



(11)

EP 3 409 658 B9

(12)

CORRECTED EUROPEAN PATENT SPECIFICATION

(15) Correction information:

Corrected version no 1 (W1 B1)
Corrections, see
Claims EN 8, 10

(48) Corrigendum issued on:
17.07.2024 Bulletin 2024/29(45) Date of publication and mention
of the grant of the patent:
06.03.2024 Bulletin 2024/10(21) Application number: **17744379.3**(22) Date of filing: **27.01.2017**

(51) International Patent Classification (IPC):
C07C 229/46 (2006.01) A61K 31/197 (2006.01)
A61K 31/397 (2006.01) A61K 31/402 (2006.01)
A61K 31/472 (2006.01) A61K 31/55 (2006.01)
A61P 21/00 (2006.01) A61P 25/00 (2006.01)
A61P 25/18 (2006.01) A61P 25/28 (2006.01)
A61P 27/02 (2006.01) A61P 31/00 (2006.01)
A61P 35/00 (2006.01) A61P 37/02 (2006.01)
A61P 43/00 (2006.01) C07D 205/04 (2006.01)
C07D 207/16 (2006.01) C07D 217/04 (2006.01)
C07D 217/16 (2006.01) C07D 223/06 (2006.01)

(52) Cooperative Patent Classification (CPC):
C07D 205/04; A61K 31/197; A61K 31/397;
A61K 31/402; A61K 31/472; A61K 31/55;
A61P 21/00; A61P 25/00; A61P 25/18;
A61P 25/28; A61P 27/02; A61P 29/00;
A61P 31/00; A61P 35/00; A61P 37/02; (Cont.)

(86) International application number:
PCT/JP2017/002911(87) International publication number:
WO 2017/131149 (03.08.2017 Gazette 2017/31)(54) **TETRAHYDRONAPHTHALENE DERIVATIVE**

TETRAHYDRONAPHTHALINDERIVAT
DÉRIVÉ DE TÉTRAHYDRONAPHTALÈNE

(84) Designated Contracting States:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB
GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO
PL PT RO RS SE SI SK SM TR

(30) Priority: **29.01.2016 JP 2016015064**(43) Date of publication of application:
05.12.2018 Bulletin 2018/49(73) Proprietor: **ONO Pharmaceutical Co., Ltd.**
Osaka-shi, Osaka 541-8526 (JP)

(72) Inventors:

- WATANABE, Toshihide**
Mishima-gun
Osaka 618-8585 (JP)

- KUSUMI, Kensuke**
Mishima-gun
Osaka 618-8585 (JP)
- INAGAKI, Yuichi**
Tsukuba-shi
Ibaraki 300-4247 (JP)

(74) Representative: **Grünecker Patent- und**
Rechtsanwälte
PartG mbB
Leopoldstraße 4
80802 München (DE)

(56) References cited:
EP-A1- 0 026 848 EP-A1- 0 035 868
EP-A2- 0 270 947 WO-A1-03/011862
WO-A1-2007/129745 WO-A1-2014/129796
WO-A1-90/15047 WO-A2-2006/085149

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

WO-A2-2016/108045	JP-A- 2004 532 834
JP-A- 2005 532 275	JP-A- 2007 506 661
JP-A- 2009 114 107	JP-A- 2009 520 688
JP-A- 2012 530 108	JP-A- 2013 519 732
US-A- 5 912 342	US-A1- 2010 240 671
US-A1- 2015 203 493	US-A1- 2015 376 173

- MCDERMED J D ET AL: "SYNTHESIS AND PHARMACOLOGY OF SOME 2-AMINOTETRALINS. DOPAMINE RECEPTOR AGONISTS", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 18, no. 4, 1 January 1975 (1975-01-01), pages 362 - 367, XP002067369, ISSN: 0022-2623, DOI: 10.1021/JM00238A008
- EMERIT M B ET AL: "Irreversible blockade of central 5-HT^{1A} receptor binding sites by the photoaffinity probe 8-methoxy-3'-nap-amino-pat", EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER SCIENCE, NL, vol. 127, no. 1-2, 1 August 1986 (1986-08-01), pages 67 - 81, XP023750423, ISSN: 0014-2999, [retrieved on 19860801], DOI: 10.1016/0014-2999(86)90207-4
- KAMIYA S ET AL: "A NOVEL SERIES OF THROMBOXANE A₂ SYNTHETASE INHIBITORS WITH FREE RADICAL SCAVENGING AND ANTI-PEROXIDATIVE ACTIVITIES", CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, JP, vol. 49, no. 5, 1 May 2001 (2001-05-01), pages 563 - 571, XP002973344, ISSN: 0009-2363, DOI: 10.1248/CPB.49.563

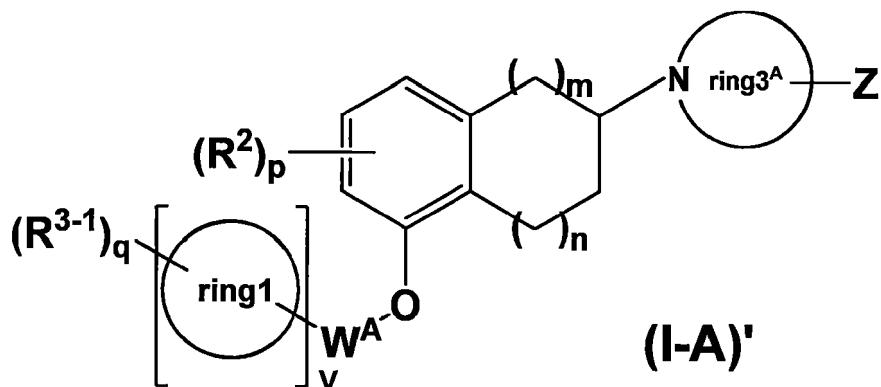
- SKIDMORE,J. ET AL.: "Optimization of Sphingosine-1-phosphate-1 Receptor Agonists: Effects of Acidic, Basic, and Zwitterionic Chemotypes on Pharmacokinetic and Pharmacodynamic Profiles", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 24, 26 December 2014 (2014-12-26), pages 10424 - 10442, XP055191848

(52) Cooperative Patent Classification (CPC): (Cont.)
 A61P 37/06; A61P 43/00; C07C 229/46;
 C07D 207/16; C07D 217/04; C07D 217/16;
 C07D 217/26; C07D 223/06; C07D 223/16;
 C07D 403/12; C07D 405/12; C07D 417/12

Description

TECHNICAL FIELD

5 [0001] The present invention relates to a compound represented by general formula (I-1):



wherein, all the symbols have the same meanings as described below, or a pharmaceutically acceptable salt thereof (hereinafter occasionally abbreviated as the compound of the present invention).

BACKGROUND ART

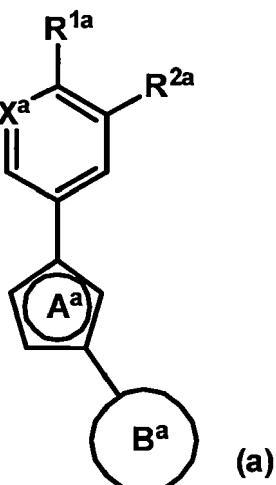
[0002] Sphingosine-1-phosphate [(2S,3R,4E)-2-amino-3-hydroxyoctadec-4-enyl-1-phosphate; hereinafter occasionally abbreviated as S1P] is a lipid which is synthesized by metabolic turnover of sphingolipids in cells and by the extracellular action of a secreted sphingosine kinase. It is proposed that sphingosine-1-phosphate acts as an intercellular communication mediator as well as an intracellular second messenger.

[0003] Among S1P receptors, with regard to S1Ps (EDG-8) receptor, it is known that S1P₅ (EDG-8) receptor is highly expressed in oligodendrocytes (oligodendroglia) and oligodendrocyte progenitor cells (see Non Patent Literatures 1 and 2). Oligodendrocytes are a kind of glial cells which form the myelin sheaths (myelin) by binding to the axons of nerve cells. Accordingly, it is considered that a compound which has an S1P₅ receptor binding activity, and can mediate the function of an S1P₅ receptor, is useful for treating neurodegenerative disease such as schizophrenia because the compound promotes the regeneration of myelin which has disappeared (demyelination) in nerve cells.

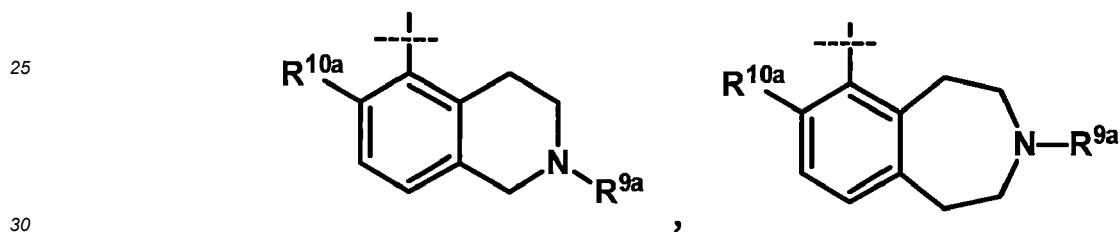
[0004] In addition, it is known that S1P₅ receptor is highly expressed also in natural killer (NK) cells and it is revealed that the migration of NK cells is induced by the activation of S1P₅ receptor (see Non Patent Literature 3).

[0005] Further, S1P₅ receptor is highly expressed in patrolling monocytes which are known to be involved in the tumor immunity, and therefore, there is a possibility that the activation of the tumor immunity is induced by the activation of S1P₅ receptor (see Non Patent Literatures 4 and 5).

[0006] Incidentally, as compounds of prior arts to the present invention, the following compounds are known. It is disclosed that a compound represented by general formula (a):

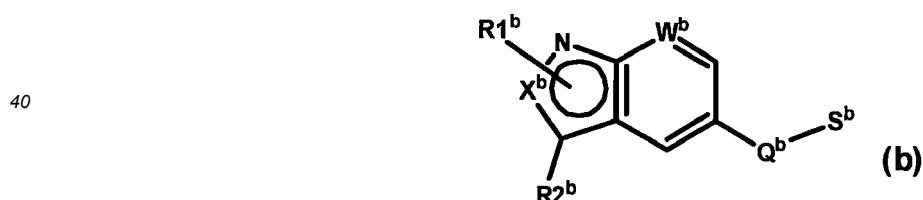


(wherein, X^a represents CH or N, R^{1a} represents a C3-6 cycloalkyl group which has a fluorine substituent(s), R^{2a} represents a hydrogen atom, a halogen atom, a cyano group or a trifluoromethyl group, A^a represents a 5-membered heterocyclic ring which is chosen between thiazole, thiadiazole or the like, B^a represents bicyclic ring which is chosen between a substituent as shown below;

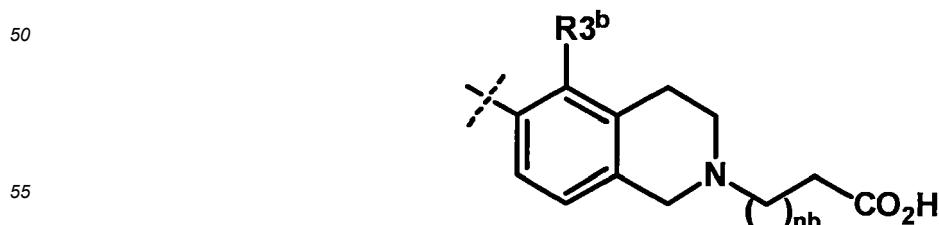


(wherein, R^{9a} represents a C1-4 alkyl group which has at least one hydroxy group substituent, R^{10a} represents a hydrogen atom or a C1-3 alkyl group which may be substituted with a halogen atom) (provided that the definition of each of groups is excerpted) has an S1P₁ agonist activity (see Patent Literature 1).

35 [0007] Also, it is known that a compound represented by general formula (b):



45 (wherein, X^b represents C or N, R^{1b} represents H or an alkyl group which may have a substituent(s), R^{2b} represents H, an alkyl group which may have a substituent(s), a halogen atom or the like, W^b represents C, N or a C-alkoxy group, Q^b represents CH₂O or the like, S^b represents a substituent as shown below;



(wherein, R^{3b} represents H, an alkyl group, a halogen atom or the like, n represents 0 to 3) (provided that the definition

of each of groups is excerpted)) has an S1P agonist activity (see Patent Literature 2).

5 Patent Literature 3 relates to the use of compounds described therein in the treatment of amyloid-related diseases.
Patent Literature 4 relates to 2-aminotetralins and pharmaceutically acceptable acid addition salts thereof, which
are useful to treat central nervous system disorders, hypertension, diabetes, sexual impotency and to control appetite.
Patent Literature 5 relates to substituted basic 2-aminotetralins and their use as medicaments.
Patent Literature 6 relates to compounds effective in the treatment or prophylaxis of HIV infection.

10 [0008] None of prior arts discloses or suggests that the compound of the present invention has a selective S1P₅
binding activity and modulates the function of an S1P₅ receptor.

CITATIONS LISTS

15 Patent Literatures

[0009]

Patent Literature 1: WO 2010/146105 A
Patent Literature 2: WO 2014/129796 A
20 Patent Literature 3: WO 2006/085149 A2
Patent Literature 4: WO 90/15047 A1
Patent Literature 5: EP 0 270 947 A2
Patent Literature 6: WO 03/011862 A1

25 Non Patent Literatures

[0010]

30 Non Patent Literature 1: The Journal of Neuroscience, Vol. 25, No. 6, pages 1459- 1469, 2005
Non Patent Literature 2: The FASEB Journal, Vol. 21, pages 1503- 1514, 2007
Non Patent Literature 3: Nature Immunology, Vol. 8, No. 12, pages 1337- 1344, 2007
Non Patent Literature 4: European Journal of Immunology, Vol. 43, pages 1667- 1675, 2013
Non Patent Literature 5: Science, Vol. 350, No. 6263, pages 985- 990, 2015

35 SUMMARY OF INVENTION

TECHNICAL PROBLEMS

40 [0011] An object of the present invention is to provide a compound which has a selective S1Ps receptor binding activity
and modulates the function of an S1P₅ receptor.

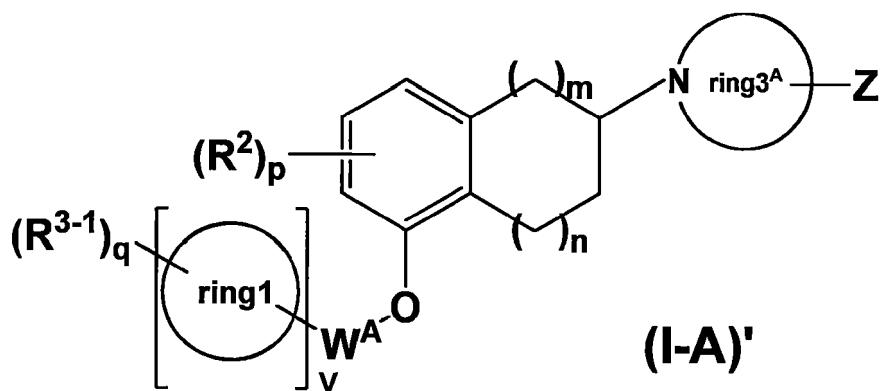
SOLUTIONS TO PROBLEMS

45 [0012] The present inventors have carried out intensive studies to find out a compound which has improved affinity
to an S1P₅ receptor in order to achieve the above-described object. As a result, the present inventors have found
surprisingly that with regard to a compound of the present invention has a selective S1P₅ receptor binding activity and
modulates the function of an S1P₅ receptor, and have completed the present invention.
The subject matter of the invention is as set out in the appended claims.

[0013] In other words, the present invention provides a compound represented by general formula (I-A)':

50

55



15 wherein.

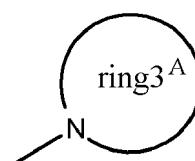
20 W^A represents (1) a C1-12 alkylene group, (2) a C2-12 alkenylene group, (3) a C2-12 alkynylene group, (4) -C1-12 alkylene-O-, (5) -C2-12 alkenylene-O-, (6) -C2-12 alkynylene-O-, (7) -C1-12 alkylene-ring2-, (8)-C2-12 alkenylene-ring2- or (9) -C2-12 alkynylene-ring2-, wherein, an alkylene group, an alkenylene group and an alkynylene group may be substituted with one to five halogen atoms,

R² represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group or (5) a C1-4 haloalkoxy group,

25 R³⁻¹ represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group, (5) a C1-4 haloalkoxy group, (6) a nitrile group, (7) -S-C1-4 alkyl group, (8)-S-C1-4 haloalkyl group or (9) an oxo group, provided that the C1-4 alkyl group or the C1-4 haloalkyl group represented by R³⁻¹ is branched chain, C1-2 alkyl groups branched from the same carbon atom may be taken together with a carbon atom to which they are bound, to form a C3-4 saturated carbocyclic ring,

30 Z represents (1) a carboxyl group which may be substituted with a C1-8 alkyl group, (2) a hydroxy group which may be substituted with a C1-8 alkyl group, (3) a hydroxamic acid group which may be substituted with a C1-8 alkyl group, (4) a sulfonic acid group which may be substituted with a C1-8 alkyl group, (5) a boronic acid group which may be substituted with a C1-8 alkyl group, (6) a carbamoyl group which may be substituted with a C1-8 alkyl group, (7) a sulfamoyl group which may be substituted with a C1-8 alkyl group, (8) a sulfoximine group which may be substituted with a C1-8 alkyl group or (9) a tetrazolyl group.

35 substituted with a C₁-C₆ alky, g, cap or (3) a tetraacyclic group, ring 1 represents (1) a C₃-10 carbocyclic ring or (2) a 3- to 10-membered heterocyclic ring, ring 2 represents (1) a C₃-7 carbocyclic ring or (2) a 3- to 7-membered heterocyclic ring.



represents a 3- to 7-membered nitrogen-containing saturated heterocyclic ring

45 m represents an integer of 0 to 2,

n represents an integer of 0 to 2,

p represents an integer of 0 to 3,

q represents an integer of 0 to 5.

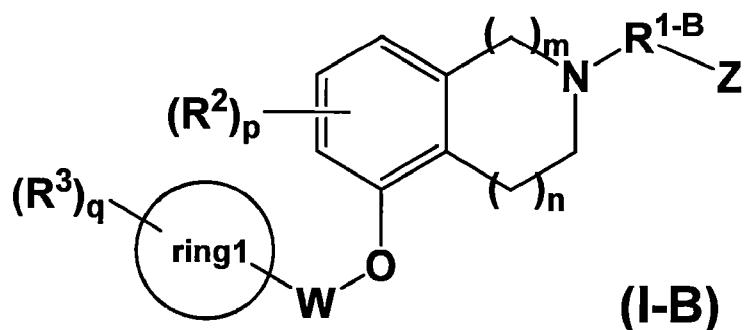
v represents an integer of 1.

50 when p is 2 or more, a plurality of R^2 s may be the same or different, and

when p is 2 or more, a plurality of R³s may be the same or different, and when q is 2 or more, a plurality of R³⁻¹s may be the same or different.

or a pharmaceutically acceptable salt thereof.

[0014] The present invention also provides a compound represented by general formula (I-B)



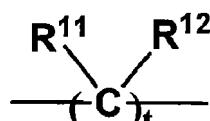
wherein,

W represents (1) a C1-6 alkylene group, (2) a C2-6 alkenylene group, (3) a C2-6 alkynylene group, (4) a -C1-6 alkylene-O-, (5) a -C2-6 alkenylene-O-, (6) a -C2-6 alkynylene-O- or (7) a -C1-6 alkylene-ring2-,
 R^{1-B} represents -L- or -L-ring3^B-,

R² represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group or (5) a C1-4 haloalkoxy group,

R³ represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group, (5) a C1-4 haloalkoxy group, (6) a nitrile group, (7) a -S-C1-4 alkyl group, or (8) a -S-C 1-4 haloalkyl group, provided that the C1-4 alkyl group or the C1-4 haloalkyl group represented by R³ is branched chain, C1-2 alkyl groups branched from the same carbon atom may be taken together with a carbon atom to which they are bound, to form a C3-4 saturated carbocyclic ring,

L represents (1) a bond or (2) a group represented by general formula



wherein, R¹¹ and R¹² each represent independently a hydrogen atom or a C1-4 alkyl group, or R¹¹ and R¹² may be taken together with a carbon atom to which they are bound, to form a C3-7 carbocyclic ring, and t represents an integer of 1 to 6,

Z represents (1) a carboxyl group which may be substituted with a C1-8 alkyl group, (2) a hydroxy group which may be substituted with a C1-8 alkyl group, (3) a hydroxamic acid group which may be substituted with a C1-8 alkyl group, (4) a sulfonic acid group which may be substituted with a C1-8 alkyl group, (5) a boronic acid group which may be substituted with a C1-8 alkyl group, (6) a carbamoyl group which may be substituted with a C1-8 alkyl group, (7) a sulfamoyl group which may be substituted with a C1-8 alkyl group, (8) a sulfoximine group which may be substituted with a C1-8 alkyl group or (9) a tetrazolyl group,

ring 1 represents a C3-10 carbocyclic ring,

ring 2 represents (1) a C3-7 carbocyclic ring or (2) a 3- to 7-membered heterocyclic ring,

ring 3^B represents a C3-7 carbocyclic ring,

m represents an integer of 0 to 2,

n represents an integer of 0 to 2,

p represents an integer of 0 to 3,

q represents an integer of 0 to 5,

when p is 2 or more, a plurality of R²s may be the same or different,

when q is 2 or more, a plurality of R³s may be the same or different and

when t is 2 or more, a plurality of R¹¹s may be the same or different, and

when t is 2 or more, a plurality of R¹²s may be the same or different,

or a pharmaceutically acceptable salt thereof.

55 [0015] Further provided is a pharmaceutical composition comprising the compound represented by general formula (I-A)' or the compound represented by general formula (I-B), or a pharmaceutically acceptable salt thereof.

The invention also provides the compound represented by general formula (I-A)' or the compound represented by general formula (I-B), or a pharmaceutically acceptable salt thereof for use in a method for preventing and/or treating a SIPs-

mediated disease, wherein the SIPs-mediated disease is neurodegenerative disease, autoimmune disease, infection or cancer. Preferred embodiments of the present invention are set forth in the dependent claims.

ADVANTAGEOUS EFFECTS OF INVENTION

[0016] The compound of the present disclosure has a selective S1P₅ receptor binding activity and modulates the function of an S1P₅ receptor, and therefore, the compound of the invention can be used in a method for treating S1P₅-mediated disease, for example, neurodegenerative disease, autoimmune disease, infection and cancer. The references to methods of treatment in the subsequent paragraphs of this description are to be interpreted as references to the compounds and pharmaceutical compositions of the present invention for use in a method for treatment of the human or animal body by therapy.

DESCRIPTION OF EMBODIMENTS

[0017] The present invention will be described in detail hereinbelow.

[0018] In the present invention, a halogen atom includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

[0019] In the present invention, a C1-8 alkyl group includes a linear or branched C1-8 alkyl group. Examples of the C1-8 alkyl group include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 1-methylbutyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, 1-methylhexyl, 1-ethylpentyl, 2-ethylpentyl, 1-propylbutyl, 2-methyl-3-hexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1-ethyl-1-methylbutyl, 1-methyl-2-ethylbutyl, 1-ethyl-2-methylbutyl, 1-ethyl-3-methylbutyl, 1,1-dimethylpentyl, 1,1,3-trimethylbutyl, 1,1-diethylpropyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3-ethylpentyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-ethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 1-propylpentyl, 2-propylpentyl, 1,5-dimethylhexyl, 1-ethyl-4-methylpentyl, 1-propyl-3-methylbutyl, 1,1-dimethylhexyl, 1-ethyl-1-methylpentyl and 1,1-diethylbutyl groups.

[0020] In the present invention, a C1-4 alkyl group includes a linear or branched C1-4 alkyl group. Examples of the C1-4 alkyl group include methyl, ethyl, propyl, butyl, isopropyl, isobutyl, sec-butyl and tert-butyl groups.

In the present invention, a C1-2 alkyl group includes methyl and ethyl groups.

[0021] In the present invention, a C1-4 haloalkyl group includes a fluoromethyl group, a chloromethyl group, a bromomethyl group, a iodomethyl group, a difluoromethyl group, a trifluoromethyl group, a 1-fluoroethyl group, a 2-fluoroethyl group, a 2-chloroethyl group, a pentafluoroethyl group, a 1-fluoropropyl group, a 2-chloropropyl group, a 3-fluoropropyl group, a 3-chloropropyl group, a 4,4,4-trifluorobutyl group and a 4-bromobutyl group.

[0022] In the present invention, a C1-4 alkoxy group includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy groups.

[0023] In the present invention, a C1-4 haloalkoxy group includes a trifluoromethoxy group, a trichloromethoxy group, a chloromethoxy group, a bromomethoxy group, a fluoromethoxy group, a iodomethoxy group, a difluoromethoxy group, a dibromomethoxy group, a 2-chloroethoxy group, a 2,2,2-trifluoroethoxy group, a 2,2,2-trichloroethoxy group, a 3-bromopropoxy group, a 3-chloropropoxy group, a 2,3-dichloropropoxy group, a 1-fluorobutoxy group, a 4-fluorobutoxy group and a 1-chlorobutoxy group.

[0024] In the present invention, examples of a C1-12 alkylene group includes methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene, decylene, undecylene and dodecylene groups.

In the present invention, examples of a C1-6 alkylene group means methylene, ethylene, propylene, butylene, pentylene and hexylene groups.

[0025] In the present invention, examples of a C2-12 alkenylene group includes ethenylene, propenylene, butenylene, pentenylene, hexenylene, heptenylene, octenylene, nonenylene, decenylene, undecenylene, dodecenylene, butadienylene, pentadienylene, hexadienylene, heptadienylene, octadienylene, nonadienylene, decadienylene, undecadienylene and dodecadienylene groups.

[0026] In the present invention, examples of a C2-6 alkenylene group includes ethenylene, propenylene, butenylene, pentenylene, hexenylene, butadienylene, pentadienylene and hexadienylene groups.

[0027] In the present invention, examples of a C2-12 alkynylene group includes ethynylene, propynylene, butynylene, pentynylene, hexynylene, heptynylene, octynylene, nonynylene, decynylene, undecynylene, dodecynylene, butadiynylene, pentadiynylene, hexadiynylene, heptadiynylene, octadiynylene, nonadiynylene, decadiynylene, undecadiynylene and dodecadiynylene groups.

[0028] In the present invention, examples of a C2-6 alkynylene group includes ethynylene, propynylene, butynylene, pentynylene, hexynylene, butadiynylene, pentadiynylene and hexadiynylene groups.

[0029] In the present invention, examples of an acidic group includes a carboxyl group, a hydroxy group, a hydroxamic acid group, a sulfonic acid group, a boronic acid group, a carbamoyl group, a sulfamoyl group, a sulfoxime group ($-SH(=O)(=NH)$) and a tetrazolyl group.

[0030] In the present invention, a C3-10 carbocyclic ring refers to a carbocyclic ring which is a C3-10 monocyclic or bicyclic carbocyclic ring and which may be partially or wholly saturated. Examples of the C3-10 carbocyclic ring include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene, pentalene, perhydralentalene, azulene, perhydroazulene, indene, perhydroindene, indane, naphthalene, dihydronaphthalene, tetrahydronaphthalene and perhydronaphthalene.

[0031] In the present invention, a C3-10 carbocyclic ring include a bridged carbocyclic ring. Examples of a C3-10 bridged carbocyclic ring include bicyclo[4.2.0]octa-1,3,5-triene, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hepta-2-ene, bicyclo[3.1.1]heptane, bicyclo[3.1.1]hepta-2-ene, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, bicyclo[2.2.2]octa-2-ene, adamantane, noradamantine and cubane ring.

[0032] In the present invention, a 3- to 10-membered heterocyclic ring refers to a partially or wholly saturated 3- to 10-membered monocyclic or bicyclic heterocyclic ring which contains 1 to 5 heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom. Examples of the 3- to 10-membered heterocyclic ring include pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, thiophene, thiopyran, thiepine, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzimidazole, chromene, benzofurazan, benzothiadiazole, benzotriazole, aziridine, azetidine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydropiazepine, tetrahydropiazepine, perhydropiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, thiirane, thietane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepine, tetrahydrothiepine, perhydrothiepine, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydroxadiazine, tetrahydroxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydro-naphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorpholine, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, dioxolane, dioxane, dithiolane, dithiane, dioxaindane, benzodioxane, chromane, benzodithiolane and benzodithiane rings.

[0033] In the present invention, a C3-7 carbocyclic ring means a C3-7 monocyclic carbocyclic ring which may be partially or wholly saturated, for example, the C3-7 carbocyclic ring include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclopentene, cyclohexene, cycloheptene, cyclobutadiene, cyclopentadiene, cyclohexadiene, cycloheptadiene and benzene rings.

[0034] In the present invention, a C3-7 saturated carbocyclic ring include cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane rings.

In the present invention, a C3-4 saturated carbocyclic ring include cyclopropane and cyclobutane rings.

[0035] In the present invention, a 3- to 7-membered heterocyclic ring includes a 3- to 7-membered unsaturated heterocyclic ring and a 3- to 7-membered saturated heterocyclic ring. Examples of the 3- to 7-membered heterocyclic ring include aziridine, azetidine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydroadiazepine, tetrahydroadiazepine, perhydro-

diazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, thirane, thietane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepine, tetrahydrothiepine, perhydrothiepine, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, thiophene, thiopyran, thiepine, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine and thiadiazepine rings.

[0036] In the present invention, examples of the 3- to 7-membered saturated heterocyclic ring include aziridine, azetidine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, thirane, thietane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepine, tetrahydrothiepine, perhydrothiepine, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane rings.

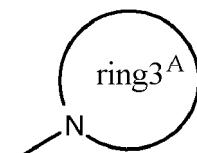
[0037] In the present invention, the 3- to 7-membered nitrogen-containing saturated heterocyclic ring means the 3- to 7-membered saturated heterocyclic ring which contains at least 1 nitrogen atom. Examples of the 3- to 7-membered nitrogen-containing saturated heterocyclic ring include aziridine, azetidine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, dihydroisoxazole, tetrahydroisoxazole (oxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane rings.

[0038] In the present invention, ring1 is preferably a C3-10 carbocyclic ring and cyclobutane, cyclohexane, benzene, bicyclo[4.2.0]octa-1,3,5-triene, indane, naphthalene or tetrahydronaphthalene ring is even more preferable.

[0039] In the present invention, ring2 is preferably a C3-7 carbocyclic ring and a cyclopropane ring is even more preferable.

[0040] In the present invention, ring3^B is preferably a C3-7 saturated carbocyclic ring which may be substituted with a C1-4 alkyl group, and cyclopropane, cyclobutane or cyclopentane ring is even more preferable.

[0041] In the present invention,



is a 3- to 7-membered nitrogen-containing saturated heterocyclic ring which may be substituted with a C1-4 alkyl group, and azetidine or pyrrolidine ring is even more preferable.

[0042] In the present invention, compounds described in Examples are more preferable. In the present invention, 4-[6-(3-Phenylpropoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid, 4-[6-[2-(1-Naphthyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid or 1-[8-[2-(1-Naphthyl)ethoxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid is more preferable.

[Isomers]

[0043] Unless otherwise specifically indicated, all isomers are included in the present invention. For example, an alkyl group includes linear and branched ones. In addition, all of geometric isomers due to double bond(s), ring(s) and fused ring(s) ((E)-, (Z)-, cis- and trans-), optical isomers due to the presence of asymmetric carbon atom(s) (R-, S-, α - and, β -configurations, enantiomer(s) and diastereomer(s)), optically active substances having optical rotation (D-, L-, d- and 1-forms), polar substances by chromatographic separation (more polar and less polar substances), compounds in equilibrium, rotational isomers, a mixture thereof in any proportion and a racemic mixture are included in the present invention. In addition, tautomers are all included in the present invention.

[0044] Further, optical isomers in the present invention may include, not only 100%-pure isomers, but also less than 50%-pure optical isomers.

[0045] In the present invention, unless otherwise specified, the symbol:  represents that a substituent binds to the back side on the paper surface (in other words, α -configuration), the symbol:  represents that a substituent

binds to the front side on the paper surface (in other words, β -configuration), and the symbol:  represents α -configuration, β -configuration or a mixture thereof at an appropriate ratio, as would be apparent to those skilled in the art.

[0046] The compound represented by general formula (I-A)' or the compound represented by general formula (I-B) can be converted into a corresponding pharmaceutically acceptable salt by a known method. The pharmaceutically acceptable salt is preferably a water-soluble salt. Examples of the appropriate salt include a salt of an alkali metal (such as potassium and sodium), a salt of an alkaline earth metal (such as calcium and magnesium), an ammonium salt, a salt of a pharmaceutically acceptable organic amine (such as tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)aminomethane, lysine, arginine and N-methyl-D-glucamine) as well as an acid addition salt (such as a salt of an inorganic acid (such as a hydrochloride, a hydrobromide, a hydroiodide, a sulfate, a phosphate and a nitrate) and a salt of an organic acid (such as an acetate, a trifluoroacetate, a lactate, a tartrate, an oxalate, a fumarate, a maleate, a benzoate, a citrate, a methanesulfonate, an ethanesulfonate, a benzenesulfonate, a toluenesulfonate, an isethionate, and a glucuronate and a gluconate)).

[0047] The compound represented by general formula (I-A)' or the compound represented by general formula (I-B) or a pharmaceutically acceptable salt thereof can be also converted into a solvate. The solvate is preferably a low-toxicity and water-soluble solvate. Examples of the appropriate solvate include a solvate of water and a solvate of an alcohol based solvent (such as a solvate of ethanol).

[0048] The compound represented by general formula (I-A)' or the compound represented by general formula (I-B) can be converted into a corresponding N-oxide by a known method. An N-oxide of the compound represented by general formula (I-1) represents a compound obtained by oxidation a nitrogen atom in the compound represented by general formula (I-1). In addition, the N-oxide of the compound represented by general formula (I) may be further converted to the above-described alkali (alkaline earth) metal salt, the ammonium salt, the organic amine salt or the acid addition salt.

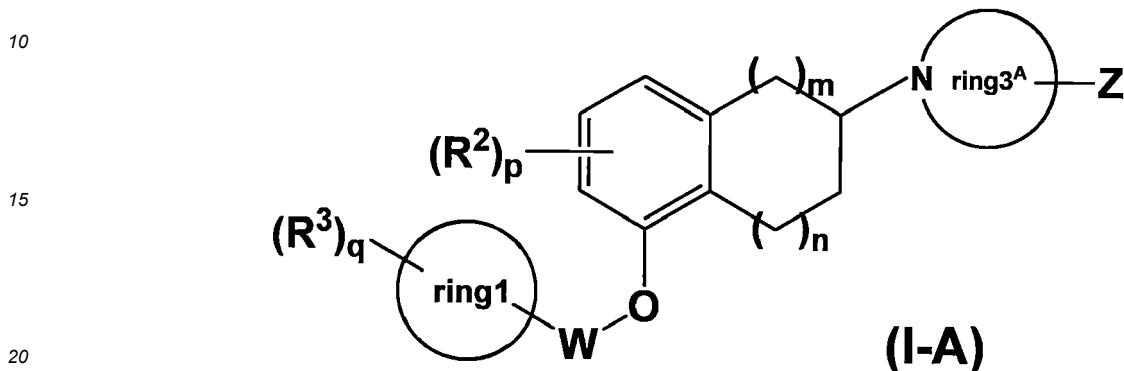
[0049] The compound represented by the general formula (I-A)' or the compound represented by general formula (I-B) can form a cocrystal with an appropriate cocrystal former. As the cocrystal, pharmaceutically acceptable cocrystal that is formed with a pharmaceutically acceptable cocrystal former is preferable. The cocrystal is defined as a crystal that is formed of two or more different molecules by intermolecular interaction that is different from ionic bond. Furthermore, the cocrystal may be a composite of a neutral molecule and a salt. The cocrystal can be prepared by a well-known method, for example, melting crystallization, recrystallization from a solvent, or physically pulverizing the components together. Appropriate cocrystal formers include ones described in WO2006/007448, for example, 4-aminobenzoic acid, 4-aminopyridine, adenine, alanine, and acetyl salicylic acid can be mentioned.

[0050] Furthermore, the compound represented by general formula (I-A)' or the compound represented by general formula (I-B) may also be labeled by an isotope (for example, ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , ^{125}I).

[Processes for the preparation of the compound of the present invention]

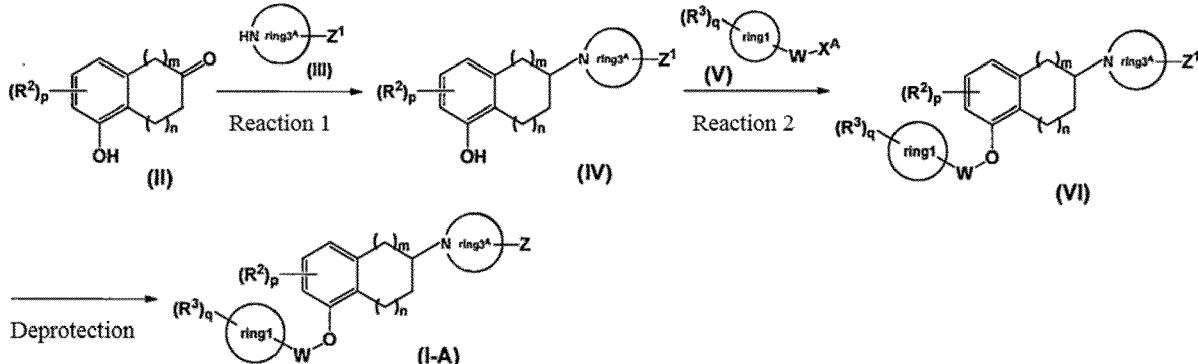
[0051] The compound of the present invention can be prepared by a known method. For example, the compound of the present invention can be prepared by appropriately improving a method described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc., 1999) or the methods described in Examples or combining these methods.

[0052] A compound represented by general formula (I-A):



wherein, ring3A represents a 3- to 7-membered nitrogen-containing saturated heterocyclic ring, W represents (1) a C1-6 alkylene group, (2) a C2-6 alkenylene group, (3) a C2-6 alkynylene group, (4) a -C1-6 alkylene-O-, (5) a -C2-6 alkenylene-O-, (6) a -C2-6 alkynylene-O- or (7) a -C1-6 alkylene-ring2-, R³ represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group, (5) a C1-4 haloalkoxy group, (6) a nitrile group, (7) a -S-C1-4 alkyl group, or (8) a -S-C1-4 haloalkyl group, provided that the C1-4 alkyl group or the C1-4 haloalkyl group represented by R³ is branched chain, C1-2 alkyl groups branched from the same carbon atom may be taken together with a carbon atom to which they are bound, to form a C3-4 saturated carbocyclic ring, and all the symbols represent the same meanings as described above, can be prepared by Reaction Scheme 1 shown below.

Reaction Scheme 1



wherein, X^A represents a halogen atom or a hydroxyl group, Z¹ represents an acidic group which may be protected, and other symbols have the same meanings as described above.

[0053] In Reaction Scheme 1, Reaction 1 can be performed by subjecting a compound represented by general formula (II) and a compound represented by general formula (III) to a reductive amination reaction. The reductive amination reaction is known, and for example, is performed in an organic solvent (such as dichloroethane, dichloromethane, tetrahydrofuran, toluene and N,N-dimethylformamide) using a compound represented by general formula (III) in the presence of a reducing agent (such as sodium triacetoxyborohydride, sodium cyanoborohydride and pinacolborane) at a temperature of 0 to 70°C.

[0054] In Reaction Scheme 1, Reaction 2 can be performed by subjecting a compound represented by general formula (IV) and a compound represented by general formula (V) to an etherification reaction. The etherification reaction is known, and can be carried out by (1) substituent reaction when X^A is a halogen atom, and (2) mitsunobu reaction when X^A is a hydroxyl group.

(1) Substituent reaction, for example, is performed by a reaction in an organic solvent (such as N,N-dimethylforma-

5 mide, N,N-dimethylacetamide, dimethyl sulfoxide, chloroform, dichloromethane, diethyl ether, tetrahydrofuran and methyl t-butyl ether) in the presence of a hydroxide of an alkali metal (such as sodium hydroxide, potassium hydroxide and lithium hydroxide), a hydroxide of an alkaline earth metal (such as barium hydroxide and calcium hydroxide), a carbonate (such as sodium carbonate and potassium carbonate), an aqueous solution thereof or a mixture thereof at 0 to 100°C.

10 (2) Mitsunobu reaction, for example, is performed by a reaction in an organic solvent (such as dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, benzene and toluene) in the presence of an azo compound (such as diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate, 1,1'-(azodicarbonyl)dipiperidine (ADDP), 1,1'-azobis(N,N-dimethylformamide) and phosphine compound (such as triphenylphosphine, tributylphosphine, trimethylphosphine, polymer-bounded triphenylphosphine) at 0 to 100°C.

[0055] In Reaction Scheme 1, a compound represented by general formula (I-A) can be produced by subjecting a compound represented by general formula (VI) prepared in Reaction 2 to a deprotection reaction.

[0056] The deprotection reaction is known, and for example, is performed by a method shown below (1) a deprotection reaction by alkaline hydrolysis, (2) a deprotection reaction under an acidic condition, (3) a deprotection reaction by hydrogenolysis, (4) a deprotection reaction of a silyl group, (5) a deprotection reaction by using a metal, (6) a deprotection reaction by using a metal complex.

[0057] These methods are described specifically as follows.

20 (1) A deprotection reaction by alkaline hydrolysis is performed, for example, in an organic solvent (such as methanol, tetrahydrofuran and dioxane), by using a hydroxide of an alkali metal (such as sodium hydroxide, potassium hydroxide and lithium hydroxide), a hydroxide of an alkaline earth metal (such as barium hydroxide and calcium hydroxide), a carbonate (such as sodium carbonate and potassium carbonate), an aqueous solution thereof or a mixture thereof at 0 to 40°C.

25 (2) A deprotection reaction under an acidic condition is performed, for example, in an organic solvent (such as dichloromethane, chloroform, dioxane, ethyl acetate, methanol, isopropyl alcohol, tetrahydrofuran and anisole), in an organic acid (such as acetic acid, trifluoroacetic acid, methanesulfonic acid and p-tosylic acid), an inorganic acid (such as hydrochloric acid and sulfuric acid) or a mixture thereof (such as hydrobromic acid/acetic acid) in the presence or absence of 2,2,2-trifluoroethanol at 0 to 100°C.

30 (3) A deprotection reaction by hydrogenolysis is performed, for example, in a solvent (such as an ether-based solvent (such as tetrahydrofuran, dioxane, dimethoxyethane and diethyl ether), an alcohol-based solvent (such as methanol and ethanol), a benzene-based solvent (such as benzene and toluene), a ketone-based solvent (such as acetone and methyl ethyl ketone), a nitrile-based solvent (such as acetonitrile), an amide-based solvent (such as N,N-dimethylformamide), water, ethyl acetate, acetic acid or a mixed solvent of two or more of them), in the presence of a catalyst (such as a palladium-carbon, a palladium black, a palladium hydroxide-carbon, a platinum oxide and a Raney nickel), under hydrogen atmosphere at a normal pressure or under pressurization or in the presence of ammonium formate, at 0 to 200°C.

35 (4) A deprotection reaction of a silyl group is performed, for example, in a water-miscible organic solvent (such as tetrahydrofuran and acetonitrile), by using tetrabutylammonium fluoride at 0 to 40°C. In addition, a deprotection reaction of a silyl group is performed, for example, in an organic acid (such as acetic acid, trifluoroacetic acid, methanesulfonic acid and p-tosylic acid), an inorganic acid (such as hydrochloric acid and sulfuric acid) or a mixture thereof (such as hydrobromic acid/acetic acid) at -10 to 100°C.

40 (5) A deprotection reaction by using a metal is performed, for example, in an acidic solvent (such as acetic acid, a buffer solution of pH 4.2 to 7.2 or a mixed solution of such a solution and an organic solvent such as tetrahydrofuran), in the presence of powdery zinc, if necessary, while applying an ultrasonic wave, at 0 to 40°C.

45 (6) A deprotection reaction by using a metal complex is performed, for example, in an organic solvent (such as dichloromethane, N,N-dimethylformamide, tetrahydrofuran, ethyl acetate, acetonitrile, dioxane and ethanol), water or a mixed solvent thereof, in the presence of a trapping reagent (such as tributyltin hydride, triethylsilane, dimedone, morpholine, diethylamine and pyrrolidine), an organic acid (such as acetic acid, formic acid and 2-ethylhexanoic acid) and/or a salt of an organic acid (such as sodium 2-ethylhexanoate and potassium 2-ethylhexanoate), in the presence or absence of a phosphine-based reagent (such as triphenylphosphine), by using a metal complex (such as tetrakis(triphenylphosphine)palladium (0), bis(triphenylphosphine)palladium (II) dichloride, palladium (II) acetate and chlorotris(triphenylphosphine)rhodium (I)), at 0 to 40°C.

55 [0058] In addition to the above-described methods, a deprotection reaction can be performed, for example, by a method described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999.

[0059] Examples of the protecting group of a hydroxy group include a methyl group, a trityl group, a methoxymethyl (MOM) group, a 1-ethoxyethyl (EE) group, a methoxyethoxymethyl (MEM) group, a 2-tetrahydropyranyl (THP) group,

a trimethylsilyl (TMS) group, a triethylsilyl (TES) group, a t-butyldimethylsilyl (TBDMS) group, a t-butyldiphenylsilyl (TB-DPS) group, an acetyl (Ac) group, a pivaloyl group, a benzoyl group, a benzyl (Bn) group, a p-methoxybenzyl group, an allyloxycarbonyl (Alloc) group, and a 2,2,2-trichloroethoxycarbonyl (Troc) group.

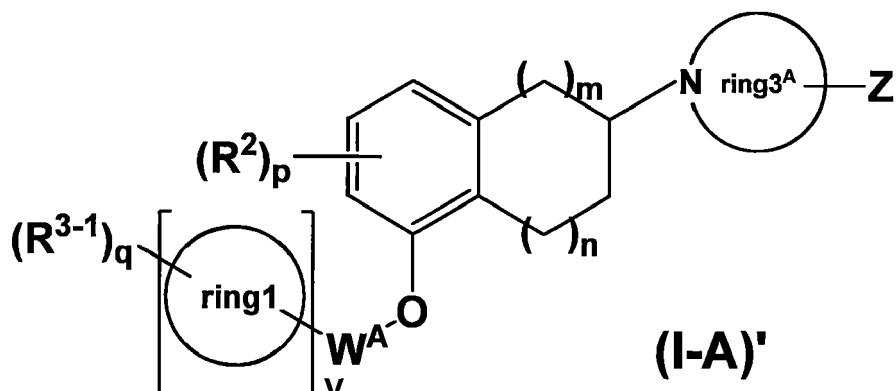
[0060] The protecting groups described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999 can be used.

[0061] In general formula (I-1), a compound in which both X^1 and X^2 is CH_2 , R^1 is $-\text{L}-\text{ring3-}$, L is a bond, Y is $-\text{O}-$ and ring3 is a 3- to 7-membered nitrogen-containing saturated heterocyclic ring, i.e., a compound represented by general formula (I-A)':

10

15

20



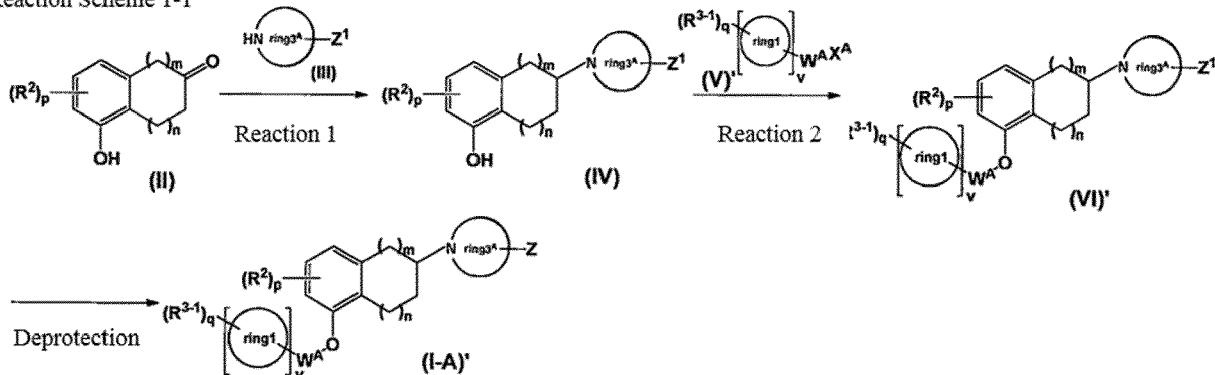
25

wherein, all the symbols represent the same meanings as described above can be prepared by Reaction Scheme 1-1 shown below.

30
Reaction Scheme 1-1

35

40



wherein, all the symbols represent the same meanings as described above.

[0062] In Reaction Scheme 1-1, a compound represented by general formula (VI)' can be prepared by the same method according to the above Reaction 2 using a compound represented by general formula (IV) and a compound represented by general formula (V)'.

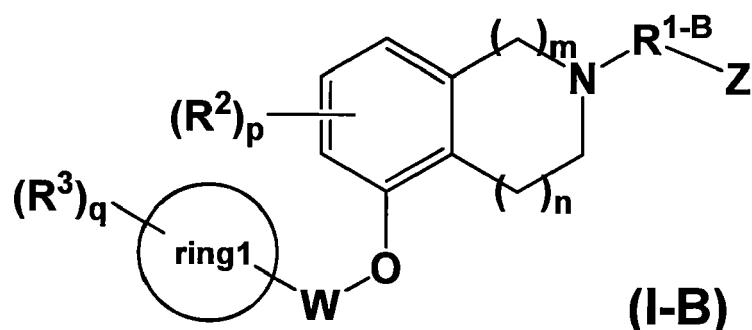
[0063] In Reaction Scheme 1-1, a compound represented by general formula (I-A)' can be prepared by subjecting a compound represented by general formula (VI)' to an above mentioned deprotection reaction.

[0064] A compound represented by general formula (I-B) wherein, R^{1-B} represents $-\text{L}-$ or $-\text{L}-\text{ring3}^B-$, ring3^B represents a C3-7 carbocyclic ring and other symbols represent the same meanings as described above can be prepared by Reaction Scheme 2 shown below.

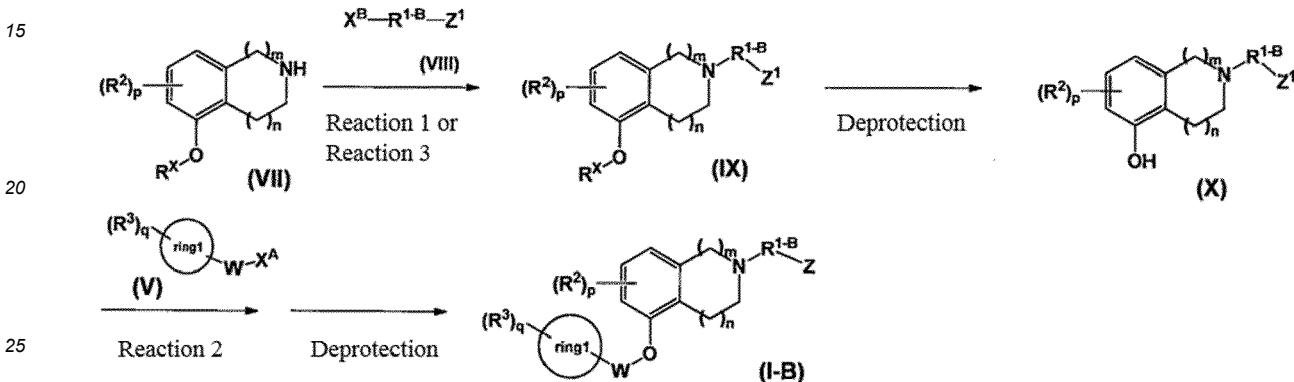
55

5

10



Reaction Scheme 2



wherein, R^X represents a protecting group of a hydroxy group, X^B represents a halogen atom or an oxo group and other symbols represent the same meanings as described above.

[0065] In a compound represented by general formula (VIII), when R^{1-B} represents $-L-$, a compound represented by general formula (IX) can be prepared by subjecting a compound represented by general formula (VII) and a compound represented by general formula (VIII) to Reaction 3. Reaction 3 is known, and for example, is performed in an organic solvent (such as *N,N*-dimethylformamide, dimethylacetamide, dimethyl sulfoxide, chloroform, diethyl ether, tetrahydrofuran and methyl *t*-butyl ether), in the presence of base (such as potassium carbonate and sodium carbonate), at 0 to 100°C.

[0066] In a compound represented by general formula (VIII), when R^{1-B} represents $-L\text{-ring}3^B-$, a compound represented by general formula (IX) can be prepared by subjecting a compound represented by general formula (VII) and a compound represented by general formula (VIII) to an above mentioned Reaction 1.

[0067] A compound represented by general formula (X) can be prepared by subjecting a compound represented by general formula (IX) to an above mentioned Deprotection reaction.

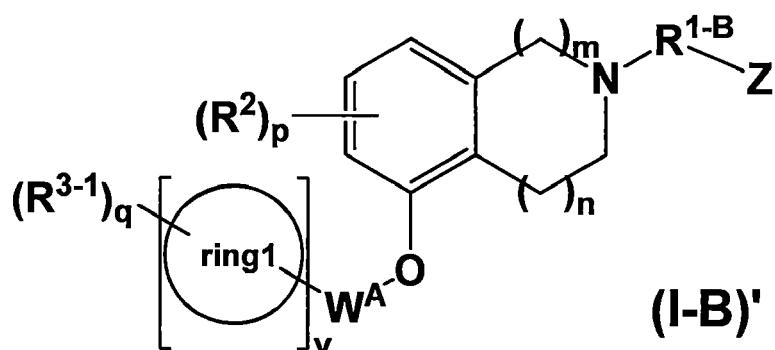
[0068] A compound represented by general formula (I-B) can be prepared by subjecting the compound represented by general formula (X) and the compound represented by the general formula (V) to the above mentioned Reaction 2 and, if necessary, subjecting to Deprotection reaction.

[0069] A compound represented by general formula (I-B)'

45

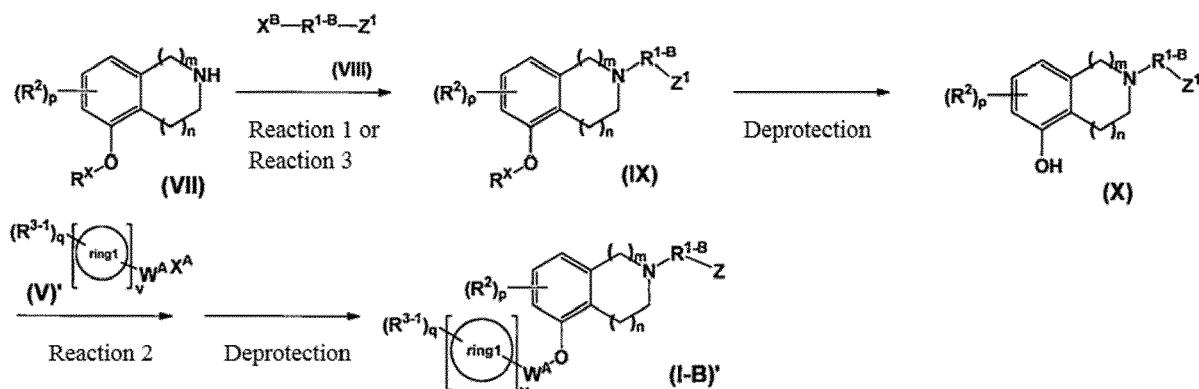
50

55



wherein, all the symbols represent the same meanings as described above can be prepared by Reaction Scheme 2-1 shown below.

Reaction Scheme 2-1



wherein, all the symbols represent the same meanings as described above.

[0070] A compound represented by general formula (I-B)' can be prepared by subjecting the compound represented by general formula (X) and the compound represented by general formula (V)' to the above mentioned Reaction 2 and, if necessary, subjecting to Deprotection reaction.

[0071] In the present specification, the compound used as the starting material in each of the reactions, for example, the compound represented by general formula (II), (III), (V), (V)', (VII) or (VIII) is known or can be easily prepared by a known method.

[0072] In the present specification, a reaction which involves heating in each of the reactions can be performed by using a water bath, an oil bath, a sand bath or a microwave as apparent to those skilled in the art.

[0073] In the present specification, a solid phase-supported reagent which is supported by a macromolecular polymer (such as polystyrene, polyacrylamide, polypropylene and polyethylene glycol) may be used appropriately, in each of the reactions.

[0074] In the present specification, the reaction product in each of the reactions can be purified by a conventional purification means. Examples of the purification means include distillation under a normal pressure or reduced pressure, high performance liquid chromatography which uses silica gel or magnesium silicate, thin-layer chromatography, an ion exchange resin, a scavenger resin, column chromatography, washing, an. The purification may be performed at each of reactions or may be performed after the completion of several reactions.

[Toxicity]

[0075] The toxicity of the compound of the present invention is sufficiently low, and the compound of the present invention can be used as a pharmaceutical safely.

[Application to pharmaceuticals]

[0076] The compound of the present invention has an S1Ps (EDG-8) receptor binding activity and modulate the function of it, and therefore, can be used in a method for preventing and/or treating S1P₅-mediated disease. Examples of the S1P₅-mediated disease include neurodegenerative disease, autoimmune disease, infection, and cancer.

[0077] In addition, the compound of the present invention has an S1P₅ (EDG-8) receptor binding activity and modulate the function of it, and therefore, can be used in a method for preventing and/or treating cancer through the activating action of the tumor immunity.

[0078] In the present invention, examples of the neurodegenerative disease include anxiety-related disease (social anxiety disorder, anxiety neurosis, obsessive-compulsive disorder and Post-Traumatic Stress Disorder (PTSD)), poly-glutamine disease, retinitis pigment neurosis, convulsion, panic disorder, sleep disorder, depression, reactive depression, epilepsy, Parkinson's disease, parkinsonian syndrome, Down's syndrome, schizophrenia, autonomic ataxia, Huntington's disease, Alzheimer's disease, affective disorder (including depressive disorder and bipolar disorder), cognitive impairment, migraine, tension-type headache, cluster headache, dissociative disorder, amyotrophic lateral sclerosis, neuromyelitis optica, optic neuritis, acute disseminated encephalomyelitis, allergic encephalomyelitis, Marchiafava-Bignami disease, Binswanger's disease, progressive multifocal leukoencephalopathy, postinfectious encephalitis, central pontine myelinolysis, adrenoleukodystrophy, multiple system atrophy, Krabbe disease, metachromatic leukodystrophy,

Alexander's disease, Canavan disease, Cockayne syndrome, Pelizaeus-Merzbacher disease, Hurler's syndrome, Lowe syndrome, spinal cord injury, transverse myelitis, spinocerebellar degeneration, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barre syndrome, phenylketonuria, Refsum's disease, Charcot-Marie-Tooth disease, Gaucher's disease, Niemann-Pick disease, multiple sclerosis, fragile X syndrome, autism, insomnia, nervous cough, psychogenic convulsive seizure, psychogenic syncopal attack, writer's cramp, spasmodic torticollis, and neuropathy.

[0079] In the present invention, examples of the autoimmune disease include inflammatory bowel disease, arthritis, lupus, rheumatism, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, type 1 diabetes mellitus, myasthenia gravis, Hashimoto's thyroiditis, iodine thyroiditis, Basedow's disease, Sjogren's syndrome, Addison disease, opsoclonus-myoclonus syndrome, ankylosing spondylitis, antiphospholipid syndrome, aplastic anemia, autoimmune hepatitis, celiac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, scleroderma, primary biliary cirrhosis, Reiter's disease, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue syndrome, autonomic neuropathy, endometriosis, interstitial cystitis, myotonia, vulvodynia, and systemic lupus erythematosus.

[0080] In the present invention, examples of the infection include symptoms which are developed by the infection of a normal cell in vivo with a pathogenic microorganism and proliferation of the pathogenic microorganism. Representative examples of the pathogenic microorganism include one or more kinds of a virus, a bacterium, and a fungus. The above-described pathogenic microorganism also includes a rickettsia, a chlamydia, a protozoan, and a parasite.

[0081] In the present invention, examples of the virus which related to infection include human hepatitis virus (such as hepatitis B virus, hepatitis C virus, hepatitis A virus or hepatitis E virus), human retrovirus, human immunodeficiency virus (such as HIV1 or HIV2), human T-cell leukemia virus, human T-lymphotropic virus (such as HTLV1 or HTLV2), herpes simplex virus type 1, herpes simplex virus type 2, Epstein-Barr (EB) virus, cytomegalovirus, varicella-zoster virus, human herpesvirus (such as human herpesvirus 6), poliovirus, measles virus, rubella virus, Japanese encephalitis virus, mumps virus, influenza virus, common cold virus (such as adenovirus, enterovirus or rhinovirus), virus which causes severe acute respiratory syndrome (SARS), Ebola virus, West Nile virus, flavivirus, echovirus, Coxsackie virus, coronavirus, respiratory syncytial virus, rotavirus, norovirus, sapovirus, measles virus, parvovirus, vaccinia virus, HTL virus, dengue virus, papilloma virus, molluscum contagiosum virus, rabies virus, JC virus, arbovirus, encephalitis virus, hanta-virus, and Ebola virus.

[0082] In the present invention, examples of the bacterium which related to infection include *Vibrio cholerae*, *Salmonella enterica*, *Escherichia coli*, *Legionella*, *Bacillus anthracis*, *Helicobacter pylori*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, nontuberculous mycobacteria, *Staphylococcus*, *Streptococcus*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Serratia*, *Corynebacterium diphtheriae*, *Brucella*, *Bartonella henselae*, *Erysipelothrix rhusiopathiae*, *Actinomyces*, *Borrelia burgdorferi*, *Clostridium perfringens*, *Shigella dysenteriae*, *Yersinia pestis*, *Clostridium tetani*, and *Enterobacter*.

[0083] In the present invention, examples of the fungus which related to infection include *Candida*, *Aspergillus*, *Cryptococcus*, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Paracoccidioides*, and *Sporothrix*.

[0084] In the present invention, examples of the protozoan which related to infection include *Plasmodium*, and *Toxoplasma gondii*.

[0085] In the present invention, examples of the parasite which related to infection include *Entamoeba histolytica*, *Ascaris lumbricoides*, *Babesia*, *Cryptosporidium*, *Giardia lamblia*, *Ancylostoma*, *Enterobius vermicularis*, *Schistosoma*, *Cestoda*, *Trichinella spiralis*, and *Trichuris trichiura*.

[0086] In the present invention, examples of other microorganisms which related to infection include *Mycoplasma*, and *Spirochaeta*.

[0087] In the present invention, examples of cancer include cancer associated with cerebral nerve (such as pediatric brain tumors (for example, neuroblastoma, medulloblastoma, astrocytoma (juvenile pilocytic astrocytoma), ependymoma, craniopharyngioma, germ cell tumors, optic nerve glioma, choroid plexus papilloma and pontine glioma), adult brain tumors (for example, adult astrocytoma, adult malignant astrocytoma, adult glioblastoma, adult ependymoma, adult malignant ependymoma, adult malignant oligodendrogloma, adult medulloblastoma, adult meningioma and adult malignant meningioma), glioma (for example, astrocytoma, oligodendrogloma, ependymoma and brain stem glioma), pituitary adenoma, acoustic schwannoma, retinoblastoma and uveal malignant melanoma), respiratory tract cancer (such as pharyngeal cancer (for example, nasopharyngeal cancer, oropharyngeal cancer and hypopharyngeal cancer), laryngeal cancer, nasal sinus cancer, lung cancer (for example, small cell cancer and non-small-cell cancer), thymoma and mesothelioma), gastrointestinal cancer (such as esophageal cancer, gastric cancer, duodenal cancer and large bowel cancer (for example, colon cancer, rectal cancer and anal cancer)), oral cancer (such as gingival cancer, tongue cancer and salivary gland cancer), urinary system cancer (such as penile cancer, renal pelvis · ureter cancer, renal cell cancer, testicular tumor, prostate cancer and bladder cancer), cancers that affect women (such as vulvar cancer, uterine cancer (for example, cervical cancer and endometrial cancer), uterine sarcoma, trophoblastic disease (for example, hydatidiform mole, choriocarcinoma, placental-site trophoblastic tumor and persistent trophoblastic disease), vaginal cancer, breast

cancer, breast sarcoma, ovarian cancer and ovarian germ cell tumor), skin cancer (such as melanoma (malignant melanoma) (for example, malignant lentiginous melanoma, superficial spreading melanoma, nodular melanoma, acral lentiginous melanoma and erosive melanoma), mycosis fungoides, squamous cell carcinoma, basal cell carcinoma, premonitory signs of skin cancer · intraepidermal carcinoma (for example, actinic keratosis, Bowen's disease and Paget's disease), lymphomatoid papulosis, cutaneous CD30 positive anaplastic large cell lymphoma, Sezary syndrome and cutaneous B-cell lymphoma), bone and muscle cancer (such as osteosarcoma, soft tissue sarcoma, rhabdomyosarcoma, synovial sarcoma and liposarcoma), thyroid cancer, carcinoid, liver cancer (hepatoma), hepatoblastoma, bile duct cancer, gallbladder cancer, pancreatic cancer, pancreatic endocrine tumors (such as insulinoma, gastrinoma and VIPoma), carcinoma of unknown primary, hereditary tumors · familial tumors (such as hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, hereditary breast cancer, ovarian cancer syndrome, Li-Fraumeni syndrome, hereditary melanoma, Wilms' tumor, hereditary papillary renal cell carcinoma, von Hippel-Lindau syndrome and multiple endocrine neoplasia), leukemia (such as acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, chronic myeloid leukemia · chronic myeloproliferative disorder, adult T-cell leukemia-lymphoma, chronic lymphocytic leukemia and small lymphocytic lymphoma), multiple myeloma, primary macroglobulinemia, malignant lymphoma (such as Hodgkin's lymphoma, intermediate- and high-grade lymphomas, Burkitt's lymphoma, lymphoblastic lymphoma, follicular lymphoma, mantle-cell lymphoma, and MALT (Mucosa-Associated Lymphoid Tissue) lymphoma and NK (natural killer) cell lymphoma).

[0088] The compound of the present invention may be administered as a combined medicine by being combined with other drug(s) for the purpose of:

- 20 1) complementation and/or enhancement of the preventing and/or treating effect of the compound,
- 2) improvement in kinetics · absorption, and reduction of the dose of the compound, and/or
- 3) reduction of the side effect of the compound.

[0089] The combined medicine of the compound of the present invention with other drug(s) may be administered in the form of a compounding agent in which both ingredients are compounded in a preparation or may be administered by means of separate preparations. The case of being administered by means of separate preparations includes simultaneous administration and administrations with a time difference. In addition, in the case of the administrations with a time difference, the compound of the present invention may be firstly administered, followed by administration of the other drug(s). Alternatively, the other drug(s) may be firstly administered, followed by administration of the compound of the present invention. A method for administering the compound of the present invention and that for administering the other drug(s) may be the same or different.

[0090] The disease which exhibits preventing and/or treating effect by the above-mentioned combined medicine may be any disease in which the preventing and/or treating effect of the compound of the present invention is complemented and/or enhanced by the other drug(s). In addition, the other drug(s) which is combined with the compound of the present invention includes not only those which have been found up to now but also those which will be found in future.

[0091] Examples of the other drug(s) for complementation and/or enhancement of the preventing and/or treating effect of the compound of the present invention on neurodegenerative disease include an acetylcholinesterase inhibitor, a nicotinic receptor modulator, a suppressor of production, secretion, accumulation, agglutination and/or deposition of β amyloid protein (such as a β secretase inhibitor, a γ secretase inhibitor, a drug having β amyloid protein agglutination inhibitory action, a β amyloid vaccine and a catabolic enzyme of β amyloid), an activator of brain function (such as an activator of brain metabolism and a cerebral circulation improving drug), a dopamine receptor agonist (a dopamine receptor stimulant), a dopamine release accelerating drug (a dopamine secretion accelerating drug or a dopamine release accelerating drug), a dopamine uptake inhibitor, a dopamine agonist, a dopamine antagonist, lithium carbonate, a serotonergic agonist, a serotonin antagonist (such as a 5-HT_{2A} antagonist, a 5-HT₃ antagonist, a 5-HT₄ antagonist and a 5-HT₇ antagonist), a monoamine oxidase (MAO) inhibitor, an aromatic L-amino acid decarboxylase inhibitor (DCI), a norepinephrine (noradrenaline) supplement, an anticholinergic drug, a catechol-O-methyltransferase (COMT) inhibitor, a therapeutic drug for amyotrophic lateral sclerosis, a therapeutic drug for hyperlipidemia, an apoptosis inhibitor, a nerve regeneration · differentiation accelerating drug, an antihypertensive drug, a therapeutic drug for diabetes, a therapeutic drug for diabetic complication, an antidepressant (such as a tricyclic antidepressant and a tetracyclic antidepressant), an antianxiety drug, an antiepileptic drug, an anticonvulsant drug, an antispasmodic drug, a nonsteroidal antiinflammatory drug, an anti-cytokine drug (such as a TNF inhibitor and an MAP kinase inhibitor), a steroid, a sex hormone or a derivative thereof (such as progesterone, estradiol and estradiol benzoate), a thyroid hormone, a parathyroid hormone (such as PTH), a calcium channel blocker (a calcium antagonist), a calcium receptor antagonist, an opioid receptor agonist, an N-methyl-D-2-amino-5-D-aspartate (NMDA) receptor antagonist, a VR-1 receptor agonist, a neuromuscular junction blocking drug, a cannabinoid-2 receptor agonist, a GABA receptor modulator (such as a GABA receptor agonist), a GABAB receptor modulator, prostaglandins, a cholecystokinin antagonist, a nitric oxide synthase (NOS) inhibitor, a local anesthetic, a neurotrophic factor (such as neurotrophin, TGF- β superfamily, a neurokinin family and a growth factor), a

sympathomimetic drug, a parasympathomimetic drug, a sympatholytic drug, a prostaglandin receptor antagonist, a prostaglandin receptor agonist, a carbonic anhydrase inhibitor, a hyperosmotic drug, a vasodilator drug, a metabolic activator, a diuretic drug (such as a thiazide diuretic drug, a loop diuretic drug and a potassium-sparing diuretic drug), a peripheral blood flow improving drug, an immunosuppressive drug, an immunoglobulin, an α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainic acid receptor antagonist, an Rho-kinase inhibitor, vitamins (such as vitamin B6 and vitamin B12), a cyclooxygenase (COX)-2 inhibitor, an anti-dizziness drug, a therapeutic drug for anemia, a therapeutic drug for heavy metal poisoning, a muscarinic receptor agonist, an aldose reductase inhibitor, a nerve regeneration accelerating drug, a protein kinase C (PKC) inhibitor, an advanced glycation end product (AGE) inhibitor, a reactive oxygen species scavenger, and a muscle relaxant.

[0092] Examples of the other drug(s) for complementation and/or enhancement of the preventing and/or treating effect of the compound of the present invention on autoimmune disease include an immunosuppressive drug, a steroid, a disease-modifying antirheumatic drug, an elastase inhibitor, a cannabinoid-2 receptor agonist, a prostaglandin, a prostaglandin synthase inhibitor, a phosphodiesterase inhibitor, a metalloprotease inhibitor, an adhesion molecule inhibitor, an anti-cytokine protein preparation such as an anti-TNF- α preparation, an anti-IL-1 preparation and an anti-IL-6 preparation, a cytokine inhibitor, a nonsteroidal antiinflammatory drug, and an anti-CD 20 antibody.

[0093] Examples of the other drug(s) for complementation and/or enhancement of the preventing and/or treating effect of the compound of the present invention on infection include an antiviral drug, an antibiotic, an antifungal drug, an antiparasitic drug, and an antiprotozoal drug.

[0094] Examples of the other drug(s) for complementation and/or enhancement of the preventing and/or treating effect of the compound of the present invention on cancer include an alkylating drug, an antimetabolite, an anticarcinogenic antibiotic, a plant alkaloid drug, a hormonal drug, a platinum compound, an anti-CD 20 antibody and other anticancer agents. Furthere, for the purpose of complementation and/or enhancement of the preventing and/or treating effect of the compound of the present invention on cancer, for example, radiation therapy, and cell therapy (such as chimeric antigen receptor-expressing T cell (CAR-T) therapy, and T cell receptor (TCR) therapy), may be used together.

[0095] The compound of the present invention or the combined medicine is administered as a solid agent for internal use or a solution for oral administration (internal use), a sustained-release preparation in oral administration, or injectables, external preparations, inhalants or suppositories for parenteral administration.

[0096] The solid preparations for oral administration (internal use) includs, for example, tablets, pills, capsules, powders and granulars. The capsules include hard capsules and soft capsules.

[0097] The oral solid preparation as an oral preparation is prepared, for example, by mixing an active ingredient with an excipient (such as lactose, mannitol, glucose, microcrystalline cellulose and starch), a bonding agent (such as hydroxypropyl cellulose, polyvinylpyrrolidone and magnesium aluminometasilicate), a disintegrating agent (such as calcium cellulose glycolate), a lubricant (such as magnesium stearate), a stabilizer, and a solubilizing agent (such as glutamic acid and aspartic acid) by a routine procedure. In addition, if necessary, the active ingredient may be coated with a coating agent (such as white soft sugar, gelatin, hydroxypropyl cellulose and hydroxypropyl methylcellulose phthalate) or may be coated with two or more layers. Further, capsules of substances which can be absorbed, such as gelatin, are also included.

[0098] The liquid for oral administration (internal use) includes pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs. In such the liquid formulations, one or more active substances are dissolved, suspended or emulsified in diluents (e.g. purified water, ethanol, or mixed liquids of them) which are generally used. Further, this liquid formulation may contain wetting agents, suspending agents, emulsifiers, sweeteners, flavors, fragrances, preservatives or buffers.

[0099] And, sustained-release preparations in oral administration are also effective. A gel forming substance used in these sustained-release preparations is a substance which is swollen while containing a solvent, thereby, mutually linking colloidal particles thereof to have a three dimensional network structure, and can form a jelly-like body which has no flowability. The substance is mainly used as binders, thickeners and sustained-release bases from a view point of preparations. For example, gum arabic, agar, polyvinyl pyrrolidone, sodium alginate, alginic acid propylene glycol ester, carboxyvinyl polymer, carboxymethylcellulose, carboxymethylcellulose sodium, guar gum, gelatin, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, methylcellulose or hydroxyethylmethylcellulose can be used.

[0100] Injectables for parenteral administration include solutions, suspensions, emulsions and solid injectables which are used by dissolving or suspending in a solvent upon use. Injectables are used by dissolving, suspending or emulsifying one or more active substances in a solvent. As the solvent, for example, distilled water for injection, physiological saline, vegetable oil, alcohols such as propylene glycol, polyethylene glycol, and ethanol, and a combination of them are used. Further, the injectables may contain stabilizers, solubilization aids (e.g. glutamic acid, aspartic acid, Polysorbate 80 (registered trademark)), suspending agents, emulsifiers, soothing agents, buffers or preservatives. These are produced by sterilization or a sterile operation method at a final step. Alternatively, injectables can be also used as aseptic solid agents (e.g. lyophilized products are produced, and dissolved in distilled water for injection or other solvent which has been sterilized or are aseptic, before use thereof).

[0101] A dosage form of the external preparations for parenteral administration includes, for example, spraying agents, inhalants, sprays, aerosols, ointments, gels, creams, fomentations, patches, liniments and nose drops. These contain one or more active substances, and prepared by the known method or formulation which is ordinarily used.

5 [0102] Spraying agents, inhalants and Sprays may contain stabilizers such as sodium hydrogen sulfite and buffers imparting isotonicity, for example, isotonics such as sodium chloride, sodium citrate or citric acid, in addition to diluents which are generally used. A method of producing spraying agents is described in detail, for example, in US Patents 2868691 and 3095355.

10 [0103] The inhalants for parenteral administration include aerosols, powders for inhalation or solutions for inhalation, and the solutions for inhalation may be a form which is used by dissolving or suspending in water or other suitable medium upon use.

[0104] These inhalants are produced in accordance with the known method.

15 [0105] For example, in the case of a solution for inhalation, it is prepared by appropriately selecting antiseptics (e.g. benzalkonium chloride, paraben), colorants, buffering agents (e.g. sodium phosphate, sodium acetate), isotonizing agents (e.g. sodium chloride, concentrated glycerin), thickeners (e.g. carboxyvinyl polymer), and absorption enhancers, if necessary.

[0106] In the case of a powder for inhalation, it is prepared by appropriately selecting lubricants (e.g. stearic acid and a salt thereof), binders (e.g. starch, dextrin), excipients (e.g. lactose, cellulose), colorants, antiseptics (e.g. benzalkonium chloride, paraben) or absorption enhancers, if necessary.

20 [0107] When solutions for inhalation are administered, usually, a sprayer (e.g. atomizer, nebulizer) is used and, when powders for inhalation are administered, usually, an inhalation administration equipment for powdery drugs is used.

25 [0108] Ointments are produced by formulation which is known or ordinarily used. For example, ointments are prepared by kneading or melting one or more active substances into a base. An ointment base is selected from ointment bases which are known or originally used. For example, ointment bases selected from higher fatty acid or higher fatty acid ester (e.g. adipic acid, myristic acid, palmitic acid, stearic acid, oleic acid, adipic acid ester, myristic acid ester, palmitic acid ester, stearic acid ester, oleic acid ester), waxes (e.g. beeswax, whale wax, ceresin), surfactants (e.g. polyoxyethylene alkyl ether phosphoric acid ester), higher alcohols (e.g. cetanol, stearyl alcohol, cetostearyl alcohol), silicone oils (e.g. dimethylpolysiloxane), hydrocarbons (e.g. hydrophilic vaseline, white vaseline, purified lanolin, liquid paraffin), glycols (e.g. ethylene glycol, diethylene glycol, propylene glycol, polyethylene glycol, macrogol), vegetable oils (e.g. castor oil, olive oil, sesame oil, turpentine oil), animal oils (e.g. mink oil, yolk oil, squalane, squalene), water, absorption enhancers or rash preventing agents are used alone, or by mixing two or more kinds. Further, ointment bases may contain humectants, preservatives, stabilizers, antioxidants or flavoring agents.

30 [0109] Gel agents are produced by formulation which is known or ordinarily used. For example, gel agents are prepared by melting one or more active substances into a base. A gel base is selected from gel bases which are known or ordinarily used. For example, gel bases selected from lower alcohols (e.g. ethanol, isopropyl alcohol), gelling agents (e.g. carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, ethylcellulose), neutralizing agents (e.g. triethanolamine, diisopropanolamine), surfactants (e.g. monostearic acid polyethylene glycol), gums, water, absorption enhancers and rash preventing agents are used alone, or by mixing two or more kinds. Further, gel bases may contain preservatives, antioxidants or flavoring agents.

35 [0110] Creams are prepared by formulation which is known or ordinarily used. For example, creams are prepared by melting or emulsifying one or more active substances into a base. A cream base is selected from cream bases which are known or ordinarily used. For example, cream bases selected from higher fatty acid esters, lower alcohols, hydrocarbons, polyhydric alcohols (e.g. propylene glycol, 1,3-butylene glycol), higher alcohols (e.g. 2-hexyldecanol, cetanol), emulsifiers (e.g. polyoxyethylene alkyl ethers, fatty acid esters), water, absorption enhancers and rash preventing agents are used alone, or by mixing two or more kinds. Further, cream bases may contain preservatives, antioxidants or flavoring agents.

40 [0111] Fomentations are produced by formulation which is known or ordinarily used. For example, fomentations are produced by melting one or more active substances into a base, and spreading a melt as a kneaded product on a support. A base used for fomentation is selected from bases which are known or ordinarily used. For example, bases selected from thickeners (e.g. polyacrylic acid, polyvinyl pyrrolidone, gum arabic, starch, gelatin, methylcellulose), wetting agents (e.g. urea, glycerin, propylene glycol), fillers (e.g. kaolin, zinc oxide, talc, calcium, magnesium), water, solubilization aids, tackiness imparting agents and rash preventing agents are used alone, or by mixing two or more kinds. Further, bases used for fomentations may contain preservatives, antioxidants or flavoring agents.

45 [0112] Patches are produced by formulation which is known or ordinarily used. For example, patches are produced by melting one or more active substances into a base, and spreading a melt on a support. A base for patches is selected from bases for patches which are known or ordinarily used. For example, bases for patches selected from polymer bases, fats, oils, higher fatty acids, tackiness imparting agents and rash preventing agents are used alone, or by mixing two or more kinds. Further, bases for patches may contain preservatives, antioxidants or flavoring agents.

[0113] Liniments are produced by formulation which is known or ordinarily used. For example, liniments are prepared

by dissolving, suspending or emulsifying one or more active substances in a base selected from water, alcohols (e.g. ethanol, polyethylene glycol), higher fatty acid, glycerin, soaps, emulsifiers and suspending agents alone, or two or more kinds of them. Further, liniments may contain preservatives, antioxidants or flavoring agents.

[0114] Other composition for parenteral administration includes suppositories for rectal administration or pessaries for intravaginal administration, which contain one or more active substances, and are formulated by the conventional method.

[0115] In order to use the compound of the present invention or the combined medicine of the compound of the present invention with other drug(s) for the above-described purpose, the compound of the present invention or the combined medicine of the compound of the present invention with other drug(s) is normally administered systemically or locally, in the form of an oral preparation or a parenteral preparation. The dose varies depending on the age, the body weight, the symptom, the therapeutic effect, the method for administration, and the duration of the treatment. However, normally, the dose per adult is in the range of from 1 ng to 1,000 mg per administration, from one to several oral administrations per day or the dose per adult is in the range of from 0.1 ng to 10 mg per administration, from one to several parenteral administrations per day. Alternatively, the dose is continuously administrated intravenously for a period of time in the range of 1 to 24 hours per day. Of course, the dose varies depending on various factors as described above, and therefore, there are some cases in which a dose below the above-described dose is sufficient and there are other cases in which administration of a dose which exceeds the above-described range is required.

EXAMPLES

[0116] The present invention will be described in details by referring to Examples hereinbelow.

[0117] Concerning chromatographic separation or TLC, a solvent in parentheses corresponds to an eluting solvent or a developing solvent employed and a ratio is expressed by volume ratio.

[0118] LC-MS/ELSD was performed by any of the following conditions:

Condition A: {column: YMC Triart C₁₈ (particle size: 1.9 x 10⁻⁶ m; column length: 30 x 2.0 mm I.D.); flow rate: 1.0 mL/min; column temperature: 30°C; mobile phase (A): 0.1% trifluoroacetic acid aqueous solution; mobile phase (B): 0.1% trifluoroacetic acid-acetonitrile solution; gradient (the ratio of mobile phase (A) : mobile phase (B) is described): [0 min] 95 : 5; [0.1 min] 95 : 5; [1.2 min] 5 : 95; [1.4 min] 5 : 95; [1.41 min] 95 : 5; [1.5 min] 95 : 5; Detector: UV(PDA), ELSD, MS} or

Condition B: {column: Waters ACQUITY BEH C₁₈ (particle size: 1.7 x 10⁻⁶ m; column length: 30 x 2.1 mm I.D.); flow rate: 1.0 mL/min; column temperature: 40°C; mobile phase (A): 0.1% formic acid aqueous solution; mobile phase (B): 0.1% formic acid-acetonitrile solution; gradient (the ratio of mobile phase (A) : mobile phase (B) is described): [0 min] 95 : 5; [0.1 min] 95 : 5; [1.2 min] 5 : 95; [1.4 min] 5 : 95; [1.41 min] 95 : 5; [1.5 min] 95 : 5; Detector: UV(PDA), ELSD, MS}.

Concerning NMR, a solvent in parentheses corresponds to a solvent used for the measurement.

[0119] The compound names used in the present specification were named using Advanced Chemistry Development's ACD/Name (registered trademark) computer program which is generally denominates a compound according to the IUPAC rules or according to the IUPAC nomenclature.

Example 1 (Reference): Methyl 1-(5-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-3-azetidinecarboxylate

[0120] Methyl azetidine-3-carboxylate hydrochloride (111 mg) (CAS registry number: 100202-39-9) and sodium triacetoxyborohydride (260 mg) were added to a Methylene chloride solution (5 mL) of 5-hydroxy-3,4-dihydronaphthalen-2(1H)-one (100 mg) (CAS registry number: 35697-10-0), and the mixture was stirred at room temperature for 16 hours. The reaction solution was diluted with water, and extracted with methylene chloride.

The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was washed with saturated saline, and thereafter, was dried with anhydrous sodium sulfate. The solution was filtrated and distilled off to give the title compound (100 mg) having the following physical properties. The obtained compound was used in the next reaction without purification.

MS (M+H): 262.

Example 2: Methyl 1-[5-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylate

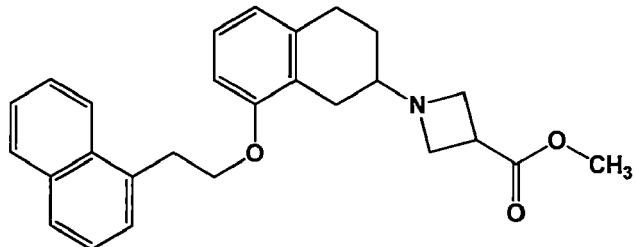
[0121] (E)-1-(3-chloroprop-1-en-1-yl)-4-(trifluoromethyl)benzene (111 mg) was added to an N,N-dimethylformamide

(DMF) (3 mL) mixture solution containing the compound (110 mg) prepared in Example 1 and potassium carbonate (174 mg), and the mixture was stirred at 70°C for 3 hours. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was washed with saturated saline, and thereafter, was dried with anhydrous sodium sulfate. The solution was filtrated and distilled off to give the title compound (100 mg) having the following physical properties. The obtained compound was used in the next reaction without purification.

5 MS (M+H): 446.

Example 2 (1): Methyl 1-{8-[2-(1-naphthyl)ethoxy]-1,2,3,4-tetrahydro-2-naphthalenyl}-3-azetidinecarboxylate

10 [0122]

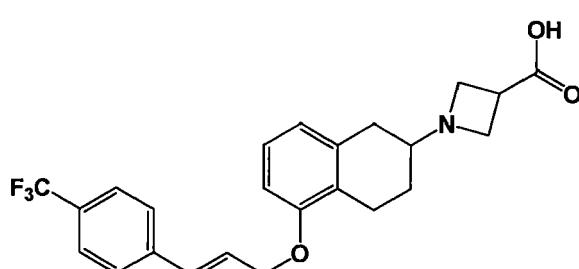


[0123] A procedure for a purpose similar to that for Example 2 was carried out by using a corresponding alcohol in place of the compound prepared in Example 1, and a corresponding halide in place of (E)-1-(3-chloroprop-1-en-1-yl)-4-(trifluoromethyl)benzene to give the title compound having the following physical properties.

25 (LC-MS/ELSD):(Retention time:0.92 minutes, Condition A);
 MS (M+H):416;
¹H-NMR (CDCl₃):δ 8.10, 7.86, 7.75, 7.56-7.36, 7.02, 6.67, 6.62, 4.30, 3.74, 3.65-3.52, 3.42-3.24, 2.88-2.61, 2.46-2.34, 2.15, 1.89-1.77, 1.50-1.33.

30 Example 3: 1-[5-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

35 [0124]



[0125] Lithium hydroxide (36 mg) was added to a solution (ethanol (1 mL), tetrahydrofuran (THF) (1 mL) and water (1 mL)) containing the compound (100 mg) prepared in Example 2. The reaction mixture was stirred at room temperature for 16 hours. After that, the solvent was distilled, and the residue liquid was acidified with 2N hydrochloric acid. The resulting solution was purified by reversed phase silica gel column chromatography (water:acetonitrile=10:0→4:6) to give the title compound (60 mg) having the following physical properties.

50 (LC-MS/ELSD):(Retention time:0.94 minutes, Condition A);
 MS (M+H): 432;
¹H-NMR (CD₃OD):δ 7.61, 7.14, 6.89-6.81, 6.76, 6.63, 4.75, 4.47-4.38, 3.69-3.62, 3.19, 3.04, 2.80-2.70, 2.27-2.24, 1.77-1.66.

Example 3(1) - 3(5)

[0126] A procedure for a purpose similar to that for Example 1 → Example 2 → Example 3 was carried out by using 5-hydroxy-3,4-dihydro-naphthalen-2(1H)-one or a corresponding alcohol, methyl azetidine-3-carboxylate hydrochloride or a corresponding amine, and (E)-1-(3-chloroprop-1-en-1-yl)-4-(trifluoromethyl)benzene or a corresponding halide to give the following Example compounds.

Example 3 (1): 1-[5-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-pyrrolidinecarboxylic acid

[0127]

(LC-MS/ELSD):(Retention time:0.94 minutes, Condition A);
MS (M+H): 446.

Example 3 (2): 1-[8-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0128]

(LC-MS/ELSD):(Retention time:0.86 minutes, Condition B);
MS (M+H): 432.

Example 3 (3): 3-{Methyl[8-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,2,3,4-tetrahydro-2-naphthalenyl]amino}propanoic acid

[0129]

(LC-MS/ELSD):(Retention time:0.86 minutes, Condition B);
MS (M+H): 434.

Example 3 (4): 1-[8-(3-Phenylpropoxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0130]

(LC-MS/ELSD):(Retention time:0.86 minutes, Condition A);
MS (M+H): 366.

Example 3 (5): 1-{8-[2-(1-Naphthyl)ethoxy]-1,2,3,4-tetrahydro-2-naphthalenyl}-3-azetidinecarboxylic acid

[0131]

(LC-MS/ELSD):(Retention time:0.88 minutes, Condition A);
MS (M+H): 402.

Example 4 (Reference): Ethyl (2E)-3-[4-(trifluoromethyl)phenyl]acrylate

[0132] To a suspension of sodium hydride (1.38 g) in THF (40 mL), a solution of triethylphosphonoacetate (7.73 g) in THF (10 mL) was added at 0°C, and the reaction mixture was stirred at room temperature for 30 minutes. To the reaction solution, 4-(Trifluoromethyl)benzaldehyde (CAS registry number:455-19-6) was added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into 10% aqueous sodium hydrogen sulfate solution, and extracted with ethyl acetate two times. The organic layer was washed with an aqueous saturated sodium bicarbonate solution and an saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:0→9:1) to give the title compound (5.92 g) having the following physical properties.

TLC:Rf 0.78 (hexane:ethyl acetate=8:2);
¹H-NMR(CDCl₃):δ 7.69, 7.64, 6.51, 4.28, 1.35.

Example 5 (Reference): (2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-ol

[0133] To a solution of the compound (5.91 g) prepared in Example 4 in THF (120 mL), 1M toluene solution (50.8 mL) of diisobutylaluminium hydride was added at 0°C, and the mixture was stirred at 0°C for 30 minutes. The reaction mixture was poured into 2N hydrochloric acid, and extracted with ethyl acetate two times. The organic layer was washed with water, and saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20→55:45) to give the title compound (4.46 g) having the following physical properties.

10 TLC:Rf 0.17 (hexane:ethyl acetate=8:2);
¹H-NMR(CDCl₃):δ 7.56, 7.47, 6.66, 6.46, 4.37, 1.53.

Example 6 (Reference): 2-[4-(Trifluoromethyl)phenoxy]ethanol

15 [0134] To a solution of 4-(trifluoromethyl)phenol (500 mg) (CAS registry number:402-45-9) in DMF (15mL), potassium carbonate (853 mg) and 2-bromoethanol (771 mg) was added, and the mixture was stirred at 80°C for 16 hours. The reaction mixture was poured into water, and extracted with ethyl acetate two times. The organic layer was washed with an saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=85: 15 →45:55) to give the title compound (226 mg) having the following physical properties.

20 ¹H-NMR(CDCl₃):δ 7.55, 6.99, 4.15-4.10, 4.03-3.96, 1.98.

Example 7 (Reference): (2Z)-3-Phenyl-2-propen-1-ol

25 [0135] To a solution of 3-phenyl-2-propyn-1-ol (800 mg) (CAS registry number: 1504-58-1) and quinoline (780 mg) in ethanol (20 mL), Lindlar's catalyst (160 mg) was added and the mixture was stirred at room temperature for 1 hour under hydrogen atmosphere. The reaction mixture was filtered through Celite (trade name) and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=90: 10→60:40) to give the title compound (548 mg) having the following physical properties.

30 ¹H-NMR(CDCl₃):δ 7.39-7.19, 6.58, 5.89, 4.45, 1.47.

Example 8 (Reference): rel-[(1R,2S)-2-Phenylcyclopropyl]methanol

35 [0136] 1M diethyl zinc solution in hexane (8.9 mL) was diluted with dichloromethane (7.0 mL) and cooled to 0°C. Trifluoroacetic acid (0.689 mL) was added to the solution, and the mixture was stirred at 0°C for 20 minutes. To the mixture diiodomethane (0.719 mL) was added, and the obtained mixture was stirred at 0°C for 20 minutes. A solution of the compound (400 mg) prepared in Example 7 in dichloromethane (3 mL) was added to the obtained mixture and the reaction mixture was stirred at 0°C for 30 minutes, and 3 hours at room temperature. The reaction mixture was poured into 1N hydrochloric acid, and extracted with ethyl acetate two times. The organic layer was washed with saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=90: 10→60:40) to give the title compound (57.8 mg) having the following physical properties.

40 ¹H-NMR(CDCl₃):δ 7.36, 7.16, 3.48, 3.27, 2.29, 1.51, 1.05, 0.88.

Example 9 (Reference): 5-(Benzylxy)-3,4-dihydro-1(2H)-naphthalenone

45 [0137] Under nitrogen atmosphere, the mixture solution of 5-hydroxy-3,4-dihydronaphthalen-1(2H)-one (10.1 g) (CAS registry number:28315-93-7), benzylbromide (12.8 g) and potassium carbonate (10.3 g) in DMF (100 mL) was stirred at room temperature for 4 hours. The mixture solution was diluted with ethyl acetate, water was added thereto, and the reaction mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water, 5% aqueous lithium chloride solution and saturated saline, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0→60:40) to give the title compound (13.8 g) having the following physical properties.

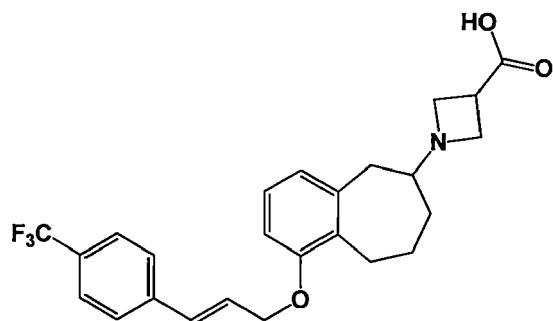
50 MS (M+H): 253.

Example 10 (Reference): 5-(Benzylxy)-1-methylene-1,2,3,4-tetrahydronaphthalene

55 [0138] To a suspension of the compound (7.83 g) prepared in Example 9 and methyltriphenylphosphoniumiodide (13.8

g) in THF (100 mL), potassium tert-butoxide (46.5 mL, 1M solution in THF) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture, cold water was poured, and the mixture was extracted with ethyl acetate. The organic layer was sequentially washed with water and saturated saline, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 → 80:20) to give the title compound (6.57 g) having the following physical properties.

⁵ ¹⁰ ¹⁵ ²⁰ ²⁵ ³⁰ ³⁵ ⁴⁰ ⁴⁵ ⁵⁰ ⁵⁵ ¹ ² ³ ⁴ ⁵ ⁶ ⁷ ⁸ ⁹ ¹⁰ ¹¹ ¹² ¹³ ¹⁴ ¹⁵ ¹⁶ ¹⁷ ¹⁸ ¹⁹ ²⁰ ²¹ ²² ²³ ²⁴ ²⁵ ²⁶ ²⁷ ²⁸ ²⁹ ³⁰ ³¹ ³² ³³ ³⁴ ³⁵ ³⁶ ³⁷ ³⁸ ³⁹ ⁴⁰ ⁴¹ ⁴² ⁴³ ⁴⁴ ⁴⁵ ⁴⁶ ⁴⁷ ⁴⁸ ⁴⁹ ⁵⁰ ⁵¹ ⁵² ⁵³ ⁵⁴ ⁵⁵ ⁵⁶ ⁵⁷ ⁵⁸ ⁵⁹ ⁶⁰ ⁶¹ ⁶² ⁶³ ⁶⁴ ⁶⁵ ⁶⁶ ⁶⁷ ⁶⁸ ⁶⁹ ⁷⁰ ⁷¹ ⁷² ⁷³ ⁷⁴ ⁷⁵ ⁷⁶ ⁷⁷ ⁷⁸ ⁷⁹ ⁸⁰ ⁸¹ ⁸² ⁸³ ⁸⁴ ⁸⁵ ⁸⁶ ⁸⁷ ⁸⁸ ⁸⁹ ⁹⁰ ⁹¹ ⁹² ⁹³ ⁹⁴ ⁹⁵ ⁹⁶ ⁹⁷ ⁹⁸ ⁹⁹ ¹⁰⁰ ¹⁰¹ ¹⁰² ¹⁰³ ¹⁰⁴ ¹⁰⁵ ¹⁰⁶ ¹⁰⁷ ¹⁰⁸ ¹⁰⁹ ¹¹⁰ ¹¹¹ ¹¹² ¹¹³ ¹¹⁴ ¹¹⁵ ¹¹⁶ ¹¹⁷ ¹¹⁸ ¹¹⁹ ¹²⁰ ¹²¹ ¹²² ¹²³ ¹²⁴ ¹²⁵ ¹²⁶ ¹²⁷ ¹²⁸ ¹²⁹ ¹³⁰ ¹³¹ ¹³² ¹³³ ¹³⁴ ¹³⁵ ¹³⁶ ¹³⁷ ¹³⁸ ¹³⁹ ¹⁴⁰ ¹⁴¹ ¹⁴² ¹⁴³ ¹⁴⁴ ¹⁴⁵ ¹⁴⁶ ¹⁴⁷ ¹⁴⁸ ¹⁴⁹ ¹⁵⁰ ¹⁵¹ ¹⁵² ¹⁵³ ¹⁵⁴ ¹⁵⁵ ¹⁵⁶ ¹⁵⁷ ¹⁵⁸ ¹⁵⁹ ¹⁶⁰ ¹⁶¹ ¹⁶² ¹⁶³ ¹⁶⁴ ¹⁶⁵ ¹⁶⁶ ¹⁶⁷ ¹⁶⁸ ¹⁶⁹ ¹⁷⁰ ¹⁷¹ ¹⁷² ¹⁷³ ¹⁷⁴ ¹⁷⁵ ¹⁷⁶ ¹⁷⁷ ¹⁷⁸ ¹⁷⁹ ¹⁸⁰ ¹⁸¹ ¹⁸² ¹⁸³ ¹⁸⁴ ¹⁸⁵ ¹⁸⁶ ¹⁸⁷ ¹⁸⁸ ¹⁸⁹ ¹⁹⁰ ¹⁹¹ ¹⁹² ¹⁹³ ¹⁹⁴ ¹⁹⁵ ¹⁹⁶ ¹⁹⁷ ¹⁹⁸ ¹⁹⁹ ²⁰⁰ ²⁰¹ ²⁰² ²⁰³ ²⁰⁴ ²⁰⁵ ²⁰⁶ ²⁰⁷ ²⁰⁸ ²⁰⁹ ²¹⁰ ²¹¹ ²¹² ²¹³ ²¹⁴ ²¹⁵ ²¹⁶ ²¹⁷ ²¹⁸ ²¹⁹ ²²⁰ ²²¹ ²²² ²²³ ²²⁴ ²²⁵ ²²⁶ ²²⁷ ²²⁸ ²²⁹ ²³⁰ ²³¹ ²³² ²³³ ²³⁴ ²³⁵ ²³⁶ ²³⁷ ²³⁸ ²³⁹ ²⁴⁰ ²⁴¹ ²⁴² ²⁴³ ²⁴⁴ ²⁴⁵ ²⁴⁶ ²⁴⁷ ²⁴⁸ ²⁴⁹ ²⁵⁰ ²⁵¹ ²⁵² ²⁵³ ²⁵⁴ ²⁵⁵ ²⁵⁶ ²⁵⁷ ²⁵⁸ ²⁵⁹ ²⁶⁰ ²⁶¹ ²⁶² ²⁶³ ²⁶⁴ ²⁶⁵ ²⁶⁶ ²⁶⁷ ²⁶⁸ ²⁶⁹ ²⁷⁰ ²⁷¹ ²⁷² ²⁷³ ²⁷⁴ ²⁷⁵ ²⁷⁶ ²⁷⁷ ²⁷⁸ ²⁷⁹ ²⁸⁰ ²⁸¹ ²⁸² ²⁸³ ²⁸⁴ ²⁸⁵ ²⁸⁶ ²⁸⁷ ²⁸⁸ ²⁸⁹ ²⁹⁰ ²⁹¹ ²⁹² ²⁹³ ²⁹⁴ ²⁹⁵ ²⁹⁶ ²⁹⁷ ²⁹⁸ ²⁹⁹ ³⁰⁰ ³⁰¹ ³⁰² ³⁰³ ³⁰⁴ ³⁰⁵ ³⁰⁶ ³⁰⁷ ³⁰⁸ ³⁰⁹ ³¹⁰ ³¹¹ ³¹² ³¹³ ³¹⁴ ³¹⁵ ³¹⁶ ³¹⁷ ³¹⁸ ³¹⁹ ³²⁰ ³²¹ ³²² ³²³ ³²⁴ ³²⁵ ³²⁶ ³²⁷ ³²⁸ ³²⁹ ³³⁰ ³³¹ ³³² ³³³ ³³⁴ ³³⁵ ³³⁶ ³³⁷ ³³⁸ ³³⁹ ³⁴⁰ ³⁴¹ ³⁴² ³⁴³ ³⁴⁴ ³⁴⁵ ³⁴⁶ ³⁴⁷ ³⁴⁸ ³⁴⁹ ³⁵⁰ ³⁵¹ ³⁵² ³⁵³ ³⁵⁴ ³⁵⁵ ³⁵⁶ ³⁵⁷ ³⁵⁸ ³⁵⁹ ³⁶⁰ ³⁶¹ ³⁶² ³⁶³ ³⁶⁴ ³⁶⁵ ³⁶⁶ ³⁶⁷ ³⁶⁸ ³⁶⁹ ³⁷⁰ ³⁷¹ ³⁷² ³⁷³ ³⁷⁴ ³⁷⁵ ³⁷⁶ ³⁷⁷ ³⁷⁸ ³⁷⁹ ³⁸⁰ ³⁸¹ ³⁸² ³⁸³ ³⁸⁴ ³⁸⁵ ³⁸⁶ ³⁸⁷ ³⁸⁸ ³⁸⁹ ³⁹⁰ ³⁹¹ ³⁹² ³⁹³ ³⁹⁴ ³⁹⁵ ³⁹⁶ ³⁹⁷ ³⁹⁸ ³⁹⁹ ⁴⁰⁰ ⁴⁰¹ ⁴⁰² ⁴⁰³ ⁴⁰⁴ ⁴⁰⁵ ⁴⁰⁶ ⁴⁰⁷ ⁴⁰⁸ ⁴⁰⁹ ⁴¹⁰ ⁴¹¹ ⁴¹² ⁴¹³ ⁴¹⁴ ⁴¹⁵ ⁴¹⁶ ⁴¹⁷ ⁴¹⁸ ⁴¹⁹ ⁴²⁰ ⁴²¹ ⁴²² ⁴²³ ⁴²⁴ ⁴²⁵ ⁴²⁶ ⁴²⁷ ⁴²⁸ ⁴²⁹ ⁴³⁰ ⁴³¹ ⁴³² ⁴³³ ⁴³⁴ ⁴³⁵ ⁴³⁶ ⁴³⁷ ⁴³⁸ ⁴³⁹ ⁴⁴⁰ ⁴⁴¹ ⁴⁴² ⁴⁴³ ⁴⁴⁴ ⁴⁴⁵ ⁴⁴⁶ ⁴⁴⁷ ⁴⁴⁸ ⁴⁴⁹ ⁴⁵⁰ ⁴⁵¹ ⁴⁵² ⁴⁵³ ⁴⁵⁴ ⁴⁵⁵ ⁴⁵⁶ ⁴⁵⁷ ⁴⁵⁸ ⁴⁵⁹ ⁴⁶⁰ ⁴⁶¹ ⁴⁶² ⁴⁶³ ⁴⁶⁴ ⁴⁶⁵ ⁴⁶⁶ ⁴⁶⁷ ⁴⁶⁸ ⁴⁶⁹ ⁴⁷⁰ ⁴⁷¹ ⁴⁷² ⁴⁷³ ⁴⁷⁴ ⁴⁷⁵ ⁴⁷⁶ ⁴⁷⁷ ⁴⁷⁸ ⁴⁷⁹ ⁴⁸⁰ ⁴⁸¹ ⁴⁸² ⁴⁸³ ⁴⁸⁴ ⁴⁸⁵ ⁴⁸⁶ ⁴⁸⁷ ⁴⁸⁸ ⁴⁸⁹ ⁴⁹⁰ ⁴⁹¹ ⁴⁹² ⁴⁹³ ⁴⁹⁴ ⁴⁹⁵ ⁴⁹⁶ ⁴⁹⁷ ⁴⁹⁸ ⁴⁹⁹ ⁵⁰⁰ ⁵⁰¹ ⁵⁰² ⁵⁰³ ⁵⁰⁴ ⁵⁰⁵ ⁵⁰⁶ ⁵⁰⁷ ⁵⁰⁸ ⁵⁰⁹ ⁵¹⁰ ⁵¹¹ ⁵¹² ⁵¹³ ⁵¹⁴ ⁵¹⁵ ⁵¹⁶ ⁵¹⁷ ⁵¹⁸ ⁵¹⁹ ⁵²⁰ ⁵²¹ ⁵²² ⁵²³ ⁵²⁴ ⁵²⁵ ⁵²⁶ ⁵²⁷ ⁵²⁸ ⁵²⁹ ⁵³⁰ ⁵³¹ ⁵³² ⁵³³ ⁵³⁴ ⁵³⁵ ⁵³⁶ ⁵³⁷ ⁵³⁸ ⁵³⁹ ⁵⁴⁰ ⁵⁴¹ ⁵⁴² ⁵⁴³ ⁵⁴⁴ ⁵⁴⁵ ⁵⁴⁶ ⁵⁴⁷ ⁵⁴⁸ ⁵⁴⁹ ⁵⁵⁰ ⁵⁵¹ ⁵⁵² ⁵⁵³ ⁵⁵⁴ ⁵⁵⁵ ⁵⁵⁶ ⁵⁵⁷ ⁵⁵⁸ ⁵⁵⁹ ⁵⁵¹⁰ ⁵⁵¹¹ ⁵⁵¹² ⁵⁵¹³ ⁵⁵¹⁴ ⁵⁵¹⁵ ⁵⁵¹⁶ ⁵⁵¹⁷ ⁵⁵¹⁸ ⁵⁵¹⁹ ⁵⁵²⁰ ⁵⁵²¹ ⁵⁵²² ⁵⁵²³ ⁵⁵²⁴ ⁵⁵²⁵ ⁵⁵²⁶ ⁵⁵²⁷ ⁵⁵²⁸ ⁵⁵²⁹ ⁵⁵²¹⁰ ⁵⁵²¹¹ ⁵⁵²¹² ⁵⁵²¹³ ⁵⁵²¹⁴ ⁵⁵²¹⁵ ⁵⁵²¹⁶ ⁵⁵²¹⁷ ⁵⁵²¹⁸ ⁵⁵²¹⁹ ⁵⁵²²⁰ ⁵⁵²²¹ ⁵⁵²²² ⁵⁵²²³ ⁵⁵²²⁴ ⁵⁵²²⁵ ⁵⁵²²⁶ ⁵⁵²²⁷ ⁵⁵²²⁸ ⁵⁵²²⁹ ⁵⁵²²¹⁰ ⁵⁵²²¹¹ ⁵⁵²²¹² ⁵⁵²²¹³ ⁵⁵²²¹⁴ ⁵⁵²²¹⁵ ⁵⁵²²¹⁶ ⁵⁵²²¹⁷ ⁵⁵²²¹⁸ ⁵⁵²²¹⁹ ⁵⁵²²²⁰ ⁵⁵²²²¹ ⁵⁵²²²² ⁵⁵²²²³ ⁵⁵²²²⁴ ⁵⁵²²²⁵ ⁵⁵²²²⁶ ⁵⁵²²²⁷ ⁵⁵²²²⁸ ⁵⁵²²²⁹ ⁵⁵²²²¹⁰ ⁵⁵²²²¹¹ ⁵⁵²²²¹² ⁵⁵²²²¹³ ⁵⁵²²²¹⁴ ⁵⁵²²²¹⁵ ⁵⁵²²²¹⁶ ⁵⁵²²²¹⁷ ⁵⁵²²²¹⁸ ⁵⁵²²²¹⁹ ⁵⁵²²²²⁰ ⁵⁵²²²²¹ ⁵⁵²²²²² ⁵⁵²²²²³ ⁵⁵²²²²⁴ ⁵⁵²²²²⁵ ⁵⁵²²²²⁶ ⁵⁵²²²²⁷ ⁵⁵²²²²⁸ ⁵⁵²²²²⁹ ⁵⁵²²²²¹⁰ ⁵⁵²²²²¹¹ ⁵⁵²²²²¹² ⁵⁵²²²²¹³ ⁵⁵²²²²¹⁴ ⁵⁵²²²²¹⁵ ⁵⁵²²²²¹⁶ ⁵⁵²²²²¹⁷ ⁵⁵²²²²¹⁸ ⁵⁵²²²²¹⁹ ⁵⁵²²²²²⁰ ⁵⁵²²²²²¹ ⁵⁵²²²²²² ⁵⁵²²²²²³ ⁵⁵²²²²²⁴ ⁵⁵²²²²²⁵ ⁵⁵²²²²²⁶ ⁵⁵²²²²²⁷ ⁵⁵²²²²²⁸ ⁵⁵²²²²²⁹ ⁵⁵²²²²²¹⁰ ⁵⁵²²²²²¹¹ ⁵⁵²²²²²¹² ⁵⁵²²²²²¹³ ⁵⁵²²²²²¹⁴ ⁵⁵²²²²²¹⁵ ⁵⁵²²²²²¹⁶ ⁵⁵²²²²²¹⁷ ⁵⁵²²²²²¹⁸ ⁵⁵²²²²²¹⁹ ⁵⁵²²²²²²⁰ ⁵⁵²²²²²²¹ ⁵⁵²²²²²²² ⁵⁵²²²²²²³ ⁵⁵²²²²²²⁴ ⁵⁵²²²²²²⁵ ⁵⁵²²²²²²⁶ ⁵⁵²²²²²²⁷ ⁵⁵²²²²²²⁸ ⁵⁵²²²²²²⁹ ⁵⁵²²²²²²¹⁰ ⁵⁵²²²²²²¹¹ ⁵⁵²²²²²²¹² ⁵⁵²²²²²²¹³ ⁵⁵²²²²²²¹⁴ ⁵⁵²²²²²²¹⁵ ⁵⁵²²²²²²¹⁶ ⁵⁵²²²²²²¹⁷ ⁵⁵²²²²²²¹⁸ ⁵⁵²²²²²²¹⁹ ⁵⁵²²²²²²²⁰ ⁵⁵²²²²²²²¹ ⁵⁵²²²²²²²² ⁵⁵²²²²²²²³ ⁵⁵²²²²²²²⁴ ⁵⁵²²²²²²²⁵ ⁵⁵²²²²²²²⁶ ⁵⁵²²²²²²²⁷ ⁵⁵²²²²²²²⁸ ⁵⁵²²²²²²²⁹ ⁵⁵²²²²²²²¹⁰ ⁵⁵²²²²²²²¹¹ ⁵⁵²²²²²²²¹² ⁵⁵²²²²²²²¹³ ⁵⁵²²²²²²²¹⁴ ⁵⁵²²²²²²²¹⁵ ⁵⁵²²²²²²²¹⁶ ⁵⁵²²²²²²²¹⁷ ⁵⁵²²²²²²²¹⁸ ⁵⁵²²²²²²²¹⁹ ⁵⁵²²²²²²²²⁰ ⁵⁵²²²²²²²²¹ ⁵⁵²²²²²²²²² ⁵⁵²²²²²²²²³ ⁵⁵²²²²²²²²⁴ ⁵⁵²²²²²²²²⁵ ⁵⁵²²²²²²²²⁶ ⁵⁵²²²²²²²²⁷ ⁵⁵²²²²²²²²⁸ ⁵⁵²²²²²²²²⁹ ⁵⁵²²²²²²²²¹⁰ ⁵⁵²²²²²²²²¹¹ ⁵⁵²²²²²²²²¹² ⁵⁵²²²²²²²²¹³ ⁵⁵²²²²²²²²¹⁴ ⁵⁵²²²²²²²²¹⁵ ⁵⁵²²²²²²²²¹⁶ ⁵⁵²²²²²²²²¹⁷ ⁵⁵²²²²²²²²¹⁸ ⁵⁵²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²⁰ ⁵⁵²²²²²²²²²¹ ⁵⁵²²²²²²²²²² ⁵⁵²²²²²²²²²³ ⁵⁵²²²²²²²²²⁴ ⁵⁵²²²²²²²²²⁵ ⁵⁵²²²²²²²²²⁶ ⁵⁵²²²²²²²²²⁷ ⁵⁵²²²²²²²²²⁸ ⁵⁵²²²²²²²²²⁹ ⁵⁵²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²¹² ⁵⁵²²²²²²²²²¹³ ⁵⁵²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²¹ ⁵⁵²²²²²²²²²²² ⁵⁵²²²²²²²²²²³ ⁵⁵²²²²²²²²²²⁴ ⁵⁵²²²²²²²²²²⁵ ⁵⁵²²²²²²²²²²⁶ ⁵⁵²²²²²²²²²²⁷ ⁵⁵²²²²²²²²²²⁸ ⁵⁵²²²²²²²²²²⁹ ⁵⁵²²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²²¹² ⁵⁵²²²²²²²²²²¹³ ⁵⁵²²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²²¹ ⁵⁵²²²²²²²²²²²² ⁵⁵²²²²²²²²²²²³ ⁵⁵²²²²²²²²²²²⁴ ⁵⁵²²²²²²²²²²²⁵ ⁵⁵²²²²²²²²²²²⁶ ⁵⁵²²²²²²²²²²²⁷ ⁵⁵²²²²²²²²²²²⁸ ⁵⁵²²²²²²²²²²²⁹ ⁵⁵²²²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²²²¹² ⁵⁵²²²²²²²²²²²¹³ ⁵⁵²²²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²²²¹ ⁵⁵²²²²²²²²²²²²² ⁵⁵²²²²²²²²²²²²³ ⁵⁵²²²²²²²²²²²²⁴ ⁵⁵²²²²²²²²²²²²⁵ ⁵⁵²²²²²²²²²²²²⁶ ⁵⁵²²²²²²²²²²²²⁷ ⁵⁵²²²²²²²²²²²²⁸ ⁵⁵²²²²²²²²²²²²⁹ ⁵⁵²²²²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²²²²¹² ⁵⁵²²²²²²²²²²²²¹³ ⁵⁵²²²²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²²²²¹ ⁵⁵²²²²²²²²²²²²²² ⁵⁵²²²²²²²²²²²²²³ ⁵⁵²²²²²²²²²²²²²⁴ ⁵⁵²²²²²²²²²²²²²⁵ ⁵⁵²²²²²²²²²²²²²⁶ ⁵⁵²²²²²²²²²²²²²⁷ ⁵⁵²²²²²²²²²²²²²⁸ ⁵⁵²²²²²²²²²²²²²⁹ ⁵⁵²²²²²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²²²²²¹² ⁵⁵²²²²²²²²²²²²²¹³ ⁵⁵²²²²²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²²²²²¹ ⁵⁵²²²²²²²²²²²²²²² ⁵⁵²²²²²²²²²²²²²²³ ⁵⁵²²²²²²²²²²²²²²⁴ ⁵⁵²²²²²²²²²²²²²²⁵ ⁵⁵²²²²²²²²²²²²²²⁶ ⁵⁵²²²²²²²²²²²²²²⁷ ⁵⁵²²²²²²²²²²²²²²⁸ ⁵⁵²²²²²²²²²²²²²²⁹ ⁵⁵²²²²²²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²²²²²²¹² ⁵⁵²²²²²²²²²²²²²²¹³ ⁵⁵²²²²²²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²²²²²²¹ ⁵⁵²²²²²²²²²²²²²²²² ⁵⁵²²²²²²²²²²²²²²²³ ⁵⁵²²²²²²²²²²²²²²²⁴ ⁵⁵²²²²²²²²²²²²²²²⁵ ⁵⁵²²²²²²²²²²²²²²²⁶ ⁵⁵²²²²²²²²²²²²²²²⁷ ⁵⁵²²²²²²²²²²²²²²²⁸ ⁵⁵²²²²²²²²²²²²²²²⁹ ⁵⁵²²²²²²²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²²²²²²²¹² ⁵⁵²²²²²²²²²²²²²²²¹³ ⁵⁵²²²²²²²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²²²²²²²¹ ⁵⁵²²²²²²²²²²²²²²²²² ⁵⁵²²²²²²²²²²²²²²²²³ ⁵⁵²²²²²²²²²²²²²²²²⁴ ⁵⁵²²²²²²²²²²²²²²²²⁵ ⁵⁵²²²²²²²²²²²²²²²²⁶ ⁵⁵²²²²²²²²²²²²²²²²⁷ ⁵⁵²²²²²²²²²²²²²²²²⁸ ⁵⁵²²²²²²²²²²²²²²²²⁹ ⁵⁵²²²²²²²²²²²²²²²²¹⁰ ⁵⁵²²²²²²²²²²²²²²²²¹¹ ⁵⁵²²²²²²²²²²²²²²²²¹² ⁵⁵²²²²²²²²²²²²²²²²¹³ ⁵⁵²²²²²²²²²²²²²²²²¹⁴ ⁵⁵²²²²²²²²²²²²²²²²¹⁵ ⁵⁵²²²²²²²²²²²²²²²²¹⁶ ⁵⁵²²²²²²²²²²²²²²²²¹⁷ ⁵⁵²²²²²²²²²²²²²²²²¹⁸ ⁵⁵²²²²²²²²²²²²²²²²¹⁹ ⁵⁵²²²²²²²²²²²²²²²²²⁰ ⁵⁵²²²²²²²²²²²²²²²²²¹ ⁵⁵²²



15 [0144] A procedure for a purpose similar to that for Example 3 was carried out by using the compound prepared in Example 14 to give the title compound having the following physical properties.

(LC-MS/ELSD):(Retention time:0.95 minutes, Condition A);
MS (M+H): 446.

20 Example 15 (1): 1-[1-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl]-3-pyrrolidinocarboxylic acid

25 [0145] A procedure for a purpose similar to that for Example 12 → Example 13 → Example 14 → Example 15 was carried out by using the compound prepared in Example 11 and a corresponding amine derivitive in place of methyl azetidine-3-carboxylate hydrochloride to give the title compound having the following physical properties.

(LC-MS/ELSD):(Retention time:0.96 minutes, Condition A);
MS (M+H): 460.

30 Example 16 (Reference): Ethyl 4-(6-methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoate

35 [0146] To a solution of 6-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (1.0 g) (CAS registry number:90047-53-3) in DMF (15 mL), potassium carbonate (1.56 g) and ethyl 4-bromobutanoate (1321 mg) were added, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water, and extracted with ethyl acetate two times. The organic layer was washed with saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=60:40 → 10:90) to give the title compound (1.37 g) having the following physical properties.

¹H-NMR(CDCl₃):δ 7.07, 6.74, 6.72, 4.13, 3.79, 3.05-2.95, 2.94-2.86, 2.65-2.54, 2.51, 2.37, 1.83, 1.26.

40 Example 17 (Reference): Ethyl 4-(6-hydroxy-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoate

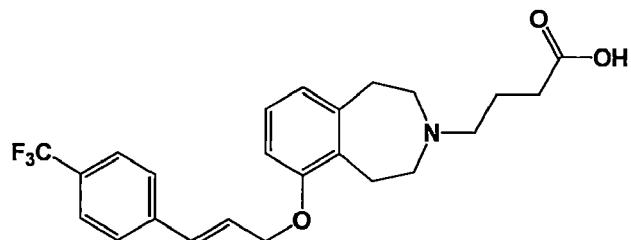
45 [0147] To a dichloromethane (23 mL) solution of the compound (1.37 g) prepared in Example 16, 1M borontribromide solution in dichloromethane (9.4 mL) was added at 0°C, and the mixture was stirred at 0°C for 2 hours. To the reaction mixture, 1M borontribromide solution in dichloromethane (4.7 mL) was added, and the mixture was stirred at 0°C for another 2 hours. The reaction mixture was poured into an aqueous saturated sodium bicarbonate solution, and extracted with ethyl acetate two times. The organic layer was washed with water and saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=70:30 → 20:70) to give the title compound (591 mg) having the following physical properties.

¹H-NMR(CDCl₃):δ 6.95, 6.68, 6.62, 4.13, 3.05-2.95, 2.95-2.85, 2.71-2.58, 2.53, 2.35, 1.86, 1.26.

50 Example 18: 4-[6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

55 [0148]

5



10 [0149] A procedure for a purpose similar to that for Example 14 → Example 3 was carried out by using the compound prepared in Example 17 and the compound prepared in Example 5 to give the title compound having the following physical properties.

15 (LC-MS/ELSD):(Retention time:0.92 minutes, Condition A);
MS ($\text{M}+\text{H}$): 434.

Example 18 (1) - 18 (45)

20 [0150] A procedure for a purpose similar to that for Example 16 → Example 17 → Example 18 was carried out by using 6-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine or a corresponding dihydroisoquinoline compound, ethyl 4-bromobutanoate or a corresponding ester halide compound, and any one compound selected from the following (i) to (iv) ((i) the compound prepared in Example 5, (ii) the compound prepared in Example 6, (iii) the compound prepared in Example 8, (iv) a corresponding alcohol compound in place of (i) to (iii)) to give the following compounds of Examples.

25 Example 18 (1): 4-[5-[2-(2-naphthyl)ethoxy]-3,4-dihydro-2(1H)-isoquinolinyl]butanoic acid trifluoroacetate

[0151]

30 (LC-MS/ELSD):(Retention time:0.81 minutes, Condition B);
MS ($\text{M}+\text{H}$): 390.

Example 18 (2): 4-[8-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl]oxy)-3,4-dihydro-2(1H)-isoquinolinyl]butanoic acid trifluoroacetate

35 **[0152]**

(LC-MS/ELSD):(Retention time:0.83 minutes, Condition B);
MS ($\text{M}+\text{H}$): 420.

40 Example 18 (3): 4-[5-[(2E)-3-(4-Isopropylphenyl)-2-propen-1-yl]oxy]-3,4-dihydro-2(1H)-isoquinolinyl]butanoic acid

[0153]

45 (LC-MS/ELSD):(Retention time:0.96 minutes, Condition A);
MS ($\text{M}+\text{H}$): 394.

Example 18 (4): 4-[5-((2E)-3-[4-(Difluoromethoxy)phenyl]-2-propen-1-yl]oxy)-3,4-dihydro-2(1H)-isoquinolinyl]butanoic acid

50 **[0154]**

(LC-MS/ELSD):(Retention time:0.86 minutes, Condition A);
MS ($\text{M}+\text{H}$): 418.

55 Example 18 (5): 4-[5-((2E)-3-[4-(2,2,2-Trifluoroethyl)phenyl]-2-propen-1-yl]oxy)-3,4-dihydro-2(1H)-isoquinolinyl]butanoic acid

[0155]

(LC-MS/ELSD):(Retention time:0.93 minutes, Condition A);
 MS (M+H): 434.

5 Example 18 (6): 4-[5-[(2E)-3-{4-[1-(Trifluoromethyl)cyclopropyl]phenyl}-2-propen-1-yl]oxy]-3,4-dihydro-2(1H)-isoquinolinyl]butanoic acid

[0156]

10 (LC-MS/ELSD):(Retention time:0.98 minutes, Condition A);
 MS (M+H): 460.

Example 18 (7): [6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl]oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid

15 **[0157]**

(LC-MS/ELSD):(Retention time:0.91 minutes, Condition A);
 MS (M+H): 406.

20 Example 18 (8): 3-[6-(1(2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl]oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid

[0158]

25 (LC-MS/ELSD):(Retention time:0.92 minutes, Condition A);
 MS (M+H): 420.

Example 18 (9): 5-[6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl]oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]pentanoic acid

30 **[0159]**

(LC-MS/ELSD):(Retention time:0.93 minutes, Condition A);
 MS (M+H): 448.

35 Example 18 (10): 4-(6-{2-[4-(Trifluoromethyl)phenoxy]ethoxy}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

[0160]

40 (LC-MS/ELSD):(Retention time:0.80 minutes, Condition B);
 MS (M+H): 438;
¹H-NMR (CDCl₃):δ 7.57, 7.13, 7.01, 6.82, 6.78, 4.41-4.27, 3.30-2.52, 1.92-1.81.

45 Example 18 (11): 4-[6-(3-Phenylpropoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0161]

(LC-MS/ELSD):(Retention time:0.79 minutes, Condition B);
 MS (M+H): 368;
¹H-NMR (CD₃OD):δ 7.34-7.24, 7.23-7.15, 7.09, 6.76-6.70, 3.94, 3.60-2.50, 2.19-2.04, 1.96-1.86.

Example 18 (12): 4-[6-(2-Phenoxyethoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0162]

55 (LC-MS/ELSD):(Retention time:0.71 minutes, Condition B);
 MS (M+H): 370;
¹H-NMR (CD₃OD):δ 7.35-7.27, 7.13, 7.01-6.89, 6.84, 6.76, 4.31, 3.32-2.70, 2.63-2.56, 1.97-1.85.

Example 18 (13): 2,2-Dimethyl-4-[6-(3-phenylpropoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0163]

5 (LC-MS/ELSD):(Retention time:0.91 minutes, Condition A);
MS (M+H): 396.

Example 18 (14): 4-[6-(3-Cyclohexylpropoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

10 **[0164]**

(LC-MS/ELSD):(Retention time:0.95 minutes, Condition B);
MS (M+H): 374.

15 Example 18 (15): 4-[6-((2E)-3-[4-(Difluoromethoxy)phenyl]-2-propen-1-yl}oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0165]

20 (LC-MS/ELSD):(Retention time:0.82 minutes, Condition B);
MS (M+H): 432.

Example 18 (16): 4-[6-(1,2,3,4-Tetrahydro-2-naphthalenylmethoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

25

[0166]

(LC-MS/ELSD):(Retention time:0.86 minutes, Condition B);
MS (M+H): 394.

30

Example 18 (17): 4-[6-(2,3-Dihydro-1H-inden-2-ylmethoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

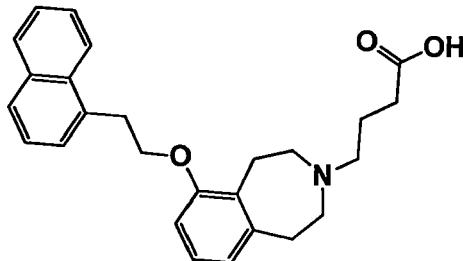
[0167]

35 (LC-MS/ELSD):(Retention time:0.82 minutes, Condition B);
MS (M+H): 380.

Example 18 (18): 4-{6-[2-(1-Naphthyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

40

[0168]



(LC-MS/ELSD):(Retention time:0.83 minutes, Condition B);
MS (M+H): 404;

55 ¹ H-NMR (CD₃ OD):δ 8.07, 7.87, 7.79-7.72, 7.56-7.39, 7.04, 6.75-6.66, 4.28, 3.56, 3.30-2.50, 2.00-1.86.

Example 18 (19): 4-{6-[2-(2-Naphthyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0169]

(LC-MS/ELSD):(Retention time:0.83 minutes, Condition B);
MS (M+H): 404.

5 Example 18 (20): 4-[6-[2-(1,2,3,4-Tetrahydro-1-naphthalenyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0170]

10 (LC-MS/ELSD):(Retention time:0.90 minutes, Condition B);
MS (M+H): 408.

Example 18 (21): rel-4-(6-[(1R,2S)-2-Phenylcyclopropyl]methoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

15 **[0171]**

(LC-MS/ELSD):(Retention time:0.85 minutes, Condition A);
MS (M+H): 380.

20 Example 18 (22): 4-[6-(2-Phenylethoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0172]

25 (LC-MS/ELSD):(Retention time:0.81 minutes, Condition A);
MS (M+H): 354.

Example 18 (23): 4-[6-(4-Phenylbutoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

30 **[0173]**

35 (LC-MS/ELSD):(Retention time:0.90 minutes, Condition A);
MS (M+H): 382.

Example 18 (24): 4-[6-[(5-Phenylpentyl)oxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

40 **[0174]**

45 (LC-MS/ELSD):(Retention time:0.94 minutes, Condition A);
MS (M+H): 396.

Example 18 (25): 4-[6-(Bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

50 **[0175]**

55 (LC-MS/ELSD):(Retention time:0.83 minutes, Condition A);
MS (M+H): 366.

Example 18 (26): 4-[6-[2-(Bicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0176]

55 (LC-MS/ELSD):(Retention time:0.88 minutes, Condition A);
MS (M+H): 380.

Example 18 (27): 3-{6-[2-(1-Naphthyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}propanoic acid

[0177]

5 (LC-MS/ELSD):(Retention time:0.83 minutes, Condition B);
MS (M+H): 390.

Example 18 (28) (Reference): 4-(6-Butoxy1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

10 [0178]

(LC-MS/ELSD):(Retention time:0.77 minutes, Condition A);
MS (M+H):306.

15 Example 18 (29) (Reference): 4-[6-(Pentyloxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0179]

20 (LC-MS/ELSD):(Retention time:0.82 minutes, Condition A);
MS (M+H):320.

Example 18 (30) (Reference): 4-[6-(Hexyloxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0180]

25 (LC-MS/ELSD):(Retention time:0.87 minutes, Condition A);
MS (M+H):334.

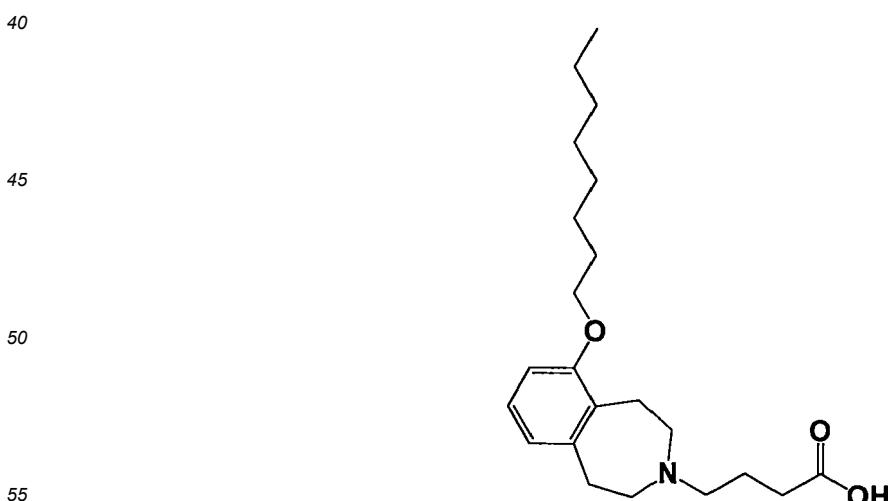
30 Example 18 (31) (Reference): 4-[6-(Heptyloxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0181]

35 (LC-MS/ELSD):(Retention time:0.93 minutes, Condition A);
MS (M+H):348.

Example 18 (32) (Reference): 4-[6-(Octyloxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0182]



(LC-MS/ELSD):(Retention time:0.97 minutes, Condition A);
MS (M+H):362;

1 H-NMR (CD₃ OD):δ 7.06, 6.80, 6.71, 3.89, 3.75-3.55, 3.18-2.86, 2.84-2.65, 2.37, 2.03-1.88, 1.76-1.62, 1.47-1.34, 1.34-1.13, 0.81.

5 Example 18 (33) (Reference): 4-{6-[(4,5,5-Trifluoro-4-penten-1-yl)oxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0183]

10 (LC-MS/ELSD):(Retention time:0.78 minutes, Condition A);
MS (M+H):372.

Example 18 (34) (Reference): 4-{6-[(5-Methylhexyl)oxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

15 [0184]

15 (LC-MS/ELSD):(Retention time:0.91 minutes, Condition A);
MS (M+H):347.

20 Example 18 (35): 4-{6-[3-(3-Pyridinyl)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0185]

25 (LC-MS/ELSD):(Retention time:0.53 minutes, Condition A);
MS (M+H):368.

Example 18 (36): 4-{6-[3-(2-Pyridinyl)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0186]

30 (LC-MS/ELSD):(Retention time:0.51 minutes, Condition A);
MS (M+H):368.

Example 18 (37): 4-[6-(2-Cyclobutylethoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

35 [0187]

(LC-MS/ELSD):(Retention time:0.83 minutes, Condition A);
MS (M+H):331.

40 Example 18 (38): 4-{6-[3-(4-Fluorophenyl)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0188]

45 (LC-MS/ELSD):(Retention time:0.85 minutes, Condition A);
MS (M+H):385;
1 H-NMR (CD₃ OD):δ 7.24, 7.19, 7.02, 6.89, 6.84, 4.01, 3.89-3.62, 3.29-3.18, 3.16-2.75, 2.83, 2.50, 2.18-2.01.

Example 18 (39): 4-{6-[3-(1,3-Thiazol-5-yl)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

50 [0189]

(LC-MS/ELSD):(Retention time:0.63 minutes, Condition A);
MS (M+H):374.

55 Example 18 (40): 4-{6-[3-(1,2-Thiazol-4-yl)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0190]

(LC-MS/ELSD):(Retention time:0.71 minutes, Condition A);
MS (M+H):374.

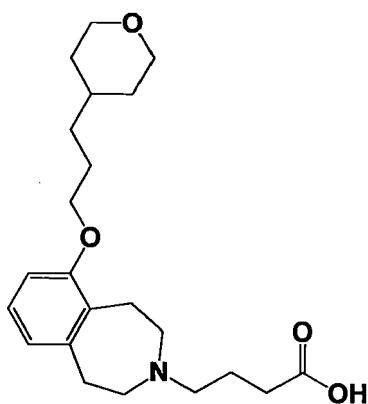
Example 18 (41): 4-{6-[3-(2-Oxo-1-pyrrolydiny)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0191]

(LC-MS/ELSD):(Retention time:0.60 minutes, Condition A);
MS (M+H):374.

Example 18 (42): 4-{6-[3-(tetrahydro-2H-pyran-4-yl)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0192]



(LC-MS/ELSD):(Retention time:0.75 minutes, Condition A);
MS (M+H):375;

¹ H-NMR (CD₃ OD):δ 7.19, 6.93, 6.84, 4.01, 3.95, 3.87-3.66, 3.44, 3.30-3.18, 3.18-2.96, 2.94-2.77, 2.49, 2.14-1.99, 1.91-1.79, 1.69, 1.65-1.52, 1.51-1.39, 1.29.

Example 18 (43): 4-(6-{2-[2-(Trifluoromethyl)phenyl]ethoxy}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

[0193]

(LC-MS/ELSD):(Retention time:0.87 minutes, Condition A);
MS (M+H):421;

¹ H-NMR (CD₃ OD):δ 7.72, 7.63-7.55, 7.45, 7.19, 6.94, 6.85, 4.33-4.21, 3.82-3.62, 3.29-2.99, 2.98-2.71, 2.49, 2.13-1.97.

Example 18 (44) (Reference): 4-(6-{[(4S)-4-Methylhexyl]oxyl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butane

[0194]

(LC-MS/ELSD):(Retention time:0.91 minutes, Condition A);
MS (M+H):347.

Example 18 (45): 4-{6-[3-(1-methyl-1H-pyrazole-4-yl)propoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}butanoic acid

[0195]

(LC-MS/ELSD):(Retention time:0.64 minutes, Condition A);
MS (M+H):371.

Example 19 (Reference): 2-Methyl-2-propenyl 6-hydroxy-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate

[0196] To a solution of 6-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (200 mg) in dichloromethane (5.0 mL), 1M boron tribromide solution in dichloromethane (2.54 mL) was added at 0°C, and the mixture was stirred at 0°C for 5 hours.

5 The reaction mixture was cooled to -78°C, methanol was added thereto, and the reaction mixture was stirred at -78°C for 15 minutes. The reaction mixture was warmed to room temperature, stirred for a while and concentrated under reduced pressure. To a THF (5.0 mL) suspension of the obtained residue, 2N sodium hydroxide (1.41 mL) and di-tert-butyl dicarbonate (265 mg) were added, and the mixture was stirred at room temperature for 6 hours. The reaction mixture was poured into 1N hydrochloric acid, and extracted with ethyl acetate two times. The organic layer was washed with saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0→75:25) to give the title compound (286 mg) having the following physical properties.

10 $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 6.97, 6.71, 6.64, 4.91, 3.60-3.50, 3.02-2.94, 2.93-2.86, 1.48.

15 Example 20: 2-Methyl-2-propenyl-6-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate

[0197] A procedure for a purpose similar to that for Example 14 was carried out by using the compound prepared in Example 19 and the compound prepared in Example 5 to give the title compound (286 mg) having the following physical properties.

20 $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.58, 7.51, 7.08, 7.83-6.71, 6.51, 4.70, 3.62-3.48, 3.12-3.00, 2.98-2.86, 1.47.

Example 21 (Reference): 6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride

25 **[0198]** To a methanol (1.0 mL) solution of the compound (190 mg) prepared in Example 20, ethyl acetate (1.0 mL) suspension, 4N hydrochloric acid (6.0 mL) was added at 0°C, and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure to give the title compound (157 mg) having the following physical properties.

30 $^1\text{H-NMR}(\text{DMSO-d}_6):\delta$ 9.05, 7.71, 7.14, 6.97, 6.89-6.79, 6.69, 4.75, 3.26-2.99.

Example 22 (1): Methyl 3-[6-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-benzazepin-3-yl]cyclobutanecarboxylate (low polar form)

35 Example 22 (2): Methyl 3-[6-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-benzazepin-3-yl]cyclobutanecarboxylate (high polar form)

[0199] A procedure for a purpose similar to that for Example 1 was carried out by using the compound prepared in Example 21 and Methyl 3-oxocyclobutanecarboxylate (CAS registry number:695-95-4) in place of Methyl azetidine-3-carboxylate hydrochloride to give the title compound having the following physical properties.

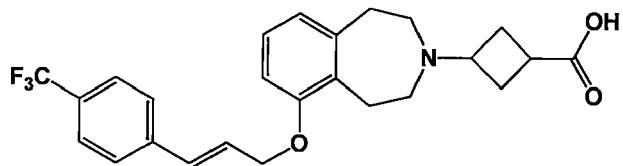
(Example 22 (1)) $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.58, 7.51, 7.06, 6.78, 6.77, 6.73, 6.51, 4.68, 3.68, 3.15-3.00, 2.95-2.85, 2.80-2.67, 2.51-2.28, 2.25-2.11.

(Example 22 (2)) $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.58, 7.51, 7.07, 6.79, 6.78, 6.74, 6.51, 4.69, 3.71, 3.20-2.82, 2.55-2.18.

45 Example 23 (1): 3-[6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]cyclobutanecarboxylic acid (low polar form)

50 Example 23 (2): 3-[6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]cyclobutanecarboxylic acid (high polar form)

[0200]



[0201] A procedure for a purpose similar to that for Example 3 was carried out by using the compound prepared in Example 22 (1) or Example 22 (2) to give the title compound having the following physical properties, respectively.

10 Example 23 (1): (LC-MS/ELSD):(Retention time:0.85 minutes, Condition B);
MS (M+H): 446.

Example 23 (2): (LC-MS/ELSD):(Retention time:0.86 minutes, Condition B);
MS (M+H): 446.

15 Example 23 (3) - 23 (9)

[0202] A procedure for a purpose similar to that for Example 19 → Example 20 → Example 21 → Example 22(1) or 22(2) → Example 23(1) or 23(2) was carried out by using 6-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine, the compound prepared in Example 5 or a corresponding alcohol compound and 3-oxocyclobutanecarboxylate or a corresponding cyclic ketone compound to give the following compounds of Examples.

20 Example 23 (3): rel-(1R,2R)-2-[(6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]methylcyclopropanecarboxylic acid

25 [0203]

(LC-MS/ELSD):(Retention time:0.85 minutes, Condition B);
MS (M+H): 446.

30 Example 23 (4): rel-(1R,2S)-2-[(6-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]methylcyclopropanecarboxylic acid

35 [0204]

(LC-MS/ELSD):(Retention time:0.86 minutes, Condition B);
MS (M+H): 446.

40 Example 23 (5): 1-Methyl-3-[6-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]cyclobutanecarboxylic acid (high polar form)

45 [0205]

(LC-MS/ELSD):(Retention time:0.94 minutes, Condition A);
MS (M+H): 460.

Example 23 (6): 1-Methyl-3-[6-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]cyclobutanecarboxylic acid (low polar form)

50 [0206]

(LC-MS/ELSD):(Retention time:0.95 minutes, Condition A);
MS (M+H): 460.

55 Example 23 (7): 3-[6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]cyclopentanecarboxylic acid

[0207]

(LC-MS/ELSD):(Retention time:0.93 minutes, Condition A);
MS (M+H): 460.

5 Example 23 (8): 3-{6-[2-(1-Naphthyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}cyclobutanecarboxylic acid (low polar form)

[0208]

10 (LC-MS/ELSD):(Retention time:0.88 minutes, Condition A);
MS (M+H): 416.

15 Example 23 (9): 3-{6-[2-(1-Naphthyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}cyclobutanecarboxylic acid (high polar form)

[0209]

(LC-MS/ELSD):(Retention time:0.87 minutes, Condition A);
MS (M+H): 416.

20 Example 24 (Reference): 2-Methyl-2-propanyl-6-hydroxy-7-(hydroxymethyl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate

25 **[0210]** To a water (2.0 mL) suspension of the compound (132 mg) prepared in Example 19, butanol (0.4 mL) and disodium 3,7-dioxide-2,4,6,8,9-pentaoxa-1,3,5,7-tetraborabicyclo[3.3.1]nonane (404 mg) were added, and the mixture was stirred at 60°C for 10 minutes. To the reaction mixture, 37% aqueous formaldehyde solution (1.0 mL) was added, and the mixture was stirred at 60°C for 72 hours. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate two times. The organic layer was washed with water and saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10→50:50) to give the title compound (80.1 mg) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.68, 6.78, 6.62, 4.84, 3.58-3.48, 3.05-2.98, 2.90-2.82, 2.23, 1.48.

30 Example 25 (Reference): 2-Methyl-2-propanyl 6-hydroxy-7-Methyl-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate

35 **[0211]** To a methanol (3.0 mL) solution of the compound (78 mg) prepared in Example 24, palladiumplatinum (ASCA-2 (trade name), 15 mg) was added, and the mixture was stirred at room temperature for 1 hour under hydrogen atmosphere. The reaction mixture was filtered through Celite (trade name) and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0→75:25) to give the title compound (71.2 mg) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 6.88, 6.63, 4.65, 3.60-3.50, 3.03-2.95, 2.91-2.82, 2.23, 1.47.

40 Example 26: 2-Methyl-2-propanyl 7-Methyl-6-(3-phenylpropoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-carboxylate

45 **[0212]** A procedure for a purpose similar to that for Example 14 was carried out by using the compound prepared in Example 25 and 3-phenyl-1-propanol in place of the compound prepared in Example 5 to give the title compound having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.35-7.17, 6.93, 6.79, 3.69, 3.57-3.42, 2.94, 2.89-2.79, 2.25, 2.14, 1.49.

Example 27: 7-Methyl-6-(3-phenylpropoxy)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride

50 **[0213]** A procedure for a purpose similar to that for Example 21 was carried out by using the compound prepared in Example 26 to give the title compound having the following physical properties. $^1\text{H-NMR}(\text{CD}_3\text{OD}):\delta$ 7.32-7.14, 7.02, 6.88, 3.70, 3.29-3.21, 3.21-3.11, 3.11-3.03, 2.85, 2.23, 2.14.

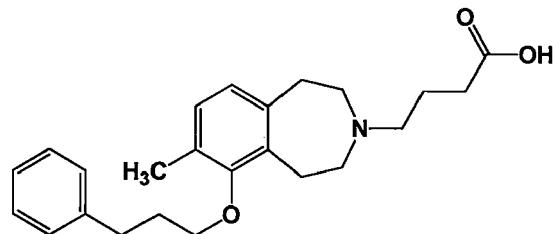
55 Example 28 (Reference): Ethyl 4-[7-Methyl-6-(3-phenylpropoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoate

[0214] A procedure for a purpose similar to that for Example 16 was carried out by using the compound prepared in Example 27 and ethyl 4-bromobutanoate to give the title compound having the following physical properties. $^1\text{H-NMR}(\text{CD}_3\text{OD}):\delta$ 7.34-7.15, 6.90, 6.76, 4.13, 3.69, 3.02-2.92, 2.92-2.78, 2.68-2.51, 2.48, 2.35, 2.24, 2.13, 1.84, 1.26.

Example 29: 4-[7-Methyl-6-(3-phenylpropoxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0215]

5



10

[0216] A procedure for a purpose similar to that for Example 3 was carried out by using the compound prepared in Example 28 to give the title compound having the following physical properties.

15

(LC-MS/ELSD):(Retention time:0.87 minutes, Condition A);

MS (M+H): 382.

20 Example 30 (Reference): Ethyl 4-(6-[(trifluoromethyl)sulfonyloxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoate

[0217] Diisopropylethylamine (0.374 mL) and N,N-bis(trifluoromethylsulfonyl)aniline (580 mg) were added to a dichloromethane (1.5 mL) solution of the compound (150 mg) prepared in Example 17 at 0°C, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water, and extracted with ethyl acetate two times. The organic layer was washed with saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=85:15→55:45) to give the title compound (179 mg) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.20-7.05, 4.14, 3.04-2.92, 2.70-2.60, 2.51, 2.38, 1.84, 1.27.

30 Example 31 (Reference): Ethyl 4-[6-(4-phenyl-1-butyn-1-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoate

[0218] 4-phenyl-1-butyne (38.2 mg), trimethylamine (0.27 mL), copper iodide (1.9 mg) and bis(triphenylphosphine)palladium dichloride (6.9 mg) were added to a DMF (0.5 mL) solution of the compound (40 mg) prepared in Example 30, and the mixture was stirred at 50°C for 16 hours. The reaction mixture was purified by silica gel column chromatography (hexane:ethyl acetate=90:10→50:50) and preparative TLC (hexane:ethyl acetate=60:40) to give the title compound (7.5 mg) having the following physical properties.

$^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.37-7.18, 7.03-6.96, 4.14, 3.12-3.05, 2.96-2.84, 2.72, 2.65-2.51, 2.48, 2.36, 1.84, 1.27.

40 Example 32 (Reference): Ethyl 4-[6-(4-phenylbutyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoate

40

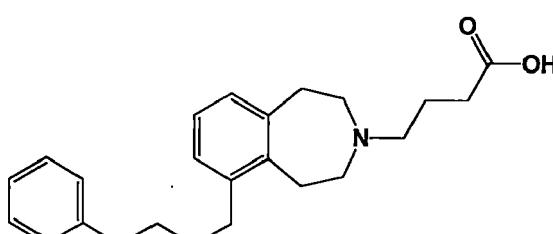
[0219] A procedure for a purpose similar to that for Example 25 was carried out by using the compound prepared in Example 31 to give the title compound having the following physical properties.

$^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.29-7.23, 7.20-7.14, 7.03-6.90, 4.14, 2.92-2.85, 2.66-2.57, 2.53, 2.46, 2.35, 1.83, 1.76-1.44, 1.26.

45 Example 33 (Reference): 4-[6-(4-Phenylbutyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

[0220]

50



55

[0221] A procedure for a purpose similar to that for Example 3 was carried out by using the compound prepared in

Example 32 to give the title compound having the following physical properties.

(LC-MS/ELSD):(Retention time:0.88 minutes, Condition B);
MS (M+H): 366.

5

Example 34 (Reference): Sodium [1-(Hydroxymethyl)cyclopropyl]acetate

[0222] A ethanol (10 mL) and water (1.0 mL) solution of 2-[1-(hydroxymethyl)cyclopropyl]acetonitrile (1.0 g) (CAS registry number: 152922-71-9) was treated with sodium hydroxide (1.4 g), and the obtained mixture was stirred at 90°C for 16 hours. The reaction mixture was concentrated under reduced pressure to give the title compound (1.2 g) having the following physical properties. $^1\text{H-NMR}$ (DMSO-d₆): δ 3.17, 2.04, 3.30-0.22, 0.21-0.18.

[0223] Sulfuric acid (0.5 mL) was added to a ethanol (10 mL) solution of the compound (1.2 g) prepared in Example 34, and the mixture was stirred at 90°C for 2 hours. The reaction mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with water and saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (900 mg) having the following physical properties. $^1\text{H-NMR}$ (DMSO-d₆): δ 4.52, 4.03, 3.25, 2.32, 1.75, 0.47.

20

Example 35 (Reference): Ethyl [1-(Hydroxymethyl)cyclopropyl]acetate

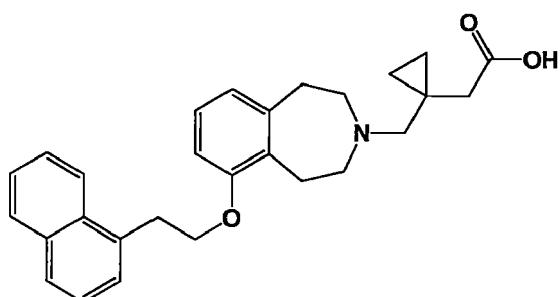
[0224] Tetrabromomethane (1.2 g) and triphenylphosphine (1.0 g) were added to a methylene chloride (6 mL) solution of the compound (500 mg) prepared in Example 35 at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with saturated saline, dried with anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=100:0→70:30) to give the title compound (450 mg) having the following physical properties. $^1\text{H-NMR}$ (DMSO-d₆): δ 4.07, 3.60, 2.43, 1.18, 0.43 3.60, 2.469-0.64.

30

Example 37: [1-({6-[2-(1-Naphthyl)ethoxy]-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl}methyl)cyclopropyl]acetic acid

[0225]

35



45

[0226] A procedure for a purpose similar to that for Example 18 was carried out by using the compound prepared in Example 36 and a correspondind alcohol compound in place of the compound prepared in Example 5 to give the title compound having the following physical properties.

50

(LC-MS/ELSD):(Retention time:0.87 minutes, Condition B);
MS (M+H): 430.

Example 38 (Reference): 5-Methoxy-3,4-dihydro-2(1H)-naphthalenone oxime

[0227] Sodium acetate (2.79 g) and hydroxylamine hydrochloride (2.37 g) were added to a ethanol (60 mL) solution of 5-methoxytetralin-2-one (2.00 g), and the mixture was stirred at 70°C for 1.5 hours. Water was added to the reaction mixture, and ethanol was reduced by concentration under reduced pressure. Saturated saline was added to the resulting mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was dried with anhydrous magnesium

sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0→70:30) to give the title compound (1.77 g) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.16, 6.80, 6.72, 3.83, 3.82, 2.89, 2.52.

5 Example 39 (Reference): 6-Methoxy-1,2,4,5-tetrahydro-3H-2-benzazepin-3-one

[0228] A THF (1.5 mL) suspension of the compound (1.00 g) prepared in Example 38 was added to a mixture solution of thionyl chloride (10 mL) and THF (5.0 mL) at 0°C, and the mixture was stirred at 0°C for 1.5 hours. The reaction mixture was poured into water and extracted twice with ethyl acetate. The organic layer was washed with an aqueous saturated sodium bicarbonate solution and saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=20:80→0:100→ethyl acetate:methanol=80:20) to give the title compound (500 mg) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.14, 6.83, 6.71, 6.14, 4.38, 3.83, 3.06, 2.82.

15 Example 40 (Reference): 6-Methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine

[0229] To a THF (6.0 mL) suspension of lithium aluminium hydride (164 mg), a THF (15.0 mL) suspension of the compound (550 mg) prepared in Example 39 was slowly added at 80°C, and the mixture was stirred at 80°C for 15 minutes. The reaction mixture was cooled to room temperature, added an aqueous saturated sodium sulfate solution and THF, and the mixture was stirred at room temperature for 30 minutes. Anhydrous magnesium sulfate was added to the reaction mixture, and the mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound (433 mg) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.07, 6.77, 6.75, 3.93, 3.80, 3.21, 3.04, 1.66.

25 Example 41 (Reference): 4-(Benzylxy)-1-indanone

[0230] Potassium carbonate (3.5 g) was added to a acetonitrile (40 mL) solution of 4-hydroxy-1-indanone (1.5 g) (CAS registry number:40731-98-4) and benzylbromide (1.45 mL). The reaction mixture was refluxed for 3 hours, filtered, and the filtrate was concentrated under vacuum to give the title compound (2.2 g) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.48-7.28, 7.09, 5.17, 3.10, 2.73-2.65.

Example 42 (Reference): 4-(Benzylxy)-1-indanol

[0231] Sodium borohydride (0.64 g) was added to a methanol (20 mL) and THF (20 mL) solution of the compound (2.0 g) prepared in Example 41 at 0°C. The reaction mixture was stirred at room temperature for 4 hours, and quenched with saturated ammonium chloride. The reaction mixture was extracted with ethyl acetate, dried with anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under vacuum to give the title compound (1.8 g) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.44-7.32, 7.23-7.19, 7.04, 6.82, 5.27-5.25, 5.11, 3.08-3.05, 2.83-2.81, 2.52-2.48, 2.00-1.94, 1.69.

40 Example 43 (Reference): 7-(Benzylxy)-1H-indene

[0232] P-toluenesulfonic acid (7 mg) was added to a toluene (40 mL) solution of the compound (1.0 g) prepared in Example 42, and the mixture was heated under reflux, and water was removed by azeotropic distillation using Dean-Stark apparatus for 4 hours. The reaction mixture was quenched with an aqueous saturated sodium bicarbonate solution, extracted with ethyl acetate, dried with anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0→20:80) to give the title compound (0.6 g) having the following physical properties. $^1\text{H-NMR}(\text{CDCl}_3):\delta$ 7.36-7.30, 7.25-7.21, 7.07, 6.87-6.85, 6.79, 6.58-6.56, 5.18, 3.42.

50 Example 44 (Reference): 4-(Benzylxy)-1,2-indanediol

[0233] Water (2.5 mL) and N-methylmorpholine N-oxide (632 mg) were added to an acetone (10 mL) solution of the compound (600 mg) prepared in Example 43. After 5 minutes stirred, a tert-butylalcohol (1.0 mL) solution of osmium tetroxide (34 mg) was added dropwise to the mixture, and the mixture was stirred at room temperature for 2 hours. The solvent was concentrated under reduced pressure, and the obtained residue was dissolved in ethyl acetate, and the solution was washed with 1N aqueous sodium thiosulfate solution and saturated saline. The organic layer was dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give the title compound (450 mg) having the

following physical properties.

¹ H-NMR (CDCl₃): δ 7.41-7.30, 7.23, 7.06, 6.84, 5.09, 5.02, 4.54-4.52, 3.15-3.10, 3.00-2.95, 2.52, 2.36.

Example 45 (Reference): 4-(Benzylxy)-1,3-dihydro-2H-inden-2-one

[0234] P-toluenesulfonic acid (5 mg) was added to a toluene (50 mL) solution of the compound (750 mg) prepared in Example 44, and the mixture was heated under reflux, and water was removed by azeotropic distillation using Dean-Stark apparatus for 4 hours. The reaction mixture was stirred at room temperature for 4 hours, quenched with an aqueous saturated sodium bicarbonate solution, extracted with ethyl acetate, dried with anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0→20:80) to give the title compound (400 mg) having the following physical properties. ESI-MS m/z 280 [C₁₆H₁₄O₂ + H + CH₃CN]⁺.

Example 46 (Reference): Methyl 1-[4-(benzylxy)-2,3-dihydro-1H-inden-2-yl]-3-azetidinecarboxylate

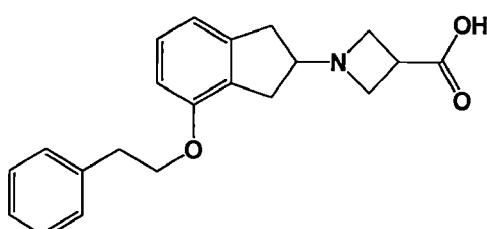
[0235] A procedure for a purpose similar to that for Example 1 was carried out by using the compound prepared in Example 45 and methyl azetidine-3-carboxylate hydrochloride to give the title compound having the following physical properties. ¹ H-NMR (CDCl₃): δ 7.40-7.31, 7.09, 6.81, 6.70, 5.07, 3.70, 3.61-3.58, 3.32-3.24, 3.00-2.93, 2.75-2.71.

Example 47 (Reference): Methyl 1-(4-hydroxy-2,3-dihydro-1H-inden-2-yl)-3-azetidinecarboxylate

[0236] A procedure for a purpose similar to that for Example 13 was carried out by using the compound prepared in Example 46 to give the title compound having the following physical properties. ¹ H-NMR (CDCl₃): δ 7.01, 6.76, 6.56, 3.71, 3.64-3.60, 3.35-3.27, 3.00-2.87, 2.75-2.64.

Example 48: 1-[4-(2-Phenylethoxy)-2,3-dihydro-1H-inden-2-yl]-3-azetidinecarboxylic acid

[0237]



[0238] A procedure for a purpose similar to that for Example 14 → Example 3 was carried out by using the compound prepared in Example 47 and 2-phenylethanol in place of the compound prepared in Example 5 to give the title compound having the following physical properties.

(LC-MS/ELSD):(Retention time:0.78 minutes, Condition A);
MS (M+H): 338.

Example 48 (1) - 48 (2)

[0239] A procedure for a purpose similar to that for Example 47 was carried out by using the compound prepared in Example 47 and corresponding alcohol derivative in place of 2-phenylethanol to give the title compound having the following physical properties.

Example 48 (1): 1-[4-(3-Phenylpropoxy)-2,3-dihydro-1H-inden-2-yl]-3-azetidinecarboxylic acid

[0240]

(LC-MS/ELSD):(Retention time:0.83 minutes, Condition A);
MS (M+H): 352.

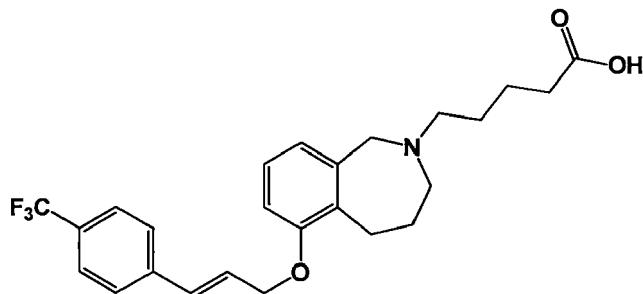
Example 48 (2): 1-[4-(4-Phenylbutoxy)-2,3-dihydro-1H-inden-2-yl]-3-azetidinecarboxylic acid

[0241]

5 (LC-MS/ELSD):(Retention time:0.87 minutes, Condition A);
MS (M+H): 366.

Example 49: 5-[6-((2E)-3-[4-(Trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]pen-
10 tanoic acid

[0242]



25 [0243] A procedure for a purpose similar to that for Example 16 → Example 17 → Example 18 was carried out by using the compound prepared in Example 40, ethyl 5-bromopentanoate in place of ethyl 4-bromobutanoate, and the compound prepared in Example 5 to give the title compound having the following physical properties.

30 (LC-MS/ELSD):(Retention time:0.92 minutes, Condition A);
MS (M+H): 448.

35 Example 50 (1): Methyl 1-{8-[2-(1-naphthyl)ethoxy]-1,2,3,4-tetrahydro-2-naphthalenyl}-3-azetidinecarboxylate (the first peak)

40 Example 50 (2): Methyl 1-{8-[2-(1-naphthyl)ethoxy]-1,2,3,4-tetrahydro-2-naphthalenyl}-3-azetidinecarboxylate (the second peak)

[0244] The optical resolution of the compound prepared in Example 2(1) was carried out by using SFC (Supercritical Fluid Chromatography): {column:DAICEL CHIRALPAK IB (column length:10 x 250 mm);flow rate:30mL/min; column temperature:35°C; mobile phase: carbon dioxide:methanol:diethylamine=85: 15:0.015; detector:UV to give the title compound having the following physical properties.

45 ¹ H-NMR (CDCl₃):δ 8.10, 7.86, 7.75, 7.56-7.36, 7.02, 6.67, 6.62, 4.30, 3.74, 3.65-3.52, 3.42-3.24, 2.88-2.61, 2.46-2.34, 2.15, 1.89-1.77, 1.50-1.33.

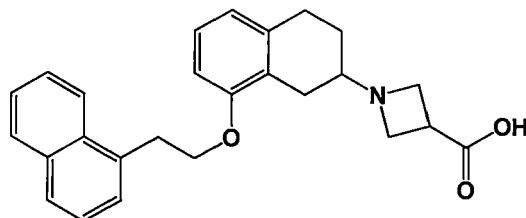
(the first peak) Retention time:4.52 minutes;

(the second peak) Retention time:5.94 minutes.

Example 51 (1): (-)-1-{8-[2-(1-Naphthyl)ethoxy]-1,2,3,4-tetrahydro-2-naphthalenyl}-3-azetidinecarboxylic acid

Example 51 (2): (+)-1-{8-[2-(1-Naphthyl)ethoxy]-1,2,3,4-tetrahydro-2-naphthalenyl}-3-azetidinecarboxylic acid

50 [0245]



[0246] A procedure for a purpose similar to that for Example 3 was carried out by using the compound prepared in Example 50 (1) or Example 50 (2) to give the title compound having the following physical properties. Further, Example 51 (1) and Example 51 (2) were derived from Example 50 (1) and Example 50 (2) respectively.

15 (LC-MS/ELSD):(Retention time:0.85 minutes, Condition B);

MS (M+H): 402.

Example 51 (1): $[\alpha]_D = -52.7$ (DMF, c=1.0);

Example 51 (2): $[\alpha]_D = +53.4$ (DMF, c=1.0).

20 Example 52 (Reference): 1-[8-(Hexyloxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

25 **[0247]** A procedure for a purpose similar to that for Example 1 → Example 17 was carried out by using 8-methoxy-3,4-dihydronaphthalen-2(1H)-one in place of 5-hydroxy-3,4-dihydronaphthalene-2(1H)-one, and a procedure for a purpose similar to that for Example 14 → Example 3 was carried out by using 1-hexanol in place of the compound prepared in Example 5 to give the title compound having the following physical properties.

25 (LC-MS/ELSD):(Retention time:0.88 minutes, Condition A);

MS (M+H):332.

30 Example 52 (1) - (8)

35 **[0248]** A procedure for a purpose similar to that for Example 52 was carried out by using a corresponding alcohol compound in place of 1-hexanol to give the following compounds of Examples.

40 Example 52 (1) (Reference): 1-[8-(Heptyloxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

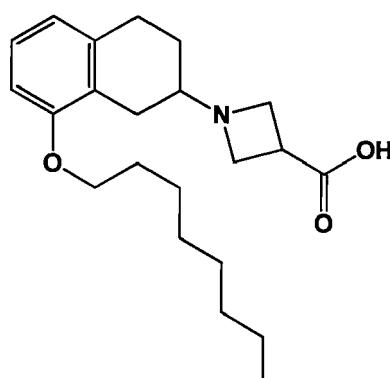
45 **[0249]**

45 (LC-MS/ELSD):(Retention time:0.92 minutes, Condition A);

MS (M+H):346.

50 Example 52 (2) (Reference): 1-[8-(Octyloxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

55 **[0250]**



(LC-MS/ELSD):(Retention time:0.97 minutes, Condition A);

MS (M+H):360;

¹ H-NMR (CD₃ OD):δ 7.10, 6.74, 6.71, 4.36-4.18, 4.04-3.91, 3.63-3.49, 3.45-3.34, 3.17, 2.96-2.79, 2.41, 2.23-2.10, 1.85-1.71, 1.70-1.58, 1.58-1.44, 1.44-1.23, 0.90.

5

Example 52 (3) (Reference): 1-[8-(Nonyloxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0251]

10 (LC-MS/ELSD):(Retention time: 1.02 minutes, Condition A);

MS (M+H):374;

¹ H-NMR (CD₃ OD):δ 7.10, 6.74, 6.71, 4.36-4.18, 4.04-3.91, 3.63-D):δ 7.10, 6.74, 6.71, 4.36-4.18, 4.04- 3.91, 3.63 10, 1.85- 1.71, 1.70 - 1.58, 1.58- 1.44, 1.44- 1.23, 0.89.

15 Example 52 (4) (Reference): 1-[8-(Decyloxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0252]

20 (LC-MS/ELSD):(Retention time: 1.07 minutes, Condition A);

MS (M+H):388.

Example 52 (5) (Reference): 1-[8-(Undecyloxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0253]

25

(LC-MS/ELSD):(Retention time: 1.12 minutes, Condition A);

MS (M+H):402.

30 Example 52 (6): 1-[8-[3-(1,2-Thiazol-4-yl)propoxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0254]

35

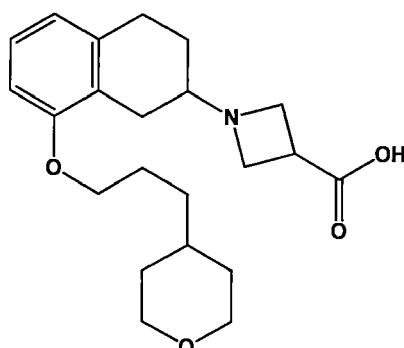
(LC-MS/ELSD):(Retention time:0.73 minutes, Condition A);

MS (M+H):373

35 Example 52 (7): 1-[8-[3-(Tetrahydro-2H-pyran-4-yl)propoxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0255]

40



50

55 (LC-MS/ELSD):(Retention time:0.76 minutes, Condition A);

MS (M+H):374;

¹ H-NMR (CD₃ OD):δ 7.12, 6.77, 6.74, 4.36- 4.15, 4.07- 3.91, 3.58-D):δ 7.12, 6.77, 6.74, 4.36-4.15, 4.07- 3.91, 3.58 thalenyl]-3-azetidinecarboxylic acid.70 - 1.58, 1.58-, 2.46 1.22.

Example 52 (8): 1-[8-(3-Cyclohexylpropoxy)-1,2,3,4-tetrahydro-2-naphthalenyl]-3-azetidinecarboxylic acid

[0256]

5 (LC-MS/ELSD):(Retention time:0.97 minutes, Condition A);
 MS (M+H):372;
 $^1\text{H-NMR}$ (CD_3OD): δ 7.12, 6.76, 6.74, 4.37- 4.18, 4.07- 3.91, 3.63-D): δ 7.12, 6.76, 6.74, 4.37-4.18, 4.07- 3.91, 3.63
 carboxylic acid-3-azetidinecarboxylic acid.70 - 1.58, 1.58- 0.89.

10 Example 53 (Reference): Methyl 1-(5-Chloro-8-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)azetidine-3-carboxylate trifluoroacetate(1/1)

15 [0257] A DMF (0.5 mL) solution of N-chlorosuccinimide (51 mg) was added to a DMF (0.5 mL) solution of methyl 1-(8-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)azetidine3-carboxylate (100 mg) under ice cooling, and the mixture was
 20 stirred at room temperature for 16 hours. The reaction mixture was poured into an aqueous saturated sodium bicarbonate solution, and extracted twice with ethyl acetate. The organic layer was washed with saturated saline, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=60:40→20:80), and then, purified by reversed phase liquid chromatography (0.1% trifluoroacetic acid (TFA)-containing water/0.1% TFA-containing acetonitrile) to give the title compound (10 mg)
 25 having the following physical properties. $^1\text{H-NMR}$ (DMSO-d_6): δ 10.45-10.20, 9.89, 7.11, 6.69, 4.60 - 4.15, 3.85- 3.47, 3.09- 2.95, 2.67- δ 10.45-10.2 2.23, 2.20 - 2.03, 1.68- 1.42.

Example 54: 1-{5-Chloro-8-[2-(naphthalen-1-yl)ethoxy]-1,2,3,4-tetrahydronaphthalen-2-yl}azetidine-3-carboxylic acid trifluoroacetate(1:1)

25 [0258] A procedure for a purpose similar to that for Example 14 was carried out by using the compound prepared in Example 53 in place of the compound prepared in Example 13, and 2-(naphthalen-1-yl)ethanol in place of the compound prepared in Example 5. 2N sodium hydroxide (0.05 mL) was added to a methanol (0.1 mL) and dimethoxyethane (0.1 mL) solution of the resulting compound (8 mg), and the mixture was stirred at room temperature for 4 hours. 2N hydrochloric acid (0.05 mL) was added to the reaction mixture, and the reaction mixture was purified by reversed phase liquid chromatography (0.1% TFA-containing water/0.1% TFA-containing acetonitrile) to give the title compound (3.2 mg) having the following physical properties.

35 (LC-MS/ELSD):(Retention time:0.92 minutes, Condition A);
 MS (M+H):435.

[0259] Biological Experimental Examples will be described hereinbelow, and the effects of the compound of the present invention were confirmed based on the experimental methods.

40 Biological Experimental Example 1: Measurement of the inhibitory action of the compound of the present invention on binding of [^{33}P]-S1P to SIPs (EDG-8).

45 [0260] A reaction was carried out in a 96-well microplate by using membrane fractions of Chinese hamster ovary (CHO) cells each of which was made to overexpress human S1P₁ (EDG-1) or human SIPs gene respectively, in an amount of the membrane fraction of 1 mg protein/mL. To each of the wells, 100 μL of a vehicle (DMSO) solution or a two-fold concentration-ligand solution each of which was diluted with Binding Buffer (50 mmol/L, Tris pH 7.5, 5 mmol/L, MgCl_2 , 0.5% BSA and Complete EDTA free (1 tablet/50 mL)), and 50 μL of 0.16 nmol/L [^{33}P]-S1P (manufactured by American Radiolabeled Chemicals, Inc.) diluted with Binding Buffer were added. Thereafter, the membrane fraction solutions (50 μL) was added to the wells and the reaction was carried out at room temperature for 60 minutes. After the reaction, suction filtration was carried out by using a 96-well UNIFILTER, and the 96-well microplate was washed with Wash Buffer (50 mmol/L, Tris pH 7.5, 0.5% BSA) (150 mL), and thereafter, was dried at 60°C for 45 minutes. MicroScint (trade name) 20 (50 μL /well) was added and the plate was covered with TopSeal-A, and thereafter, the radioactivity was measured by using TopCount (manufactured by PerkinElmer Inc.).

55 [Results]

[0261] The compound of the present invention exhibited the inhibitory activity (IC50 value) as shown in the following table on binding of [^{33}P]-S1P to SIPs. In addition, the binding activities of the compounds of the present invention to

S1P₁ of [³³P]-S1P are shown in Table 1. Further, the symbols in the Table 1 represent the value of IC50 is A: 1 nM or more and less than 100 nM, B: 100 nM or more and less than 1000 nM, C: 1 μ M to 3 μ M, D: >10 μ M and E: >30 μ M, respectively. As a result, it was found that all the compounds of the present invention had high S1P₅ receptor binding activity, and a selective S1P₅ receptor binding activity against SIPi receptor binding activity.

5

10

15

20

25

30

35

40

45

50

55

[Table 1]

Example No.	S1P ₅ binding activity (IC50)	S1P ₁ binding activity (IC50)
Example 18 (1)	C	E
Example 18 (2)	C	E
Example 18 (3)	C	E
Example 18 (4)	C	E
Example 18 (8)	B	D
Example 49	C	E
Example 3 (1)	C	E
Example 18 (10)	A	D
Example 3 (3)	B	E
Example 18 (14)	B	D
Example 18 (16)	B	D
Example 18 (18)	A	D
Example 18 (22)	B	D
Example 18 (24)	A	D
Example 18 (26)	B	D
Example 3 (4)	A	D
Example 23 (8)	A	D
Example 29	A	D
Example 51 (1)	A	D
Example 51 (2)	A	D
Example 37	B	D
Example 48	B	E
Example 18 (32)	B	D
Example 18 (42)	B	D

Biological Example 2: Evaluation of S 1Ps receptor modulatory activities of the compound of the present invention by monitoring the concentration of produced intracellular cyclic AMP

[0262] CHO cells which were made to overexpress human SIPs (EDG-8) gene were cultured in Ham's F12 Medium (manufactured by Gibco-BRL) containing 10% FBS (fetal bovine serum), penicillin/streptomycin and geneticin (0.25 mg/mL). The medium was removed from the cultured cells, the cultured cells were washed once with phosphate-buffered saline, and the cultured cells were treated with a vehicle (DMSO) solution or a compound solution each of which was diluted with Buffer (Hanks' balanced salt solution containing 20 mmol/L HEPES, 0.1 or 0.2% BSA, 1 mmol/L IBMX and 5 μ mol/L forskolin) at 37°C for 30 minutes. Thereafter, the cultured cells were washed once with phosphate-buffered saline, lysis of the cells, and the concentration of cyclic AMP in the cell lysate were measured by using cAMP Assay Kit (Cisbio Bioassays).

[Results]

[0263] As a result, it was found that the compound of the present invention had a selective S1Ps receptor modulatory activity. Further, the symbol in the Table 2 represents the value of EC50 is A: 1 nM or more and less than 100 nM.

5

[Table 2]

Example No.	S1P ₅ receptor modulatory activity (EC50)
Example 18 (11)	A
Example 18 (18)	A
Example 3 (5)	A

10

[Preparation Examples]

Preparation Example 1

[0264] The following components were mixed in a conventional manner and compressed to give 10,000 tablets each containing 10 mg of the active component.

20

- 4-{5-[2-(2-naphthyl)ethoxy]-3,4-dihydro-2(1H)-isoquinolinyl}butanoic acid trifluoroacetate ... 100 g
- Carboxymethyl cellulose calcium (a disintegrating agent)... 20 g
- Magnesium stearate (a lubricant)... 10 g
- Microcrystalline cellulose... 870 g

25

Preparation Example 2

[0265] The following components were mixed in a conventional manner. Thereafter, the mixture was filtered through a dust filter, and 5 ml aliquots were charged into ampules. The ampules were heat sterilized by an autoclave to give 10,000 ampules each containing 20 mg of the active component.

30

- 1-[5-((2E)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl)oxy]-1,2,3,4-tetrahydro-2-naphthalenyl]-3-pyrrolidinecarboxylic acid... 200g
- Mannitol... 20 g
- Distilled water... 50 L

35

INDUSTRIAL APPLICABILITY

[0266] The compound of the present invention has a selective S1P₅ receptor binding activity and modulates the function of an S1P₅ receptor, and therefore, can be used in a method for treating S1P₅-mediated disease, for example, neurodegenerative disease.

40

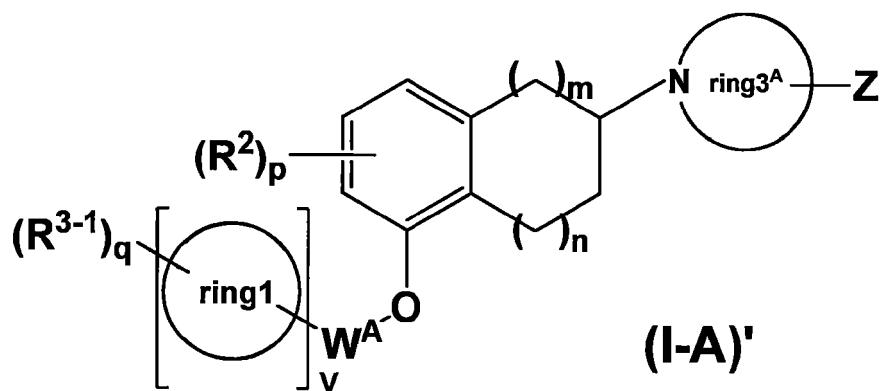
Claims

45

1. A compound represented by general formula (I-A):

50

55



wherein,

20

W^A represents (1) a C1-12 alkylene group, (2) a C2-12 alkenylene group, (3) a C2-12 alkynylene group, (4) -C1-12 alkylene-O-, (5) -C2-12 alkenylene-O-, (6) -C2-12 alkynylene-O-, (7) -C1-12 alkylene-ring2-, (8)-C2-12 alkenylene-ring2- or (9) -C2-12 alkynylene-ring2-, wherein, an alkylene group, an alkenylene group and an alkynylene group may be substituted with one to five halogen atoms,

25

R² represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group or (5) a C1-4 haloalkoxy group,

30

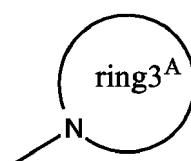
R³⁻¹ represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group, (5) a C1-4 haloalkoxy group, (6) a nitrile group, (7) -S-C1-4 alkyl group, (8) -S-C1-4 haloalkyl group or (9) an oxo group, provided that the C1-4 alkyl group or the C1-4 haloalkyl group represented by R³⁻¹ is branched chain, C1-2 alkyl groups branched from the same carbon atom may be taken together with a carbon atom to which they are bound, to form a C3-4 saturated carbocyclic ring,

35

Z represents (1) a carboxyl group which may be substituted with a C1-8 alkyl group, (2) a hydroxy group which may be substituted with a C1-8 alkyl group, (3) a hydroxamic acid group which may be substituted with a C1-8 alkyl group, (4) a sulfonic acid group which may be substituted with a C1-8 alkyl group, (5) a boronic acid group which may be substituted with a C1-8 alkyl group, (6) a carbamoyl group which may be substituted with a C1-8 alkyl group, (7) a sulfamoyl group which may be substituted with a C1-8 alkyl group, (8) a sulfoxime group which may be substituted with a C1-8 alkyl group or (9) a tetrazolyl group,

ring 1 represents (1) a C3-10 carbocyclic ring or (2) a 3- to 10-membered heterocyclic ring,

ring 2 represents (1) a C3-7 carbocyclic ring or (2) a 3- to 7-membered heterocyclic ring,



45

represents a 3- to 7-membered nitrogen-containing saturated heterocyclic ring,

m represents an integer of 0 to 2,

n represents an integer of 0 to 2,

p represents an integer of 0 to 3,

q represents an integer of 0 to 5,

v represents an integer of 1,

50

when p is 2 or more, a plurality of R²s may be the same or different, and

when q is 2 or more, a plurality of R³⁻¹s may be the same or different, or a pharmaceutically acceptable salt thereof.

55

2. The compound according to claim 1, wherein, W^A represents (1) a C1-6 alkylene group, (2) a C2-6 alkenylene group, (3) a C2-6 alkynylene group, (4) a -C1-6 alkylene-O-, (5) a -C2-6 alkenylene-O-, (6) a -C2-6 alkynylene-O- or (7) a -C1-6 alkylene-ring2-,

and the other symbols have the same meanings as described in claim 1,

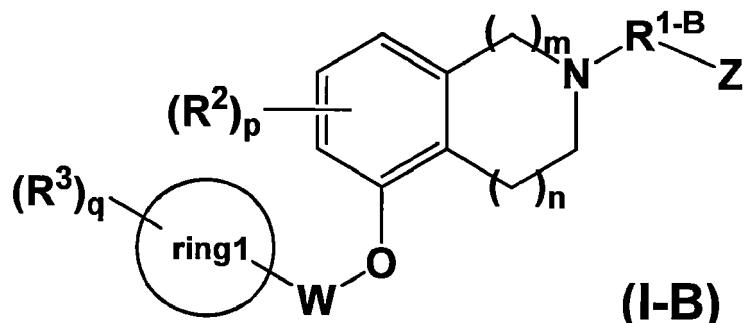
or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein ring 1 is a C3-10 carbocyclic ring, or a pharmaceutically acceptable salt thereof.

5

4. A compound represented by general formula (I-B)

10



15

20

wherein,

W represents (1) a C1-6 alkylene group, (2) a C2-6 alkenylene group, (3) a C2-6 alkynylene group, (4) a -C1-6 alkylene-O-, (5) a -C2-6 alkenylene-O-, (6) a -C2-6 alkynylene-O- or (7) a -C1-6 alkylene-ring2-,
 R^{1-B} represents -L- or -L-ring3^B-,

25

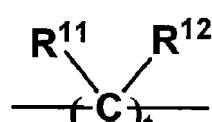
R² represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group or (5) a C1-4 haloalkoxy group,

R³ represents (1) a halogen atom, (2) a C1-4 alkyl group, (3) a C1-4 haloalkyl group, (4) a C1-4 alkoxy group, (5) a C1-4 haloalkoxy group, (6) a nitrile group, (7) a -S-C1-4 alkyl group, or (8) a -S-C1-4 haloalkyl group, provided that the C1-4 alkyl group or the C1-4 haloalkyl group represented by R³ is branched chain, C1-2 alkyl groups branched from the same carbon atom may be taken together with a carbon atom to which they are bound, to form a C3-4 saturated carbocyclic ring,

30

L represents (1) a bond or (2) a group represented by general formula

35



40

wherein, R¹¹ and R¹² each represent independently a hydrogen atom or a C1-4 alkyl group, or R¹¹ and R¹² may be taken together with a carbon atom to which they are bound, to form a C3-7 carbocyclic ring, and t represents an integer of 1 to 6,

45

Z represents (1) a carboxyl group which may be substituted with a C1-8 alkyl group, (2) a hydroxy group which may be substituted with a C1-8 alkyl group, (3) a hydroxamic acid group which may be substituted with a C1-8 alkyl group, (4) a sulfonic acid group which may be substituted with a C1-8 alkyl group, (5) a boronic acid group which may be substituted with a C1-8 alkyl group, (6) a carbamoyl group which may be substituted with a C1-8 alkyl group, (7) a sulfamoyl group which may be substituted with a C1-8 alkyl group, (8) a sulfoxime group which may be substituted with a C1-8 alkyl group or (9) a tetrazolyl group,

ring 1 represents a C3-10 carbocyclic ring,

50

ring 2 represents (1) a C3-7 carbocyclic ring or (2) a 3- to 7-membered heterocyclic ring,

ring 3^B represents a C3-7 carbocyclic ring,

m represents an integer of 0 to 2,

n represents an integer of 0 to 2,

p represents an integer of 0 to 3,

55

q represents an integer of 0 to 5,

when p is 2 or more, a plurality of R²s may be the same or different,

when q is 2 or more, a plurality of R³s may be the same or different and

when t is 2 or more, a plurality of R¹¹s may be the same or different, and

when t is 2 or more, a plurality of R^{12} s may be the same or different, or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 to 4, wherein Z is a carboxyl group which may be substituted with a C1-8 alkyl group, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising the compound represented by general formula (I-A)' according to claim 1 or the compound represented by general formula (I-B) according to claim 4, or a pharmaceutically acceptable salt thereof.

15. The pharmaceutical composition according to claim 6, which is an $S1P_5$ binder and/or modulator.

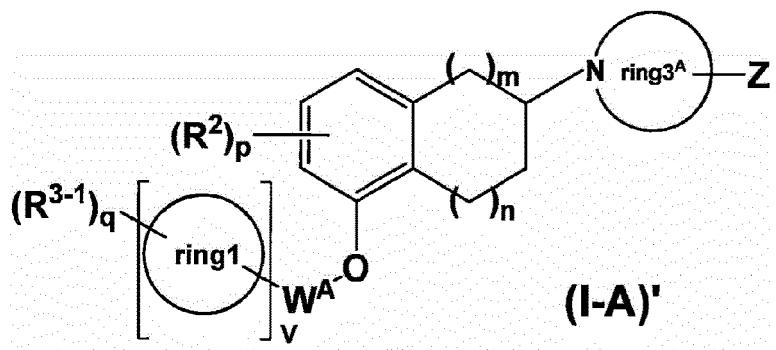
20. The pharmaceutical composition according to claim 6 for use in a method for preventing and/or treating a $S1P_5$ -mediated disease, wherein the $S1P_5$ -mediated disease is neurodegenerative disease, autoimmune disease, infection or cancer.

25. The pharmaceutical composition for use according to claim 8, wherein the neurodegenerative disease is schizophrenia, Binswanger's disease, multiple sclerosis, neuromyelitis optica, Alzheimer's disease, cognitive impairment, amyotrophic lateral sclerosis or spinocerebellar atrophy.

30. The compound represented by general formula (I-A)' according to claim 1 or the compound represented by general formula (I-B) according to claim 4, or a pharmaceutically acceptable salt thereof for use in a method for preventing and/or treating a $S1P_5$ -mediated disease, wherein the $S1P_5$ -mediated disease is neurodegenerative disease, autoimmune disease, infection or cancer.

Patentansprüche

1. Verbindung, dargestellt durch die allgemeine Formel (I-A)':



wobei W^A (1) eine C1-12-Alkylengruppe, (2) eine C2-12-Alkenylengruppe, (3) eine C2-12-Alkinylengruppe, (4) -C1-12-Alkylen-O-, (5) -C2-12-Alkenylen-O-, (6) -C2-12-Alkinylen-O-, (7) -C1-12-Alkylen-Ring2-, (8) -C2-12-Alkenylen-Ring2- oder (9) -C2-12-Alkinylen-Ring2- ist, wobei eine Alkylengruppe, eine Alkenylengruppe und eine Alkinylengruppe mit ein bis fünf Halogenatomen substituiert sein können,

R^2 (1) ein Halogenatom, (2) eine C1-4-Alkylgruppe, (3) eine C1-4-Haloalkylgruppe, (4) eine C1-4-Alkoxygruppe oder (5) eine C1-4-Haloalkoxygruppe ist,

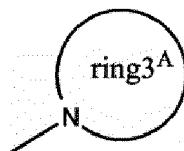
R^{3-1} (1) ein Halogenatom, (2) eine C1-4-Alkylgruppe, (3) eine C1-4-Haloalkylgruppe, (4) eine C1-4-Alkoxygruppe, (5) eine C1-4-Haloalkoxygruppe, (6) eine Nitrilgruppe, (7) -S-C1-4-Alkylgruppe, (8) -S-C1-4-Haloalkylgruppe oder (9) eine Oxogruppe ist, vorausgesetzt, dass die C1-4-Alkylgruppe oder die C1-4-Haloalkylgruppe, die durch R^{3-1} dargestellt wird, verzweigtkettig ist, wobei C1-2-Alkylgruppen, die von demselben Kohlenstoffatom abgezweigt sind, zusammen mit einem Kohlenstoffatom, an das sie gebunden sind, genommen werden können, um einen gesättigten C3-4-carbocyclischen Ring zu bilden,

Z (1) eine Carboxylgruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (2) eine Hydroxygruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (3) eine Hydroxamsäuregruppe, die mit einer C1-8-Alkylgruppe

substituiert sein kann, (4) eine Sulfonsäuregruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (5) eine Boronsäuregruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (6) eine Carbamoylgruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (7) eine Sulfamoylgruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (8) eine Sulfoximin-Gruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, oder (9) eine Tetrazolylgruppe ist,

5 Ring 1 (1) ein carbocyclischer C3-10-Ring oder (2) ein 3- bis 10-gliedriger heterocyclischer Ring ist,
Ring 2 (1) ein carbocyclischer C3-7-Ring oder (2) ein 3- bis 7-gliedriger heterocyclischer Ring ist,

10



15 ein 3- bis 7-gliedriger, stickstoffhaltiger gesättigter heterocyclischer Ring ist,

m eine ganze Zahl von 0 bis 2 ist,

n eine ganze Zahl von 0 bis 2 ist,

p eine ganze Zahl von 0 bis 3 ist,

q eine ganze Zahl von 0 bis 5 ist,

20 v eine ganze Zahl von 1 ist,

wenn p 2 oder mehr ist, eine Vielzahl von R² gleich oder unterschiedlich sein können und,

wenn q 2 oder mehr ist, eine Vielzahl von R³⁻¹ gleich oder unterschiedlich sein können,

oder ein pharmazeutisch verträgliches Salz davon.

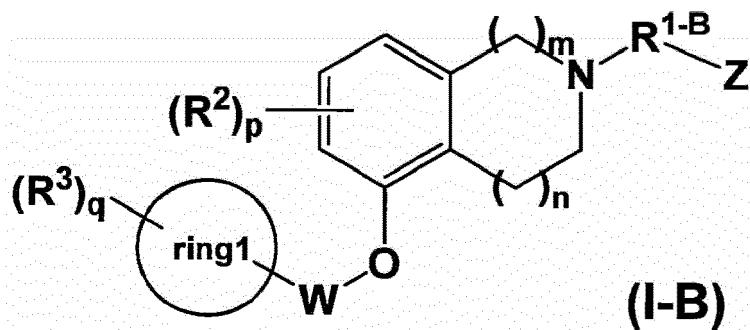
25 2. Verbindung gemäß Anspruch 1, wobei W^A (1) eine C1-6-Alkylengruppe, (2) eine C2-6-Alkenylengruppe, (3) eine C2-6-Alkinylengruppe, (4) ein -C1-6-Alkylen-O-, (5) ein -C2-6-Alkenylen-O-, (6) ein -C2-6-Alkinylen-O- oder (7) ein -C1-6-Alkylen-Ring2- ist,

30 und die anderen Symbole die gleiche Bedeutung wie in Anspruch 1 beschrieben haben,
oder ein pharmazeutisch verträgliches Salz davon.

35 3. Verbindung gemäß Anspruch 1 oder 2, wobei Ring 1 ein carbocyclischer C3-10-Ring ist, oder ein pharmazeutisch verträgliches Salz davon.

40 4. Verbindung, dargestellt durch die allgemeine Formel (I-B)

40



50

wobei

W (1) eine C1-6-Alkylengruppe, (2) eine C2-6-Alkenylengruppe, (3) eine C2-6-Alkinylengruppe, (4) ein -C1-6-Alkylen-O-, (5) ein -C2-6-Alkenylen-O-, (6) ein -C2-6-Alkinylen-O- oder (7) ein -C1-6-Alkylen-Ring2- ist,
R^{1-B}-L- oder -L-Ring3^{B-}, ist

55 R² (1) ein Halogenatom, (2) eine C1-4-Alkylgruppe, (3) eine C1-4-Haloalkylgruppe, (4) eine C1-4-Alkoxygruppe oder (5) eine C1-4-Haloalkoxygruppe ist,

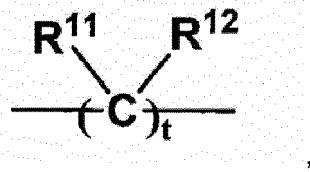
R³ (1) ein Halogenatom, (2) eine C1-4-Alkylgruppe, (3) eine C1-4-Haloalkylgruppe, (4) eine C1-4-Alkoxygruppe, (5) eine C1-4-Haloalkoxygruppe, (6) eine Nitrilgruppe, (7) eine -S-C1-4-Alkylgruppe oder (8) eine -S-C1-4-

Haloalkylgruppe ist,

vorausgesetzt, dass die C1-4-Alkylgruppe oder die C1-4-Haloalkylgruppe, die durch R³ dargestellt ist, verzweigtkettig ist, wobei C1-2-Alkylgruppen, die von demselben Kohlenstoffatom abgezweigt sind, zusammen mit einem Kohlenstoffatom, an das sie gebunden sind, genommen werden können, um einen gesättigten carbocyclischen C3-4-Ring zu bilden,

5 L (1) eine Bindung oder (2) eine Gruppe ist, dargestellt durch die allgemeine Formel

10



15 wobei R¹¹ und R¹² jeweils unabhängig voneinander ein Wasserstoffatom oder eine C1-4-Alkylgruppe sind, oder R¹¹ und R¹², zusammen mit einem Kohlenstoffatom, an das sie gebunden sind, genommen werden können, um einen carbocyclischen C3-7-Ring zu bilden, und t eine ganze Zahl von 1 bis 6 ist,

20 Z (1) eine Carboxylgruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (2) eine Hydroxygruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (3) eine Hydroxamsäuregruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (4) eine Sulfonsäuregruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (5) eine Boronsäuregruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (6) eine Carbamoylgruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (7) eine Sulfamoylgruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, (8) eine Sulfoximin-Gruppe, die mit einer C1-8-Alkylgruppe substituiert sein kann, oder (9) eine Tetrazolylgruppe ist,

25 Ring 1 ein carbocyclischer C3-10-Ring ist,

Ring 2 (1) ein carbocyclischer C3-7-Ring oder (2) ein 3- bis 7-gliedriger heterocyclischer Ring ist,

Ring 3^B ein carbocyclischer C3-7-Ring ist,

m eine ganze Zahl von 0 bis 2 ist,

n eine ganze Zahl von 0 bis 2 ist,

30 p eine ganze Zahl von 0 bis 3 ist,

q eine ganze Zahl von 0 bis 5 ist,

wenn p 2 oder mehr ist, eine Vielzahl von R² gleich oder unterschiedlich sein können,

wenn q 2 oder mehr ist, eine Vielzahl von R³ gleich oder unterschiedlich sein können, und

35 wenn 12 oder mehr ist, eine Vielzahl von R¹¹ gleich oder unterschiedlich sein können, und

wenn 12 oder mehr ist, eine Vielzahl von R¹² gleich oder unterschiedlich sein können,

oder ein pharmazeutisch verträgliches Salz davon.

40 5. Verbindung gemäß einem der Ansprüche 1 bis 4, wobei Z eine Carboxylgruppe ist, die mit einer C1-8-Alkylgruppe substituiert sein kann, oder ein pharmazeutisch verträgliches Salz davon.

45 6. Pharmazeutische Zusammensetzung, umfassend die Verbindung, dargestellt durch die allgemeine Formel (I-A)' gemäß Anspruch 1, oder die Verbindung, dargestellt durch die allgemeine Formel (I-B) gemäß Anspruch 4, oder ein pharmazeutisch verträgliches Salz davon.

50 7. Pharmazeutische Zusammensetzung gemäß Anspruch 6, bei der es sich um ein S1P₅-Bindemittel und/oder einen S1P₅-Modulator handelt.

8. Pharmazeutische Zusammensetzung gemäß Anspruch 6 zur Verwendung bei einem Verfahren zum Vorbeugen und/oder Behandeln einer durch S1P₅ vermittelten Erkrankung, wobei es sich bei der durch S1P₅ vermittelten Erkrankung um eine neurodegenerative Erkrankung, eine Autoimmunerkrankung, eine Infektion oder Krebs handelt.

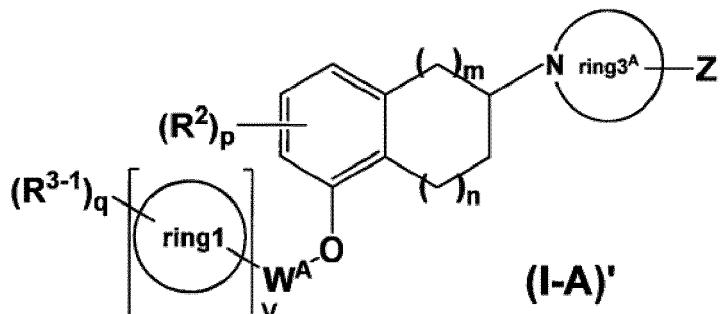
55 9. Pharmazeutische Zusammensetzung zur Verwendung gemäß Anspruch 8, wobei es sich bei der neurodegenerativen Erkrankung um Schizophrenie, Binswanger-Erkrankung, Multiple Sklerose, Neuromyelitis optica, Alzheimer-Erkrankung, kognitive Beeinträchtigung, amyotrophe Lateralsklerose oder spinozerebelläre Ataxie handelt.

10. Verbindung, dargestellt durch die allgemeine Formel (I-A)' gemäß Anspruch 1, oder Verbindung, dargestellt durch die allgemeine Formel (I-B) gemäß Anspruch 4, oder pharmazeutisch verträgliches Salz davon zur Verwendung bei einem Verfahren zum Vorbeugen und/oder Behandeln einer durch S1P₅ vermittelten Erkrankung, wobei es sich

bei der durch S1P₅ vermittelten Erkrankung um eine neurodegenerative Erkrankung, eine Autoimmunerkrankung, eine Infektion oder Krebs handelt.

5 **Revendications**

1. Composé représenté par la formule générale (I-A)':



dans laquelle,

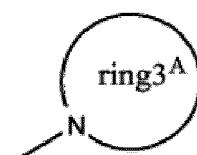
25 W^A représente (1) un groupe alkylène en C1-12, (2) un groupe alcénylène en C2-12, (3) un groupe alcynylène en C2-12, (4) -(alkylène en C1-12)-O-, (5) -(alcénylène en C2-12)-O-, (6) -(alcynylène en C2-12)-O-, (7) -(alkylène en C1-12)-ring2-, (8) -(acénylène en C2-12)-ring2- ou (9) -(alcynylène en C2-12)-ring2-, dans lesquels un groupe alkylène, un groupe alcénylène et un groupe alcynylène peuvent être substitués par un à cinq atomes d'halogène,

30 R^2 représente (1) un atome d'halogène, (2) un groupe alkyle en C1-4, (3) un groupe haloalkyle en C1-4, (4) un groupe alcoxy en C1-4 ou (5) un groupe haloalcoxy en C1-4,

35 R^{3-1} représente (1) un atome d'halogène, (2) un groupe alkyle en C1-4, (3) un groupe haloalkyle en C1-4, (4) un groupe alcoxy en C1-4, (5) un groupe haloalcoxy en C1-4, (6) un groupe nitrile, (7) un groupe -S- alkyle en C1-4, (8) un groupe -S- haloalkyle en C1-4 ou (9) un groupe oxo, à condition que le groupe alkyle en C1-4 ou que le groupe haloalkyle en C1-4 représenté par R^{3-1} soit à chaîne ramifiée, des groupes alkyle en C1-2 se ramifiant à partir du même atome de carbone pouvant être pris ensemble avec un atome de carbone auquel ils sont liés, pour former un noyau carbocyclique saturé en C3-4,

40 Z représente (1) un groupe carboxyle qui peut être substitué par un groupe alkyle en C1-8, (2) un groupe hydroxy qui peut être substitué par un groupe alkyle en C1-8, (3) un groupe acide hydroxamique qui peut être substitué par un groupe alkyle en C1-8, (4) un groupe acide sulfonique qui peut être substitué par un groupe alkyle en C1-8, (5) un groupe acide boronique qui peut être substitué par un groupe alkyle en C1-8, (6) un groupe carbamoyle qui peut être substitué par un groupe alkyle en C1-8, (7) un groupe sulfamoyle qui peut être substitué par un groupe alkyle en C1-8, (8) un groupe sulfoxymine qui peut être substitué par un groupe alkyle en C1-8 ou (9) un groupe tétrazolyte,

45 « ring1 » représente (1) un noyau carbocyclique en C3-10 ou (2) un noyau hétérocyclique de 3 à 10 chaînons, « ring 2 » représente (1) un noyau carbocyclique en C3-7 ou (2) un noyau hétérocyclique de 3 à 7 chaînons,



représente un noyau hétérocyclique saturé azoté de 3 à 7 chaînons,

55 m représente un entier de 0 à 2,

n représente un entier de 0 à 2,

p représente un entier de 0 à 3,

q représente un entier de 0 à 5,

v représente un entier égal à 1,

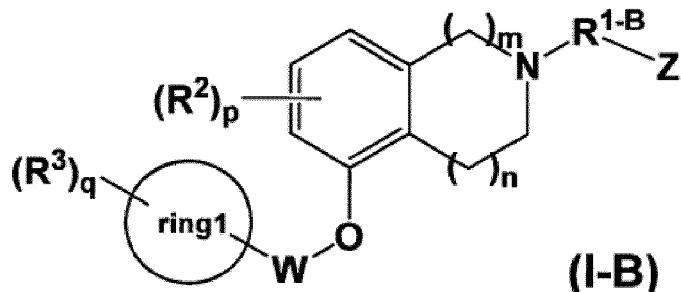
lorsque p vaut 2 ou plus, une pluralité de R² peuvent être identiques ou différents, et lorsque q vaut 2 ou plus, une pluralité de R³⁻¹ peuvent être identiques ou différents, ou sel pharmaceutiquement acceptable de celui-ci.

5 2. Composé selon la revendication 1, dans lequel W^A représente (1) un groupe alkylène en C1-6, (2) un groupe alcényle en C2-6, (3) un groupe alcynyle en C2-6, (4) un -(alkylène en C1-6)-O-, (5) un -(alcényle en C2-6)-O-, (6) un -(alcynyle en C2-6)-O- ou (7) un -(alkylène en C1-6)-ring2-,

10 et les autres symboles ont les mêmes significations que celles décrites à la revendication 1, ou sel pharmaceutiquement acceptable de celui-ci.

15 3. Composé selon la revendication 1 ou 2, dans lequel « ring 1 » est un noyau carbocyclique en C3-10, ou sel pharmaceutiquement acceptable de celui-ci.

4. Composé représenté par la formule générale (I-B)



dans laquelle,

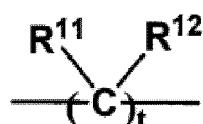
30 W représente (1) un groupe alkylène en C1-6, (2) un groupe alcényle en C2-6, (3) un groupe alcynyle en C2-6, (4) un -(alkylène en C1-6)-O-, (5) un -(alcényle en C2-6)-O-, (6) un -(alcynyle en C2-6)-O- ou (7) un -(alkylène en C1-6)-ring2-,

R^{1-B} représente -L- ou -L-ring3^B-,

35 R² représente (1) un atome d'halogène, (2) un groupe alkyle en C1-4, (3) un groupe haloalkyle en C1-4, (4) un groupe alcoxy en C1-4 ou (5) un groupe haloalcoxy en C1-4,

35 R³ représente (1) un atome d'halogène, (2) un groupe alkyle en C1-4, (3) un groupe haloalkyle en C1-4, (4) un groupe alcoxy en C1-4, (5) un groupe haloalcoxy en C1-4, (6) un groupe nitrile, (7) un groupe -S-alkyle en C1-4, ou (8) un groupe -S-haloalkyle en C1-4, à condition que le groupe alkyle en C1-4 ou que le groupe haloalkyle en C1-4 représenté par R³⁻¹ soit à chaîne ramifiée, des groupes alkyle en C1-2 se ramifiant à partir du même atome de carbone pouvant être pris ensemble avec un atome de carbone auquel ils sont liés, pour former un noyau carbocyclique saturé en C3-4,

40 R représente (1) une liaison ou (2) un groupe représenté par la formule générale



50 dans laquelle R¹¹ et R¹² représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C1-4, ou R¹¹ et R¹² peuvent être pris ensemble avec un atome de carbone auquel ils sont liés, pour former un noyau carbocyclique en C3-7, et t représente un entier de 1 à 6,

55 Z représente (1) un groupe carboxyle qui peut être substitué par un groupe alkyle en C1-8, (2) un groupe hydroxy qui peut être substitué par un groupe alkyle en C1-8, (3) un groupe acide hydroxamique qui peut être substitué par un groupe alkyle en C1-8, (4) un groupe acide sulfonique qui peut être substitué par un groupe alkyle en C1-8, (5) un groupe acide boronique qui peut être substitué par un groupe alkyle en C1-8, (6) un groupe carbamoyle qui peut être substitué par un groupe alkyle en C1-8, (7) un groupe sulfamoyle qui peut être substitué par un groupe alkyle en C1-8, (8) un groupe sulfoxamine qui peut être substitué par un groupe alkyle en C1-8

ou (9) un groupe tétrazolyle,
 « ring1 » représente un noyau carbocyclique en C3-10,
 « ring 2 » représente (1) un noyau carbocyclique en C3-7 ou (2) un noyau hétérocyclique de 3 à 7 chaînons,
 « ring 3^B » représente un noyau carbocyclique en C3-7,
 m représente un entier de 0 à 2,
 n représente un entier de 0 à 2,
 p représente un entier de 0 à 3,
 q représente un entier de 0 à 5,
 lorsque p vaut 2 ou plus, une pluralité de R² peuvent être identiques ou différents, lorsque q vaut 2 ou plus,
 une pluralité de R³ peuvent être identiques ou différents, lorsque t vaut 2 ou plus, une pluralité de R¹¹ peuvent
 être identiques ou différents, et
 lorsque t vaut 2 ou plus, une pluralité de R¹² peuvent être identiques ou différents, ou sel pharmaceutiquement
 acceptable de celui-ci.

5

10

15

20

25

30

35

40

45

50

55

- 5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel Z est un groupe carboxyle qui peut être substitué par un groupe alkyle en C1-8, ou sel pharmaceutiquement acceptable de celui-ci.
- 6. Composition pharmaceutique comprenant le composé représenté par la formule générale (I-A)' selon la revendication 1 ou le composé représenté par la formule générale (I-B) selon la revendication 4, ou un sel pharmaceutiquement acceptable de ceux-ci.
- 7. Composition pharmaceutique selon la revendication 6, qui est un agent se liant à et/ou modulant S1P₅.
- 8. Composition pharmaceutique selon la revendication 6 destinée à être utilisée dans un procédé de prévention et/ou de traitement d'une maladie médiée par S1P₅, la maladie médiée par S1P₅ étant une maladie neurodégénérative, une maladie autoimmune, une infection ou un cancer.
- 9. Composition pharmaceutique destinée à être utilisée selon la revendication 8, la maladie neurodégénérative étant une schizophrénie, la maladie de Binswanger, une sclérose en plaques, une neuromyélite optique, la maladie d'Alzheimer, un déficit cognitif, une sclérose latérale amyotrophique ou une ataxie spinocérébelleuse.
- 10. Composé représenté par la formule générale (I-A)' selon la revendication 1 ou composé représenté par la formule générale (I-B) selon la revendication 4, ou sel pharmaceutiquement acceptable de ceux-ci destinés à être utilisés dans un procédé de prévention et/ou de traitement d'une maladie médiée par S1P₅, la maladie médiée par S1P₅ étant une maladie neurodégénérative, une maladie autoimmune, une infection ou un cancer.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 2010146105 A [0009]
- WO 2014129796 A [0009]
- WO 2006085149 A2 [0009]
- WO 9015047 A1 [0009]
- EP 0270947 A2 [0009]
- WO 03011862 A1 [0009]
- WO 2006007448 A [0049]
- US 2868691 A [0102]
- US 3095355 A [0102]

Non-patent literature cited in the description

- *The Journal of Neuroscience*, 2005, vol. 25 (6), 1459-1469 [0010]
- *The FASEB Journal*, 2007, vol. 21, 1503-1514 [0010]
- *Nature Immunology*, 2007, vol. 8 (12), 1337-1344 [0010]
- *European Journal of Immunology*, 2013, vol. 43, 1667-1675 [0010]
- *Science*, 2015, vol. 350 (6263), 985-990 [0010]
- **RICHARD C. LAROCK**. Comprehensive Organic Transformations: A Guide to Functional Group Preparations. John Wiley & Sons Inc, 1999 [0051]
- **T. W. GREENE**. Protective Groups in Organic Synthesis. Wiley, 1999 [0058] [0060]
- *CHEMICAL ABSTRACTS*, 100202-39-9 [0120]
- *CHEMICAL ABSTRACTS*, 35697-10-0 [0120]
- *CHEMICAL ABSTRACTS*, 455-19-6 [0132]
- *CHEMICAL ABSTRACTS*, 402-45-9 [0134]
- *CHEMICAL ABSTRACTS*, 1504-58-1 [0135]
- *CHEMICAL ABSTRACTS*, 28315-93-7 [0137]
- *CHEMICAL ABSTRACTS*, 90047-53-3 [0146]
- *CHEMICAL ABSTRACTS*, 695-95-4 [0199]
- *CHEMICAL ABSTRACTS*, 152922-71-9 [0222]
- *CHEMICAL ABSTRACTS*, 40731-98-4 [0230]