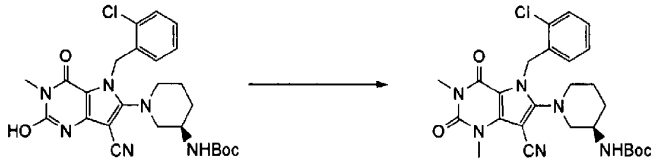
[0218]

Reference Example 6

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0219]

[Formula 98]



Potassium carbonate (700 mg) and methyl iodide (0.34 ml) were added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-2-hydroxy-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (1.3 g) in N,N-dimethylformamide, and the resulting mixture was stirred at 25°C for 4 hours. After the reaction, water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (1.1 g) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 1H), 7.25-7.13 (m, 2H), 6.56-6.48 (m, 1H), 5.69 (d, J = 16.5 Hz, 1H), 5.59 (d, J = 16.5 Hz, 1H), 3.76 (s, 3H), 3.75-3.65 (m, 1H), 3.50-3.41 (m, 1H), 3.35 (s, 3H), 3.01-2.84 (m, 3H), 1.89-1.78 (m, 1H), 1.69-1.45 (m, 3H), 1.42 (s, 9H).

MS (ESI+) 527 (M^++1, 100%).

[0220]

Reference Example 7

N-(1-{(3R)-3-[(tert-Butoxycarbonyl)amino]-piperidin-1-yl}-2,2-dicyanovinyl)glycine ethyl ester

[0221]

[Formula 99]

Glycine methyl ester hydrochloride (3.3 g) and triethylamine (3.7 ml) were added to a solution of tert-butyl {(3R)-1-[2,2-dicyano-1-(methylthio)vinyl]-piperidin-3-yl}carbamate (1.3 g) in ethanol (30 ml), and the resulting mixture was heated under reflux. After 4 hours, triethylamine (1.5 ml) was added thereto, followed by heating under reflux for another 7 hours. After the reaction solution was cooled to 25°C, a saturated aqueous sodium hydrogencarbonate solution was added thereto, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and

then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 3/1 to 1/1) to obtain the title compound (360 mg) as a white amorphous substance.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (brs, 1H), 4.58 (brd, 1H), 4.27 (q, J= 7.1 Hz, 2H), 4.15 (dd, J= 1.0, 5.2 Hz, 2H), 3.84-3.79 (m, 1H), 3.69-3.58 (m, 2H), 3.40-3.30 (m, 1H), 3.28-3.18 (m, 1H), 2.05-1.95 (m, 1H), 1.89-1.79 (m, 1H), 1.74-1.63 (m, 1H), 1.60-1.49 (m, 1H), 1.45 (s, 9H) 1.32 (t, J= 7.1 Hz, 3H).

MS (ESI+) 378 (M^++1, 10%).

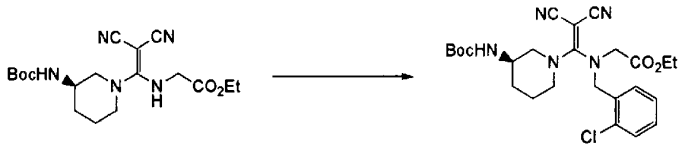
[0222]

Reference Example 8

N-{1-{(3R)-3-[(tert-Butoxycarbonyl)amino]-piperidin-1-yl}-2,2-dicyanovinyl)-N-(2-chlorobenzyl)glycine ethyl ester

[0223]

[Formula 100]



A solution of N-(1-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-2,2-dicyanovinyl)glycine ethyl ester (300 mg), 2-chlorobenzyl bromide (0.15 ml) and potassium carbonate (330 mg) in acetone (4 ml) was stirred at 25°C for 24

hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with an aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 5/1 to 1/1) to obtain the title compound (340 mg) as a white amorphous substance.

MS (ESI+) 502 (M^++1, 25%).

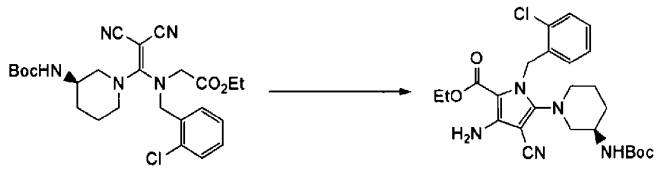
[0224]

Reference Example 9

Ethyl 3-amino-5-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-4-cyano-1H-pyrrole-2-carboxylate

[0225]

[Formula 101]



A solution of N-(1-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-2,2-dicyanovinyl)-N-(2-chlorobenzyl)glycine ethyl ester (320 mg) in tetrahydrofuran (5 ml) was cooled to 0°C, followed by adding thereto sodium hydride (33 mg), and the resulting mixture was stirred for 1 hour while being

warmed to 25°C. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 3/1 to 1/1) to obtain the title compound (300 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 1H), 7.21-7.09 (m, 2H), 6.57-6.49 (m, 1H), 5.47-5.30 (m, 2H), 4.07 (q, J = 7.0 Hz, 2H), 3.76-3.64 (m, 1H), 3.40-3.30 (m, 1H), 3.00-2.82 (m, 3H), 1.87-1.74 (m, 1H), 1.72-1.46 (m, 3H), 1.41 (s, 9H), 1.07 (t, J= 7.0 Hz, 3H).

MS (ESI+) 502 (M^++1, 29%).

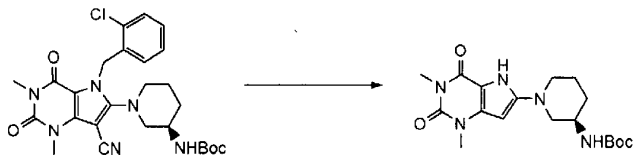
[0226]

Reference Example 10

tert-Butyl [(3R)-1-(1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl)piperidin-3-yl]carbamate

[0227]

[Formula 102]



Under ice-cooling, water (2 ml) and

concentrated sulfuric acid (4 ml) were added to tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (300 mg), and the resulting mixture was stirred at 140°C. After 3 hours, the reaction solution was cooled to 0°C and adjusted to pH 8 or higher by dropwise addition of a 5N aqueous potassium carbonate solution. The reaction solution was extracted with chloroform and the organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered, and the filtrate was concentrated under reduced pressure. To the resulting residue were added di-tert-butyl dicarbonate (372 mg), 1,4-dioxane (5 ml) and a saturated aqueous sodium hydrogencarbonate solution (5 ml), and the resulting mixture was stirred at room temperature for 8 hours. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. To the resulting residue was added diethyl ether, followed by filtration, and the precipitate was washed with hexane to obtain the title compound (200 mg) as a light-yellow solid.
^{1}H NMR (400 MHz, DMSO-d_6) δppm 11.07 (s, 1H), 6.90 (d, J= 8.0 Hz, 1H), 5.44 (s, 1H), 3.71-3.53 (m, 2H), 3.47-3.35 (m, 1H), 3.31 (s, 3H), 3.19 (s, 3H), 2.76-2.65 (m,

1H), 2.62-2.53 (m, 1H), 1.85-1.65 (m, 2H), 1.57-1.28 (m, 2H), 1.44 (s, 9H).

MS (ESI+) 378 (M^++1, 100%).

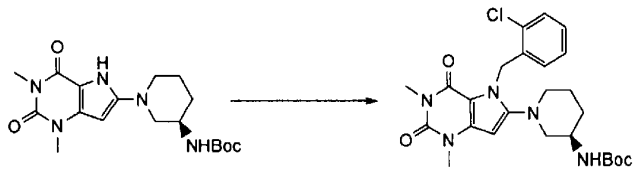
[0228]

Reference Example 11

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0229]

[Formula 103]



A solution of tert-butyl [(3R)-1-(1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl)piperidin-3-yl]carbamate (60 mg), 2-chlorobenzyl bromide (32 µl) and potassium carbonate (44 mg) in N,N-dimethylformamide (2 ml) was stirred at room temperature for 2 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered, and the filtrate was concentrated under reduced pressure and purified by a preparative thin-layer chromatography (hexane / ethyl acetate = 1/2) to obtain the title compound (10 mg) as

a white amorphous substance.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.36 (m, 1H), 7.18-7.07 (m, 2H), 6.51-6.42 (m, 1H), 5.67 (d, J = 16.8 Hz, 1H), 5.59 (s, 1H), 5.56 (d, J = 16.8 Hz, 1H), 3.85-3.74 (m, 1H), 3.48 (s, 3H), 3.36 (s, 3H), 3.12-3.03 (m, 1H), 2.82-2.62 (m, 3H), 1.80-1.47 (m, 4H), 1.43 (s, 9H).

MS (ESI+) 502 (M^++1, 100%).

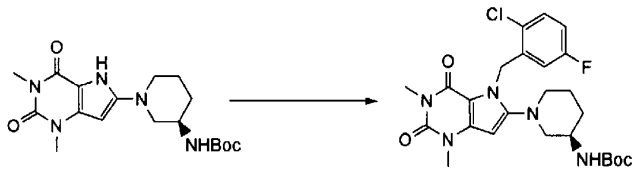
[0230]

Reference Example 12

tert-Butyl {1-[5-(2-chloro-5-fluorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0231]

[Formula 104]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 13.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 1H), 6.92-6.83 (m, 1H), 6.22-6.13 (m, 1H), 5.62 (d, J = 17.0 Hz, 1H), 5.61 (s, 1H), 5.52 (d, J = 17.0 Hz, 1H), 3.85-3.72 (m, 1H), 3.48 (s, 3H), 3.35 (s, 3H), 3.14-3.03 (m, 1H), 2.83-2.64 (m, 3H), 1.79-1.45 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 520 (M^++1, 100%).

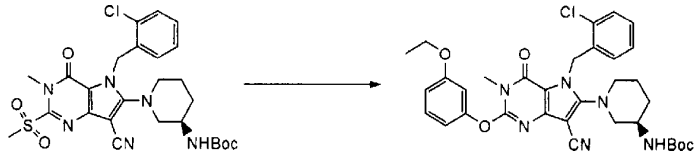
[0232]

Reference Example 13

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-2-(3-ethoxyphenoxy)-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidine-3-yl}carbamate

[0233]

[Formula 105]



A solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-3-methyl-2-(methylsulfonyl)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidine-3-yl}carbamate (110 mg), 3-ethoxyphenol (31 µl) and potassium carbonate (39 mg) in N,N-dimethylformamide (2 ml) was stirred at 50°C for 1 hour. After the reaction solution was allowed to cool, a saturated aqueous ammonium chloride solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 3/1 to 1/1) to obtain the title compound (86 mg) as a white solid.

MS (ESI+) 633 (M^++1, 100%).

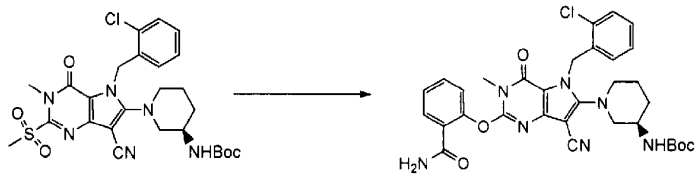
[0234]

Reference Example 14

tert-Butyl {(3R)-1-[2-[2-(aminocarbonyl)phenoxy]-5-(2-chlorobenzyl)-7-cyano-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidine-3-yl}carbamate

[0235]

[Formula 106]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 1.

MS (ESI+) 632 (M^++1, 100%).

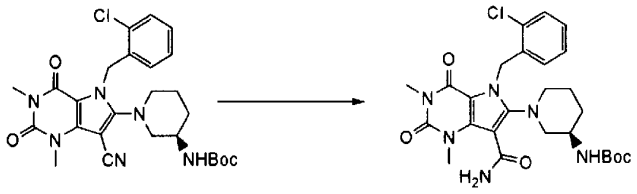
[0236]

Reference Example 15

tert-Butyl {(3R)-1-[7-(aminocarbonyl)-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0237]

[Formula 107]



To a mixed solution of dimethyl sulfoxide (250 ml) and water (25 ml) were added tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (17.9 g) and potassium carbonate (4.7 g). In a water bath, an aqueous hydrogen peroxide solution (a 30-35% aqueous solution, 17 ml) was added dropwise and the resulting mixture was stirred at 25°C for 15 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed three times with water and then once with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure to obtain the title compound (15.6 g) as a light-yellow amorphous substance.

MS (ESI+) 545 (M^++1, 100%).

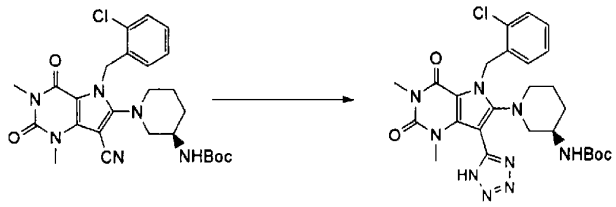
[0238]

Reference Example 16

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-7-(1H-tetrazol-5-yl)-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0239]

[Formula 108]



Sodium azide (154 mg) and ammonium chloride (125 mg) were added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-cyano-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (250 mg) in N,N-dimethylformamide (4 ml), and the resulting mixture was stirred at 150°C for 8 hours. Sodium azide (154 mg) and ammonium chloride (125 mg) were further added thereto and stirred for another 6 hours. After the reaction solution was cooled to 25°C, a 10% aqueous potassium hydrogensulfate solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by HPLC to obtain the title compound (23 mg) as a white solid.

MS (ESI+) 570 (M^++1, 100%).

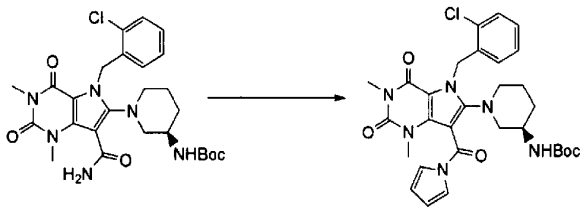
[0240]

Reference Example 17

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-7-(1H-pyrrolo-1-ylcarbonyl)-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0241]

[Formula 109]



After tert-butyl {(3R)-1-[7-(aminocarbonyl)-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (12.6 g) and 2,5-dimethoxytetrahydrofuran (150 ml) were stirred at 25°C, thionyl chloride (1.7 ml) was added dropwise thereto and the resulting mixture was stirred at 40°C for 6 hours. After the reaction solution was cooled to 25°C, a saturated aqueous sodium hydrogencarbonate solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 2/1) to obtain the title compound (15.9 g) as a yellow amorphous

substance.

MS (ESI+) 595 (M^++1, 100%).

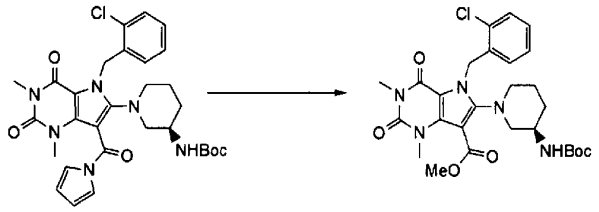
[0242]

Reference Example 18

Methyl 6-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

[0243]

[Formula 110]



Sodium methoxide (a 28% methanol solution, 0.2 ml) was added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-7-(1H-pyrrolo-1-ylcarbonyl)-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (410 mg) in methanol (5 ml), and the resulting mixture was stirred at 60°C for 2 hours. After the reaction solution was cooled to 25°C, a saturated aqueous ammonium chloride solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then

filtered and the filtrate was concentrated under reduced pressure to obtain the title compound (380 mg) as a white amorphous substance.

MS (ESI+) 560 (M^++1, 100%).

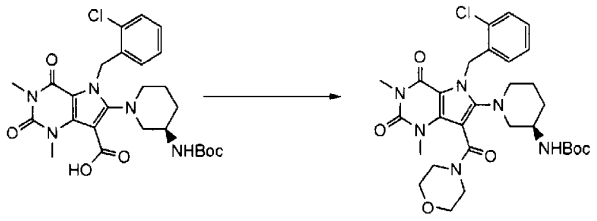
[0244]

Reference Example 19

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-7-(morpholin-4-ylcarbonyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0245]

[Formula 111]



1-Hydroxybenzotriazole (117 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (147 mg), triethylamine (0.21 ml) and morpholine (63 µl) were added to a solution of 6-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid (140 mg) in N,N-dimethylformamide (3 ml), and the resulting mixture was stirred at 25°C for 20 hours. A saturated aqueous ammonium chloride solution was added

to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a preparative thin-layer chromatography (hexane / ethyl acetate = 2/1) to obtain the title compound (106 mg) as a white solid.
MS (ESI+) 615 (M^++1, 100%).

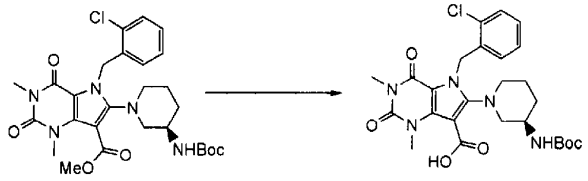
[0246]

Reference Example 20

6-{(3R)-3-[(tert-Butoxycarbonyl)amino]piperidin-1-yl}-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid

[0247]

[Formula 112]



A 1M aqueous sodium hydroxide solution (10 ml) was added to a solution of methyl 6-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

(2.08 g) in 1,4-dioxane (10 ml), and the resulting mixture was stirred at 80°C for 5 hours. After the reaction solution was cooled to 25°C, a saturated aqueous ammonium chloride solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure to obtain the title compound (1.95 g) as a light-yellow amorphous substance.
MS (ESI+) 546 (M^++1, 100%).

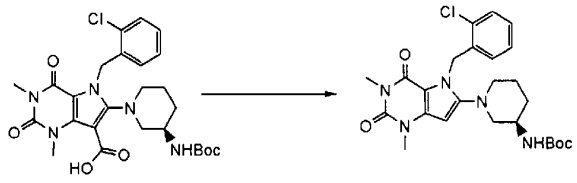
[0248]

Reference Example 21

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0249]

[Formula 113]



In acetonitrile (5 ml) was dissolved 6-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylic

acid (350 mg), and the solution was stirred at 80°C for 1 hour. The reaction solution was cooled to 25°C and concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (270 mg) as a white amorphous substance.

MS (ESI+) 402 (M^++1, 100%).

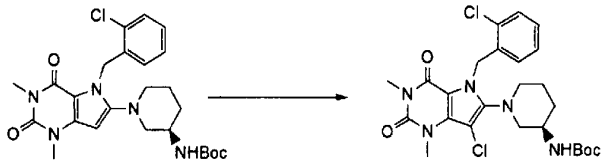
[0250]

Reference Example 22

tert-Butyl {(3R)-1-[7-chloro-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0251]

[Formula 114]



To a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (1.00 g) in N,N-dimethylformamide (20 ml) was added N-chlorosuccinimide (294 mg), and the resulting mixture was stirred overnight at room temperature. The reaction solution was adjusted to pH

2 with a 10% aqueous potassium hydrogensulfate solution and extracted with ethyl acetate (200 ml). The organic layer was washed with a 10% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 2/1) to obtain the title compound (917 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 1H), 7.20-7.10 (m, 2H), 6.42 (d, J = 6.6 Hz, 1H), 5.78-5.70 (m, 2H), 3.79 (s, 3H), 3.59-3.55 (m, 1H), 3.36 (s, 3H), 3.12-2.80 (m, 4H), 1.64-1.43 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 536(M^++1, 100%).

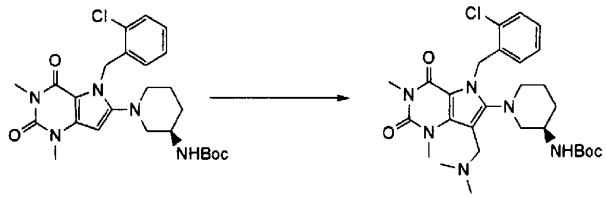
[0252]

Reference Example 23

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-[(dimethylamino)methyl]-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0253]

[Formula 115]



Paraformaldehyde (600 mg) and a 50% aqueous dimethylamine solution (1.80 g) were added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (1.00 g) in a mixture of ethanol (10 ml) and acetic acid (5 ml), and the resulting mixture was stirred with heating at 80°C. After the reaction solution was cooled to 25°C, toluene (30 ml) was added thereto and the resulting mixture was concentrated under reduced pressure. This procedure was repeated three times. The resulting residue was acidified with a 10% aqueous potassium hydrogensulfate solution and extracted twice with chloroform (100 ml). The organic layer was dried over sodium sulfate and filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/2) to obtain the title compound (913 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 7.3 Hz, 1H), 7.18-7.07 (m, 2H), 6.31 (d, J = 7.5 Hz, 1H), 5.71-5.58 (m, 2H), 3.84 (s, 3H), 3.46-3.12 (m, 4H), 3.36 (s, 3H), 2.89-2.64 (m, 3H), 2.22 (s, 6H), 1.79-1.45 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 559(M^++1, 43%).

[0254]

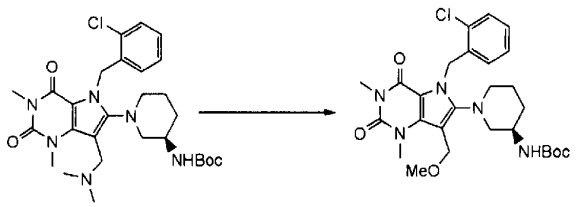
Reference Example 24

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-(methoxymethyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-

tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0255]

[Formulation 116]



Methyl iodide (25 µl) was added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-[(dimethylamino)methyl]-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (112 mg) in acetone (5 ml), and the resulting mixture was stirred overnight in a sealed tube at room temperature. The reaction solution was concentrated under reduced pressure, and to a solution of the resulting residue in methanol (2 ml) was added 28% methanol methoxide (2 ml), followed by stirring with heating at 60°C for 4 hours. The methanol was distilled off under reduced pressure and the residue was adjusted to pH 2 with an aqueous potassium hydrogensulfate solution and extracted with ethyl acetate (100 ml). The organic layer was washed with a 10% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting

residue was purified by a thin-layer silica gel column chromatography (hexane / ethyl acetate = 1/5) to obtain the title compound (26 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 7.7 Hz, 1H), 7.18-7.07 (m, 2H), 6.37 (d, J = 7.0 Hz, 1H), 5.71-5.60 (m, 2H), 4.67-4.64 (m, 1H), 4.40 (s, 3H), 3.72 (s, 3H), 3.71-3.69 (m, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 3.35-3.30 (m, 1H), 2.82-2.78 (m, 3H), 1.80-1.45 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 546(M^++1, 36%).

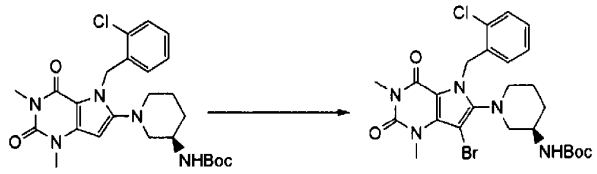
[0256]

Reference Example 25

tert-Butyl {(3R)-1-[7-bromo-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0257]

[Formula 117]



To a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (1.00 g) in N,N-dimethylformamide (20 ml) was added N-bromosuccinimide (392 mg), and the

resulting mixture was stirred overnight at room temperature. The reaction solution was adjusted to pH 2 with a 10% aqueous potassium hydrogensulfate solution and extracted with ethyl acetate (200 ml). The organic layer was washed with a 10% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 2/1) to obtain the title compound (1.143 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.3 Hz, 1H), 7.20-7.10 (m, 2H), 6.40 (d, J = 7.1 Hz, 1H), 5.76 (s, 2H), 4.97-4.95 (m, 1H), 3.83 (s, 3H), 3.67-3.59 (m, 1H), 3.36 (s, 3H), 3.23-2.82 (m, 3H), 2.54-2.52 (m, 1H), 1.91-1.89 (m, 1H), 1.71-1.51 (m, 3H), 1.43 (sm, 9H).
MS (ESI+) 582(M^++1, 52%).

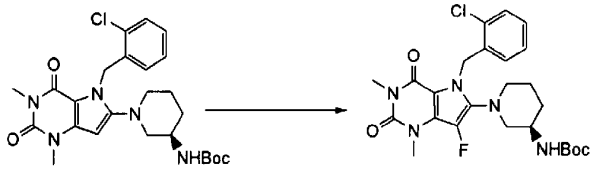
[0258]

Reference Example 26

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-fluoro-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0259]

[Formula 118]



Xenon fluoride (56 mg) was added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (1.00 g) in acetonitrile (10 ml), and the resulting mixture was stirred overnight at room temperature. After a saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, the acetonitrile was distilled off under reduced pressure, and the residue was extracted twice with chloroform (50 ml). The organic layer was dried over sodium sulfate and filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a thin-layer silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (8 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 1H), 7.20-7.11 (m, 2H), 6.46 (d, J = 6.8 Hz, 1H), 5.69 (d, J = 16.3 Hz, 1H), 5.59 (d, J = 16.3 Hz, 1H), 4.73-4.69 (m, 1H), 3.76-3.74 (m, 1H), 3.61 (s, 3H), 3.36 (s, 3H), 3.29-3.25 (m, 1H), 2.78-2.76 (m, 3H), 1.69-1.45 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 520(M^++1, 17%).

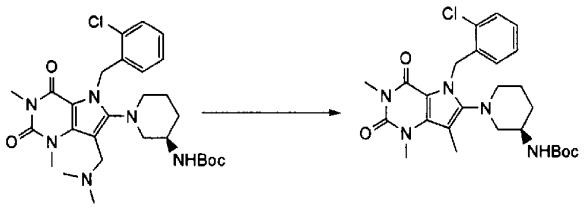
[0260]

Reference Example 27

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3,7-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0261]

[Formula 119]



Methyl iodide (38 µl) was added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-[(dimethylamino)methyl]-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (168 mg) in acetone (4 ml), and the resulting mixture was stirred overnight in a sealed tube at room temperature. The reaction solution was concentrated under reduced pressure, and to a solution of the resulting residue in tetrahydrofuran (5 ml) was added a 1N aqueous sodium hydroxide solution (3 ml), followed by stirring with heating at 60°C for 3 hours. The tetrahydrofuran was distilled off under reduced pressure and water was added to the residue, followed by two runs of extraction with chloroform (50 ml). The organic layer was dried over sodium sulfate and filtered and the filtrate was concentrated under reduced pressure. Then, a solution of the resulting residue in dichloromethane (6 ml) was added dropwise to an ice-cooled solution of triethylsilane (144 µl) and methanesulfonic acid (60 µl) in dichloromethane (10 ml), and the resulting mixture was stirred at 0°C for 1 hour.

A 10% aqueous potassium carbonate solution was added thereto, followed by two runs of extraction with chloroform (50 ml). The organic layer was dried over sodium sulfate and filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (101 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 7.3 Hz, 1H), 7.17-7.07 (m, 2H), 6.35 (d, J = 6.7 Hz, 1H), 5.70 (s, 1H), 4.93-4,91 (m, 1H), 4.93-4,91 (m, 1H), 3.75-3.73 (m, 1H), 3.70 (s, 3H), 3.36 (s, 3H), 3.31-3.29 (m, 1H), 2.90-2.63 (m, 3H), 2.33 (s, 3H), 1.92-1.90 (m, 1H), 1.63-1.46 (m, 3H), 1.42 (s, 9H).

MS (ESI+) 516(M^++1, 61%).

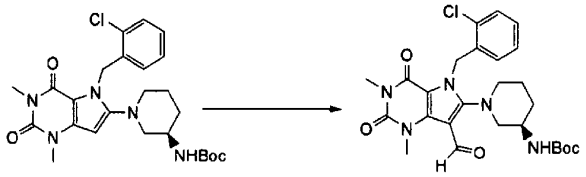
[0262]

Reference Example 28

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-formyl-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0263]

[Formula 120]



Phosphorus oxychloride (551 µl) was added to dimethylformamide (10 ml) at room temperature and stirred for 5 minutes. A solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (502 mg) in N,N-dimethylformamide (1 ml) was added to the reaction solution, and the resulting mixture was stirred at room temperature for 3 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate (100 ml). The organic layer was washed with a 10% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (290 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.43-7.40 (m, 1H), 7.23-7.12 (m, 2H), 6.46 (d, J = 7.1 Hz, 1H), 5.80 (d, J = 16.0 Hz, 1H), 5.59 (d, J = 16.0 Hz, 1H), 4.61-4.59 (m, 1H), 3.84 (s, 3H), 3.66-3.64 (m, 1H), 3.38 (s, 3H), 3.37-3.31 (m, 1H), 2.90-2.85 (m, 3H), 1.88-1.85 (m, 1H), 1.59-1.55 (m, 3H), 1.42 (s, 9H).

MS (ESI+) 530(M^++1, 39%).

[0264]

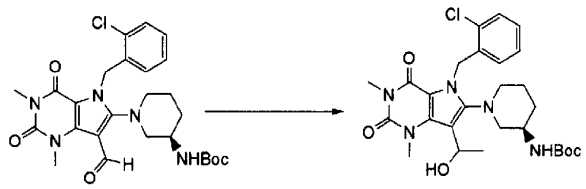
Reference Example 29

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-(1-hydroxyethyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-

tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0265]

[Formula 121]



A solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-formyl-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (132 mg) in tetrahydrofuran (4 ml) was cooled to 0°C, followed by adding thereto methylmagnesium bromide (417 µl), and the resulting mixture was stirred at 0°C for 2 hours. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by two runs of extraction with chloroform (50 ml). The organic layer was dried over sodium sulfate and filtered and the filtrate was concentrated under reduced pressure to obtain a crude product of the title compound (167 mg).

MS (ESI+) 546 (M^++1, 46%).

[0266]

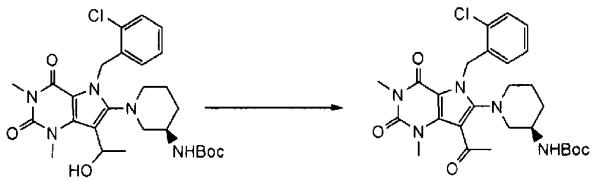
Reference Example 30

tert-Butyl {(3R)-1-[7-acetyl-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-

yl}carbamate

[0267]

[Formula 122]



Manganese dioxide (0.66 g) was added to a solution of crude tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-(1-hydroxyethyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (167 mg) in dichloromethane (5 ml), and the resulting mixture was stirred overnight at room temperature. Then, the reaction solution was heated to 45°C and stirred for 3 hours. The reaction solution was filtered through Celite and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (33 mg).

MS (ESI+) 546(M^++1, 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 1H), 7.22-7.11 (m, 2H), 6.43-6.40 (m, 1H), 5.77-5.60 (m, 2H), 5.54-5.51 (m, 1H), 3.62-3.60 (m, 1H), 3.42 (s, 3H), 3.36 (s, 3H), 3.34-3.32 (m, 1H), 2.79-2.65 (m, 3H), 2.59 (s, 3H), 1.88-1.82 (m, 1H), 1.65-1.48 (m, 2H), 1.42 (s, 9H).

MS (ESI+) 544(M^++1, 34%).

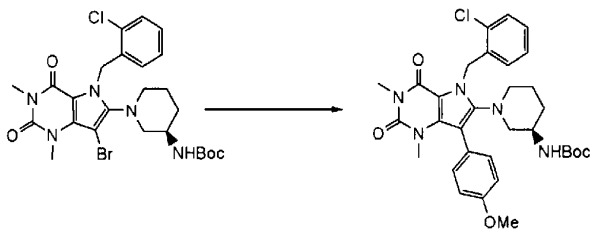
[0268]

Reference Example 31

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0269]

[Formula 123]



Bis(dibenzylideneacetone)palladium (18 mg), tri-tert-butylphosphonium tetrafluoroborate (22 mg), potassium phosphate (329 mg) and 4-methoxyphenylboronic acid (236 mg) were added to a solution of tert-butyl {(3R)-1-[7-bromo-5-(2-chlorobenzyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (90 mg) in dioxane (4 ml), and the resulting mixture was stirred with heating at 50°C for 15 hours. The reaction solution was filtered through Celite and washed with tetrahydrofuran and the filtrate was concentrated under reduced pressure. A 10% aqueous potassium carbonate solution was added to the residue, followed by two runs of extraction with chloroform (50 ml). The organic layer was dried over

sodium sulfate and filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 2/1) to obtain the title compound (10 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 1H), 7.26-7.10 (m, 4H), 6.92 (d, J = 8.8 Hz, 1H), 6.52-6.50 (m, 1H), 5.80 (d, J = 16.7 Hz, 1H), 5.66 (d, J = 16.7 Hz, 1H), 3.87 (s, 3H), 3.52-3.50 (m, 1H), 3.37 (s, 3H), 3.07 (s, 3H), 2.80-2.40 (m, 4H), 1.62-1.39 (m, 4H), 1.38 (s, 9H).

MS (ESI+) 608(M^++1, 76%).

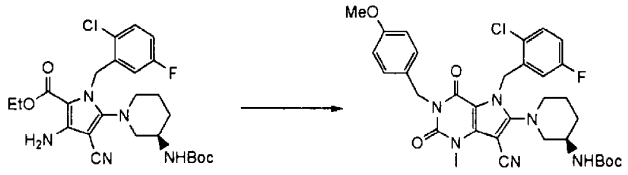
[0270]

Reference Example 32

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-7-cyano-3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0271]

[Formula 124]



4-Methoxybenzyl isocyanate (0.5 ml) and potassium carbonate (486 mg) were added to a solution of ethyl 3-amino-5-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-1-(2-chloro-5-fluorobenzyl)-4-

cyano-1H-pyrrole-2-carboxylate (920 mg) in pyridine (1 ml), and the resulting mixture was stirred at 130°C for 6 hours. 4-Methoxybenzyl isocyanate (2.0 ml) was added thereto, followed by stirring with heating for another 24 hours. The reaction solution was cooled to 25°C and then concentrated under reduced pressure and water was added to the residue, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (15 ml), followed by adding thereto potassium carbonate (486 mg) and methyl iodide (0.33 ml), and the resulting mixture was stirred at 25°C for 3 hours. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate) to obtain the title compound (750 mg) as a light-yellow amorphous substance.

MS (ESI+) 651 (M^++1, 100%).

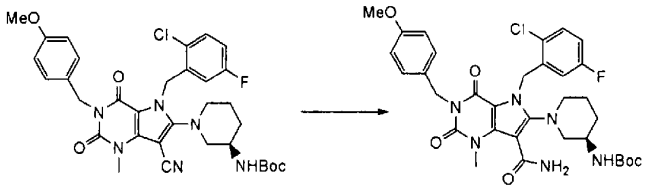
[0272]

Reference Example 33

tert-Butyl {(3R)-1-[7-(aminocarbonyl)-5-(2-chloro-5-fluorobenzyl)-3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0273]

[Formula 125]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 15.

MS (ESI+) 669 (M^++1, 100%).

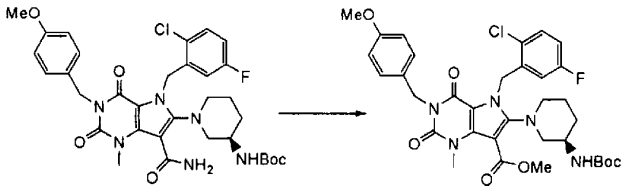
[0274]

Reference Example 34

Methyl 6-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-5-(2-chloro-5-fluorobenzyl)-3-(4-methoxybenzyl}-1-methyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

[0275]

[Formula 126]



The title compound was synthesized from a corresponding compound by the same process as in Reference Examples 17 and 18.

MS (ESI+) 684 (M^++1, 100%).

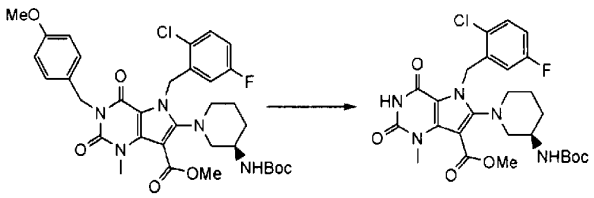
[0276]

Reference Example 35

Methyl 6-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-5-(2-chloro-5-fluorobenzyl)-1-methyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

[0277]

[Formula 127]



Under a nitrogen atmosphere, a solution of aluminum chloride (395 mg) in anisole (1.5 ml) was added to methyl 6-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-5-(2-chloro-5-fluorobenzyl)-3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate (260 mg), and the resulting mixture was stirred at 65°C for 4 hours. After the reaction solution was cooled to 25°C, 1N hydrochloric acid was added thereto and the aqueous layer was washed with ethyl acetate. The aqueous layer was neutralized with a 1N aqueous sodium hydroxide

solution and extracted with chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. To the resulting residue were added di-tert-butyl dicarbonate (415 mg), 1,4-dioxane (4 ml) and a saturated aqueous sodium hydrogencarbonate solution (4 ml) and the resulting mixture was stirred at 25°C for 16 hours. Water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. To the resulting residue was added diethyl ether/hexane and the resulting mixture was filtered and then washed with hexane to obtain the title compound (121 mg) as a light-yellow solid.

MS (ESI+) 564 (M^++1, 100%).

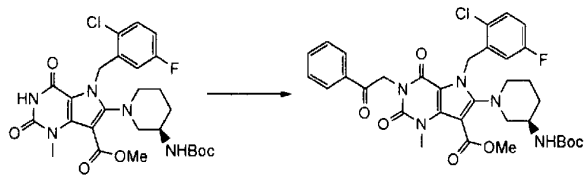
[0278]

Reference Example 36

Methyl 6-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-5-(2-chloro-5-fluorobenzyl)-1-methyl-2,4-dioxo-3-(2-oxo-2-phenylethyl)-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

[0279]

[Formula 128]



A solution of methyl 6-{(3R)-3-[(tert-butoxycarbonyl}amino]piperidin-1-yl}-5-(2-chloro-5-fluorobenzyl)-1-methyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylate (50 mg), α-bromoacetophenone (27 mg) and potassium carbonate (25 mg) in N,N-dimethylformamide was stirred at 25°C for 14 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a preparative thin-layer chromatography (hexane / ethyl acetate = 2/1) to obtain the title compound (51 mg) as a white solid.
MS (ESI+) 682 (M^++1, 100%).

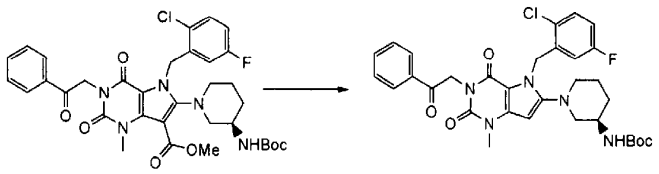
[0280]

Reference Example 37

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-1-methyl-2,4-dioxo-3-(2-oxo-2-phenylethyl)-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0281]

[Formula 129]



The title compound was synthesized from a corresponding compound by the same process as in Reference Examples 20 and 21.

MS (ESI+) 624 (M^++1, 100%).

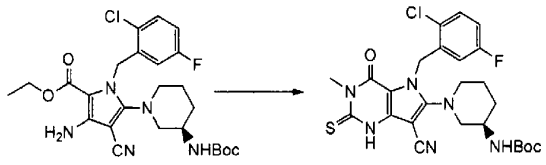
[0282]

Reference Example 38

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-7-cyano-3-methyl-4-oxo-2-thioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0283]

[Formula 130]



Methyl isothiocyanate (7.36 ml) and potassium carbonate (14.86 g) were added to a solution (200 ml) of ethyl 3-amino-5-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-1-(2-chloro-5-fluorobenzyl)-4-

cyano-1H-pyrrole-2-carboxylate (27.96 g) in pyridine, and the resulting mixture was stirred with heating at 130°C for 13 hours. After the reaction solution was cooled to 25°C, toluene (50 ml) was added thereto and the resulting mixture was concentrated under reduced pressure. This procedure was repeated three times. The resulting residue was adjusted to pH 2 with an aqueous potassium hydrogensulfate solution and the solid precipitated was collected by filtration and washed with water and then hexane. The solid thus obtained was dried at 45°C under reduced pressure to obtain the title compound (28.56 g).

MS (ESI+) 547 (M^++1, 86%).

[0284]

Reference Example 39

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-7-cyano-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0285]

[Formula 131]

Sodium tungstate dihydrate (0.91 g) was added to a solution of tert-butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-7-cyano-3-methyl-4-oxo-2-thioxo-2,3,4,5-

tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (1.51 g) in a mixture of methanol (9 ml), acetic acid (3 ml) and water (1 ml), and a 30% aqueous hydrogen peroxide solution (0.29 ml) was added dropwise thereto at room temperature and stirred for 2 hours. After the reaction mixture was allowed to cool, the methanol was distilled off under reduced pressure and the residue was adjusted to pH 9 with an aqueous potassium carbonate solution. A 10% aqueous sodium hydrogensulfite solution was added thereto and stirred for 30 minutes, followed by extraction with ethyl acetate (200 mL). The organic layer was washed with a 10% aqueous potassium carbonate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was dried under reduced pressure to obtain the title compound (1.61 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.41-7.36 (m, 1H), 6.96-6.89 (m, 1H), 6.20 (d, J = 7.5 Hz, 1H), 5.70 (d, J = 16.7 Hz, 1H), 5.59 (d, J = 16.7 Hz, 1H), 4.53-4.51 (m, 1H), 3.74-3.69 (m, 1H), 3.55 (s, 3H), 3.52-3.46 (m, 1H), 3.05-2.94 (m, 3H), 1.88-1.85 (m, 1H), 1.70-1.60 (m, 3H), 1.41 (s, 9H).

MS (ESI+) 515(M^++1, 66%).

[0286]

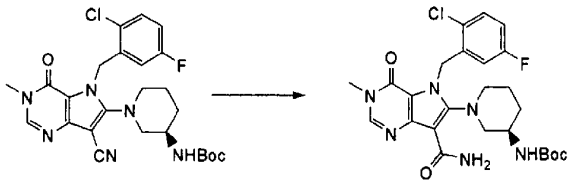
Reference Example 40

tert-Butyl {(3R)-1-[7-(aminocarbonyl)-5-(2-chloro-5-fluorobenzyl)-3-methyl-4-oxo-4,5-dihydro-3H-

pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0287]

[Formula 132]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 15.

MS (ESI+) 533 (M^++1, 73%).

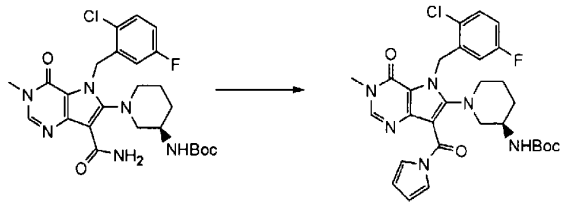
[0288]

Reference Example 41

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-3-methyl-4-oxo-7-(1H-pyrrolo-1-ylcarbonyl)-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0289]

[Formula 133]



The title compound was synthesized from a corresponding compound by the same process as in

Reference Example 17.

MS (ESI+) 583 (M^++1, 100%).

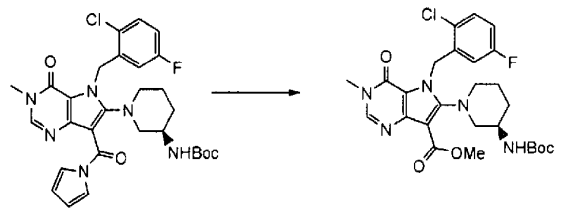
[0290]

Reference Example 42

Methyl 6-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-5-(2-chloro-5-fluorobenzyl)-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carboxylate

[0291]

[Formula 134]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 18.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.40-7.35 (m, 1H), 6.93-6.86 (m, 1H), 6.03 (d, J = 7.1 Hz, 1H), 5.85 (d, J = 16.8 Hz, 1H), 5.74 (d, J = 16.8 Hz, 1H), 4.68-4.66 (m, 1H), 3.98 (s, 3H), 3.68-3.66 (m, 1H), 3.56 (s, 3H), 3.33-3.31 (m, 1H), 2.97-2.93 (m, 3H), 1.83-1.81 (m, 1H), 1.65-1.56 (m, 3H), 1.41 (s, 9H).

MS (ESI+) 548(M^++1, 41%).

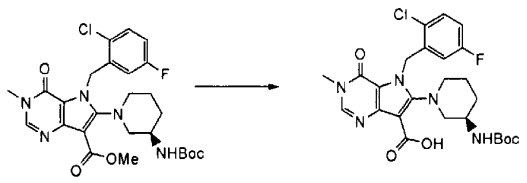
[0292]

Reference Example 43

6-{(3R)-3-[(tert-Butoxycarbonyl)amino]-piperidin-1-yl}-5-(2-chloro-5-fluorobenzyl)-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid

[0293]

[Formula 135]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 20.

MS (ESI+) 534 (M^++1, 6%).

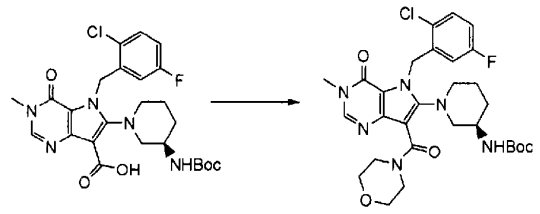
[0294]

Reference Example 44

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-3-methyl-7-(morpholin-4-ylcarbonyl)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0295]

[Formula 136]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 19.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.39-7.34 (m, 1H), 6.92-6.87 (m, 1H), 6.21-6.19 (m, 1H), 5.74 (d, J = 16.6 Hz, 1H), 5.59 (d, J = 16.6 Hz, 1H), 4.60-4.58 (m, 1H), 3.92-3.71 (m, 7H), 3.57-3.51 (m, 2H), 3.54 (s, 3H), 3.30-3.28 (m, 1H), 2.87-2.76 (m, 3H), 1.78-1.57 (m, 4H), 1.41 (s, 9H).

MS (ESI+) 603(M^++1, 19%).

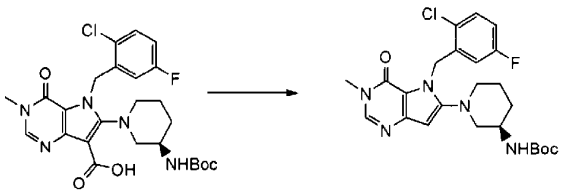
[0296]

Reference Example 45

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0297]

[Formula 137]



The title compound was synthesized from a corresponding compound by the same process as in Reference Example 21.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.37-7.32 (m, 1H), 6.90-6.83 (m, 1H), 6.09 (d, J = 9.3 Hz, 1H), 6.06 (s, 1H), 5.73 (d, J = 16.9 Hz, 1H), 5.62 (d, J = 16.9

Hz, 1H), 4.69-4.65 (m, 1H), 3.80-3.78 (m, 1H), 3.54 (s, 3H), 3.13-3.08 (m, 1H), 2.77-2.74 (m, 3H), 1.72-1.60 (m, 4H), 1.42 (s, 9H).

MS (ESI+) 490(M^++1, 71%).

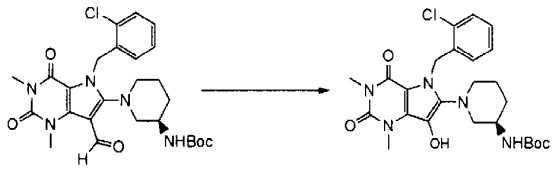
[0298]

Reference Example 46

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-hydroxy-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0299]

[Formula 138]



Methanesulfonic acid (21 µl) and a 30% aqueous hydrogen peroxide solution (54 µl) were added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-formyl-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (132 mg) in methanol (4 ml), and the resulting mixture was stirred at room temperature for 2 hours. A 10% aqueous sodium sulfite solution was added to the reaction solution, followed by extraction with ethyl acetate (50 ml). The organic layer was dried over sodium sulfate and filtered and the filtrate was concentrated under reduced pressure. The resulting

residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/2) to obtain the title compound (54 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δppm 7.35 (d, J = 7.5 Hz, 1H), 7.17-7.07 (m, 2H), 6.37 (d, J = 6.8 Hz, 1H), 5.86 (brs, 1H), 5.60-5.56 (m, 2H), 4.82 (brs, 1H), 3.71 (s, 3H), 3.65-3.63 (m, 1H), 3.37 (s, 3H), 3.35-3.33 (m, 1H), 2.84-2.70 (m, 3H),1.95-1.93 (m, 1H), 1.62-1.41 (m, 3H), 1.41 (m, 9H).

MS (ESI+) 518(M^++1, 82%).

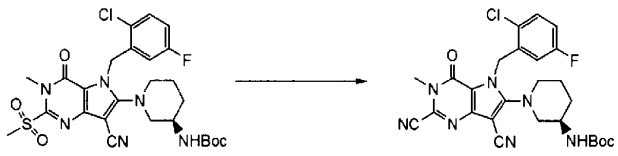
[0300]

Reference Example 47

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-2,7-dicyano-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0301]

[Formula 139]



An aqueous solution (2 ml) of sodium cyanide (338 mg) was added to a solution of tert-butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-7-cyano-3-methyl-2-(methylsulfonyl)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (890 mg) in

tetrahydrofuran (10 ml), and the resulting mixture was stirred at room temperature for 3 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate (200 ml). The organic layer was washed with a 10% aqueous potassium carbonate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 2/1) to obtain the title compound (758 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.37 (m, 1H), 6.99-6.91 (m, 1H), 6.19 (d, J = 7.3 Hz, 1H), 5.68 (d, J = 16.7 Hz, 1H), 5.57 (d, J = 16.7 Hz, 1H), 4.52-4.49 (m, 1H), 3.78 (s, 3H), 3.72-3.70 (m, 1H), 3.55-3.50 (m, 1H), 3.10-3.06 (m, 2H), 3.00-2.93 (m, 1H), 1.91-1.89 (m, 1H), 1.74-1.58 (m, 3H), 1.41 (s, 9H).

MS (ESI+) 540(M^++1, 11%).

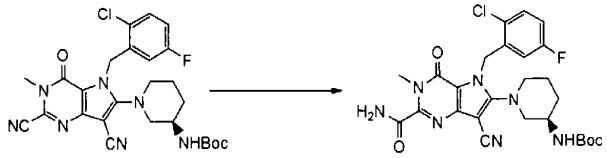
[0302]

Reference Example 48

tert-Butyl {(3R)-1-[2-(aminocarbonyl)-5-(2-chloro-5-fluorobenzyl)-7-cyano-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0303]

[Formula 140]



Potassium carbonate (42 mg) and then an aqueous hydrogen peroxide solution (a 30-35% aqueous solution, 170 µl) were added dropwise to a solution of tert-butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-2,7-dicyano-3-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (162 mg) in a mixture of dimethyl sulfoxide (10 ml) and water (2 ml), and the resulting mixture was stirred overnight at room temperature. A 10% aqueous sodium sulfite solution was added to the reaction solution, followed by extraction with ethyl acetate (200 ml). The organic layer was washed with a 10% aqueous potassium carbonate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (77 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.42-7.37 (m, 1H), 6.97-6.91 (m, 1H), 6.21 (d, J = 7.0 Hz, 1H), 5.84 (s, 1H), 5.71 (d, J = 16.7 Hz, 1H), 5.60 (d, J = 16.7 Hz, 1H), 4.58-4.55 (m, 1H), 3.87 (s, 3H), 3.75-3.73 (m, 1H), 3.54-3.49 (m, 1H), 3.05-2.95 (m, 3H), 1.87-1.85 (m,

1H), 1.70-1.66 (m, 3H), 1.42 (s, 9H).

MS (ESI+) 458(M^++1, 100%).

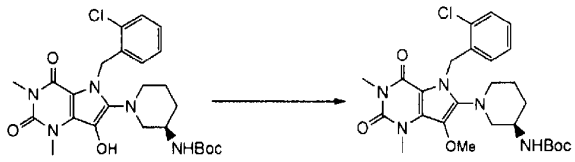
[0304]

Reference Example 49

tert-Butyl {(3R)-1-[5-(2-chlorobenzyl)-7-methoxy-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0305]

[Formula 141]



Potassium carbonate (41 mg) and methyl iodide (13 µl) were added to a solution of tert-butyl {(3R)-1-[5-(2-chlorobenzyl)-7-hydroxy-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (50 mg) in N,N-dimethylformamide (2 ml), and the resulting mixture was stirred at room temperature for 5 hours. A 10% aqueous potassium hydrogensulfate solution was added to the reaction solution, followed by extraction with ethyl acetate (100 ml). The organic layer was washed with a 10% aqueous potassium hydrogensulfate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting

residue was purified by a preparative thin-layer chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (17 mg).

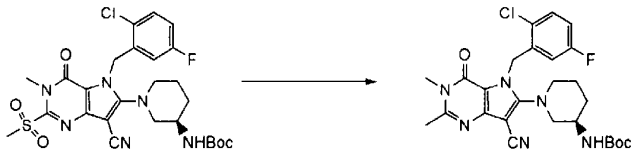
MS (ESI+) 532 (M^++1, 69%).

Reference Example 50

tert-Butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-7-cyano-2,3-dimethyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate

[0306]

[Formula 142]



A solution of tert-butyl {(3R)-1-[5-(2-chloro-5-fluorobenzyl)-7-cyano-3-methyl-2-(methylsulfonyl)-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-6-yl]piperidin-3-yl}carbamate (890 mg) in tetrahydrofuran (2 ml) was cooled to 0°C and a 3M methylmagnesium bromide/diethyl ether solution (333 µl) was added dropwise thereto. After 30 minutes, the reaction solution was warmed to room temperature and stirred for 1 hour. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate (100 ml). The organic layer was washed with a saturated aqueous

sodium chloride solution, dried over sodium sulfate and then filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane / ethyl acetate = 1/1) to obtain the title compound (64 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.35 (m, 1H), 6.95-6.88 (m, 1H), 6.18 (d, J = 6.9 Hz, 1H), 5.68 (d, J = 16.8 Hz, 1H), 5.57 (d, J = 16.8 Hz, 1H), 4.58-4.55 (m, 1H), 3.78-3.74 (m, 1H), 3.54 (s, 3H), 3.50-3.45 (m, 1H), 3.04-2.94 (m, 3H), 2.63 (s, 3H), 1.88-1.83 (m, 1H), 1.68-1.62 (m, 2H), 1.43-1.41 (m, 1H), 1.41 (s, 9H).
MS (ESI+) 529(M^++1, 100%).

[0307]

In vitro DPP-IV inhibitory effect measurement test

Human serum containing DPP-IV enzyme was diluted finally 9- to 20- fold with assay buffer and added to a microassay plate. Each of solutions of each test compound having various concentrations was added thereto, followed by adding thereto a substrate (Glycyl-L-Proline 4-Methyl-Coumaryl-7-Amide, Peptide Laboratories Co., Ltd.) to a final concentration of 10 to 100 μM, and the reaction was carried out at room temperature. Acetic acid was added thereto to a final concentration of 0.5% to terminate the reaction, and the intensity of fluorescence at an excitation wavelength of 360 nm and a measuring wavelength of 460 nm was measured by the use of a fluorescent plate reader. A compound concentration for 50% inhibition

was calculated as an IC_{50} value from enzyme inhibiting activity values obtained by adding each test compound to a plurality of concentrations.

[308]

[Table 1]

Test Compound	Human DPP IV inhibiting activity IC_{50} (nM)	Test compound	Human DPPIV inhibiting activity IC_{50} (nM)
Example 1	76	Example 34	5.8
Example 2	21	Example 37	10
Example 3	26	Example 38	5.3
Example 4	28	Example 39	4.1
Example 5	15	Example 40	6.8
Example 6	1.9	Example 41	4.1
Example 7	60	Example 42	5.7
Example 8	7.4	Example 43	6.9
Example 14	55	Example 44	9.0
Example 18	12	Example 45	4.8
Example 19	7.1	Example 46	5.6
Example 20	4.3	Example 56	31
Example 24	44	Example 60	28
Example 25	7.6	Example 61	85
Example 26	3.2	Example 62	56
Example 27	9.8	Example 63	27
Example 28	6.4	Example 64	13
Example 29	5.7	Example 65	6.2
Example 30	4.7	Example 66	5.5
Example 31	5.0	Example 70	3800
Example 32	7.5	Example 72	1200
Example 33	12.0		

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INDUSTRIAL APPLICABILITY

[0309]

The present invention makes it possible to provide compounds that have DPP-IV inhibitory activity and possess improved safety, non-toxicity and the like.

The present inventive compounds are useful for the suppression of postprandial hyperglycemia in prediabetes, the treatment of non-insulin dependent diabetes, the treatment of autoimmune diseases such as arthritis and articular rheumatism, the treatment of intestinal mucosa diseases, growth acceleration, the inhibition of transplantation rejection, the treatment of obesity, the treatment of eating disorder, the treatment of HIV infection, the suppression of cancer metastasis, the treatment of prostatomegaly, the treatment of periodontitis, and the treatment of osteoporosis.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

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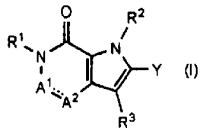
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound represented by the formula (I):

[Formula 1]



(I)

wherein R^1 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

the solid line and dotted line between A^1 and A^2 indicate a double bond (A^1=A^2) or a single bond (A^1-A^2) ;

A^1 is a group represented by the formula C(R^4) and A^2 is a nitrogen atom, in the case of the solid line and dotted line between A^1 and A^2 being a double bond (A^1=A^2);

A^1 is a group represented by the formula C=O and A^2 is a group represented by the formula N(R^5), in the case of the solid line and dotted line between A^1 and A^2 being a single bond (A^1-A^2) ;

R^2 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroarylalkyl group, an optionally substituted alkenyl group or an optionally substituted alkynyl group;

R^3 is a hydrogen atom, a halogen atom, a cyano group, a formyl group, a carboxyl group, an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroarylalkyl group, an optionally substituted alkylcarbonyl group, an optionally substituted cycloalkylcarbonyl group, an optionally substituted aroyl group, an optionally

substituted heteroarylcarbonyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted carbamoyl group, a hydroxyl group, an optionally substituted alkoxy group, or the formula: -Rd-C(O)O-Re wherein Rd is a single bond, an alkylene group or an alkenylene group and Re is tetrahydrofuranyl, cinnamyl, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-(tert-butyl)-2-oxo-1,3-dioxolen-4-ylmethyl or the formula: - $CH(R^{4a})OC(O)R^{4b}$ wherein R^{4a} is a hydrogen atom, an alkyl group, an alkenyl group, a cycloalkyl group or an alkoxy group and R^{4b} is an optionally substituted alkyl group, an optionally substituted alkenyl group, a cycloalkyl group, a cycloalkyloxy group, an optionally substituted alkoxy group, an optionally substituted alkenyloxy group, a 2-indanyloxy group, a 5-indanyloxy group or an optionally substituted aryloxy group;

R^4 is a hydrogen atom, a hydroxyl group, a halogen atom, a cyano group, a formyl group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkyloxy group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, an optionally substituted arylthio group, an optionally substituted arylsulfinyl group, an optionally substituted arylsulfonyl group, an optionally substituted alkylthio group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, an optionally substituted alkylcarbonyl group, an optionally substituted nitrogen-containing saturated heterocyclic group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyloxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, or the formula: -Rd-C(O)O-Re wherein Rd and Re are as defined above;

R^5 is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally

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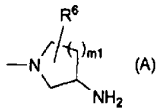
substituted vinyl group, an optionally substituted nitrogen-containing saturatedheterocyclic group, or an optionally substituted heteroaryl group;

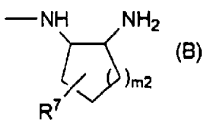
-Y is a group represented by any of the formula (A), formula (B), formula (C) and formula (D) shown below:

[Formula 2]



wherein m1 is 0, 1, 2 or 3, and R^6 is absent or one or two R^6s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group, or two R^6s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring;

[Formula 3]



wherein m2 is 0, 1, 2 or 3, and R^7 is absent or one or two R^7s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an

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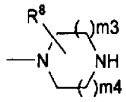
optionally substituted carbamoyl group, or two R^7s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring;

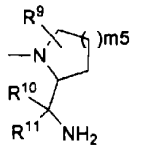
[Formula 4]



(C)

wherein m3 and m4 are independently 0 or 1, and R^8 is absent or one or two R^8s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group, or two R^8s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring; and

[Formula 5]



(D)

wherein m5 is 1, 2 or 3, R^9 is absent or one or two R^9s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an

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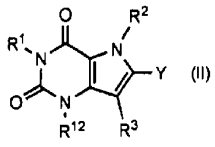
optionally substituted carbamoyl group, or two R^9s, when taken together, represent methylene or ethylene and may bind to two carbon atoms constituting the ring, to form a new ring, and R^{10} and R^{11} are independently a hydrogen atom, methyl, ethyl, propyl, or isopropyl, or R^{10} and R^{11}, when taken together, represent cyclopropyl, cyclobutyl or cyclopentyl,

a prodrug of said compound, or a pharmaceutically acceptable salt of said compound or prodrug.

2. A compound according to claim 1, which is represented by the formula (II):

[Formula 6]

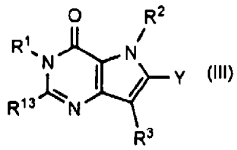


(II)

wherein R^1, R^2, R^3 and Y are as defined in claim 1 and R^{12} is a hydrogen atom, an optionally substituted alkyl group or an optionally substituted aryl group, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

3. A compound according to claim 1, which is represented by the formula (III):

[Formula 7]



(III)

wherein R^1, R^2, R^3 and Y are as defined in claim 1 and R^{13} is a hydrogen atom, a hydroxyl group, a cyano group, a carboxyl group, an optionally substituted alkyl group,

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an optionally substituted cycloalkyl group, an optionally substituted alkoxy group, an optionally substituted cycloalkyloxy group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, an optionally substituted alkylcarbonyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyloxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, an optionally substituted alkylsulfonyl group, or the formula: -Rd-C(O)O-Re wherein Rd and Re are as defined in claim 1, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

4. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to claim 3, wherein R^{13} is a hydrogen atom, a hydroxyl group, a cyano group, a carboxyl group, a trifluoromethyl group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aroyl group, an optionally substituted alkylcarbonyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyloxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, an optionally substituted alkylsulfonyl group, or the formula: -Rd-C(O)O-Re wherein Rd and Re are as defined in claim 1.

5. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 4, wherein R^2 is a group represented by any of the following formula (E), formula (F), formula (G), formula (H), formula (I) and formula (J):

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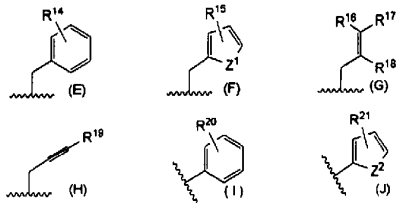
[Formula 8]



wherein each of Z^1 and Z^2 is an oxygen atom, the formula S(O)p or the formula $N(R^{22})$;

each of R^{14} and R^{20} is absent or one or two R^{14}s and/or one or two R^{20}s are present and are independently a halogen atom, a hydroxyl group, a formyl group, a carboxyl group, a cyano group, an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group, a haloalkoxy group, an optionally substituted amino group, an optionally substituted carbamoyl group, an alkoxycarbonyl group, an optionally substituted alkylcarbonyl group, a cycloalkylcarbonyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted nitrogen-containing heteroaryl group, or two R^{14}s or two R^{20}s, when taken together, represent a C_{1-3} alkylenedioxy group;

each of R^{15} and R^{21} is absent or one or two R^{15}s and/or one or two R^{21}s are present and are independently a halogen atom, a cyano group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group or a haloalkoxy group;

R^{16} is methyl, ethyl, a chlorine atom or a bromine atom;

R^{17} is a hydrogen atom, methyl, ethyl, a chlorine atom or a bromine atom;

R^{18} is a hydrogen atom, methyl or ethyl;

R^{19} is a hydrogen atom, methyl, ethyl, cyclopropyl or cyclobutyl;

p is 0, 1 or 2; and

R^{22} is a hydrogen atom or an alkyl group.

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6. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 5, wherein -Y is a group represented by the formula (A) in which m1 is 1 or 2, or -Y is a group represented by the formula (B) in which m2 is 1 or 2, or -Y is a group represented by the formula (C) in which each of m3 and m4 is 1.

7. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 6, wherein R^2 is a group represented by any of the formula (E), formula (H) and formula (I).

8. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 7, wherein R^1 is a hydrogen atom, an optionally substituted C_1-C_3 alkyl group or an optionally substituted aryl group, and the substituent(s) of the optionally substituted alkyl group is selected from fluorine atom, optionally substituted aroyl groups, carboxyl group, optionally substituted alkoxycarbonyl groups, optionally substituted aryl groups and optionally substituted aryloxy groups.

9. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 7, wherein R^1 is a group represented by the formula: -Ra-Rb-Rc in which

Ra is an alkylene group;

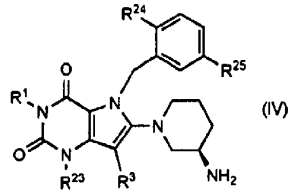
Rb is a single bond or a carbonyl group; and

Rc is an optionally substituted alkyl group, an optionally substituted alkoxy group, an optionally substituted aryl group, an optionally substituted aryloxy group or an optionally substituted heteroarylamino group.

10. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 7, wherein R^1 is a hydrogen atom, methyl or ethyl.

11. A compound according to claim 1, which is represented by the formula (IV):

[Formula 9]

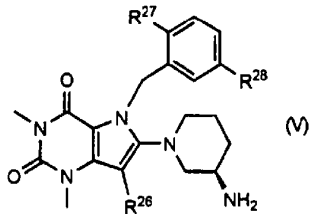


(IV)

wherein R^1 and R^3 are as defined in claim 1; R^{23} is a hydrogen atom or an optionally substituted alkyl group; R^{24} is a halogen atom, a cyano group, a carbamoyl group, a methyl group, a trifluoromethyl group, a difluoromethyl group, a monofluoromethyl group, a methoxy group, a trifluoromethoxy group, difluoromethoxy group or a monofluoromethoxy group; and R^{25} is a hydrogen atom, a fluorine atom or a chlorine atom, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

12. A compound according to claim 1, which is represented by the formula (V):

[Formula 10]



(V)

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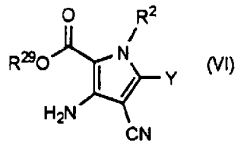
wherein R^{26} is a hydrogen atom, a cyano group, an optionally substituted alkyl group, an optionally substituted carbamoyl group, a hydroxyl group or an optionally substituted alkoxy group; R^{27} is a chlorine atom, a bromine atom, a cyano group, a carbamoyl group, a methyl group, a trifluoromethyl group, a difluoromethyl group, a monofluoromethyl group, a methoxy group, a trifluoromethoxy group, difluoromethoxy group or a monofluoromethoxy group; and R^{28} is a hydrogen atom or a fluorine atom, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

13. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to claim 12, wherein R^{27} is a chlorine atom or a cyano group.

14. A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to either claim 12 or claim 13, wherein R^{26} is a hydrogen atom or an optionally substituted carbamoyl group.

15. A compound represented by the formula (VI):

[Formula 11]



(VI)

wherein R^2 and Y are as defined in claim 1 and R^{29} is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally

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substituted alkynyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group or an optionally substituted heteroarylalkyl group, a prodrug of the compound or a pharmaceutically acceptable salt of the compound or prodrug.

16. A pharmaceutical composition comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 14 as an active ingredient.

17. A dipeptidyl peptidase IV inhibitor comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 14 as an active ingredient.

18. A pharmaceutical composition for the treatment of diabetes comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 14 as an active ingredient.

19. Use of a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 14 in the manufacture of a dipeptidyl peptidase IV inhibitor.

20. Use of a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 14 in the manufacture of a pharmaceutical composition for the treatment of diabetes.

21. A method for treating diabetes comprising administering an effective amount of a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of claims 1 to 14 to a patient who needs the treatment.

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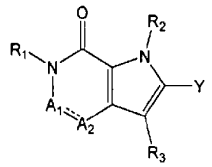
22. Use of a compound according to claim 15 in the manufacture of a dipeptidyl peptidase IV inhibitor or in the manufacture of a compound according to any one of claims 1 to 14.

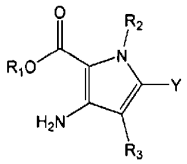
23. A process for preparing a compound of formula (I):



(I)

wherein R_1, R_2, R_3, A_1, A_2 and Y, for formula (I) are as defined in claim 1, and wherein the process comprises the steps of:

(i) reacting in an organic solvent an isocyanate or isothiocyanate compound with a compound of formula (VIa), wherein R_1, R_2, R_3 and Y, are as defined in claim 1:



(VIa)

in the presence of a base to obtain a reaction product; and

(ii) reacting the product obtained from (i) with a base and a source of methyl anion in an organic solvent, and (iii) performing an aqueous work up of the product to form the compound of formula (I).

24. The process of claim 23, wherein the source of methyl anion is methyl iodide.

25. The process of claim 23 or claim 24, wherein the step (ii) is carried out a temperature between 50 and 160°C.

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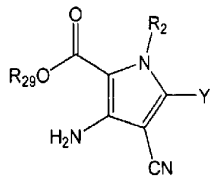
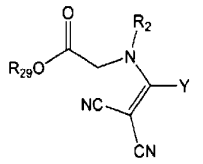
26. A process for preparing a compound of formula (VI):



(VI)

wherein R_2, R_{29} and Y, for formula (VI) are as defined in claim 15, and wherein the process comprises the steps of:

(i) reacting in an organic solvent a compound of formula (VIb), where R_1, R_2, R_3 and Y, are as defined in claim 1:



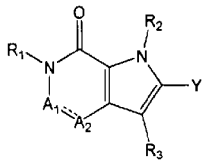
(VIb)

with a strong base to obtain a reaction product; and

(ii) performing an aqueous work up of the product obtained from (i) to form the compound of formula (VI).

27. The process of claim 26, wherein the strong base is a hydride.

28. A compound of formula (I):



(I)

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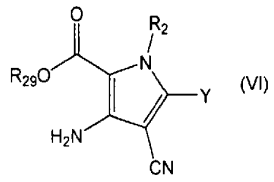
, a dipeptidyl peptidase IV inhibitor comprising the compound, a process for preparing the compound, a pharmaceutical composition comprising the compound, use of the compound in the manufacture of a medicament for the treatment of diabetes, or a method of treating diabetes comprising administering an effective amount of the compound to a patient in need thereof, substantially as herein described with reference to the accompanying Examples.

29. A compound of formula (VI):



(VI)

or a process for preparing the compound, substantially as herein described with reference to the accompanying Examples.