

DESCRIPTION

Title of Invention: TETRAHYDROOXEPINOPYRIDINE COMPOUND

5 **Technical Field**

[0001]

The present invention relates to a tetrahydrooxepinopyridine compound which has a positive allosteric modulating activity (PAM activity) on an $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nACh receptor), and can be expected as an active ingredient of a
10 pharmaceutical composition, in particular, a pharmaceutical composition for treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, cognitive impairment associated with schizophrenia (CIAS), negative symptoms of schizophrenia, inflammatory diseases, or pain.

15 **Background Art**

[0002]

The nicotinic acetylcholine receptor (nACh receptor) is a pentamer consisting of five subunits (α , β , γ , ϵ , or δ) in which these subunits are circularly arranged to constitute an ion channel having cation selectivity (Nature, 2003, vol. 423, pp. 949-955). With
20 regard to the nACh receptor, it is known that there are a plurality of subtypes such as a muscle type ($\alpha 1\beta 1\gamma\delta$), a ganglion type ($\alpha 3\beta 4$), and a central nervous system (CNS) type ($\alpha 7$, $\alpha 4\beta 2$). Binding of an endogenous ligand acetylcholine to the nACh receptor leads to opening of an ion channel, which plays an important role in the expression or regulation of various physiological functions such as muscle contraction, inflammation, synaptic
25 transmission and plasticity.

[0003]

An $\alpha 7$ nACh receptor out of CNS type nACh receptors is present primarily in the cerebral cortex and hippocampus, and is believed to be involved in higher brain functions such as memory and learning. In fact, an $\alpha 7$ nACh receptor agonist has been reported to
30 have various pharmacological effects such as improvement of Alzheimer's disease or CIAS (International Journal of Molecular Sciences, 2012, vol. 13, pp. 2219-2238), improvement of negative symptoms of schizophrenia (The American Journal of Psychiatry, 2008, vol. 165, pp. 1040-1047), inhibition of inflammatory responses (British Journal of Pharmacology, 2007, vol. 151, pp. 915-929), and exhibition of analgesic effects (British
35 Journal of pharmacology, 2012, vol. 167, pp. 421-435). Therefore, a compound stimulating the $\alpha 7$ nACh receptor is considered to be promising as an agent for preventing or treating a disease such as dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.

[0004]

On the other hand, it is known that the $\alpha 7$ nACh receptor exhibits higher Ca^{2+} ion permeability and is readily susceptible to desensitization in response to agonist stimulation when compared with other nACh receptor subtypes (Neuron, 1990, vol. 5, pp. 847-856).

5 Therefore, with respect to agonists, there is a possibility of problems associated with attenuation of drug efficacy due to desensitization.

[0005]

A positive allosteric modulator (PAM) is a group of compounds which themselves have no agonist activity and have an effect of enhancing the intensity of signals transmitted to cells by a receptor. In recent years, drug discovery research on PAMs for an $\alpha 7$ nACh receptor has been energetically proceeding with the aim of improving cognitive impairment seen in Alzheimer's disease patients and schizophrenia patients. In fact, it has become apparent that a plurality of PAMs for an $\alpha 7$ nACh receptor have cognitive function improving effects in various preclinical cognitive models (Biochemical Pharmacology, 10 2007, vol. 74, pp. 1155-1163). From the foregoing, it can be expected that PAMs for an $\alpha 7$ nACh receptor will become a drug for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.

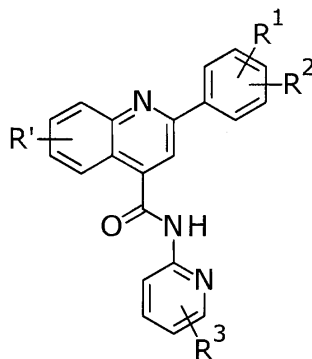
[0006]

20 Up to now, compounds controlling an $\alpha 7$ nACh receptor have been reported.

[0007]

Patent Document 1 discloses that a compound represented by the following general formula or a pharmaceutically acceptable salt thereof is a modulator of an nACh receptor, and there is a description regarding use in the treatment of diseases associated with cholinergic neurons in the CNS or peripheral nervous system (PNS). 25

[Chem. 1]

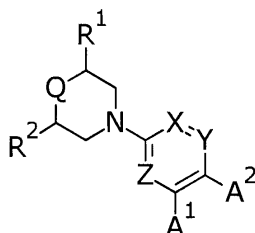


30 (For symbols in the formula, refer to Patent Document 1)

[0008]

Patent Document 2 discloses that a compound represented by the following general formula or a pharmaceutically acceptable salt thereof is an $\alpha 7$ nACh receptor modulator, and there is a description regarding use in the treatment of pain, psychotic disorder, cognitive impairment, or Alzheimer's disease.

5 [Chem. 2]

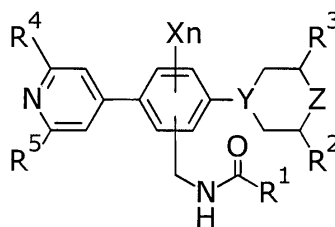


10 (In the formula, each of X, Y or Z is selected from CH and N. For the other symbols, refer to Patent Document 2)

[0009]

Patent Document 3 discloses that a compound represented by the following general formula, an optical isomer, or acid addition salt thereof is a PAM of nACh receptors.

15 [Chem. 3]



20 (In the formula, X is fluoro or chloro; and n is 0, 1 or 2. For the other symbols, refer to Patent Document 3)

Related Art

Patent Document

[0010]

25 [Patent Document1] WO 2010/020672

[Patent Document2] WO 2012/055942

[Patent Document3] WO 2012/113850

Disclosure of Invention

Problems to Be Solved by the Invention

[0011]

Provided is a compound which has a PAM activity on an $\alpha 7$ nACh receptor, and can be expected as an active ingredient of a pharmaceutical composition, in particular, a pharmaceutical composition for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.

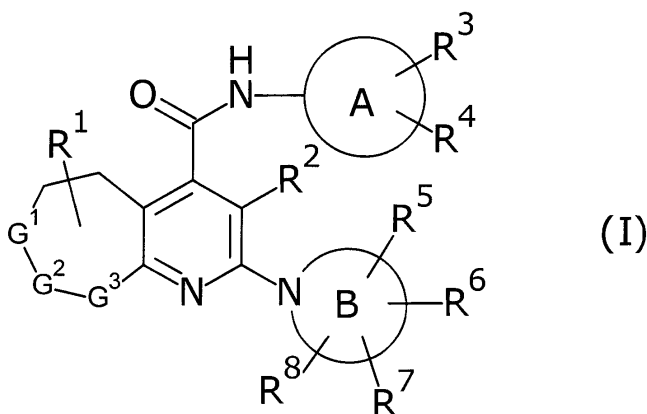
Means for Solving the Problems

[0012]

The present inventors have conducted extensive studies on a compound having a PAM activity on an $\alpha 7$ nACh receptor, and as a result, they have found that the tetrahydrooxepinopyridine compound of the present invention has a PAM activity on an $\alpha 7$ nACh receptor, thereby completing the present invention.

That is, the present invention relates to a compound of the formula (I) or a salt thereof, as well as a pharmaceutical composition comprising a compound of the formula (I) or a salt thereof and a pharmaceutically acceptable excipient.

[Chem. 4]



(In the formula,

R^1 is H or lower alkyl,

R^2 is H or CN,

any one of G^1 , G^2 , and G^3 is O, and the other two of G^1 , G^2 , and G^3 are CH_2 ,

ring A is aryl, or nitrogen-containing heteroaryl,

ring B is cyclic amino,

R^3 and R^4 are the same as or different each other, and are H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, -O-halo-lower alkyl, cycloalkyl, CN, OH, -N(lower alkyl)₂, or -C(=O)NH₂,

R^5 , R^6 , R^7 and R^8 are the same as or different from each other, and are H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN, or

in the case where R^5 and R^6 are bonded to the same carbon atom, R^5 and R^6 may form cycloalkane or cyclic ether together with the carbon atom, and may form a spiro ring together with Ring B, or

ring B may form 6,7-dihydro[1,3]oxazolo[4,5-c]pyridin-5(4H)-yl together with R^5 and R^6 .)

In addition, unless otherwise specified, when symbols in a certain chemical formula in the present specification are also used in another chemical formula, the same symbol represents the same meaning.

[0013]

Moreover, the present invention relates to:

(1) a pharmaceutical composition comprising a compound of the formula (I) or a salt thereof, which is a positive allosteric modulator on an $\alpha 7$ nicotinic acetylcholine receptor;

and

(2) a pharmaceutical composition for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain, comprising a compound of the formula (I) or a salt thereof.

(3) Here, the pharmaceutical composition includes an agent for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain, comprising a compound of the formula (I) or a salt thereof.

Further, the present invention relates to:

(4) use of a compound of the formula (I) or a salt thereof for the manufacture of a pharmaceutical composition for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain;

(5) use of a compound of the formula (I) or a salt thereof for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain;

(6) a compound of the formula (I) or a salt thereof for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain; and

(7) a method for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain, comprising administering to a subject an effective amount of a compound of the formula (I) or a salt thereof.

Meanwhile, the term "subject" is a human being or another animal in need of prevention or treatment thereof, and according to one embodiment, a human being in need of prevention or treatment thereof.

5 Effects of the Invention

[0014]

A compound of the formula (I) or a salt thereof has a PAM activity on an $\alpha 7$ nACh receptor, and can be expected to be used as an agent for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of
10 schizophrenia, inflammatory diseases, or pain.

Embodiments for Carrying Out the Invention

[0015]

Hereinafter, the present invention will be described in detail.

15 As used herein, the term "lower alkyl" is a linear or branched alkyl having 1 to 6 carbon atoms (hereinafter, also referred to as C₁₋₆ alkyl). For example, the lower alkyl is methyl, ethyl, n-propyl, isopropyl, n-butyl, or the like. In one embodiment, the lower alkyl is C₁₋₂ alkyl. In one embodiment, the lower alkyl is methyl.

[0016]

20 The "lower alkylene" is a linear or branched C₁₋₆ alkylene (hereinafter, also referred to as C₁₋₆ alkylene), for example, methylene, ethylene, propylene, -C(CH₃)₂-, or the like; and in one embodiment, -C(CH₃)₂-.

[0017]

The "halogen" is F, Cl, Br, or I; and in one embodiment, F.

25 [0018]

The "halo-lower alkyl" is C₁₋₆ alkyl substituted with one or more halogen atoms; in one embodiment, C₁₋₆ alkyl substituted with 1 to 5 halogen atoms; in one embodiment, C₁₋₆ alkyl substituted with 1 to 3 halogen atoms; in one embodiment, CF₃ or CHF₂; and in one embodiment, CF₃.

30 [0019]

The "cycloalkane" is a saturated hydrocarbon ring having 3 to 7 ring atoms (hereinafter, also referred to as C₃₋₇ cycloalkane), for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, or the like; in one embodiment, C₃₋₆ cycloalkane; and in one embodiment, cyclopropane.

35 [0020]

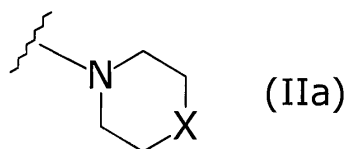
The "cycloalkyl" is a saturated hydrocarbon ring group having 3 to 7 ring atoms (hereinafter, also referred to as C₃₋₇ cycloalkyl), for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or the like; in one embodiment, C₃₋₆ cycloalkyl; and

in one embodiment, cyclopropyl.

[0021]

The “cyclic amino” is a group in which one or more ring atoms are substituted with nitrogen atoms in cycloalkyl having 5 to 7 ring atoms, which has a bond on one of the nitrogen atoms. Here, some of carbon atoms of ring atoms may be substituted with oxygen atoms. In one embodiment, the cyclic amino is 5- or 6-membered cyclic amino; in one embodiment, a group of the formula (IIa):

[Chem. 5]



wherein X is CH₂, O, or a bond; in one embodiment, a group of the formula (IIa) wherein X is CH₂ or O; in one embodiment, a group of the formula (IIa) wherein X is CH₂ or a bond; in one embodiment, a group of the formula (IIa) wherein X is CH₂; in one embodiment, a group of the formula (IIa) wherein X is O; and in one embodiment, a group of the formula (IIa) wherein X is a bond.

[0022]

The “cyclic ether” is a saturated ring having 3 to 8 ring atoms and containing only 1 or 2 oxygen atoms as a heteroatom, for example, oxirane, oxetane, oxolane, dioxolane, oxane, dioxane, oxepane, oxocane, or the like; in one embodiment, 3- to 6-membered cyclic ether; and in one embodiment, oxetane.

[0023]

The “aryl” is an aromatic hydrocarbon ring group formed by removing one hydrogen atom from a monocyclic or bicyclic aromatic hydrocarbon ring having 6 to 10 carbon atoms (hereinafter, also referred to as C₆₋₁₀ aryl), for example, phenyl or naphthyl; and in one embodiment, phenyl.

[0024]

The “nitrogen-containing heteroaryl” is a group formed by removing one hydrogen atom from a monocyclic or bicyclic aromatic hetero ring, which has one or more nitrogen atoms as ring atoms and may further have one or more oxygen atoms or sulfur atoms as ring atoms. Examples thereof include (a) oxazolyl, isoxazolyl, isothiazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, triazolyl, and the like; (b) pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like; and (c) benzothiazolyl, benzimidazolyl, thiazolopyridyl, and the like.

[0025]

The "nitrogen-containing monocyclic heteroaryl" is a monocyclic nitrogen-containing heteroaryl, for example, the above (a) or (b).

The "nitrogen-containing 5-membered heteroaryl" is 5-membered nitrogen-containing heteroaryl, for example, the above (a).

5 The "nitrogen-containing 6-membered heteroaryl" is 6-membered nitrogen-containing heteroaryl, for example, the above (b).

The "nitrogen-containing bicyclic heteroaryl" is bicyclic nitrogen-containing heteroaryl, for example, the above (c).

[0026]

10 One embodiment of the "nitrogen-containing heteroaryl" may be shown below. An example thereof is nitrogen-containing monocyclic heteroaryl, or nitrogen-containing bicyclic heteroaryl; in one embodiment, nitrogen-containing monocyclic heteroaryl, or nitrogen-containing bicyclic heteroaryl in which nitrogen-containing monocyclic heteroaryl is fused with a benzene ring or a pyridine ring; in one embodiment, nitrogen-
15 containing monocyclic heteroaryl; in one embodiment, nitrogen-containing 6-membered heteroaryl; in one embodiment, nitrogen-containing 6-membered heteroaryl having one or two nitrogen atoms as ring atoms; in one embodiment, nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms; in one embodiment, pyridyl, pyridazinyl or pyrazinyl; in one embodiment, pyridyl; and in one embodiment, pyridazinyl.

20 [0027]

One embodiment of the present invention is shown below. In the present specification, particularly in terms of embodiments, "a compound of the formula (I) or a salt thereof" may be simply referred to as "a compound of the formula (I)" in some cases. In the present specification, particularly in terms of embodiments, "a compound or a salt
25 thereof" may be simply referred to as "a compound" in some cases.

(1) A compound of the formula (I) wherein R^1 is H.

(2) A compound of the formula (I) wherein R^2 is H.

(3) A compound of the formula (I) wherein G^1 is O, and G^2 and G^3 are CH_2 .

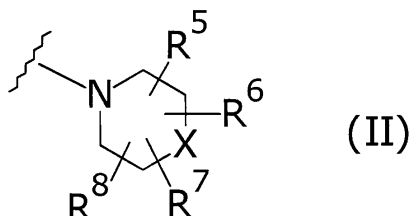
(4) A compound of the formula (I) wherein ring A is phenyl or nitrogen-containing
30 heteroaryl. In one embodiment, a compound of the formula (I) wherein ring A is phenyl, nitrogen-containing monocyclic heteroaryl, or nitrogen-containing bicyclic heteroaryl. In one embodiment, a compound of the formula (I) wherein ring A is nitrogen-containing monocyclic heteroaryl. In one embodiment, a compound of the formula (I) wherein ring A is nitrogen-containing 6-membered heteroaryl having one or two nitrogen atoms as ring
35 atoms. In one embodiment, a compound of the formula (I) wherein ring A is pyridyl. In one embodiment, a compound of the formula (I) wherein ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms.

[0028]

(5) A compound of the formula (I) wherein ring B is 5- or 6-membered cyclic amino.

(5-1) A compound of the formula (I) wherein ring B and R^5 , R^6 , R^7 , and R^8 (hereinafter, also referred to as R^5 to R^8) are the formula (II):

[Chem. 6]

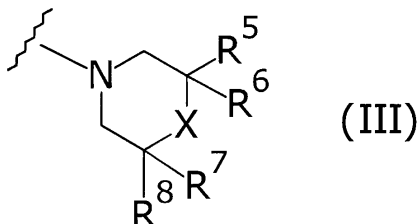


X is CH_2 , O, or a bond, and in the case where X is CH_2 , R^5 and R^6 may be substituted with X. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (II), and X is CH_2 , O, or a bond. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (II), and in the case where X is CH_2 , R^5 and R^6 are substituted with X. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (II), and X is CH_2 or O. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (II), and X is O. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (II), and X is CH_2 . In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (II), and X is bond.

[0029]

(5-2) A compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (III):

[Chem. 7]



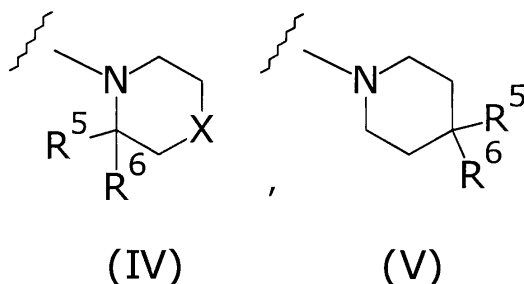
and X is CH_2 , O, or a bond. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (III), and X is CH_2 or O. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the formula (III), and X is O. In one embodiment, a compound of the formula (I) wherein ring B and R^5 to R^8 are the

formula (III), and X is CH₂.

[0030]

(5-3) A compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (IV) or the formula (V):

[Chem. 8]

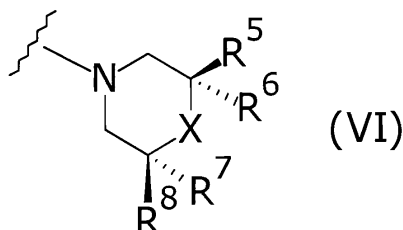


and X is CH₂ or a bond. In one embodiment, a compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (IV) or the formula (V), and X is a bond. In one embodiment, a compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (IV) or the formula (V), and X is CH₂. In one embodiment, a compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (IV), and X is CH₂ or a bond. In one embodiment, a compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (IV), and X is a bond. In one embodiment, a compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (IV), and X is CH₂. In one embodiment, a compound of the formula (I) wherein ring B and R⁵ to R⁸ is the formula (V).

[0031]

(5-4) A compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (VI):

[Chem. 9]



and X is CH₂ or O. In one embodiment, a compound of the formula (I) wherein ring B and R⁵ to R⁸ are the formula (VI), and X is O.

[0032]

(5-5) A compound of the formula (I) wherein ring B forms 6,7-

dihydro[1,3]oxazolo[4,5-c]pyridin-5(4H)-yl together with R^5 and R^6 .

[0033]

(6) A compound of the formula (I) wherein R^3 is H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, -O-halo-lower alkyl, cycloalkyl, CN, OH, -N(lower alkyl)₂, or -C(=O)NH₂. In one embodiment, a compound of the formula (I) wherein R^3 is H or lower alkyl. In one embodiment, a compound of the formula (I) wherein R^3 is H. In one embodiment, a compound of the formula (I) wherein R^3 is lower alkyl.

(7) A compound of the formula (I) wherein R^4 is H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, -O-halo-lower alkyl, cycloalkyl, CN, OH, -N(lower alkyl)₂, or -C(=O)NH₂. In one embodiment, a compound of the formula (I) wherein R^4 is H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, cycloalkyl or CN. In one embodiment, a compound of the formula (I) wherein R^4 is halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, cycloalkyl or CN. In one embodiment, a compound of the formula (I) wherein R^4 is H, halogen, lower alkyl, or -O-lower alkyl. In one embodiment, a compound of the formula (I) wherein R^4 is halogen, lower alkyl, or -O-lower alkyl. In one embodiment, a compound of the formula (I) wherein R^4 is H or halogen. In one embodiment, a compound of the formula (I) wherein R^4 is H. In one embodiment, a compound of the formula (I) wherein R^4 is halogen. In one embodiment, a compound of the formula (I) wherein R^4 is lower alkyl. In one embodiment, the compound of the formula (I) wherein R^4 is -O-lower alkyl.

(8) A compound of the formula (I) wherein R^5 is H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN. In one embodiment, a compound of the formula (I) wherein R^5 is H, halogen, lower alkyl, or halo-lower alkyl. In one embodiment, a compound of the formula (I) wherein R^5 is halogen or lower alkyl. In one embodiment, a compound of the formula (I) wherein R^5 is halogen. In one embodiment, a compound of the formula (I) wherein R^5 is lower alkyl. In one embodiment, a compound of the formula (I) wherein R^5 is halo-lower alkyl. In one embodiment, a compound of the formula (I) wherein R^5 is CH₃.

(9) A compound of the formula (I) wherein R^6 is H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN. In one embodiment, a compound of the formula (I) wherein R^6 is H, halogen, lower alkyl, or halo-lower alkyl. In one embodiment, a compound of the formula (I) wherein R^6 is H or lower alkyl. In one embodiment, a compound of the formula (I) wherein R^6 is lower alkyl. In one embodiment, a compound of the formula (I) wherein R^6 is H.

(10) A compound of the formula (I) wherein in the case where R^5 and R^6 are bonded to the same carbon atom, R^5 and R^6 form cycloalkane or cyclic ether together with the carbon atom, and form a spiro ring together with ring B. In one embodiment, a

compound of the formula (I) wherein in the case where R^5 and R^6 are bonded to the same carbon atom, R^5 and R^6 form C_{3-6} cycloalkane or 3- to 6-membered cyclic ether together with the carbon atom, and form a spiro ring together with ring B. In one embodiment, a compound of the formula (I) wherein in the case where R^5 and R^6 are bonded to the same carbon atom, R^5 and R^6 form cycloalkane together with the carbon atom.

(11) A compound of the formula (I) wherein R^7 is H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN. In one embodiment, a compound of the formula (I) wherein R^7 's are the same as or different from each other, and are H, halogen, lower alkyl, or halo-lower alkyl. In one embodiment, a compound of the formula (I) wherein R^7 is H or lower alkyl. In one embodiment, a compound of the formula (I) wherein R^7 is lower alkyl. In one embodiment, a compound of the formula (I) wherein R^7 is H.

(12) A compound of the formula (I) wherein R^8 is H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN. In one embodiment, a compound of the formula (I) wherein R^8 is H, halogen, lower alkyl, or halo-lower alkyl. In one embodiment, a compound of the formula (I) wherein R^8 is H or lower alkyl. In one embodiment, a compound of the formula (I) wherein R^8 is lower alkyl. In one embodiment, a compound of the formula (I) wherein R^8 is CH_3 . In one embodiment, a compound of the formula (I) wherein R^8 is H.

(13) The compound of the formula (I) which is a non-contradictory combination of two or more of the groups described in the above (1) to (12).

[0034]

Examples of the combination described in the above (13) include the following embodiments.

(14) A compound of the formula (I) wherein R^3 and R^4 are the same as or different from each other, and are H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, -O-halo-lower alkyl, cycloalkyl, CN, OH, -N(lower alkyl)₂, or -C(=O)NH₂.

(15) A compound of the formula (I) wherein R^5 to R^8 are the same as or different from each other, and are H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN, or

in the case where R^5 and R^6 are bonded to the same carbon atom, R^5 and R^6 may form C_{3-6} cycloalkane or 3- to 6-membered cyclic ether together with the carbon atom, and may form a spiro ring together with ring B, or

ring B may form 6,7-dihydro[1,3]oxazolo[4,5-c]pyridin-5(4H)-yl together with R^5 and R^6 .

(16) A compound of the formula (I) wherein R^5 to R^8 are the same as or different from each other, and are H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN, A compound of the formula (I) wherein R^5 to R^8 are the same as or different from each

other, and are H, halogen, lower alkyl, or halo-lower alkyl. A compound of the formula (I) wherein R^5 to R^8 are the same as or different from each other, and are H, lower alkyl, or halo-lower alkyl.

- (17) A compound of the formula (I) wherein R^5 is halo-lower alkyl, and R^6 , R^7 , and R^8 are H. In one embodiment, a compound of the formula (I) wherein R^5 , R^6 , R^7 and R^8 are lower alkyl. In one embodiment, a compound of the formula (I) wherein R^5 and R^8 are lower alkyl, and R^6 and R^7 are H. In one embodiment, a compound of the formula (I) wherein R^5 and R^8 are CH_3 , and R^6 and R^7 are H.

[0035]

- Further, specific examples of the combination described in the above (13) include the following embodiments.

(A) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is pyridyl, ring B and R^5 to R^8 are the formula (III), X is O, R^3 is H, R^4 is halogen, R^5 is lower alkyl, R^6 is H, R^7 is H, and R^8 is lower alkyl.

(B) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is pyridyl, ring B and R^5 to R^8 are the formula (III), X is O, R^3 is H, R^4 is lower alkyl, R^5 is lower alkyl, R^6 is H, R^7 is H, and R^8 is H.

(C) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are the formula (IV), X is a bond, R^3 is H or lower alkyl, R^4 is lower alkyl or -O-lower alkyl, R^5 is lower alkyl, R^6 is H, R^7 is H, and R^8 is H.

(D) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are the formula (IV), X is a bond, R^3 is H, R^4 is -O-lower alkyl, R^5 is lower alkyl, R^6 is H, R^7 is H, and R^8 is H.

(E) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are the formula (IV), X is a bond, R^3 is H, R^4 is lower alkyl, R^5 is lower alkyl, R^6 is H, R^7 is H, and R^8 is H.

(F) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are the formula (IV), X is a bond, R^3 is lower alkyl, R^4 is lower alkyl, R^5 is lower alkyl, R^6 is H, R^7 is H, and R^8 is H.

(G) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are a group of the formula (V), R^3 is H, R^4 is H, R^5 is halogen, and each of R^6 , R^7 and R^8 is H.

(H) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are the formula (III), X is CH_2 , R^3 is H, R^4 is H, R^5 is lower alkyl, R^6 is H, R^7 is H, and R^8 is lower alkyl.

5 (I) A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is pyridyl, ring B and R^5 to R^8 are the formula (III), X is O, R^3 is H, R^4 is halogen, R^5 is halogen, R^6 is H, R^7 is H, and R^8 is H.

[0036]

Further, other specific examples of the combination of the above (13) include the
10 following embodiments.

[1] A compound of the formula (I) wherein R^1 is H, R^2 is H, G^1 is O, each of G^2 and G^3 is CH_2 , ring A is phenyl or nitrogen-containing heteroaryl, and ring B is 5- or 6-membered cyclic amino.

[2] The compound according to [1], wherein ring A is nitrogen-containing
15 monocyclic heteroaryl, R^3 is H or lower alkyl, R^4 is H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, -O-halo-lower alkyl, cycloalkyl, CN, OH, -N(lower alkyl)₂, or -C(=O)NH₂, and R^5 to R^8 are the same as or different from each other, and are H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN.

[2-1] The compound according to [1], wherein ring A is nitrogen-containing
20 monocyclic heteroaryl, R^3 is H or lower alkyl, R^4 is H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, cycloalkyl, or CN.

[2-2] The compound according to [1], wherein ring A is nitrogen-containing monocyclic heteroaryl, R^3 is H or lower alkyl, R^4 is H, halogen, lower alkyl, or -O-lower alkyl.

25 [3] The compound according to [1] or [2], wherein ring B and R^5 to R^8 are the formula (II), X is CH_2 , O, or a bond, in the case where X is CH_2 , R^5 and R^6 may be substituted with X, and R^5 to R^8 are the same as or different from each other, and are H, halogen, lower alkyl, or halo-lower alkyl.

[4] The compound according to [3], wherein X is CH_2 or O.

30 [5] The compound according to [3], wherein X is bond.

[6] The compound according to [4], wherein ring A is nitrogen-containing 6-membered heteroaryl having one or two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are the formula (III), R^5 is halogen or lower alkyl, R^6 is H, R^7 is H, and R^8 is H or lower alkyl.

35 [7] The compound according to [6], wherein ring A is pyridyl, X is CH_2 , R^5 is halogen, and R^8 is H.

[8] The compound according to [6], wherein ring A is pyridyl, X is O, R^5 is lower alkyl, and R^8 is lower alkyl.

[9] The compound according to [5], wherein ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as ring atoms, ring B and R^5 to R^8 are the formula (IV), R^5 is halogen or lower alkyl, R^6 is H, R^7 is H, and R^8 is H.

5 [10] The compound according to [1], wherein ring B and R^5 to R^8 are the formula (II), X is CH_2 or O.

[11] The compound according to [10], wherein ring A, R^3 , R^4 and R^5 to R^8 are each of the groups described in [2].

[12] The compound according to [11], R^5 to R^8 are the same as or different from each other, and are H, halogen, lower alkyl, or halo-lower alkyl.

10 [13] The compound according to [12], wherein R^3 is H or lower alkyl, R^4 is H, halogen, lower alkyl, or -O-lower alkyl.

[14] The compound according to [13], wherein ring B and R^5 to R^8 are the formula (III).

15 [15] The compound according to [1], wherein ring B and R^5 to R^8 are the formula (II), X is bond.

[16] The compound according to [15], wherein ring A, R^3 , R^4 and R^5 to R^8 are each of the groups described in [2].

[17] The compound according to [16], R^5 to R^8 are the same as or different from each other, and are H, halogen, lower alkyl, or halo-lower alkyl.

20 [18] The compound according to [17], wherein R^3 is H or lower alkyl, R^4 is H, halogen, lower alkyl, or -O-lower alkyl.

[19] The compound according to [18], wherein ring B and R^5 to R^8 are the formula (IV).

25 [20] The compound according to any one of [3] to [19], wherein [2] is [2-1] or [2-2].

[21] The compound according to any one of [1] to [20], wherein X is CH_2 .

[22] The compound according to any one of [1] to [20], wherein X is O.

[0037]

30 Further, still other specific examples of the combination of the above (13) include the following embodiments.

[a] A compound of the formula (I) wherein R^5 to R^8 are the same as or different from each other, and are H, halogen, lower alkyl, or halo-lower alkyl,

wherein R^5 and R^6 , taken together with the same carbon atom to which they are bonded, may form cycloalkane.

35 [b] The compound according to [a], wherein G^1 is O, G^2 and G^3 are CH_2 , ring B and R^5 to R^8 are the formula (II), and X is CH_2 or O.

[c] The compound according to [b], wherein ring B and R^5 to R^8 are the formula (III), and X is CH_2 or O.

[d] The compound according to [c], wherein ring A is phenyl or nitrogen-containing monocyclic heteroaryl, and the nitrogen-containing monocyclic heteroaryl is a group which may be fused with a benzene ring or a pyridine ring.

[e] The compound according to [d], wherein R¹ is H, and R² is H.

5 [f] The compound according to [e], wherein R³ and R⁴ are the same as or different from each other, and are H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, -O-halo-lower alkyl, C₃₋₆ cycloalkyl or CN, and R⁵ to R⁸ are the same as or different from each other, and are H, lower alkyl, or halo-lower alkyl.

10 [g] The compound according to [f], wherein R¹ is H, R² is H, G¹ is O, G² and G³ are CH₂, ring A is nitrogen-containing 6-membered heteroaryl having one or two nitrogen atoms, ring B and R⁵ to R⁸ are the formula (III), X is O, R³ is H, R⁴ is H or halogen, and R⁵ to R⁸ are the same as or different from each other, and are H, lower alkyl, or halo-lower alkyl.

15 [h] The compound according to [g], wherein ring B and R⁵ to R⁸ are the formula (VI), one of R⁵ and R⁶ is halo-lower alkyl and the other one is H, and R⁷ and R⁸ are H.

[i] The compound according to [g], wherein ring B and R⁵ to R⁸ are the formula (VI), and R⁵, R⁶, R⁷, and R⁸ are lower alkyl.

[j] The compound according to [g], wherein ring B and R⁵ to R⁸ are the formula (VI), R⁵ and R⁸ are lower alkyl, and R⁶ and R⁷ are H.

20 [0038]

Specific examples of the compound encompassed by the present invention include compounds of the formula (I) or salts thereof selected from the group consisting of the following.

25 N-(pyridazin-3-yl)-2-[(3S)-3-(trifluoromethyl)piperidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

N-(pyridazin-3-yl)-2-[(3R)-3-(trifluoromethyl)piperidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

N-(pyridazin-3-yl)-2-(2,2,6,6-tetramethylmorpholin-4-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

30 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-(5-fluoropyridin-2-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

35 N-(6-methoxypyridazin-3-yl)-2-[(2R)-2-methylpyrrolidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

N-(6-methylpyrazin-2-yl)-2-[(2S)-2-methylpyrrolidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

2-[(2R)-2-ethylmorpholin-4-yl]-N-(6-methylpyridin-3-yl)-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

N-(5,6-dimethylpyrazin-2-yl)-2-[(2R)-2-methylpyrrolidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

N-(3-cyanophenyl)-2-[(3S)-3-methoxypyrrolidin-1-yl]-5,6,8,9-

5 tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

2-(4-fluoropiperidin-1-yl)-N-(pyridazin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-

b]pyridine-4-carboxamide,

N-(5-chloropyridin-2-yl)-2-(4-fluoropiperidin-1-yl)-5,6,8,9-tetrahydrooxepino[4,5-

b]pyridine-4-carboxamide,

10 N-(5,6-dimethylpyrazin-2-yl)-2-[(2S)-2-methylpyrrolidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

2-[(2S)-2-methylpiperidin-1-yl]-N-(pyridazin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-

b]pyridine-4-carboxamide,

2-[(2S)-2-methylpiperidin-1-yl]-N-(pyrazin-2-yl)-5,6,8,9-tetrahydrooxepino[4,5-

15 b]pyridine-4-carboxamide, and

N-(5-chloropyridin-2-yl)-2-[(3S)-3-fluoropiperidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide.

[0039]

Specific examples of the compound encompassed by the present invention include
20 compounds of the formula (I) or salts thereof selected from the group consisting of the following.

N-(pyridazin-3-yl)-2-[(3S)-3-(trifluoromethyl)piperidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide fumarate,

N-(pyridazin-3-yl)-2-[(3R)-3-(trifluoromethyl)piperidin-1-yl]-5,6,8,9-

25 tetrahydrooxepino[4,5-b]pyridine-4-carboxamide fumarate,

N-(pyridazin-3-yl)-2-(2,2,6,6-tetramethylmorpholin-4-yl)-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride,

2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-(5-fluoropyridin-2-yl)-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

30 N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride,

N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide p-toluenesulfonate,

N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-

35 tetrahydrooxepino[4,5-b]pyridine-4-carboxamide benzenesulfonate,

N-(6-methoxypyridazin-3-yl)-2-[(2R)-2-methylpyrrolidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide phosphate,

N-(6-methylpyrazin-2-yl)-2-[(2S)-2-methylpyrrolidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride,

2-[(2R)-2-ethylmorpholin-4-yl]-N-(6-methylpyridin-3-yl)-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride,

N-(5,6-dimethylpyrazin-2-yl)-2-[(2R)-2-methylpyrrolidin-1-yl]-5,6,8,9-

5 tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride,

N-(3-cyanophenyl)-2-[(3S)-3-methoxypyrrolidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride,

2-(4-fluoropiperidin-1-yl)-N-(pyridazin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-

b]pyridine-4-carboxamide hydrochloride,

10 N-(5-chloropyridin-2-yl)-2-(4-fluoropiperidin-1-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,

N-(5,6-dimethylpyrazin-2-yl)-2-[(2S)-2-methylpyrrolidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride,

2-[(2S)-2-methylpiperidin-1-yl]-N-(pyridazin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-

15 b]pyridine-4-carboxamide hydrochloride,

2-[(2S)-2-methylpiperidin-1-yl]-N-(pyrazin-2-yl)-5,6,8,9-tetrahydrooxepino[4,5-

b]pyridine-4-carboxamide hydrochloride, and

N-(5-chloropyridin-2-yl)-2-[(3S)-3-fluoropiperidin-1-yl]-5,6,8,9-

tetrahydrooxepino[4,5-b]pyridine-4-carboxamide benzenesulfonate.

20 [0040]

The compound of the formula (I) may exist in the form of tautomers or geometrical isomers depending on the kind of substituents. In the present specification, the compound of the formula (I) may be described in only one form of isomers, yet the present invention includes any other isomers, isolated forms of the isomers, or a mixture thereof.

25

In addition, the compound of the formula (I) may have asymmetric carbon atoms or axis chirality in some cases, and correspondingly, it may exist in the form of optical isomers. The present invention also includes an isolated form of the optical isomers of the compound of the formula (I) or a mixture thereof.

30 [0041]

Further, the present invention also includes a pharmaceutically acceptable prodrug of the compound represented by the formula (I). The pharmaceutically acceptable prodrug is a compound having a group that can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like through solvolysis or under physiological conditions. Examples of the group forming the prodrug include the groups described in, for example, Progress in Medicine, 1985, vol. 5, 2157-2161 and "Pharmaceutical Research and Development" (Hirokawa-Shoten Ltd.) 1990, Vol. 7 (Molecular Design) pp. 163 to 198.

35

[0042]

Moreover, the salt of the compound of the formula (I) is a pharmaceutically acceptable salt of the compound of the formula (I) and may form an acid addition salt or a salt with a base depending on the kind of substituents. Specific examples thereof include
5 acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; and acid addition salts with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid,
10 ethanesulfonic acid, benzenesulfonic acid (besylic acid), p-toluenesulfonic acid (4-methylbenzenesulfonic acid, tosic acid), aspartic acid, and glutamic acid.

[0043]

The present invention further includes various hydrates or solvates, and polymorphic crystal substances of a compound of the formula (I) and a salt thereof. In
15 addition, the present invention also includes compounds labeled with various radioactive or non-radioactive isotopes.

[0044]

As used herein, the term "CIAS" refers to cognitive impairment associated with schizophrenia.

20 The "negative symptoms of schizophrenia" refers to negative symptoms in schizophrenia.

[0045]

(Preparation Methods)

The compound of the formula (I) and a salt thereof can be prepared using the
25 characteristics based on the basic structure or the type of substituent thereof and by using various known synthesis methods. During the preparation, replacing the relevant functional group with a suitable protective group (a group that can be easily converted into the relevant functional group) at the stage of starting materials or intermediates may be effective depending on the type of the functional group in the production in some cases.
30 Examples of such a protective group include those described in by Peter G M. Wuts and Theodora W. Greene, "Greene's Protective Groups in Organic Synthesis (4th edition), 2006", and the like, and one of these may be appropriately selected depending on reaction conditions. A desired compound can be obtained by introducing the protective group to carry out a reaction, and then by eliminating the protective group as necessary.

35 In addition, the prodrug of the compound of the formula (I) can be prepared by introducing a specific group at the stage from a starting material to an intermediate or by further carrying out the reaction using the obtained compound of the formula (I), just as in the case of the above-mentioned protective group. The reaction can be carried out using

methods known to those skilled in the art, such as ordinary esterification, amidation, dehydration, and the like.

Hereinbelow, the representative preparation methods for the compound of the formula (I) will be described. Each of the preparation methods may also be carried out with reference to the References. Further, the preparation methods of the present invention are not limited to the examples as shown below.

[0046]

The following abbreviations may be used in some cases in the present specification.

- 10 AcOEt: ethyl acetate, AcCl: acetyl chloride, brine: saturated brine, BINAP: 1,1'-binaphthalene-2,2'-diylbis (diphenylphosphine), nBuLi: n-butyllithium, tBuOH: tert-butyl alcohol, Comins reagent: N-(5-chloro-2-pyridyl)triflimide, DIPEA: N,N-diisopropylethylamine, DMAP: N,N-dimethyl-4-aminopyridine, DME: dimethoxyethane, DMF: N,N-dimethylformamide, DMSO: dimethylsulfoxide, dppf: 1,1'-
- 15 bis(diphenylphosphino)ferrocene, EtOH: ethanol, Et₂O: diethyl ether, Et₃N: triethylamine, FM: fumaric acid, Ghosez reagent: 1-chloro-N,N,2-trimethyl-1-propenyl amine, Grubbs catalyst: benzylidene [1,3-bis (2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium, HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide
- 20 hexafluorophosphate, HOBt: 1-hydroxybenzotriazole, iPr₂O: diisopropyl ether, iPrOH: 2-propanol, KHMDS: potassium hexamethyldisilazide, KOtBu: potassium tert-butoxide, LDA: lithium diisopropylamide, LHMDs: lithium hexamethyldisilazide, LiTMP: lithium 2,2,6,6-tetramethylpiperidide, McMurry's reagent: 1,1,1-trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide, MeCN: acetonitrile, MeOH: methanol,
- 25 MgSO₄: anhydrous magnesium sulfate, NBS: N-bromosuccinimide, NMP: N-methyl-2-pyrrolidone, NaHMDS: sodium hexamethyldisilazide, Na₂SO₄: anhydrous sodium sulfate, NaOtBu: sodium tert-butoxide, OsO₄-NaIO₄: osmium tetroxide-sodium periodate, Pd(OAc)₂: palladium acetate (II), Pd(dba)₂: bis(dibenzylideneacetone)palladium (0), Pd₂(dba)₃: tris(dibenzylideneacetone)palladium (0), Pd(PPh₃)₄:
- 30 tetrakis(triphenylphosphine)palladium (0), Pd/C: palladium on carbon, Pd(OH)₂/C: palladium hydroxide on carbon, Pt/C: platinum on carbon, PyCLU: 1-(chloro-1-pyrrolidyl methylene)pyrrolidinium hexafluorophosphate, TBAF: tetra-n-butylammonium fluoride, TBAI: tetrabutylammonium iodide, TCFH: chloro-N,N,N',N'-tetramethyl formamidinium hexafluorophosphate, TFFH: fluoro-N,N,N',N'-tetramethyl- formamidinium
- 35 hexafluorophosphate, THF: tetrahydrofuran, Tf₂O: (CF₃SO₂)₂O, Wilkinson complex: chlorotris(triphenylphosphine)rhodium (I), WSC hydrochloride: N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride, tBu₂BINAP: 1,1'-binaphthalen-2-yl(di-tert-butyl) phosphine, silica gel CC: silica gel column

chromatography.

[0047]

In this specification, in particular the chemical structural formula, the following abbreviations may be used in some cases.

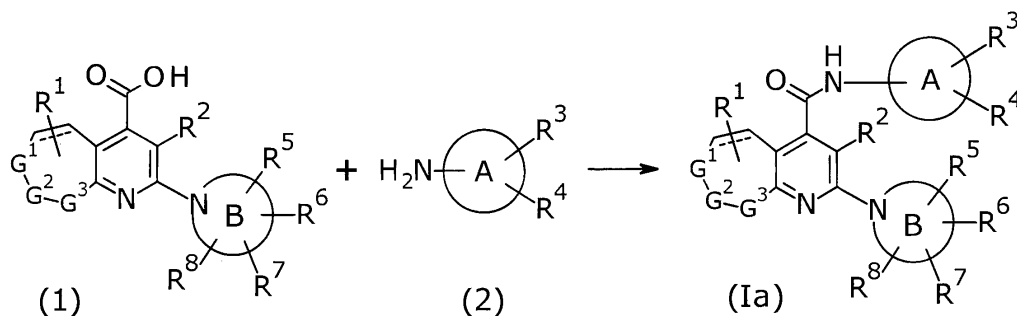
5 Ac: $\text{CH}_3\text{C}(=\text{O})$, BOC: tert-butoxycarbonyl, Et: C_2H_5 , Me: CH_3 , OMe: OCH_3 , Tf: CF_3SO_2 , PMB: p-methoxybenzyl.

[0048]

(First preparation method)

[Chem. 10]

10



(In the formula, ---- represents a single bond or a double bond. The same shall apply hereinafter).

15 (The compound (I) of the present invention is a compound wherein ---- in the compound (Ia) is a single bond).

[1] The compound (Ia) can be prepared by amidation of the compound (1) and the compound (2). This reaction can be carried out by preparing an acid halide as an intermediate from carboxylic acid and a halogenating reagent in a solvent inert to the reaction and adding a base and an amine thereto. Further, depending on the substrate, an acid halide may be isolated once. The solvents that can be used are aromatic hydrocarbons such as toluene and the like, halogenated hydrocarbons such as CH_2Cl_2 , CHCl_3 , and the like, ethers such as Et_2O , THF, and the like, DMF, DMSO, AcOEt, MeCN, water, and mixed solvents thereof. The halogenating reagents that can be used are a Ghosez reagent, PyCLU, TCFH, TFFH, SOCl_2 , POCl_3 , and the like. Additionally, this reaction may be carried out by adding a small amount of DMF to SOCl_2 . The base that can be used is an organic base such as pyridine and the like.

The activated intermediate of the carboxy group may be mixed acid anhydride or active ester, or the like, in addition to the above-mentioned acid halide.

30 As another preparation method, a method using a condensing agent may be used. This reaction can be carried out in a solvent inert to the reaction by adding a condensing agent and a base. The condensing agent that can be used is WSC hydrochloride, HATU,

or the like. The solvent that can be used is halogenated hydrocarbons, NMP, or the like. The base that can be used is an organic base such as pyridine, Et₃N, DIPEA, DMAP, or the like, or an inorganic base such as K₂CO₃, Na₂CO₃, KOH, or the like. The reaction may proceed smoothly in some cases with the addition of HOBt or the like during the reaction.

[Literature] "Organic Syntheses", 1980, vol. 59, p. 26.

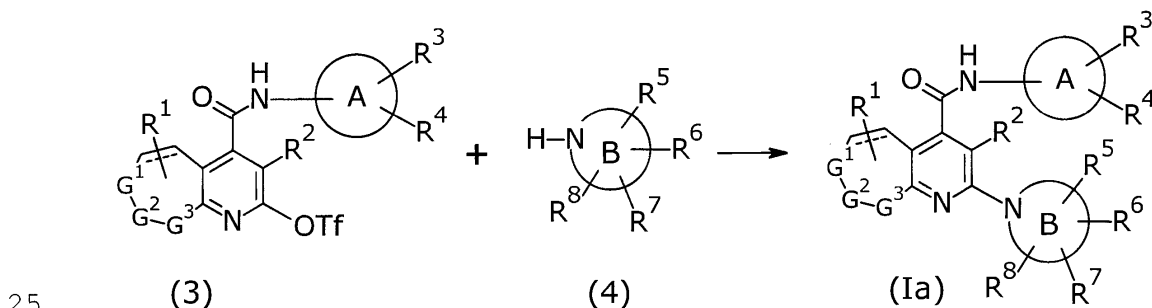
[2] The compound (I) of the present invention can also be prepared by hydrogenation of a compound wherein ---- in the compound (Ia) is a double bond. Further, the reduction may be carried out at a stage that does not affect other functional groups in any step from a starting material to a desired product, or a compound wherein ---- is a single bond can be used from starting materials. The hydrogenation can be carried out under a hydrogen atmosphere in a solvent inert to the reaction in the presence of a metal catalyst. The solvent that can be used is alcohols such as MeOH, or the like. The metal catalyst that can be used include a palladium catalyst such as Pd/C, Pd(OH)₂/C, or the like, a platinum catalyst such as Pt/C or the like, a nickel catalyst such as Raney nickel or the like, a rhodium catalyst such as Wilkinson complex or the like, and an iron catalyst such as reduced iron or the like. As a hydrogen source, formic acid or ammonium formate may be used in place of hydrogen gas.

[Literature] "Reductions in Organic Chemistry", 2nd edition, ACS Monograph: 188, ACS, 1996; and "Courses in Experimental Chemistry (5th edition)", Volume 19 (2005), edited by The Chemical Society of Japan (Maruzen Publishing Co. Ltd.)

[0049]

(Second preparation method)

[Chem. 11]



The compound (Ia) can be prepared from the compound (3) and the compound (4). This reaction can be carried out in a solvent inert to the reaction or without a solvent at room temperature to under heating to reflux. The solvent that can be used is aromatic hydrocarbons, ethers, halogenated hydrocarbons, alcohols such as EtOH or the like, DMF, DMSO, AcOEt, MeCN, NMP, water, and mixed solvents thereof. Further, the reaction may proceed smoothly in some cases by the addition of an organic base or an inorganic

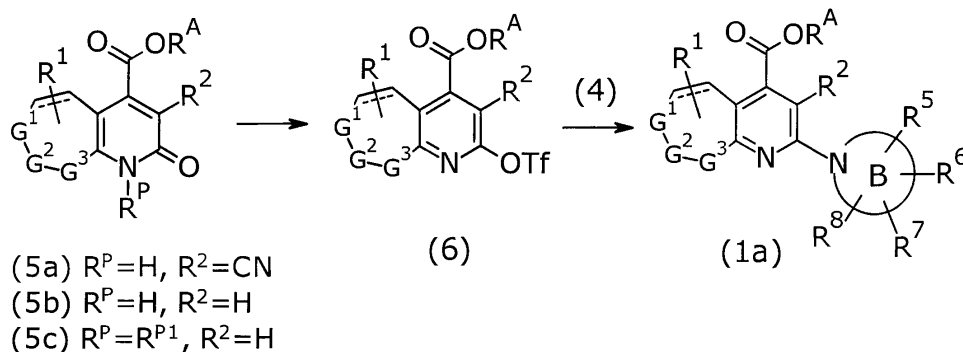
base during the reaction.

[0050]

(Starting material preparation method 1)

[Chem. 12]

5



(In the formula, R^A represents a protecting group of the carboxy group. R^P represents H or R^{P1}, and R^{P1} represents a protecting group of the amide group. The same shall apply hereinafter).

The compound (1a) can be prepared using the compound (5a), (5b) or (5c) as a starting material. R^{P1} is, for example, a PMB group or the like. The compound (6) can be prepared by triflation of the compound (5a), (5b) or (5c). An example of R^A is lower alkyl or the like, and an example of R^{P1} is PMB or the like. This reaction can be carried out in a halogenated hydrocarbon solvent such as CH₂Cl₂ or the like using a triflating reagent, an inorganic base or an organic base such as pyridine or the like. The triflating reagent that can be used is Tf₂O, McMurry's reagent, a Comins reagent, or the like. The compound (1a) can be prepared from the compound (6) and the compound (4). This reaction may employ the conditions of the above-mentioned second preparation method.

The compound (1) can be prepared by deprotecting the compound (1a). This reaction can be carried out in a solvent inert to the reaction or without a solvent at room temperature to under heating to reflux. The solvent that can be used is aromatic hydrocarbons, ethers, halogenated hydrocarbons, alcohols such as EtOH or the like, DMF, DMSO, AcOEt, MeCN, NMP, water, and mixed solvents thereof. The reaction may proceed smoothly in some cases by adding an organic base or an inorganic base during the reaction.

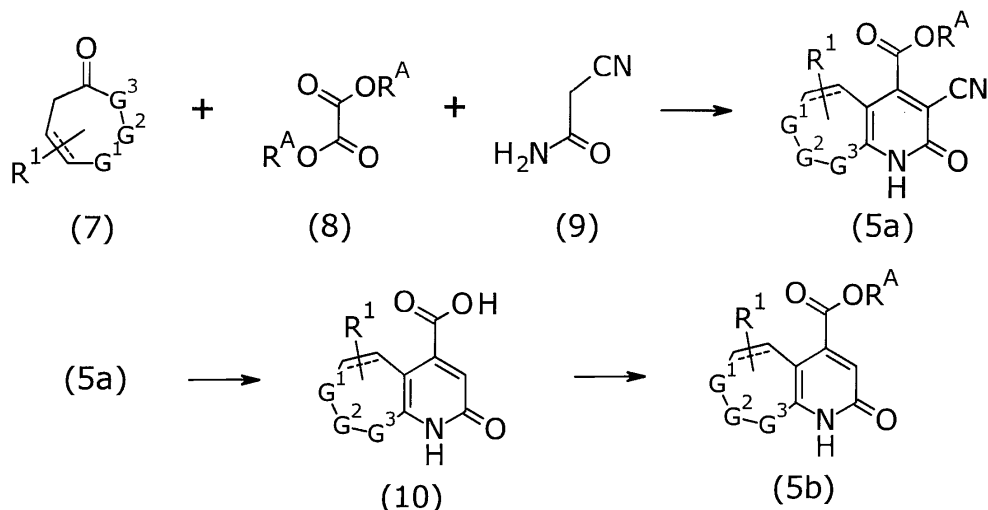
Further, in preparing the compound (1a) from the compound (5a), (5b) or (5c), the compound (1a) may also be prepared without isolation of the compound (6) depending on the substrate.

[0051]

(Starting material preparation method 2)

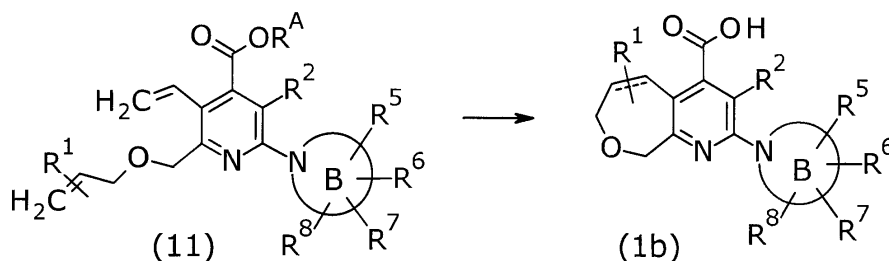
30

[Chem. 13]



- 5 The compound (5b) can be prepared using the compound (7) as a starting material. The compound (5a) can be prepared from the compound (7), the compound (8) and the compound (9). This reaction can be carried out in a solvent inert to the reaction in the presence of a base under heating. The solvent that can be used is alcohols such as EtOH or the like. The base that can be used is an inorganic base such as KOtBu or the like.
- 10 The compound (5b) can be prepared via the compound (10) from the compound (5a). The compound (10) can be prepared from the compound (5a). This reaction proceeds with simultaneous occurrence of CN group elimination and deprotection. This reaction can be carried out in a concentrated hydrochloric acid under heating. The compound (5b) can be prepared by re-protecting the carboxy group of the compound (10).

15 [0052]
(Starting material preparation method 3)
[Chem. 14]



20

(In the formula, R¹ represents a substitution with a vinyl group of the side chain. The same shall apply hereinafter).

The compound (1b) can be prepared from the compound (11). This reaction is a

ring-closing metathesis reaction. This reaction can be carried out in a solvent inert to the reaction in the presence of a catalyst at room temperature to under heating. The solvent that can be used is halogenated solvents such as CH_2Cl_2 or the like, or aromatic hydrocarbons. The catalyst that can be used is a Grubbs catalyst, or the like.

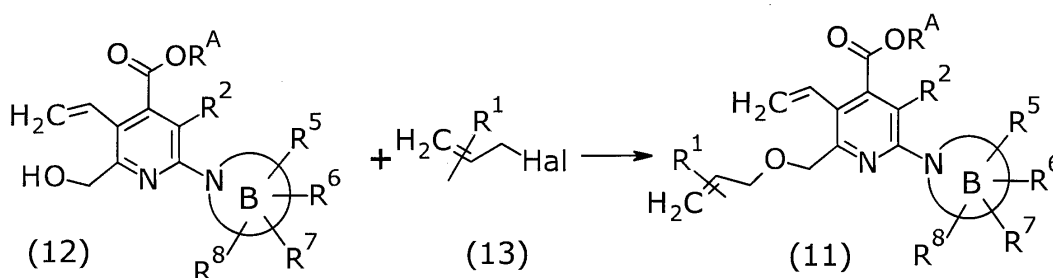
The resulting oxepane has a double bond. The compound in which the double bond of oxepane is a single bond can be prepared by hydrogenation also described in the first preparation method [2].

[Literature] "Angewandte Chemie International Edition", 2006, vol. 45, pp. 3760 to 3765; and "Courses in Experimental Chemistry (5th edition)", Volume 19 (2005), edited by The Chemical Society of Japan (Maruzen Publishing Co. Ltd.)

[0053]

(Starting material preparation method 4)

[Chem. 15]



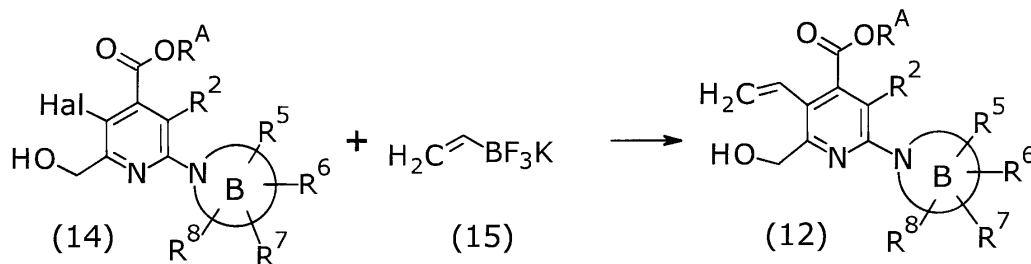
(In the formula, Hal is halogen. The same shall apply hereinafter).

The compound (11) can be prepared from the compound (12) and the compound (13). The reaction can be carried out in a solvent inert to the reaction in the presence of a base at room temperature to under heating to reflux. The solvent that can be used is aromatic hydrocarbons, ethers, halogenated hydrocarbons, DMF, DMSO, AcOEt, MeCN and mixed solvents thereof. The base that can be used is an organic base, an inorganic base such as NaH, or the like. The reaction may proceed smoothly in some cases by a phase transfer catalyst such as TBAI or the like.

[0054]

(Starting material preparation method 5)

[Chem. 16]



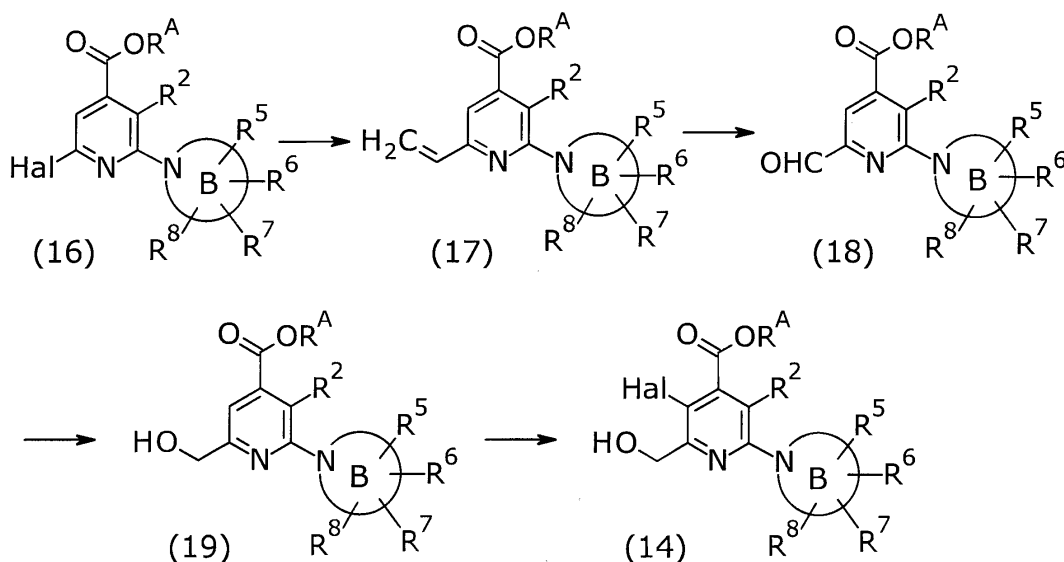
The compound (12) can be prepared from the compound (14) and the compound (15). This reaction can be carried out in a solvent inert to the reaction in the presence of a palladium catalyst and a base under heating. The solvent that can be used is a mixed solvent of an organic solvent and water, for example, THF-H₂O, dioxane-H₂O, toluene-EtOH-H₂O, DME-H₂O, or the like. The palladium catalyst that can be used is Pd(PPh₃)₄ or the like. The inorganic base that can be used is KF, CsF or NaHCO₃. The organic base that can be used is Et₃N or the like.

[Literature] "Journal of Organic Chemistry", 2006, vol. 71(26), pp. 9681 to 9686; and *ibid.*, 2009, vol. 74(6), pp. 2321 to 2327.

[0055]

(Starting material preparation method 6)

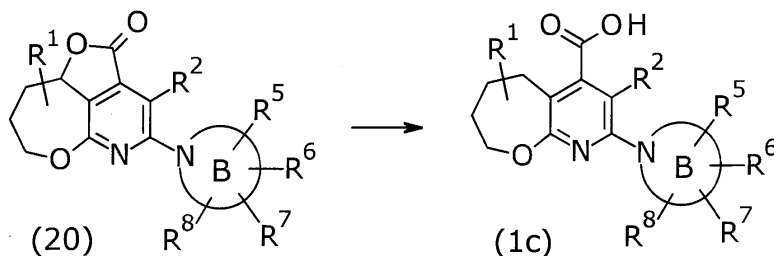
[Chem. 17]



The compound (14) can be prepared using the compound (16) as a starting material. The compound (17) can be prepared from the compound (16) and the compound (15) described above. The same conditions as in Starting material preparation method 5 can be used. The compound (18) can be prepared from the compound (17). This reaction is oxidative cleavage using an oxidizing agent such as OsO₄-NaIO₄ or the like and may employ conventional conditions. The compound (19) can be prepared from

the compound (18). This reaction is reduction and may employ NaBH_4 or the like as a reducing agent. The compound (14) can be prepared from the compound (19). This reaction is halogenation. This reaction may employ a halogenating agent such as N-halosuccinimide or the like as a reagent.

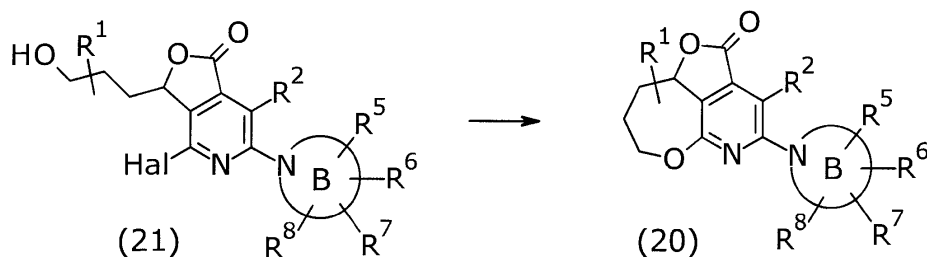
5 [0056]
(Starting material preparation method 7)
[Chem. 18]



10

The compound (1c) can be prepared from the compound (20). This reaction is hydrogenation. This reaction may employ the conditions described in the first preparation method [2].

[0057]
15 (Starting material preparation method 8)
[Chem. 19]



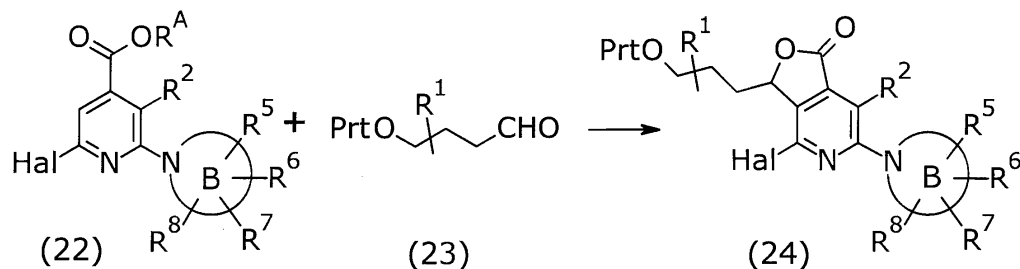
20 The compound (20) can be prepared from the compound (21). This reaction is ether synthesis of so-called Buchwald-Hartwig cross-coupling. This reaction can be carried out in a solvent inert to the reaction in the presence of a base, a palladium catalyst and a phosphine ligand at room temperature. The solvent that can be used is aromatic hydrocarbons such as toluene or the like. The palladium catalyst that can be used is
25 $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{dba})_2$, or the like. The base that can be used is an inorganic base such as Cs_2CO_3 , NaOtBu , or the like. The phosphine ligand that can be used is tBu_2BINAP , ferrocenyl phosphine, or the like.

[Literature] "Angewandte Chemie International Edition", 1998, vol. 37, pp. 2046 to 2067

[0058]

(Starting material preparation method 9)

[Chem. 20]



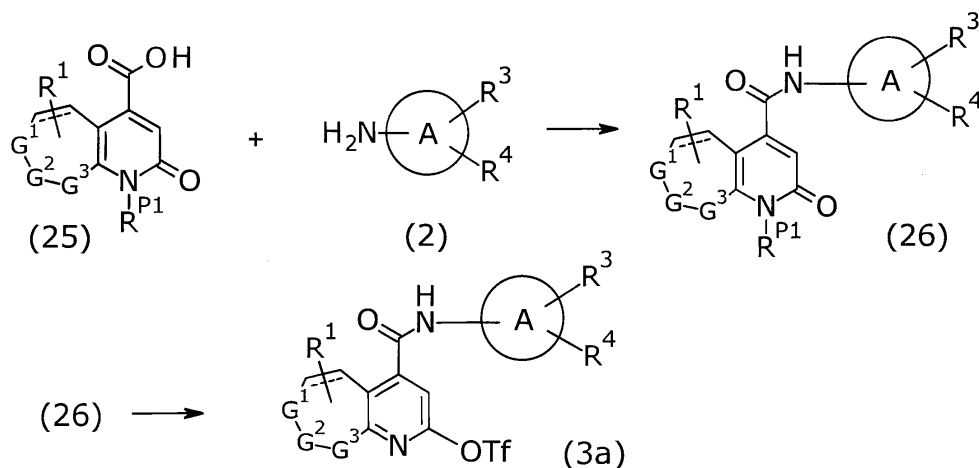
(In the formula, Prt is a protecting group)

10 The compound (24) can be prepared from the compound (22) and the compound (23). Prt is, for example, a tert-butyl(dimethyl)silyl group or the like. This reaction can be carried out in a solvent inert to the reaction in the presence of a base. The base that can be used is a lithium amide-based reagent such as LDA, LiTMP, LHMDs, or the like. The compound (21) can be prepared by deprotection of the compound (24).

[0059]

(Starting material preparation method 10)

[Chem. 21]



20 The compound (3a) can be prepared using the compound (25) as a starting material. The compound (26) can be prepared from the compound (25) and the compound (2). This reaction is amidation and may employ the conditions described in the first preparation method [1]. The compound (3a) can be prepared from the compound (26). This reaction is triflation and may employ the conditions described in the Starting

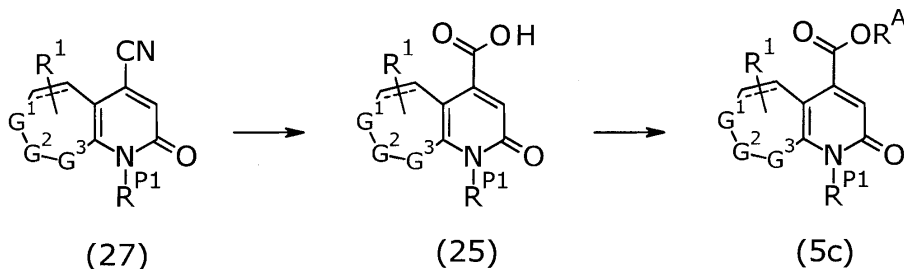
material preparation method 1.

[0060]

(Starting material preparation method 11)

[Chem. 22]

5



The compound (5c) can be prepared using the compound (27) as a starting material. The compound (25) can be prepared by hydrolysis of the compound (27).

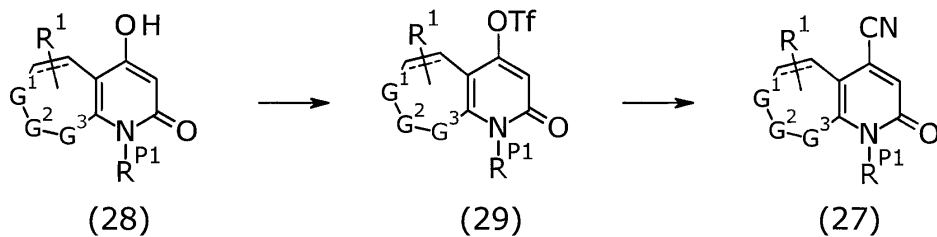
- 10 This reaction can be carried out in a solvent inert to the reaction in the presence of a base at room temperature to under heating for several hours to overnight. The solvent that can be used is an alcohol. The base that can be used is an aqueous NaOH solution or the like.

- The compound (5c) can be prepared from the compound (25). This reaction can be generally carried out in a solvent inert to the reaction in the presence of halogenated alkyl and a base at room temperature to under heating for several hours to overnight. The solvent that can be used is MeCN or the like. The halogenated alkyl is $R^A X$ (X is a leaving group such as Cl, Br, I, or the like), and an example of R^A is methyl. The base that can be used is an inorganic base such as K_2CO_3 or the like.

[0061]

- 20 (Starting material preparation method 12)

[Chem. 23]



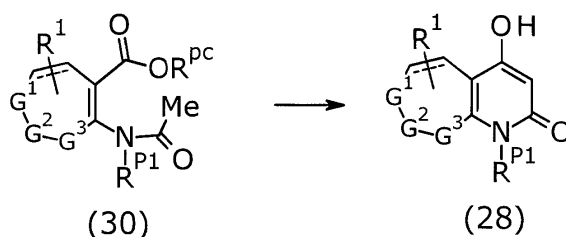
- 25 The compound (27) can be prepared using the compound (28) as a starting material. The compound (29) can be prepared from the compound (28). This reaction can be carried out in the same manner as in the above-mentioned Starting material preparation method 1. The compound (27) can be prepared from the compound (29). This reaction can be carried out in a solvent inert to the reaction in the presence of a CN

source, a palladium catalyst, a phosphine ligand, $\text{CH}_3\text{SO}_2\text{Na}$ and the like under heating for several hours to overnight. The solvent that can be use is DMF, H_2O , or the like. CN source that can be use is NaCN , KCN , $\text{Zn}(\text{CN})_2$, or the like. The palladium catalyst that can be use is $\text{Pd}_2(\text{dba})_3$, or the like. The phosphine ligand that can be used is dppf, or the like.

[0062]

(Starting material preparation method 13)

[Chem. 24]

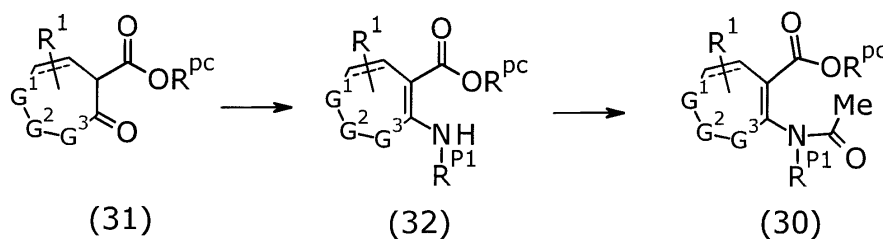


The compound (28) can be prepared from the compound (30). This reaction can be carried out for several hours to several days by adding a lithium amide reagent to the compound (30) at -30°C to -80°C , followed by elevating the temperature. The solvent that can be used is THF, toluene, or the like. The lithium amide reagent that can be used is LDA, LiTMP, LHMDs, KHMDS, or NaHMDS.

[0063]

(Starting material preparation method 14)

[Chem. 25]



The compound (30) can be prepared using the compound (31) as a starting material. The compound (32) can be prepared from the compound (31). This reaction can be carried out in a solvent inert to the reaction in the presence of $\text{R}^{\text{P}1}\text{-NH}_2$ and an acid at room temperature to under heating for one hour to several hours. The solvent that can be used is alcohols such as EtOH or the like. The acid that can be used is acetic acid. The compound (30) can be prepared by acylation of the compound (32). This reaction can be carried out in a solvent inert to the reaction under heating for several hours after adding MeC(=O)X (X is a leaving group such as Cl, Br, I, or the like) under ice-cooling.

The solvent that can be used is THF or the like.

[0064]

The compound of the formula (I) is isolated and purified as a free compound, a salt, a hydrate, a solvate, or a polymorphic crystal substance thereof. A salt of the compound of the formula (I) can be prepared by carrying out a conventional salt forming reaction.

Isolation and purification are carried out by employing ordinary chemical operations such as extraction, fractional crystallization, various types of fractional chromatography, and the like.

Various isomers can be prepared by selecting an appropriate starting compound or can be separated by using the difference in the physicochemical properties between the isomers. For example, the optical isomers can be obtained by means of a general method for designing optical resolution of racemic compounds (for example, fractional crystallization for inducing diastereomer salts with optically active bases or acids, chromatography using a chiral column or the like, and others), and further, the isomers can also be prepared from an appropriate optically active starting compound.

[0065]

Furthermore, for the sake of convenience, a concentration mol/L is expressed as M. For example, a 1 M aqueous NaOH solution means a 1 mol/L aqueous NaOH solution.

[0066]

The pharmacological activity of the compound of the formula (I) was confirmed by the following tests.

(Abbreviation)

In the following Test Examples of the present specification, the following abbreviations may be used in some cases.

AChCl: Acetylcholine chloride, ATCC: American Type Culture Collection, DMEM: Dulbecco's modified Eagle's medium, EGTA: Ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid, FBS: Fetal bovine serum, HBSS: Hank's Balanced Salt Solution, HEK293 cells: Human embryonic kidney cells, HEPES: 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, NMDA: N-methyl-D-aspartate, PNU-120596: 1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methyl-1,2-oxazol-3-yl)urea (CAS registry number: 501925-31-1). PNU-282987: N-(3R)-1-azabicyclo[2.2.2]octo-3-yl-4-chlorobenz amide (CAS registry number: 123464-89-1).

[0067]

(Materials)

The composition of the buffer used in Test Example 1 is shown.

Assay buffer: HBSS buffer containing 1.25 mM probenecid.

[0068]

Test Example 1 Evaluation for human $\alpha 7$ nACh receptor using FLIPR

The PAM activity of a test drug was evaluated in terms of Ca^{2+} dye-based fluorescence intensity for an intracellular calcium response in the presence of an $\alpha 7$ nACh receptor-selective agonist PNU-282987 (CAS registry number: 123464-89-1, Tocris) using a FLIPR tetra (Molecular Devices).

In the case where a concentration-response curve has been obtained in which the logarithm of a concentration of a test drug is on the abscissa and the ratio of a response (hereinafter, also referred to as calcium response) is on the ordinate, this test drug has been determined to have a PAM activity.

In this test, the agonist (PNU-282987) elicited a calcium response only in the presence of PAM (PNU-120596).

[0069]

(Acquisition of cells transiently co-expressing human $\alpha 7$ nACh receptor/RIC3)

The coding sequence of a human $\alpha 7$ nACh receptor (accession number: NM_000746.5) was subcloned into a pCEP4 vector (Life Technologies). The coding sequence of a rat chaperone protein RIC3 (accession number: NM_001115045.3) was subcloned into a pcDNA3.1/Hygro (+) vector (Life Technologies). The resulting constructs were transfected into HEK293 cells (ATCC number: CRL-1573) by an electroporation method using Neon (Life Technologies).

[0070]

(Test method)

Concentration-response curve of human $\alpha 7$ nACh receptor with addition of test drug

The concentration-response curve of a human $\alpha 7$ nACh receptor with the addition of a test drug was produced by the following experiment.

The transiently expressing cells obtained in the manner described above were seeded at a density of 8×10^3 cells/well onto a 384-well plate (Becton Dickinson) and allowed to stand overnight at 37°C . DMEM+10% FBS was used as a medium.

On the next day, the medium was removed, and Fluo4-AM (Dojindo) prepared using an assay buffer was applied, followed by allowing to stand for 1 hour. The test drug was dissolved in DMSO and then made to a final concentration of 0.03 to 100 μM (3-fold dilutions) with an assay buffer. Similarly, PNU-120596 which is a known PAM was made to a final concentration of 0.003 to 10 μM (3-fold dilutions). PNU-282987 which is an agonist was made to a final concentration of 0.6 μM . Thereafter, the test drug was applied to the cells using a FLIPR tetra, the agonist (PNU-282987) was added 5 minutes later, and the fluorescence intensity at that time was detected.

As a control, using (1) a group with neither addition of a test drug, PAM (PNU-

120596) nor that of agonist (PNU-282987), the response thereof was set to 0%. Using (2) a group with the addition of PAM (PNU-120596) and agonist (PNU-282987), the maximum response thereof was set to 100%.

[0071]

5 (Evaluation of activity)

As a result of the tests above, some representative Example compounds of the present invention exhibited an enhanced concentration-dependent response (calcium response) when those compounds were added in the presence of an agonist (PNU-282987), and the concentration-response curve of the human $\alpha 7$ nACh receptor was obtained.

10 Further, the calcium response was not elicited with an agonist (PNU-282987) alone, or some representative Example compounds of the present invention alone. From the foregoing results, it was demonstrated that compounds of the present invention have a PAM activity on a human $\alpha 7$ nACh receptor.

To quantitatively compare the PAM activity of the test drug, an EC₂₀ value and a
15 Max value were used as activity indicators. The EC₂₀ value refers to a test drug concentration exhibiting the response intensity of 20%, in the concentration-response curve, when setting the maximum response of PAM (PNU-120596) in the presence of an agonist (PNU-282987) to 100%. The EC₂₀ value was calculated using a non-linear regression analysis from the concentration-response curve of a human $\alpha 7$ nACh receptor
20 with the addition of a test drug. The Max value refers to a maximum response value. The Max value is expressed in terms of % value of the maximum response of a test drug in the presence of an agonist (PNU-282987) relative to when the maximum response of PAM (PNU-120596) in the presence of an agonist (PNU-282987) is set to 100%.

[0072]

25 The results of some representative Example compounds of the present invention (EC₂₀ value and Max value) are shown in Table below. In the Table, No. represents a Compound No., and Ex represents an Example Compound No.

[0073]

[Table 1]

No.	EC ₂₀ (μ M)	Max (%)
Ex1	2.72	99.8
Ex7	0.512	94.8
Ex9	3.52	69.3
Ex12	4.35	96.9
Ex18	1.02	79.2

30

[0074]

Test Example 2 Electrophysiological evaluation for human $\alpha 7$ nACh receptor

The PAM activity of a test drug was evaluated by a current response in the presence of an $\alpha 7$ nACh receptor agonist Acetylcholine chloride (Sigma) (hereinafter, also referred to as AChCl) using Qpatch HTX (Biolin Scientific) or Qube (Biolin Scientific). This test cannot detect a small current response of AChCl alone. The current response can be detected only in the case where the test drug has a PAM activity.

[0075]

(Materials)

The composition of extracellular fluid and intracellular fluid used in Test Example 2 is shown below.

Extracellular fluid (pH 7.4): NaCl 145 mM, KCl 4 mM, HEPES 10 mM, CaCl_2 2 mM, MgCl_2 1 mM.

Intracellular fluid (pH 7.2): KF 120 mM, KCl 20 mM, EGTA 0.1 mM, HEPES 10mM, MgCl_2 2 mM.

[0076]

(Acquisition of cells transiently co-expressing human $\alpha 7$ nACh receptor/RIC3)

The cells were obtained in the same manner as in Test Example 1.

[0077]

(Test method)

Response of human $\alpha 7$ nACh receptor with addition of test drug

The response of a human $\alpha 7$ nACh receptor with the addition of a test drug was measured by the following experiment. Transient expression cells obtained by the method described above were subjected to the experiment after allowing to stand overnight at 37°C. The test drug was dissolved in DMSO, and then made to a final concentration of 3 μM using extracellular fluid. The agonist AChCl was made to a final concentration of 100 μM . The membrane potential was voltage-clamped at -90 mV. The current response was measured by multi-hole mode at the time of simultaneous addition of the test drug and AChCl to the cells, using QPatch HTX or Qube.

[0078]

(Evaluation of activity)

As a result of the tests above, the case where an inward current response specific to a human $\alpha 7$ nACh receptor was obtained when 3 μM of a test drug had been added was determined as positive, and the case where a specific current response was not observed was determined as negative. It should be noted that, when the agonist concentration is 0, the current response was not observed even with the addition of a test drug.

[0079]

The results of some representative Example compounds of the present invention are shown in Table below. In the Table, No. represents a Compound No., Ex represents an Example Compound No., and Dat.1 represents Determination.

[0080]

[Table 2]

No.	Dat.1	No.	Dat.1
Ex18	positive	Ex51	positive
Ex36	positive	Ex55	positive
Ex40	positive	Ex69	positive
Ex46	positive	Ex70	positive
Ex48	positive	Ex76	positive
Ex50	positive		

[0081]

5 Test Example 3 Y-maze test

The improving effect of the compound of the present invention on cognitive impairment was evaluated using a Y-maze test which is an experimental system of spontaneous alternation behavior.

[0082]

10 (Experimental device)

As a Y-maze, a maze, in which three tracks having a length of one arm of 40 cm, a height of a wall of 13 cm, a width of a bottom of 3 cm, and a width of a top of 10 cm are each joined in the Y shape at a degree of 120, was used.

[0083]

15 (Test Method)

A test drug (0.1, 0.3, 1, 3 and 10 mg/kg, suspended in 0.5% methyl cellulose) was orally administered once to a 5- to 6-week old ddY male mice (n=8, Japan SLC, Inc.) at 0.5 or one hour before the Y maze test started, and further, MK-801 (Sigma), which is an NMDA receptor antagonist causing cognitive impairment, was intraperitoneally
20 administered at a dose of 0.15 mg/kg at 20 minutes before the Y-maze test started.

Further, for the mice in a control group, a vehicle (0.5% methyl cellulose) was used instead of a test drug, and physiological saline, not MK-801, was used.

For the mice in the MK-801 control group, a vehicle (0.5% methyl cellulose) was used instead of the test drug.

25 The above-described mice were allowed to explore freely for 8 minutes after being placed at an end of one track in the Y-maze. The number of times the mice entered the track was counted, and taken as a total entry number. The number of times the mice successively entered different three tracks (for example, when taking three arms as a, b, and c, respectively, a case where the order of the track that entered was "abccbacab" was
30 counted as 4) was considered as a spontaneous alternation behavior number. The

spontaneous alternation behavior rate was calculated by the following calculation and used as an index for a spontaneous alternation behavior:

Spontaneous alternation behavior rate=[spontaneous alternation behavior number/(total number of entries-2)] $\times$ 100

5 A higher index value indicates the maintenance of short-term memory.

[0084]

(Data Analysis)

A test for significant difference between the control group and the MK-801 control group was carried out by a Student's t-test. Further, a test for significant difference
10 between the test drug-administered group and the MK-801 control group was carried out by a Dunnett's type multiple comparison test, and an improving effect of the test drug on learning disorder was determined. With $P<0.05$ in each test, it was determined that there is a significant difference.

[0085]

15 The results that representative Example compounds of the present invention significantly improved the spontaneous alternation behavior are shown in Table below. In the Table, No. represents a Compound No., Ex represents an Example Compound No., and Dat.2 represents an effective dose.

[0086]

20 [Table 3]

No.	Dat.2
Ex18	1, 3, 10 mg/kg
Ex37	0.3, 1, 3, 10 mg/kg
Ex76	1, 3, 10 mg/kg

[0087]

As a result of the tests above, a PAM activity on an $\alpha 7$ nACh receptor was confirmed in the representative compounds of the formula (I). Further, as a result of the
25 tests above, it was confirmed that the representative compounds of the formula (I) are effective in a Y-maze test. Therefore, it can be expected that the compound of the formula (I) can be used for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.

30 [0088]

A pharmaceutical composition containing one or two or more kinds of a compound of the formula (I) or a salt thereof as an active ingredient can be prepared using excipients that are commonly used in the art, that is, pharmaceutical excipients, pharmaceutical carriers, and the like according to a conventionally used method.

Administration can be accomplished either by oral administration via tablets, pills, capsules, granules, powders, solutions, and the like, or parenteral administration injections, such as intraarticular, intravenous or intramuscular injections, suppositories, transdermal liquid preparations, ointments, transdermal patches, transmucosal liquid preparations, transmucosal patches, inhalers, and the like.

[0089]

As the solid composition for oral administration, tablets, powders, granules, or the like may be used. In such a solid composition, one or two or more active ingredient(s) are mixed with at least one inactive excipient. In a conventional method, the composition may contain inactive additives, such as a lubricant, a disintegrating agent, a stabilizer, or a solubilization assisting agent. If necessary, tablets or pills may be coated with sugar or a film of a gastric or enteric coating substance.

The liquid composition for oral administration contains pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and also contains commonly used inert diluents, for example, purified water or EtOH. In addition to the inert diluent, the liquid composition may also contain auxiliary agents, such as a solubilization assisting agent, a moistening agent, and a suspending agent, sweeteners, flavors, aromatics, and antiseptics.

[0090]

The injections for parenteral administration include sterile aqueous or non-aqueous solution preparations, suspensions and emulsions. The aqueous solvent includes, for example, distilled water for injection and physiological saline. Examples of the non-aqueous solvent include alcohols such as EtOH. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent, or a solubilizing aid. These are sterilized, for example, by filtration through a bacteria retaining filter, blending of a bactericide, or irradiation. In addition, these can also be used by preparing a sterile solid composition, and dissolving or suspending it in sterile water or a sterile solvent for injection prior to use.

[0091]

Examples of the agent for external use includes ointments, plasters, creams, jellies, patches, sprays, lotions, eye drops, eye ointments, and the like. The agents contain generally used ointment bases, lotion bases, aqueous or non-aqueous liquid preparations, suspensions, emulsions, or the like.

[0092]

As the transmucosal agents such as an inhaler and a transnasal agent, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with a conventionally known method. For example, a known excipient, and also a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizing agent, a thickening

agent, or the like may be appropriately added thereto. For the administration, an appropriate device for inhalation or insufflation can be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with a pharmaceutically acceptable carrier, using a known device or sprayer, such as a measured administration inhalation device, and the like. A dry powder inhaler or the like may be for single or multiple administration use, and a dry powder or a powder-containing capsule may be used. Alternatively, this may be in a form such as a pressurized aerosol spray which uses an appropriate ejection agent, for example, a suitable gas such as chlorofluoroalkane, carbon dioxide, and the like, or other forms.

10 [0093]

In general oral administration, the daily dose is suitably about 0.001 to 100 mg/kg, preferably 0.003 to 30 mg/kg, and more preferably 0.01 to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 divided portions. In the case of intravenous administration, the daily dose is suitably about 0.001 to 10 mg/kg per body weight, once a day or two or more times a day. In addition, a transmucosal agent is administered at a dose of about 0.001 to 10 mg/kg per body weight, once a day or two or more times a day. The dose is appropriately determined in response to the individual case by taking the symptoms, the age, and the gender, and the like into consideration.

20 [0094]

Although varying depending on administration routes, dosage forms, administration sites, or the types of excipients and additives, the pharmaceutical composition of the present invention contains 0.01% to 100% by weight, and in one embodiment, 0.01% to 50% by weight of one or more kinds of the compound of the formula (I) or a salt thereof, which is an active ingredient.

25 [0095]

The compound of the formula (I) can be used in combination with various agents for treating or preventing the diseases for which the compound of the formula (I) is considered to be effective. The combined preparation may be administered simultaneously, or separately and continuously, or at a desired time interval. The preparations to be co-administered may be a blend, or may be formulated individually.

Examples

[0096]

Hereinbelow, the preparation methods for the compound of the formula (I) will be described in more detail with reference to Examples. Further, the present invention is not limited to the compounds described in the following Examples. Furthermore, the preparation methods for the starting compounds will be described in Preparation Examples.

[0097]

Furthermore, the following abbreviations may be used in some cases in the present specification, for example, Tables below.

No. : Compound No., No./Inf : Compound No./ (salt and optical activity information of the compound), Pr : Preparation Example No., Ex : Example No., Ref : preparation process (indicating that the compound was prepared by the process which is similar to the compound of Example No. or Preparation Example No. described in the column), Str : Chemical structural formula, Dat : Physicochemical data, ESI⁺ : m/z value ([M+H]⁺, unless otherwise specified) in ESI-MS⁺, APCI/ESI⁺ : m/z value ([M+H]⁺, unless otherwise specified) in the simultaneous measurement of APCI-MS⁺ and ESI-MS⁺, and NMR1 : δ (ppm) measured by ¹H-NMR at 400MHz in DMSO-d₆ solvent. NMR signals show a representative signal.

FM : fumaric acid, TS : p-toluene sulfonic acid (tosic acid), BS : benzene sulfonic acid (besylic acid), and PA : phosphoric acid.

In No./Inf, for example, "Ex1/FM, CHR" indicates that the compound Ex1 is fumarate, optically active.

In Ref, for example, the "Ex1" in the Ex2 column indicates that Example compound Ex2 was prepared in the same manner as in the method described in Ex1.

[0098]

Preparation Example 1

EtOH (150 mL) was added to KOtBu (27 g) at room temperature, and stirred until dissolved. Diethyl oxalate (35 g) was added to the reaction mixture, and oxepan-4-one (23.99 g) was added thereto. The reaction mixture was stirred for 10 minutes at room temperature and stirred for 45 minutes at 70°C. 2-cyanoacetamide (20 g) was added to the reaction mixture at 70°C, followed by cooling to room temperature and stirring at room temperature for 1 day. 1M hydrochloric acid (240 mL) was added to the reaction mixture which was then extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and then concentrated under reduced pressure to give a mixture (26.9 g) of ethyl 3-cyano-2-oxo-1,2,5,7,8,9-hexahydrooxepino[4,3-b]pyridine-4-carboxylate and ethyl 3-cyano-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylate.

[0099]

Preparation Example 2

Concentrated hydrochloric acid (200 mL) was added to a mixture (26.9 g) of ethyl 3-cyano-2-oxo-1,2,5,7,8,9-hexahydrooxepino[4,3-b]pyridine-4-carboxylate and ethyl 3-cyano-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylate which was then stirred 120°C for 1 day. The reaction mixture was concentrated under reduced pressure. EtOH (500 mL) was added to the residue which was then concentrated under reduced pressure to give a mixture (21.5 g) of 2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylic acid and 2-oxo-1,2,5,7,8,9-hexahydrooxepino[4,3-b]pyridine-4-carboxylic

acid.

[0100]

Preparation Example 3

A mixture of the mixture (19 g) of 2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylic acid and 2-oxo-1,2,5,7,8,9-hexahydrooxepino[4,3-b]pyridine-4-carboxylic acid, EtOH (200 mL), and concentrated sulfuric acid (18 g) was stirred at 90°C for 8 hours. The reaction mixture was concentrated under reduced pressure, and H₂O was added thereto, followed by extraction with AcOEt. The organic layer was dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel CC (CHCl₃/MeOH) to give ethyl 2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylate (2.36 g).

[0101]

Preparation Example 4

Pyridine (270 µL) and Tf₂O (550 µL) were added to a mixture of ethyl 2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylate (700 mg) and CH₂Cl₂ (10 mL) under ice-cooling, followed by stirring under ice-cooling for 3 hours. The reaction mixture was diluted with CHCl₃, and H₂O was added to carry out liquid separation. The organic layer was washed with brine, dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified using silica gel CC (hexane/AcOEt) to give ethyl 2-{[(trifluoromethyl)sulfonyl]oxy}-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (1.04 g).

[0102]

Preparation Example 5

3-(trifluoromethyl)piperidine (750 mg) was added to a mixture of ethyl 2-{[(trifluoromethyl)sulfonyl]oxy}-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (600 mg) and DMSO (5 mL) which was then stirred at room temperature for 3 days. 3-(trifluoromethyl)piperidine (200 µL) was further added to reaction mixture which was then stirred overnight at 40°C. H₂O was added to the reaction mixture, followed by extraction with AcOEt. The organic layer was washed with H₂O-brine (1:1), dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give ethyl 2-[3-(trifluoromethyl)piperidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (174 mg).

[0103]

Preparation Example 6

Pyridine (0.788 g) was added to a mixture of ethyl 2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylate (2 g) and CH₂Cl₂ (10 mL), and Tf₂O (2.8 g) was then added thereto under ice-cooling. The reaction mixture was stirred under ice-cooling for 2 hours. The reaction mixture was diluted with CHCl₃, and H₂O was added

thereto, followed by extraction with CHCl_3 . The organic layer was washed with brine, dried over MgSO_4 , and then concentrated under reduced pressure. The resulting residue was dissolved in DMSO (10 mL), and (2R,6S)-2,6-dimethylmorpholine (7 mL) was added thereto. The reaction mixture was stirred overnight at 40°C . The reaction mixture was diluted with AcOEt, and H_2O was added thereto, followed by extraction with AcOEt. The organic layer was washed successively with H_2O and brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give ethyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (0.562 g).

[0104]

Preparation Example 7

A mixture of ethyl 2-{[(trifluoromethyl)sulfonyl]oxy}-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (850 mg), 1,4-dioxane (17 mL), 2,2,6,6-tetramethylmorpholine (660 mg), (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one-palladium (3:2) (210 mg), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (2.66 g), and Cs_2CO_3 (1.5 g) was stirred at 140°C for 1 hour using a microwave reactor. After the reaction mixture was diluted with AcOEt and H_2O , the insoluble material was removed by filtration and then the filtrate was separated. The organic layer was washed with brine, dried over MgSO_4 , and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give ethyl 2-(2,2,6,6-tetramethylmorpholin-4-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (495 mg).

[0105]

Preparation Example 8

A 1M NaOH aqueous solution (2 mL) was added to an EtOH (30 mL) solution of ethyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (300 mg), followed by stirring at 60°C for 1 hour. The reaction mixture was cooled to room temperature, and 1M hydrochloric acid (2 mL) was added thereto. The reaction mixture was concentrated under reduced pressure, and H_2O was added thereto, followed by stirring at room temperature for 10 minutes. The solid was collected by filtration, washed with H_2O , and then dried under reduced pressure to give 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylic acid (200 mg).

[0106]

Preparation Example 9

A mixture of methyl 2-chloro-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]isonicotinate (4.54 g), potassium trifluoro(vinyl)borate (3.2 g), a [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane adduct (900 mg), Et_3N (4.5 mL), and isopropanol (90 mL) was stirred under a nitrogen atmosphere at

80°C for 18 hours. AcOEt and H₂O were added to the reaction mixture which was then extracted with AcOEt. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-vinylisonicotinate (4.19 g).

5 [0107]

Preparation Example 10

OsO₄ (2.5% tBuOH solution, 10.3 mL) was added to a mixture of methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-vinylisonicotinate (3.03 g), THF (90 mL) and H₂O (30 mL) which was then stirred at room temperature for 10 minutes. NaIO₄ (6.99 g)
10 was added to the reaction mixture which was then stirred at room temperature for 3 hours. AcOEt and H₂O were added to the reaction mixture which was then extracted with AcOEt. The organic layer was sequentially washed with a 20% Na₂S₂O₃ aqueous solution and brine, dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give methyl 2-[(2R,6S)-2,6-
15 dimethylmorpholin-4-yl]-6-formylisonicotinate (2.67 g).

[0108]

Preparation Example 11

NaBH₄ (400 mg) was added under a nitrogen atmosphere and under ice-cooling to a mixture of methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-formylisonicotinate (2.67
20 g) and THF (80 mL) which was then stirred at room temperature from 0°C for 3.5 hours. AcOEt and a saturated NH₄Cl aqueous solution were added to the reaction mixture which was then extracted with AcOEt. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure to give methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-(hydroxymethyl)isonicotinate (2.70 g).

25 [0109]

Preparation Example 12

NBS (1.83 g) was added to a mixture of methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-(hydroxymethyl)isonicotinate (2.69 g) and MeCN(80 mL) which was then stirred at room temperature for 14 hours. AcOEt and H₂O were added to
30 the reaction mixture which was then extracted with AcOEt. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give methyl 3-bromo-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-(hydroxymethyl)isonicotinate (2.33 g).

[0110]

35 Preparation Example 13

A mixture of methyl 3-bromo-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-(hydroxymethyl)isonicotinate (800 mg), potassium trifluoro(vinyl)borate (600 mg), a [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane adduct (330

mg), Et₃N (850 µL) and butan-1-ol (16 mL) was stirred under a nitrogen atmosphere at 100°C for 5.5 hours. CHCl₃ and H₂O were added to the reaction mixture which was then extracted with CHCl₃. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give methyl 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-(hydroxymethyl)-3-vinylisonicotinate (634 mg).

[0111]

Preparation Example 14

Sodium hydride (55% mineral oil dispersion, 225 mg) was added under a nitrogen atmosphere and under ice-cooling to a mixture of methyl 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-(hydroxymethyl)-3-vinylisonicotinate (630 mg) and DMF (19 mL) which was then stirred at room temperature for 20 minutes. 3-bromoprop-1-ene (440 µL) was added under ice-cooling to the reaction mixture which was then stirred at room temperature from 0°C for 21 hours. A saturated NH₄Cl solution and CHCl₃ were added to the reaction mixture which was then extracted with CHCl₃. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure. A 1M NaOH aqueous solution (5.2 mL) and THF (10 mL) were added to the residue which was then stirred at 80°C for 2 hours. 1M hydrochloric acid (5.2 mL) was added to the reaction mixture which was then stirred at room temperature for 5 minutes. H₂O and CHCl₃ were added to the reaction mixture which was then extracted with CHCl₃. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (CHCl₃/MeOH) to give 2-[(allyloxy)methyl]-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-vinylisonicotinic acid (579 mg).

[0112]

Preparation Example 15

A Grubbs catalyst (75 mg) was added under a nitrogen atmosphere to a mixture of 2-[(allyloxy)methyl]-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-vinylisonicotinic acid (577 mg) and CH₂Cl₂ (170 mL) which was then stirred for 4 hours under heating to reflux. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel CC (CHCl₃/MeOH). EtOH (15 mL) and Pd/C with 10% water content (180 mg) were added to the residue which was then stirred under a hydrogen atmosphere at room temperature for 12 hours. The reaction mixture was diluted with MeOH, filtered through Celite, and concentrated under reduced pressure to give 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,7,9-tetrahydrooxepino[3,4-b]pyridine-4-carboxylic acid (477 mg).

[0113]

Preparation Example 16

DIPEA (6.5 mL) and (2R,6S)-2,6-dimethylmorpholine (3.5 mL) were added to a

1,4-dioxane (78 mL) solution of methyl 2,6-dichloroisonicotinate (4.0 g) which was then stirred at 100°C for 12 hours. H₂O and AcOEt were added to the reaction mixture which was then extracted with AcOEt. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by CC (hexane/AcOEt) to give methyl 2-chloro-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]isonicotinate (4.54 g).

[0114]

Preparation Example 17

A mixture of 2,2,6,6-tetramethylpiperidine (0.624 g) and THF (5 mL) was cooled in a dry ice-acetone bath, and nBuLi (2.6M hexane solution, 1.65 mL) was added thereto, followed by warming to -20°C and stirring for 10 minutes. The reaction mixture was cooled in a dry ice-acetone bath to which a THF (5 mL) solution of methyl 2-chloro-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]isonicotinate (1.0 g) was added dropwise, followed by stirring at the same temperature for 1 hour. A THF (5 mL) solution of 4-{[tert-butyl(dimethyl)silyl]oxy}butanal (1.0 g) was added to the reaction mixture at the same temperature, followed by gradual warming to room temperature and stirring for 4 hours. H₂O and brine were added to the reaction mixture which was then extracted with AcOEt and concentrated under reduced pressure. THF (6 mL) and TBAF (1M THF solution, 6 mL) were added to the residue which was then stirred at room temperature for 5 hours. H₂O and brine were added to the reaction mixture which was then extracted with AcOEt. The organic layer was dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give 4-chloro-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-(3-hydroxypropyl)furo[3,4-c]pyridin-1(3H)-one (0.277 g).

[0115]

Preparation Example 18

A mixture of 4-chloro-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-3-(3-hydroxypropyl)furo[3,4-c]pyridin-1(3H)-one (0.30 g), toluene (3 mL), Cs₂CO₃ (0.45 g), Pd(OAc)₂ (20 mg), and 1,1'-binaphthalen-2-yl(di-tert-butyl)phosphine (40 mg) was stirred in a microwave reactor under an argon atmosphere at 120°C for 4 hours. The reaction mixture was allowed to cool to room temperature and then purified by silica gel CC (hexane/AcOEt) to give 4-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-7,8,9,9a-tetrahydro-2H-1,6-dioxo-5-azabenz[cd]azulen-2-one (120 mg).

[0116]

Preparation Example 19

A mixture of 4-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-7,8,9,9a-tetrahydro-2H-1,6-dioxo-5-azabenz[cd]azulen-2-one (75 mg), MeOH (10 mL), and 10% Pd/C (0.1 g) was stirred under a hydrogen atmosphere of 3.4 atmospheric pressure at room temperature for 5 hours. The reaction mixture was filtered through Celite, and then concentrated under reduced pressure. MeOH (20 mL) and 10% Pd/C (0.35 g) were added to residue which

was then stirred under a hydrogen atmosphere of 3.6 atmospheric pressure at room temperature for 18 hours. The reaction mixture was filtered through Celite, concentrated under reduced pressure, and dried to give 8-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2,3,4,5-tetrahydrooxepino[2,3-b]pyridine-6-carboxylic acid (58 mg).

5 [0117]

Preparation Example 20

1-(4-methoxyphenyl)methanamine (91.1 g) and AcOH (16 g) were added to a mixture of ethyl 5-oxooxepane-4-carboxylate (103 g) and EtOH (500 mL) which was then stirred at 50°C for 5 hours. The reaction mixture was concentrated under reduced
10 pressure. AcOEt and H₂O were added to the residue which was then extracted with AcOEt. The organic layer was sequentially washed with saturated a NaHCO₃ aqueous solution and brine, dried over MgSO₄, concentrated under reduced pressure, and then dried to give ethyl 5-[(4-methoxybenzyl)amino]-2,3,6,7-tetrahydrooxepine-4-carboxylate (169 g).

15 [0118]

Preparation Example 21

NaH (60% mineral oil dispersion, 13.2 g) was added under ice-cooling to a mixture of ethyl 5-[(4-methoxybenzyl)amino]-2,3,6,7-tetrahydrooxepine-4-carboxylate (77.6 g) and THF (620 mL) which was then stirred at the same temperature for 10 minutes,
20 and AcCl (27 mL) was added thereto, followed by stirring at 0°C to room temperature for 6.3 hours. Under ice-cooling, the reaction mixture was added to a mixture of 1M hydrochloric acid (153 mL), brine (153 mL) and ice (150 g). AcOEt was added to the reaction mixture. The organic layer was collected, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over MgSO₄, and
25 concentrated under reduced pressure to give ethyl 5-[acetyl(4-methoxybenzyl)amino]-2,3,6,7-tetrahydrooxepine-4-carboxylate (85.1 g).

[0119]

Preparation Example 22

LHMDS (1.1M THF solution, 240 mL) was added to a mixture of ethyl 5-
30 [acetyl(4-methoxybenzyl)amino]-2,3,6,7-tetrahydrooxepine-4-carboxylate (91.9 g) and THF (200 mL) at -65°C, followed by stirring for 1 hour, and LHMDS (1.1M THF solution, 260 mL) was added thereto, followed by further stirring at -65°C for 1 hour. H₂O and hexane were added to the reaction mixture, followed by stirring at room temperature, and the aqueous layer was collected. Concentrated hydrochloric acid (46 mL) was added to
35 the aqueous layer which was then stirred. The precipitated solid was collected by filtration, and then dried under reduced pressure to give 4-hydroxy-1-(4-methoxybenzyl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridin-2(1H)-one (30 g).

[0120]

Preparation Example 23

2-aminoethyl hydrogen sulfate (40 g) was added under ice-cooling to a mixture of KOH (17 g) and H₂O (12 mL) which was then stirred at room temperature for 30 minutes, and a MeOH solution (2 mL) of (2R)-2-ethyloxirane (2 g) was added dropwise thereto.

- 5 After stirring at room temperature for 2 hours, an aqueous solution (12 mL) of KOH (31 g) was added under ice-cooling, followed by stirring at 50°C for 12 hours. The reaction solution was filtered through Celite. Di-tert-butyl dicarbonate (6 g) was added to the filtrate which was then stirred at room temperature for 2 hours. The reaction mixture was extracted with AcOEt, and the organic layer was dried over Na₂SO₄, and then concentrated
10 under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give tert-butyl (2R)-2-ethylmorpholine-4-carboxylate (1.0 g).

[0121]

Preparation Example 24

- 1,1,1-trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide (37.11
15 g) was added to a mixture of 4-hydroxy-1-(4-methoxybenzyl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridin-2(1H)-one (32.95 g) and DMF (165 mL) which was then stirred at room temperature. Et₃N (16 mL) was added to the reaction mixture which was then stirred at room temperature for 1 hour. H₂O was added under ice-cooling to the reaction mixture which was then stirred and collected by filtration to give 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridin-4-yl
20 trifluoromethanesulfonate (43.4 g).

[0122]

Preparation Example 25

- Under an argon atmosphere at 90°C, Pd₂(dba)₃ (291 mg), dppf (422 mg), 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridin-4-yl
25 trifluoromethanesulfonate (27.5 g), Zn (CN)₂ (4.47 g), and H₂O (1.4 mL) were added to DMF (140 mL) which was then stirred at 110°C for 3 hours. NH₄Cl (25% aqueous solution)-28% aqueous NH₃-H₂O (4:1:4, 80 mL) was added under ice-cooling to the reaction mixture which was then stirred. The precipitated solid was collected by
30 filtration, washed with water, and then dried under reduced pressure to give 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carbonitrile (13.2 g).

[0123]

Preparation Example 26

- 35 A mixture of 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carbonitrile (17 g), EtOH (12 mL), and a 3M NaOH aqueous solution (45 mL) was stirred at 85°C for 15 hours. The reaction mixture was filtered through Celite. Toluene was added to the filtrate which was then stirred and separated. Activated carbon

(purified Shirasagi (registered trademark), 3.7 g) was added to the aqueous layer which was then stirred and filtered through Celite. 3M hydrochloric acid (45 mL) was added under ice-cooling to the filtrate which was then stirred. The precipitated solid was collected by filtration, and then dried under reduced pressure to give 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylic acid (16.7 g).

[0124]

Preparation Example 27

K₂CO₃ (14 g) and CH₃I (21.6 g) were added to a mixture of 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylic acid (16.7 g) and CH₃CN (167 mL) which was then stirred at 45°C for 4.5 hours. The insoluble material of the reaction mixture was separated by filtration, and then the filtrate was concentrated under reduced pressure. H₂O was added to the residue which was then stirred at room temperature and stirred under ice-cooling. The precipitated solid was collected by filtration to give methyl 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylate (16.3 g).

[0125]

Preparation Example 28

Under a nitrogen atmosphere, a mixture of CH₂Cl₂ (110 mL) and Tf₂O (36.7 g) was added to a mixture of methyl 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylate (22.3 g), CH₂Cl₂ (220 mL), and pyridine (15.4 g) which was then stirred under ice-cooling for 2 hours, and Tf₂O (5.5 g) was further added thereto, followed by stirring at the same temperature for 1 hour. Hexane and AcOEt were added to the reaction mixture which was then concentrated under reduced pressure, and hexane, AcOEt and H₂O were added thereto, followed by liquid separation. The organic layer was sequentially washed with a saturated NaHCO₃ aqueous solution and H₂O, and concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give methyl 2-[[[(trifluoromethyl)sulfonyl]oxy]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (22.3 g).

[0126]

Preparation Example 29

(2R,6S)-2,6-dimethylmorpholine (13.9 g) was added to a mixture of methyl 2-[[[(trifluoromethyl)sulfonyl]oxy]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate (8.55 g) and DMSO (43 mL) which was then stirred at 50°C for 17 hours. Hexane-AcOEt (1:1) was added to the reaction mixture, and H₂O was added thereto under ice-cooling, followed by stirring at room temperature. The organic layer was collected, and the aqueous layer was extracted with hexane-AcOEt (1:1). The combined organic layer was washed with a 1% citric acid aqueous solution and 20% physiological saline, dried over MgSO₄, and concentrated under reduced pressure. AcOEt (18 mL) and seed crystals

of methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate hydrochloride were added to the residue, and hydrogen chloride (4M AcOEt solution, 6.7 mL) was added thereto under ice-cooling, followed by stirring at room temperature for 20 minutes. iPr₂O (38 mL) was added to the reaction mixture which was then stirred at room temperature for 18 hours. The precipitate was collected by filtration, and then dried under reduced pressure to give methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate hydrochloride (6.46 g).

[0127]

Preparation Example 30

A 50% NaOH aqueous solution (6.23 mL) was added to a MeOH (170 mL) solution of methyl 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylate hydrochloride (17.0 g) which was then stirred at 50°C for 7 hours. MeOH (50 mL) was added to the reaction mixture, and under ice-cooling, concentrated H₂SO₄ (2.43 g) was added thereto, and then CHCl₃ and Na₂SO₄ were added. The reaction mixture was stirred at room temperature. The reaction mixture was filtered through Celite and washed with CHCl₃-MeOH (4:1). The filtrate was concentrated under reduced pressure. CHCl₃-MeOH (9:1) was added to the residue, and the insoluble material was separated by filtration. The filtrate was concentrated under reduced pressure. MeCN was added to the residue which was then stirred under heating to reflux. The precipitated solid was collected by filtration, and then dried under reduced pressure to give 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylic acid (12.2 g).

[0128]

Preparation Example 31

A Ghosez reagent (4.87 g) was added under ice-cooling to a mixture of 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylic acid (8 g) and CH₂Cl₂ (120 mL) which was then stirred at room temperature for 2 hours. Further, a mixture of 5-chloropyridine-2-amine (3.44 g), pyridine (5.76 g) and CH₂Cl₂ (40 mL) was added under ice-cooling to the reaction mixture which was then stirred at room temperature for 1 day. H₂O was added to the reaction mixture which was then extracted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄, and then concentrated under reduced pressure. The residue was washed with iPrOH under heating to reflux, collected by filtration, and then dried under reduced pressure to give N-(5-chloropyridin-2-yl)-1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxamide (5.30 g).

[0129]

Preparation Example 32

A mixture of 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylic acid (3 g), WSC hydrochloride (2.1 g), pyridazine-3-amine (1.1 g), MeCN (30 mL), Et₃N (1.1 g), and HOBt (1.35 g) was stirred at 60°C for 1 day. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel CC (CHCl₃/MeOH) to give 1-(4-methoxybenzyl)-2-oxo-N-(pyridazin-3-yl)-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxamide (3.55 g).

[0130]

Preparation Example 33

A mixture of 1-(4-methoxybenzyl)-2-oxo-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxylic acid (980 mg), pyrazine-2-amine (567 mg), WSC hydrochloride (685 mg), DMAP (730 mg) and CH₂Cl₂ (30 mL) was stirred at 50°C for 1 day. The reaction mixture was concentrated under reduced pressure, and purified by silica gel CC (CHCl₃/MeOH) to give 1-(4-methoxybenzyl)-2-oxo-N-(pyrazin-2-yl)-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxamide (662 mg).

[0131]

Preparation Example 34

Under an argon atmosphere, a mixture of CH₂Cl₂ (10 mL) and Tf₂O (4.92 g) was added under ice-cooling to a mixture of 1-(4-methoxybenzyl)-2-oxo-N-(pyridazin-3-yl)-1,2,5,6,8,9-hexahydrooxepino[4,5-b]pyridine-4-carboxamide (3.55 g), CH₂Cl₂ (50 mL) and pyridine (2.1 g), followed by stirring at the same temperature for 2 hours, and further, under ice-cooling, Tf₂O (740 mg) was added thereto, followed by stirring at room temperature for 1 day. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt) to give 4-(pyridazin-3-ylcarbonyl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridin-2-yl trifluoromethanesulfonate (1.61 g).

[0132]

Preparation Example 35

Hydrogen chloride (4M AcOEt solution, 3 mL) was added to a MeOH solution (10 mL) of tert-butyl (2R)-2-ethylmorpholine-4-carboxylate (1.0 g) at room temperature, followed by stirring at the same temperature for 14 hours. The reaction solution was concentrated under reduced pressure to give (2R)-2-ethylmorpholine hydrochloride (800 mg).

[0133]

Example 1

DIPEA (120 μL) was added to a mixture of 2-[(3S)-3-(trifluoromethyl)piperidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylic acid (120 mg), pyridazine-3-amine (70 mg), HATU (200 mg) and NMP (6 mL) which was then stirred at 60°C for 2 days. The reaction mixture was allowed to cool to room temperature and H₂O was added

thereto, followed by extraction with AcOEt. The organic layer was dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel CC (CHCl₃/MeOH), and then purified by silica gel CC (hexane/AcOEt). The resulting compound was dissolved in a mixed solution of EtOH-Et₂O, and fumaric acid (33 mg) was added thereto. The precipitate was collected by filtration to give N-(pyridazin-3-yl)-2-[(3S)-3-(trifluoromethyl)piperidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide fumarate (107 mg).

[0134]

Example 9

A mixture of 2-(2,2,6,6-tetramethylmorpholin-4-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylic acid (99 mg), pyridazine-3-amine (26 mg), WSC hydrochloride (114 mg), DMAP (72 mg) and CH₂Cl₂ (3 mL) was stirred at 50°C for 3 hours. The reaction mixture was diluted with CHCl₃, purified by silica gel CC (CHCl₃/MeOH), and then purified by silica gel CC (hexane/AcOEt). The resulting compound was dissolved in AcOEt (5 mL), and hydrogen chloride (4M AcOEt solution, 70 µL) was added thereto, followed by stirring at room temperature. The mixture was concentrated under reduced pressure to give N-(pyridazin-3-yl)-2-(2,2,6,6-tetramethylmorpholin-4-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride (32 mg).

[0135]

Example 18

A mixture of 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxylic acid (100 mg), CH₂Cl₂ (3 mL), and a Ghosez reagent (87 µL) was stirred at room temperature for 30 minutes. 5-chloropyridine-2-amine (51 mg) and pyridine (52 µL) were added to the reaction mixture which was then stirred at room temperature for 3 hours. The reaction mixture was diluted with CHCl₃, purified by silica gel CC (CHCl₃/MeOH), and then purified by silica gel CC (hexane/AcOEt). EtOH (2 mL) and hydrogen chloride (4M AcOEt solution, 1 mL) were added to the resulting compound which was then stirred at room temperature for 30 minutes. The mixture was concentrated under reduced pressure. The residue was solidified with EtOH and Et₂O to give N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride (26.6 mg).

[0136]

Example 32

2-butanone (5 mL) and p-toluene sulfonic acid monohydrate (43 mg) were added to N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide (104 mg), followed by stirring at room temperature for 30 minutes. The mixture was concentrated under reduced pressure. 2-

butanone (10 mL) was added to the residue and H₂O (1 mL) was added thereto at 60°C, followed by stirring. The mixture was stirred at room temperature for 1 day. Then, the precipitated solid was collected by filtration and dried under reduced pressure to give N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide p-toluenesulfonate (64 mg).

[0137]

Example 33

2-butanone (5.0 mL) and benzene sulfonic acid (41 mg) were added to N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide (108 mg), followed by stirring at 60°C for 30 minutes. The mixture was concentrated under reduced pressure. 2-butanone (5 mL) was added to the residue which was then stirred at 60°C, followed by stirring at room temperature for 1 day. The precipitated solid was collected by filtration and dried under reduced pressure to give N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide benzenesulfonate (104 mg).

[0138]

Example 69

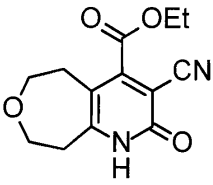
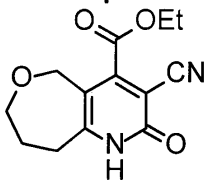
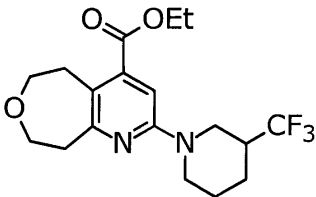
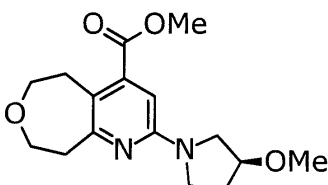
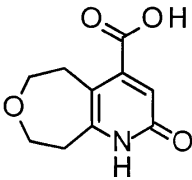
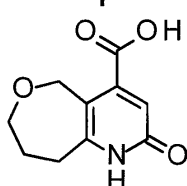
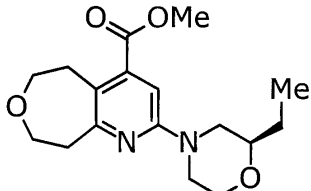
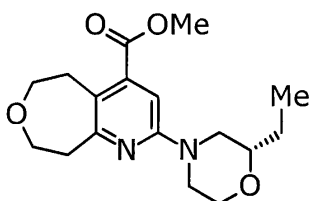
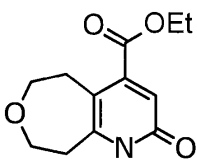
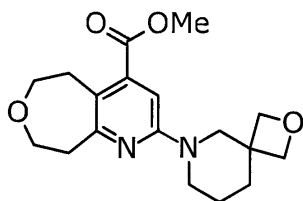
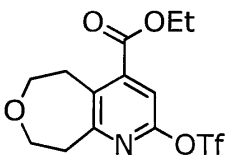
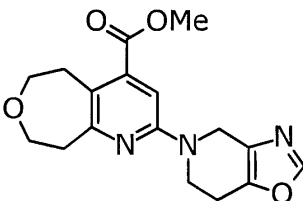
(2S)-2-methylpiperidine (83 mg) and DIPEA (71 mg) were added to a mixture of 4-(pyridazin-3-ylcarbamoyl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridin-2-yl trifluoromethanesulfonate (70 mg) and NMP (1 mL) which was then stirred in a microwave reactor at 180°C for 30 minutes. The reaction mixture was diluted with AcOEt, and H₂O was added thereto, followed by liquid separation. The organic layer was washed with brine, dried over MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel CC (hexane/AcOEt). The resulting compound was suspended in EtOH (5 mL) to which hydrogen chloride (4M AcOEt solution, 1 mL) was then added, followed by stirring at room temperature for 15 minutes and concentration under reduced pressure. Et₂O was added to the residue, and the insoluble material was collected by filtration and dried under reduced pressure to give 2-[(2S)-2-methylpiperidin-1-yl]-N-(pyridazin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide hydrochloride (22 mg).

[0139]

Compounds of Preparation Examples and Examples shown in Tables below were prepared in the same manner as in Preparation Examples or Examples described above.

[0140]

[Table 4]

No. /Inf	Str	No. /Inf	Str
Pr1	 + 	Pr5	
		Pr5-1 /CHR	
Pr2	 + 	Pr5-2 /CHR	
		Pr5-3 /CHR	
Pr3		Pr5-4	
Pr4		Pr5-5	

[0141]

[Table 5]

No. /Inf	Str	No. /Inf	Str
Pr5-6 /CHR		Pr6	
Pr5-7 /CHR		Pr6-1 /CHR	
Pr5-8 /CHR		Pr6-2 /CHR	
Pr5-9		Pr6-3	
Pr5-10		Pr7	

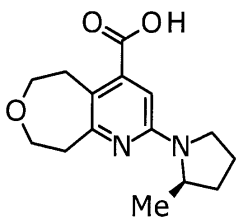
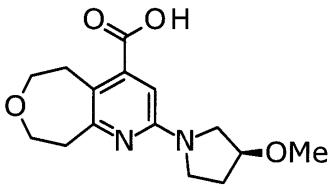
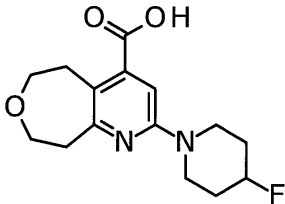
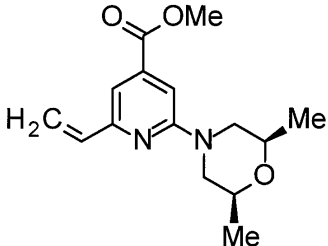
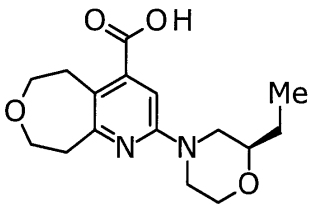
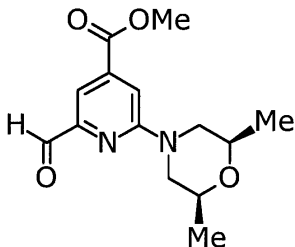
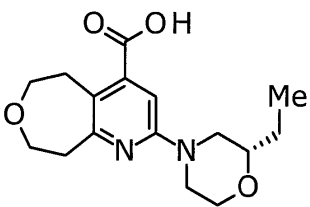
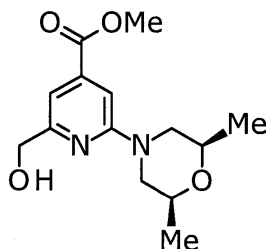
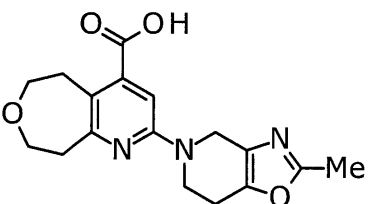
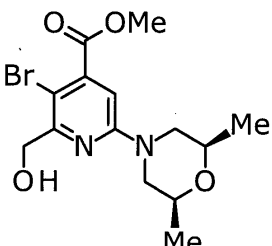
[0142]

[Table 6]

No. /Inf	Str	No. /Inf	Str
Pr7-1		Pr8-5	
Pr8		Pr8-6	
Pr8-1 /CHR		Pr8-7	
Pr8-2 /CHR		Pr8-8 /CHR	
Pr8-3		Pr8-9 /CHR	
Pr8-4		Pr8-10	

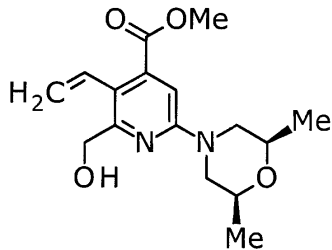
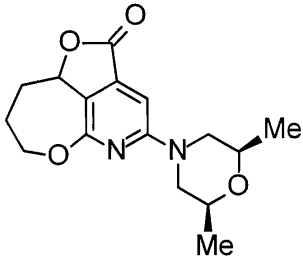
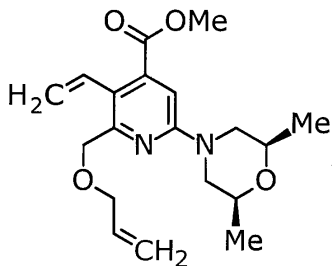
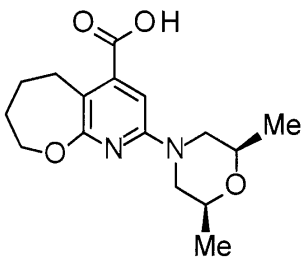
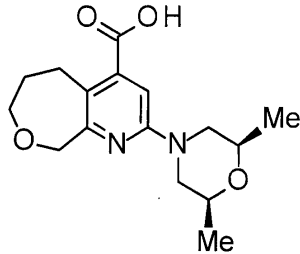
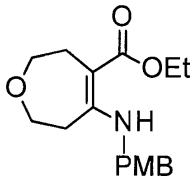
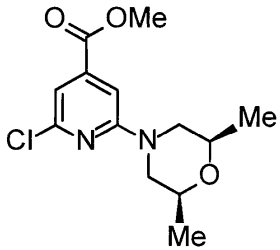
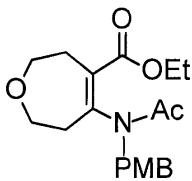
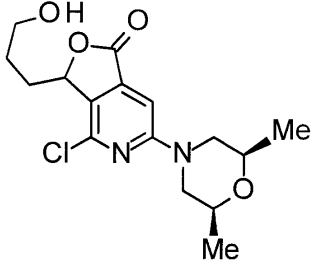
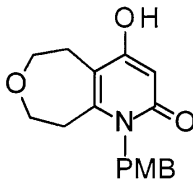
[0143]

[Table 7]

No. /Inf	Str	No. /Inf	Str
Pr8-11 /CHR		Pr8-16 /CHR	
Pr8-12		Pr9	
Pr8-13 /CHR		Pr10	
Pr8-14 /CHR		Pr11	
Pr8-15		Pr12	

[0144]

[Table 8]

No. /Inf	Str	No. /Inf	Str
Pr13		Pr18	
Pr14		Pr19	
Pr15		Pr20	
Pr16		Pr21	
Pr17		Pr22	

[0145]

[Table 9]

No. /Inf	Str	No. /Inf	Str
Pr23 /CHR		Pr27	
Pr23-1 /CHR		Pr28	
Pr24		Pr29 /HCl	
Pr25		Pr30	
Pr26		Pr31	

[0146]

[Table 10]

No. /Inf	Str	No. /Inf	Str
Pr 31-1		Pr 34-1	
Pr32		Pr 34-2	
Pr 32-1		Pr 34-3	
Pr 32-2		Pr 34-4	
Pr33		Pr 34-5	
Pr34		Pr35 /HCl CHR	
		Pr35-1 /HCl CHR	

[0147]

[Table 11]

No. /Inf	Str	No. /Inf	Str
Ex1 /FM CHR		Ex6	
Ex2 /HCl		Ex7 /FM CHR	
Ex3 /HCl		Ex8 /FM	
Ex4		Ex9 /HCl	
Ex5		Ex10	

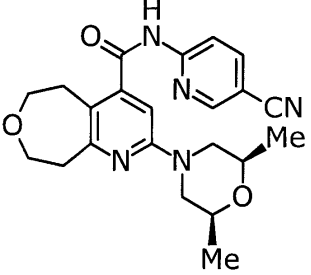
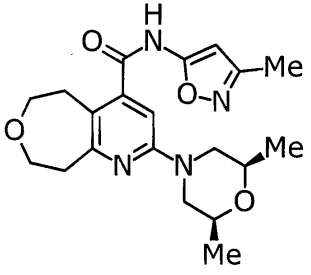
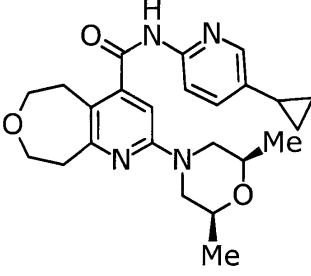
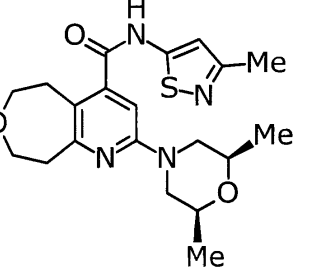
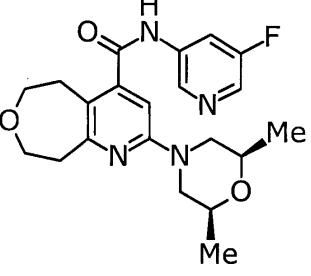
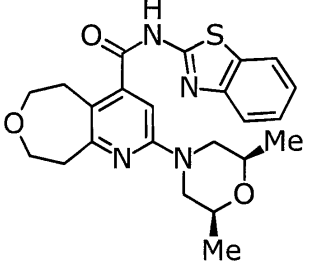
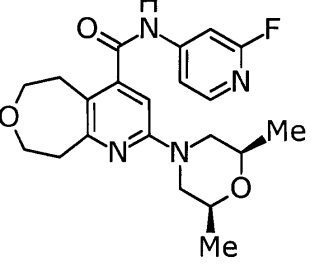
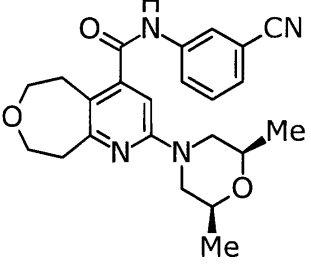
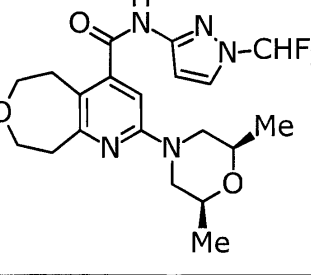
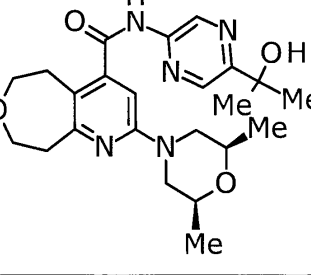
[0148]

[Table 12]

No. /Inf	Str	No. /Inf	Str
Ex11		Ex16	
Ex12		Ex17 /HCl	
Ex13		Ex18 /HCl	
Ex14		Ex19 /FM	
Ex15		Ex20	

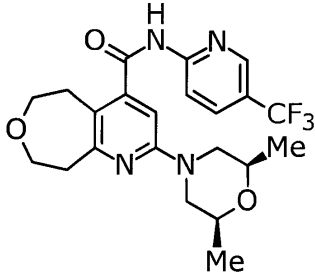
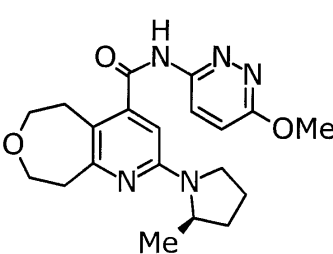
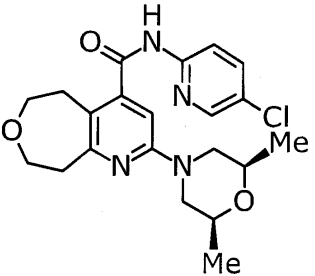
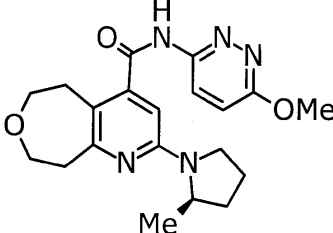
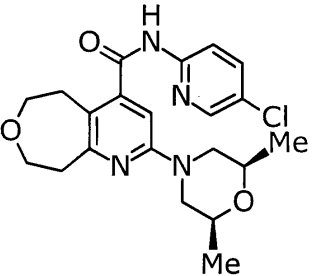
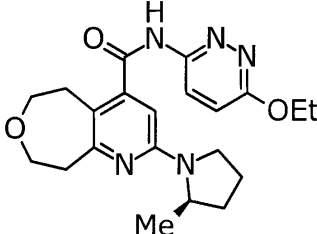
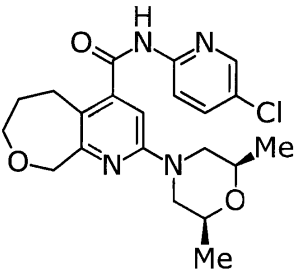
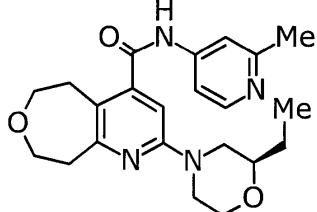
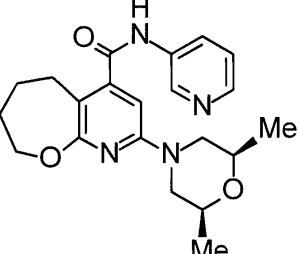
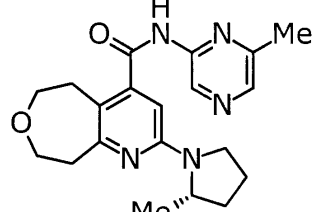
[0149]

[Table 13]

No. /Inf	Str	No. /Inf	Str
Ex21		Ex26	
Ex22		Ex27	
Ex23		Ex28	
Ex24		Ex29	
Ex25		Ex30	

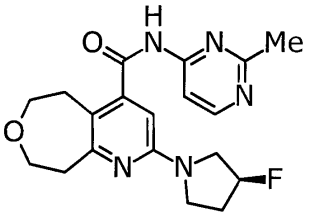
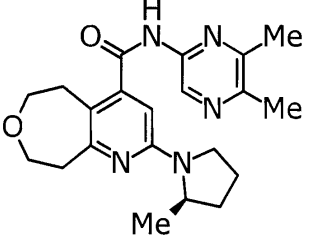
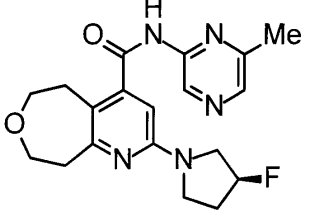
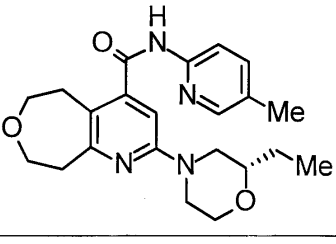
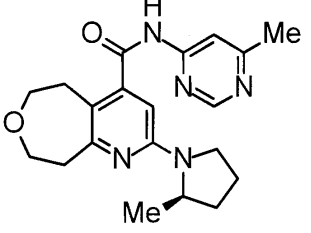
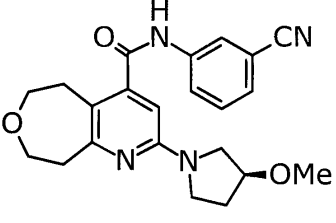
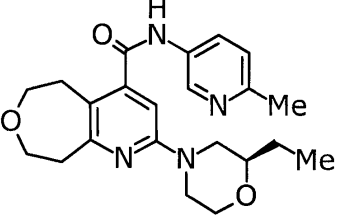
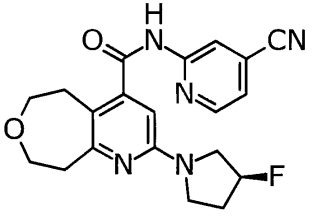
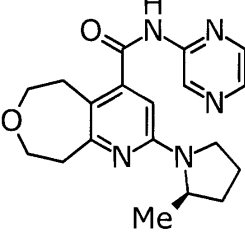
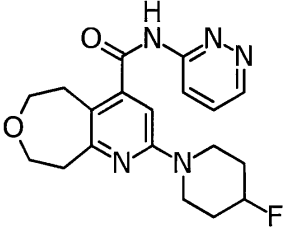
[0150]

[Table 14]

No. /Inf	Str	No. /Inf	Str
Ex31 /HCl		Ex36 /CHR	
Ex32 /TS		Ex37 /PA CHR	
Ex33 /BS		Ex38 /CHR	
Ex34		Ex39 /HCl CHR	
Ex35		Ex40 /HCl CHR	

[0151]

[Table 15]

No. /Inf	Str	No. /Inf	Str
Ex41 /CHR		Ex46 /HCl CHR	
Ex42 /CHR		Ex47 /HCl CHR	
Ex43 /HCl CHR		Ex48 /HCl CHR	
Ex44 /HCl CHR		Ex49 /CHR	
Ex45 /CHR		Ex50	

[0152]

[Table 16]

No. /Inf	Str	No. /Inf	Str
Ex51		Ex56 /HCl	
Ex52 /CHR		Ex57	
Ex53		Ex58	
Ex54 /HCl CHR		Ex59	
Ex55 /HCl CHR		Ex60	

[0153]

[Table 17]

No. /Inf	Str	No. /Inf	Str
Ex61 /HCl		Ex66 /HCl CHR	
Ex62 /HCl		Ex67	
Ex63 /CHR		Ex68 /HCl	
Ex64		Ex69 /HCl CHR	
Ex65 /HCl		Ex70 /HCl CHR	

[0154]

[Table 18]

No. /Inf	Str	No. /Inf	Str
Ex71 /HCl CHR		Ex75 /BS CHR	
Ex72 /HCl CHR		Ex76 /BS CHR	
Ex73 /HCl CHR		Ex77 /CHR	
Ex74 /HCl CHR		Ex78 /HCl	

[0155]

[Table 19]

No.	Ref	Dat		No.	Ref	Dat	
Pr1	Pr1	ESI+	263	Pr9	Pr9	ESI+	277
Pr2	Pr2	APCI/ESI+	210	Pr10	Pr10	ESI+	279
Pr3	Pr3	ESI+	238	Pr11	Pr11	ESI+	281
Pr4	Pr4	APCI/ESI+	370	Pr12	Pr12	ESI+	361
Pr5	Pr5	ESI+	373	Pr13	Pr13	ESI+	307
Pr5-1	Pr5	ESI+	307	Pr14	Pr14	ESI+	333
Pr5-2	Pr5	ESI+	321	Pr15	Pr15	ESI+	307
Pr5-3	Pr5	ESI+	321	Pr16	Pr16	ESI+	285,287
Pr5-4	Pr5	ESI+	333	Pr17	Pr17	ESI+	341
Pr5-5	Pr5	APCI/ESI+	330	Pr18	Pr18	ESI+	305
Pr5-6	Pr5	ESI+	295	Pr19	Pr19	APCI/ESI+	307
Pr5-7	Pr5	ESI+	291	Pr20	Pr20	ESI+	306
Pr5-8	Pr5	ESI+	291	Pr21	Pr21	ESI+	348
Pr5-9	Pr5	APCI/ESI+	309	Pr22	Pr22	APCI/ESI+	302
Pr5-10	Pr5	ESI+	344	Pr23	Pr23	ESI+	238[M+Na] ⁺
Pr6	Pr6	ESI+	335	Pr23-1	Pr23	ESI+	238[M+Na] ⁺
Pr6-1	Pr6	ESI+	373	Pr24	Pr24	APCI/ESI+	434
Pr6-2	Pr6	ESI+	373	Pr25	Pr25	ESI+	311
Pr6-3	Pr6	ESI+	331	Pr26	Pr26	ESI+	330
Pr7	Pr7	APCI/ESI+	363	Pr27	Pr27	ESI+	344
Pr7-1	Pr7	APCI/ESI+	379	Pr28	Pr28	ESI+	356
Pr8	Pr8	ESI+	307	Pr29	Pr29	ESI+	321
Pr8-1	Pr8	ESI+	345	Pr30	Pr30	ESI+	307
Pr8-2	Pr8	ESI+	345	Pr31	Pr31	ESI+	440,442
Pr8-3	Pr8	ESI+	351	Pr31-1	Pr31	ESI+	421
Pr8-4	Pr8	ESI+	335	Pr32	Pr32	ESI+	407
Pr8-5	Pr8	ESI+	303	Pr32-1	Pr32	ESI+	437
Pr8-6	Pr8	ESI+	345	Pr32-2	Pr32	ESI+	421
Pr8-7	Pr8	ESI+	319	Pr33	Pr33	ESI+	407
Pr8-8	Pr8	ESI+	281	Pr34	Pr34	ESI+	419
Pr8-9	Pr8	ESI+	277	Pr34-1	Pr34	ESI+	452,454
Pr8-10	Pr8	ESI+	316	Pr34-2	Pr34	ESI+	449
Pr8-11	Pr8	ESI+	277	Pr34-3	Pr34	ESI+	419
Pr8-12	Pr8	ESI+	295	Pr34-4	Pr34	ESI+	433
Pr8-13	Pr8	ESI+	307	Pr34-5	Pr34	ESI+	433
Pr8-14	Pr8	ESI+	307	Pr35	Pr35	ESI+	116
Pr8-15	Pr8	ESI+	330	Pr35-1	Pr35	ESI+	116
Pr8-16	Pr8	ESI+	293				

[0156]

[Table 20]

No.	Ref	Dat		No.	Ref	Dat	
Ex1	Ex1	ESI+	422	Ex40	Ex9	ESI+	368
Ex2	Ex1	ESI+	383	Ex41	Ex9	ESI+	372
Ex3	Ex1	ESI+	386	Ex42	Ex9	ESI+	372
Ex4	Ex1	ESI+	403	Ex43	Ex9	APCI/ESI+	368
Ex5	Ex1	ESI+	384	Ex44	Ex18	ESI+	397
Ex6	Ex1	ESI+	417	Ex45	Ex18	ESI+	354
Ex7	Ex1	ESI+	422	Ex46	Ex18	ESI+	382
Ex8	Ex1	ESI+	380	Ex47	Ex9	ESI+	397
Ex9	Ex9	ESI+	412	Ex48	Ex18	ESI+	393
Ex10	Ex9	ESI+	383	Ex49	Ex18	ESI+	382
Ex11	Ex9	ESI+	384	Ex50	Ex18	ESI+	372
Ex12	Ex9	ESI+	401	Ex51	Ex18	ESI+	405,407
Ex13	Ex9	ESI+	457	Ex52	Ex18	ESI+	381
Ex14	Ex9	ESI+	389	Ex53	Ex18	ESI+	463
Ex15	Ex9	ESI+	414	Ex54	Ex18	ESI+	371
Ex16	Ex9	ESI+	428	Ex55	Ex18	ESI+	382
Ex17	Ex9	ESI+	445,447	Ex56	Ex18	ESI+	401
Ex18	Ex18	ESI+	417,419	Ex57	Ex18	ESI+	389
Ex19	Ex18	ESI+	424	Ex58	Ex18	ESI+	375
Ex20	Ex18	ESI+	401	Ex59	Ex18	ESI+	385
Ex21	Ex18	ESI+	408	Ex60	Ex18	ESI+	440
Ex22	Ex18	ESI+	423	Ex61	Ex18	ESI+	401
Ex23	Ex18	ESI+	401	Ex62	Ex18	ESI+	386
Ex24	Ex18	ESI+	401	Ex63	Ex18	ESI+	382
Ex25	Ex18	ESI+	422	Ex64	Ex18	APCI/ESI+	401
Ex26	Ex18	ESI+	387	Ex65	Ex18	ESI+	401
Ex27	Ex18	ESI+	403	Ex66	Ex18	ESI+	397
Ex28	Ex18	ESI+	439	Ex67	Ex18	ESI+	393
Ex29	Ex18	ESI+	407	Ex68	Ex18	ESI+	393
Ex30	Ex18	ESI+	442	Ex69	Ex69	ESI+	368
Ex31	Ex18	ESI+	451	Ex70	Ex69	ESI+	368
Ex32	Ex32	ESI+	417,419	Ex71	Ex69	ESI+	368
Ex33	Ex33	APCI/ESI+	417	Ex72	Ex69	ESI+	382
Ex34	Ex1	ESI+	417,419	Ex73	Ex69	ESI+	382
Ex35	Ex1	ESI+	383	Ex74	Ex69	ESI+	382
Ex36	Ex1	ESI+	384	Ex75	Ex69	ESI+	405,407
Ex37	Ex1	ESI+	384	Ex76	Ex69	ESI+	405,407
Ex38	Ex1	ESI+	398	Ex77	Ex69	ESI+	409
Ex39	Ex1	ESI+	397	Ex78	Ex18	APCI/ESI+	372

[0157]

[Table 21]

No.	Dat
Ex1	NMR1:1.44-1.61(2H,m),1.72-1.83(1H,m),1.92-2.05(1H,m),2.75-2.91(4H,m),3.00-3.10(2H,m),3.60-3.76(4H,m),4.17-4.24(1H,m),4.57-4.65(1H,m),6.63(1H,s),6.82(1H,s),7.74(1H,dd,J=9.0,4.8Hz),8.39(1H,d,J=8.7Hz),9.02(1H,dd,J=4.7,1.4Hz),11.5(1H,s),13.1(1H,brs)
Ex7	NMR1:1.46-1.59(2H,m),1.72-1.81(1H,m),1.95-2.04(1H,m),2.78-2.90(4H,m),3.03-3.10(2H,m),3.61-3.75(4H,m),4.17-4.24(1H,m),4.58-4.64(1H,m),6.63(1.6H,s),6.82(1H,s),7.74(1H,dd,J=9.0,4.8Hz),8.39(1H,d,J=9.0Hz),9.02(1H,dd,J=4.7,1.5Hz),11.5(1H,s),13.1(1.6H,brs)
Ex9	NMR1:1.19(12H,s),2.78-2.86(2H,m),3.11(2H,brs),3.44(4H,s),3.63-3.68(2H,m),3.68-3.74(2H,m),6.83(1H,brs),8.41-8.47(2H,m),9.41(1H,s),11.29(1H,s)
Ex12	NMR1:1.15(6H,d,J=6.2Hz),2.35(2H,dd,J=12.6,10.7Hz),2.76-2.86(2H,m),3.00-3.09(2H,m),3.54-3.73(6H,m),4.11-4.20(2H,m),6.69(1H,brs),7.74-7.83(1H,m),8.15-8.24(1H,m),8.33-8.38(1H,m),11.01(1H,brs)
Ex18	NMR1:1.15(6H,d,J=6.4Hz),2.39-2.54(2H,m),2.78-2.85(2H,m),3.08-3.19(2H,m),3.55-3.68(4H,m),3.68-3.74(2H,m),4.19(2H,d,J=11.9Hz),6.87(1H,brs),7.97(1H,dd,J=8.9,2.7Hz),8.20(1H,d,J=8.9Hz),8.41(1H,d,J=2.5Hz),11.17(1H,brs)
Ex37	NMR1:1.17(3H,d,J=6.2Hz),1.61-1.72(1H,m),1.85-2.08(3H,m),2.75-2.86(2H,m),2.96-3.08(2H,m),3.22-3.34(1H,m),3.42-3.53(1H,m),3.56-3.76(4H,m),4.00(3H,s),4.06-4.18(1H,m),6.30(1H,s),7.29(1H,d,J=9.6Hz),8.28(1H,d,J=9.4Hz),11.3(1H,s)
Ex40	NMR1:1.19(3H,d,J=6.2Hz),1.71-1.82(1H,m),1.96-2.21(3H,m),2.46(3H,s),2.79-2.89(2H,m),3.16-3.96(8H,m),4.40(1H,brs),7.06(1H,brs),8.37(1H,s),9.24(1H,s),11.51(1H,brs)
Ex55	NMR1:1.19(3H,d,J=6.2Hz),1.70-1.82(1H,m),1.95-2.20(3H,m),2.45(3H,s),2.48(3H,s),2.79-2.88(2H,m),3.60-3.69(2H,m),3.69-3.80(2H,m),3.81-4.14(4H,m),4.39(1H,brs),7.01(1H,brs),9.10(1H,s),11.35(1H,brs)
Ex70	NMR1:1.13-1.21(3H,m),1.40-1.54(1H,m),1.54-1.82(5H,m),2.86(2H,brs),3.28(2H,brs),3.60-3.70(2H,m),3.70-3.78(2H,m),4.12(1H,brs),7.13(1H,brs),8.41-8.51(2H,m),9.41(1H,brs),11.45(1H,brs)

[0158]

[Table 22]

No.	Dat
Ex76	NMR1:1.48-1.64(1H,m),1.70-2.01(3H,m),2.73-2.87(2H,m),3.03-3.20(2H,m),3.35-3.47(1H,m),3.52-3.81(6H,m),3.90(1H,brs),4.70-4.89(1H,m),6.93(1H,brs),7.25-7.35(3H,m),7.55-7.62(2H,m),7.97(1H,dd,J=8.8,2.6Hz),8.20(1H,d,J=8.7Hz),8.42(1H,d,J=2.5Hz),11.21(1H,s)
Ex78	NMR1:1.65-1.81(2H,m),1.85-2.04(2H,m),2.79-2.91(2H,m),3.07-3.21(2H,m),3.26-4.10(8H,m),4.79-5.02(1H,m),6.99(1H,s),7.77(1H,dd,J=9.0,4.7Hz),8.40(1H,d,J=9.1Hz),9.04(1H,d,J=4.7Hz),11.64(1H,s)

5 Industrial Applicability

[0159]

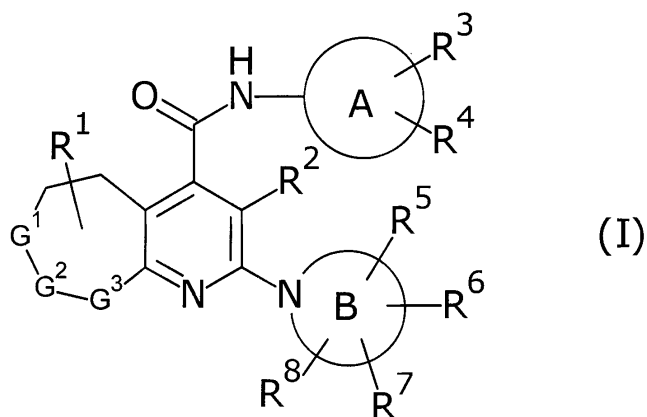
A compound of the formula (I) or a salt thereof has a positive allosteric modulating activity (PAM activity) on an $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nACh receptor), and can be expected as an agent for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.

Claims

[Claim 1] A compound of the formula (I) or a salt thereof:

[Chem. 26]

5



(In the formula,

R^1 is H or lower alkyl,

10

R^2 is H or CN,

any one of G^1 , G^2 , and G^3 is O, and the other two of G^1 , G^2 , and G^3 are CH_2 ,

ring A is aryl, or nitrogen-containing heteroaryl,

ring B is cyclic amino,

R^3 and R^4 are the same as or different each other, and are H, halogen, lower alkyl,

15

-lower alkylene-OH, halo-lower alkyl, -O-lower alkyl, -O-halo-lower alkyl, cycloalkyl, CN, OH, -N(lower alkyl)₂, or -C(=O)NH₂,

R^5 , R^6 , R^7 and R^8 are the same as or different from each other, and are H, halogen, lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN, or

20 in the case where R^5 and R^6 are bonded to the same carbon atom, R^5 and R^6 may form cycloalkane or cyclic ether together with the carbon atom, and may form a spiro ring together with Ring B, or

ring B may form 6,7-dihydro[1,3]oxazolo[4,5-c]pyridin-5(4H)-yl together with R^5 and R^6 .)

25

[Claim 2] The compound or a salt thereof according to claim 1, wherein

R^1 is H,

R^2 is H,

G^1 is O,

G^2 and G^3 are CH_2 ,

30

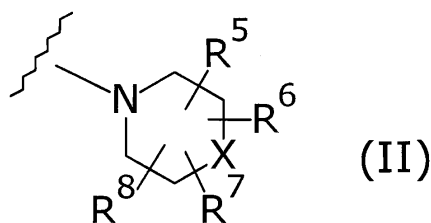
ring A is phenyl, or nitrogen-containing heteroaryl,

ring B is 5- or 6-membered cyclic amino, and
 R^5 , R^6 , R^7 and R^8 are the same as or different from each other, and are H, halogen,
 lower alkyl, halo-lower alkyl, -O-lower alkyl, or CN.

- 5 [Claim 3] The compound or a salt thereof according to claim 2, wherein
 ring A is nitrogen-containing monocyclic heteroaryl,
 R^3 is H or lower alkyl, and
 R^4 is H, halogen, lower alkyl, -lower alkylene-OH, halo-lower alkyl, -O-lower
 alkyl, -O-halo-lower alkyl, cycloalkyl, CN, OH, -N(lower alkyl)₂, or -C(=O)NH₂.

10

- [Claim 4] The compound or a salt thereof according to claim 2 or 3, wherein
 ring B and R^5 , R^6 , R^7 , and R^8 are the formula (II):
 [Chem. 27]



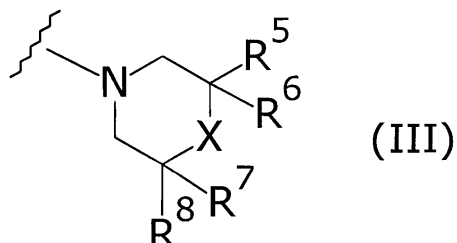
15

- X is CH₂, O, or a bond,
 in the case where X is CH₂, R^5 and R^6 may be substituted with X, and
 R^5 , R^6 , R^7 , and R^8 are the same as or different from each other, and are H, halogen,
 20 lower alkyl, or halo-lower alkyl.

- [Claim 5] The compound or a salt thereof according to claim 4, wherein
 X is CH₂ or O.

- 25 [Claim 6] The compound or a salt thereof according to claim 4, wherein
 X is bond.

- [Claim 7] The compound or a salt thereof according to claim 5, wherein
 ring A is nitrogen-containing 6-membered heteroaryl having one or two nitrogen
 30 atoms as ring atoms,
 ring B, and, R^5 , R^6 , R^7 , and R^8 are the formula (III):
 [Chem. 28]



R^5 is halogen or lower alkyl,

R^6 is H,

5 R^7 is H, and

R^8 is H or lower alkyl.

[Claim 8] The compound or a salt thereof according to claim 7, wherein
ring A is pyridyl,

10 X is CH_2 ,

R^5 is halogen, and

R^8 is H.

[Claim 9] The compound or a salt thereof according to claim 7, wherein
15 ring A is pyridyl,

X is O,

R^5 is lower alkyl, and

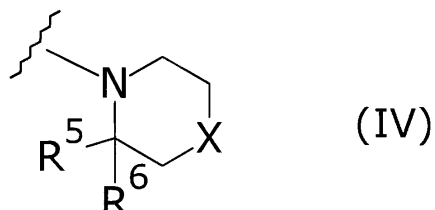
R^8 is lower alkyl.

20 [Claim 10] The compound or a salt thereof according to claim 6, wherein
ring A is nitrogen-containing 6-membered heteroaryl having two nitrogen atoms as
ring atoms,

ring B, and, R^5 , R^6 , R^7 , and R^8 are the formula (IV):

[Chem. 29]

25



R^5 is halogen or lower alkyl,

R^6 is H,

30 R^7 is H, and

R⁸ is H.

[Claim 11] The compound or a salt thereof according to claim 1, which is selected from the group consisting of:

- 5 N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
N-(6-methoxypyridazin-3-yl)-2-[(2R)-2-methylpyrrolidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
N-(6-methylpyrazin-2-yl)-2-[(2S)-2-methylpyrrolidin-1-yl]-5,6,8,9-
10 tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
2-[(2R)-2-ethylmorpholin-4-yl]-N-(6-methylpyridin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
2-(4-fluoropiperidin-1-yl)-N-(pyridazin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
15 N-(5,6-dimethylpyrazin-2-yl)-2-[(2S)-2-methylpyrrolidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
2-[(2S)-2-methylpiperidin-1-yl]-N-(pyridazin-3-yl)-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
2-[(2S)-2-methylpiperidin-1-yl]-N-(pyrazin-2-yl)-5,6,8,9-tetrahydrooxepino[4,5-
20 b]pyridine-4-carboxamide, and,
N-(5-chloropyridin-2-yl)-2-[(3S)-3-fluoropiperidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide,
or a salt thereof.

- 25 [Claim 12] The compound or a salt thereof according to claim 11, which is N-(5-chloropyridin-2-yl)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide or a salt thereof.

- 30 [Claim 13] The compound or a salt thereof according to claim 11, which is N-(6-methoxypyridazin-3-yl)-2-[(2R)-2-methylpyrrolidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide or a salt thereof.

- 35 [Claim 14] The compound or a salt thereof according to claim 11, which is N-(5-chloropyridin-2-yl)-2-[(3S)-3-fluoropiperidin-1-yl]-5,6,8,9-tetrahydrooxepino[4,5-b]pyridine-4-carboxamide or a salt thereof.

[Claim 15] A pharmaceutical composition comprising the compound or the salt thereof according to claim 1, and a pharmaceutically acceptable excipient.

- [Claim 16] The pharmaceutical composition according to claim 15, which is a positive allosteric modulator on an $\alpha 7$ nicotinic acetylcholine receptor.
- 5 [Claim 17] The pharmaceutical composition according to claim 15, which is a pharmaceutical composition for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.
- 10 [Claim 18] Use of the compound or the salt thereof according to claim 1 for the manufacture of a pharmaceutical composition for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.
- 15 [Claim 19] Use of the compound or the salt thereof according to claim 1, for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.
- [Claim 20] The compound or the salt thereof according to claim 1, for preventing or
20 treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia, inflammatory diseases, or pain.
- [Claim 21] A method for preventing or treating dementia, cognitive impairment, schizophrenia, Alzheimer's disease, CIAS, negative symptoms of schizophrenia,
25 inflammatory diseases, or pain, comprising administering an effective amount of the compound or the salt thereof according to claim 1 to a subject.