

DESCRIPTION

Title of the Invention: HETEROCYCLIC COMPOUND

Technical Field

5 [0001]

The present invention relates to a heterocyclic compound having a monoacylglycerol lipase (sometimes to be abbreviated as "MAGL" in the present specification) inhibitory action, a pharmaceutical composition containing same and the like.

10 [0002]

(Background of the Invention)

Arachidonic acid (sometimes to be abbreviated as "AA" in the present specification), and eicosanoid, which is a product in vivo, have been reported to cause inflammation in the
15 central nervous system and peripheral [non-patent document 1: Science, vol. 294, pages 1871-1875, 2001]. An inhibitor that suppresses arachidonic acid production pathway, and eicosanoid production pathway is promising as a therapeutic drug for inflammatory diseases, and non-steroidal anti-inflammatory
20 drugs such as cyclooxygenase inhibitor and the like have been used as therapeutic drugs for inflammatory pain. However, when a cyclooxygenase inhibitor is used for a long time, digestive tract disorders are sometimes developed as side effects, thus posing a problem. In addition, circulatory side effects such
25 as myocardial infarction, cerebral infarction and the like also pose problems in recent years.

[0003]

Neuroinflammation accompanied by activation of glial cells has been suggested to be a pathological change
30 characteristic of neurodegenerative diseases (e.g., Alzheimer's disease etc.) [non-patent document 2: Molecular Neurobiology (Mol. Neurobiol), vol. 41, pages 115-128, 2010]. It has been reported that anti-inflammatory drugs suppress activation of glial cells and suppress neurodegenerative progression in an
35 animal model of tau overexpression (human variant tau

transgenic mouse etc.) which is a pathological characteristic of Alzheimer's disease [non-patent document 3: Neuron, vol. 53, pages 337-351, 2007]. In addition, the effectiveness of suppression of neuroinflammation for the treatment of neurodegenerative diseases such as Alzheimer's disease and the like has been suggested [non-patent document 4: Nature Reviews Neurology (Nat. Rev. Neurol.), vol. 6, pages 193-201, 2010], and a therapeutic drug that suppresses neuroinflammation is promising as a therapeutic or prophylactic drug for neurodegenerative diseases.

[0004]

Monoacylglycerol lipase (MAGL) is an enzyme that hydrolyzes monoacylglycerol into fatty acid and glycerol. In the central nervous system, the substrate of MAGL is 2-arachidonoylglycerol (also referred to as 2-AG in the present specification) which is decomposed into arachidonic acid and glycerol [non-patent document 5: Chemistry and Physics of Lipids (Chem phys Lipids) vol. 121, pages 149-158, 2002]. In recent years, suppression of production of arachidonic acid and eicosanoids, suppression of activation of glial cell, suppression of production of inflammatory cytokine, and a decreasing action on the accumulation of A β plaque which is a pathologic finding of Alzheimer's disease have been reported in a crossbred animal of MAGL deficient mouse and amyloid β (to be also referred to as A β in the present specification) overexpressing animal model (APP/PS1 double transgenic mouse etc.) [non-patent document 6: Cell Report (Cell Rep.), vol. 1, pages 617-623, 2012], and an inhibitor etc. that suppress the action of MAGL are promising as a therapeutic or prophylactic drug for Alzheimer's disease.

[0005]

In addition, as receptors of 2-AG, which is a substrate of MAGL, cannabinoid receptor 1 (to be referred to as CB1 in the present specification), and cannabinoid receptor 2 (to be referred to as CB2 in the present specification) have been

identified [non-patent document 7: Biochemical Pharmacology (Biochem. Pharmacol.) vol. 50, 83-90, 1995]. CB1 is mainly expressed in the brain region [non-patent document 8: Molecular Pharmacology (Mol. Pharmacol.), vol. 34, pages 605-613, 1988],
5 and CB2 is expressed in immunocyte, and microglial cell in the brain region [non-patent document 9: Neuroscience Letters (Neurosci. Lett.), vol. 396, pages 113-116, 2006]. In recent years, it has been reported that CB1 receptor agonist improves cognition function [non-patent document 10: Journal of
10 Alzheimer's Disease (J. Alzheimers. Dis.), vol. 30, pages 439-459, 2012], and 2-AG, which is the substrate of MAGL, shows a protective action against nerve cell death due to A β [non-patent document 11: Neuroscience, vol. 178, pages 159-168, 2011]. Therefore, MAGL inhibitor that suppresses decomposition
15 of 2-AG is promising as a therapeutic or prophylactic drug that suppresses neuroinflammation, nerve cell death, A β accumulation and the like observed in Alzheimer's disease and having not only a symptomatic relief action but also a disease-modifying action.

20 [0006]

Parkinson's disease, which is one of the neurodegenerative diseases, is a disease associated with movement disorders caused by the degeneration of midbrain substantia nigra dopamine nerve cells, for which activation of
25 glial cell has been reported [non-patent document 12: Annals of Neurology (Ann. Neurol.) vol. 57, pages 168-175, 2005]. While 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is known to induce midbrain substantia nigra dopamine nerve cell death, it has been
30 reported to show a protective action against nerve cell death in MAGL deficient mouse [non-patent document 13: Science, vol. 334, pages 809-813, 2011]. Therefore, an inhibitor etc. that suppress the action of MAGL are promising as new therapeutic drugs for Parkinson's disease.

35 [0007]

Amyotrophic lateral sclerosis (to be referred to as ALS in the present specification) is a disease associated with degeneration of motor neuron, and an effective treatment method does not exist at present. Activation of glial cell in ALS has
5 been reported [non-patent document 14: Neurobiology of Disease (Neurobiol. Dis.) vol. 15, pages 601-609, 2004]. It has also been reported that activation of CB2 suppresses progression of the disease in mutant superoxide dismutase overexpression mouse, which is an animal model of ALS [non-patent document 15:
10 European Journal of Pharmacology (Eur. J. Pharmacol.), vol. 542, pages 100-105, 2006]. In addition, it has been reported that neuroinflammation in MAGL deficient mouse is suppressed by decreasing arachidonic acid, which is a product of MAGL in the living body [non-patent document 13: Science, vol. 334, pages
15 809-813, 2011]. Therefore, an MAGL inhibitor is promising as a new therapeutic drug for ALS.

[0008]

Huntington's disease which is one of the neurodegenerative diseases is a disease wherein a neurological
20 function is lost by nerve cell death and neuroinflammation due to polyglutamine aggregation. It has been reported that activation of CB2 suppresses neuroinflammation and shows a neuroprotective action in R6/2 mouse which is an animal model of Huntington's disease [non-patent document 16: Brain, vol.
25 132, pages 3152-3164, 2009]. In addition, it has been reported that neuroinflammation is suppressed by decreasing arachidonic acid, which is a resultant product of MAGL, in MAGL deficient mouse [non-patent document 13: Science, vol. 334, pages 809-813, 2011]. Therefore, an MAGL inhibitor is promising as a new
30 therapeutic drug for Huntington's disease.

[0009]

2-AG, which is a substrate of MAGL, has been reported to suppress progression of the disease state in an autoimmune encephalomyelitis model, i.e., an animal model of multiple
35 sclerosis which is one of the central demyelination diseases

[non-patent document 17: Brain Research (Brain Res.), vol. 1390, pages 126-141, 2011]. In addition, it has been reported that neuroinflammation is suppressed in MAGL deficient mouse by decreasing arachidonic acid, which is a resultant product of
5 MAGL [non-patent document 13: Science, vol. 334, pages 809-813, 2011]. Therefore, an MAGL inhibitor is promising as a new therapeutic drug for multiple sclerosis.

[0010]

Traumatic brain injury (TBI) is a condition exerting an
10 extremely harmful influence on the health of individuals, and an effective treatment method does not exist at present. 2-AG, which is a substrate of MAGL, has been reported to have a protective action against nerve cell death in a closed head injury animal model [non-patent document 18: Nature, vol. 413,
15 pages 527-531, 2001]. Therefore, an MAGL inhibitor is promising as a new therapeutic or prophylactic drug for traumatic brain injury.

[0011]

Glaucoma most often causes loss of eyesight, and is
20 considered a serious social problem. 2-AG, which is a substrate of MAGL, has been reported to activate aqueous outflow in an intraocular perfusion model [non-patent document 19: Experimental Eye Research (Exp. Eye Res.), vol. 87, pages 106-114, 2008]. Therefore, an MAGL inhibitor is promising as a
25 new therapeutic or prophylactic drug for glaucoma.

[0012]

Anxiety disorder is a mental disease that occurs highly frequently, and greatly influences the quality of life. 2-AG, which is a substrate of MAGL, has been reported to show an
30 anti-anxiety action in an elevated plus maze test, which is an effective test system of anxiety disorder [non-patent document 20: Behavioural Brain Research (Behav. Brain Res.), vol. 252, pages 10-17, 2013]. Therefore, an MAGL inhibitor is promising as a new therapeutic drug for anxiety disorders.

35 [0013]

2-AG, which is a substrate of MAGL, has been reported to show an antinociceptive effect in a formalin test [non-patent document 21: British Journal of Pharmacology, vol. 150, pages 693-701, 2007]. In addition, 2-AG has been reported to show
5 effect in a mechanical hyperalgesia test which is a carcinomatous pain model [non-patent document 22: Pharmacological Research (Pharmacol. Res.), vol. 64, pages 60-67, 2011]. Therefore, an MAGL inhibitor is promising as a new therapeutic drug for inflammatory pain and nervous pain.

10 [0014]

Epilepsy greatly influences daily life. It is known that neuroinflammation has been induced in the hippocampus of temporal lobe epilepsy patients, and neuroinflammation accompanied by activation of glial cells is involved in
15 convulsive attack [non-patent document 23: Nature Medicine (Nature Med.), vol. 16, pages 413-419, 2010]. 2-AG, which is a substrate of MAGL, has a suppressive action on pentylenetetrazole-induced convulsive attack, which is an acute convulsion model [non-patent document 24: Neurochemical
20 Research (Neurochem. Res.), vol. 36, pages 1520-1525, 2011]. Therefore, an MAGL inhibitor is promising as a new therapeutic drug for epilepsy.

[0015]

Depression is a disease that occurs highly frequently in
25 the modern society, and greatly influences the quality of life. 2-AG, which is a substrate of MAGL, has been reported to show an anti-depression action on chronical stress model which is an effective test system of depression [non-patent document 25: Neuropsychopharmacology, vol. 39, pages 1763-1776, 2014].
30 Therefore, an MAGL inhibitor is promising as a new therapeutic drug for depression.

[0016]

Migraine is a disease that occurs highly frequently in the modern society, and greatly influences the quality of life.
35 One of the factors that develop migraine is neuroinflammation.

Activation of CB2 has been reported to have an analgesic action in nitroglycerin-administered rat, which is an effective test system of migraine [non-patent document 26: Journal of Headache and Pain, vol. 15, No. 14, 2014]. Therefore, an MAGL inhibitor
5 is promising as a new therapeutic drug for migraine.

[0017]

Cerebral edema is a disease developed in association with various encephalopathies. One of the causes of cerebral edema is collapse of blood-brain barrier. Arachidonic acid and
10 eicosanoids are known to collapse blood-brain barrier [non-patent document 27: Brain Research, vol. 1298, pages 13-23, 2009]. An inhibitor that suppresses the action of MAGL decreases production of arachidonic acid by MAGL. Therefore, an MAGL inhibitor is promising as a new therapeutic drug for
15 cerebral edema.

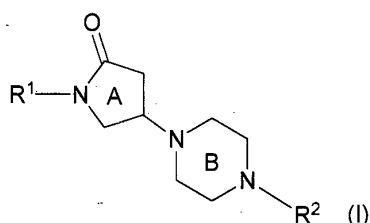
[0018]

Cerebral ischemia is one factor causing the onset of cerebral infarction. 2-AG, which is a substrate of MAGL, has been reported to have a brain protective action in a test
20 system effective for cerebral ischemia [non-patent document 28: Brain Research, vol. 1474, pages 91-99, 2012]. Therefore, an MAGL inhibitor is promising as a new therapeutic drug for cerebral ischemia.

[0019]

25 As the heterocyclic compound, the following compounds are known. Patent Document 1 describes that a compound represented by the following formula (I):

[0020]



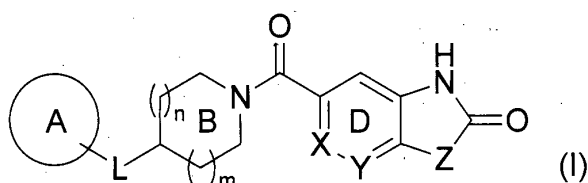
30 [0021]

wherein each symbol is as defined in patent document 1, is an

MAGL inhibitor and useful for the treatment, improvement or prophylaxis of neurodegenerative disease, anxiety disorder, pain or epilepsy.

Patent Document 2 describes that a compound represented
5 by the following formula (I):

[0022]

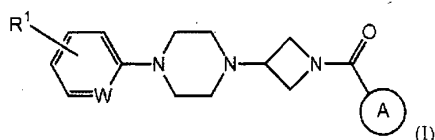


[0023]

wherein each symbol is as defined in patent document 2, is an
10 MAGL inhibitor and useful for the prophylaxis or treatment of
neurodegenerative diseases (e.g., Alzheimer's disease,
Parkinson's disease, Huntington's disease, amyotrophic lateral
sclerosis, traumatic brain injury, glaucoma, multiple sclerosis
etc.), anxiety disorder, pains (e.g., inflammatory pain,
15 cancerous pain, neurogenic pain etc.), epilepsy, depression and
the like.

Patent Document 3 describes that a compound represented
by the following formula (I):

[0024]



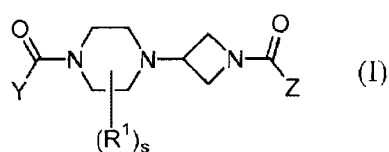
20

[0025]

wherein each symbol is as defined in patent document 3, is an
MAGL inhibitor and useful for the treatment of pain and the
like.

25 Patent Document 4 describes that a compound represented
by the following formula (I):

[0026]

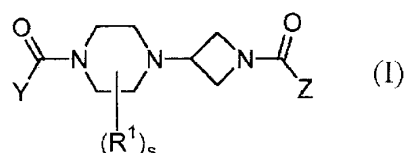


[0027]

wherein each symbol is as defined in patent document 4, is an
 MAGL inhibitor and useful for the treatment of pain and the
 5 like.

Patent Document 5 describes that a compound represented
 by the following formula (I):

[0028]

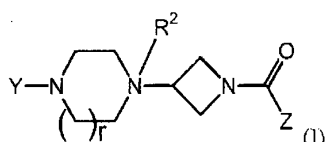


10 [0029]

wherein each symbol is as defined in patent document 5, is an
 MAGL inhibitor and useful for the treatment of pain and the
 like.

Patent Document 6 describes that a compound represented
 15 by the following formula (I):

[0030]

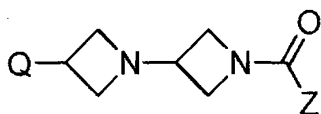


[0031]

wherein each symbol is as defined in patent document 6, is an
 20 MAGL inhibitor and useful for the treatment of pain and the
 like.

Patent Document 7 describes that a compound represented
 by the following formula:

[0032]

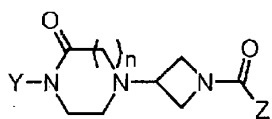


[0033]

wherein each symbol is as defined in patent document 7, is useful as an MAGL inhibitor.

5 Patent Document 8 describes that a compound represented by the following formula:

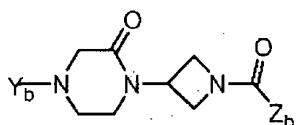
[0034]



[0035]

10 wherein each symbol is as defined in patent document 8, and the following formula:

[0036]

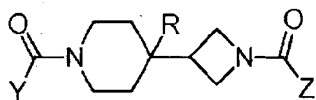


[0037]

15 wherein each symbol is as defined in patent document 8, are useful as an MAGL inhibitor.

Patent Document 9 describes that a compound represented by the following formula:

[0038]



20

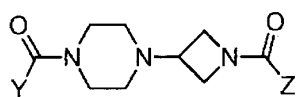
[0039]

wherein each symbol is as defined in patent document 9, is useful as an MAGL inhibitor.

Patent Document 10 describes that a compound represented

by the following formula (I):

[0040]



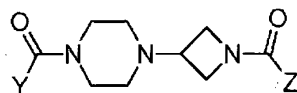
(I)

[0041]

5 wherein each symbol is as defined in patent document 10, is an MAGL inhibitor and useful for the treatment, improvement or prophylaxis of metabolic diseases (obesity, diabetes).

Patent Document 11 describes that a compound represented by the following formula (I):

10 [0042]



(I)

[0043]

wherein each symbol is as defined in patent document 11, is an MAGL inhibitor and useful for the treatment, improvement or
15 prophylaxis of metabolic diseases (obesity, diabetes).

Document List

Patent Document

[0044]

- Patent Document 1: WO 2015/099196
20 Patent Document 2: WO 2016/158956
Patent Document 3: WO 2010/124122
Patent Document 4: WO 2010/124082
Patent Document 5: WO 2010/124086
Patent Document 6: WO 2010/124121
25 Patent Document 7: WO 2012/030907
Patent Document 8: WO 2012/044613
Patent Document 9: WO 2012/054716
Patent Document 10: WO 2013/049289
Patent Document 11: WO 2013/049293

Non-Patent Document

[0045]

Non-Patent document 1: Science, vol. 294, pages 1871-1875, 2001

Non-Patent document 2: Molecular Neurobiology (Mol. Neurobiol.),

5 vol. 41, pages 115-128, 2010

Non-Patent document 3: Neuron, vol. 53, pages 337-351, 2007

Non-Patent document 4: Nature Reviews Neurology (Nat. Rev.

Neurol.), vol. 6, pages 193-201, 2010

Non-Patent document 5: Chemistry and Physics of Lipids (Chem

10 phys Lipids) vol. 121, pages 149-158, 2002

Non-Patent document 6: Cell Report (Cell Rep.), vol. 1, page

617-623, 2012

Non-Patent document 7: Biochemical Pharmacology (Biochem.

Pharmacol.) vol. 50, 83-90, 1995

15 Non-Patent document 8: Molecular Pharmacology (Mol. Pharmacol.),

vol. 34, pages 605-613, 1988

Non-Patent document 9: Neuroscience Letters (Neurosci. Lett.),

vol. 396, pages 113-116, 2006

Non-Patent document 10: Journal of Alzheimer's Disease (J.

20 Alzheimers. Dis.), vol. 30, pages 439-459, 2012

Non-Patent document 11: Neuroscience, vol. 178, pages 159-168,

2011

Non-Patent document 12: Annals of Neurology (Ann. Neurol.) vol.

57, pages 168-175, 2005

25 Non-Patent document 13: Science, vol. 334, pages 809-813, 2011

Non-Patent document 14: Neurobiology of Disease (Neurobiol.

Dis.) vol. 15, pages 601-609, 2004

Non-Patent document 15: European Journal of Pharmacology (Eur.

J. Pharmacol.), vol. 542, pages 100-105, 2006

30 Non-Patent document 16: Brain, vol. 132, pages 3152-3164, 2009

Non-Patent document 17: Brain Research (Brain Res.), vol. 1390,

pages 126-141, 2011

Non-Patent document 18: Nature, vol. 413, pages 527-531, 2001

Non-Patent document 19: Experimental Eye Research (Exp. Eye

35 Res.), vol. 87, pages 106-114, 2008

- Non-Patent document 20: Behavioural Brain Research (Behav. Brain Res.), vol. 252, pages 10-17, 2013
- Non-Patent document 21: British Journal of Pharmacology, vol. 150, pages 693-701, 2007
- 5 Non-Patent document 22: Pharmacological Research (Pharmacol. Res.), vol. 64, pages 60-67, 2011
- Non-Patent document 23: Nature Medicine (Nature Med.), vol. 16, pages 413-419, 2010
- Non-Patent document 24: Neurochemical Research (Neurochem. Res.), vol. 36, pages 1520-1525, 2011
- 10 Non-Patent document 25: Neuropsychopharmacology, vol. 39, pages 1763-1776, 2014
- Non-Patent document 26: Journal of Headache and Pain, vol. 15, No. 14, 2014
- 15 Non-Patent document 27: Brain Research, vol. 1298, pages 13-23, 2009
- Non-Patent document 28: Brain Research, vol. 1474, pages 91-99, 2012

Summary of the Invention

20 Problems to be Solved by the Invention

[0046]

An object of the present invention is to provide a compound having an MAGL inhibitory action, which is expected to be useful as an agent for the prophylaxis or treatment of

25 neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, traumatic brain injury, glaucoma, multiple sclerosis etc.), anxiety disorder, pains (e.g., inflammatory pain, cancerous pain, neurogenic pain etc.), epilepsy, depression and

30 the like.

Means of Solving the Problems

[0047]

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that

35 a compound represented by the following formula (I) has an MAGL

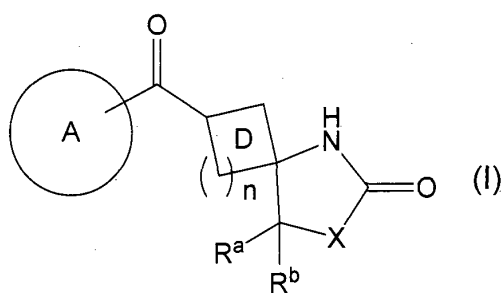
inhibitory action, and therefore, is expected to be useful as an agent for the prophylaxis or treatment of neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, traumatic brain injury, glaucoma, multiple sclerosis etc.), anxiety disorder, pains (e.g., inflammatory pain, cancerous pain, neurogenic pain etc.), epilepsy, depression and the like, which resulted in the completion of the present invention.

[0048]

10 Accordingly, the present invention provides the following.

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

[0049]



[0050]

15 wherein

Ring A is an optionally further substituted ring,

Ring D is an optionally further substituted ring,

n is 1 or 2,

X is -O-, -CR¹R²-, -CR¹R²-O-, -O-CR¹R²- or -NR³-,

20 R¹, R² and R³ are each independently a hydrogen atom or a substituent, and

R^a and R^b are each independently a hydrogen atom or a C₁₋₆ alkyl group optionally substituted by halogen atom(s),

or a salt thereof (hereinafter sometimes to be referred to as

25 compound (I)).

[0051]

[2] The compound or salt of the above-mentioned [1], wherein

Ring D is a cyclobutane ring;

n is 1;

X is -O-; and

R^a and R^b are both hydrogen atoms.

[0052]

[3] The compound or salt of the above-mentioned [1], or [2],
5 wherein Ring A is an optionally further substituted 3- to 14-
membered non-aromatic heterocycle.

[0053]

[4] The compound or salt of the above-mentioned [1], wherein
Ring A is a 3- to 14-membered non-aromatic heterocycle
10 optionally further substituted by 1 to 3 substituents selected
from

(a) a C₁₋₆ alkyl group optionally substituted by 1 to 3
substituents selected from

(i) a C₆₋₁₄ aryloxy group optionally substituted by 1 to 3
15 substituents selected from

(I) a halogen atom,
(II) an optionally halogenated C₁₋₆ alkyl group,
(III) a C₃₋₁₀ cycloalkyl group,
(IV) a 3- to 14-membered non-aromatic heterocyclic
20 group optionally substituted by 1 to 3 halogen atoms,
and

(V) a cyano group,
(ii) a C₆₋₁₄ aryl group optionally substituted by 1 to 3
substituents selected from

(I) a halogen atom, and
25 (II) an optionally halogenated C₁₋₆ alkyl group,
(iii) a halogen atom, and
(iv) a C₇₋₁₆ aralkyloxy group optionally substituted by 1
to 3 substituents selected from

(I) a halogen atom, and
30 (II) a C₁₋₆ alkyl group,

(b) a C₇₋₁₆ aralkyloxy group optionally substituted by 1 to 3
substituents selected from

(i) a halogen atom,
35 (ii) an optionally halogenated C₁₋₆ alkyl group, and

- (iii) an optionally halogenated C₁₋₆ alkoxy group,
(c) a C₂₋₆ alkenyl group optionally substituted by 1 to 3
substituents selected from
(i) a C₆₋₁₄ aryl group optionally substituted by 1 to 3
substituents selected from
(I) a halogen atom, and
(II) an optionally halogenated C₁₋₆ alkyl group, and
(ii) a halogen atom,
(d) a C₆₋₁₄ aryloxy group optionally substituted by 1 to 3
halogen atoms, and
(e) a 3- to 14-membered non-aromatic heterocyclic group
optionally substituted by 1 to 3 substituents selected from
(i) a halogen atom, and
(ii) an optionally halogenated C₁₋₆ alkyl group;
- 15 Ring D is a C₄₋₅ cycloalkane;
n is 1 or 2;
X is -O-, -CH₂- or -O-CH₂-; and
R^a and R^b are both hydrogen atoms.
[0054]
- 20 [5] The compound or salt of any of the above-mentioned [1],
wherein
Ring A is
(1) an azetidine ring optionally further substituted by 1 to 3
substituents selected from
(a) a benzyloxy group optionally substituted by 1 to 3
substituents selected from
(i) a halogen atom, and
(ii) an optionally halogenated C₁₋₆ alkyl group,
(2) a piperidine ring optionally further substituted by 1 to 3
substituents selected from
(a) a C₁₋₆ alkyl group optionally substituted by 1 to 3
substituents selected from
(i) a phenoxy group optionally substituted by 1 to 3
substituents selected from
(I) a halogen atom,
- 35

- (II) an optionally halogenated C₁₋₆ alkyl group, and
(III) an azetidiny group optionally substituted by 1 to 3 halogen atoms,
(ii) a phenyl group optionally substituted by 1 to 3 halogen atoms, and
(iii) a halogen atom, and
(b) a dihydrobenzofuryl group optionally substituted by 1 to 3 substituents selected from
(i) a halogen atom, and
(ii) an optionally halogenated C₁₋₆ alkyl group, or
(3) a 7-azaspiro[3.5]nonane ring optionally further substituted by 1 to 3 substituents selected from
(a) a phenoxy group optionally substituted by 1 to 3 halogen atoms;
15 Ring D is a cyclobutane ring;
n is 1;
X is -O-; and
R^a and R^b are both hydrogen atoms.
[0055]
20 [6] The compound or salt of any of the above-mentioned [1], wherein
Ring A is
(1) an azetidine ring further substituted by 1 to 3 substituents selected from
(a) a benzyloxy group substituted by 1 to 3 substituents selected from
(i) a halogen atom, and
(ii) an optionally halogenated C₁₋₆ alkyl group;
Ring D is a cyclobutane ring;
30 n is 1;
X is -O-; and
R^a and R^b are both hydrogen atoms.
[0056]
[7] (2s,4s)-2-((3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-

azaspiro[3.4]octan-6-one, or a salt thereof.

[8] (2s,4s)-2-((3-((2-Methyl-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one, or a salt thereof.

5 [9] (2s,4s)-2-((3-((3-Chloro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one, or a salt thereof.

[0057]

[10] A medicament comprising the compound or salt of any of the
10 above-mentioned [1] to [9].

[11] The medicament of the above-mentioned [10], which is a monoacylglycerol lipase inhibitor.

[12] The medicament of the above-mentioned [10], which is an agent for the prophylaxis or treatment of Alzheimer's disease,
15 Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, anxiety disorder, pain, epilepsy or depression.

[0058]

[13] Use of the compound or salt of any of the above-mentioned
20 [1] to [9] for the production of an agent for the prophylaxis or treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, anxiety disorder, pain, epilepsy or depression.

[14] The compound or salt of the compound or salt of any of the
25 above-mentioned [1] to [9] for use in the prophylaxis or treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, anxiety disorder, pain, epilepsy or depression.

[0059]

30 [15] A method of inhibiting monoacylglycerol lipase in a mammal, which comprises administering an effective amount of the compound or salt of any of the above-mentioned [1] to [9] to the mammal.

[16] A method for the prophylaxis or treatment of Alzheimer's
35 disease, Parkinson's disease, Huntington's disease, amyotrophic

lateral sclerosis, multiple sclerosis, anxiety disorder, pain, epilepsy or depression in a mammal, which comprises administering an effective amount of the compound or salt of any of the above-mentioned [1] to [9] to the mammal.

5 **Effect of the Invention**

[0060]

According to the present invention, a compound having a superior MAGL inhibitory action, which is expected to be useful as an agent for the prophylaxis or treatment of

10 neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, traumatic brain injury, glaucoma, multiple sclerosis etc.), anxiety disorder, pains (e.g., inflammatory pain, cancerous pain, neurogenic pain etc.), epilepsy, depression and

15 the like can be provided.

[0061]

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

20 [0062]

The definition of each substituent used in the present specification is described in detail in the following. Unless otherwise specified, each substituent has the following definition.

25 In the present specification, examples of the "halogen atom" include fluorine, chlorine, bromine and iodine.

In the present specification, examples of the "C₁₋₆ alkyl group" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl,

30 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkyl group" include a C₁₋₆ alkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms.

35 Specific examples thereof include methyl, chloromethyl,

difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, tetrafluoroethyl, pentafluoroethyl, propyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, 5 isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl and 6,6,6-trifluorohexyl.

In the present specification, examples of the "C₂₋₆ alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2- 10 butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl and 5-hexenyl.

In the present specification, examples of the "C₂₋₆ alkynyl group" include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3- 15 pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and 4-methyl-2-pentynyl.

In the present specification, examples of the "C₃₋₁₀ cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, 20 bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl and adamantyl.

In the present specification, examples of the "optionally halogenated C₃₋₁₀ cycloalkyl group" include a C₃₋₁₀ cycloalkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include cyclopropyl, 2,2- 25 difluorocyclopropyl, 2,3-difluorocyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

In the present specification, examples of the "C₃₋₁₀ cycloalkenyl group" include cyclopropenyl, cyclobutenyl, 30 cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

In the present specification, examples of the "C₆₋₁₄ aryl group" include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl and 9-anthryl.

In the present specification, examples of the "C₇₋₁₆ aralkyl group" include benzyl, phenethyl, naphthylmethyl and 35

phenylpropyl.

[0063]

In the present specification, examples of the "C₁₋₆ alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkoxy group" include a C₁₋₆ alkoxy group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "C₃₋₁₀ cycloalkyloxy group" include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy.

In the present specification, examples of the "C₁₋₆ alkylthio group" include methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio and hexylthio.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkylthio group" include a C₁₋₆ alkylthio group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio and hexylthio.

In the present specification, examples of the "C₁₋₆ alkyl-carbonyl group" include acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 3-methylbutanoyl, 2-methylbutanoyl, 2,2-dimethylpropanoyl, hexanoyl and heptanoyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkyl-carbonyl group" include a C₁₋₆ alkyl-carbonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include acetyl, chloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl,

butanoyl, pentanoyl and hexanoyl.

In the present specification, examples of the "C₁₋₆ alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, 5 isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl.

In the present specification, examples of the "C₆₋₁₄ aryl-carbonyl group" include benzoyl, 1-naphthoyl and 2-naphthoyl.

In the present specification, examples of the "C₇₋₁₆ 10 aralkyl-carbonyl group" include phenylacetyl and phenylpropionyl.

In the present specification, examples of the "5- to 14-membered aromatic heterocyclylcarbonyl group" include nicotinoyl, isonicotinoyl, thenoyl and furoyl.

15 In the present specification, examples of the "3- to 14-membered non-aromatic heterocyclylcarbonyl group" include morpholinylcarbonyl, piperidinylcarbonyl and pyrrolidinylcarbonyl.

[0064]

20 In the present specification, examples of the "mono- or di-C₁₋₆ alkyl-carbamoyl group" include methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl and N-ethyl-N-methylcarbamoyl.

In the present specification, examples of the "mono- or 25 di-C₇₋₁₆ aralkyl-carbamoyl group" include benzylcarbamoyl and phenethylcarbamoyl.

In the present specification, examples of the "C₁₋₆ alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec- 30 butylsulfonyl and tert-butylsulfonyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkylsulfonyl group" include a C₁₋₆ alkylsulfonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include 35 methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl,

ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl and hexylsulfonyl.

In the present specification, examples of the "C₆₋₁₄ arylsulfonyl group" include phenylsulfonyl, 1-naphthylsulfonyl
5 and 2-naphthylsulfonyl.

[0065]

In the present specification, examples of the "substituent" include a halogen atom, a cyano group, a nitro group, an optionally substituted hydrocarbon group, an
10 optionally substituted heterocyclic group, an acyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, an optionally substituted thiocarbamoyl group, an optionally substituted sulfamoyl group, an optionally substituted hydroxy group, an optionally substituted sulfanyl
15 (SH) group and an optionally substituted silyl group.

In the present specification, examples of the "hydrocarbon group" (including "hydrocarbon group" of "optionally substituted hydrocarbon group") include a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₃₋₁₀
20 cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group.

[0066]

In the present specification, examples of the "optionally substituted hydrocarbon group" include a hydrocarbon group
25 optionally having substituent(s) selected from the following Substituent group A.

[Substituent group A]

- (1) a halogen atom,
- (2) a nitro group,
- 30 (3) a cyano group,
- (4) an oxo group,
- (5) a hydroxy group,
- (6) an optionally halogenated C₁₋₆ alkoxy group,
- (7) a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthoxy),
- 35 (8) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy),

- (9) a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy),
- (10) a 3- to 14-membered non-aromatic heterocyclyloxy group (e.g., morpholinylloxy, piperidinylloxy),
- 5 (11) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetoxy, propanoyloxy),
- (12) a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy),
- (13) a C₁₋₆ alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, 10 ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy),
- (14) a mono- or di-C₁₋₆ alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, dimethylcarbamoyloxy, diethylcarbamoyloxy),
- (15) a C₆₋₁₄ aryl-carbamoyloxy group (e.g., phenylcarbamoyloxy, 15 naphthylcarbamoyloxy),
- (16) a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy),
- (17) a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., morpholinylcarbonyloxy, piperidinylcarbonyloxy),
- 20 (18) an optionally halogenated C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, trifluoromethylsulfonyloxy),
- (19) a C₆₋₁₄ arylsulfonyloxy group optionally substituted by a C₁₋₆ alkyl group (e.g., phenylsulfonyloxy, toluenesulfonyloxy),
- (20) an optionally halogenated C₁₋₆ alkylthio group,
- 25 (21) a 5- to 14-membered aromatic heterocyclic group,
- (22) a 3- to 14-membered non-aromatic heterocyclic group,
- (23) a formyl group,
- (24) a carboxy group,
- (25) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- 30 (26) a C₆₋₁₄ aryl-carbonyl group,
- (27) a 5- to 14-membered aromatic heterocyclylcarbonyl group,
- (28) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group,
- (29) a C₁₋₆ alkoxy-carbonyl group,
- 35 (30) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, 1-

- naphthyloxycarbonyl, 2-naphthyloxycarbonyl),
(31) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl),
(32) a carbamoyl group,
5 (33) a thiocarbamoyl group,
(34) a mono- or di-C₁₋₆ alkyl-carbamoyl group,
(35) a C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl),
(36) a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl, thienylcarbamoyl),
10 (37) a 3- to 14-membered non-aromatic heterocyclylcarbamoyl group (e.g., morpholinylcarbamoyl, piperidinylcarbamoyl),
(38) an optionally halogenated C₁₋₆ alkylsulfonyl group,
(39) a C₆₋₁₄ arylsulfonyl group,
(40) a 5- to 14-membered aromatic heterocyclylsulfonyl group
15 (e.g., pyridylsulfonyl, thienylsulfonyl),
(41) an optionally halogenated C₁₋₆ alkylsulfinyl group,
(42) a C₆₋₁₄ arylsulfinyl group (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl),
(43) a 5- to 14-membered aromatic heterocyclylsulfinyl group
20 (e.g., pyridylsulfinyl, thienylsulfinyl),
(44) an amino group,
(45) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, N-ethyl-N-methylamino),
25 (46) a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino),
(47) a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino),
(48) a C₇₋₁₆ aralkylamino group (e.g., benzylamino),
30 (49) a formylamino group,
(50) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino, propanoylamino, butanoylamino),
(51) a (C₁₋₆ alkyl)(C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-methylamino),
35 (52) a C₆₋₁₄ aryl-carbonylamino group (e.g., phenylcarbonylamino,

- naphthylcarbonylamino),
- (53) a C₁₋₆ alkoxy-carbonylamino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino),
- 5 (54) a C₇₋₁₆ aralkyloxy-carbonylamino group (e.g., benzyloxycarbonylamino),
- (55) a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino),
- (56) a C₆₋₁₄ arylsulfonylamino group optionally substituted by a
- 10 C₁₋₆ alkyl group (e.g., phenylsulfonylamino, toluenesulfonylamino),
- (57) an optionally halogenated C₁₋₆ alkyl group,
- (58) a C₂₋₆ alkenyl group,
- (59) a C₂₋₆ alkynyl group,
- 15 (60) a C₃₋₁₀ cycloalkyl group,
- (61) a C₃₋₁₀ cycloalkenyl group, and
- (62) a C₆₋₁₄ aryl group.
- [0067]

The number of the above-mentioned substituents in the

20 "optionally substituted hydrocarbon group" is, for example, 1 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

In the present specification, examples of the

25 "heterocyclic group" (including "heterocyclic group" of "optionally substituted heterocyclic group") include (i) an aromatic heterocyclic group, (ii) a non-aromatic heterocyclic group and (iii) a 7- to 10-membered bridged heterocyclic group, each containing, as a ring-constituting atom besides carbon

30 atom, 1 to 4 heteroatoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0068]

In the present specification, examples of the "aromatic heterocyclic group" (including "5- to 14-membered aromatic

35 heterocyclic group") include a 5- to 14-membered (preferably 5-

to 10-membered) aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 heteroatoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the "aromatic heterocyclic group" include 5- or 6-membered monocyclic aromatic heterocyclic groups such as thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, tetrazolyl, triazinyl and the like; and 8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocyclic groups such as benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, imidazopyridinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyrazinyl, imidazopyrimidinyl, thienopyrimidinyl, furopyrimidinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, pyrazolotriazinyl, naphtho[2,3-b]thienyl, phenoxathiinyl, indolyl, isoindolyl, 1H-indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like.

[0069]

In the present specification, examples of the "non-aromatic heterocyclic group" (including "3- to 14-membered non-aromatic heterocyclic group") include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 heteroatoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the "non-aromatic heterocyclic group" include 3- to 8-membered monocyclic non-aromatic

heterocyclic groups such as aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, tetrahydrothienyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, oxazolinyl, oxazolidinyl, pyrazolinyl, 5 pyrazolidinyl, thiazolinyl, thiazolidinyl, tetrahydroisothiazolyl, tetrahydrooxazolyl, tetrahydroisooxazolyl, piperidinyl, piperazinyl, tetrahydropyridinyl, dihydropyridinyl, dihydrothiopyranyl, tetrahydropyrimidinyl, tetrahydropyridazinyl, dihydropyranyl, 10 tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, azepanyl, diazepanyl, azepinyl, oxepanyl, azocanyl, diazocanyl and the like; and 9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocyclic groups such as dihydrobenzofuranyl, 15 dihydrobenzimidazolyl, dihydrobenzoxazolyl, dihydrobenzothiazolyl, dihydrobenzisoctiazolyl, dihydronaphtho[2,3-b]thienyl, tetrahydroisoquinolyl, tetrahydroquinolyl, 4H-quinoliziny, indolinyl, isoindolinyl, tetrahydrothieno[2,3-c]pyridinyl, tetrahydrobenzazepinyl, 20 tetrahydroquinoxalinyl, tetrahydrophenanthridinyl, hexahydrophenothiazinyl, hexahydrophenoxazinyl, tetrahydrophthalazinyl, tetrahydronaphthyridinyl, tetrahydroquinazolinyl, tetrahydrocinnolinyl, tetrahydrocarbazolyl, tetrahydro- β -carbolinyl, 25 tetrahydroacrydinyl, tetrahydrophenazinyl, tetrahydrothioxanthenyl, octahydroisoquinolyl and the like.

[0070]

In the present specification, preferable examples of the "7- to 10-membered bridged heterocyclic group" include 30 quinuclidinyl and 7-azabicyclo[2.2.1]heptanyl.

In the present specification, examples of the "nitrogen-containing heterocyclic group" include a "heterocyclic group" containing at least one nitrogen atom as a ring-constituting atom.

35 In the present specification, examples of the "optionally

substituted heterocyclic group" include a heterocyclic group optionally having substituent(s) selected from the above-mentioned Substituent group A.

The number of the substituents in the "optionally substituted heterocyclic group" is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0071]

In the present specification, examples of the "acyl group" include a formyl group, a carboxy group, a carbamoyl group, a thiocarbamoyl group, a sulfinoyl group, a sulfo group, a sulfamoyl group and a phosphono group, each optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a 5- to 14-membered aromatic heterocyclic group and a 3- to 14-membered non-aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from a halogen atom, an optionally halogenated C₁₋₆ alkoxy group, a hydroxy group, a nitro group, a cyano group, an amino group and a carbamoyl group".

Examples of the "acyl group" also include a hydrocarbon-sulfonyl group, a heterocyclylsulfonyl group, a hydrocarbon-sulfinyl group and a heterocyclylsulfinyl group.

Here, the hydrocarbon-sulfonyl group means a hydrocarbon group-bonded sulfonyl group, the heterocyclylsulfonyl group means a heterocyclic group-bonded sulfonyl group, the hydrocarbon-sulfinyl group means a hydrocarbon group-bonded sulfinyl group and the heterocyclylsulfinyl group means a heterocyclic group-bonded sulfinyl group.

Preferable examples of the "acyl group" include a formyl group, a carboxy group, a C₁₋₆ alkyl-carbonyl group, a C₂₋₆ alkenyl-carbonyl group (e.g., crotonoyl), a C₃₋₁₀ cycloalkyl-carbonyl group (e.g., cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl); a C₃₋₁₀ cycloalkenyl-carbonyl group (e.g., 2-cyclohexenecarbonyl), a

C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl), a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl), a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl), a sulfinio group, a C₁₋₆ alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl), a sulfo group, a C₁₋₆ alkylsulfonyl group, a C₆₋₁₄ arylsulfonyl group, a phosphono group and a mono- or di-C₁₋₆ alkylphosphono group (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono).

[0072]

In the present specification, examples of the "optionally substituted amino group" include an amino group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-

membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a
5 mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group and a C₆₋₁₄ arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted amino group include an amino group, a mono- or di-(optionally
10 halogenated C₁₋₆ alkyl) amino group (e.g., methylamino, trifluoromethylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino), a mono- or di-C₂₋₆ alkenylamino group (e.g., diallylamino), a mono- or di-C₃₋₁₀ cycloalkylamino group (e.g., cyclopropylamino, cyclohexylamino), a mono- or di-
15 C₆₋₁₄ arylamino group (e.g., phenylamino), a mono- or di-C₇₋₁₆ aralkylamino group (e.g., benzylamino, dibenzylamino), a mono- or di-(optionally halogenated C₁₋₆ alkyl)-carbonylamino group (e.g., acetylamino, propionylamino), a mono- or di-C₆₋₁₄ aryl-carbonylamino group (e.g., benzoylamino), a mono- or di-C₇₋₁₆
20 aralkyl-carbonylamino group (e.g., benzylcarbonylamino), a mono- or di-5- to 14-membered aromatic heterocyclylcarbonylamino group (e.g., nicotinoylamino, isonicotinoylamino), a mono- or di-3- to 14-membered non-aromatic heterocyclylcarbonylamino group (e.g.,
25 piperidinylcarbonylamino), a mono- or di-C₁₋₆ alkoxy-carbonylamino group (e.g., tert-butoxycarbonylamino), a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino), a carbamoylamino group, a (mono- or di-C₁₋₆ alkyl-carbamoyl) amino group (e.g., methylcarbamoylamino), a
30 (mono- or di-C₇₋₁₆ aralkyl-carbamoyl) amino group (e.g., benzylcarbamoylamino), a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino), a C₆₋₁₄ arylsulfonylamino group (e.g., phenylsulfonylamino), a (C₁₋₆ alkyl)(C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-
35 methylamino) and a (C₁₋₆ alkyl)(C₆₋₁₄ aryl-carbonyl) amino group

(e.g., N-benzoyl-N-methylamino).

[0073]

In the present specification, examples of the "optionally substituted carbamoyl group" include a carbamoyl group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted carbamoyl group include a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl, cyclohexylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbonyl-carbamoyl group (e.g., acetylcarbamoyl, propionylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-carbamoyl group (e.g., benzoylcarbamoyl) and a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl).

[0074]

In the present specification, examples of the "optionally substituted thiocarbamoyl group" include a thiocarbamoyl group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-

membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which
5 optionally has 1 to 3 substituents selected from Substituent group "A".

Preferable examples of the optionally substituted thiocarbamoyl group include a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, 10 ethylthiocarbamoyl, dimethylthiocarbamoyl, diethylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or 15 di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-thiocarbamoyl group (e.g., acetylthiocarbamoyl, propionylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl- 20 thiocarbamoyl group (e.g., benzoylthiocarbamoyl) and a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl).

[0075]

In the present specification, examples of the "optionally substituted sulfamoyl group" include a sulfamoyl group 25 optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- 30 to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which 35 optionally has 1 to 3 substituents selected from Substituent

group A".

Preferable examples of the optionally substituted sulfamoyl group include a sulfamoyl group, a mono- or di-C₁₋₆ alkyl-sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-methylsulfamoyl), a mono- or di-C₂₋₆ alkenyl-sulfamoyl group (e.g., diallylsulfamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-sulfamoyl group (e.g., cyclopropylsulfamoyl, cyclohexylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-sulfamoyl group (e.g., phenylsulfamoyl), a mono- or di-C₇₋₁₆ aralkyl-sulfamoyl group (e.g., benzylsulfamoyl, phenethylsulfamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-sulfamoyl group (e.g., acetylsulfamoyl, propionylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-sulfamoyl group (e.g., benzoylsulfamoyl) and a 5- to 14-membered aromatic heterocyclisulfamoyl group (e.g., pyridylsulfamoyl).
[0076]

In the present specification, examples of the "optionally substituted hydroxy group" include a hydroxy group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group and a C₆₋₁₄ arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted hydroxy group include a hydroxy group, a C₁₋₆ alkoxy group, a C₂₋₆ alkenyloxy group (e.g., allyloxy, 2-butenyloxy, 2-pentenylloxy, 3-hexenyloxy), a C₃₋₁₀ cycloalkyloxy group (e.g., cyclohexyloxy), a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthyloxy), a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy, phenethylloxy), a C₁₋₆ alkyl-

carbonyloxy group (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy), a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy), a C₇₋₁₆ aralkyl-carbonyloxy group (e.g., benzylcarbonyloxy), a 5- to 14-membered aromatic
5 heterocyclylcarbonyloxy group (e.g., nicotinoyloxy), a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., piperidinylcarbonyloxy), a C₁₋₆ alkoxy-carbonyloxy group (e.g., tert-butoxycarbonyloxy), a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy), a carbamoyloxy group,
10 a C₁₋₆ alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy), a C₇₋₁₆ aralkyl-carbamoyloxy group (e.g., benzylcarbamoyloxy), a C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy) and a C₆₋₁₄ arylsulfonyloxy group (e.g., phenylsulfonyloxy).

15 [0077]

In the present specification, examples of the "optionally substituted sulfanyl group" include a sulfanyl group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group and a 5- to 14-membered aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from Substituent group A" and a halogenated sulfanyl group.

25 Preferable examples of the optionally substituted sulfanyl group include a sulfanyl (-SH) group, a C₁₋₆ alkylthio group, a C₂₋₆ alkenylthio group (e.g., allylthio, 2-butenylthio, 2-pentenylthio, 3-hexenylthio), a C₃₋₁₀ cycloalkylthio group (e.g., cyclohexylthio), a C₆₋₁₄ arylthio group (e.g., phenylthio, naphthylthio), a C₇₋₁₆ aralkylthio group (e.g., benzylthio, phenethylthio), a C₁₋₆ alkyl-carbonylthio group (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio, pivaloylthio), a C₆₋₁₄ aryl-carbonylthio group (e.g., benzoylthio), a 5- to 14-membered aromatic heterocyclylthio
30 group (e.g., pyridylthio) and a halogenated thio group (e.g.,

pentafluorothio).

[0078]

In the present specification, examples of the "optionally substituted silyl group" include a silyl group optionally
5 having "1 to 3 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted silyl
10 group include a tri-C₁₋₆ alkylsilyl group (e.g., trimethylsilyl, tert-butyl(dimethyl)silyl).

[0079]

In the present specification, examples of the
"hydrocarbon ring" include a C₆₋₁₄ aromatic hydrocarbon ring, C₃₋₁₀
15 cycloalkane and C₃₋₁₀ cycloalkene.

In the present specification, examples of the "C₆₋₁₄ aromatic hydrocarbon ring" include benzene and naphthalene.

In the present specification, examples of the "C₃₋₁₀ cycloalkane" include cyclopropane, cyclobutane, cyclopentane,
20 cyclohexane, cycloheptane and cyclooctane.

In the present specification, examples of the "C₃₋₁₀ cycloalkene" include cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene and cyclooctene.

In the present specification, examples of the
25 "heterocycle" include an aromatic heterocycle and a non-aromatic heterocycle, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0080]

30 In the present specification, examples of the "aromatic heterocycle" include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen
35 atom. Preferable examples of the "aromatic heterocycle"

include 5- or 6-membered monocyclic aromatic heterocycles such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 5 1,2,4-thiadiazole, 1,3,4-thiadiazole, triazole, tetrazole, triazine and the like; and 8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocycles such as benzothiophene, benzofuran, benzimidazole, benzoxazole, benzisoxazole, 10 benzothiazole, benzisothiazole, benzotriazole, imidazopyridine, thienopyridine, furopyridine, pyrrolopyridine, pyrazolopyridine, oxazolopyridine, thiazolopyridine, imidazopyrazine, imidazopyrimidine, thienopyrimidine, furopyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, 15 oxazolopyrimidine, thiazolopyrimidine, pyrazolopyrimidine, pyrazolotriazine, naphtho[2,3-b]thiophene, phenoxathiin, indole, isoindole, 1H-indazole, purine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β -carboline, phenanthridine, 20 acridine, phenazine, phenothiazine, phenoxazine and the like. [0081]

In the present specification, examples of the "non-aromatic heterocycle" include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocycle containing, as a 25 ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. Preferable examples of the "non-aromatic heterocycle" include 3- to 8-membered monocyclic non-aromatic heterocycles such as aziridine, oxirane, thiirane, azetidine, 30 oxetane, thietane, tetrahydrothiophene, tetrahydrofuran, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, oxazoline, oxazolidine, pyrazoline, pyrazolidine, thiazoline, thiazolidine, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, piperazine, 35 tetrahydropyridine, dihydropyridine, dihydrothiopyran,

tetrahydropyrimidine, tetrahydropyridazine, dihydropyran, tetrahydropyran, tetrahydrothiopyran, morpholine, thiomorpholine, azepane, diazepane, azepine, azocane, diazocane, oxepane and the like; and

5 9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocycles such as dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzothiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, 4H-quinolizine,
10 indoline, isoindoline, tetrahydrothieno[2,3-c]pyridine, tetrahydrobenzazepine, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiazine, hexahydrophenoxazine, tetrahydrophthalazine, tetrahydronaphthylidine, tetrahydroquinazoline,
15 tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro- β -carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxanthene, octahydroisoquinoline and the like.

In the present specification, examples of the "nitrogen-containing heterocycle" include a "heterocycle" containing at
20 least one nitrogen atom as a ring-constituting atom.

In the present specification, examples of the "C₆₋₁₄ aromatic hydrocarbon ring" include anthracene, phenanthrene, acenaphthylene, in addition to those exemplified as the above-mentioned "C₆₋₁₄ aromatic hydrocarbon ring".

25 [0082]

The definition of each symbol in the formula (I) is explained in detail in the following.

[0083]

Ring A is an optionally further substituted ring.

30 Examples of the "ring" of the "optionally further substituted ring" for Ring A include a hydrocarbon ring and a heterocycle.

[0084]

The "ring" of the "optionally further substituted ring"
35 for Ring A is optionally further substituted, for example, by

substituent(s) selected from the above-mentioned Substituent Group A. The number of the substituents is, for example, 1 to 3. When the number of the substituents is 2 or more, the respective substituents may be the same or different.

5 [0085]

Ring A is preferably an optionally further substituted 3- to 14-membered non-aromatic heterocycle, more preferably an optionally further substituted 3- to 14-membered nitrogen-containing non-aromatic heterocycle, further more preferably an
10 optionally further substituted 3- to 8-membered monocyclic nitrogen-containing non-aromatic heterocycle (preferably piperidine, azetidine) or an optionally further substituted 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) nitrogen-containing non-aromatic heterocycle (preferably 7-
15 azaspiro[3.5]nonane). Particularly preferred is an azetidine ring.

[0086]

Specifically, Ring A is preferably a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 14-membered
20 nitrogen-containing non-aromatic heterocycle, more preferably a 3- to 8-membered monocyclic nitrogen-containing non-aromatic heterocycle (e.g., piperidine, azetidine) or a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) nitrogen-containing non-aromatic heterocycle (e.g., 7-
25 azaspiro[3.5]nonane)) optionally further substituted by 1 to 3 substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl)

optionally substituted by 1 to 3 substituents selected from

(i) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally
30 substituted by 1 to 3 substituents selected from

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

(II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl, trifluoromethyl, 2-fluoroethyl),

35 (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), and

- (IV) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., azetidiny)) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (ii) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
- (iii) a halogen atom (e.g., a fluorine atom),
- (b) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
- (iii) an optionally halogenated C₁₋₆ alkoxy group (e.g., trifluoromethoxy),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from
- (i) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and
- (ii) a halogen atom (e.g., a fluorine atom),
- (d) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
- (e) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic

group (e.g., dihydrobenzofuryl)) optionally substituted by 1 to 3 substituents selected from

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

5 (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl).

[0087]

Ring A is more preferably

(1) a piperidine ring optionally further substituted by 1 to 3
10 substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl)

optionally substituted by 1 to 3 substituents selected from

(i) a phenoxy group optionally substituted by 1 to 3 substituents selected from

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

(II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl, 2-fluoroethyl),

(III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), and

20 (IV) an azetidiny group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(ii) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and

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

(b) a benzyloxy group optionally substituted by 1 to 3 halogen atoms (e.g., a chlorine atom), and

(c) a dihydrobenzofuryl group optionally substituted by 1 to 3 substituents selected from

30 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and

(ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),

(2) an azetidine ring optionally further substituted by 1 to 3
35 substituents selected from

- (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from
- (i) a phenoxy group optionally substituted by 1 to 3 substituents selected from
 - (I) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom),
 - (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl, trifluoromethyl), and
 - (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
 - (ii) a phenyl group optionally substituted by 1 to 3 substituents selected from
 - (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
 - (iii) a halogen atom (e.g., a fluorine atom),
- (b) a benzyloxy group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
 - (iii) an optionally halogenated C₁₋₆ alkoxy group (e.g., trifluoromethoxy), and
- (c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from
- (i) a phenyl group optionally substituted by 1 to 3 substituents selected from
 - (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - (II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and
 - (ii) a halogen atom (e.g., a fluorine atom), or
- (3) a 7-azaspiro[3.5]nonane ring optionally further substituted by 1 to 3 substituents selected from

(a) a phenoxy group optionally substituted by 1 to 3
halogen atoms (e.g., a fluorine atom, a chlorine atom).

[0088]

Ring A is further more preferably

5 (1) a piperidine ring optionally further substituted by 1 to 3
substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally
substituted by 1 to 3 substituents selected from

(i) a phenoxy group optionally substituted by 1 to 3
10 substituents selected from

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

(II) an optionally halogenated C₁₋₆ alkyl group (e.g.,
2-fluoroethyl), and

15 (III) an azetidiny group optionally substituted by 1
to 3 halogen atoms (e.g., a fluorine atom).

[0089]

Ring A is still more preferably

(1) a piperidine ring optionally further substituted by 1 to 3
20 substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted
by 1 to 3 substituents selected from

(i) a phenoxy group optionally substituted by 1 to 3
substituents selected from

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

(II) an optionally halogenated C₁₋₆ alkyl group (e.g.,
2-fluoroethyl), and

(III) an azetidiny group optionally substituted by 1
30 to 3 halogen atoms (e.g., a fluorine atom).

[0090]

In another embodiment, Ring A is preferably a 3- to 14-
membered non-aromatic heterocycle (preferably a 3- to 14-
membered nitrogen-containing non-aromatic heterocycle, more
35 preferably a 3- to 8-membered monocyclic nitrogen-containing

non-aromatic heterocycle (e.g., piperidine, azetidine, pyrrolidine) or a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) nitrogen-containing non-aromatic heterocycle (e.g., 7-azaspiro[3.5]nonane)) optionally further
5 substituted by 1 to 3 substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl) optionally substituted by 1 to 3 substituents selected from

(i) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 substituents selected from

10 (I) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom),

(II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl, trifluoromethyl, 2-fluoroethyl),

(III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

15 (IV) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., azetidiny)) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

20 (V) a cyano group,

(ii) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

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

25 (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),

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

(iv) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy) optionally substituted by 1 to 3 substituents selected from

30 (I) a halogen atom (e.g., a chlorine atom), and

(II) a C₁₋₆ alkyl group (e.g., methyl),

(b) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy) optionally substituted by 1 to 3 substituents selected from

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

- (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
- (iii) an optionally halogenated C₁₋₆ alkoxy group (e.g., trifluoromethoxy),
- 5 (c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from
 - (i) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
 - (I) a halogen atom (e.g., a fluorine atom, a chlorine
 - 10 atom), and
 - (II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and
 - (ii) a halogen atom (e.g., a fluorine atom),
 - (d) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally
 - 15 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
 - (e) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic
 - 20 group (e.g., dihydrobenzofuryl)) optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - (ii) an optionally halogenated C₁₋₆ alkyl group (e.g.,
 - 25 methyl, trifluoromethyl).

[0091]

- In this embodiment, Ring A is more preferably
- (1) an azetidine ring optionally further substituted by 1 to 3 substituents selected from
 - 30 (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from
 - (i) a phenoxy group optionally substituted by 1 to 3 substituents selected from
 - (I) a halogen atom (e.g., a fluorine atom, a chlorine
 - 35 atom, a bromine atom),

- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl, trifluoromethyl), and
- (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
- (ii) a phenyl group optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),
- (iii) a halogen atom (e.g., a fluorine atom), and
- (iv) a benzyloxy group optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a chlorine atom), and
- (II) a C₁₋₆ alkyl group (e.g., methyl),
- (b) a benzyloxy group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
- (iii) an optionally halogenated C₁₋₆ alkoxy group (e.g., trifluoromethoxy), and
- (c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from
- (i) a phenyl group optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and
- (ii) a halogen atom (e.g., a fluorine atom),
- (2) a piperidine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl) optionally substituted by 1 to 3 substituents selected from

- (i) a phenoxy group optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - 5 (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl, 2-fluoroethyl),
 - (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
 - (IV) an azetidiny group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - 10 (V) a cyano group,
- (ii) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
- (iii) a halogen atom (e.g., a fluorine atom),
- 15 (b) a benzyloxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
- (c) a dihydrobenzofuryl group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - 20 (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),
- (3) a 7-azaspiro[3.5]nonane ring optionally further substituted by 1 to 3 substituents selected from
- 25 (a) a phenoxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), or
- (4) a pyrrolidine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted
 - 30 by 1 to 3 substituents selected from a phenoxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
 - (b) a benzyloxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom).
- 35 [0092]

- In this embodiment, Ring A is further more preferably
- (1) an azetidine ring optionally further substituted by 1 to 3 substituents selected from
 - (a) a benzyloxy group optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),
 - 10 (2) a piperidine ring optionally further substituted by 1 to 3 substituents selected from
 - (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from
 - (i) a phenoxy group optionally substituted by 1 to 3 substituents selected from
 - 15 (I) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (II) an optionally halogenated C₁₋₆ alkyl group (e.g., 2-fluoroethyl), and
 - 20 (III) an azetidiny group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (ii) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
 - 25 (iii) a halogen atom (e.g., a fluorine atom), and
 - (b) a dihydrobenzofuryl group optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), or
 - 30 (3) a 7-azaspiro[3.5]nonane ring optionally further substituted by 1 to 3 substituents selected from
 - (a) a phenoxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom).
- 35 [0093]

In this embodiment, Ring A is still more preferably
(1) an azetidine ring further substituted by 1 to 3
substituents selected from

(a) a benzyloxy group substituted by 1 to 3 substituents
5 selected from

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

(ii) an optionally halogenated C₁₋₆ alkyl group (e.g.,
methyl, trifluoromethyl).

10 [0094]

Ring D is an optionally further substituted ring.

Examples of the "ring" of the "optionally further
substituted ring" for Ring D include a hydrocarbon ring.

The "ring" is preferably C₄₋₅ cycloalkane, more preferably
15 cyclobutane.

[0095]

The "ring" of the "optionally further substituted ring"
for Ring D is optionally further substituted, for example, by
substituent(s) selected from the above-mentioned Substituent
20 Group A. The number of the substituents is, for example, 1 to
3. When the number of the substituents is 2 or more, the
respective substituents may be the same or different.

[0096]

Ring D is preferably an optionally further substituted
25 C₄₋₅ cycloalkane (preferably cyclobutane).

Ring D is more preferably a C₄₋₅ cycloalkane (preferably
cyclobutane).

[0097]

n is 1 or 2.

30 n is preferably 1.

[0098]

X is -O-, -CR¹R²-, -CR¹R²-O-, -O-CR¹R²- or -NR³-.

R¹, R² and R³ are each independently a hydrogen atom or a
substituent.

35 Examples of the substituent include a substituent selected

from the Substituent Group A.

[0099]

When X is $-\text{CR}^1\text{R}^2-\text{O}-$, the carbon atom in the $-\text{CR}^1\text{R}^2-\text{O}-$ is bonded to the adjacent carbon atom that R^a and R^b are bonded to, and the oxygen atom in the $-\text{CR}^1\text{R}^2-\text{O}-$ is bonded to the adjacent carbon atom of the carbonyl group.

[0100]

When X is $-\text{O}-\text{CR}^1\text{R}^2-$, the oxygen atom in the $-\text{O}-\text{CR}^1\text{R}^2-$ is bonded to the adjacent carbon atom that R^a and R^b are bonded to, and the carbon atom in the $-\text{O}-\text{CR}^1\text{R}^2-$ is bonded to the adjacent carbon atom of the carbonyl group.

[0101]

X is preferably $-\text{O}-$, $-\text{CR}^1\text{R}^2-$ or $-\text{O}-\text{CR}^1\text{R}^2-$.

R^1 and R^2 are preferably both hydrogen atoms.

X is more preferably $-\text{O}-$, $-\text{CH}_2-$ or $-\text{O}-\text{CH}_2-$.

X is further more preferably $-\text{O}-$.

[0102]

R^a and R^b are each independently a hydrogen atom or a C_{1-6} alkyl group optionally substituted by halogen atom(s).

R^a and R^b are preferably both hydrogen atoms.

[0103]

The combination of Ring D, n, X, R^a and R^b is preferably

Ring D is a C_{4-5} cycloalkane (preferably cyclobutane);

n is 1 or 2;

X is $-\text{O}-$, $-\text{CH}_2-$ or $-\text{O}-\text{CH}_2-$; and

R^a and R^b are both hydrogen atoms,

more preferably

Ring D is a cyclobutane ring;

n is 1;

X is $-\text{O}-$; and

R^a and R^b are both hydrogen atoms.

[0104]

Preferable examples of compound (I) include the following compounds.

[0105]

[Compound A-1]

Compound (I) wherein

Ring A is an optionally further substituted 3- to 14-membered
5 non-aromatic heterocycle (preferably an optionally further
substituted 3- to 14-membered nitrogen-containing non-aromatic
heterocycle, more preferably an optionally further substituted
3- to 8-membered monocyclic nitrogen-containing non-aromatic
heterocycle (preferably piperidine, azetidine) or an optionally
10 further substituted 9- to 14-membered fused polycyclic
(preferably bi- or tri-cyclic) nitrogen-containing non-aromatic
heterocycle (preferably 7-azaspiro[3.5]nonane));

Ring D is an optionally further substituted C₄₋₅ cycloalkane
(preferably cyclobutane);

15 n is 1 or 2;

X is -O-, -CR¹R²- or -O-CR¹R²-;

R¹ and R² are each independently a hydrogen atom or a
substituent; and

R^a and R^b are each independently a hydrogen atom or a C₁₋₆ alkyl
20 group optionally substituted by halogen atom(s).

[0106]

[Compound B-1]

Compound (I) wherein

Ring A is a 3- to 14-membered non-aromatic heterocycle
25 (preferably a 3- to 14-membered nitrogen-containing non-
aromatic heterocycle, more preferably a 3- to 8-membered
monocyclic nitrogen-containing non-aromatic heterocycle (e.g.,
piperidine, azetidine) or a 9- to 14-membered fused polycyclic
(preferably bi- or tri-cyclic) nitrogen-containing non-aromatic
30 heterocycle (e.g., 7-azaspiro[3.5]nonane)) optionally further
substituted by 1 to 3 substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl)

optionally substituted by 1 to 3 substituents selected from

(i) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally
35 substituted by 1 to 3 substituents selected from

- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom),
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl, trifluoromethyl, 2-fluoroethyl),
- 5 (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), and
- (IV) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., azetidiny)) optionally substituted by 1 to 3 halogen atoms (e.g.,
- 10 a fluorine atom),
- (ii) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- 15 (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
- (iii) a halogen atom (e.g., a fluorine atom),
- (b) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy) optionally substituted by 1 to 3 substituents selected from
- 20 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
- (iii) an optionally halogenated C₁₋₆ alkoxy group (e.g.,
- 25 trifluoromethoxy),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from
- (i) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- 30 (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and
- (ii) a halogen atom (e.g., a fluorine atom),
- 35 (d) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally

substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and

(e) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 9- to 14-membered fused polycyclic

5 (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydrobenzofuryl)) optionally substituted by 1 to 3 substituents selected from

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

10 (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl);

Ring D is a C₄₋₅ cycloalkane (preferably cyclobutane);

n is 1 or 2;

X is -O-, -CH₂- or -O-CH₂-; and

15 R^a and R^b are both hydrogen atoms.

[0107]

[Compound C-1]

Compound (I) wherein

Ring A is

20 (1) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl)

optionally substituted by 1 to 3 substituents selected from

(i) a phenoxy group optionally substituted by 1 to 3

25 substituents selected from

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

(II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl, 2-fluoroethyl),

30 (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), and

(IV) an azetidiny group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(ii) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom),

35 and

- (iii) a halogen atom (e.g., a fluorine atom),
(b) a benzyloxy group optionally substituted by 1 to 3
halogen atoms (e.g., a chlorine atom), and
(c) a dihydrobenzofuryl group optionally substituted by 1 to
5 3 substituents selected from
(i) a halogen atom (e.g., a fluorine atom, a chlorine
atom), and
(ii) an optionally halogenated C₁₋₆ alkyl group (e.g.,
methyl, trifluoromethyl),
10 (2) an azetidine ring optionally further substituted by 1 to 3
substituents selected from
(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally
substituted by 1 to 3 substituents selected from
(i) a phenoxy group optionally substituted by 1 to 3
15 substituents selected from
(I) a halogen atom (e.g., a fluorine atom, a chlorine
atom, a bromine atom),
(II) an optionally halogenated C₁₋₆ alkyl group (e.g.,
methyl, ethyl, trifluoromethyl), and
20 (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
(ii) a phenyl group optionally substituted by 1 to 3
substituents selected from
(I) a halogen atom (e.g., a fluorine atom, a chlorine
atom), and
25 (II) an optionally halogenated C₁₋₆ alkyl group (e.g.,
methyl, trifluoromethyl), and
(iii) a halogen atom (e.g., a fluorine atom),
(b) a benzyloxy group optionally substituted by 1 to 3
substituents selected from
30 (i) a halogen atom (e.g., a fluorine atom, a chlorine
atom),
(ii) an optionally halogenated C₁₋₆ alkyl group (e.g.,
methyl, trifluoromethyl), and
(iii) an optionally halogenated C₁₋₆ alkoxy group (e.g.,
35 trifluoromethoxy), and

(c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from

(i) a phenyl group optionally substituted by 1 to 3 substituents selected from

5 (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and

(II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and

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

10 (3) a 7-azaspiro[3.5]nonane ring optionally further substituted by 1 to 3 substituents selected from

(a) a phenoxy group optionally substituted by 1 to 3

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

Ring D is a C₄₋₅ cycloalkane (preferably cyclobutane);

15 n is 1 or 2;

X is -O-, -CH₂- or -O-CH₂-; and

R^a and R^b are both hydrogen atoms.

[0108]

[Compound D-1]

20 Compound (I) wherein

Ring A is

(1) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

25 (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from

(i) a phenoxy group optionally substituted by 1 to 3 substituents selected from

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

30 (II) an optionally halogenated C₁₋₆ alkyl group (e.g., 2-fluoroethyl), and

(III) an azetidiny group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom);

Ring D is a cyclobutane ring;

35 n is 1;

X is -O-; and

R^a and R^b are both hydrogen atoms.

[0109]

[Compound E-1]

5 Compound (I) wherein

Ring A is

(1) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

10 (a) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 substituents selected from

(i) a phenoxy group optionally substituted by 1 to 3 substituents selected from

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

15 (II) an optionally halogenated C₁₋₆ alkyl group (e.g., 2-fluoroethyl), and

(III) an azetidiny group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom);

Ring D is a cyclobutane ring;

20 n is 1;

X is -O-; and

R^a and R^b are both hydrogen atoms.

[0110]

[Compound B-2]

25 Compound (I) wherein

Ring A is a 3- to 14-membered non-aromatic heterocycle

(preferably a 3- to 14-membered nitrogen-containing non-

aromatic heterocycle, more preferably a 3- to 8-membered

30 monocyclic nitrogen-containing non-aromatic heterocycle (e.g., piperidine, azetidine, pyrrolidine) or a 9- to 14-membered

fused polycyclic (preferably bi- or tri-cyclic) nitrogen-

containing non-aromatic heterocycle (e.g., 7-

azaspiro[3.5]nonane)) optionally further substituted by 1 to 3 substituents selected from

35 (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl)

optionally substituted by 1 to 3 substituents selected from

(i) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 substituents selected from

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

(II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl, trifluoromethyl, 2-fluoroethyl),

(III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

(IV) a 3- to 14-membered non-aromatic heterocyclic

group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., azetidiny))

optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(V) a cyano group,

(ii) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from

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

(II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),

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

(iv) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy) optionally substituted by 1 to 3 substituents selected from

(I) a halogen atom (e.g., a chlorine atom), and

(II) a C₁₋₆ alkyl group (e.g., methyl),

(b) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy) optionally substituted by 1 to 3 substituents selected from

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

(ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and

(iii) an optionally halogenated C₁₋₆ alkoxy group (e.g., trifluoromethoxy),

(c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from

- (i) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - (II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and
- (ii) a halogen atom (e.g., a fluorine atom),
- (d) a C₆₋₁₄ aryloxy group (e.g., phenoxy) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
- (e) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydrobenzofuryl)) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl);
- Ring D is a C₄₋₅ cycloalkane (preferably cyclobutane);
- n is 1 or 2;
- X is -O-, -CH₂- or -O-CH₂-; and
- R^a and R^b are both hydrogen atoms.

[0111]

25 [Compound C-2]

Compound (I) wherein

Ring A is

- (1) an azetidine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from
 - (i) a phenoxy group optionally substituted by 1 to 3 substituents selected from
 - (I) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom),

- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, ethyl, trifluoromethyl), and
- (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
- (ii) a phenyl group optionally substituted by 1 to 3
5 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),
- 10 (iii) a halogen atom (e.g., a fluorine atom), and
- (iv) a benzyloxy group optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a chlorine atom), and
- (II) a C₁₋₆ alkyl group (e.g., methyl),
- 15 (b) a benzyloxy group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl), and
- 20 (iii) an optionally halogenated C₁₋₆ alkoxy group (e.g., trifluoromethoxy), and
- (c) a C₂₋₆ alkenyl group (e.g., vinyl) optionally substituted by 1 to 3 substituents selected from
- 25 (i) a phenyl group optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (II) an optionally halogenated C₁₋₆ alkyl group (e.g., trifluoromethyl), and
- 30 (ii) a halogen atom (e.g., a fluorine atom),
- (2) a piperidine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl)
- 35 optionally substituted by 1 to 3 substituents selected from

- (i) a phenoxy group optionally substituted by 1 to 3 substituents selected from
- (I) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - 5 (II) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl, 2-fluoroethyl),
 - (III) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
 - (IV) an azetidiny group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - 10 (V) a cyano group,
- (ii) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
- (iii) a halogen atom (e.g., a fluorine atom),
- 15 (b) a benzyloxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
- (c) a dihydrobenzofuryl group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - 20 (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),
- (3) a 7-azaspiro[3.5]nonane ring optionally further substituted by 1 to 3 substituents selected from
- 25 (a) a phenoxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), or
- (4) a pyrrolidine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted
 - 30 by 1 to 3 substituents selected from a phenoxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and
 - (b) a benzyloxy group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom);
- 35 Ring D is a C₄₋₅ cycloalkane (preferably cyclobutane);

n is 1 or 2;

X is -O-, -CH₂- or -O-CH₂-; and

R^a and R^b are both hydrogen atoms.

[0112]

5 [Compound D-2]

Compound (I) wherein

Ring A is

(1) an azetidine ring optionally further substituted by 1 to 3 substituents selected from

10 (a) a benzyloxy group optionally substituted by 1 to 3 substituents selected from

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

15 (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl),

(2) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

(a) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from

20 (i) a phenoxy group optionally substituted by 1 to 3 substituents selected from

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

25 (II) an optionally halogenated C₁₋₆ alkyl group (e.g., 2-fluoroethyl), and

(III) an azetidinyll group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

30 (ii) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom), and

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

(b) a dihydrobenzofuryl group optionally substituted by 1 to 3 substituents selected from

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

35 (ii) an optionally halogenated C₁₋₆ alkyl group (e.g.,

methyl, trifluoromethyl), or

(3) a 7-azaspiro[3.5]nonane ring optionally further substituted by 1 to 3 substituents selected from

(a) a phenoxy group optionally substituted by 1 to 3

5 halogen atoms (e.g., a fluorine atom, a chlorine atom);

Ring D is a cyclobutane ring;

n is 1;

X is -O-; and

R^a and R^b are both hydrogen atoms.

10 [0113]

[Compound E-2]

Compound (I) wherein

Ring A is

(1) an azetidine ring further substituted by 1 to 3

15 substituents selected from

(a) a benzyloxy group substituted by 1 to 3 substituents selected from

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

20 (ii) an optionally halogenated C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl);

Ring D is a cyclobutane ring;

n is 1;

X is -O-; and

25 R^a and R^b are both hydrogen atoms.

[0114]

[Compound F]

(2s,4s)-2-((3-((2-fluoro-4-

(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-

30 azaspiro[3.4]octan-6-one, or a salt thereof.

[Compound G]

(2s,4s)-2-((3-((2-methyl-4-

(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-

azaspiro[3.4]octan-6-one, or a salt thereof.

35 [Compound H]

(2s,4s)-2-((3-((3-chloro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one, or a salt thereof.

[0115]

5 Specific examples of compound (I) include the compounds of Examples 1 to 130.

[0116]

When compound (I) is a salt, examples of the salt include metal salts, ammonium salts, salts with organic base, salts
10 with inorganic acid, salts with organic acid, and salts with basic or acidic amino acid. Preferable examples of the metal salt include alkali metal salts such as sodium salts, potassium salts and the like; alkali earth metal salts such as calcium salts, magnesium salts, barium salts and the like; and
15 aluminum salts. Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of
20 the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic
25 acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salts with basic amino acid include salts with arginine, lysine, ornithine and the like. Preferable examples of the
30 salt with acidic amino acid include salts with aspartic acid, glutamic acid and the like. Among them, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, examples of the salt include inorganic salts such as alkali metal salts (e.g., sodium salt,
35 potassium salt etc.), alkaline earth metal salts (e.g.,

calcium salt, magnesium salt etc.) and the like, ammonium salt etc., and when a compound has a basic functional group, examples of the salt include salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, and salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

10 When compound (I) contains isomers such as tautomers, optical isomers, stereoisomers, position isomers and rotational isomers, any of isomers or mixture are also encompassed in the compound of the present invention. Further, when compound (I) contains an optical isomer, the optical
15 isomer separated from the racemate is encompassed in compound (I).

Compound (I) can be obtained in the crystal form. Either single crystalline form or crystalline mixture can be encompassed in compound (I).

20 Compound (I) can be a pharmaceutically acceptable co-crystal or a co-crystal salt. The co-crystal or co-crystal salt as used herein means a crystalline material composed of two or more unique solids at room temperature, each of which has distinctive physical characteristics such as structure,
25 melting point, and heats of fusion, hygroscopicity, solubility, and stability. A co-crystal or a co-crystal salt can be produced according to co-crystallization method known per se.

Compound (I) may be a solvate (e.g., a hydrate) or a non-solvate and both are encompassed in compound (I).

30 Compounds labeled with or substituted by isotopes (e.g., ^2H , ^3H , ^{11}C , ^{14}C , ^{18}F , ^{35}S , ^{125}I , etc.) are also encompassed in compound (I). The compound labeled with or substituted by isotopes can be used as, for example, a tracer used for Positron Emission Tomography (PET) (PET tracer), and are

expected to be useful in the field of medical diagnosis and the like.

[0117]

The production method of the compound of the present invention is explained below.

[0118]

The raw material compound and reagent used and the compound obtained in each step in the following production method may be each in a form of a salt, and examples of such salt include those similar to the salts of the compound of the present invention and the like.

[0119]

When the compound obtained in each step is a free form, it can be converted to the objective salt according to a method known per se. When the compound obtained in each step is a salt, it can be converted to the objective free form or the other salt according to a method known per se.

[0120]

The compound obtained in each step can be used directly as the reaction mixture or as a crude product for the next reaction. Alternatively, the compound obtained in each step can be isolated and purified from a reaction mixture according to a method known per se, for example, a separation means such as concentration, crystallization, recrystallization, distillation, solvent extraction, fractional distillation, column chromatography and the like.

[0121]

When the raw material compound and reagent used in each step are commercially available, the commercially available product can also be used directly.

[0122]

In the reaction in each step, while the reaction time varies depending on the kind of the reagent and solvent to be used, it is generally 1 min - 48 hr, preferably 10 min - 8 hr, unless otherwise specified.

[0123]

In the reaction in each step, while the reaction temperature varies depending on the kind of the reagent and solvent to be used, it is generally -78°C - 300°C, preferably -
5 78°C - 150°C, unless otherwise specified.

[0124]

In the reaction in each step, while the pressure varies depending on the kind of the reagent and solvent to be used, it is generally 1 atm - 20 atm, preferably 1 atm - 3 atm,
10 unless otherwise specified.

[0125]

Microwave synthesizer such as Initiator manufactured by Biotage and the like may be used for the reaction in each step. While the reaction temperature varies depending on the kind of
15 the reagent and solvent to be used, it is generally room temperature - 300°C, preferably 50°C - 250°C, unless otherwise specified. While the reaction time varies depending on the kind of the reagent and solvent to be used, it is generally 1 min - 48 hr, preferably 1 min - 8 hr, unless otherwise
20 specified.

[0126]

In the reaction in each step, the reagent is used in an amount of 0.5 equivalents - 20 equivalents, preferably 0.8 equivalents - 5 equivalents, relative to the substrate, unless
25 otherwise specified. When the reagent is used as a catalyst, the reagent is used in an amount of 0.001 equivalent - 1 equivalent, preferably 0.01 equivalent - 0.2 equivalent, relative to the substrate. When the reagent is used as a reaction solvent, the reagent is used in a solvent amount.

30 [0127]

Unless otherwise specified, the reaction in each step is carried out without solvent, or by dissolving or suspending the raw material compound in a suitable solvent. Examples of the solvent include those described in Examples and the
35 following solvents.

- alcohols: methanol, ethanol, tert-butyl alcohol, 2-methoxyethanol and the like;
ethers: diethyl ether, diphenyl ether, tetrahydrofuran, 1,2-dimethoxyethane and the like;
5 aromatic hydrocarbons: chlorobenzene, toluene, xylene and the like;
saturated hydrocarbons: cyclohexane, hexane and the like;
amides: N,N-dimethylformamide, N-methylpyrrolidone and the like;
10 halogenated hydrocarbons: dichloromethane, carbon tetrachloride and the like;
nitriles: acetonitrile and the like;
sulfoxides: dimethyl sulfoxide and the like;
aromatic organic bases: pyridine and the like;
15 anhydrides: acetic anhydride and the like;
organic acids: formic acid, acetic acid, trifluoroacetic acid and the like;
inorganic acids: hydrochloric acid, sulfuric acid and the like;
20 esters: ethyl acetate and the like;
ketones: acetone, methyl ethyl ketone and the like;
water.

The above-mentioned solvent can be used in a mixture of two or more kinds thereof in an appropriate ratio.

25 [0128]

When a base is used for the reaction in each step, examples thereof include those described in Examples and the following bases.

- inorganic bases: sodium hydroxide, magnesium hydroxide, sodium
30 carbonate, calcium carbonate, sodium hydrogen carbonate and the like;
organic bases: triethylamine, diethylamine, pyridine, 4-dimethylaminopyridine, N,N-dimethylaniline, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-7-undecene,
35 imidazole, piperidine and the like;

metal alkoxides: sodium ethoxide, potassium tert-butoxide and the like;

alkali metal hydrides: sodium hydride and the like;

metal amides: sodium amide, lithium diisopropylamide, lithium

5 hexamethyldisilazide and the like;

organic lithiums: n-butyllithium and the like.

[0129]

When an acid or an acid catalyst is used for the reaction in each step, examples thereof include those described in

10 Examples and the following acids and acid catalysts.

inorganic acids: hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid and the like;

organic acids: acetic acid, trifluoroacetic acid, citric acid, p-toluenesulfonic acid, 10-camphorsulfonic acid and the like;

15 Lewis acid: boron trifluoride diethyl ether complex, zinc iodide, anhydrous aluminum chloride, anhydrous zinc chloride, anhydrous iron chloride and the like.

[0130]

Unless otherwise specified, the reaction in each step is carried out according to a method known per se, for example, the method described in Jikken Kagaku Kouza, 5th Edition, vol.13-19 (the Chemical Society of Japan ed.); Shin Jikken Kagaku Kouza, vol.14-15 (the Chemical Society of Japan ed.); Fine Organic Chemistry, Revised 2nd Edition (L. F. Tietze, Th.

25 Eicher, Nankodo); Organic Name Reactions, the Reaction Mechanism and Essence, Revised Edition (Hideo Togo, Kodansha); ORGANIC SYNTHESSES Collective Volume I-VII (John Wiley & Sons Inc.); Modern Organic Synthesis in the Laboratory A Collection of Standard Experimental Procedures (Jie Jack Li, OXFORD UNIVERSITY); Comprehensive Heterocyclic Chemistry III, Vol.1 - Vol.14 (Elsevier Japan); Strategic Applications of Named Reactions in Organic Synthesis (translated by Kiyoshi Tomioka, Kagakudojin); Comprehensive Organic Transformations (VCH Publishers Inc.), 1989, or the like, or the method described
35 in Examples.

[0131]

In each step, the protection or deprotection reaction of an functional group is carried out according to a method known per se, for example, the method described in "Protective
5 Groups in Organic Synthesis, 4th Ed", Wiley-Interscience, Inc., 2007 (Theodora W. Greene, Peter G. M. Wuts); "Protecting Groups 3rd Ed." Thieme, 2004 (P.J. Kocienski), or the like, or the method described in Examples.

Examples of the protecting group for a hydroxy group of
10 an alcohol and the like and a phenolic hydroxy group include ether-type protecting groups such as methoxymethyl ether, benzyl ether, tert-butyldimethylsilyl ether, tetrahydropyranyl ether and the like; carboxylate ester-type protecting groups such as acetate ester and the like; sulfonate ester-type
15 protecting groups such as methanesulfonate ester and the like; carbonate ester-type protecting groups such as tert-butylcarbonate and the like, and the like.

Examples of the protecting group for a carbonyl group of an aldehyde include acetal-type protecting groups such as
20 dimethylacetal and the like; cyclic acetal-type protecting groups such as 1,3-dioxane and the like, and the like.

Examples of the protecting group for a carbonyl group of a ketone include ketal-type protecting groups such as dimethylketal and the like; cyclic ketal-type protecting
25 groups such as 1,3-dioxane and the like; oxime-type protecting groups such as O-methyloxime and the like; hydrazone-type protecting groups such as N,N-dimethylhydrazone and the like, and the like.

Examples of the protecting group for a carboxyl group
30 include ester-type protecting groups such as methyl ester and the like; amide-type protecting groups such as N,N-dimethylamide and the like, and the like.

Examples of the protecting group for a thiol include ether-type protecting groups such as benzyl thioether and the

like; ester-type protecting groups such as thioacetate ester, thiocarbonate, thiocarbamate and the like, and the like.

Examples of the protecting group for an amino group and an aromatic heterocycle such as imidazole, pyrrole, indole and
5 the like include carbamate-type protecting groups such as benzyl carbamate and the like; amide-type protecting groups such as acetamide and the like; alkyl amine-type protecting groups such as N-triphenylmethylamine and the like; sulfonamide-type protecting groups such as methanesulfonamide
10 and the like, and the like.

The protecting groups can be removed according to a method known per se, for example, by employing a method using acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride,
15 palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide) and the like, a reduction method, and the like.

[0132]

When reduction reaction is carried out in each step,
20 examples of the reducing agent to be used include metal hydrides such as lithium aluminum hydride, sodium triacetoxyborohydride, sodium cyanoborohydride, diisobutylaluminum hydride (DIBAL-H), sodium borohydride, tetramethylammonium triacetoxyborohydride and the like;
25 boranes such as borane tetrahydrofuran complex and the like; Raney nickel; Raney cobalt; hydrogen; formic acid; triethylsilane and the like. When carbon-carbon double bond or triple bond is reduced, a method using a catalyst such as palladium-carbon, Lindlar's catalyst and the like may be
30 employed.

[0133]

When oxidation reaction is carried out in each step, examples of the oxidizing agent to be used include peroxides such as m-chloroperbenzoic acid (mCPBA), hydrogen peroxide,
35 tert-butylhydroperoxide and the like; perchlorates such as

tetrabutylammonium perchlorate and the like; chlorates such as sodium chlorate and the like; chlorites such as sodium chlorite and the like; periodates such as sodium periodate and the like; hypervalent iodine reagents such as iodosylbenzene and the like; reagents containing manganese such as manganese dioxide, potassium permanganate and the like; leads such as lead tetraacetate and the like; reagents containing chromium such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), Jones reagent and the like; halogen compounds such as N-bromosuccinimide (NBS) and the like; oxygen; ozone; sulfur trioxide-pyridine complex; osmium tetroxide; selenium dioxide; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the like.

[0134]

When radical cyclization reaction is carried out in each step, examples of the radical initiator to be used include azo compounds such as azobisisobutyronitrile (AIBN) and the like; water-soluble radical initiators such as 4-4'-azobis-4-cyanopentanoic acid (ACPA) and the like; triethylboron in the presence of air or oxygen; benzoyl peroxide and the like.

Examples of the radical reagent to be used include tributylstannane, tris(trimethylsilyl)silane, 1,1,2,2-tetraphenyldisilane, diphenylsilane, samarium iodide and the like.

[0135]

When Wittig reaction is carried out in each step, examples of the Wittig reagent to be used include alkylidene phosphoranes and the like. The alkylidene phosphoranes can be prepared according to a method known per se, for example, by reacting a phosphonium salt with a strong base.

[0136]

When Horner-Emmons reaction is carried out in each step, examples of the reagent to be used include phosphonoacetates such as methyl dimethylphosphonoacetate, ethyl diethylphosphonoacetate and the like; and bases such as alkali metal hydrides, organic lithiums and the like.

[0137]

When Friedel-Crafts reaction is carried out in each step, a combination of a Lewis acid and an acid chloride or a combination of a Lewis acid and an alkylating agent (e.g., an alkyl halide, an alcohol, an olefin etc.) is used as a reagent. Alternatively, an organic acid or an inorganic acid can also be used instead of a Lewis acid, and an anhydride such as acetic anhydride and the like can also be used instead of an acid chloride.

10 [0138]

When aromatic nucleophilic substitution reaction is carried out in each step, a nucleophile (e.g., an amine, imidazole etc.) and a base (e.g., an inorganic base, an organic base etc.) are used as a reagent.

15 [0139]

When nucleophilic addition reaction by a carbo anion, nucleophilic 1,4-addition reaction (Michael addition reaction) by a carbo anion or nucleophilic substitution reaction by a carbo anion is carried out in each step, and examples of the base to be used for generation of the carbo anion include organic lithiums, metal alkoxides, inorganic bases, organic bases and the like.

[0140]

When Grignard reagent is carried out in each step, examples of the Grignard reagent to be used include arylmagnesium halides such as phenylmagnesium bromide and the like; and alkylmagnesium halides such as methylmagnesium bromide and the like. The Grignard reagent can be prepared according to a method known per se, for example, by reacting an alkyl halide or an aryl halide with a metal magnesium in an ether or tetrahydrofuran as a solvent.

[0141]

When Knoevenagel condensation reaction is carried out in each step, a compound having an activated methylene group with two electron withdrawing groups (e.g., malonic acid, diethyl

malonate, malononitrile etc.) and a base (e.g., an organic base, a metal alkoxide, an inorganic base) are used as a reagent.

[0142]

5 When Vilsmeier-Haack reaction is carried out in each step, phosphoryl chloride and an amide derivative (e.g., N,N-dimethylformamide etc.) are used as a reagent.

[0143]

 When azidation reaction of an alcohol, an alkyl halide or
10 a sulfonate is carried out in each step, examples of the azidating agent to be used include diphenylphosphorylazide (DPPA), trimethylsilylazide, sodium azide and the like. For example, for the azidation reaction of an alcohol, a method using diphenylphosphorylazide and 1,8-
15 diazabicyclo[5.4.0]undec-7-ene (DBU), a method using trimethylsilylazide and a Lewis acid, and the like are employed.

[0144]

 When reductive amination reaction is carried out in each
20 step, examples of the reducing agent to be used include sodium triacetoxyborohydride, sodium cyanoborohydride, hydrogen, formic acid and the like. When the substrate is an amine compound, examples of the carbonyl compound to be used include paraformaldehyde, aldehydes such as acetaldehyde and the like,
25 and ketones such as cyclohexanone and the like. When the substrate is a carbonyl compound, examples of the amine to be used include ammonia, primary amines such as methylamine and the like; secondary amines such as dimethylamine and the like, and the like.

30 [0145]

 When Mitsunobu reaction is carried out in each step, an azodicarboxylate (e.g., diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) etc.) and a phosphine such as triphenylphosphine, tri-n-butylphosphine and the like are
35 used as a reagent.

[0146]

When esterification reaction, amidation reaction or urea formation reaction is carried out in each step, examples of the reagent to be used include acyl halides such as acid chlorides, acid bromides and the like; activated carboxylic acids such as anhydrides, activated esters, sulfates and the like. Examples of the activating agent of the carboxylic acid include carbodiimide condensing agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and the like; triazine condensing agents such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n-hydrate (DMT-MM) and the like; carbonate condensing agents such as 1,1-carbonyldiimidazole (CDI) and the like; diphenylphosphoryl azide (DPPA); benzotriazol-1-yloxy-trisdimethylaminophosphonium salt (BOP reagent); 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent); thionyl chloride; lower alkyl haloformates such as ethyl chloroformate and the like; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); sulfuric acid; combinations thereof and the like. When carbodiimide condensing agent is used, an additive such as 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP) and the like may be added to the reaction system.

[0147]

When coupling reaction is carried out in each step, examples of the metal catalyst to be used include palladium compounds such as palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), dichlorobis(triethylphosphine)palladium(II), tris(dibenzylideneacetone)dipalladium(0), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride, palladium(II) acetate and the like; nickel compounds such as tetrakis(triphenylphosphine)nickel(0) and the like; rhodium

compounds such as tris(triphenylphosphine)rhodium(III) chloride and the like; cobalt compounds; copper compounds such as copper oxide, copper(I) iodide and the like; platinum compounds and the like. In addition, a base can be added to the reaction system, and examples thereof include inorganic bases, metal alkoxides and the like.

[0148]

When thiocarbonylation reaction is carried out in each step, phosphorus pentasulfide is typically used as the thiocarbonylating agent. Alternatively, a reagent having a 1,3,2,4-dithiadiphosphetane-2,4-disulfide structure (e.g., 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson reagent) etc.) can also be used instead of phosphorus pentasulfide.

[0149]

When Wohl-Ziegler reaction is carried out in each step, examples of the halogenating agent to be used include N-iodosuccinimide, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), bromine, sulfuryl chloride and the like. In addition, the reaction can be accelerated by subjecting a radical initiator such as heat, light, benzoyl peroxide, azobisisobutyronitrile and the like to the reaction system reaction.

[0150]

When halogenation reaction of a hydroxy group is carried out in each step, examples of the halogenating agent to be used include hydrohalic acids and acid halides of inorganic acids, specifically, hydrochloric acid, thionyl chloride, phosphorus oxychloride and the like for chlorination, 48% hydrobromic acid and the like for bromination. In addition, a method of producing an alkyl halide by reacting an alcohol with triphenylphosphine and carbon tetrachloride or carbon tetrabromide or the like can be employed. Alternatively, a method of producing an alkyl halide via two step comprising converting an alcohol to the corresponding sulfonate, and then

reacting the sulfonate with lithium bromide, lithium chloride or sodium iodide can also be employed.

[0151]

When Arbuzov reaction is carried out in each step,
5 examples of the reagent to be used include alkyl halides such as ethyl bromoacetate and the like; and phosphites such as triethyl phosphite, tri(isopropyl) phosphite and the like.

[0152]

When sulfonate esterification reaction is carried out in
10 each step, examples of the sulfonating agent to be used include methanesulfonyl chloride, p-toluenesulfonyl chloride, methanesulfonic anhydride, p-toluenesulfonic anhydride and the like.

[0153]

15 When hydrolysis reaction is carried out in each step, an acid or a base is used as a reagent. For acid hydrolysis reaction of tert-butyl ester, formic acid, triethylsilane and the like may be added to reductively-trap tert-butyl cation which is by-produced.

20 [0154]

When dehydration reaction is carried out in each step, examples of the dehydrating agent to be used include sulfuric acid, diphosphorus pentaoxide, phosphorus oxychloride, N,N'-dicyclohexylcarbodiimide, alumina, polyphosphoric acid and the
25 like.

[0155]

When alkylation reaction is carried out in each step, examples of the base to be used include potassium carbonate, tripotassium phosphate, triethylamine, N,N-
30 diisopropylethylamine, pyridine, sodium ethoxide, potassium tert-butoxide, sodium hydride, lithiumhexamethyldisilazide, sodium hexamethyldisilazide, n-butyllithium and the like.

[0156]

When deoxofluorination reaction is carried out in each
35 step, examples of the fluorinating agent to be used include

bis(2-methoxyethyl)aminosulfur trifluoride, diethylaminosulfur trifluoride, 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride, N,N-diethyl-S,S-difluorosulfiliminium tetrafluoroborate, difluoro-4-morpholinylsulfonium tetrafluoroborate and the like.

5 [0157]

Compound (I), naming structures shown by Compounds (7), (12), (18), (23), (28a) or (28b) as Ring A, can be produced according Production Methods A to E explained below.

Each symbol in the formulas of the schemes is as defined
10 above, unless otherwise specified. In the formulas, m and k are each independently 0 or 1. R⁴ to R⁸ are each independently a hydrogen atom or an optionally substituted C₁₋₆ alkyl group (e.g., methyl, etc.). R⁹ and R¹⁰ are each an optionally substituted C₁₋₆ alkyl group (e.g., methyl, etc.). Rings E, F,
15 G, H, J, L, W, Y, Z₁ and Z₂ are each an optionally further substituted ring. P¹ to P⁵ are each a "protecting group for an amino group". Examples of the "protecting group for an amino group" include tert-butoxycarbonyl group and the like, in addition to those exemplified as the above-mentioned protecting
20 group for an amino group. LG¹ to LG⁵ are each a "leaving group". Examples of the "leaving group" include a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom etc.), an optionally halogenated C₁₋₆ alkylsulfonyloxy group (e.g., methanesulfonyloxy,
25 ethanesulfonyloxy, trifluoromethanesulfonyloxy etc.), an optionally substituted C₆₋₁₄ arylsulfonyloxy group [e.g., a C₆₋₁₄ arylsulfonyloxy group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl, etc.), a C₁₋₆ alkoxy group (e.g., methoxy, etc.) and a nitro group, and the
30 like, and specific examples thereof include benzenesulfonyloxy, m-nitrobenzenesulfonyloxy, p-toluenesulfonyloxy, naphthylsulfonyloxy and the like] and the like.

R⁴ - R⁸ and Rings E, G, H, J, L, W, Y, Z₁ and Z₂ are partial structures of Ring A, and therefore the definitions of
35 each partial structure do not go beyond the definition of ring

A as a whole. In other words, compounds (7), (12), (18), (23), (28a) and (28b) are included in the scope of Ring A.

[0158]

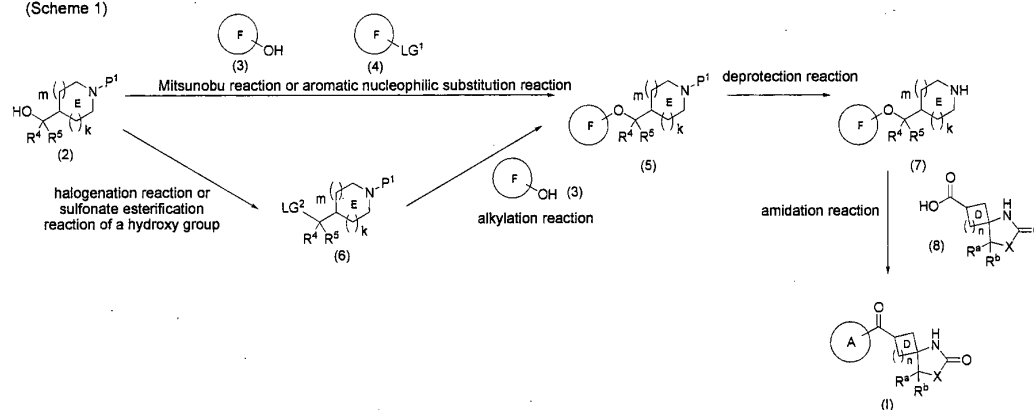
[Production Method A]

5 [0159]

Compound (I) can be produced from compound (2) according to the following method.

[0160]

(Scheme 1)



10 [0161]

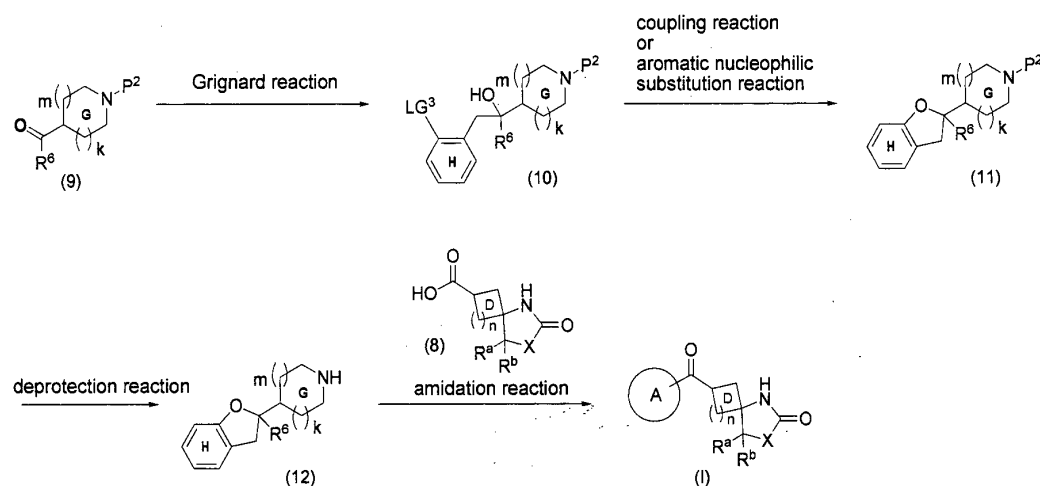
[Production Method B]

[0162]

Compound (I) can also be produced from compound (9) according to the following method.

15 [0163]

(Scheme 2)



[0164]

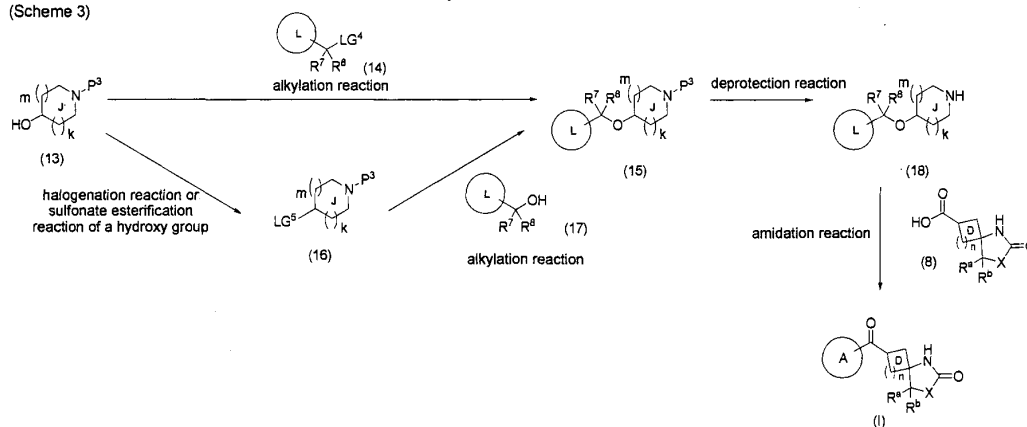
[Production Method C]

[0165]

Compound (I) can also be produced from compound (13) according to the following method.

5 [0166]

(Scheme 3)



[0167]

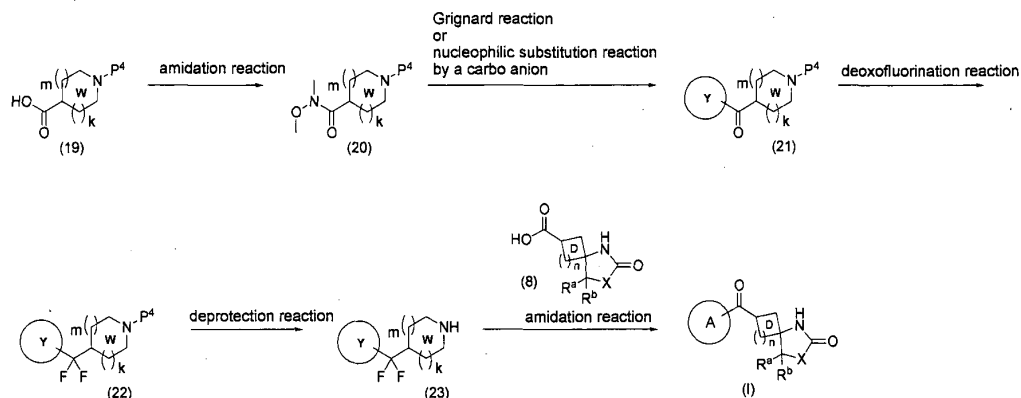
[Production Method D]

[0168]

Compound (I) can also be produced from compound (19) according to the following method.

[0169]

(Scheme 4)



[0170]

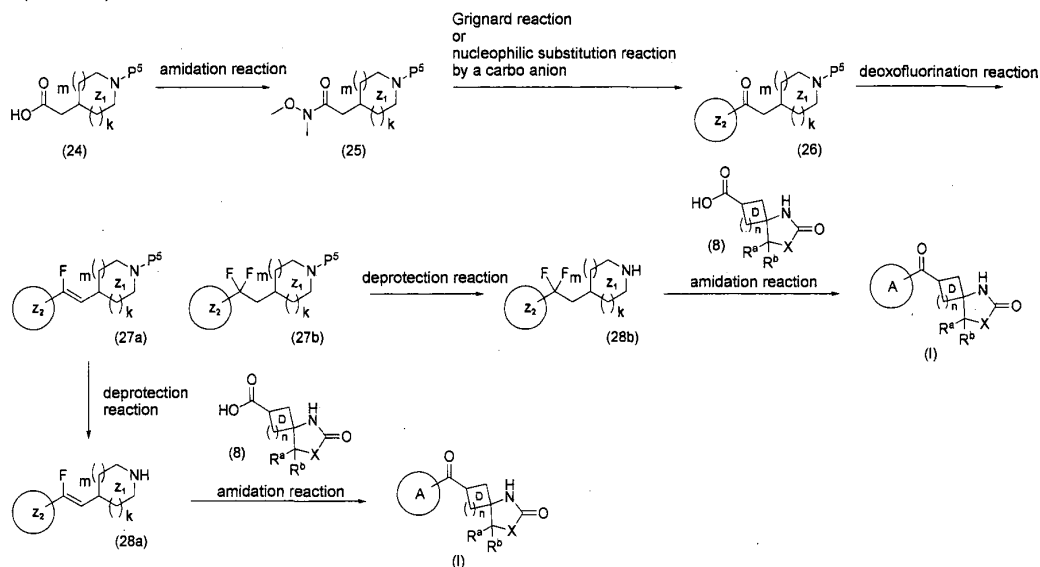
15 [Production Method E]

[0171]

Compound (I) can also be produced from compound (24) according to the following method.

[0172]

(Scheme 5)

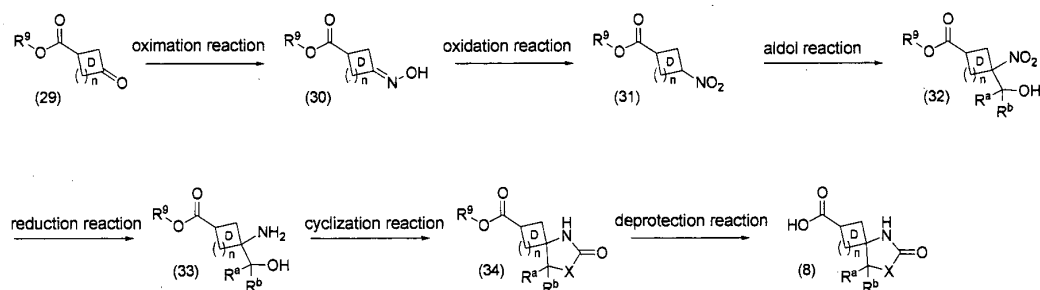


[0173]

Carboxylic acid (8) used in each production method can be produced from compound (29) according to the following method.

5 [0174]

(Scheme 6)



[0175]

Compound (30) can be produced by subjecting compound (29) to an oximation reaction. Examples of the oximating agent include hydroxylamine, hydroxylamine hydrochloride and the like. In addition, a base may be added to the reaction system, and examples of the base include sodium acetate and the like. Compound (32) can be produced by subjecting compound (31) to an aldol reaction in the presence of a base. Examples of the electrophile include formalin, acetaldehyde and the like, and examples of the base include triethylamine and the like.

Compound (34) can be produced by subjecting compound (33) to a cyclization reaction in the presence of a base. Examples of the cyclizing agent include triphosgene, chloroacetyl chloride and the like, and examples of the base include

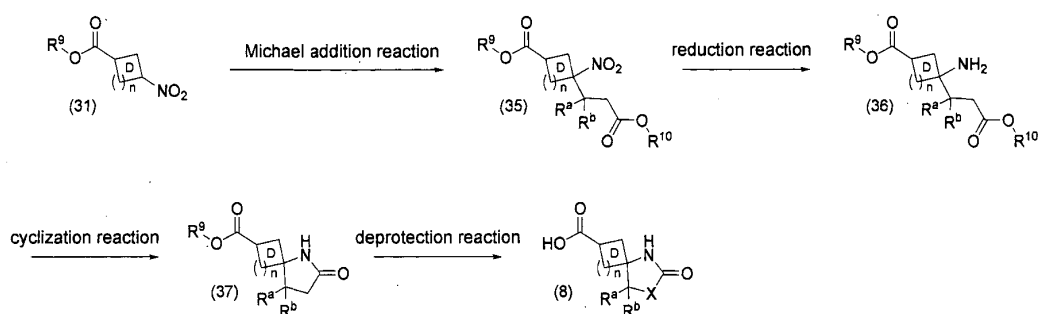
5 triethylamine and the like.

[0176]

Carboxylic acid (8) used in each production method can also be produced from compound (31) according to the following method.

10 [0177]

(Scheme 7)



[0178]

Compound (37) can be produced by subjecting compound (35) to a reduction reaction, followed by a cyclization reaction.

15 Examples of the reducing agent include a combination of sodium borohydride and nickel(II) chloride hexahydrate; Raney nickel under hydrogen atmosphere; and the like. The cyclization reaction proceeds in the presence of a base. Examples of the base include potassium carbonate and the like.

20 [0179]

The starting compound and/or production intermediate for compound (I) may form a salt. While the salt is not particularly limited as long as the reaction can be performed, examples thereof include those similar to the salts optionally

25 formed by compound (I) and the like, and the like.

As for the configurational isomers (E, Z forms) of compound (I), they can be isolated and purified when

isomerization occurs, for example, according to a conventional separation means such as extraction, recrystallization, distillation, chromatography and the like to obtain a pure compound. In addition, the corresponding pure isomer can also
5 be obtained by isomerizing a double bond using heating, an acid catalyst, a transition metal complex, a metal catalyst, a radical catalyst, light irradiation, a strong base catalyst and the like, according to the method described in Shin Jikken Kagaku Kouza 14 (The Chemical Society of Japan ed.), pages 251
10 to 253, 4th Edition Jikken Kagaku Kouza 19 (The Chemical Society of Japan ed.), pages 273 to 274 or a method analogous thereto.

[0180]

Compound (I) contains a stereoisomer depending on the
15 kind of a substituent, and each stereoisomer and a mixture thereof are encompassed in the present invention.

Compound (I) may be a hydrate or a non-hydrate.

When desired, compound (I) can be synthesized by performing deprotection reaction, acylation reaction,
20 alkylation reaction, hydrogenation reaction, oxidation reaction, reduction reaction, reaction of carbon chain extension, halogenation reaction, substituent exchange reaction, coupling reaction, nucleophilic addition reaction by a carbo anion, Grignard reagent and deoxofluorination reaction singly or two
25 or more thereof in combination.

When the objective product is obtained as a free form by the above-mentioned reaction, it can be converted to a salt according to a conventional method, or when the objective product is obtained as a salt, it can be converted to a free
30 form or other salt according to a conventional method. The thus-obtained compound (I) can also be isolated and purified from a reaction mixture according to a known method such as phase transfer, concentration, solvent extraction, distillation, crystallization, recrystallization, chromatography and the like.

35 When compound (I) contains a configurational isomer, a

diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification methods, if desired. In addition, when compound (I) is racemic, d-form and l-form can be isolated according to a conventional
5 optical resolution.

[0181]

The thus-obtained compound (I), other reaction intermediate therefor and starting compounds thereof can be isolated and purified from a reaction mixture according to a
10 method known per se, for example, extraction, concentration, neutralization, filtration, distillation, recrystallization, column chromatography, thin layer chromatography, preparative high performance liquid chromatography (preparative HPLC), moderate-pressure preparative liquid chromatography (moderate-
15 pressure preparative LC) and the like.

[0182]

A salt of compound (I) can be produced according to a method known per se. For example, when compound (I) is a basic compound, it can be produced by adding an inorganic acid or
20 organic acid, or when compound (I) is an acidic compound, by adding an organic base or inorganic base.

When compound (I) contains an optical isomer, each optical isomer and a mixture thereof are encompassed in the scope of the present invention, and these isomers can be
25 subjected to optical resolution or can be produced respectively, according to a method known per se, if desired.

When compound (I) contains a configurational isomer, a diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification
30 methods, if desired. In addition, when compound (I) is racemic, S-form and R-form can be isolated according to a conventional optical resolution.

When compound (I) contains a stereoisomer, each isomer and a mixture thereof are encompassed in the present invention.
35 r and s mean steric configuration based on a

pseudoasymmetric center, which is defined by IUPAC nomenclature, not mean R and S steric configuration based on an asymmetric center.

[0183]

- 5 The compound of the present invention is expected to be useful for mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.) as an agent for the prophylaxis or treatment of diseases, for example,
- 10 (1) psychiatric diseases [e.g., depression, major depression, bipolar depression, dysthymic disorder, emotional disorder (seasonal affective disorder and the like), recurrent depression, postpartum depression, stress disorder, depression symptom, mania, anxiety, generalized anxiety disorder, anxiety syndrome, panic disorder, phobia, social phobia, social anxiety
- 15 disorder, obsessive disorder, post-traumatic stress syndrome, post-traumatic stress disorder, Tourette syndrome, autism, fragile X syndrome, Rett syndrome, adjustment disorder, bipolar disorder, neurosis, schizophrenia (e.g., positive symptom, negative symptom, cognitive impairment), chronic fatigue
- 20 syndrome, anxiety neurosis, compulsive neurosis, panic disorder, epilepsy, anxiety disorder, anxiety, anxious mental state, emotional abnormality, cyclothymia, nervous erethism, faint, addiction, low sex drive, attention deficit hyperactivity disorder (ADHD), psychotic major depression, refractory major
- 25 depression, treatment-resistant depression, depressive disorder, catalepsy, hebephrenic schizophrenia, paranoid schizophrenia],
- (2) neurodegenerative diseases [e.g., Alzheimer's disease, Alzheimer-type senile dementia, Parkinson's disease, Huntington's disease, multi-infarct dementia, frontotemporal
- 30 dementia, dementia Parkinson's type, progressive supranuclear palsy, Pick's syndrome, Niemann-Pick syndrome, corticobasal degeneration, Down's disease, vascular dementia, postencephalitic parkinsonism, Lewy body dementia, HIV dementia, amyotrophic lateral sclerosis (ALS), motor neurogenesis disease
- 35 (MND), Creutzfeldt-Jakob disease or prion disease, cerebral

- palsy, progressive supranuclear palsy, traumatic brain injury, glaucoma, multiple sclerosis, neuromyelitis optica (NMO), postoperative cognitive dysfunction (POCD), postoperative delirium (POD), delirium],
- 5 (3) age-related cognition memory disorders [e.g., age-related memory disorders, senile dementia],
- (4) sleep disorders [e.g., intrinsic sleep disorders (e.g., psychophysiological insomnia and the like), extrinsic sleep disorder, circadian rhythm disorders (e.g., time zone change
- 10 syndrome (jet lag), shift work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome, advanced sleep phase syndrome, non-24-hour sleep-wake and the like), parasomnia, sleep disorders associated with internal medical or psychiatric disorder (e.g., chronic obstructive pulmonary
- 15 diseases, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, schizophrenia, depression, anxiety neurosis), stress insomnia, insomnia, insomniac neurosis, sleep apnea syndrome],
- (5) respiratory depression caused by anesthetics, traumatic
- 20 disease, or neurodegenerative disease and the like,
- (6) traumatic brain injury, cerebral apoplexy, neurotic anorexia, eating disorder, anorexia nervosa, hyperorexia, other eating disorder, alcohol dependence, alcohol abuse, alcoholic amnesia, alcohol paranoia, alcohol preference, alcohol
- 25 withdrawal, alcoholic insanity, alcohol poisoning, alcoholic jealousy, alcoholic mania, alcohol-dependent psychiatric disorder, alcoholic insanity, pharmacophilia, pharmacophobia, pharmacomania, drug withdrawal, stress headache, catatonic headache, diabetic neuropathy, obesity, diabetes, muscular
- 30 spasm, Meniere's disease, autonomic ataxia, alopecia, glaucoma, hypertension, cardiac disease, tachycardia, congestive cardiac failure, hyperventilation, bronchial asthma, apnea, sudden infant death syndrome, inflammatory disease, allergic disease, impotence, climacteric disorder, infertility, neoplasms (e.g.,
- 35 cancer, liver neoplasms, colonic neoplasms, breast neoplasms,

prostatic neoplasms, neuroblastoma, bone neoplasms, mouth
neoplasms, mastocytoma, cholangiocarcinoma, Lewis lung
carcinoma etc.), immunodeficiency syndrome caused by HIV
infection, immunodeficiency syndrome caused by stress,
5 cerebrospinal meningitis, acromegaly, incontinence, metabolic
syndrome, osteoporosis, peptic ulcer, irritable bowel syndrome,
inflammatory bowel disease, ulcerative colitis, Crohn's disease,
stress gastrointestinal disorder, stress vomiting, diarrhea,
constipation, postoperative ileus, rheumatoid arthritis,
10 osteoarthritis, functional dyspepsia, hyperalgesia, insulin
resistance, dementia pugilistica, nausea, vomiting, neoplasm
metastasis, brain injuries, seizure, body weight changes,
weight gain, weight loss, colitis, alcoholism, hypothermia,
fatty liver, atherosclerosis, infection, muscle spasticity,
15 hypertension, stroke, malignant migrating partial seizures of
infancy, diabetes mellitus, type 2 diabetes mellitus,
dyslipidaemia, visceral obesity, ocular hypotension, anorexia,
fibrosis, myocardial infarction, cachexia, induced psychotic
disorder, ataxia, AIDS wasting syndrome, cirrhotic
20 cardiomyopathy, uremic pruritus, neurobehavioral manifestations,
Tubulointerstitial nephritis and uveitis syndrome, interstitial
cystitis, retinitis pigmentosa, autoimmune diseases, coronary
artery disease, aspirin-induced asthma, platelet storage pool
deficiency, diabetic embryopathy, Arthus type urticaria, asthma,
25 toxic oil syndrome, otitis and the like,

(7) pain (e.g., inflammatory pain, cancerous pain, neuropathic
pain, acute pain, pain associated with peripheral neuropathy,
central pain, fibromyalgia, vasoocclusive painful crises in
sickle cell disease, multiple sclerosis-mediated spasticity or
30 pain, functional chest pain, complex regional pain syndrome
etc.),

(8) migraine,

(9) cerebral edema,

(10) cerebral ischemia, ischemia, and the like.

35 [0184]

Since the compound of the present invention has a superior MAGL inhibitory action, a superior prophylactic or therapeutic effect for the above-mentioned diseases may be expected.

5 [0185]

Since the compound of the present invention has a superior MAGL inhibitory action, a superior prophylactic or therapeutic effect for neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, traumatic brain injury, glaucoma, multiple sclerosis etc.), anxiety disorder, pains (e.g., inflammatory pain, cancerous pain, neurogenic pain etc.), epilepsy, depression and the like, particularly Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, anxiety disorder, pain, epilepsy or depression may be expected.

[0186]

Compound (I) can be used as a prodrug.

[0187]

20 A prodrug of compound (I) means a compound which is converted to compound (I) with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to compound (I) with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to compound (I) by hydrolysis etc. due to gastric acid, etc.

[0188]

A prodrug for compound (I) may be a compound obtained by subjecting an amino group in compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by 30 subjecting an amino group in compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation, etc.); a compound obtained by subjecting a hydroxy

group in compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in compound (I) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting a carboxyl group in compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation, etc.) and the like. Any of these compounds can be produced from compound (I) by a method known per se. The prodrug of compound (I) may be a compound that converts to compound (I) under physiological conditions as described in Development of Pharmaceutical Products, vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

[0189]

The compound of the present invention is superior in vivo kinetics (e.g., plasma drug half-life, intracerebral transferability, metabolic stability), shows low toxicity (e.g., more superior as a medicament in terms of acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, drug interaction, carcinogenicity etc.). The compound of the present invention is directly used as a medicament or a pharmaceutical composition mixed with a pharmaceutically acceptable carrier or the like to be orally or parenterally administered to mammals (e.g., humans, monkeys, cows, horses, pigs, mice, rats, hamsters, rabbits, cats, dogs, sheep and goats) in safety. Examples of the "parenteral" include intravenous, intramuscular, subcutaneous, intra-organ, intranasal, intradermal, instillation, intracerebral,

intrarectal, intravaginal, intraperitoneal and intratumor administrations, administration to the vicinity of tumor etc. and direct administration to the lesion.

[0190]

5 While the dose of the compound of the present invention varies depending on the administration route, symptom and the like, when, for example, the compound is orally administered to a patient with Alzheimer's disease (adult, body weight 40 - 80 kg, for example, 60 kg), it is, for example, 0.001 - 1000 mg/kg
10 body weight/day, preferably 0.01 - 100 mg/kg body weight/day, more preferably 0.1 - 10 mg/kg body weight/day. This amount can be administered in 1 to 3 portions per day.

[0191]

A medicament containing the compound of the present
15 invention can be used alone or as a pharmaceutical composition containing the compound of the present invention and a pharmaceutically acceptable carrier according to a method known per se as a production method of a pharmaceutical preparation (e.g., the method described in the Japanese Pharmacopoeia etc.).
20 A medicament containing the compound of the present invention can be safely administered in the form of, for example, tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating tablet, buccal and the like), pill, powder, granule, capsule (including soft capsule,
25 microcapsule), troche, syrup, liquid, emulsion, suspension, release control preparation (e.g., immediate-release preparation, sustained-release preparation, sustained-release microcapsule), aerosol, film (e.g., orally disintegrating film, oral mucosa-adhesive film), injection (e.g., subcutaneous
30 injection, intravenous injection, intramuscular injection, intraperitoneal injection), drip infusion, transdermal absorption type preparation, ointment, lotion, adhesive preparation, suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparation, pulmonary preparation
35 (inhalant), eye drop and the like, orally or parenterally (e.g.,

intravenous, intramuscular, subcutaneous, intraorgan,
intranasal, intradermal, instillation, intracerebral,
intrarectal, intravaginal, intraperitoneal administrations, and
administration to the lesion).

5 [0192]

As the aforementioned "pharmaceutically acceptable
carrier", various organic or inorganic carriers conventionally
used as preparation materials (starting materials) can be used.
For example, excipient, lubricant, binder, disintegrant and the
10 like are used for solid preparations, and solvent, solubilizing
agent, suspending agent, isotonicity agent, buffer, soothing
agent and the like are used for liquid preparations. Where
necessary, preparation additives such as preservative,
antioxidant, colorant, sweetening agent and the like can also
15 be used.

Examples of the excipient include lactose, sucrose, D-
mannitol, starch, corn starch, crystalline cellulose, light
anhydrous silicic acid and the like.

Examples of the lubricant include magnesium stearate,
20 calcium stearate, talc, colloidal silica and the like.

Examples of the binder include crystalline cellulose,
white sugar, D-mannitol, dextrin, hydroxypropylcellulose,
hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch,
sucrose, gelatin, methylcellulose, carboxymethylcellulose
25 sodium and the like.

Examples of the disintegrant include starch,
carboxymethylcellulose, carboxymethylcellulose calcium, sodium
carboxymethyl starch, L-hydroxypropylcellulose and the like.

Examples of the solvent include water for injection,
30 alcohol, propylene glycol, Macrogol, sesame oil, corn oil,
olive oil and the like.

Examples of the solubilizing agent include polyethylene
glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol,
trisaminomethane, cholesterol, triethanolamine, sodium
35 carbonate, sodium citrate and the like. Examples of the

suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; and the like.

Examples of the isotonicity agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like.

Examples of the buffer include buffer solutions such as phosphates, acetates, carbonates, citrates and the like.

Examples of the soothing agent include benzyl alcohol and the like.

Examples of the preservative include p-oxybenzoates, chlorobutanol, benzyl alcohol, phenylethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Examples of the antioxidant include sulfite, ascorbic acid, α -tocopherol and the like.

[0193]

While the pharmaceutical composition varies according to the dosage form, administration method, carrier and the like, it can be produced according to a conventional method by adding the compound of the present invention in a proportion of generally 0.01 - 100% (w/w), preferably 0.1 - 95% (w/w), of the total amount of the preparation.

[0194]

The compound of the present invention can be used in combination with other active ingredients (hereinafter to be abbreviated as concomitant drug).

[0195]

Examples of the concomitant drug include the following. benzodiazepine (chlordiazepoxide, diazepam, potassium clorazepate, lorazepam, clonazepam, alprazolam etc.), L-type calcium channel inhibitor (pregabalin etc.), tricyclic or

tetracyclic antidepressant (imipramine hydrochloride, amitriptyline hydrochloride, desipramine hydrochloride, clomipramine hydrochloride etc.), selective serotonin reuptake inhibitor (fluvoxamine maleate, fluoxetine hydrochloride, 5 citalopram hydrobromide, sertraline hydrochloride, paroxetine hydrochloride, escitalopram oxalate etc.), serotonin-noradrenaline reuptake inhibitor (venlafaxine hydrochloride, duloxetine hydrochloride, desvenlafaxine hydrochloride etc.), noradrenaline reuptake inhibitor (reboxetine mesylate etc.), 10 noradrenaline-dopamine reuptake inhibitor (bupropion hydrochloride etc.), mirtazapine, trazodone hydrochloride, nefazodone hydrochloride, bupropion hydrochloride, setiptiline maleate, 5-HT_{1A} agonist (buspirone hydrochloride, tandospirone citrate, osetozotan hydrochloride etc.), 5-HT₃ antagonist 15 (Cyamemazine etc.), heart non-selective β inhibitor (propranolol hydrochloride, oxprenolol hydrochloride etc.), histamine H₁ antagonist (hydroxyzine hydrochloride etc.), therapeutic drug for schizophrenia (chlorpromazine, haloperidol, sulpiride, clozapine, trifluoperazine hydrochloride, 20 fluphenazine hydrochloride, olanzapine, quetiapine fumarate, risperidone, aripiprazole etc.), CRF antagonist, other antianxiety drug (meprobamate etc.), tachykinin antagonist (MK-869, saredutant etc.), medicament that acts on metabotropic glutamate receptor, CCK antagonist, β 3 adrenaline antagonist 25 (amibegron hydrochloride etc.), GAT-1 inhibitor (tiagabine hydrochloride etc.), N-type calcium channel inhibitor, carbonic anhydrase II inhibitor, NMDA glycine moiety agonist, NMDA antagonist (memantine etc.), peripheral benzodiazepine receptor agonist, vasopressin antagonist, vasopressin V1b antagonist, 30 vasopressin V1a antagonist, phosphodiesterase inhibitor, opioid antagonist, opioid agonist, uridine, nicotinic acid receptor agonist, thyroid hormone (T₃, T₄), TSH, TRH, MAO inhibitor (phenelzine sulfate, tranlycypromine sulfate, moclobemide etc.), 5-HT_{2A} antagonist, 5-HT_{2A} inverse agonist, COMT inhibitor 35 (entacapone etc.), therapeutic drug for bipolar disorder

(lithium carbonate, sodium valproate, lamotrigine, riluzole, felbamate etc.), cannabinoid CB1 antagonist (rimonabant etc.), FAAH inhibitor, sodium channel inhibitor, anti-ADHD drug (methylphenidate hydrochloride, methamphetamine hydrochloride etc.), therapeutic drug for alcoholism, therapeutic drug for autism, therapeutic drug for chronic fatigue syndrome, therapeutic drug for spasm, therapeutic drug for fibromyalgia syndrome, therapeutic drug for headache, therapeutic drug for insomnia (etizolam, zopiclone, triazolam, zolpidem, ramelteon, 10 indiplon etc.), therapeutic drug for quitting smoking, therapeutic drug for myasthenia gravis, therapeutic drug for cerebral infarction, therapeutic drug for mania, therapeutic drug for hypersomnia, therapeutic drug for pain, therapeutic drug for dysthymia, therapeutic drug for autonomic ataxia, 15 therapeutic drug for male and female sexual dysfunction, therapeutic drug for migraine, therapeutic drug for pathological gambler, therapeutic drug for restless legs syndrome, therapeutic drug for substance addiction, therapeutic drug for alcohol-related syndrome, therapeutic drug for 20 irritable bowel syndrome, therapeutic drug for Alzheimer's disease (donepezil, galanthamine, memantine, rivastigmine etc.), therapeutic drug for Parkinson's disease (levodopa, carbidopa, benserazide, selegiline, zonisamide, entacapone, amantadine, talipexole, pramipexole, apomorphine, cabergoline, 25 bromocriptine, istradefylline, trihexyphenidyl, promethazine, pergolide, etc.), therapeutic drug for Huntington's disease (chlorpromazine hydrochloride, haloperidol, reserpine etc.), therapeutic drug for ALS (riluzole etc., neurotrophic factor etc.), therapeutic drug for multiple sclerosis (molecular 30 target drug such as fingolimod, interferon beta 1b, natalizumab and the like, etc.), antiepilepsy drug (phenytoin, carbamazepine, phenobarbital, primidone, zonisamide, sodium valproate, ethosuximide, diazepam, nitrazepam, clonazepam, clobazam, gabapentin, topiramate, lamotrigine, levetiracetam, 35 stiripentol, rufinamide, etc.), therapeutic drug for lipid

abnormality such as cholesterol-lowering drug (statin series (pravastatin sodium, atorvastatin, simvastatin, rosuvastatin etc.), fibrate (clofibrate etc.), squalene synthetase inhibitor), therapeutic drug for abnormal behavior or
5 suppressant of dromomania due to dementia (sedatives, antianxiety drug etc.), apoptosis inhibitor, antiobesity drug, therapeutic drug for diabetes, therapeutic drug for hypertension, therapeutic drug for hypotension, therapeutic drug for rheumatism (DMARD), anti-cancer agent, therapeutic
10 drug for parathyroid (PTH), calcium receptor antagonist, sex hormone or a derivative thereof (progesterone, estradiol, estradiol benzoate etc.), neuronal differentiation promoter, nerve regeneration promoter, non-steroidal anti-inflammatory drug (meloxicam, tenoxicam, indomethacin, ibuprofen, celecoxib,
15 rofecoxib, aspirin etc.), steroid (dexamethasone, cortisone acetate etc.), anti-cytokine drug (TNF inhibitor, MAP kinase inhibitor etc.), antibody medicament, nucleic acid or nucleic acid derivative, aptamer drug and the like.

[0196]

- 20 By combining the compound of the present invention and a concomitant drug, a superior effect such as
- (1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,
 - 25 (2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),
 - (3) the period of treatment can be set longer by selecting a concomitant drug having different action and mechanism from the
30 compound of the present invention,
 - (4) a sustained treatment effect can be designed by selecting a concomitant drug having different action and mechanism from the compound of the present invention,
 - (5) a synergistic effect can be afforded by a combined use of
35 the compound of the present invention and a concomitant drug,

and the like, can be achieved.

[0197]

Hereinafter the compound of the present invention and a concomitant drug used in combination are referred to as the
5 "combination agent of the present invention".

When using the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention or a pharmaceutical
10 composition thereof and the concomitant drug or a pharmaceutical composition thereof can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be
15 appropriately selected depending on an administration subject, administration route, disease, combination and the like.

The administration mode of the concomitant drug of the present invention is not particularly restricted, and it is sufficient that the compound of the present invention and the concomitant
20 drug are combined in administration. Examples of such administration mode include the following methods:

(1) administration of a single preparation obtained by simultaneously processing the compound of the present invention and the concomitant drug, (2) simultaneous administration of
25 two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by the same administration route, (3) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately
30 produced, by the same administration route in a staggered manner, (4) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different administration routes, (5) administration of two
35 kinds of preparations of the compound of the present invention

and the concomitant drug, which have been separately produced, by different administration routes in a staggered manner (for example, administration in the order of the compound of the present invention and the concomitant drug, or in the reverse order) and the like.

[0198]

The combination agent of the present invention exhibits low toxicity. For example, the compound of the present invention or (and) the aforementioned concomitant drug can be combined with a pharmacologically acceptable carrier according to the known method to prepare a pharmaceutical composition such as tablets (including sugar-coated tablet and film-coated tablet), powders, granules, capsules (including soft capsule), liquids, injections, suppositories, sustained-release agents, etc. These compositions can be administered safely orally or non-orally (e.g., topical, rectal, intravenous administration etc.). Injection can be administered intravenously, intramuscularly, subcutaneously, or by intraorgan administration or directly to the lesion.

Examples of the pharmacologically acceptable carriers usable for the production of a combination agent of the present invention, various organic or inorganic carrier substances conventionally used as preparation materials can be mentioned. For solid preparations, for example, excipient, lubricant, binder and disintegrant can be used. For liquid preparations, for example, solvent, solubilizing agent, suspending agent, isotonic agent, buffering agent, soothing agent and the like can be used. Where necessary, an appropriate amount of conventional preservative, antioxidant, colorant, sweetening agent, adsorbent, wetting agent and the like can be used as appropriate.

Examples of the excipient include lactose, sucrose, D-mannitol, starch, corn starch, crystalline cellulose, light anhydrous silicic acid and the like.

Examples of the lubricant include magnesium stearate,

calcium stearate, talc, colloidal silica and the like.

Examples of the binder include crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch,
5 sucrose, gelatin, methylcellulose, carboxymethylcellulose sodium and the like.

Examples of the disintegrant include starch, carboxymethylcellulose, carboxymethylcellulose calcium, sodium carboxymethyl starch, L-hydroxypropylcellulose and the like.

10 Examples of the solvent include water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil and the like.

Examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol,
15 trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like.

Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride,
20 benzetonium chloride, glycerin monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; and the like.

25 [0199]

Examples of the isotonic agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like.

Examples of the buffering agent include buffer solutions such as phosphates, acetates, carbonates, citrates and the like.

30 Examples of the soothing agent include benzyl alcohol and the like.

Examples of the preservative include p-oxybenzoates, chlorobutanol, benzyl alcohol, phenylethyl alcohol, dehydroacetic acid, sorbic acid and the like.

35 Examples of the antioxidant include sulfite, ascorbic

acid, α -tocopherol and the like.

[0200]

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

For example, the content of the compound of the present invention in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably from about 0.5 to about 20 wt%, based on the preparation.

The content of the concomitant drug in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably from about 0.5 to about 20 wt%, based on the preparation.

The content of additives such as a carrier and the like in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 1 to about 99.99 wt%, preferably from about 10 to about 90 wt%, based on the preparation.

When the compound of the present invention and a concomitant drug are separately formulated into preparations, the contents thereof are similar to the above.

Example

[0201]

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

In the following Examples, the "room temperature" generally means about 10°C to about 35°C. The ratios indicated

for mixed solvents are volume mixing ratios, unless otherwise specified. % means wt%, unless otherwise specified.

In silica gel column chromatography, NH means use of aminopropylsilane-bonded silica gel. In HPLC (high performance liquid chromatography), C18 means use of octadecyl-bonded silica gel.

The ratios of elution solvents are volume mixing ratios, unless otherwise specified.

[0202]

10 In Examples, the following abbreviations are used.

mp: melting point

MS: mass spectrum

M: mol concentration

N: normality

15 CDCl₃: deuteriochloroform

DMSO-d₆: deuterodimethyl sulfoxide

¹H NMR: proton nuclear magnetic resonance

LC/MS: liquid chromatograph mass spectrometer

ESI: Electron Spray Ionization

20 APCI: atmospheric pressure chemical ionization

ADDP: 1,1'-(azodicarbonyl)dipiperidine

DIPEA: N,N-diisopropylethylamine

DMF: N,N-dimethylformamide

DMA: N,N-dimethylacetamide

25 DMSO: dimethyl sulfoxide

EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
hydrochloride

HATU: 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium
hexafluorophosphate

30 HOBt: 1-hydroxybenzotriazole

HOBt-H₂O: 1-hydroxybenzotriazole monohydrate

IPA: 2-propanol

IPE: diisopropyl ether

p-TsOH-H₂O: p-toluenesulfonic acid monohydrate

35 TEA: triethylamine

THF: tetrahydrofuran

[0203]

¹H NMR was measured by Fourier-transform type NMR. For the analysis, ACD/SpecManager (trade name) and the like were used. Peaks with very mild protons such as a hydroxy group, an amino group and the like are not described.

MS was measured by LC/MS. As ionization method, ESI method or APCI method was used. The data indicates actual measured value (found). Generally, molecular ion peaks ([M+H]⁺, [M-H]⁻ and the like) are observed. For example, in the case of a compound having a tert-butoxycarbonyl group, a peak after elimination of a tert-butoxycarbonyl group or a tert-butyl group may be observed as a fragment ion. In the case of a compound having a hydroxy group, a peak after elimination of H₂O may be observed as a fragment ion. In the case of a salt, a molecular ion peak or fragment ion peak of free form is generally observed.

The unit of sample concentration (c) for optical rotation ([α]_D) is g/100 mL.

Elemental analysis value (Anal.) was described as calculated value (Calcd) and actual measured value (Found).

Powder X-RAY diffraction pattern was measured using Cu-Kα characteristic X-ray of Rigaku Ultima IV, and characteristic peak was described.

[0204]

Example 1

(2s,4r)-2-((4-((2-chloro-4-fluorophenoxy)methyl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one

[0205]

A) tert-butyl 4-((2-chloro-4-fluorophenoxy)methyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (2.50 g), 2-chloro-4-fluorophenol (1.49 mL) and tri-n-butylphosphine (3.47 mL) in THF (50 mL) was added ADDP (3.52 g) at 0°C, and the reaction mixture was stirred at room

temperature for 18 hr. The reaction mixture was passed through a pad of silica gel/NH silica gel, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to
5 give the title compound (3.81 g).

¹H NMR (300 MHz, CDCl₃) δ 1.21-1.38 (2H, m), 1.42-1.51 (9H, m), 1.78-2.11 (3H, m), 2.64-2.85 (2H, m), 3.75-3.97 (2H, m), 4.04-4.37 (2H, m), 6.80-7.00 (2H, m), 7.05-7.16 (1H, m).

[0206]

10 B) 4-((2-chloro-4-fluorophenoxy)methyl)piperidine hydrochloride

To a solution of tert-butyl 4-((2-chloro-4-fluorophenoxy)methyl)piperidine-1-carboxylate (3.81 g) in ethyl acetate (30 mL) was added 4N hydrogen chloride-ethyl acetate solution (22.2 mL), and the reaction mixture was stirred at
15 room temperature for 14 hr. The resulting precipitate was collected, washed with ethyl acetate, and dried under reduced pressure to give the title compound (2.09 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.43-1.62 (2H, m), 1.84-1.98 (2H, m), 2.01-2.17 (1H, m), 2.83-2.97 (2H, m), 3.23-3.36 (2H, m),
20 3.93 (2H, d, J = 6.2 Hz), 7.13-7.26 (2H, m), 7.39-7.48 (1H, m), 8.81 (2H, brs).

[0207]

C) ethyl 3-(hydroxyimino)cyclobutanecarboxylate

A mixture of ethyl 3-oxocyclobutanecarboxylate (25.6 g),
25 hydroxylamine hydrochloride (15.0 g), sodium acetate (17.7 g) and ethanol (200 mL) was heated under reflux for 18 hr. The mixture was allowed to be cooled to room temperature, the precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was diluted
30 with ethyl acetate/water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and passed through a pad of silica gel, and the filtrate was concentrated under reduced pressure. The residue was purified
35 by silica gel column chromatography (ethyl acetate/hexane) to

give the title compound (25.1 g).

¹H NMR (300 MHz, CDCl₃) δ1.28 (3H, t, J = 7.2 Hz), 3.04-3.32 (5H, m), 4.19 (2H, q, J = 7.2 Hz), 7.73 (1H, s).

[0208]

5 D) ethyl 3-nitrocyclobutanecarboxylate

To a mixture of ethyl 3-(hydroxyimino)cyclobutanecarboxylate (5.00 g), disodium hydrogenphosphate (45.2 g), urea hydrogen peroxide (8.98 g) and acetonitrile (60 mL) was added dropwise a solution of
10 trifluoroacetic anhydride (27.0 mL) in acetonitrile (40 mL) over 20 min at 80°C, and the mixture was stirred at the same temperature for 1.8 hr. The mixture was allowed to be cooled to room temperature, diluted with ethyl acetate/water, and extracted with ethyl acetate. The organic layer was washed
15 with water and saturated brine, dried over anhydrous sodium sulfate, and passed through a pad of silica gel, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.38 g).

20 ¹H NMR (300 MHz, CDCl₃) δ1.28 (3H, t, J = 7.2 Hz), 2.72-3.04 (5H, m), 4.19 (2H, q, J = 7.1 Hz), 4.77-4.92 (1H, m).

[0209]

E) ethyl trans-3-(3-methoxy-3-oxopropyl)-3-nitrocyclobutanecarboxylate

25 To a solution of ethyl 3-nitrocyclobutanecarboxylate (0.560 g) and methyl acrylate (0.349 mL) in acetonitrile (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.242 mL) at 0°C, and the mixture was stirred at the same temperature for 20 min. The reaction was quenched with aqueous ammonium chloride
30 solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title
35 compound (0.180 g).

¹H NMR (300 MHz, CDCl₃) δ 1.28 (3H, t, J = 7.2 Hz), 2.24-2.33 (2H, m), 2.41-2.50 (2H, m), 2.56-2.66 (2H, m), 2.99-3.11 (2H, m), 3.15-3.29 (1H, m), 3.68 (3H, s), 4.18 (2H, q, J = 7.2 Hz). [0210]

5 F) (2s,4r)-2-((4-((2-chloro-4-fluorophenoxy)methyl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one

To a mixture of ethyl trans-3-(3-methoxy-3-oxopropyl)-3-nitrocyclobutanecarboxylate (0.195 g), nickel(II) chloride hexahydrate (0.179 g) and methanol (2 mL) was added sodium
10 borohydride (0.142 g) at -10°C in 3 parts. The mixture was stirred at the same temperature for 2 hr, and the reaction was quenched with aqueous potassium carbonate solution (0.416 g/1 mL) at 0°C. The mixture was stirred at 0°C for 3 hr, and then at room temperature for 2 hr, and passed through a Celite pad.
15 The filtrate was concentrated under reduced pressure, and the residue was dissolved in THF (2 mL)/methanol (2 mL)/water (1 mL). To the solution was added 2M aqueous sodium hydroxide solution (0.752 mL), and the mixture was stirred overnight at room temperature. The mixture was acidified with 6M
20 hydrochloric acid (pH 4), and concentrated under reduced pressure to give a crude carboxylic acid.

A mixture of the obtained carboxylic acid, 4-((2-chloro-4-fluorophenoxy)methyl)piperidine hydrochloride (0.210 g), HOBT-H₂O (0.138 g), EDCI (0.173 g), DIPEA (0.654 mL) and DMF
25 (10 mL) was stirred at room temperature for 2 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and passed through a pad of NH silica gel, and the filtrate was concentrated under
30 reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane and methanol/ethyl acetate), and the obtained crude crystals were recrystallized from ethyl acetate/IPA/heptane to give the title compound (0.165 g).

35 ¹H NMR (300 MHz, DMSO-d₆) δ 1.06-1.31 (2H, m), 1.71-1.86 (2H, m),

1.91-2.15 (5H, m), 2.25-2.40 (4H, m), 2.54-2.67 (1H, m), 2.91-3.07 (1H, m), 3.12-3.26 (1H, m), 3.60-3.73 (1H, m), 3.83-3.99 (2H, m), 4.34-4.48 (1H, m), 7.12-7.21 (2H, m), 7.38-7.48 (1H, m), 8.12 (1H, s).

5 [0211]

Example 4

(2s,4s)-2-((4-(5-fluoro-2-methyl-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)

10 [0212]

A) tert-butyl 3-oxocyclobutanecarboxylate

To a solution of 3-oxocyclobutanecarboxylic acid (250 g) in THF (1.5 L) were added tert-butanol (228 g) and 4-dimethylaminopyridine (148 g) at room temperature, and a solution of N,N'-dicyclohexylcarbodiimide (497 g) in THF (0.5 L) was added dropwise thereto over 30 min, and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and the mixture was washed with 1M hydrochloric acid, saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was diluted with petroleum ether, the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to give the title compound (250 g).

¹H NMR (500 MHz, CDCl₃) δ 1.48 (9H, s), 3.12-3.14 (1H, m), 3.21-3.27 (2H, m), 3.33-3.35 (2H, m).

[0213]

30 B) tert-butyl 3-(hydroxyimino)cyclobutanecarboxylate

To a solution of tert-butyl 3-oxocyclobutanecarboxylate (500 g) in ethanol (9 L) were added sodium acetate (976 g) and hydroxylamine hydrochloride (409 g) at room temperature, and the reaction mixture was heated under reflux for 4 hr. The reaction mixture was filtered through Celite, and the filtrate

was concentrated under reduced pressure. The residue was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (500 g).

^1H NMR (400 MHz, CDCl_3) δ 1.46 (9H, s), 3.09-3.16 (5H, m), 6.83 (1H, brs).

[0214]

C) (1s,3s)-tert-butyl 3-(hydroxymethyl)-3-nitrocyclobutanecarboxylate

To a mixture of urea hydrogen peroxide (305 g) and acetonitrile (2 L) was added dropwise a solution of trifluoroacetic anhydride (454 mL) in acetonitrile (1 L) over 1 hr at -10°C , and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added dropwise to a solution of tert-butyl 3-(hydroxyimino)cyclobutanecarboxylate (200 g) and disodium hydrogenphosphate (1080 g) in acetonitrile (2 L) over 30 min at 80°C , and the reaction mixture was stirred at 80°C for 30 min. The reaction mixture was filtered through Celite. The filtrate was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give tert-butyl 3-nitrocyclobutanecarboxylate (140 g).

To a solution of the obtained tert-butyl 3-nitrocyclobutanecarboxylate (300 g) in acetonitrile (4 L) was added formaldehyde (37% aqueous solution, 243 mL) at room temperature, and TEA (211 mL) was added dropwise thereto at 0°C . The reaction mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (180 g).

^1H NMR (500 MHz, CDCl_3) δ 1.45 (9H, s), 2.57-2.62 (m, 3H), 2.79-2.86 (1H, m), 2.92-2.96 (2H, m), 4.02 (2H, d, $J = 4.5$ Hz).

[0215]

D) (1s,3s)-tert-butyl 3-amino-3-(hydroxymethyl)cyclobutanecarboxylate

A mixture of (1s,3s)-tert-butyl 3-(hydroxymethyl)-3-nitrocyclobutanecarboxylate (210 g), Raney nickel (20.0 g) and IPA (2 L) was subjected to hydrogenation at 70°C at 50 bar for 3 hr. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was washed with n-pentane to give the title compound (150 g).

¹H NMR (500 MHz, CDCl₃) δ 1.44 (9H, s), 1.99-2.03 (2H, m), 2.27-2.32 (2H, m), 2.68 (1H, quin, J = 8.6 Hz), 3.48 (2H, d, J = 4.5 Hz).

[0216]

E) (2s,4s)-tert-butyl 6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylate

To a solution of (1s,3s)-tert-butyl 3-amino-3-(hydroxymethyl)cyclobutanecarboxylate (120 g) in THF (3.0 L) was added TEA (177 mL) at room temperature, followed by the dropwise addition of a solution of triphosgene (62.0 g) in THF (0.5 L) at -10°C, and the reaction mixture was stirred at -10°C for 30 min. The reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (110 g).

¹H NMR (500 MHz, CDCl₃) δ 1.45 (9H, s), 2.46-2.53 (4H, m), 2.72 (1H, quin, J = 8.0 Hz), 4.34 (2H, s), 5.80 (1H, brs).

[0217]

F) (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid

To (2s,4s)-tert-butyl 6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylate (110 g) was added trifluoroacetic acid (1 L)

cooled in advance at 0°C, and the reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was azeotroped with toluene three times. The residue was stirred
5 in n-pentane, collected by filtration, and dried under reduced pressure to give the title compound (76.0 g).

¹H NMR (500 MHz, DMSO-d₆) δ 2.33-2.39 (4H, m), 2.73 (1H, quin, J = 9.1 Hz), 4.34 (2H, s), 8.09 (1H, s), 12.24 (1H, brs).

[0218]

10 G) tert-butyl 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine-1-carboxylate

A mixture of 2-bromo-5-fluorobenzyl bromide (23.1 g), iodine (10 mg), magnesium (4.81 g) and diethyl ether (150 mL) was heated under reflux until the color of the iodine
15 disappeared, and stirred at room temperature for 1.5 hr. The reaction mixture was added dropwise to a solution of tert-butyl 4-acetyl-piperidine-1-carboxylate (9.78 g) in diethyl ether (30 mL) at 0°C, and the mixture was stirred at room temperature for 1.5 hr. The reaction was quenched with aqueous ammonium
20 chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). A degassed
25 mixture of the obtained residue, palladium acetate (0.406 g), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.13 g), potassium carbonate (8.33 g) and toluene (100 mL) was heated under reflux for 24 hr. The reaction mixture was diluted with ethyl acetate, and filtered through a pad of NH silica gel
30 short. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (6.63 g).

¹H NMR (300 MHz, CDCl₃) δ 1.14-1.33 (2H, m), 1.36 (3H, s), 1.45
35 (9H, s), 1.64-1.86 (3H, m), 2.57-2.73 (2H, m), 2.80 (1H, d, J =

16.0 Hz), 3.13 (1H, d, J = 16.1 Hz), 4.06-4.33 (2H, m), 6.61 (1H, dd, J = 8.6, 4.2 Hz), 6.73-6.87 (2H, m).

[0219]

H) 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine
5 hydrochloride

To a solution of tert-butyl 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine-1-carboxylate (6.60 g) in methanol (50 mL) was added 2N hydrogen chloride-methanol solution (98 mL), and the mixture was stirred at room
10 temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with ethyl acetate to give the title compound (5.02 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.31 (3H, s), 1.38-1.61 (2H, m), 1.72-1.99 (3H, m), 2.71-2.96 (3H, m), 3.12-3.21 (1H, m), 3.25-
15 3.34 (2H, m), 6.68 (1H, dd, J = 8.7, 4.2 Hz), 6.84-6.94 (1H, m), 7.06 (1H, dd, J = 8.4, 2.7 Hz), 8.59 (1H, brs), 8.86 (1H, brs).

[0220]

I) 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine

To a suspension of 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine hydrochloride (3.00 g) in THF
20 (30 mL) was added 2M aqueous sodium hydroxide solution (6.62 mL) at 0°C, and the mixture was stirred at 0°C for 30 min. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and
25 saturated brine, dried over anhydrous sodium sulfate, and filtered through a pad of NH silica gel, and the filtrate was concentrated under reduced pressure to give the title compound (2.35 g).

¹H NMR (300 MHz, CDCl₃) δ 1.17-1.34 (2H, m), 1.36 (3H, s), 1.57 (1H, brs), 1.65-1.83 (3H, m), 2.51-2.66 (2H, m), 2.78 (1H, d, J = 16.0 Hz), 3.07-3.22 (3H, m), 6.60 (1H, dd, J = 8.6, 4.2 Hz), 6.72-6.87 (2H, m).

[0221]

J) 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine
35 (optical isomer)

A racemate (3.40 g) of 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine was resolved by HPLC (column: CHIRALPAK AD (trade name), 50 mm I.D. x 500 mm L, manufactured by Daicel Chemical Industries, mobile phase:

5 hexane/ethanol/diethylamine = 850/150/1) to give the title compound (1.45 g) having a longer retention time.

¹H NMR (300 MHz, CDCl₃) δ 1.16-1.39 (5H, m), 1.56 (1H, s), 1.65-1.84 (3H, m), 2.53-2.66 (2H, m), 2.78 (1H, d, J = 16.0 Hz), 3.07-3.22 (3H, m), 6.60 (1H, dd, J = 8.6, 4.2 Hz), 6.72-6.86
10 (2H, m).

[0222]

K) (2s,4s)-2-((4-(5-fluoro-2-methyl-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)

15 A mixture of (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (43 mg), 4-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-2-yl)piperidine (optical isomer) (59.1 mg), HOBT-H₂O (46.2 mg), EDCI (57.8 mg), DIPEA (0.158 mL) and DMF (1.5 mL) was stirred at room temperature for 2.5 hr. The
20 reaction mixture was diluted with water, and extracted with ethyl acetate/IPA. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and
25 methanol/ethyl acetate), and recrystallized from ethyl acetate/IPA/heptane to give the title compound (57 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.95-1.18 (2H, m), 1.28 (3H, s), 1.61-1.91 (3H, m), 2.23-2.43 (5H, m), 2.77-3.06 (3H, m), 3.16 (1H, d, J = 16.4 Hz), 3.76-3.89 (1H, m), 4.35 (2H, d, J = 2.6
30 Hz), 4.39-4.51 (1H, m), 6.66 (1H, dd, J = 8.7, 4.3 Hz), 6.81-6.91 (1H, m), 7.01 (1H, dd, J = 8.3, 2.8 Hz), 8.01 (1H, s).

[0223]

Example 49

(2s,4s)-2-((4-((2-chloro-4-(3-fluoroazetidin-1-yl)phenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-
35

azaspiro[3.4]octan-6-one

[0224]

A) tert-butyl 4-((4-bromo-2-chlorophenoxy)methyl)piperidine-1-carboxylate

5 To a suspension of 60% sodium hydride (0.223 g) in DMA (10 mL) was added tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (1.00 g) at 0°C. The mixture was stirred at room temperature for 30 min. To the mixture was added 4-bromo-2-chloro-1-fluorobenzene (0.679 mL) at room temperature, and the
10 mixture was stirred overnight at 60°C. The mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column
15 chromatography (ethyl acetate/hexane) to give the title compound (1.78 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.11-1.26 (2H, m), 1.39 (9H, s), 1.68-1.81 (2H, m), 1.86-1.98 (1H, m), 2.62-2.89 (2H, m), 3.89-4.03 (4H, m), 7.08-7.15 (1H, m), 7.44-7.51 (1H, m), 7.64-7.68
20 (1H, m).

[0225]

B) tert-butyl 4-((2-chloro-4-(3-fluoroazetidin-1-yl)phenoxy)methyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-((4-bromo-2-chlorophenoxy)methyl)piperidine-1-carboxylate (665 mg), 3-
25 fluoroazetidine hydrochloride (238 mg), potassium carbonate (908 mg) and L-proline (76 mg) in DMSO (5 mL) was added copper(I) iodide (62.6 mg) at room temperature. The mixture was heated under microwave irradiation at 120°C for 2 hr. The
30 reaction mixture was poured into water at room temperature, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl
35 acetate/hexane) to give the title compound (248 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.07-1.26 (2H, m), 1.39 (9H, s), 1.68-1.97 (3H, m), 2.64-2.86 (2H, m), 3.72-3.88 (4H, m), 3.90-4.16 (4H, m), 5.29-5.61 (1H, m), 6.36-6.43 (1H, m), 6.53-6.58 (1H, m), 6.96-7.04 (1H, m).

5 [0226]

C) (2s,4s)-2-((4-((2-chloro-4-(3-fluoroazetidin-1-yl)phenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

A mixture of tert-butyl 4-((2-chloro-4-(3-fluoroazetidin-10 1-yl)phenoxy)methyl)piperidine-1-carboxylate (248 mg) and trifluoroacetic acid (2 mL) was stirred at 0°C for 30 min under dried atmosphere using a calcium chloride tube. The reaction mixture was concentrated under reduced pressure. A mixture of the obtained residue, (2s,4s)-6-oxo-7-oxa-5-15 azaspiro[3.4]octane-2-carboxylic acid (106 mg), HATU (354 mg), TEA (0.864 mL) and DMF (5 mL) was stirred overnight at room temperature. The mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate,20 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate), and recrystallized from DMSO/ethyl acetate to give the title compound (191 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.98-1.25 (2H, m), 1.69-1.86 (2H,25 m), 1.88-2.05 (1H, m), 2.22-2.45 (4H, m), 2.55-2.65 (1H, m), 2.89-3.09 (2H, m), 3.70-3.90 (5H, m), 4.02-4.17 (2H, m), 4.30-4.43 (3H, m), 5.28-5.60 (1H, m), 6.37-6.44 (1H, m), 6.54-6.59 (1H, m), 6.95-7.05 (1H, m), 8.04 (1H, s).

[0227]

30 Example 51

(2s,4s)-2-((4-(1,1-diphenylethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

[0228]

A) tert-butyl 4-(hydroxydiphenylmethyl)piperidine-1-carboxylate

35 To a mixture of diphenyl(piperidin-4-yl)methanol (10.0 g),

TEA (6.76 mL) and THF (100 mL) was added di-tert-butylidicarbonate (9.46 mL), and the mixture was stirred at room temperature for 14 hr. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with heated ethyl acetate/heptane to give the title compound (13.1 g).

¹H NMR (300 MHz, CDCl₃) δ 1.24-1.55 (13H, m), 2.05 (1H, s), 2.48-2.81 (3H, m), 3.98-4.30 (2H, m), 7.16-7.23 (2H, m), 7.24-7.35 (4H, m), 7.42-7.50 (4H, m).

10 [0229]

B) tert-butyl 4-(fluorodiphenylmethyl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(hydroxydiphenylmethyl)piperidine-1-carboxylate (5.00 g) in toluene (50 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (3.26 mL) at 0°C, and the mixture was stirred at room temperature for 2.5 hr. The reaction was quenched with saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.80 g).

¹H NMR (300 MHz, CDCl₃) δ 1.37-1.51 (13H, m), 2.34-2.77 (3H, m), 3.99-4.25 (2H, m), 7.17-7.48 (10H, m).

25 [0230]

C) tert-butyl 4-(1,1-diphenylethyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(fluorodiphenylmethyl)piperidine-1-carboxylate (1.69 g) in toluene (15 mL) was added trimethylaluminium (1.8M toluene solution, 5.08 mL), and the mixture was stirred at room temperature for 1 hr. The reaction was quenched with methanol and aqueous Rochelle salt solution at 0°C, and the mixture was stirred at room temperature for 12 hr. The mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous

sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (565 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.02-1.22 (2H, m), 1.42 (9H, s),
5 1.49-1.61 (2H, m), 1.64 (3H, s), 2.30-2.44 (1H, m), 2.60-2.81
(2H, m), 3.98-4.24 (2H, m), 7.09-7.32 (10H, m).

[0231]

D) 4-(1,1-diphenylethyl)piperidine hydrochloride

To a solution of tert-butyl 4-(1,1-
10 diphenylethyl)piperidine-1-carboxylate (560 mg) in ethyl
acetate (7 mL) was added 4N hydrogen chloride-ethyl acetate
solution (3.83 mL), and the mixture was stirred at room
temperature for 18 hr. The resulting precipitate was collected,
washed with ethyl acetate, and dried under reduced pressure to
15 give the title compound (411 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.24-1.43 (2H, m), 1.48-1.66 (5H, m),
2.66-2.79 (1H, m), 2.87-3.02 (2H, m), 3.17-3.28 (2H, m), 7.10-
7.38 (10H, m), 8.49 (2H, brs).

[0232]

20 E) (2s,4s)-2-((4-(1,1-diphenylethyl)piperidin-1-yl)carbonyl)-7-
oxa-5-azaspiro[3.4]octan-6-one

A mixture of (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-
carboxylic acid (198 mg), 4-(1,1-diphenylethyl)piperidine
hydrochloride (350 mg), HOBT-H₂O (213 mg), EDCI (267 mg), DIPEA
25 (0.727 mL) and DMF (7 mL) was stirred at room temperature for
24 hr. Water was added thereto, and the resulting precipitate
was collected, washed with water, and dried under reduced
pressure. The obtained solid was triturated with heated
ethanol/water to give the title compound (423 mg).

30 ¹H NMR (300 MHz, DMSO-d₆) δ 0.82-1.08 (2H, m), 1.34-1.66 (5H,
m), 2.17-2.69 (6H, m), 2.85-3.04 (2H, m), 3.68-3.82 (1H, m),
4.26-4.42 (3H, m), 7.05-7.37 (10H, m), 7.99 (1H, s).

[0233]

Example 57

35 (2s,4s)-2-((4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidin-1-

yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)
[0234]

A) 4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidine

A mixture of tert-butyl 4-(1-
5 ((methylsulfonyl)oxy)ethyl)piperidine-1-carboxylate (1.82 g),
2,3,6-trifluorophenol (0.877 g), cesium carbonate (5.79 g) and
DMF (10 mL) was stirred overnight at 60°C. The mixture was
poured into water, and extracted with ethyl acetate. The
organic layer was washed with water and saturated brine, dried
10 over anhydrous magnesium sulfate, and concentrated under
reduced pressure. The residue was purified by silica gel
column chromatography (ethyl acetate/hexane). The obtained
residue was dissolved in ethyl acetate (10 mL), and 4N hydrogen
chloride-ethyl acetate solution (10 mL) was added thereto. The
15 mixture was stirred at room temperature for 2 hr. The mixture
was concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (NH,
methanol/ethyl acetate) to give the title compound (0.800 g).
¹H NMR (300 MHz, DMSO-d₆) δ 1.09-1.33 (5H, m), 1.53-2.03 (4H,
20 m), 2.36-2.48 (2H, m), 2.89-3.03 (2H, m), 4.05-4.19 (1H, m),
7.10-7.29 (2H, m).

[0235]

B) (2s,4s)-2-((4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidin-1-
yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

25 A mixture of 4-(1-(2,3,6-
trifluorophenoxy)ethyl)piperidine (167 mg), (2s,4s)-6-oxo-7-
oxa-5-azaspiro[3.4]octane-2-carboxylic acid (110 mg), EDCI (185
mg), HOBt (104 mg), TEA (0.448 mL) and DMF (5 mL) was stirred
overnight at room temperature. The reaction mixture was poured
30 into water, and extracted with ethyl acetate. The organic
layer was washed with water and saturated brine, dried over
anhydrous magnesium sulfate, and concentrated under reduced
pressure. The residue was purified by silica gel column
chromatography (NH, methanol/ethyl acetate), and recrystallized
35 from ethyl acetate/hexane to give the title compound (188 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.06-1.34 (5H, m), 1.63-1.95 (3H, m), 2.22-2.59 (5H, m), 2.86-3.11 (2H, m), 3.76-3.92 (1H, m), 4.10-4.23 (1H, m), 4.32-4.51 (3H, m), 7.12-7.30 (2H, m), 8.03 (1H, s).

5 [0236]

C) (2s,4s)-2-((4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer).

A racemate (800 mg) of (2s,4s)-2-((4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one was resolved by HPLC (column: CHIRALPAK AD (trade name), 50 mm I.D. x 500 mmL, manufactured by Daicel Chemical Industries, mobile phase: hexane/ethanol = 350/650), and the compound having a longer retention time was recrystallized from ethyl acetate/hexane to give the title
10 compound (394 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.06-1.34 (5H, m), 1.63-1.95 (3H, m), 2.22-2.59 (5H, m), 2.86-3.11 (2H, m), 3.76-3.92 (1H, m), 4.10-4.23 (1H, m), 4.32-4.51 (3H, m), 7.12-7.30 (2H, m), 8.03 (1H, s).

20 [0237]

Example 58

(2s,4s)-2-((4-(5-fluoro-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

25 [0238]

A) tert-butyl 4-((2-bromo-5-fluorophenyl)acetyl)piperidine-1-carboxylate

To a mixture of magnesium (0.134 g), iodine (0.019 g) and diethyl ether (15 mL) was added dropwise a solution of 1-bromo-2-(bromomethyl)-4-fluorobenzene (1.18 g) in diethyl ether (15 mL) over 30 min, while vigorously stirring and keeping the internal temperature at 25 to 28°C. The reaction mixture was stirred for additional 10 min. The mixture was cooled to 0°C, and a solution of tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (1 g) in
35

diethyl ether (15 mL) was slowly added dropwise thereto at 0°C. The mixture was stirred at room temperature for 3 hr. The reaction was quenched with saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate.

5 The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (0.977 g).

10 ¹H NMR (300 MHz, DMSO-d₆) δ 1.27-1.38 (2H, m), 1.39 (9H, s), 1.77-1.94 (2H, m), 2.65-2.93 (3H, m), 3.84-4.00 (2H, m), 4.05 (2H, s), 7.10 (1H, td, J = 8.6, 3.2 Hz), 7.22 (1H, dd, J = 9.6, 3.2 Hz), 7.62 (1H, dd, J = 8.9, 5.5 Hz).

[0239]

15 B) tert-butyl 4-(3-(2-bromo-5-fluorophenyl)-1,1,1-trifluoro-2-hydroxypropan-2-yl)piperidine-1-carboxylate

To a mixture of tert-butyl 4-((2-bromo-5-fluorophenyl)acetyl)piperidine-1-carboxylate (977 mg), (trifluoromethyl)trimethylsilane (0.397 mL) and THF (10 mL) was
20 added tetra-n-butylammonium fluoride (1M THF solution, 0.244 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hr. Additional (trifluoromethyl)trimethylsilane (0.397 mL) and tetra-n-butylammonium fluoride (1M THF solution, 2.44 mL) were added
25 thereto at room temperature, and the mixture was stirred at room temperature over weekend. The mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate,
30 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (245 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.20-1.33 (2H, m), 1.38 (9H, s), 1.73-1.93 (3H, m), 2.53-2.69 (2H, m), 3.11 (2H, s), 4.03 (2H, q,
35 J = 7.1 Hz), 6.14 (1H, s), 7.08 (1H, td, J = 8.5, 3.2 Hz), 7.41

(1H, dd, J = 10.5, 3.1 Hz), 7.62 (1H, dd, J = 8.9, 5.7 Hz).

[0240]

C) tert-butyl 4-(5-fluoro-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidine-1-carboxylate

5 To a mixture of tert-butyl 4-(3-(2-bromo-5-fluorophenyl)-1,1,1-trifluoro-2-hydroxypropan-2-yl)piperidine-1-carboxylate (245 mg), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (64.9 mg), potassium carbonate (216 mg) and toluene (15 mL) was added palladium acetate (23.4 mg) under argon atmosphere. The
10 mixture was heated under reflux at 120°C for 3 days. The mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced
15 pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (50.0 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.10-1.29 (2H, m), 1.38 (9H, s), 1.55-1.75 (2H, m), 2.12-2.31 (1H, m), 2.73 (2H, brs), 3.26-3.36
20 (1H, m), 3.45-3.59 (1H, m), 3.91-4.07 (2H, m), 6.83-6.92 (1H, m), 6.93-7.03 (1H, m), 7.10 (1H, dd, J = 8.2, 2.7 Hz).

[0241]

D) (2s,4s)-2-((4-(5-fluoro-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-
25 azaspiro[3.4]octan-6-one

tert-Butyl 4-(5-fluoro-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidine-1-carboxylate (50.0 mg) was dissolved in 4N hydrogen chloride-ethyl acetate solution (3 mL) at room temperature. The solution was stirred at room
30 temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DMF (5 mL), and (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (22.0 mg), HOBt-H₂O (23.6 mg), EDCI (29.5 mg) and DIPEA (0.081 mL) were added thereto. The mixture was stirred at room
35 temperature for 5 hr. The mixture was poured into saturated

aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel
5 column chromatography (methanol/ethyl acetate) to give the title compound (42.0 mg).

¹H NMR (300 MHz, DMSO-d₆) δ1.09-1.32 (2H, m), 1.55-1.80 (2H, m), 2.18-2.45 (6H, m), 2.86-3.06 (2H, m), 3.25-3.37 (1H, m), 3.45-3.56 (1H, m), 3.83 (1H, d, J = 12.8 Hz), 4.27-4.48 (3H, m),
10 6.84-6.91 (1H, m), 6.93-7.03 (1H, m), 7.07-7.15 (1H, m), 8.02 (1H, d, J = 2.3 Hz).

[0242]

Example 62

(2s,4s)-2-((2-(2-chloro-4-fluorophenoxy)-7-azaspiro[3.5]non-7-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one
15

[0243]

A) benzyl 2-(2-chloro-4-fluorophenoxy)-7-azaspiro[3.5]nonane-7-carboxylate

To a solution of 2-chloro-4-fluorophenol (0.456 g) and
20 benzyl 2-((methylsulfonyl)oxy)-7-azaspiro[3.5]nonane-7-carboxylate (1 g) in DMA (20 mL) was added potassium carbonate (0.587 g) at room temperature. The mixture was stirred overnight at 80°C. The mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with
25 ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (806 mg).

30 ¹H NMR (300 MHz, DMSO-d₆) δ1.47-1.60 (4H, m), 1.76-1.89 (2H, m), 2.37-2.47 (2H, m), 3.23-3.45 (4H, m), 4.80 (1H, quin, J = 6.7 Hz), 5.06 (2H, s), 6.98 (1H, dd, J = 9.2, 5.0 Hz), 7.07-7.20 (1H, m), 7.27-7.45 (6H, m).

[0244]

35 B) 2-(2-chloro-4-fluorophenoxy)-7-azaspiro[3.5]nonane

hydrochloride

To a mixture of benzyl 2-(2-chloro-4-fluorophenoxy)-7-azaspiro[3.5]nonane-7-carboxylate (806 mg) and thioanisole (1 mL) was added trifluoroacetic acid (9 mL) at room temperature.

5 The mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and 4N hydrogen chloride-ethyl acetate solution (0.998 mL) was added thereto. The mixture was triturated with ethyl acetate/hexane to give the title compound
10 (400 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.68-1.81 (4H, m), 1.82-1.94 (2H, m), 2.38-2.49 (2H, m), 2.97 (4H, d, J = 18.5 Hz), 4.79 (1H, quin, J = 6.8 Hz), 6.99 (1H, dd, J = 9.2, 5.0 Hz), 7.16 (1H, ddd, J = 9.1, 8.2, 3.1 Hz), 7.43 (1H, dd, J = 8.3, 3.0 Hz), 8.65 (2H,
15 brs).

[0245]

C) (2s,4s)-2-((2-(2-chloro-4-fluorophenoxy)-7-azaspiro[3.5]non-7-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

A mixture of (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-
20 carboxylic acid (55.9 mg), 2-(2-chloro-4-fluorophenoxy)-7-azaspiro[3.5]nonane hydrochloride (100 mg), HOBT-H₂O (60.0 mg), EDCI (75 mg), DIPEA (0.205 mL) and DMF (2 mL) was stirred at room temperature for 5 hr. The mixture was poured into saturated sodium hydrogencarbonate, and extracted with ethyl
25 acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with ethyl acetate to give the title compound (105 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.38-1.60 (4H, m), 1.75-1.93 (2H, m),
30 2.18-2.44 (6H, m), 2.90-3.09 (1H, m), 3.20-3.48 (4H, m), 4.36 (2H, d, J = 4.0 Hz), 4.80 (1H, quin, J = 6.7 Hz), 6.99 (1H, dd, J = 9.3, 5.1 Hz), 7.14 (1H, td, J = 8.6, 3.1 Hz), 7.42 (1H, dd, J = 8.3, 3.0 Hz), 8.02 (1H, s).

[0246]

35 Example 64

(2s,4s)-2-((4-((2-fluoro-4-(2-fluoroethyl)phenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one
[0247]

5 A) methyl 2-(3-fluoro-4-hydroxyphenyl)acetate

A mixture of 2-(3-fluoro-4-hydroxyphenyl)acetic acid (2.2 g), conc. sulfuric acid (3 mL) and methanol (20 mL) was heated under reflux for 2 days. The mixture was concentrated under reduced pressure. The residue was basified with saturated aqueous sodium hydrogencarbonate solution at 0°C. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (2.31 g).

15 MS: [M-H]⁻ 182.9.

[0248]

B) tert-butyl 4-((2-fluoro-4-(2-methoxy-2-oxoethyl)phenoxy)methyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (2.46 g), methyl 2-(3-fluoro-4-hydroxyphenyl)acetate (2.31 g) and tri-n-butylphosphine (3.41 mL) in THF (50 mL) was added ADDP (3.45 g) at 0°C. The mixture was stirred at room temperature for 2 hr. The mixture was filtered through a pad of NH silica gel, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.51 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.06-1.25 (2H, m), 1.39 (9H, s), 1.66-1.82 (2H, m), 1.85-2.03 (1H, m), 2.63-2.86 (2H, m), 3.60 (3H, s), 3.62 (2H, s), 3.84-3.91 (2H, m), 3.92-4.04 (2H, m), 6.94-7.03 (1H, m), 7.05-7.16 (2H, m).

[0249]

C) 2-(4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methoxy)-3-fluorophenyl)acetic acid

35 A mixture of tert-butyl 4-((2-fluoro-4-(2-methoxy-2-

oxoethyl)phenoxy)methyl)piperidine-1-carboxylate (1000 mg), 2M aqueous sodium hydroxide solution (2.62 mL) and methanol (10 mL) was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure. The residue
5 was neutralized with 1M hydrochloric acid at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (885 mg).

10 ¹H NMR (300 MHz, DMSO-d₆) δ 1.05-1.23 (2H, m), 1.40 (9H, s), 1.67-1.80 (2H, m), 1.86-2.01 (1H, m), 2.59-2.94 (2H, m), 3.51 (2H, s), 3.86-3.91 (2H, m), 3.92-4.04 (2H, m), 6.94-7.02 (1H, m), 7.04-7.15 (2H, m), 12.32 (1H, brs).

[0250]

15 D) tert-butyl 4-((2-fluoro-4-(2-hydroxyethyl)phenoxy)methyl)piperidine-1-carboxylate

A mixture of 2-(4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methoxy)-3-fluorophenyl)acetic acid (885 mg), borane-THF complex (1M THF solution, 5.06 mL) and THF (20 mL) was stirred
20 at 60°C for 1.5 hr. The reaction was quenched with 1M hydrochloric acid, and the mixture was stirred at 60°C for 1 hr. The THF was evaporated under reduced pressure. The residue was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium
25 sulfate, and concentrated under reduced pressure to give the title compound (734 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.05-1.23 (2H, m), 1.39 (9H, s), 1.67-1.79 (2H, m), 1.84-1.97 (1H, m), 2.59-2.85 (4H, m), 3.49-3.60 (2H, m), 3.82-3.90 (2H, m), 3.91-4.03 (2H, m), 4.60 (1H, t, J = 5.3 Hz), 6.90-6.98 (1H, m), 6.99-7.12 (2H, m).

[0251]

E) (2s,4s)-2-((4-((2-fluoro-4-(2-fluoroethyl)phenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

35 To a solution of tert-butyl 4-((2-fluoro-4-(2-

hydroxyethyl)phenoxy)methyl)piperidine-1-carboxylate (684 mg) in acetonitrile (20 mL) was added diethylaminosulfur trifluoride (0.772 mL) at 0°C. The mixture was stirred at 0°C for 1 hr under dried atmosphere using a calcium chloride tube.

5 The reaction was quenched with saturated aqueous sodium hydrogencarbonate solution at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue

10 was purified by silica gel column chromatography (ethyl acetate/hexane). A mixture of the obtained residue and trifluoroacetic acid (10 mL) was stirred at 0°C for 30 min under dried atmosphere using a calcium chloride tube. The reaction mixture was concentrated under reduced pressure. To a

15 solution of the obtained residue, TEA (1.35 mL) and (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (331 mg) in DMF (10 mL) was added HATU (883 mg) at room temperature. The mixture was stirred overnight at room temperature under dried atmosphere using a calcium chloride tube. The reaction mixture

20 was poured into water at room temperature, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate).

25 The obtained solid was recrystallized from ethyl acetate/heptane to give the title compound (90 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.99-1.22 (2H, m), 1.69-1.84 (2H, m), 1.93-2.09 (1H, m), 2.25-2.43 (4H, m), 2.55-2.65 (1H, m), 2.82-2.89 (1H, m), 2.90-3.09 (3H, m), 3.74-3.85 (1H, m), 3.86-3.91 (2H, m), 4.31-4.42 (3H, m), 4.51 (1H, t, J = 6.4 Hz), 4.67 (1H, t, J = 6.2 Hz), 6.96-7.19 (3H, m), 8.04 (1H, s).

[0252]

Example 95

(2s,4s)-2-((3-((3-chloro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-

35

azaspiro[3.4]octan-6-one

[0253]

A) (3-chloro-4-(trifluoromethyl)phenyl)methanol

A solution of 3-chloro-4-(trifluoromethyl)benzoic acid
5 (1.97 g) in THF (29.2 mL) was cooled to 0°C under argon
atmosphere. To this mixture was added dropwise borane-THF
complex (1M THF solution, 17.6 mL) over 10 min at 0°C. The
reaction mixture was stirred at room temperature for 17 hr.
The reaction was quenched with methanol at 0°C, and the mixture
10 was stirred at room temperature for 1 hr. The solvent was
evaporated under reduced pressure, and the mixture was
partitioned between water and ethyl acetate. The organic layer
was washed with saturated brine, dried over anhydrous magnesium
sulfate, and filtered through a short pad of silica gel/NH
15 silica gel, and the filtrate was concentrated under reduced
pressure to give the title compound (1.84 g).

¹H NMR (300 MHz, DMSO-d₆) δ 4.52-4.68 (2H, m), 5.52 (1H, t, J =
5.8 Hz), 7.43-7.53 (1H, m), 7.63 (1H, s), 7.82 (1H, d, J = 8.1
Hz).

20 [0254]

B) 3-chloro-4-(trifluoromethyl)benzyl methanesulfonate

To a solution of (3-chloro-4-
(trifluoromethyl)phenyl)methanol (1.84 g) and TEA (2.82 mL) in
THF (30.7 mL) was added dropwise methanesulfonyl chloride (1.43
25 mL) at 0°C, and the mixture was stirred at room temperature for
3 hr. The mixture was partitioned between water and ethyl
acetate. The organic layer was washed with water and saturated
brine, dried over anhydrous sodium sulfate, and filtered
through a short pad of silica gel, and the filtrate was
30 concentrated under reduced pressure to give the title compound
(2.53 g).

¹H NMR (300 MHz, DMSO-d₆) δ 3.31 (3H, s), 5.37 (2H, s), 7.63 (1H,
dd, J = 8.1, 0.8 Hz), 7.81 (1H, s), 7.93 (1H, d, J = 8.1 Hz).

[0255]

35 C) tert-butyl 3-((3-chloro-4-

(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate

To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (1.45 g) in DMF (15.7 mL) was added 60% sodium hydride (0.402 g) under argon atmosphere at 0°C. The mixture was stirred at 0°C for 5 min. To the reaction mixture was added dropwise a solution of 3-chloro-4-(trifluoromethyl)benzyl methanesulfonate (2.53 g) in DMF (5.23 mL). The reaction mixture was stirred at room temperature for 3 hr. The reaction was quenched with saturated aqueous ammonium chloride solution, and the mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.66 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.38 (9H, s), 3.73 (2H, dd, J = 9.4, 3.4 Hz), 3.94-4.10 (2H, m), 4.30-4.41 (1H, m), 4.53 (2H, s), 7.52 (1H, d, J = 7.6 Hz), 7.69 (1H, s), 7.85 (1H, d, J = 8.1 Hz).

[0256]

D) 3-((3-chloro-4-(trifluoromethyl)benzyl)oxy)azetidine tosylate

A solution of tert-butyl 3-((3-chloro-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate (340 mg) and p-TsOH-H₂O (194 mg) in ethyl acetate (4.65 mL) was heated under reflux for 2 hr. The mixture was allowed to be cooled to room temperature, and the resulting solid was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (351 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.29 (3H, s), 3.89 (2H, dd, J = 12.1, 4.9 Hz), 4.10-4.22 (2H, m), 4.38-4.52 (1H, m), 4.58 (2H, s), 7.11 (2H, d, J = 7.7 Hz), 7.42-7.49 (2H, m), 7.53 (1H, d, J = 8.1 Hz), 7.73 (1H, s), 7.88 (1H, d, J = 8.3 Hz), 8.58 (2H, brs).
[0257]

E) (2s,4s)-2-((3-((3-chloro-4-

(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

A mixture of 3-((3-chloro-4-(trifluoromethyl)benzyl)oxy)azetidine tosylate (351 mg),
5 (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (137 mg), EDCI (169 mg), HOBT-H₂O (135 mg), DIPEA (0.42 mL) and DMF (2.67 mL) was stirred at room temperature for 3 hr. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine, dried over
10 anhydrous magnesium sulfate, and filtered through a short pad of NH silica gel, and the filtrate was concentrated under reduced pressure. The residue was washed with IPE/ethyl acetate to give the title compound (149 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.20-2.39 (4H, m), 2.69-2.79 (1H, m),
15 3.71 (1H, dd, J = 10.5, 3.7 Hz), 3.95 (1H, dd, J = 9.7, 3.7 Hz), 3.99-4.08 (1H, m), 4.21-4.30 (1H, m), 4.34 (2H, s), 4.38-4.46 (1H, m), 4.55 (2H, s), 7.52 (1H, d, J = 8.7 Hz), 7.70 (1H, s), 7.86 (1H, d, J = 8.3 Hz), 8.09 (1H, s).

[0258]

20 Example 112

(2s,4s)-2-((4-((2-chloro-4-fluorophenyl)(difluoro)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

[0259]

25 A) tert-butyl 4-(2-chloro-4-fluorobenzoyl)piperidine-1-carboxylate

To a solution of 2-chloro-4-fluoriodobenzene (11.6 g) in THF (80 mL) was added dropwise isopropylmagnesium chloride-lithium chloride complex (1.3M THF solution, 34.8 mL) over 20
30 min at -78°C, and the mixture was stirred at -15°C for 1.5 hr. To this mixture was added tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (6.16 g), and the mixture was stirred at room temperature for 48 hr. The reaction was quenched with aqueous ammonium chloride solution
35 at 0°C, and the mixture was extracted with ethyl acetate. The

organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title
5 compound (3.41 g).

¹H NMR (300 MHz, CDCl₃) δ 1.46 (9H, s), 1.54-1.71 (2H, m), 1.79-1.94 (2H, m), 2.72-2.94 (2H, m), 3.17-3.31 (1H, m), 4.01-4.19 (2H, m), 7.01-7.09 (1H, m), 7.17 (1H, dd, J = 8.5, 2.5 Hz), 7.39 (1H, dd, J = 8.6, 5.9 Hz).

10 [0260]

B) tert-butyl 4-((2-chloro-4-fluorophenyl)difluoromethyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(2-chloro-4-fluorobenzoyl)piperidine-1-carboxylate (1.95 g) in toluene (6
15 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (15.8 mL), and the mixture was stirred at 80°C for 18 hr. The reaction was quenched with aqueous sodium hydrogencarbonate solution at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated
20 brine, dried over anhydrous sodium sulfate, and filtered through a pad of NH silica gel/silica gel, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.63 g).

25 ¹H NMR (300 MHz, CDCl₃) δ 1.36-1.67 (13H, m), 2.41-2.75 (3H, m), 4.07-4.28 (2H, m), 6.99-7.08 (1H, m), 7.20 (1H, dd, J = 8.3, 2.6 Hz), 7.51 (1H, dd, J = 8.9, 6.0 Hz).

[0261]

C) 4-((2-chloro-4-fluorophenyl)difluoromethyl)piperidine
30 hydrochloride

To a solution of tert-butyl 4-((2-chloro-4-fluorophenyl)difluoromethyl)piperidine-1-carboxylate (1.63 g) in ethyl acetate (8 mL) was added 4N hydrogen chloride-ethyl acetate solution (11.2 mL), and the mixture was stirred at room
35 temperature for 1 hr. The resulting precipitate was collected,

washed with ethyl acetate, and dried under reduced pressure to give the title compound (1.18 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.57-1.76 (4H, m), 2.67-2.97 (3H, m), 3.23-3.34 (2H, m), 7.34-7.44 (1H, m), 7.59-7.70 (2H, m), 8.93 (2H, brs).

[0262]

D) (2s,4s)-2-((4-((2-chloro-4-fluorophenyl)(difluoro)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

To a mixture of (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (0.570 g), 4-((2-chloro-4-fluorophenyl)difluoromethyl)piperidine hydrochloride (1.00 g), HOBT-H₂O (0.612 g), EDCI (0.766 g), DIPEA (2.09 mL) and DMF (7 mL) was stirred at room temperature for 18 hr. The mixture was diluted with water, and extracted with ethyl acetate/IPA. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtered through a pad of NH silica gel/silica gel, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethanol/heptane to give the title compound (0.920 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.11-1.38 (2H, m), 1.48-1.64 (2H, m), 2.21-2.58 (5H, m), 2.61-2.82 (1H, m), 2.86-3.09 (2H, m), 3.75-3.89 (1H, m), 4.32-4.46 (3H, m), 7.31-7.43 (1H, m), 7.57-7.68 (2H, m), 8.03 (1H, s).

[0263]

Example 97

(2s,4s)-2-((3-((3-chloro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

[0264]

A) tert-butyl 3-((3-chloro-4-methylbenzyl)oxy)azetidine-1-carboxylate

To a solution of 3-chloro-4-methylbenzoic acid (1.50 g) in THF (29 mL) was added dropwise borane-THF complex (1M THF solution, 17.6 mL) over 10 min under argon atmosphere at 0°C, and the reaction mixture was stirred at room temperature for 16

hr. The reaction was quenched with methanol at 0°C, and the mixture was stirred at room temperature for 1 hr. The organic solvent was evaporated under reduced pressure, and the residue was partitioned between water and ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtered through a pad of silica gel and NH silica gel. The filtrate was concentrated under reduced pressure to give crude (3-chloro-4-methylphenyl)methanol (1.39 g).

10 To a solution of the obtained (3-chloro-4-methylphenyl)methanol (1.39 g) and TEA (2.72 mL) in THF (30 mL) was added dropwise methanesulfonyl chloride (1.37 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hr, and partitioned between water and ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give crude 3-chloro-4-methylbenzyl methanesulfonate (2.23 g).

20 To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (1.40 g) in DMF (15 mL) was added sodium hydride (60%, 387 mg) under argon atmosphere at 0°C, and the mixture was stirred at 0°C for 5 min. To the reaction mixture was added dropwise a solution of the obtained crude 3-chloro-4-methylbenzyl methanesulfonate (2.08 g) in DMF (5.0 mL), and the mixture was stirred at room temperature for 3 hr. The reaction was quenched with saturated aqueous ammonium chloride solution, and the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.12 g).

35 ¹H NMR (300 MHz, DMSO-d₆) δ 1.37 (9H, s), 2.32 (3H, s), 3.68 (2H, d, J = 5.3 Hz), 3.93-4.06 (2H, m), 4.26-4.34 (1H, m), 4.39 (2H,

s), 7.21 (1H, dd, J = 7.7, 1.5 Hz), 7.33 (1H, d, J = 7.9 Hz), 7.39 (1H, d, J = 1.5 Hz).

[0265]

B) 3-((3-chloro-4-methylbenzyl)oxy)azetidine 4-methylbenzenesulfonate

A solution of tert-butyl 3-((3-chloro-4-methylbenzyl)oxy)azetidine-1-carboxylate (2.12 g) and p-TsOH-H₂O (1.42 g) in ethyl acetate (34 mL) was heated under reflux for 2 hr. After the mixture was allowed to be cooled to room temperature, the solid was collected and washed with ethyl acetate to give the title compound (2.32 g).

¹H NMR (300 MHz, DMSO-d₆) δ2.29 (3H, s), 2.32 (3H, s), 3.84 (2H, dd, J = 12.1, 5.1 Hz), 4.06-4.17 (2H, m), 4.36-4.47 (3H, m), 7.06-7.15 (2H, m), 7.22 (1H, dd, J = 7.6, 1.6 Hz), 7.35 (1H, d, J = 7.9 Hz), 7.42 (1H, d, J = 1.5 Hz), 7.44-7.50 (2H, m), 8.58 (2H, brs).

[0266]

C) (2s,4s)-2-((3-((3-chloro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

To a solution of 3-((3-chloro-4-methylbenzyl)oxy)azetidine 4-methylbenzenesulfonate (400 mg), (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (196 mg) and HOBt-H₂O (183 mg) in DMF (5.0 mL) were added EDCI (260 mg) and TEA (0.218 mL) at 0°C, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed with 1M hydrochloric acid, 10% aqueous potassium carbonate solution and saturated brine, and dried over anhydrous sodium sulfate. The solution was filtered through NH silica gel, and the filtrate was concentrated under reduced pressure. The residue was crystallized from ethanol/water to give the title compound (290 mg).

¹H NMR (300 MHz, DMSO-d₆) δ2.19-2.41 (7H, m), 2.64-2.80 (1H, m), 3.60-3.69 (1H, m), 3.85-4.05 (2H, m), 4.17-4.28 (1H, m), 4.31-4.43 (5H, m), 7.21 (1H, dd, J = 7.7, 1.5 Hz), 7.30-7.36 (1H, m),

7.39 (1H, d, J = 1.3 Hz), 8.09 (1H, s).

mp 118°C

powder X-RAY crystal diffraction pattern (diffraction angle
2θ): 5.3°, 10.6°, 15.5°, 16.5°, 17.9°, 18.3°, 21.3°, 22.0°,
5 22.9°

[0267]

Example 6

(2s,4s)-2-((3-((2-fluoro-4-
(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-
10 azaspiro[3.4]octan-6-one

[0268]

A) (2-fluoro-4-(trifluoromethyl)phenyl)methanol

To a solution of 2-fluoro-4-(trifluoromethyl)benzoic acid
(2.00 g) and 4-methylmorpholine (1.59 mL) in THF (20 mL) was
15 added chloroethyl formate (1.20 mL) at room temperature, and
the mixture was stirred for 1 hr. To the reaction mixture was
added dropwise a solution of sodium borohydride (1.27 g) in
water (10 mL) at 0°C, and the mixture was stirred at room
temperature for 2 hr. The reaction mixture was poured into
20 saturated aqueous sodium hydrogencarbonate solution, and
extracted with ethyl acetate. The organic layer was separated,
washed with saturated brine, dried over anhydrous magnesium
sulfate, and concentrated under reduced pressure. The residue
was purified by silica gel column chromatography (ethyl
25 acetate/hexane) to give the title compound (1.26 g).

¹H NMR (300 MHz, DMSO-d₆) δ4.62 (2H, d, J = 5.5 Hz), 5.49 (1H,
t, J = 5.7 Hz), 7.54-7.64 (2H, m), 7.66-7.78 (1H, m).

[0269]

B) 2-fluoro-4-(trifluoromethyl)benzyl methanesulfonate

30 To a solution of (2-fluoro-4-
(trifluoromethyl)phenyl)methanol (1.26 g) and TEA (1.09 mL) in
THF (30 mL) was added methanesulfonyl chloride (0.553 mL) at
0°C, and the mixture was stirred overnight at room temperature.
The reaction was quenched with saturated aqueous sodium
35 hydrogencarbonate solution, and the mixture was extracted with

ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (1.77 g).

5 ¹H NMR (300 MHz, CDCl₃) δ 3.30 (3H, s), 5.41 (2H, s), 7.64-7.72 (1H, m), 7.75-7.86 (2H, m).

[0270]

C) tert-butyl 3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate

10 To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (1.12 g) in DMF (20 mL) was added sodium hydride (60%, 311 mg) at 0°C, and the mixture was stirred at room temperature for 10 min. To the reaction mixture was added a solution of 2-fluoro-4-(trifluoromethyl)benzyl methanesulfonate
15 (1.77 g) in DMF (10 mL), and the mixture was stirred overnight at 60°C. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and
20 concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.73 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.37 (9H, s), 3.71 (2H, dd, J = 9.1, 3.4 Hz), 3.98-4.09 (2H, m), 4.38 (1H, tt, J = 6.4, 4.0 Hz),
25 4.57 (2H, s), 7.57-7.77 (3H, m).

[0271]

D) 3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)azetidine 4-methylbenzenesulfonate

A mixture of tert-butyl 3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate (1.73 g),
30 p-TsOH-H₂O (1.04 g) and ethyl acetate (30 mL) was heated under reflux for 1.5 hr. The precipitate was collected by filtration, and washed with ethyl acetate to give the title compound (1.93 g).

35 ¹H NMR (300 MHz, DMSO-d₆) δ 2.29 (3H, s), 3.82-3.93 (2H, m),

4.11-4.22 (2H, m), 4.43-4.55 (1H, m), 4.63 (2H, s), 7.06-7.16 (2H, m), 7.43-7.51 (2H, m), 7.60-7.77 (3H, m), 8.62 (2H, brs).
[0272]

E) (2s,4s)-2-((3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

To a mixture of 3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)azetidine 4-methylbenzenesulfonate (1.00 g), (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (406 mg), HOBt-H₂O (436 mg), EDCI (546 mg) and DMF (10 mL) was added TEA (1.32 mL) at room temperature, and the mixture was stirred overnight. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and methanol/ethyl acetate), and crystallized from ethyl acetate/hexane to give the title compound (498 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.18-2.38 (4H, m), 2.65-2.79 (1H, m), 3.68 (1H, dd, J = 10.7, 3.9 Hz), 3.93 (1H, dd, J = 8.9, 3.6 Hz), 4.04 (1H, dd, J = 10.1, 6.7 Hz), 4.20-4.30 (1H, m), 4.34 (2H, s), 4.39-4.48 (1H, m), 4.59 (2H, s), 7.57-7.65 (1H, m), 7.66-7.76 (2H, m), 8.08 (1H, s).

mp 157°C

powder X-RAY crystal diffraction pattern (diffraction angle 2θ): 4.8°, 14.5°, 16.6°, 17.4°, 19.9°, 22.6°, 26.0°, 26.5°.
[0273]

Example 93

(2s,4s)-2-((3-((2-methyl-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one
[0274]

A) 1-(bromomethyl)-2-methyl-4-(trifluoromethyl)benzene

To a solution of 2-methyl-4-(trifluoromethyl)benzoic acid (879 mg) in THF (7.0 mL) was added dropwise borane-THF complex (1M THF solution, 10.8 mL) over 30 min at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0°C, and the reaction was quenched with methanol. The mixture was concentrated under reduced pressure, and the residue was partitioned between saturated brine and ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and passed through a pad of silica gel. The filtrate was concentrated under reduced pressure to give crude (2-methyl-4-(trifluoromethyl)phenyl)methanol (895 mg).

To a solution of (2-methyl-4-(trifluoromethyl)phenyl)methanol (865 mg) in 1,2-dimethoxyethane (12 mL) was added dropwise phosphorus tribromide (0.257 mL) at 0°C, and the mixture was stirred at room temperature for 2 hr. The reaction was quenched with ice water, and the mixture was extracted with ethyl acetate/hexane. The extract was washed with water, saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtered through a pad of silica gel and NH silica gel. The filtrate was concentrated under reduced pressure to give the title compound (932 mg).

¹H NMR (300 MHz, CDCl₃) δ 2.47 (3H, s), 4.50 (2H, s), 7.37-7.59 (3H, m).

[0275]

B) tert-butyl 3-((2-methyl-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate

To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (633 mg) in DMF (9.0 mL) was added sodium hydride (60%, 190 mg) at 0°C, and the mixture was stirred for 10 min. To this reaction mixture was added dropwise a solution of 1-(bromomethyl)-2-methyl-4-(trifluoromethyl)benzene (924 mg) in DMF (3.0 mL) at 0°C, and the mixture was stirred at room temperature for 3 hr. The reaction was quenched with ice, and

the mixture was extracted with ethyl acetate. The extract was washed with water (twice) and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.15 g).

^1H NMR (300 MHz, CDCl_3) δ 1.44 (9H, s), 2.38 (3H, s), 3.88 (2H, dd, $J = 10.2, 4.1$ Hz), 4.05-4.17 (2H, m), 4.34 (1H, tt, $J = 6.4, 4.3$ Hz), 4.47 (2H, s), 7.40-7.48 (3H, m).

10 [0276]

C) 3-((2-methyl-4-(trifluoromethyl)benzyl)oxy)azetidine 4-methylbenzenesulfonate

A mixture of tert-butyl 3-((2-methyl-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate (1.15 g),
15 p-TsOH-H₂O (662 mg) and ethyl acetate (10 mL) was heated under reflux for 2 hr, and stirred at room temperature for 1 hr. The precipitate was collected by filtration, and washed with ethyl acetate to give the title compound (1.27 g).

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 2.29 (3H, s), 2.36 (3H, s), 3.87 (2H, dd, $J = 12.1, 5.3$ Hz), 4.17 (2H, dd, $J = 12.1, 6.4$ Hz), 4.41-4.53 (1H, m), 4.57 (2H, s), 7.11 (2H, d, $J = 8.3$ Hz), 7.41-7.52 (2H, m), 7.52-7.64 (3H, m), 8.61 (2H, brs).

[0277]

D) (2s,4s)-2-((3-((2-methyl-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one

To a solution of 3-((2-methyl-4-(trifluoromethyl)benzyl)oxy)azetidine 4-methylbenzenesulfonate (250 mg), (2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]octane-2-carboxylic acid (102 mg), EDCI (138 mg) and HOBt-H₂O (92.0 mg)
30 in acetonitrile (3.0 mL) was added dropwise TEA (0.200 mL) at room temperature, and the mixture was stirred for 5 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate solution/water (1:1), and extracted with
35 ethyl acetate. The extract was washed with water and saturated

brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate), and crystallized from ethyl acetate/IPE to give the title compound
5 (173 mg).

^1H NMR (300 MHz, DMSO- d_6) δ 2.17-2.43 (7H, m), 2.66-2.83 (1H, m), 3.70 (1H, dd, J = 10.5, 3.8 Hz), 3.94 (1H, dd, J = 9.0, 3.4 Hz), 4.00-4.12 (1H, m), 4.21-4.31 (1H, m), 4.34 (2H, s), 4.39-4.48 (1H, m), 4.53 (2H, s), 7.44-7.71 (3H, m), 8.10 (1H, s).

10 mp 129°C

powder X-RAY crystal diffraction pattern (diffraction angle 2θ): 6.8°, 13.7°, 15.9°, 19.9°, 20.2°, 20.5°, 21.7°, 23.4°, 25.1°

[0278]

15 The compounds of Examples 2, 3, 5, 7 to 48, 50, 52 to 56, 59 to 61, 63, 65 to 92, 94, 96, 98 to 111 and 113 to 130 in the following tables were produced according to the methods described in the above-mentioned Examples, or methods analogous thereto. The compounds of Examples are shown in the following
20 Tables 1-1 to 1-13. MS in the tables means actual measured value.

[0279]

Table 1-1

EXAMPLE	IUPAC NAME	Structure	MS
1	(2s,4r)-2-((4-((2-chloro-4-fluorophenoxy)methyl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one		395.2
2	(2r,4s)-2-((4-((2-chloro-4-fluorophenoxy)methyl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one		395.2
3	(2s,4s)-2-((4-((2-chloro-4-fluorophenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		397.1
4	(2s,4s)-2-((4-(5-fluoro-2-methyl-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		389.2
5	(2r,4s)-2-((4-(5-fluoro-2-methyl-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one (optical isomer)		387.4
6	(2s,4s)-2-((3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		403.3
7	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		411.3
8	(2s,4s)-2-((4-((2,4-dichlorophenyl)(difluoro)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		433.1
9	(2s,4s)-2-((3-((2-fluoro-4-(trifluoromethyl)phenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		403.1
10	(2s,4s)-2-((3-(1-(2-fluoro-4-(trifluoromethyl)phenoxy)ethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		417.1

[0280]

Table 1-2

11	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		411.2
12	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		411.2
13	(2s,4s)-2-((3-(1-(2-fluoro-4-(trifluoromethyl)phenoxy)ethyl)azetid in-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		417.1
14	(2s,4s)-2-((3-(1-(2-fluoro-4-(trifluoromethyl)phenoxy)ethyl)azetid in-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		417.1
15	(2s,4s)-2-((4-(1-(2,4-difluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		395.2
16	(2s,4s)-2-((4-(5,7-difluoro-2-methyl-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		407.2
17	(2r,4s)-2-((4-(1-(4-chloro-2-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one		409.2
18	(2s,4s)-2-((4-(1-(4-chloro-2-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		411.1
19	(2s,4s)-2-((4-((2-chloro-4-(trifluoromethyl)phenoxy)methyl)pipe ridin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		447.1
20	(2s,4s)-2-((4-(1-(4-fluoro-2-methylphenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		391.2

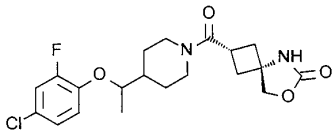
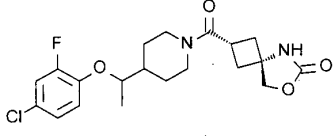
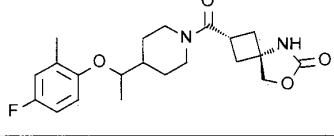
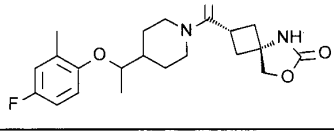
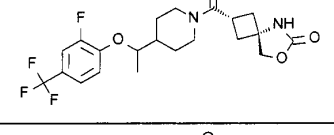
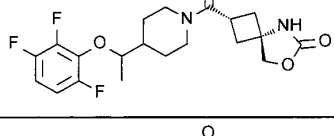
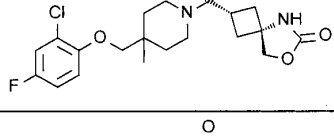
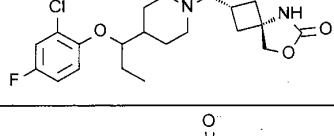
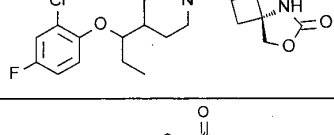
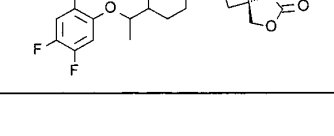
[0281]

Table 1-3

21	(2s,4s)-2-((4-(1-(2,4-difluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		395.2
22	(2s,4s)-2-((4-(1-(2,4-difluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		395.2
23	(2s,4s)-2-((4-((2-fluoro-4-methylphenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		377.2
24	(2s,4s)-2-((4-((2,4-dichlorobenzyl)oxy)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		413.0
25	(2s,4s)-2-((4-((2-chloro-4-fluorophenoxy)methyl)piperidin-1-yl)carbonyl)-8-oxa-5-azaspiro[3.5]nonan-6-one		411.2
26	(2s,4s)-2-((4-((2-fluoro-4-(trifluoromethyl)phenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		431.1
27	(2s,4s)-2-((4-(7-chloro-5-fluoro-2-methyl-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		423.1
28	(2s,4s)-2-((4-(1-(2-fluoro-4-methylphenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		391.2
29	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)propyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		425.2
30	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)-2,2,2-trifluoroethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		465.1

[0282]

Table 1-4

31	(2s,4s)-2-((4-(1-(4-chloro-2-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		411.2
32	(2s,4s)-2-((4-(1-(4-chloro-2-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		411.2
33	(2s,4s)-2-((4-(1-(4-fluoro-2-methylphenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		391.2
34	(2s,4s)-2-((4-(1-(4-fluoro-2-methylphenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		391.2
35	(2s,4s)-2-((4-(1-(2-fluoro-4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		445.3
36	(2s,4s)-2-((4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		413.2
37	(2s,4s)-2-((4-((2-chloro-4-fluorophenoxy)methyl)-4-methylpiperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		411.1
38	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)propyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		425.2
39	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)propyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		425.2
40	(2s,4s)-2-((4-(1-(2,4,5-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		413.2

[0283]

Table 1-5

41	(2s,4s)-2-((3-((5-bromo-2-fluoro-4-(trifluoromethyl)phenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		481.0
42	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)-2,2,2-trifluoroethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		465.1
43	(2s,4s)-2-((4-(1-(2-chloro-4-fluorophenoxy)-2,2,2-trifluoroethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		465.1
44	(2s,4s)-2-((4-((2-chloro-4-fluorophenoxy)methyl)-4-ethylpiperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		425.1
45	(2s,4s)-2-((4-(1-(2-fluoro-4-methylphenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		391.2
46	(2s,4s)-2-((4-(1-(2-fluoro-4-methylphenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		391.2
47	(2s,4s)-2-((4-(1-(4-cyclopropyl-2-fluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		417.2
48	(2s,4s)-2-((4-((2-chloro-4-fluorophenoxy)methyl)-4-(trifluoromethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		465.1
49	(2s,4s)-2-((4-((2-chloro-4-(3-fluoroazetidin-1-yl)phenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		452.1
50	(2s,4s)-2-((4-(diphenylmethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		405.2

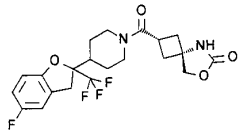
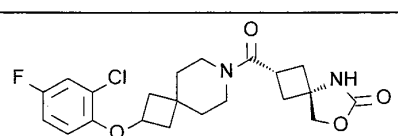
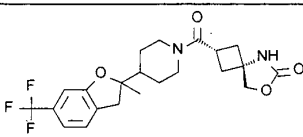
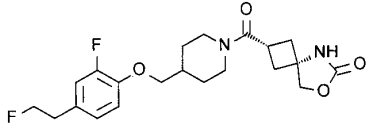
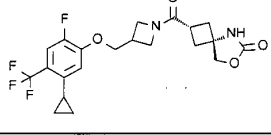
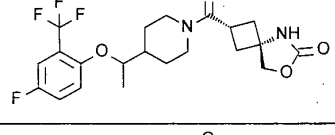
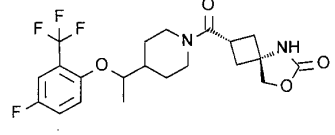
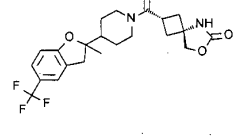
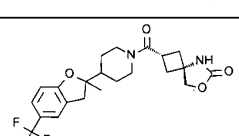
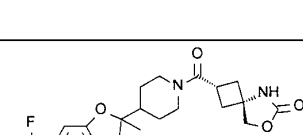
[0284]

Table 1-6

51	(2s,4s)-2-((4-(1,1-diphenylethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		419.2
52	(2s,4s)-2-((4-((2-chloro-4-fluorophenyl)(difluoro)methyl)-4-methylpiperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		431.1
53	(2s,4s)-2-((4-(2-methyl-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		439.2
54	(2s,4s)-2-((4-(1-(2,4,5-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
55	(2s,4s)-2-((4-(1-(2,4,5-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
56	(2s,4s)-2-((4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
57	(2s,4s)-2-((4-(1-(2,3,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
58	(2s,4s)-2-((4-(5-fluoro-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		443.2
59	(2s,4s)-2-((4-(1-(4-fluoro-2-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		445.2
60	(2s,4s)-2-((4-(5-fluoro-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		443.2

[0285]

Table 1-7

61	(2s,4s)-2-((4-(5-fluoro-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		443.2
62	(2s,4s)-2-((2-(2-chloro-4-fluorophenoxy)-7-azaspiro[3.5]non-7-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		423.1
63	(2s,4s)-2-((4-(2-methyl-6-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		439.2
64	(2s,4s)-2-((4-((2-fluoro-4-(2-fluoroethyl)phenoxy)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		409.1
65	(2s,4s)-2-((3-((5-cyclopropyl-2-fluoro-4-(trifluoromethyl)phenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		443.2
66	(2s,4s)-2-((4-(1-(4-fluoro-2-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		445.2
67	(2s,4s)-2-((4-(1-(4-fluoro-2-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		445.2
68	(2s,4s)-2-((4-(2-methyl-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		439.2
69	(2s,4s)-2-((4-(2-methyl-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		439.2
70	(2s,4s)-2-((4-(2-methyl-6-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		439.2

[0286]

Table 1-8

71	(2s,4s)-2-((4-(2-methyl-6-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		439.2
72	(2s,4s)-2-((3-((2-fluoro-5-methyl-4-(trifluoromethyl)phenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		417.1
73	(2r,4s)-2-((4-(1-(4-fluoro-2-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one		443.2
74	(2r,4s)-2-((4-(1-(2,3,4-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-5-azaspiro[3.4]octan-6-one		411.2
75	(2s,4s)-2-((3-((2,6-dichloro-4-fluorophenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		403.0
76	(2s,4s)-2-((3-((2-chloro-4-(trifluoromethyl)phenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		419.1
77	(2s,4s)-2-((4-(1-(2-fluoro-4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		445.2
78	(2s,4s)-2-((4-(1-(2-fluoro-4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		445.2
79	(2s,4s)-2-((3-((2,4-dichlorophenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		385.0
80	(2s,4s)-2-((4-(1-(2,3,4-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		413.2

[0287]

Table 1-9

81	(2s,4s)-2-((4-(1-(2,3,4-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
82	(2s,4s)-2-((4-(1-(2,3,4-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
83	(2s,4s)-2-((3-((3,5-bis(trifluoromethyl)phenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		453.2
84	(2s,4s)-2-((3-((2-chloro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		419.1
85	(2s,4s)-2-((4-(1-(2,4,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		413.2
86	(2s,4s)-2-((3-((5-ethyl-2-fluoro-4-(trifluoromethyl)phenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		431.1
87	(2s,4s)-2-((4-(1-(2,4,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
88	(2s,4s)-2-((4-(1-(2,4,6-trifluorophenoxy)ethyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one (optical isomer)		413.2
89	(2s,4s)-2-((3-((2,4-dichlorobenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		382.9
90	(2s,4s)-2-((3-((3,4-dichlorobenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		385.1

[0288]

Table 1-10

91	(2s,4s)-2-((3-((2,2-difluoro-2-(2-fluoro-4-(trifluoromethyl)phenyl)ethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		437.1
92	(2s,4s)-2-((3-((4-chloro-2-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		365.1
93	(2s,4s)-2-((3-((2-methyl-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		399.2
94	(2s,4s)-2-((3-((2,3-difluoro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		367.1
95	(2s,4s)-2-((3-((3-chloro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		419.1
96	(2s,4s)-2-((3-((2,3-difluoro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		421.1
97	(2s,4s)-2-((3-((3-chloro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		365.1
98	(2s,4s)-2-((3-((4-chloro-3-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		365.1
99	(2s,4s)-2-((3-((2,2-difluoro-2-(3-fluoro-4-(trifluoromethyl)phenyl)ethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		437.2
100	(2s,4s)-2-((3-((2,2-difluoro-2-(4-fluoro-3-(trifluoromethyl)phenyl)ethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		434.9

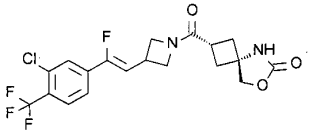
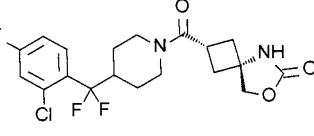
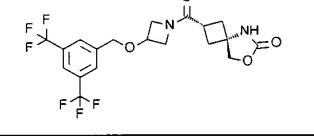
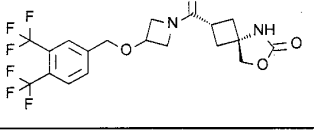
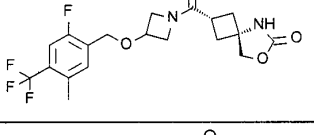
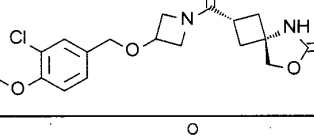
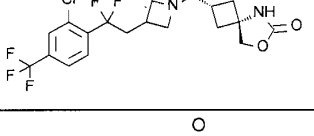
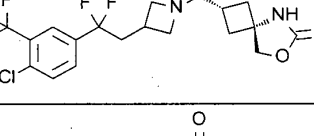
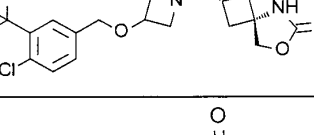
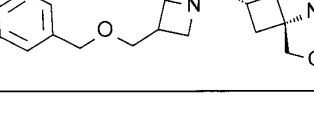
[0289]

Table 1-11

101	(2s,4s)-2-((3-((2,5-difluoro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		421.1
102	(2s,4s)-2-((3-((3-chloro-2-fluoro-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		437.1
103	(2s,4s)-2-((3-(2-(2,3-difluoro-4-(trifluoromethyl)phenyl)-2,2-difluoroethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		453.0
104	(2s,4s)-2-((3-((Z)-2-(2,3-difluoro-4-(trifluoromethyl)phenyl)-2-fluorovinyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		435.1
105	(2s,4s)-2-((3-((4-methyl-3-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		399.2
106	(2s,4s)-2-((3-((3,5-dichloro-4-fluorobenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		403.1
107	(2s,4s)-2-((3-((2-chloro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		365.1
108	(2s,4s)-2-((3-((3-methyl-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		399.2
109	(2s,4s)-2-((3-(2-(3-chloro-4-methylphenyl)-2,2-difluoroethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		399.1
110	(2s,4s)-2-((3-(2-(3-chloro-4-(trifluoromethyl)phenyl)-2,2-difluoroethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		453.1

[0290]

Table 1-12

111	(2s,4s)-2-((3-((Z)-2-(3-chloro-4-(trifluoromethyl)phenyl)-2-fluorovinyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		433.0
112	(2s,4s)-2-((4-((2-chloro-4-fluorophenyl)(difluoro)methyl)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		417.1
113	(2s,4s)-2-((3-((3,5-bis(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		453.2
114	(2s,4s)-2-((3-((3,4-bis(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		453.2
115	(2s,4s)-2-((3-((2-fluoro-5-methyl-4-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		417.1
116	(2s,4s)-2-((3-((3-chloro-4-(trifluoromethoxy)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		435.1
117	(2s,4s)-2-((3-((2-(2-chloro-4-(trifluoromethyl)phenyl)-2,2-difluoroethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		453.1
118	(2s,4s)-2-((3-((2-(4-chloro-3-(trifluoromethyl)phenyl)-2,2-difluoroethyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		453.1
119	(2s,4s)-2-((3-((4-chloro-3-(trifluoromethyl)benzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		419.1
120	(2s,4s)-2-((3-(((3-chloro-4-methylbenzyl)oxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		379.2

[0291]

Table 1-13

121	(2s,4s)-2-((3-(((4-chloro-3-methylbenzyl)oxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		379.2
122	(2s,4s)-2-((3-((2-chloro-4-fluorophenoxy)methyl)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		369.1
123	(2r,4r)-2-((3-((3-chloro-4-methylbenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		365.1
124	(2s,4s)-2-((3-((2-chloro-4-fluorobenzyl)oxy)pyrrolidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		383.1
125	(2s,4s)-2-((4-((2-chloro-4-fluorobenzyl)oxy)piperidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		397.2
126	(2s,4s)-2-((3-((2-chloro-4-fluorobenzyl)oxy)azetidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		369.1
127	(2s,4s)-2-((3-((2-chloro-4-fluorophenoxy)methyl)pyrrolidin-1-yl)carbonyl)-7-oxa-5-azaspiro[3.4]octan-6-one		383.1
128	2-((1-(((2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]oct-2-yl)carbonyl)piperidin-4-yl)methoxy)-5-(trifluoromethyl)benzonitrile		438.2
129	5-chloro-2-((1-(((2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]oct-2-yl)carbonyl)piperidin-4-yl)methoxy)benzonitrile		404.1
130	3-chloro-4-((1-(((2s,4s)-6-oxo-7-oxa-5-azaspiro[3.4]oct-2-yl)carbonyl)piperidin-4-yl)methoxy)benzonitrile		404.1

[0292]

Experimental Example 1: Cloning of human MGLL encoding MAGL protein and construction of expression plasmid

Human MGLL cDNA was obtained by PCR using human ORF Clone
5 (DNAForm; Clone ID: 100004585) as a template. For PCR, two kinds of primers:

5'-CCACCATCATCACGGATCCATGCCAGAGGAAAGTTCCCCCA-3'

[SEQ ID NO: 1]

and

10 5'-TGGTGCTCGAGTGCGGCCGCTCAGGGTGGGGACGCAGTTC-3'

[SEQ ID NO: 2]

and PrimeSTAR MAX DNA Polymerase (Takara Bio Inc.) were used, and (1) reaction at 98°C for 1 min, (2) 25 cycles of reaction at 98°C for 10 sec and 68°C for 10 sec as one cycle, and (3)
15 reaction at 72°C for 1 min were performed. The obtained PCR product was digested with Bam HI and Not I (Takara Bio Inc.), inserted into the Bam HI/Not I site of pET21HH(V) (pET21a (Novagen) inserted with His x6 and TEV Protease recognition sequence) by using Ligation High (Toyobo Co., Ltd.), and
20 introduced into ECOS™ JM109 (Nippon Gene Co., Ltd.), whereby expression plasmid pET21HH(V)/His-hMGLLv2 for Escherichia coli was constructed.

[0293]

Experimental Example 2: Preparation of recombinant
25 polyhistidine tagged human MAGL protein

Recombinant His-hMAGL protein was prepared by transforming ECOS™ Competent E. coli BL21(DE3) (Nippon Gene Co., Ltd.) with the pET21HH(V)/His-hMGLLv2 plasmid prepared above. Escherichia coli obtained by transformation was
30 inoculated to 10 mL of LB medium (1% peptone, 0.5% yeast extract, 0.5% sodium chloride, 0.01% ampicillin), and cultured at 30°C for 16 hr. The obtained culture medium (5 mL) was transplanted into a 2L Sakaguchi flask containing 1L of main fermentation medium (1.05% M9 MEDIUM BROTH (AMRESCO LLC), 0.5%
35 yeast extract, 1.5% sorbitol, 1.5% casamino acid, 0.024%

magnesium sulfate, 0.01% antifoaming agent PE-L (Wako Pure Chemical Industries, Ltd.), 0.01% ampicillin), and shaking culture at 37°C and 150 rpm was started. When the turbidity of the culture medium reached about 500 Klett unit, the culture temperature was lowered to 16°C, isopropyl- β -D-thiogalactopyranoside (IPTG) was added to a final concentration of 1 mM, and the mixture was further cultured for 19 hr. After the completion of culture, the culture medium was centrifuged (4°C, 6,000 rpm, 10 min) to give His-hMAGL-expressed Escherichia coli. Then, His-hMAGL-expressed Escherichia coli was suspended in 50 mM Tris-HCl (pH 8.0, 100 ml) containing 1% Triton X-100, 20 mM imidazole, 3 mM DTT, 5 U/mL Benzonase (Merck) and 150 mM NaCl, and the suspension was sufficiently cooled, and subjected to sonication at AMPLITUDE=60%, 15 sec/ON, 30 sec/OFF for 3 min using 3/4" solid type crushed horn of BRANSON Digital Sonifier 450 (Central Scientific Commerce, Inc.). Furthermore, the homogenate was centrifuged (4°C, 6,000 rpm, 20 min) and the supernatant was obtained. As the purification apparatus, AKTA explorer 10s (GE Healthcare Japan Corporation) was used at 4°C. To the obtained supernatant was added 5M NaCl to the final salt concentration of 0.3 M, and the mixture was flown through and adsorbed to 5 mL of Ni-NTA Superflow Cartridges (QIAGEN) equilibrated in advance with buffer A (50 mM Tris-HCl (pH 8.0) containing 0.05% TritonX-100, 1 mM DTT, 300 mM NaCl). The column was sufficiently washed with buffer A containing 20 mM imidazole and His-hMAGL was eluted with buffer A containing imidazole at a final concentration of 250 mM. The eluate was further subjected to gel filtration using HiLoad 16/600 Superdex 200 pg (GE Healthcare Japan Corporation) equilibrated with 50 mM Tris-HCl pH 8.0 containing 10% glycerol, 0.05% TritonX-100, 1 mM DTT and 150 mM NaCl. The eluted fraction was concentrated by Amicon Ultra-15 10K (Merck Millipore) to give purified His-hMAGL protein. The protein concentration was measured by BCA Protein Assay Kit (Thermo Fisher Scientific) using BSA as the standard.

[0294]

Experimental Example 3: Measurement of MAGL inhibitory activity

The His-hMAGL obtained above was diluted with enzyme reaction buffer (10 mM Tris-HCl, pH 7.5, 1 mM EDTA, 0.025 (w/v)% Triton X-100, 0.01% Bovine serum albumin) to a concentration of 7.5 ng/mL. To each well of a 384 well assay plate (Greiner 781280) was added a solution (5 μ L) of a test compound dissolved in dimethyl sulfoxide (DMSO), which was diluted with the above-mentioned enzyme reaction buffer, then His-hMAGL solution (5 μ L) diluted to a concentration of 7.5 ng/mL was added and the mixture was incubated at room temperature for 60 min. Thereafter, to each well was added 5 μ L of 150 μ M 2-arachidonylglycerol (Tocris Bioscience), and the mixture was incubated at room temperature for 10 min. Then, 10 μ L of 2% formic acid (Wako Pure Chemical Industries, Ltd.) was added to stop the reaction. Furthermore, acetonitrile (50 μ L) containing 3 μ M arachidonic acid-d8 (Cayman Chemical Company) was added and the mixture was stirred.

The amount of arachidonic acid in the obtained enzyme reaction mixture was calculated by measuring by RapidFire-mass spectrometry and correcting by the amount of arachidonic acid-d8. High Throughput online solid phase extraction was performed using RapidFire 300™ system (Agilent Technologies, Inc.). Samples were loaded on SPE C4 cartridge (Agilent Technologies, Inc.) and desalted with 0.2 (v/v)% acetic acid (Wako Pure Chemical Industries, Ltd.) in ultrapure water/acetonitrile (70/30, v/v) at a flow rate of 1.5 mL/min, eluted at a flow rate of 0.5 mL/min with 0.2(v/v)% acetic acid dissolved in acetonitrile/ultrapure water (90/10, v/v), and injected into the mass spectrometry part. The injection needle was washed with ultrapure water (500 millisecond) and acetonitrile (500 millisecond) to minimize carry-over. The suction time (injection loop 5 μ L), load/cleansing time, elution time and re-equilibration time were adjusted to 300, 3000, 4250 and 1000 milliseconds, respectively, and the total

cycle time was adjusted to about 10.0 seconds. The RapidFire300 system was controlled by RapidFire UI software version 3.6 (Agilent Technologies, Inc.).

The mass spectrometry of the resultant product was performed using API4000TM triple quadrupole mass spectrometer (AB SCIEX) equipped with an electrospray ion source (TurboIon SprayTM) in a negative selected reaction monitoring (SRM) mode. The conditions of SRM are shown below. The parameters of the instrument were optimized as follows: capillary temperature 600°C, ion spray voltage -4.5 kV, collision gas 8, curtain gas 15 psi, ion source gas 1 60 psi, ion source gas 2 60 psi. The mass spectrometer was controlled by AnalystTM software version 1.5.1 (AB SCIEX). The peak area integration was analyzed using RapidFire integrator software version 3.6 (Agilent Technologies, Inc.).

MAGL inhibitory rate (%) was calculated according to the following calculation formula.

$$(1 - (\text{arachidonic acid production amount of test compound addition group} - \text{arachidonic acid production amount of enzyme-free group}) / (\text{arachidonic acid production amount of test compound-free group} - \text{arachidonic acid production amount of enzyme-free group})) \times 100$$

The results are shown in the following Tables 2-1 and 2-2.

[0295]

Table 2-1

Example	% inhibition (10 μ M)	Example	% inhibition (10 μ M)	Example	% inhibition (10 μ M)
1	90	41	101	81	100
2	100	42	101	82	100
3	101	43	100	83	100
4	100	44	101	84	100
5	100	45	100	85	100
6	100	46	100	86	100
7	100	47	100	87	100
8	100	48	100	88	100
9	100	49	101	89	100
10	100	50	101	90	100
11	100	51	101	91	100
12	100	52	100	92	100
13	100	53	101	93	100
14	100	54	101	94	100
15	100	55	100	95	100
16	100	56	100	96	100
17	100	57	100	97	100
18	101	58	100	98	100
19	101	59	100	99	100
20	100	60	100	100	100
21	100	61	100	101	100
22	101	62	100	102	100
23	100	63	100	103	100
24	100	64	101	104	100
25	100	65	101	105	100
26	101	66	100	106	100
27	101	67	100	107	100
28	100	68	100	108	100
29	101	69	101	109	99
30	101	70	101	110	100
31	101	71	101	111	100
32	100	72	101	112	100
33	101	73	100	113	100
34	101	74	101	114	100
35	101	75	100	115	100
36	101	76	100	116	100
37	100	77	101	117	100
38	100	78	101	118	100
39	100	79	100	119	100
40	101	80	101		

[0296]

Table 2-2

Example	% inhibition (10 μ M)	Example	% inhibition (10 μ M)	Example	% inhibition (10 μ M)
120	100	124	99	128	100
121	101	125	100	129	100
122	99	126	100	130	100
123	99	127	99		

[0297]

As is clear from Table 2-1 and Table 2-2, the compound of the present invention has a MAGL inhibitory activity.

[0298]

Experimental Example 4: Measurement of intracerebral 2-AG and
5 arachidonic acid concentrations

As the mouse, 8-week-old male C57BL/6J mice (CLEA Japan, Inc.) were used (6 mice/group). Administration solutions were prepared by suspending the test compounds (compound 1 (compound of Example 6), compound 2 (compound of Example 93) and compound
10 3 (compound of Example 97)) in 0.5% methylcellulose solution (Wako Pure Chemical Industries, Ltd.). The dose of the test compound was prepared to be 3 mg/kg body weight/10 mL. The test compounds were administered by gavage at 3 mg/kg body weight. The cerebrum was isolated after the administration of
15 the test compound (isolation time after the administration of the test compound is shown in Table 3), and the cerebrum hemisphere was extracted. The obtained cerebrum hemisphere was frozen on dry ice, and the frozen tissue weight was measured.

[0299]

20 The cerebral tissue weight was measured, and cerebral tissue was homogenized with 4-fold (v/w) of isopropanol (IPA), and double diluted with IPA. To the diluted sample (200 μ L) was added internal standard solution (5 μ L) ([5,6,8,9,11,12,14,15-D8]-(5Z,8Z,11Z,14Z)-5,8,11,14-
25 eicosatetraenoic acid (AA-d₈, 0.5 nmol/mL IPA) and [5,6,8,9,11,12,14,15-D8]-(5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoyl-2-glycerol ester (2-AG-d₈, 0.5nmol/mL IPA)), and the mixture was centrifuged at 15000 rpm for 5 min. The supernatant was injected to liquid chromatographymass
30 spectrometer to perform quantitative analysis.

For liquid chromatography, Shimadzu LC20A system (Shimadzu Corporation) was used. The separation was performed by gradient elution method with mobile phase A (10 mmol/L HCOONH₄/HCOOH (100:0.2, v/v)) and mobile phase B (ethanol/IPA
35 (3:2, v/v)) using Shim-pack XR-ODS (2.2 μ m, 2.0×30 mm, Shimadzu

Corporation) at column temperature of 50°C, at flow rate of 0.5 mL/min. The gradient conditions are as follows: 0-1 min, 1% B; 1-1.2 min, 1-55% B; 1.2-2.7 min, 55-75% B; 2.7-3.5 min, 75-99% B; 3.5-6 min, 99% B; 6-8 min, 1% B.

5 For mass spectrometer, API5000 (AB SCIEX) was used. The eluate from the liquid chromatography was directly ionized by turbospray ionization method, where (5Z,8Z,11Z,14Z)5,8,11,14-eicosatetraenoic acid (AA) and AA-d₈ were measured by negative ionization mode, and (5Z,8Z,11Z,14Z)5,8,11,14-eicosatetraenoyl-
10 2-glycerol ester (2-AG) and 2-AG-d₈ were measured by positive ionization mode. Detection conditions of the mass spectrometer are shown in Table 4.

A solution for calibration curve was prepared to the concentration of 2, 5, 10, 20, 50, 100, 200, 500, 1000 nmol/mL
15 of acetonitrile. These solutions (10 µL) was mixed with 200 µL of IPA and 5 µL of internal standard solution, and the mixture was centrifuged at 15000 rpm for 5 min, and the supernatant was injected to liquid chromatography mass spectrometer to perform analysis. The calibration curve was drawn by regression line
20 with a weighting of 1/x², and the quantitativity was confirmed by accuracy of 100±20% and R²>0.99.

The results are shown in Table 5.

[0300]

As is clear from Table 5, the compounds 1, 2 and 3 was
25 migrated into brain by oral administration to C57BL/6J mice, and these compound increased significantly intracerebral 2-AG concentration, and simultaneously decreased significantly intracerebral arachidonic acid concentration, compared to control.

30

[0301]

Table 3

test compound	isolation time after the administration of test compound (hour)
compound 1	1
compound 2	1
compound 3	1

[0302]

5 Table 4

mass spectrometer parameter

target molecule	polar- ity	Q1	Q3	retention time (msec)	DP (V)	EP (V)	CE (V)	CXP (V)
arachidonic acid	-	303.2	205.2	25	-90	-11	-17	-15
arachidonic acid-d8	-	311.4	267.4	25	-175	-10	-22	-17
2-arachidonyl glycerol	+	379.3	95	25	181	10	91	14
2-arachidonyl glycerol-d8	+	387.4	294.2	25	161	10	23	18

DP: declustering potential

EP: entrance potential

CE: cleavage energy

10 CXP: collision cell exit potential

[0303]

Table 5

	2-AG concentration (nmol/g)	arachidonic acid concentration (nmol/g)
control	9.9	163.5
compound 1	124.5	31.7
compound 2	125.2	42.6
compound 3	131.9	60.9

[0304]

5 Formulation Examples

Medicaments containing the compound of the present invention as an active ingredient can be produced, for example, by the following formulations.

1. capsule

10	(1) compound obtained in Example 1	10 mg
	(2) lactose	90 mg
	(3) microcrystalline cellulose	70 mg
	(4) magnesium stearate	10 mg
	1 capsule	180 mg

15 The total amount of the above-mentioned (1), (2) and (3) and 5 mg of (4) are blended and granulated, and 5 mg of the remaining (4) is added. The whole mixture is sealed in a gelatin capsule.

[0305]

20 2. tablet

	(1) compound obtained in Example 1	10 mg
	(2) lactose	35 mg
	(3) cornstarch	150 mg
	(4) microcrystalline cellulose	30 mg
25	(5) magnesium stearate	5 mg
	1 tablet	230 mg

The total amount of the above-mentioned (1), (2) and (3), 20 mg of (4) and 2.5 mg of (5) are blended and granulated, and 10 mg of the remaining (4) and 2.5 mg of the remaining (5) are

added and the mixture is compression formed to give a tablet.

Industrial Applicability

[0306]

According to the present invention, a compound having an
5 MAGL inhibitory action, which is expected to be useful as an
agent for the prophylaxis or treatment of neurodegenerative
diseases (e.g., Alzheimer's disease, Parkinson's disease,
Huntington's disease, amyotrophic lateral sclerosis, traumatic
brain injury, glaucoma, multiple sclerosis etc.), anxiety
10 disorder, pains (e.g., inflammatory pain, cancerous pain,
neurogenic pain etc.), epilepsy, depression and the like can be
provided.

[0307]

This application is based on patent application No. 2016-
15 071181 filed on March 31, 2016 in Japan, the contents of which
are encompassed in full herein.