DESCRIPTION

Title of Invention

PHARMACEUTICAL COMPOSITION FOR TREATING OR PREVENTING ANHEDONIA

Technical Field

[0001]

The present invention relates to a pharmaceutical composition for treating or preventing anhedonia, including a selective δ opioid receptor agonist as an active ingredient.

The present application claims priority based on Japanese Patent Application No. 2024-042863 filed in Japan on March 18, 2024 and Japanese Patent Application No. 2024-134624 filed in Japan on August 9, 2024, the contents of which are incorporated herein by reference.

Background Art

[0002]

Opioids exhibit their effects by binding to opioid receptors. The opioid receptors have three subtypes, μ, δ, and κ. Compounds having activity similar to opioids are also known. Among such compounds, for example, an agonist that activates the δ opioid receptor (DOR) may also be an agonist or an antagonist for other receptors, namely the μ opioid receptor (MOR) or the κ opioid receptor (KOR), and a

compound acting on opioid receptors may have various activities. To date, various compounds have been reported as DOR agonists whose analgesic action, antidepressant action, anxiolytic action and effects on stress-related disorders have been demonstrated (Patent Literatures 1 to 8 and Non Patent Literatures 1 to 4).

[0003]

In diagnosis of major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), five or more symptoms among nine depressive symptoms, namely "depressed mood", "markedly diminished interest or pleasure", "change in weight or appetite", "insomnia or hypersomnia", "psychomotor agitation or retardation", "fatigue", "feeling of guilt or worthlessness", "diminished ability to concentrate or indecisiveness", and "recurrent thoughts of death", must be present nearly every day during the same two-week period, and one of the symptoms must be "depressed mood" or "markedly diminished interest or pleasure". "Markedly diminished interest or pleasure" is synonymous with anhedonia, and is a component of substance-related disorders, psychotic disorders, and personality disorders in addition to depressive disorders.

In the Research Domain Criteria (RDoC) (Non Patent Literature 5), anhedonia can be regarded as dysregulation

of a positive valence system, and is described as a condition including reduction in motivation and effort for reward acquisition, reduction and difficulty in maintaining positive affect upon reward acquisition, difficulty in learning relating to reward acquisition or the like. Anhedonia is clearly distinguished from depressed mood, which is a core symptom of major depression.

Conventional treatment for depression has focused on alleviation of depressed mood and negative symptoms, and little attention has been paid to loss of positive affect such as enjoyment of pleasure and joy, that is, so-called anhedonia. Anhedonia in depression is treatment-resistant, is a symptom that remains until the last among depressive symptoms, and has been reported not to be sufficiently improved by existing psychiatric treatments and psychological support methods (Non Patent Literature 6). At least at present, no antidepressant effective against anhedonia has been marketed domestically or overseas, and rather, anhedonia has been reported to attenuate the effect of selective serotonin reuptake inhibitors (SSRIs), which are first-line drugs for depression (Non Patent Literature 7), and anhedonia has been reported to predict suicidal ideation most strongly among depressive symptoms (Non Patent Literature 8). Furthermore, anhedonia is a symptom observed not only in depression but also in diseases such

as schizophrenia, Parkinson's disease, obsessive-compulsive disorder, or post-traumatic stress disorder (PTSD), and an effective therapeutic agent for anhedonia is desired.

[0004]

Animal models for evaluating anhedonia have been reported, and examples include a female urine sniffing test (FUST) (Non Patent Literature 9) and a sucrose preference test (Non Patent Literature 10). In addition, attempts to treat anhedonia by modulating opioid receptors have been reported, and evaluations have been performed with a KOR agonist (Salvinolin A), a KOR antagonist (LY-2456302), a DOR agonist/MOR agonist/partial KOR agonist (Nalmefen), or a DOR agonist (SNC80) (Non Patent Literatures 9 to 12).

[Citation List]

[Patent Documents]

[0005]

[Patent Document 1]

JP2006-522775

[Patent Document 2]

WO2001/046192

[Patent Document 3]

WO2008/001859

[Patent Document 4]

WO2013/035833

[Patent Document 5]

WO2014/021273

[Patent Document 6]

WO2014/136305

[Patent Document 7]

WO2016/148232

[Patent Document 8]

WO2022/181763

[Non-Patent Documents]

[0006]

[Non-Patent Document 1] Hayashida et al.,Tetrahedron,2011,67,6682

[Non-Patent Document 2] Kamei et al.,E.J.Pharmacol.,1995,276 ,131

[Non-Patent Document 3] Kamei et al., E.J.Pharmacol.,1997,322,27

[Non-Patent Document 4] Nagase et al.,Bioorg. Medic.Chem.Lett.,2010,20,6302

[Non-Patent Document 5] Insel et al.,Am.J.Psychiary.2010,167,748

[Non-Patent Document 6] Dunn et al.,Clinic.Psychol. Sci.,2020,8,36

[Non-Patent Document 7] Uher et al.,Psychol.Med.,2012,42,967.

[Non-Patent Document 8] Ducasse et al.,Depress

Anxiety.,2018,35,382

[Non-Patent Document 9] Scheggi et al.,Int.J.Neuropsychopharmacol.,2018,21,1049

[Non-Patent Document 10] Wu et al.,E.J.Pharmacol.,2023,942,175532

[Non-Patent Document 11] Harden et al.,Behav.Pharmacol.,2012,23,710

[Non-Patent Document 12] Page et al.,Int.J.Neuropsychopharmacol.,2019,22,735

Summary of Invention

Technical Problem

[0007]

An object of the present invention is to provide a medicine useful for treating or preventing anhedonia.

Solution to Problem

[0008]

The present inventors have conducted extensive studies to achieve the above object, as a result found that a pharmaceutical composition including a selective DOR agonist as an active ingredient, preferably a pharmaceutical composition in which the selective DOR agonist has a morphinan skeleton and the selective DOR agonist further has MOR antagonist action and KOR

antagonist action, is useful for treating or preventing anhedonia, and completed the present invention.

That is, the present invention includes the following aspects.

[0009]

[1] A pharmaceutical composition for treating or preventing anhedonia, including a selective δ opioid receptor agonist as an active ingredient.

[2] The pharmaceutical composition for treating or preventing anhedonia according to [1], wherein the selective δ opioid receptor agonist further has κ opioid receptor antagonist action.

[3] The pharmaceutical composition for treating or preventing anhedonia according to [1] or [2], wherein the selective δ opioid receptor agonist further has μ opioid receptor antagonist action and κ opioid receptor antagonist action.

[4] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [3], wherein the anhedonia is anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder (such as PTSD), autism spectrum disorder, or Alzheimer-type dementia.

[5] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [4], wherein the anhedonia is anhedonia caused by psychological stress or physical stress.

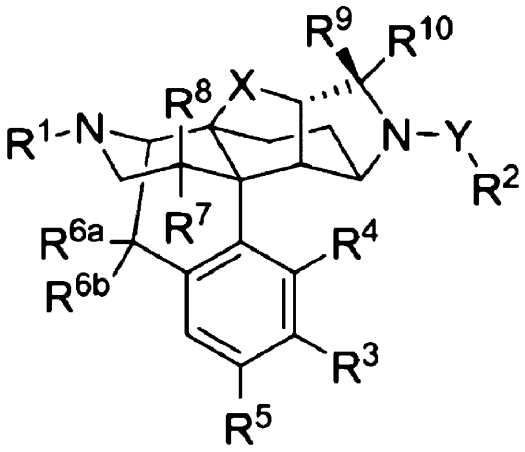
[6] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [5], suppressing suicidal ideation.

[7] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [6], wherein the anhedonia is reduced responsiveness to pleasant experiences relating to at least one selected from money, food and drink, hobbies, entertainment, travel and recreation, and desire for control, desire for approval, desire for achievement, desire for affiliation and sexual desire.

[8] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [7], wherein the selective δ opioid receptor agonist is a compound represented by the following general formula (I):

[0010]

[Chem. 1]



(I)

(wherein R^1 represents hydrogen; C_{1-10} alkyl; C_{6-10} aryl; C_{2-6} alkenyl; cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five; C_{3-6} cycloalkyl; or heteroarylalkyl in which the heteroaryl moiety includes one to four heteroatoms selected from N, O and S as ring-constituting atoms and the number of carbon atoms in the alkylene moiety is one to five,

R^2 represents a heterocycle including one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is

a ring-constituting atom of R^2,

R^3, R^4 and R^5 are the same or different, and represent hydrogen; hydroxy; halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyloxy; nitro; amino; C_{1-8} alkylamino; C_{6-10} arylamino; or acylamino in which the number of carbon atoms in the acyl moiety is two to six,

R^{6a} and R^{6b} are the same or different, and represent hydrogen; fluorine; or hydroxy, or R^{6a} and R^{6b} together represent =O,

R^7 and R^8 are the same or different, and represent hydrogen; fluorine; or hydroxy,

R^9 and R^{10} are the same or different, and represent hydrogen; C_{1-6} alkyl; C_{6-10} aryl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five; heteroarylalkyl in which the heteroaryl moiety includes one to four heteroatoms selected from N, O and S as ring-constituting atoms and the number of carbon atoms in the alkylene moiety is one to five; cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; or C_{2-6} alkenyl,

X represents O or CH_2,

and Y represents C(=O),

provided that the C_{1-10} alkyl; the alkylene moiety and the cycloalkyl moiety of the cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; the alkylene moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five; and the alkylene moiety of the heteroarylalkyl in which the heteroaryl moiety includes one to four heteroatoms selected from N, O and S as ring-constituting atoms and the number of carbon atoms in the alkylene moiety is one to five of R^1,

may be substituted with at least one substituent selected from one to six halogens; hydroxy; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyl; C_{1-6} alkanoyloxy; carboxyl; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; alkylsulfonyl in which the number of carbon atoms in the alkyl moiety is one to six; aminosulfonyl; alkylsulfinyl in which the number of carbon atoms in the alkyl moiety is one to six; alkylthio in which the number of carbon atoms in the alkyl moiety is

one to six; C_{1-6} alkoxy substituted with one to six halogens; and arylcarbonyl in which the number of carbon atoms in the aryl moiety is six to ten,

and the C_{6-10} aryl; the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1; the aryl moiety of C_{6-10} aryloxy, and the aryl moiety of C_{6-10} arylamino of R^3, R^4 and R^5; and the C_{6-10} aryl; the heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five; and the heteroaryl moiety of the heteroarylalkyl in which the heteroaryl moiety includes one to four heteroatoms selected from N, O and S as ring-constituting atoms and the number of carbon atoms in the alkylene moiety is one to five of R^9 and R^{10}

may be substituted with at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six;

halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which the number of carbon atoms in the alkyl is one to three; and methylenedioxy,

the heterocycle of R^2 may have, in addition to the oxo group, a substituent that C_{6-10} aryl of R^1 described above may have, and the pyridine 1-oxide of R^2 may have a substituent that C_{6-10} aryl of R^1 described above may have,

further, when R^1 is C_{1-10} alkyl, R^1 may be substituted with $NR^{11}R^{12}$, wherein R^{11} and R^{12} are the same or different, and are hydrogen; C_{1-10} alkyl; or aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five, or R^{11} and R^{12}, the nitrogen atom to which R^{11} and R^{12} are bonded, and further, optionally, one to two heteroatoms may together form a five- to seven-membered ring, and also the alkylene moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from phenyl or C_{1-6} alkyl substituted with one to three halogens)

or a pharmaceutically acceptable salt thereof.

[9] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [8], wherein the compound represented by the general formula (I) is a compound in which R^5, R^{6a}, R^{6b}, R^7, R^8, R^9 and R^{10} are hydrogen,

R^1 is hydrogen; C_{1-6} alkyl; C_{2-6} alkenyl; cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; or aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five,

R^2 represents a five- to seven-membered heterocycle including one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or a heterocycle in which a benzene ring is fused to the heterocycle, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is a ring-constituting atom of R^2,

R^3 and R^4 are the same or different, and are hydrogen; hydroxy; halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyloxy; amino; or acylamino in which

the number of carbon atoms in the acyl moiety is two to six,

X is CH_2,

and Y is C(=O),

provided that the C_{1-6} alkyl; the alkylene moiety and the cycloalkyl moiety of the cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; or the alkylene moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from one to six halogens; hydroxy; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyl; C_{1-6} alkanoyloxy; carboxyl; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; alkylsulfonyl in which the number of carbon atoms in the alkyl moiety is one to six; aminosulfonyl; alkylsulfinyl in which the number of carbon atoms in the alkyl moiety is one to six; alkylthio in which the number of carbon atoms in the alkyl moiety is one to six; C_{1-6} alkoxy substituted with one to six halogens; and

arylcarbonyl in which the number of carbon atoms in the aryl moiety is six to ten,

and the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1; and the aryl moiety of the C_{6-10} aryloxy of R^3 and R^4

may be substituted with at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which the number of carbon atoms in the alkyl is one to three; and methylenedioxy,

the heterocycle of R^2 may have, in addition to the oxo group, a substituent that the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 described above may

have, and the pyridine 1-oxide of R^2 may have a substituent that the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 described above may have,

further, the alkylene moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from phenyl or C_{1-6} alkyl substituted with one to three halogens.

[10] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [9], wherein the compound represented by the general formula (I) is a compound in which R^1 is C_{1-6} alkyl; cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; or aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five.

[11] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [9], wherein the compound represented by the general formula (I) is a compound in which R^1 is cycloalkylalkyl in which the

number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five.

[12] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [9], wherein the compound represented by the general formula (I) is a compound in which R^1 is C_{2-6} alkyl substituted with hydroxy; C_{1-6} alkyl substituted with one to six halogens; or C_{2-6} alkyl substituted with C_{1-6} alkoxy.

[13] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [9], wherein the compound represented by the general formula (I) is a compound in which R^1 is allyl, fluoropropyl, 2-(pyridin-3-yl)ethyl, 2-(methylsulfonyl)ethyl or 2-(aminosulfonyl)ethyl.

[14] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which R^2 is a five- to seven-membered heterocycle including one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or a heterocycle in which a benzene ring is fused to

the heterocycle, or pyridine 1-oxide.

[15] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which R^2 is pyridine 1-oxide.

[16] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyridin-2(1H)-one.

[17] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyridin-4(1H)-one.

[18] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyridazin-3(2H)-one.

[19] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyrazin-2(1H)-one.

[20] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is 4H-pyran-4-one or 2H-pyran-2-one.

[21] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is quinolin-2(1H)-one.

[22] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [13], wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyrimidin-4(3H)-one or pyrimidine-2,4(1H,3H)-dione.

[23] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [22], wherein the compound represented by the general formula (I) is a compound in which X is CH_2.

[24] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which one of R^3 and R^4 is hydroxy and the other is hydrogen.

[25] The pharmaceutical composition for treating or

preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which R^3 is halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; amino; or acylamino in which the number of carbon atoms in the acyl moiety is two to six, R^4 is hydrogen or hydroxy, and R^5 is hydrogen.

[26] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which R^3 is hydroxy; carbamoyl; or C_{1-6} alkanoyloxy, R^4 is hydrogen, and R^5 is hydrogen.

[27] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which R^3 is hydroxy, R^4 is hydrogen, and R^5 is hydrogen.

[28] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which R^3, R^4 and R^5 are all hydrogen.

[29] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [28], wherein the compound represented by the general formula (I) is a compound in which R^{6a}, R^{6b}, R^7, R^8, R^9 and R^{10} are all hydrogen.

[30] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which R^3 is halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; amino; or acylamino in which the number of carbon atoms in the acyl moiety is two to six, and R^4 is hydrogen or hydroxy.

[31] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which R^3 is hydroxy; carbamoyl; or C_{1-6} alkanoyloxy, and R^4 is hydrogen.

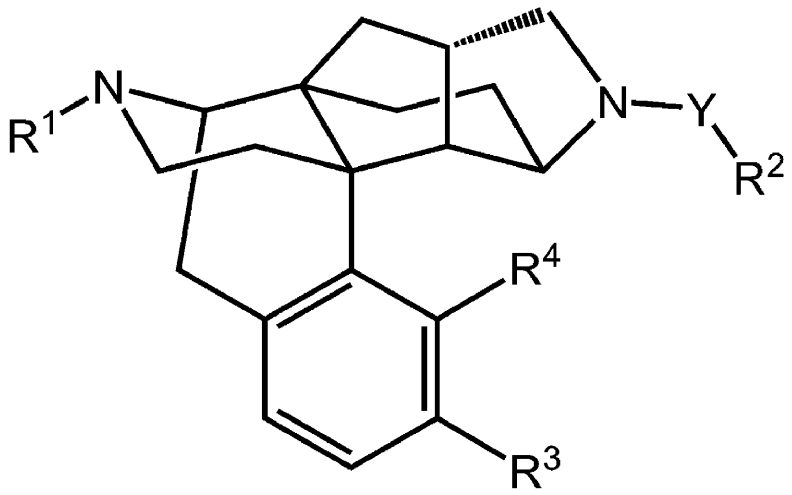
[32] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is such that R^3 is hydroxy and R^4 is hydrogen.

[33] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [23], wherein the compound represented by the general formula (I) is a compound in which R^3 and R^4 are hydrogen.

[34] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [6], wherein the compound represented by the general formula (I) is a compound represented by the following general formula (II):

[0011]

[Chem. 2]



(II)

(wherein R^1 is hydrogen; C_{1-6} alkyl; or cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five,

R^2 represents a five- to seven-membered heterocycle including one or two nitrogen atoms and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is a ring-constituting atom of R^2,

R^3 and R^4 are the same or different, and are hydrogen; hydroxy; or C_{1-6} alkoxy,

Y is C(=O),

provided that the C_{1-6} alkyl; and the alkylene moiety and the cycloalkyl moiety of the cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five of R^1

may be substituted with at least one substituent selected from one to six halogens; hydroxy; and C_{1-6} alkoxy,

and the heterocycle of R^2 may have, in addition to the oxo group,

at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which the number of carbon atoms in the alkyl is one to three; and methylenedioxy,

and the pyridine 1-oxide of R^2 may have

at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which

the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which the number of carbon atoms in the alkyl is one to three; and methylenedioxy).

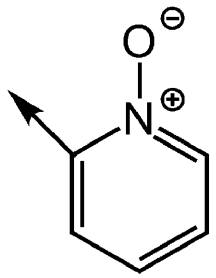
[35] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [6] and [34], wherein the compound represented by the general formula (II) is a compound in which R^1 is cycloalkylalkyl and is cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five.

[36] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [6], [34] and [35], wherein the compound represented by the general formula (II) is a compound in which R^2 is

formula (III):

[0012]

[Chem. 3]

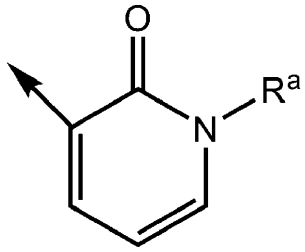


(III)

; formula (IV):

[0013]

[Chem. 4]

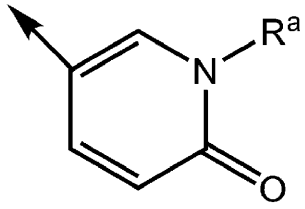


(IV)

; formula (V):

[0014]

[Chem. 5]

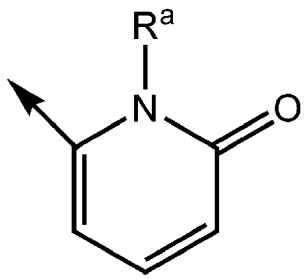


(V)

; or formula (VI):

[0015]

[Chem. 6]



(V I)

(in formulas III to VI, R^a is hydrogen or C_{1-6} alkyl, and is bonded to Y at the position of the arrow).

[37] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [6], and [34] to [36], wherein the compound represented by the general formula (II) is a compound in which R^3 is hydroxy.

[38] The pharmaceutical composition for treating or preventing anhedonia according to any one of [1] to [6], and [34] to [37], wherein the compound represented by the general formula (II) is a compound in which R^4 is hydrogen.

[39] The pharmaceutical composition for treatment or prevention according to any one of [1] to [6],and [34], wherein the compound represented by the general formula (I) is at least one compound selected from:
2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-

carbonyl)-6-methylpyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridazin-3(2H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)quinolin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-2H-pyran-2-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-4H-pyran-4-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-4(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-

10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-10-acetoxy-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-

carbonyl)pyrimidin-4(3H)-one, and

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one.

[40] The pharmaceutical composition for treatment or prevention according to any one of [1] to [6],and [34], wherein the compound represented by the general formula (I) is at least one compound selected from:

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one, and

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one.

Advantageous Effects of Invention

[0016]

According to the present invention, a pharmaceutical composition useful for treating or preventing anhedonia is provided.

Brief Description of Drawings

[0017]

[Fig. 1] Fig. 1 is a drawing showing the effect of a compound (compound number 7) on anhedonia associated with physical stress, using a sucrose preference test (**: $p < 0.01$ (Bonferroni's test after one-way analysis of variance)).

[Fig. 2] Fig. 2 is a drawing showing the effect of KNT-127 on anhedonia associated with chronic vicarious social defeat stress, using a sucrose preference test

(n.s.: no significant difference, **: $p < 0.01$ (Bonferroni's test after one-way analysis of variance)).

[Fig. 3] Fig. 3 is a drawing showing the effect of a compound (compound number 7) on anhedonia associated with chronic vicarious social defeat stress, using a sucrose preference test (n.s.: no significant difference, *: $p < 0.05$ (Bonferroni's test after one-way analysis of variance)).

[Fig. 4] Fig. 4 is a drawing showing the effect of a compound (compound number 7) on anhedonia associated with physical stress, using a female urine sniffing test (n.s.: no significant difference, *: $p < 0.05$ (Bonferroni's test after one-way analysis of variance)).

[Fig. 5] Fig. 5 is a drawing showing the effect of a compound (compound number 7) on anhedonia associated with chronic vicarious social defeat stress, using a female urine sniffing test (n.s.: no significant difference, *: $p < 0.05$, **: $p < 0.01$ (Bonferroni's test after one-way analysis of variance)).

Description of Embodiments

[0018]

Next, more detailed description is made of the present invention. Patent publications, patent application publications, non patent literatures and the like cited in

the present specification are each incorporated herein by reference in entirety for all purposes.

[0019]

1. Anhedonia

In the present specification, “anhedonia” is a symptom indicating reduced responsiveness to rewards, recreation or other pleasant experiences. Anhedonia is generally sometimes also described as reduced positive affect, reduced motivation, reduced sensitivity to reward, loss of pleasure, and the like. In the Research Domain Criteria (RDoC) (Non Patent Literature 5), anhedonia (loss of pleasure) can be regarded as dysregulation of a positive valence system, and is described as a condition including reduction in motivation and effort for reward acquisition, reduction and difficulty in maintaining positive affect upon reward acquisition, difficulty in learning relating to reward acquisition, and the like. Anhedonia may further be classified in detail as “motivational anhedonia”, which means reduction or loss of motivation to seek rewards, “consummatory anhedonia”, which means reduction or loss of a hedonic response at the stage at which a reward is obtained, or “decisional anhedonia”, which regards anhedonia not as a trait but as a problem in a dynamic decision-making process.

One aspect of the present invention is a

pharmaceutical composition for treating or preventing symptoms of anhedonia, including a selective DOR agonist as an active ingredient, and more specifically, is a pharmaceutical composition for treating or preventing symptoms of motivational anhedonia, including a selective DOR agonist as an active ingredient, or is a pharmaceutical composition for treating or preventing symptoms of consummatory anhedonia, including a selective DOR agonist as an active ingredient, or is a pharmaceutical composition for treating or preventing symptoms of decisional anhedonia, including a selective DOR agonist as an active ingredient. In one aspect of the present invention, the selective DOR agonist is a compound having a morphinan skeleton, and preferably, the selective DOR agonist is a compound further having MOR antagonist action and KOR antagonist action.

[0020]

In the present specification, examples of rewards, recreation or other pleasant experiences relating to "anhedonia" include pleasant experiences relating to at least one selected from money, food and drink, hobbies, entertainment (television programs, radio programs, reading, and the like), travel, recreation and the like, and desire for control, desire for approval, desire for achievement, desire for affiliation, sexual desire, and the

like.

[0021]

A questionnaire may be used for diagnosis of anhedonia relating to the present invention. Examples of the questionnaire include the Snaith-Hamilton pleasure scale (SHAPS) (Snaith et al., Br J Psychiatry, 1995, 167: 99), Chapman scales for physical and social anhedonia (Chapman et al., J Abnorm Psychol 85: 374-382, 1976), and questionnaires prepared for respective various diseases accompanied by anhedonia (for example, items 1 and 2 of the "Edinburgh Postnatal Depression Scale"; Cox JL, et al., Br. J. Psychiatry., 1987, 150, 782). In SHAPS, the following 14 questions are prepared.

1) Can you enjoy your favorite television programs or radio programs?

2) Do you enjoy being with family or friends?

3) Do you enjoy time for hobbies or entertainment?

4) Can you enjoy eating meals containing your favorite dishes?

5) Do you feel good when refreshed by taking a warm bath or shower?

6) Is the fragrance of flowers, sea breeze, or smell of freshly baked bread pleasant?

7) Does a person's smile soothe you?

8) Do you feel happy when you have properly groomed

yourself?

9) Do you enjoy reading books, magazines, or newspapers?

10) Do you enjoy drinking tea, coffee, or a favorite beverage?

11) Do you feel joy in small things (such as fine weather or a phone call from a friend)?

12) Are your soothed when viewing beautiful scenery?

13) Do you feel happy when you have been useful to other people?

14) Do you feel happy when praised by people?

One aspect of the present invention is a pharmaceutical composition for improving a score of a questionnaire relating to anhedonia, including a selective DOR agonist as an active ingredient. More specifically, one aspect of the present invention is a pharmaceutical composition including a selective DOR agonist as an active ingredient, for bringing about, for example, a state in which a subject finds favorite television programs or radio programs more enjoyable, a state in which the subject finds being with family or friends more enjoyable, a state in which the subject finds time for hobbies or entertainment more enjoyable, a state in which the subject can enjoy eating meals containing favorite dishes more deliciously, a state in which the subject feels that being refreshed by

taking a warm bath or shower is more pleasant, a state in which the subject finds the fragrance of flowers, sea breeze, or smell of freshly baked bread more pleasant, a state in which the subject is more soothed by a person's smile, a state in which the subject feels happier when the subject has properly groomed himself or herself, a state in which the subject finds reading books, magazines, or newspapers more enjoyable, a state in which the subject finds drinking tea, coffee, or a favorite beverage more enjoyable, a state in which the subject feels more joy in small things, a state in which the subject is more soothed when viewing beautiful scenery, a state in which the subject feels happier when the subject has been useful to other people, a state in which the subject feels happy about having a romantic relationship with a favorite member of the opposite sex, liking a member of the opposite sex, or being liked by a member of the opposite sex, or a state in which the subject feels happier when praised by people. In one aspect of the present invention, the selective DOR agonist is a compound having a morphinan skeleton, and preferably, the selective DOR agonist is a compound further having MOR antagonist action and KOR antagonist action.

[0022]

As a method for measuring anhedonia relating to the present invention, task behavior of Effort-Expenditure for

Rewards Task (EEfRT) (Treadway et al., PLoS One, 2009, 4, e65982009) may be used. In EEfRT, participants perform a task of repeatedly pressing a button within a predetermined time, and receive a reward when the task can be achieved. In addition to EEfRT, a method in which a task of Progressive Ratio Task (PRT) (Wolf et al., Schizophrenia Bulletin, 2014, 40, 1328) is used is also performed. PRT is a task in which a task of selecting the larger of two numbers displayed on a screen is performed a required number of times, and a reward is received when the task can be achieved.

One aspect of the present invention is a pharmaceutical composition for increasing a reward obtained by EEfTR or PRT, including a selective DOR agonist as an active ingredient, and for example, compared with a case where the pharmaceutical composition is not administered or before administration of the pharmaceutical composition, administration of the pharmaceutical composition preferably increases the reward by 1% or more, 3% or more, 5% or more, 10% or more, 20% or more, 30% or more, 40% or more, 50% or more, 70% or more, 100% or more, or 200% or more. In one aspect of the present invention, the selective DOR agonist is a compound having a morphinan skeleton, and preferably, the selective DOR agonist is a compound further having MOR antagonist action and KOR antagonist action.

[0023]

Anhedonia relating to the present invention is a symptom associated with many diseases. Examples of diseases accompanied by anhedonia include diseases caused by dopaminergic system disorders, diseases caused by dysfunction of a reward system, and diseases caused by cognitive dysfunction. Specific examples include depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder (such as PTSD), autism spectrum disorder and Alzheimer-type dementia. One aspect of the present invention is a pharmaceutical composition for treating or preventing anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder (such as PTSD), autism spectrum disorder or Alzheimer-type dementia, including a selective DOR agonist as an active ingredient. In one aspect of the present invention, the selective DOR agonist is a compound having a morphinan skeleton, and preferably, the selective DOR agonist is a compound further having MOR antagonist action and KOR antagonist action.

Another aspect of the present invention is a

pharmaceutical composition for treating or preventing depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder (such as PTSD), autism spectrum disorder or Alzheimer-type dementia, including a selective DOR agonist as an active ingredient, and particularly suppresses anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder (such as PTSD), autism spectrum disorder or Alzheimer-type dementia. Still another aspect of the present invention is a pharmaceutical composition for treating or preventing depression, including a selective DOR agonist as an active ingredient, and particularly suppresses anhedonia associated with depression.

[0024]

Anhedonia relating to the present invention is caused by stress, for example. In the present specification, “stress” (also referred to as “stressor”) means a stimulus from outside the body. Stress includes physical stress (such as high temperature or low temperature, humidity, noise or vibration, violence, or electric shock), chemical stress (such as lack of oxygen,

drug-induced harm, or nutritional deficiency), biological stress (such as diseases caused by pathogens, or sleep deprivation), and psychological stress (such as various types of harassment including bullying, power harassment/moral harassment, bereavement, marriage, divorce, separation, human relationships such as trouble with others, and mental suffering associated with moving, changing jobs, trouble of others, or debt). In the present specification, stress that directly affects the body, such as physical stress, chemical stress, or biological stress, is described as “physical stress”.

One aspect of the present invention is a pharmaceutical composition for treating or preventing anhedonia caused by psychological stress or physical stress, including a selective DOR agonist as an active ingredient. In one aspect of the present invention, the selective DOR agonist is a compound having a morphinan skeleton, and preferably, the selective DOR agonist is a compound further having MOR antagonist action and KOR antagonist action.

[0025]

The pharmaceutical composition for treating or preventing anhedonia according to the present invention can also be evaluated in a model obtained using animals. Examples of the animal model include FUST (Non Patent

Literature 9) and a sucrose preference test (Non Patent Literature 10).

One aspect of the present invention is a pharmaceutical composition for improving reduction in female urine sniffing behavior and/or improving reduction in sucrose preference, including a selective DOR agonist as an active ingredient. One aspect of the present invention is a pharmaceutical composition for improving sucrose preference by 5% or more, 10% or more, 15% or more, 20% or more, 25% or more, 30% or more, or to a normal level not loaded with stress, compared with a control to which the pharmaceutical composition is not administered, including a selective DOR agonist as an active ingredient. One aspect of the present invention is a pharmaceutical composition for improving reduction in female urine sniffing behavior by 5% or more, 10% or more, 15% or more, 20% or more, 25% or more, 30% or more, or to a normal level not loaded with stress, compared with a control to which the pharmaceutical composition is not administered, including a selective DOR agonist as an active ingredient.

[0026]

In the present specification, “suicidal ideation” means thoughts about suicide, special interest in suicide, or thoughts of ending one's life or no longer wishing to live, which are not necessarily accompanied by active

efforts toward suicide. Anhedonia predicts suicidal ideation most strongly among depressive symptoms.

One aspect of the present invention is a pharmaceutical composition for suppressing, improving, alleviating, treating or preventing suicidal ideation, including a selective DOR agonist as an active ingredient. One aspect of the present invention is a pharmaceutical composition for suppressing or preventing suicide, including a selective DOR agonist as an active ingredient.

In one aspect of the present invention, the selective DOR agonist is a compound having a morphinan skeleton, and preferably, the selective DOR agonist is a compound further having MOR antagonist action and KOR antagonist action.

[0027]

In the present specification, “suppression” is a concept including stopping or slowing worsening or progression of a symptom, condition or disease, and an act or means therefor, and also including improving the symptom, condition or disease, or an act or means therefor. The “worsening or progression of a symptom, condition or disease” includes worsening or progression of a “pathological” or “abnormal” symptom, condition or disease, and worsening or progression from a “healthy” or “normal” state to a “pathological” or “abnormal” symptom, condition

or disease. In one embodiment, “suppression” is stopping or slowing worsening or progression of a symptom, condition or disease, or an act or means therefor. In another embodiment, “suppression” is stopping or slowing worsening or progression of a symptom, condition or disease. Here, “improvement” is a concept including bringing a “pathological” or “abnormal” symptom, condition or disease closer to a “healthy” or “normal” state or an act or means therefor, and bringing the “pathological” or “abnormal” symptom, condition or disease into a “healthy” or “normal” state or an act or means therefor. Therefore, in one embodiment, “improvement” includes a numerical value serving as an indicator of a “pathological” or “abnormal” symptom or condition becoming smaller or becoming larger in accordance with the “improvement”, and approaching a normal value or becoming a normal value. In the present specification, “alleviation” may be a concept including the “improvement”.

In the present specification, “treatment” is a concept including eliminating, completely curing, curing or remitting a “pathological” or “abnormal” symptom, condition or disease, and an act or means therefor, including “suppressing” worsening of a “pathological” or “abnormal” symptom, condition or disease, and an act or means therefor, and also including improvement. In one

embodiment, “treatment” is eliminating, completely curing, curing or remitting a “pathological” or “abnormal” symptom, condition or disease, and an act or means therefor. In another embodiment, “treatment” is eliminating, completely curing, curing or remitting a “pathological” or “abnormal” symptom, condition or disease.

In the present specification, “prevention” is a concept including preventing onset of a “pathological” or “abnormal” symptom, condition or disease before occurrence, and an act or means therefor.

[0028]

2. δ Opioid Receptor Agonist (DOR Agonist)

In the present specification,

a “δ opioid receptor agonist” means a substance that, by binding to DOR, causes a biological response reaction that is the same as or similar to a reaction caused by an endogenous ligand.

A “selective DOR agonist” means a substance having DOR agonist action that is relatively strong as compared with μ opioid receptor agonist (MOR agonist) action and κ opioid receptor agonist (KOR agonist) action. Among such substances, a substance having DOR agonist action and having extremely weak MOR agonist action and KOR agonist action, or having none of these actions, is preferred. Furthermore, a substance having DOR agonist action, not

having MOR agonist action and KOR agonist action, and having KOR antagonist action is preferred. Furthermore, a substance having DOR agonist action, not having MOR agonist action and KOR agonist action, and having MOR antagonist action and KOR antagonist action is preferred. Here, a "MOR antagonist" or a "KOR antagonist" means a substance that binds to MOR or KOR but, unlike an endogenous ligand, does not cause a biological response reaction, and, by the binding, inhibits binding between an endogenous ligand that should otherwise bind and the receptor, and does not cause a biological response reaction of the endogenous ligand.

[0029]

By the method described in Patent Literature 7, the "selective DOR agonist" of the present invention has an EC_{50} value of 30 nM or less, 10 nM or less, 3 nM or less, 1 nM or less, 0.3 nM or less or 0.1 nM or less, and has an E_{max} of 50% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more or 99% or more with respect to the DOR agonist activity of SNC80.

[0030]

The "selective DOR agonist" of the present invention preferably further has KOR antagonist action. By the method described in Patent Literature 8, the "selective DOR agonist" of the present invention has an IC_{50} value of 100

nM or less, 30 nM or less, 20 nM or less, 15 nM or less, 10 nM or less or 5 nM or less with respect to 100 nM U-69593.

[0031]

The "selective DOR agonist" of the present invention preferably further has MOR antagonist action. By the method described in Patent Literature 8, the "selective DOR agonist" of the present invention has an IC_{50} value of 100 nM or less, 30 nM or less, 20 nM or less, 15 nM or less, 10 nM or less or 5 nM or less with respect to 30 nM DAMGO.

[0032]

The "selective DOR agonist" of the present invention preferably further has KOR antagonist action and MOR antagonist action. By the method described in Patent Literature 8, the "selective DOR agonist" of the present invention has an IC_{50} value of 100 nM or less, 30 nM or less, 20 nM or less, 15 nM or less, 10 nM or less or 5 nM or less with respect to the action of 100 nM U-69593 on KOR and the action of 30 nM DAMGO on MOR.

[0033]

In the present specification, "morphinan skeleton" means a structure of a fused ring relating to morphinan. The compound relating to the selective DOR agonist having a morphinan skeleton according to the present invention has a morphinan skeleton, may further have an added substituent, and may have another ring fused.

[0034]

One aspect of the pharmaceutical composition of the present invention includes, as an active ingredient, a selective DOR agonist that is a compound represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

[0035]

In the present specification,

examples of C_{1-6} alkyl include methyl, ethyl, propyl, i-propyl, butyl, tert-butyl, pentyl, neopentyl, hexyl and the like.

Examples of C_{1-10} alkyl include, in addition to those exemplified for the above C_{1-6} alkyl, heptyl, octyl and the like.

Examples of C_{1-6} alkyl substituted with one to three halogens include 2-chloroethyl, 2-fluoroethyl, 3-fluoropropyl, 2,2-difluoroethyl, trifluoromethyl, 3,3,3-trifluoropropyl and the like.

Examples of C_{2-6} alkenyl include 2-propenyl, 3-methyl-2-butenyl and the like.

Examples of cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five include methyl, ethyl and the like substituted with C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl

or cyclohexyl.

Examples of aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five include a benzyl group or a phenethyl group.

Examples of C_{3-6} cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

Examples of C_{6-10} aryl include phenyl, naphthyl and the like.

As heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms, five- or six-membered heteroaryl is preferred, and examples include pyridyl, furyl, imidazolyl, pyrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiazolyl and the like.

As heteroarylalkyl in which heteroaryl includes one to four heteroatoms selected from N, O and S as ring-constituting atoms and the number of carbon atoms in the alkylene moiety is one to five, heteroarylalkyl having five- or six-membered heteroaryl is preferred, and examples include (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, (furan-2-yl)methyl, (furan-3-yl)methyl, (imidazol-2-yl)methyl, (imidazol-4-yl)methyl, (imidazol-5-yl)methyl, (thiazol-2-yl)methyl, (thiazol-4-yl)methyl, (thiazol-5-yl)methyl, 2-(pyridin-2-yl)ethyl, 2-(pyridin-3-yl)ethyl, 2-(pyrazol-1-yl)ethyl, 2-(thiophen-2-

yl)ethyl, 2-(thiophen-3-yl)ethyl and the like.

[0036]

Examples of C_{1-6} alkanoyl include acetyl, propionyl and the like.

Examples of C_{1-6} alkoxy include methoxy, ethoxy, propoxy and the like.

Examples of C_{1-6} alkanoyloxy include acetoxy and the like.

Examples of alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six include methoxycarbonyl, ethoxycarbonyl and the like.

Examples of halogen include fluorine, chlorine, bromine, iodine and the like.

Examples of C_{1-6} alkoxy substituted with one to three halogens include fluoromethoxy, trifluoromethoxy and the like.

Examples of C_{1-6} alkoxy substituted with one to six halogens include, in addition to the above C_{1-6} alkoxy substituted with one to three halogens, tetrafluoroethoxy and the like.

Examples of phenylalkyl in which the number of carbon atoms in the alkyl is one to three include benzyl and the like.

Examples of C_{6-10} aryloxy include phenoxy and the like.

Examples of C_{1-8} alkylamino include methylamino, ethylamino and the like.

Examples of acylamino in which the number of carbon atoms in the acyl moiety is two to six include acetylamino and the like.

Examples of C_{6-10} arylamino include phenylamino and the like.

Examples of alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six include ethylcarbamoyl and the like.

Examples of dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six include diethylcarbamoyl and the like.

Examples of alkylsulfonyl in which the number of carbon atoms in the alkyl moiety is one to six include methylsulfonyl and the like.

Examples of alkylsulfinyl in which the number of carbon atoms in the alkyl moiety is one to six include methylsulfinyl and the like.

Examples of alkylthio in which the number of carbon atoms in the alkyl moiety is one to six include methylthio and the like.

Examples of arylcarbonyl in which the number of carbon atoms in the aryl moiety is six to ten include benzoyl and the like.

[0037]

Examples of the five- to seven-membered ring that may be formed by R^{11} and R^{12}, the nitrogen atom to which R^{11} and R^{12} are bonded, and further, optionally, one to two heteroatoms together, in the above general formula (I), include pyrrolidine, piperidine, morpholine and the like.

[0038]

Examples of the heterocycle of R^2 in the above general formula (I), the heterocycle including one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or pyridine 1-oxide, include:

(A) pyridine 1-oxide optionally substituted with one to four substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as pyridine 1-oxide or 2-methylpyridine 1-oxide,

(B) pyridin-2(1H)-one optionally substituted with one to four substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as pyridin-2(1H)-one, 1-methylpyridin-2(1H)-one, 1-ethylpyridin-2(1H)-one, 6-methylpyridin-2(1H)-one, 6-ethylpyridin-2(1H)-one or 6-trifluoromethylpyridin-2(1H)-one,

(C) pyridin-4(1H)-one optionally substituted with one to four substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as pyridin-4(1H)-one, 1-methylpyridin-4(1H)-one, 1-ethylpyridin-4(1H)-one or 1-(fluoroethyl)pyridin-4(1H)-one,

(D) pyridazin-3(2H)-one optionally substituted with one to three substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as pyridazin-3(2H)-one or 2-methylpyridazin-3(2H)-one,

(E) pyrazin-2(1H)-one optionally substituted with one to three substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as pyrazin-2(1H)-one or 1-methylpyrazin-2(1H)-one,

(F) 4H-pyran-4-one or 2H-pyran-2-one optionally substituted with one to three substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as 4H-pyran-4-one, 3-methyl-4H-pyran-4-one, 2H-pyran-2-one or 5-methyl-2H-pyran-2-one,

(G) quinolin-2(1H)-one or quinoline-1-oxide optionally substituted with one to three substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as quinolin-

2(1H)-one, 6-methylquinolin-2(1H)-one, quinoline-1-oxide or 4-methylquinoline-1-oxide, and

(H) pyrimidin-4(3H)-one or pyrimidine-2,4(1H,3H)-dione optionally substituted with one to three substituents selected from C_{1-10} alkyl substituted with one to three fluorines and unsubstituted C_{1-10} alkyl, such as pyrimidin-4(3H)-one or pyrimidine-2,4(1H,3H)-dione.

[0039]

One embodiment of present invention is a pharmaceutical composition for treating or preventing anhedonia, comprising a compound or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the compound is selected from:

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one、

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-6-methylpyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-

10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridazin-3(2H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)quinolin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-2H-pyran-2-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-4H-pyran-4-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-4(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-10-acetoxy-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-

carbonyl)pyridine 1-oxide,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidin-4(3H)-one, and

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one.

[0040]

Examples of tautomers of the compound represented by the general formula (I) include tautomers of the aforementioned heterocyclic ring as R2, containing 1 to 4 heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, containing at least one set of adjacent ring-constituting atoms bound by a double bond, and further substituted with at least one oxo group, and an example is 2-hydroxypyridine (lactim) that corresponds with 2-pyridone (lactam).

Among the compounds represented by the above general formula (I), tautomers and stereoisomers of those compounds, pharmaceutically acceptable salts thereof, or solvates of any of the above, examples of preferred pharmaceutically acceptable salts include acid addition salts, wherein specific examples of those acid addition salts include salts with organic acids or inorganic acids such as hydrochloride, sulfate, fumarate, oxalate, methanesulfonate or camphorsulfonate.

Among the compounds represented by the above general formula (I), tautomers and stereoisomers of those compounds, and pharmaceutically acceptable salts thereof, or solvates of any of the above, examples of the stereoisomers include cis and trans isomers, racemates, and optically active compounds.

Among the compounds represented by the above general

formula (I), tautomers and stereoisomers of those compounds, and pharmaceutically acceptable salts thereof, or solvates of any of the above, examples of the solvates include pharmaceutically acceptable solvates of the compound of the present invention or a salt thereof, and also include hydrates.

Further, the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate thereof may be a prodrug that has been chemically modified so as to change into the pharmacologically active substance in vivo or upon reaching the target site, thereby realizing the pharmacological effect (activation).

Examples of the prodrug, for example in those cases where the group that constitutes the prodrug exists at a hydroxy group, include typical hydroxy group protective groups such as lower acyl groups and lower alkoxycarbonyl groups, in those cases where the group that constitutes the prodrug exists at a nitrogen atom, include typical amino group protective group such as lower acyl groups and lower alkoxycarbonyl groups, or in those cases where the prodrug group is introduced at a carboxylic acid site, include a pivaloyloxymethyl (tBu-C(O)O-CH2-) group, a Medoxomil group, or a Cilexetil group.

Moreover, the compound represented by the above

general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above may be substituted with a stable isotope such as deuterium.

[0041]

The compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above can be produced, for example, in accordance with the method described in WO2018/052114 or conventional methods.

[0042]

The compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above exhibits superior agonist activity and selectivity for the DOR compared with the μ- and κ-opioid receptors.

Accordingly, the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above can be used in a pharmaceutical composition that exhibits a selective DOR agonist action.

Moreover, the compound represented by the above general formula (I), a tautomer or stereoisomer of that

compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above exhibits excellent stability relative to metabolism by human liver microsome.

Accordingly, the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above can be used as an active ingredient in an orally administered pharmaceutical composition.

[0043]

3. Pharmaceutical compositions

The pharmaceutical composition provided by the present invention may be administered either orally or parenterally to humans or other mammals, wherein examples of the parenteral administration include intravenous administration, subcutaneous administration, intramuscular administration, intra-articular administration, transmucosal administration, percutaneous administration, transnasal administration, rectal administration, or intrathecal administration.

The pharmaceutical composition provided by the present invention may be prepared by using the selective DOR agonist described above, or the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt

thereof, or a solvate of any of the above, either as is, or in a mixture with one or more pharmaceutically acceptable carriers, such as excipients (for example, lactose, D-mannitol, crystalline cellulose or glucose), binders (for example, hydroxypropylcellulose (HPC), gelatin, or polyvinylpyrrolidone (PVP)), lubricants (for example, magnesium stearate or talc), disintegrants (for example, starch, or carboxymethylcellulose calcium (CMC-Ca)), diluents (for example, injection water or physiological saline solution), or other additives as necessary (for example, pH modifiers, surfactants, solubilizers, preservatives, emulsifiers, tonicity agents, or stabilizers), and may be prepared in various formulations, including tablets, granules, powders, capsules, suspensions, injections, or suppositories. For example, in order to prepare a tablet, the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above may be mixed and formulated with an excipient (such as lactose, D-mannitol, crystalline cellulose or glucose), a disintegrant (such as starch or carboxymethylcellulose calcium (CMC-Ca)), a binder (such as hydroxypropylcellulose (HPC), gelatin or polyvinylpyrrolidone (PVP)), or a lubricant (such as magnesium stearate or talc) and the like. In order to

prepare an injection, the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above may be mixed and formulated with a dispersant (for example, a surfactant such as Tween 80, a polysaccharide such as carboxymethylcellulose, sodium alginate or hyaluronic acid, or polysorbate), a preservative (such as methylparaben or propylparaben), a tonicity agent (such as sodium chloride, mannitol, sorbitol or glucose), or a pH modifier (such as sodium phosphate or potassium phosphate) and the like.

[0044]

The pharmaceutical composition provided by the present invention may contain the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above in an amount that is effective in the treatment or prevention of anhedonia.

In one embodiment, the pharmaceutical composition provided by the present invention may contain the compound represented by the above general formula (I), a pharmaceutically acceptable solvate (such as a hydrate) of that compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable solvate (such as a hydrate) of that salt, in an amount that is effective in

the treatment or prevention of anhedonia.

In one embodiment, the pharmaceutical composition provided by the present invention may contain the compound represented by the above general formula (I), or a pharmaceutically acceptable salt of the compound, in an amount that is effective in the treatment or prevention of anhedonia.

[0045]

The dosage of the compound represented by the above general formula (I), tautomer or stereoisomer of that compound, pharmaceutically acceptable salt thereof, or solvate of any of the above may be determined appropriately in accordance with factors such as the type of salt, the administration method, and the symptoms and age of the administration subject. For example, in those cases where the compound represented by the above general formula (I), a tautomer or stereoisomer of that compound, a pharmaceutically acceptable salt thereof, or a solvate of any of the above is administered orally to a human, the dosage is typically within a range from 1 μg/day to 10 g/day, preferably from 0.01 to 2,000 mg/day, more preferably from 0.1 to 100 mg/day, whereas in the case of intravenous administration to a human, the dosage is typically within a range from 0.1 μg/day to 1 g/day, and preferably from 0.001 to 200 mg/day. Administration may be split across 1 to 3 doses per day.

[0046]

The present invention also has the following aspects.

<1a> A method for treating or preventing anhedonia, the method including administering to a subject in need thereof (for example, a mammal including a human) a therapeutically effective amount of a selective δ opioid receptor agonist;

<2a> The method according to <1a>, wherein the selective δ opioid receptor agonist further has κ opioid receptor antagonist action;

<3a> The method according to <1a> or <2a>, wherein the selective δ opioid receptor agonist further has μ opioid receptor antagonist action and κ opioid receptor antagonist action;

<4a> The method according to any one of <1a> to <3a>, wherein the anhedonia is anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder, autism spectrum disorder, or Alzheimer-type dementia;

<5a> The method according to any one of <1a> to <4a>, wherein the anhedonia is anhedonia caused by psychological stress or physical stress;

<6a> The method according to any one of <1a> to <5a>, suppressing suicidal ideation;

<7a> The method according to any one of <1a> to <6a>, wherein the anhedonia is reduced responsiveness to pleasant experiences relating to at least one selected from money, food and drink, hobbies, entertainment, travel and recreation, and desire for control, desire for approval, desire for achievement, desire for affiliation and sexual desire;

[0047]

<1b> A selective δ opioid receptor agonist, or a pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use in treating or preventing anhedonia;

<2b> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to <1b>, wherein the selective δ opioid receptor agonist further has κ opioid receptor antagonist action;

<3b> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to <1b> or <2b>, wherein the selective δ opioid receptor agonist further has μ opioid receptor antagonist action and κ opioid receptor antagonist action;

<4b> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to any one of <1b> to <3b>, wherein the anhedonia is anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder, autism spectrum disorder, or Alzheimer-type dementia;

<5b> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to any one of <1b> to <4b>, wherein the anhedonia is anhedonia caused by psychological stress or physical stress;

<6b> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to any one of <1b> to <5b>, suppressing suicidal ideation;

<7b> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to any one of <1b> to <6b>, wherein the anhedonia is reduced responsiveness to pleasant experiences relating to at least one selected from money, food and drink, hobbies,

entertainment, travel and recreation, and desire for control, desire for approval, desire for achievement, desire for affiliation and sexual desire;

[0048]

<1b'> A selective δ opioid receptor agonist, or a pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use in treating or preventing depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder (such as PTSD), autism spectrum disorder or Alzheimer-type dementia, and particularly suppressing anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder (such as PTSD), autism spectrum disorder or Alzheimer-type dementia;

<2b'> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to <1b'>, wherein the selective δ opioid receptor agonist further has κ opioid receptor antagonist action;

<3b'> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ

opioid receptor agonist as an active ingredient, for use according to <1b'> or <2b'>, wherein the selective δ opioid receptor agonist further has μ opioid receptor antagonist action and κ opioid receptor antagonist action;

<4b'> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to any one of <1b'> to <3b'>, wherein the anhedonia is anhedonia caused by psychological stress or physical stress;

<5b'> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to any one of <1b'> to <4b'>, suppressing suicidal ideation;

<6b'> The selective δ opioid receptor agonist, or the pharmaceutical composition including a selective δ opioid receptor agonist as an active ingredient, for use according to any one of <1b'> to <5b'>, wherein the anhedonia is reduced responsiveness to pleasant experiences relating to at least one selected from money, food and drink, hobbies, entertainment, travel and recreation, and desire for control, desire for approval, desire for achievement, desire for affiliation and sexual desire;

[0049]

<1c> Use of a selective δ opioid receptor agonist for manufacturing a pharmaceutical composition for treating or preventing anhedonia;

<2c> The use according to <1c>, wherein the selective δ opioid receptor agonist further has κ opioid receptor antagonist action;

<3c> The use according to <1c> or <2c>, wherein the selective δ opioid receptor agonist further has μ opioid receptor antagonist action and κ opioid receptor antagonist action;

<4c> The use according to any one of <1c> to <3c>, wherein the anhedonia is anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder, autism spectrum disorder, or Alzheimer-type dementia;

<5c> The use according to any one of <1c> to <4c>, wherein the anhedonia is anhedonia caused by psychological stress or physical stress;

<6c> The use according to any one of <1c> to <5c>, wherein the pharmaceutical composition for treating or preventing the anhedonia suppresses suicidal ideation;

<7c> The use according to any one of <1c> to <6c>, wherein the anhedonia is reduced responsiveness to pleasant

experiences relating to at least one selected from money, food and drink, hobbies, entertainment, travel and recreation, and desire for control, desire for approval, desire for achievement, desire for affiliation and sexual desire;

[0050]

<8d> The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the selective δ opioid receptor agonist is a compound represented by the general formula (I) or a pharmaceutically acceptable salt thereof;

<9d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to <8d> is a compound in which, in the compound represented by the general formula (I), R^5, R^{6a}, R^{6b}, R^7, R^8, R^9 and R^{10} are hydrogen,

R^1 is hydrogen; C_{1-6} alkyl; C_{2-6} alkenyl; cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; or aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene

moiety is one to five,

R^2 represents a five- to seven-membered heterocycle including one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or a heterocycle in which a benzene ring is fused to the heterocycle, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is a ring-constituting atom of R^2,

R^3 and R^4 are the same or different, and are hydrogen; hydroxy; halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyloxy; amino; or acylamino in which the number of carbon atoms in the acyl moiety is two to six,

X is CH_2,

and Y is C(=O),

provided that the C_{1-6} alkyl; the alkylene moiety and the cycloalkyl moiety of the cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; or the alkylene moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene

moiety is one to five of R^1 may be substituted with at least one substituent selected from one to six halogens; hydroxy; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyl; C_{1-6} alkanoyloxy; carboxyl; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; alkylsulfonyl in which the number of carbon atoms in the alkyl moiety is one to six; aminosulfonyl; alkylsulfinyl in which the number of carbon atoms in the alkyl moiety is one to six; alkylthio in which the number of carbon atoms in the alkyl moiety is one to six; C_{1-6} alkoxy substituted with one to six halogens; and arylcarbonyl in which the number of carbon atoms in the aryl moiety is six to ten,

and the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1; and the aryl moiety of the C_{6-10} aryloxy of R^3 and R^4

may be substituted with at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl;

alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which the number of carbon atoms in the alkyl is one to three; and methylenedioxy,

the heterocycle of R^2 may have, in addition to the oxo group, a substituent that the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 described above may have, and the pyridine 1-oxide of R^2 may have a substituent that the aryl moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 described above may have,

further, the alkylene moiety of the aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from phenyl or C_{1-6} alkyl substituted with one to three halogens;

<10d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to <8d> or <9d> is a compound in which R^1 is C_{1-6} alkyl; cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five; or aralkyl in which the number of carbon atoms in the aryl moiety is six to ten and the number of carbon atoms in the alkylene moiety is one to five;

<11d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <10d> is a compound in which R^1 is cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five;

<12d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound

represented by the general formula (I) according to <8d> or <9d> is a compound in which R^1 is C_{2-6} alkyl substituted with hydroxy; C_{1-6} alkyl substituted with one to six halogens; or C_{2-6} alkyl substituted with C_{1-6} alkoxy;

<13d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to <8d> or <9d> is a compound in which R^1 is allyl, fluoropropyl, 2-(pyridin-3-yl)ethyl, 2-(methylsulfonyl)ethyl or 2-(aminosulfonyl)ethyl;

[0051]

<14d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <13d> is a compound in which R^2 is a five- to seven-membered heterocycle including one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or a heterocycle in which a

benzene ring is fused to the heterocycle, or pyridine 1-oxide;

<15d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which R^2 is pyridine 1-oxide;

<16d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which the heterocycle of R^2 is pyridin-2(1H)-one;

<17d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which the heterocycle of R^2 is pyridin-4(1H)-one;

<18d>

The method, use or pharmaceutical composition

according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which the heterocycle of R^2 is pyridazin-3(2H)-one;

<19d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which the heterocycle of R^2 is pyrazin-2(1H)-one;

<20d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which the heterocycle of R^2 is 4H-pyran-4-one or 2H-pyran-2-one;

<21d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which the heterocycle of

R^2 is quinolin-2(1H)-one;

<22d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <14d> is a compound in which the heterocycle of R^2 is pyrimidin-4(3H)-one or pyrimidine-2,4(1H,3H)-dione;

[0052]

<23d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> and <10d> to <22d> is a compound in which X is CH_2;

<24d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> to <23d> is a compound in which one of R^3 and R^4 is hydroxy and the other is hydrogen;

<25d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'>

to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> and <10d> to <23d> is a compound in which R^3 is halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; amino; or acylamino in which the number of carbon atoms in the acyl moiety is two to six, R^4 is hydrogen or hydroxy, and R^5 is hydrogen;

<26d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> and <10d> to <23d> is a compound in which R^3 is hydroxy; carbamoyl; or C_{1-6} alkanoyloxy, R^4 is hydrogen, and R^5 is hydrogen;

<27d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> and <10d> to <23d> is a compound in which R^3 is hydroxy, R^4 is hydrogen, and R^5 is hydrogen;

<28d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'>

to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> and <10d> to <23d> is a compound in which R^3, R^4 and R^5 are all hydrogen;

[0053]

<29d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <8d> and <10d> to <28d> is a compound in which R^{6a}, R^{6b}, R^7, R^8, R^9 and R^{10} are all hydrogen;

<30d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <9d> to <23d> is a compound in which R^3 is halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; amino; or acylamino in which the number of carbon atoms in the acyl moiety is two to six, and R^4 is hydrogen or hydroxy;

<31d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound

represented by the general formula (I) according to any one of <9d> to <23d> is a compound in which R^3 is hydroxy; carbamoyl; or C_{1-6} alkanoyloxy, and R^4 is hydrogen;

<32d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <9d> to <23d> is such that R^3 is hydroxy and R^4 is hydrogen;

<33d>

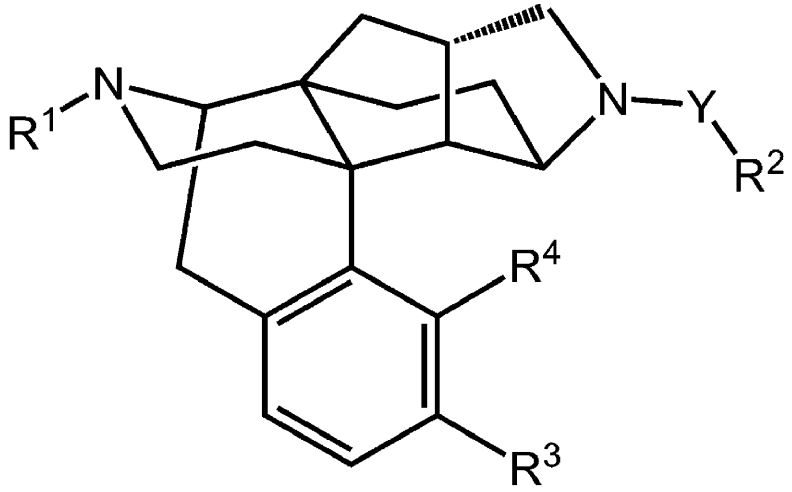
The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to any one of <9d> to <23d> is a compound in which R^3 and R^4 are hydrogen;

<34d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (I) according to <8d> is a compound represented by the following general formula (II):

[0054]

[Chem. 7]



(II)

(wherein R^1 is hydrogen; C_{1-6} alkyl; or cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five,

R^2 represents a five- to seven-membered heterocycle including one or two nitrogen atoms and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is a ring-constituting atom of R^2,

R^3 and R^4 are the same or different, and are hydrogen; hydroxy; or C_{1-6} alkoxy,

Y is C(=O),

provided that the C_{1-6} alkyl; and the alkylene moiety

and the cycloalkyl moiety of the cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from one to six halogens; hydroxy; and C_{1-6} alkoxy,

and the heterocycle of R^2 may have, in addition to the oxo group,

at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which the number of carbon atoms in the alkyl is one to three; and methylenedioxy,

and the pyridine 1-oxide of R^2 may have

at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which the number of carbon atoms in the alkoxy moiety is one to

six; carbamoyl; alkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; dialkylcarbamoyl in which the number of carbon atoms in the alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl including one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which the number of carbon atoms in the alkyl is one to three; and methylenedioxy).

[0055]

<35d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (II) according to <34d> is a compound in which R^1 is cycloalkylalkyl and is cycloalkylalkyl in which the number of carbon atoms in the cycloalkyl moiety is three to six and the number of carbon atoms in the alkylene moiety is one to five;

<36d>

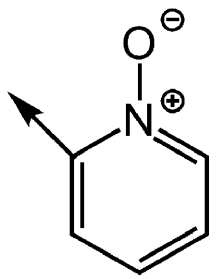
The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (II) according to <34d>

or <35d> is a compound in which R^2 is

formula (III):

[0056]

[Chem. 8]

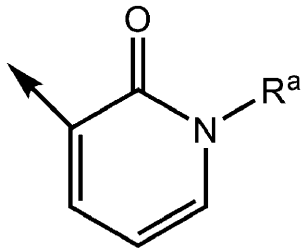


(III)

; formula (IV):

[0057]

[Chem. 9]

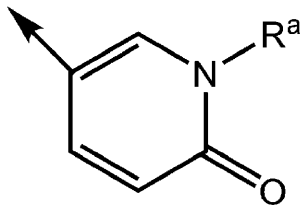


(IV)

; formula (V):

[0058]

[Chem. 10]

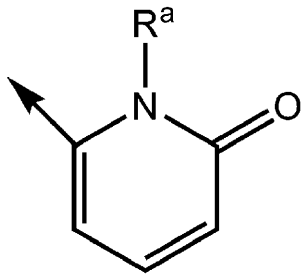


(V)

; or formula (VI):

[0059]

[Chem. 11]



(VI)

(in formulas III to VI, R^a is hydrogen or C_{1-6} alkyl, and is bonded to Y at the position of the arrow);

<37d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (II) according to any one of <34d> to <36d> is a compound in which R^3 is hydroxy;

<38d>

The method, use or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b>, <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by the general formula (II) according to any one of <34d> to <37d> is a compound in which R^4 is hydrogen;

[0060]

<39d>

The method, use, or pharmaceutical composition according to any one of <1a> to <7a>, <1b to 7b>, <1b’> to <6b’> ,and

<1c> to <7c>, wherein the compound represented by general formula (I) disclosed in <8d> is at least one compound selected from:

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-6-methylpyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-

carbonyl)pyrimidine-2,4(1H,3H)-dione,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridazin-3(2H)-one,

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)quinolin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-2H-pyran-2-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-4H-pyran-4-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-4(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one,

2-((1S,3aR,5aS,6R,11bR,11cS)-10-acetoxy-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidin-4(3H)-one, and

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one; or

[0061]

<40d>

The method, use, or pharmaceutical composition according to any one of <1a> to <7a>, <1b> to <7b> and <1b'> to <6b'>, and <1c> to <7c>, wherein the compound represented by general formula (I) disclosed in any one of <8d> and <34d> to <38d> is at least one compound selected from:

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide,

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one,

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one,

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one, and

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one.

[0062]

Next, more detailed description is made of the present invention with reference to examples, but the present invention is not limited thereto.

Names of example compounds were obtained by drawing

structural formulas using ChemDraw ver.14 manufactured by CambridgeSoft, converting the structural formulas into English names by a nomenclature algorithm installed in the software, and then translating the English names into Japanese.

Examples

[0063]

Example 1: Synthesis of compounds

The following compounds of compound numbers 1 to 39 were synthesized according to the method described in Patent Literature 7, and KNT-127 was synthesized according to the method described in Non Patent Literature 4.

[0064]

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridine 1-oxide(Compound No.1, Example 1 of Patent Document 7);

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridine 1-oxide(Compound No.2, Example 2 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-

hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-2(1H)-one(Compound No.3, Example 3 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridine 1-oxide(Compound No.4, Example 4 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-2(1H)-one (Compound No.5, Example 5 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-2(1H)-one (Compound No.6, Example 6 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-2(1H)-oneCompound No.7, Example 7 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-

hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-6-methylpyridin-2(1H)-one (Compound No.8, Example 8 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-2(1H)-one (Compound No.9, Example 9 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-2(1H)-one (Compound No.10, Example 10 of Patent Document 7);

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-2(1H)-one (Compound No.11, Example 11 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione (Compound No.12, Example 12 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-

hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-4(1H)-one (Compound No.13, Example 13 of Patent Document 7);

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-4(1H)-one (Compound No.14, Example 14 of Patent Document 7);

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-2(1H)-one (Compound No.15, Example 15 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridazin-3(2H)-one (Compound No.16, Example 16 of Patent Document 7);

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)quinolin-2(1H)-one (Compound No.17, Example 17 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-

hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-2H-pyran-2-one (Compound No.18, Example 18 of Patent Document 7);

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-4H-pyran-4-one (Compound No.19, Example 19 of Patent Document 7);

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-4(1H)-one (Compound No.20, Example 20 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyrazin-2(1H)-one (Compound No.21, Example 21 of Patent Document 7);

2-((1S,3aR,5aS,6R,11bR,11cS)-10-acetoxy-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridine 1-oxide (Compound No.22, Example 22 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-

2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one (Compound No.23, Example 23 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyrazin-2(1H)-one (Compound No.24, Example 24 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione (Compound No.25, Example 25 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-ethylpyridin-2(1H)-one (Compound No.26, Example 26 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyrimidin-4(3H)-one (Compound No.27, Example 27 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-ethylpyridin-2(1H)-one (Compound No.28, Example 28 of Patent Document 7);

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridine 1-oxide hydrochloride (Compound No.29, Example 29 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-2(1H)-one hydrochloride (Compound No.30, Example 30 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-2(1H)-one hydrochloride (Compound No.31, Example 31 of Patent Document 7);

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-6-methylpyridin-2(1H)-one hydrochloride (Compound No.32, Example 32 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-2(1H)-one hydrochloride (Compound No.33, Example 33 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methylpyridin-2(1H)-one hydrochloride (Compound No.34, Example 34 of Patent Document 7);

6-((1S,3aR,5aS,6R,11bR,11cS)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one (Compound No.35, Example 35 of Patent Document 7);

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)-1-methyl-1,2-dihydro-3H-pyrazol-3-one (Compound No.36, Example 36 of Patent Document 7);

5-chloro-3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one (Compound No.37, Example 37 of Patent Document 7);

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-

carbonyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (Compound No.38, Example 38 of Patent Document 7);
6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-methoxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e] indole-3-carbonyl)pyridin-2(1H)-one (Compound No.39, Example 39 of Patent Document 7)

[0065]

Example 2: Agonist activity of compounds against opioid receptors

The agonist activity of the compounds synthesized in Example 1 against opioid receptors was as shown in Table 1 (Patent Literature 7). KNT-127 also had similar agonist activity against DOR. The compounds shown in Table 1 were confirmed to have potent agonist activity against DOR and to have no agonist activity against μ and κ receptors or to show only very weak agonist activity against μ and κ receptors.

[0066]

[Table 1]

Compound number	δ receptor		μ receptor		κ receptor	
	EC_{50} value (nM)	E_{max} (%)	EC_{50} value (nM)	E_{max} (%)	EC_{50} value (nM)	E_{max} (%)
1	< 3	88	NC	8.3*	> 1	12
3	< 3	98	> 1	20	< 1	15

4	< 3	86	NC	5.5*	> 10	27
5	< 3	81	> 1	9.7	< 1	20
6	< 3	97	> 10	7.7	NC	3.2*
7	< 3	99	> 1	10	NC	-0.9*
8	< 3	70	> 1	8.6	< 1	21
9	< 3	74	< 1	15	< 1	14
10	< 3	74	NC	6.0*	NC	-0.7*
11	< 3	76	> 1	11	NC	-2.5*
14	< 3	95	> 1	8.1	NC	5.7*
16	< 3	92	> 1	19	< 1	29
19	< 3	91	> 1	19	NC	0.6*
28	< 3	92	> 1	16	< 1	13
31	< 3	97	> 10	7.7	NC	3.2*
32	< 3	70	> 1	8.6	< 1	21
KNT-127	< 3	95				

[0067]

N.C.: At the highest concentration (10 μM), the maximum response was not reached, and therefore the ED_{50} value was not calculated.

*: Since the maximum response was not reached at the highest concentration, the response rate at the highest concentration is shown as a reference value.

[0068]

Example 3: Antagonist activity of compounds against opioid receptors

The antagonist activity of the compounds synthesized in Example 1 against opioid receptors was as shown in Table 2 (Patent Literature 8). The compounds shown in Table 2 were confirmed to have potent antagonist activity against opioid μ and κ receptors.

[0069]

[Table 2]

Compound number	μ receptor IC_{50} (nM)	κ receptor IC_{50} (nM)
1	4.1	3.3
3	4.6	11.1
7	1.3	4.6
9	2.4	3.3
10	5.7	3.4
28	2.1	4.0

[0070]

Example 4: Preparation of social defeat stress (SDS) model mice

To examine whether the compounds of the present invention having δ opioid receptor agonist have an anhedonia-improving action in depression, two types of SDS model mice suffering from depression were prepared.

1) Physical stress (PS) mice

SDS model mice loaded with physical stress were

prepared according to the report by Golden et al. (Nat Protoc (2011) 6: 1183). Male C57BL/6J mice (Sankyo Labo Service) were purchased and housed for acclimation for 5 days or more (four to six mice/cage, 12-hour light/dark cycle (light period: 8:00 to 20:00), room temperature: 23 ± 2°C). Highly aggressive male ICR mice (Sankyo Labo Service) used as aggressors were purchased and isolated and housed in individual cages (referred to as "home cages"). Home cages having a size of 225 mm in length × 338 mm in width × 140 mm in height (manufactured by CLEA Japan, Inc.) were used. The C57BL/6J mice were randomly divided into two groups, and in one group, physical stress was loaded on each individual as follows (referred to as "PS mice"), and in another group, physical stress was not loaded (referred to as "naive mice"). One C57BL/6J mouse (6 weeks old) was allowed to be attacked by an ICR mouse (retirement age) serving as an aggressor in a home cage for 10 minutes per day for 10 consecutive days, thereby loading physical stress. The PS mice were isolated and housed for 5 days from the day after the final stress loading and were subjected to an anhedonia test. Attacks by aggressors were performed from 16:00 to 20:00 in order to minimize the influence of diurnal variation in corticosterone in the body.

[0071]

2) Chronic vicarious social defeat stress (cVSDS) mice

cVSDS model mice without physical stress loading were prepared according to the method of Sial et al. (J Neurosci Methods (2016) 258: 94). Male C57BL/6J mice (Sankyo Labo Service) were purchased and housed for acclimation for 5 days or more (four to six mice/cage, 12-hour light/dark cycle (light period: 8:00 to 20:00), room temperature: 23 ± 2°C). Highly aggressive male ICR mice (retirement age) used as aggressors were individually housed in home cages, and then highly aggressive mice were selected by screening for 3 minutes per day for 3 days. In the screening, the number of attacks was measured when male C57BL/6J mice were exposed to the home cages of the ICR mice. The C57BL/6J mice were randomly divided into two groups, and in one group, cVSDS was loaded on each individual as follows (referred to as "cVSDS mice"), and in another group, cVSDS was not loaded (referred to as "naive mice"). One C57BL/6J mouse was transferred to one side of a home cage in a state separated from an ICR mouse by a perforated transparent acrylic plate. Thereafter, another C57BL/6J mouse was transferred to the home cage and was allowed to be attacked by the ICR mouse serving as an aggressor. By carrying out this procedure for 10 minutes per day for 10 consecutive days, cVSDS was loaded on the

C57BL/6J mouse first transferred to the home cage. Different individuals were used every day as the attacking ICR mouse and the attacked C57BL/6J mouse. The cVSDS mice were isolated and housed for 38 days after the first stress loading and were subjected to an anhedonia test. Stress loading on the cVSDS mice was performed from 16:00 to 20:00 in order to minimize the influence of diurnal variation in corticosterone in the body.

[0072]

Example 5: Evaluation of anhedonia: sucrose preference test (SPT)

SPT was performed by preparing normal drinking water and a 1% sucrose solution, allowing free intake, and measuring the proportion of consumption of the sucrose solution. In a depressive state, consumption of a sucrose solution, which is a reward response, is reduced.

1) Effect on PS mice

The compound of the present application of compound number 7 was dissolved in a solvent (1% methylcellulose), and orally administered to the PS mice prepared in Example 4 described above twice daily (from 8:00 to 9:00 and from 19:00 to 20:00 (provided that it was done at 16:00 only on the final day)) for 5 days from the day after final stress loading (5 mg/kg/dose, n = 6). As control groups, only the solvent was similarly administered to PS mice or naive mice

(C57BL/6J mice) not loaded with physical stress (n = 6 each). From day 2 after the start of drug administration, in addition to normal drinking water, a 1% sucrose solution was also freely ingested for acclimation. From day 4 after the start of drug administration (22 hours before SPT), the mice were housed under water deprivation, and on day 5 after the start of drug administration, 2 hours after drug administration, normal drinking water and a 1% sucrose solution were prepared and freely ingested, and then sucrose preference (%) was calculated from the proportion of consumption of the 1% sucrose solution with respect to the total consumption (consumption of the 1% sucrose solution + consumption of drinking water) during the 2-hour test period.

As shown in Fig. 1, compared with naive mice not loaded with physical stress, PS mice were found to have significantly reduced sucrose preference and to develop anhedonia ($p < 0.01$; Bonferroni's test after one-way analysis of variance). On the other hand, administration of the compound of the present application to PS mice significantly improved the reduction in sucrose preference ($p < 0.01$; Bonferroni's test after one-way analysis of variance). In PS mice, sucrose preference had decreased to 40%, and symptoms of anhedonia were severe, but an improving effect against anhedonia was observed by

administration of the compound of the present application for 5 days. Regarding the effect of the compound of the present application on anhedonia, a possibility is considered that, in addition to agonist activity against the δ opioid receptor, antagonist activity against the κ opioid receptor and the μ opioid receptor functions.

[0073]

2) Effect on cVSDS mice (KNT-127)

KNT-127 synthesized in Example 1 was dissolved in physiological saline. Rapamycin (manufactured by LC Laboratories), which is an mTOR inhibitor, was dissolved at 0.04 mM in 5% dimethyl sulfoxide/95% physiological saline. LY294002 (manufactured by FUJIFILM Wako Pure Chemical Corporation), which is a PI3K inhibitor, was dissolved at 4 mM in 10% dimethyl sulfoxide/90% physiological saline. From day 26 after final stress loading, the cVSDS mice prepared in Example 4 described above were allowed to freely ingest, in addition to normal drinking water, a 1% sucrose solution as well for acclimation. From day 28 after final stress loading (22 hours before SPT), the cVSDS mice were housed under water deprivation. On day 29 after final stress loading, rapamycin or LY294002, or the solvent thereof, was intracerebroventricularly administered 60 minutes before the start of the test (5 μL). In addition, KNT-127 (10 mg/kg) or the solvent thereof was

subcutaneously administered 30 minutes before the start of the test. Thereafter, normal drinking water and a 1% sucrose solution were prepared and freely ingested, and then sucrose preference (%) was calculated from the proportion of consumption of the 1% sucrose solution with respect to the total consumption (consumption of the 1% sucrose solution + consumption of drinking water) during the 2-hour test period. Eight mice were used in the naive/drug solvent/inhibitor solvent group, eight mice were used in the cVSDS/drug solvent/inhibitor solvent group, eight mice were used in the cVSDS/KNT-127/inhibitor solvent group, seven mice were used in the cVSDS/KNT-127/rapamycin group, and seven mice were used in the cVSDS/KNT-127/LY294002 group.

As shown in Fig. 2, compared with naive mice not loaded with cVSDS, cVSDS mice were found to have significantly reduced sucrose preference and to develop anhedonia ($p < 0.01$; Bonferroni's test after one-way analysis of variance). On the other hand, administration of KNT-127 to cVSDS mice restored sucrose preference to the sucrose preference of naive mice, and the improving effect of KNT-127 on anhedonia became clear. Since the effect of KNT-127 on anhedonia was inhibited by rapamycin and LY-294002, involvement of mTOR and PI3K in signal transduction was suggested.

[0074]

3) Effect on cVSDS mice (compound of the present application)

The compound of the present application of compound number 7 was dissolved in a solvent (1% methylcellulose), and orally administered to the cVSDS mice prepared in Example 4 described above twice daily (from 8:00 to 9:00 and from 16:00 to 17:00 (provided that it was done at 16:00 only on the final day)) for 5 days from day 28 after final stress loading (5 mg/kg/dose, n = 7). As control groups, only the solvent was similarly administered to cVSDS mice or naive mice (C57BL/6J mice) not loaded with cVSDS (n = 6 each). From day 2 after the start of drug administration, in addition to normal drinking water, a 1% sucrose solution was also freely ingested for acclimation. From day 4 after the start of drug administration (22 hours before SPT), the mice were housed under water deprivation, and on day 5 after the start of drug administration, 2 hours after drug administration, normal drinking water and a 1% sucrose solution were prepared and freely ingested, and then sucrose preference (%) was calculated from the proportion of consumption of the 1% sucrose solution with respect to the total consumption (consumption of the 1% sucrose solution + consumption of drinking water) during the 2-hour test period.

As shown in Fig. 3, compared with naive mice not loaded with cVSDS, cVSDS mice were found to have significantly reduced sucrose preference and to develop anhedonia ($p < 0.05$; Bonferroni's test after one-way analysis of variance). On the other hand, administration of the compound of the present application to cVSDS mice tended to improve the reduction in sucrose preference ($p = 0.075$; Bonferroni's test after one-way analysis of variance), and showed sucrose preference at a level similar to that of naive mice not loaded with stress.

[0075]

Example 6: Evaluation of anhedonia: female urine sniffing test (FUST)

Next, the effect of the compound of the present application on anhedonia relating to sexual desire was examined by FUST. In a depressive state, the duration of olfactory behavior by male mice toward urine of female mice in estrus, which is motivation/reward-seeking behavior based on sexual orientation as an innate desire, is reduced.

1) Effect on PS mice

The compound of the present application of compound number 7 was dissolved in a solvent (1% methylcellulose), and orally administered to the PS mice prepared in Example 4 described above twice daily (from 8:00 to 9:00 and from

16:00 to 17:00 (provided that only the final day involved one administration)) for 5 days from the second day after final stress loading (5 mg/kg/dose, n = 12). As control groups, only the solvent was similarly administered to PS mice or naive mice (C57BL/6J mice) not loaded with physical stress (n = 9 and 10, respectively). The test was performed according to the following procedure from 2 hours after final administration. First, a cotton swab having a tip moistened with water was presented to mice for 3 minutes, and 45 minutes later, a cotton swab having a tip moistened with urine collected from females in estrus was again presented to the mice for 3 minutes, and the respective olfactory behavior times were measured.

As shown in Fig. 4, when a cotton swab moistened with water was presented, the odor sniffing behavior time of all mice was about 2 to 5 seconds, whereas when a cotton swab moistened with female urine was presented, prolongation of the odor sniffing behavior time was observed, but the odor sniffing behavior time of PS mice remained at about 60% prolongation as compared with naive mice not loaded with physical stress, and it was found that motivation/reward-seeking behavior based on sexual orientation was reduced (anhedonia had developed) ($p < 0.05$; Bonferroni's test after one-way analysis of variance). On the other hand, in the group in which the

compound of the present application was administered to PS mice, the odor sniffing behavior time toward female urine had recovered to the same extent as in naive mice (no significant difference from the naive mouse group; $p < 0.05$ versus the solvent-administered cVSDS mouse group; Bonferroni's test after one-way analysis of variance).

[0076]

2) Effect on cVSDS mice

The compound of the present application of compound number 7 was dissolved in a solvent (1% methylcellulose), and orally administered to the cVSDS mice prepared in Example 4 described above twice daily (from 8:00 to 9:00 and from 16:00 to 17:00 (provided that only the final day involved one administration)) for 5 days from day 28 after final stress loading (5 mg/kg/dose, n = 7). As control groups, only the solvent was similarly administered to cVSDS mice or naive mice (C57BL/6J mice) not loaded with cVSDS (n = 6 each). The test was performed according to the following procedure from 2 hours after final administration. First, a cotton swab having a tip moistened with water was presented to mice for 3 minutes, and 45 minutes later, a cotton swab having a tip moistened with urine collected from females in estrus was again presented to the mice for 3 minutes, and the respective olfactory behavior times were measured.

As shown in Fig. 5, when a cotton swab moistened with water was presented, the odor sniffing behavior time of all mice was about 2 to 5 seconds, whereas when a cotton swab moistened with female urine was presented, prolongation of the odor sniffing behavior time was observed, but the odor sniffing behavior time of cVSDS mice remained at about 50% prolongation as compared with naive mice not loaded with stress, and it was found that motivation/reward-seeking behavior based on sexual orientation was reduced (anhedonia had developed) ($p < 0.05$; Bonferroni's test after one-way analysis of variance). On the other hand, in the group in which the compound of the present application was administered to cVSDS mice, the odor sniffing behavior time toward female urine had recovered to the same extent as in naive mice not loaded with stress (no significant difference from the naive mouse group; $p < 0.01$ versus the solvent-administered cVSDS mouse group; Bonferroni's test after one-way analysis of variance).

Industrial Applicability

[0077]

The pharmaceutical composition of the present invention is useful for treating or preventing anhedonia associated with depression.

CLAIMS

[Claim 1]

A pharmaceutical composition for treating or preventing anhedonia, comprising a selective δ opioid receptor agonist as an active ingredient.

[Claim 2]

The pharmaceutical composition for treating or preventing anhedonia according to claim 1, wherein the selective δ opioid receptor agonist further has κ opioid receptor antagonist action.

[Claim 3]

The pharmaceutical composition for treating or preventing anhedonia according to claim 1 or 2, wherein the selective δ opioid receptor agonist further has μ opioid receptor antagonist action and κ opioid receptor antagonist action.

[Claim 4]

The pharmaceutical composition for treating or preventing anhedonia according to claim 1 or 2, wherein the anhedonia is anhedonia associated with depression, Parkinson's disease, obsessive-compulsive disorder, schizophrenia, substance use disorder, alcohol dependence, nicotine dependence, eating disorder, neurotic disorder, autism spectrum disorder, or Alzheimer-type dementia.

[Claim 5]

The pharmaceutical composition for treating or preventing anhedonia according to claim 1 or 2, wherein the anhedonia is anhedonia caused by psychological stress or physical stress.

[Claim 6]

The pharmaceutical composition for treating or preventing anhedonia according to claim 1 or 2, suppressing suicidal ideation.

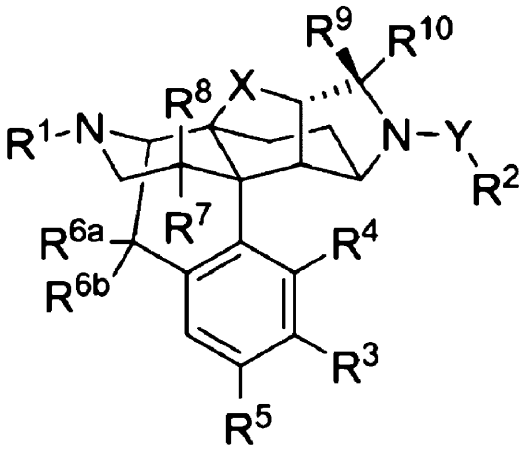
[Claim 7]

The pharmaceutical composition for treating or preventing anhedonia according to claim 1 or 2, wherein the anhedonia is reduced responsiveness to pleasant experiences relating to at least one selected from money, food and drink, hobbies, entertainment, travel and recreation, and desire for control, desire for approval, desire for achievement, desire for affiliation and sexual desire.

[Claim 8]

The pharmaceutical composition for treating or preventing anhedonia according to claim 1, wherein the selective δ opioid receptor agonist is a compound represented by a following general formula (I):

[Chem. 1]



(I)

(wherein R^1 represents hydrogen; C_{1-10} alkyl; C_{6-10} aryl; C_{2-6} alkenyl; cycloalkylalkyl in which a number of carbon atoms in a cycloalkyl moiety is three to six and a number of carbon atoms in an alkylene moiety is one to five; aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five; C_{3-6} cycloalkyl; or heteroarylalkyl in which a heteroaryl moiety comprises one to four heteroatoms selected from N, O and S as ring-constituting atoms and a number of carbon atoms in an alkylene moiety is one to five,

R^2 represents a heterocycle comprising one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is

a ring-constituting atom of R^2,

R^3, R^4 and R^5 are the same or different, and represent hydrogen; hydroxy; halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyloxy; nitro; amino; C_{1-8} alkylamino; C_{6-10} arylamino; or acylamino in which a number of carbon atoms in an acyl moiety is two to six,

R^{6a} and R^{6b} are the same or different, and represent hydrogen; fluorine; or hydroxy, or R^{6a} and R^{6b} together represent =O,

R^7 and R^8 are the same or different, and represent hydrogen; fluorine; or hydroxy,

R^9 and R^{10} are the same or different, and represent hydrogen; C_{1-6} alkyl; C_{6-10} aryl; heteroaryl comprising one to four heteroatoms selected from N, O and S as ring-constituting atoms; aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five; heteroarylalkyl in which a heteroaryl moiety comprises one to four heteroatoms selected from N, O and S as ring-constituting atoms and a number of carbon atoms in an alkylene moiety is one to five; cycloalkylalkyl in which a number of carbon atoms in a cycloalkyl moiety is three to six and a number of carbon atoms in an alkylene moiety is one to five; or C_{2-6} alkenyl,

X represents O or CH_2,

and Y represents C(=O),

provided that the C_{1-10} alkyl; an alkylene moiety and a cycloalkyl moiety of the cycloalkylalkyl in which a number of carbon atoms in the cycloalkyl moiety is three to six and a number of carbon atoms in the alkylene moiety is one to five; an alkylene moiety of the aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in the alkylene moiety is one to five; and an alkylene moiety of the heteroarylalkyl in which a heteroaryl moiety comprises one to four heteroatoms selected from N, O and S as ring-constituting atoms and a number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from one to six halogens; hydroxy; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyl; C_{1-6} alkanoyloxy; carboxyl; alkoxycarbonyl in which a number of carbon atoms in an alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; dialkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; alkylsulfonyl in which a number of carbon atoms in an alkyl moiety is one to six; aminosulfonyl; alkylsulfinyl in which a number of carbon atoms in an alkyl moiety is one to six; alkylthio in which a number of carbon atoms in an alkyl moiety is one to six; C_{1-6} alkoxy substituted with one to six halogens; and

arylcarbonyl in which a number of carbon atoms in an aryl moiety is six to ten,

and the C_{6-10} aryl; an aryl moiety of the aralkyl in which a number of carbon atoms in the aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five of R^1; an aryl moiety of the C_{6-10} aryloxy, and an aryl moiety of the C_{6-10} arylamino of R^3, R^4 and R^5; and the C_{6-10} aryl; the heteroaryl comprising one to four heteroatoms selected from N, O and S as ring-constituting atoms; an aryl moiety of the aralkyl in which a number of carbon atoms in the aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five; and a heteroaryl moiety of the heteroarylalkyl in which the heteroaryl moiety comprises one to four heteroatoms selected from N, O and S as ring-constituting atoms and a number of carbon atoms in an alkylene moiety is one to five of R^9 and R^{10}

may be substituted with at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which a number of carbon atoms in an alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; dialkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to

three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl comprising one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which a number of carbon atoms in an alkyl is one to three; and methylenedioxy,

the heterocycle of R^2 may have, in addition to the oxo group, a substituent that the C_{6-10} aryl of R^1 may have, and the pyridine 1-oxide of R^2 may have a substituent that the C_{6-10} aryl of R^1 may have,

further, when R^1 is C_{1-10} alkyl, R^1 may be substituted with $NR^{11}R^{12}$, wherein R^{11} and R^{12} are the same or different, and are hydrogen; C_{1-10} alkyl; or aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five, or R^{11} and R^{12}, a nitrogen atom to which R^{11} and R^{12} are bonded, and further, optionally, one to two heteroatoms may together form a five- to seven-membered ring, and also an alkylene moiety of the aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from phenyl or C_{1-6} alkyl substituted with one to three halogens)

or a pharmaceutically acceptable salt thereof.

[Claim 9]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound in which R^5, R^{6a}, R^{6b}, R^7, R^8, R^9 and R^{10} are hydrogen,

R^1 is hydrogen; C_{1-6} alkyl; C_{2-6} alkenyl; cycloalkylalkyl in which a number of carbon atoms in a cycloalkyl moiety is three to six and a number of carbon atoms in an alkylene moiety is one to five; or aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five,

R^2 represents a five- to seven-membered heterocycle comprising one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or a heterocycle in which a benzene ring is fused to the heterocycle, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is a ring-constituting atom of R^2,

R^3 and R^4 are the same or different, and are hydrogen; hydroxy; halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyloxy; amino; or acylamino in which

a number of carbon atoms in an acyl moiety is two to six,

X is CH_2,

and Y is C(=O),

provided that the C_{1-6} alkyl; an alkylene moiety and the cycloalkyl moiety of the cycloalkylalkyl in which a number of carbon atoms in the cycloalkyl moiety is three to six and a number of carbon atoms in the alkylene moiety is one to five; or an alkylene moiety of the aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from one to six halogens; hydroxy; C_{1-6} alkoxy; C_{6-10} aryloxy; C_{1-6} alkanoyl; C_{1-6} alkanoyloxy; carboxyl; alkoxycarbonyl in which a number of carbon atoms in an alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; dialkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; alkylsulfonyl in which a number of carbon atoms in an alkyl moiety is one to six; aminosulfonyl; alkylsulfinyl in which a number of carbon atoms in an alkyl moiety is one to six; alkylthio in which a number of carbon atoms in an alkyl moiety is one to six; C_{1-6} alkoxy substituted with one to six halogens; and arylcarbonyl in which a number of carbon atoms in an aryl moiety is six to ten,

and an aryl moiety of the aralkyl in which a number of carbon atoms in the aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five of R^1; and an aryl moiety of the C_{6-10} aryloxy of R^3 and R^4

may be substituted with at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which a number of carbon atoms in an alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; dialkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl comprising one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which a number of carbon atoms in an alkyl is one to three; and methylenedioxy,

the heterocycle of R^2 may have, in addition to the oxo group, a substituent that the aryl moiety of the aralkyl in which a number of carbon atoms in the aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five of R^1 may have, and the pyridine 1-oxide of R^2 may have a substituent that the aryl moiety of the aralkyl in which a number of carbon atoms in the aryl moiety is six to ten and a number of carbon atoms

in an alkylene moiety is one to five of R^1 may have,

further, an alkylene moiety of the aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from phenyl or C_{1-6} alkyl substituted with one to three halogens.

[Claim 10]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which R^1 is C_{1-6} alkyl; cycloalkylalkyl in which a number of carbon atoms in a cycloalkyl moiety is three to six and a number of carbon atoms in an alkylene moiety is one to five; or aralkyl in which a number of carbon atoms in an aryl moiety is six to ten and a number of carbon atoms in an alkylene moiety is one to five.

[Claim 11]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which R^1 is cycloalkylalkyl in which a number of carbon atoms in a cycloalkyl moiety is three to six and a number of carbon atoms in an alkylene moiety is one to five.

[Claim 12]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which R^1 is C_{2-6} alkyl substituted with hydroxy; C_{1-6} alkyl substituted with one to six halogens; or C_{2-6} alkyl substituted with C_{1-6} alkoxy.

[Claim 13]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which R^1 is allyl, fluoropropyl, 2-(pyridin-3-yl)ethyl, 2-(methylsulfonyl)ethyl or 2-(aminosulfonyl)ethyl.

[Claim 14]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which R^2 is a five- to seven-membered heterocycle including one to four heteroatoms selected from N, O and S and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or a heterocycle in which a benzene ring is fused to

the heterocycle, or pyridine 1-oxide.

[Claim 15]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which R^2 is pyridine 1-oxide.

[Claim 16]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyridin-2(1H)-one.

[Claim 17]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyridin-4(1H)-one.

[Claim 18]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyridazin-3(2H)-one.

[Claim 19]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyrazin-2(1H)-one.

[Claim 20]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is 4H-pyran-4-one or 2H-pyran-2-one.

[Claim 21]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is quinolin-2(1H)-one.

[Claim 22]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which the heterocycle of R^2 is pyrimidin-4(3H)-one or pyrimidine-2,4(1H,3H)-dione.

[Claim 23]

The pharmaceutical composition for treating or

preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound in which X is CH_2.

[Claim 24]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8 or 9, wherein the compound represented by the general formula (I) is a compound in which one of R^3 and R^4 is hydroxy and another is hydrogen.

[Claim 25]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound in which R^3 is halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; amino; or acylamino in which a number of carbon atoms in an acyl moiety is two to six, R^4 is hydrogen or hydroxy, and R^5 is hydrogen.

[Claim 26]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound in which R^3 is hydroxy; carbamoyl; or C_{1-6} alkanoyloxy, R^4 is hydrogen, and R^5 is hydrogen.

[Claim 27]

The pharmaceutical composition for treating or

preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound in which R^3 is hydroxy, R^4 is hydrogen, and R^5 is hydrogen.

[Claim 28]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound in which R^3, R^4 and R^5 are all hydrogen.

[Claim 29]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound in which R^{6a}, R^{6b}, R^7, R^8, R^9 and R^{10} are all hydrogen.

[Claim 30]

The pharmaceutical composition for treating or preventing anhedonia according to claim 9, wherein the compound represented by the general formula (I) is a compound in which R^3 is halogen; cyano; carbamoyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; amino; or acylamino in which a number of carbon atoms in an acyl moiety is two to six, and R^4 is hydrogen or hydroxy.

[Claim 31]

The pharmaceutical composition for treating or

preventing anhedonia according to claim 9, wherein the compound represented by the general formula (I) is a compound in which R^3 is hydroxy; carbamoyl; or C_{1-6} alkanoyloxy, and R^4 is hydrogen.

[Claim 32]

The pharmaceutical composition for treating or preventing anhedonia according to claim 9, wherein the compound represented by the general formula (I) is such that R^3 is hydroxy and R^4 is hydrogen.

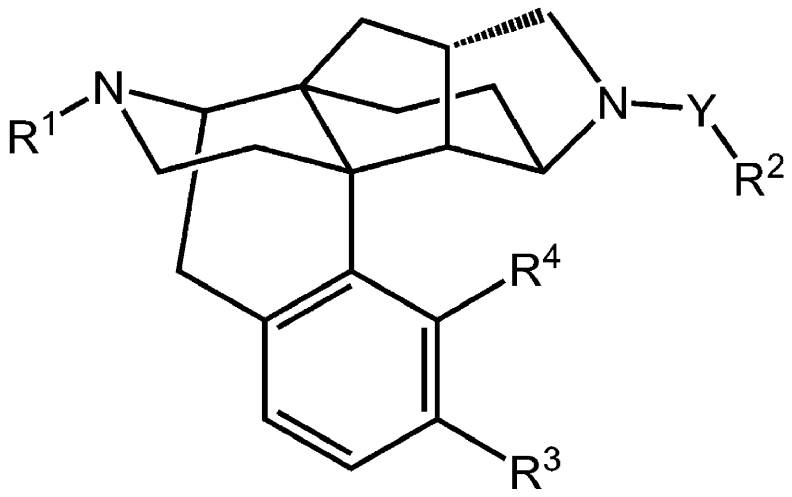
[Claim 33]

The pharmaceutical composition for treating or preventing anhedonia according to claim 9, wherein the compound represented by the general formula (I) is a compound in which R^3 and R^4 are hydrogen.

[Claim 34]

The pharmaceutical composition for treating or preventing anhedonia according to claim 8, wherein the compound represented by the general formula (I) is a compound represented by a following general formula (II):

[Chem. 2]



(II)

(wherein R^1 is hydrogen; C_{1-6} alkyl; or cycloalkylalkyl in which a number of carbon atoms in a cycloalkyl moiety is three to six and a number of carbon atoms in an alkylene moiety is one to five,

R^2 represents a five- to seven-membered heterocycle comprising one or two nitrogen atoms and at least one carbon atom as ring-constituting atoms, wherein at least one pair of the adjacent ring-constituting atoms has a double bond, and the heterocycle is further substituted with at least one oxo group, or pyridine 1-oxide,

wherein R^2 is bonded to Y via a carbon atom that is a ring-constituting atom of R^2,

R^3 and R^4 are the same or different, and are hydrogen; hydroxy; or C_{1-6} alkoxy,

Y is C(=O),

provided that the C_{1-6} alkyl; and an alkylene moiety and a cycloalkyl moiety of the cycloalkylalkyl in which a

number of carbon atoms in the cycloalkyl moiety is three to six and a number of carbon atoms in the alkylene moiety is one to five of R^1 may be substituted with at least one substituent selected from one to six halogens; hydroxy; and C_{1-6} alkoxy,

and the heterocycle of R^2 may have, in addition to the oxo group,

at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which a number of carbon atoms in an alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; dialkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl comprising one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which a number of carbon atoms in an alkyl is one to three; and methylenedioxy,

and the pyridine 1-oxide of R^2 may have

at least one substituent selected from C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyloxy; hydroxy; alkoxycarbonyl in which a number of carbon atoms in an alkoxy moiety is one to six; carbamoyl; alkylcarbamoyl in which a number of carbon atoms in an alkyl moiety is one to six; dialkylcarbamoyl in which

a number of carbon atoms in an alkyl moiety is one to six; halogen; nitro; cyano; C_{1-6} alkyl substituted with one to three halogens; C_{1-6} alkoxy substituted with one to three halogens; phenyl; heteroaryl comprising one to four heteroatoms selected from N, O and S as ring-constituting atoms; phenoxy; phenylalkyl in which a number of carbon atoms in an alkyl is one to three; and methylenedioxy).

[Claim 35]

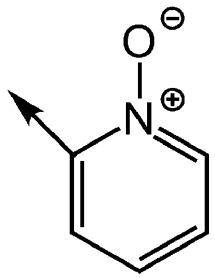
The pharmaceutical composition for treating or preventing anhedonia according to claim 34, wherein the compound represented by the general formula (II) is a compound in which R^1 is cycloalkylalkyl and is cycloalkylalkyl in which a number of carbon atoms in a cycloalkyl moiety is three to six and a number of carbon atoms in an alkylene moiety is one to five.

[Claim 36]

The pharmaceutical composition for treating or preventing anhedonia according to claim 34 or 35, wherein the compound represented by the general formula (II) is a compound in which R^2 is

formula (III):

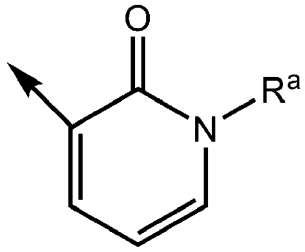
[Chem. 3]



(III)

; formula (IV):

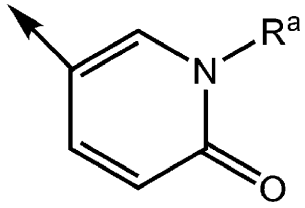
[Chem. 4]



(IV)

; formula (V):

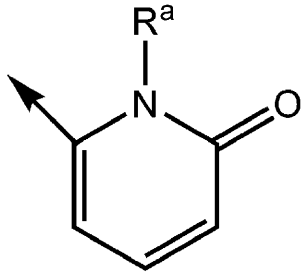
[Chem. 5]



(V)

; or formula (VI):

[Chem. 6]



(VI)

(in formulas III to VI, R^a is hydrogen or C_{1-6} alkyl,

and is bonded to Y at a position of an arrow).

[Claim 37]

The pharmaceutical composition for treating or preventing anhedonia according to claim 34 or 35, wherein the compound represented by the general formula (II) is a compound in which R^3 is hydroxy.

[Claim 38]

The pharmaceutical composition for treating or preventing anhedonia according to claim 34 or 35, wherein the compound represented by the general formula (II) is a compound in which R^4 is hydrogen.

[Claim 39]

The pharmaceutical composition for treatment or prevention according to Claim 8, wherein the compound represented by the general formula (I) is at least one compound selected from:

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide;

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide;

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-

10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one;

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide;

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one;

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one;

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-6-methylpyridin-2(1H)-one;

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one;

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one;

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione;

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one;

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-4(1H)-one;

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-

carbonyl)-1-methylpyridin-2(1H)-one;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridazin-3(2H)-one;

4-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)quinolin-2(1H)-one;

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-2H-pyran-2-one;

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-4H-pyran-4-one;

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-4(1H)-one;

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one;

2-((1S,3aR,5aS,6R,11bR,11cS)-10-acetoxy-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one;

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrazin-2(1H)-one;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidine-2,4(1H,3H)-dione;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyrimidin-4(3H)-one; and

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one.

[Claim 40]

The pharmaceutical composition for treatment or prevention according to any one of Claims 8, 34 and 35, wherein the compound represented by the general formula (I) is at least one compound selected from:

2-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridine 1-oxide;

3-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)pyridin-2(1H)-one;

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one;

6-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-

(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-methylpyridin-2(1H)-one; and

5-((1S,3aR,5aS,6R,11bR,11cS)-14-(cyclopropylmethyl)-10-hydroxy-2,3,3a,4,5,6,7,11c-octahydro-1H-6,11b-(epiminoethano)-1,5a-methanonaphtho[1,2-e]indole-3-carbonyl)-1-ethylpyridin-2(1H)-one.