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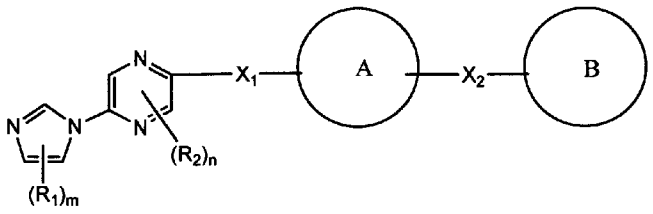
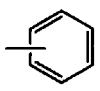
(54) Title: IMIDAZOLYLPYRAZINE DERIVATIVES



[I]



[2]

(57) Abstract: To provide a novel low-molecular-weight compound that inhibits the production of amyloid-β (Aβ). A compound represented by the formula [I]: or a pharmacologically acceptable salt or ester thereof, wherein R_1 and R_2 are the same or different and each represent a substituent selected from the following Substituent Group a1; m represents an integer of 0 to 3; n represents an integer of 0 to 2; X_1 represents a single bond or the like; X_2 represents a single bond or the like; Ring A represents a five-membered aromatic heterocyclic group or the like which contains two or more nitrogen atoms and may have 1 to 3 substituents selected from the following Substituent Group b1; and Ring B represents a monocyclic or fused cyclic aromatic ring group such as the formula [2] which may have 1 to 3 substituents selected from the following Substituent Group c1, is effective as a therapeutic agent for a disease such as Alzheimer's disease. Substituent Group a1: a C1-6 alkyl group and the like Substituent Group b1: a C1-6 alkyl group and the like Substituent Group c1: an amino group and the like

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DESCRIPTION

TITLE OF THE INVENTION: IMIDAZOLYLPYRAZINE DERIVATIVES

TECHNICAL FIELD

[0001]

The present invention relates to a pharmaceutical, more particularly, to a polycyclic imidazolylpyrazine derivative effective for the treatment of a neurodegenerative disease caused by amyloid-β (hereinafter referred to as Aβ) such as Alzheimer's disease or Down's syndrome and a medicine, in particular, a medicine for the treatment of a disease caused by Aβ comprising the compound as an active ingredient.

BACKGROUND ART

[0002]

Alzheimer's disease is a disease characterized by degeneration and loss of neurons as well as formation of senile plaques and neurofibrillary degeneration. Currently, Alzheimer's disease is treated only with symptomatic treatment using a symptom improving agent typified by an acetylcholinesterase inhibitor, and a fundamental remedy to inhibit progression of the disease has not yet been developed. It is necessary to develop a method for controlling the cause of the onset of pathology in order to create a fundamental remedy for Alzheimer's disease.

It is assumed that Aβ-proteins as metabolites of amyloid precursor proteins (hereinafter referred to as APP) are highly involved in degeneration and loss of neurons and onset of symptoms of dementia (see NON-PATENT DOCUMENTS 1 and 2, for example). Main molecular species of Aβ-protein are Aβ40 consisting of 40 amino acids and Aβ42 with two amino acids added at the C-terminal. The Aβ40 and Aβ42 are known to have high aggregability (see NON-PATENT DOCUMENT 3, for example) and to be main components of senile plaques (see NON-PATENT DOCUMENTS 3, 4 and 5, for example). Further, it is known that the Aβ40 and Aβ42 are increased by mutation in APP and presenilin genes which is observed in familial Alzheimer's disease (see NON-PATENT DOCUMENTS 6, 7 and 8, for example). Accordingly, a compound that reduces the production of Aβ40 and Aβ42 is expected as a progression inhibitor or prophylactic agent for Alzheimer's disease.

Aβ is produced by cleaving APP by β-secretase and subsequently by γ-secretase. For this reason, attempts have been made to create γ-secretase and β-secretase inhibitors in order

to reduce Aβ production. Many of these secretase inhibitors already known are, for example, peptides and peptide mimetics such as L-685,458 (see NON-PATENT DOCUMENT 9, for example), LY-411,575 (see NON-PATENT DOCUMENTS 10, 11 and 12, for example) and LY-450,139 (see NON-PATENT DOCUMENTS 13, 14 and 15). Nonpeptidic compounds are, for example, MRK-560 (see NON-PATENT DOCUMENTS 16 and 17) and compounds having a plurality of aromatic rings as disclosed in PATENT DOCUMENTS 1 and 2. However, the compound represented by the formula (VI) as disclosed in page 17 of the specification differs from the compound of the present invention in that the compound is limited to a compound having a 2-aminothiazolyl group as a main structure.

And the compound represented by the formula (I) as disclosed in page 6 of the specification of PATENT DOCUMENT 2 differs from the compound of the present invention in that the former compound does not have pyrazine ring in the partial structure defined as Ar_2.

PRIOR ART DOCUMENTS

PATENT DOCUMENTS

[0003]

PATENT DOCUMENT 1: WO 2004/110350

PATENT DOCUMENT 2: WO 2007/102580

NON-PATENT DOCUMENTS

[0004]

NON-PATENT DOCUMENT 1: Klein WL, and seven others, Alzheimer's disease-affected brain: Presence of oligomeric Aβ ligands (ADDLs) suggests a molecular basis for reversible memory loss, Proceeding of the National Academy of Science USA, 2003, Sep, 2; 100 (18), p. 10417-10422.

NON-PATENT DOCUMENT 2: Nitsch RM, and sixteen others, Antibodies against β-amyloid slow cognitive decline in Alzheimer's disease, Neuron, 2003, May 22; 38, p. 547-554.

NON-PATENT DOCUMENT 3: Jarrett JT, and two others, The carboxy terminus of the β amyloid PROTEIN is critical for the seeding of amyloid formation: Implications for the pathogenesis of Alzheimers' disease, Biochemistry, 1993, 32 (18), p. 4693-4697.

NON-PATENT DOCUMENT 4: Glenner GG, and one other, Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein, Biochemical and Biophysical Research Communications, 1984, May 16, 120 (3), p. 885-890.

NON-PATENT DOCUMENT 5: Masters CL, and five others, Amyloid plaque core protein in

Alzheimer disease and Down syndrome, Proceeding of the National Academy of Science USA, 1985, Jun, 82 (12), p. 4245-4249.

NON-PATENT DOCUMENT 6: Gouras GK, and eleven others, Intraneuronal Aβ42 accumulation in human brain, American Journal of Pathology, 2000, Jan, 156 (1), p. 15-20.

NON-PATENT DOCUMENT 7: Scheuner D, and twenty others, Secreted amyloid β-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease, Nature Medicine, 1996, Aug, 2 (8), p. 864-870.

NON-PATENT DOCUMENT 8: Forman MS, and four others, Differential effects of the swedish mutant amyloid precursor protein on β-amyloid accumulation and secretion in neurons and nonneuronal cells, The Journal of Biological Chemistry, 1997, Dec, 19, 272 (51), p. 32247-32253.

NON-PATENT DOCUMENT 9: Shearman MS, and nine others, L-685, 458, an Aspartyl Protease Transition State Mimic, Is a Potent Inhibitor of Amyloid β-Protein Precursor γ-Secretase Activity, Biochemistry, 2000, Aug, 1, 39 (30), p. 8698-8704.

NON-PATENT DOCUMENT 10: Shearman MS, and six others, Catalytic Site-Directed γ-Secretase Complex Inhibitors Do Not Discriminate Pharmacologically between Notch S3 and β-APP Clevages, Biochemistry, 2003, Jun, 24, 42 (24), p. 7580-7586.

NON-PATENT DOCUMENT 11: Lanz TA, and three others, Studies of Aβ pharmacodynamics in the brain, cerebrospinal fluid, and plasma in young (plaque-free) Tg2576 mice using the γ-secretase inhibitor N2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyethanoyl]-N1-[(7S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-L-alaninamide (LY-411575), The Journal of Pharmacology and Experimental Therapeutics, 2004, Apr, 309 (1), p. 49-55.

NON-PATENT DOCUMENT 12: Wong GT, and twelve others, Chronic treatment with the γ-secretase inhibitor LY-411, 575 inhibits β-amyloid peptide production and alters lymphopoiesis and intestinal cell differentiation, The Journal of Biological Chemistry, 2004, Mar, 26, 279 (13), p. 12876-12882.

NON-PATENT DOCUMENT 13: Gitter BD, and ten others, Stereoselective inhibition of amyloid beta peptide secretion by LY450139, a novel functional gamma secretase inhibitor, Neurology of Aging 2004, 25, sup2, p. 571.

NON-PATENT DOCUMENT 14: Lanz TA, and eighteen others, Concentration-dependent modulation of amyloid-β in vivo and in vitro using the γ-secretase inhibitor, LY-450139, The Journal of Pharmacology and Experimantal Therapeutics, 2006, Nov, 319 (2) p. 924-933.

NON-PATENT DOCUMENT 15: Siemers ER, and thirteen others, Effects of a γ-secretase inhibitor in a randamized study of patients with Alzheimer disease, Neurology, 2006, 66, p. 602-604.

NON-PATENT DOCUMENT 16: Best JD, and nine others, In vivo characterization of Aβ (40) changes in brain and cerebrospinal fluid using the novel γ-secretase inhibitor N-[cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexyl]-1,1,1-trifluoromethanesulphonlamide (MK-560) in the rat, The Journal of Pharmacology and Experimantal Therapeutics, 2006, May 317 (2) p. 786-790.

NON-PATENT DOCUMENT 17: Best JD, and thirteen others The novel γ-secretase inhibitor N-[cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexyl]-1,1,1-trifluoromethanesulphonlamide (MK-560) reduces amylid plaque deposition without evidence notch-related pathology in the Tg2576 mouse, The Journal of Pharmacology and Experimantal Therapeutics, 2007, Feb, 320 (2) p. 552-558.

SUMMARY OF THE INVENTION

PROBLEM TO BE SOLVED BY THE INVENTION

[0005]

As described above, a compound that inhibits the production of Aβ40 and Aβ42 from APP has been expected as a therapeutic or prophylactic agent for a disease caused by Aβ which is typified by Alzheimer's disease. However, a nonpeptidic compound having high efficacy which inhibits the production of Aβ40 and Aβ42 has not yet been known. Accordingly, there is a need for a novel low-molecular-weight compound that inhibits the production of Aβ40 and Aβ42.

MEANS FOR SOLVING THE PROBLEM

[0006]

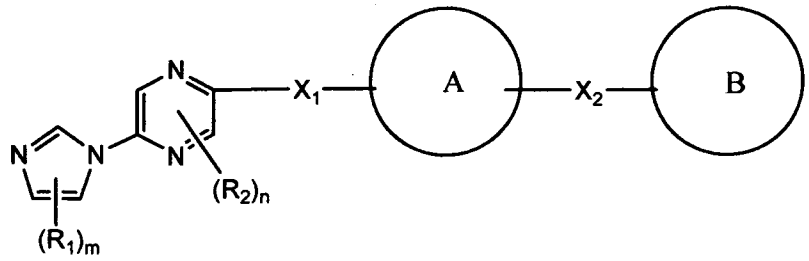
As a result of extensive studies, the present inventors have found a nonpeptidic polycyclic compound that inhibits the production of Aβ40 and Aβ42 from APP and thus found a therapeutic agent for a disease caused by Aβ which is typified by Alzheimer's disease. This finding has led to the accomplishment of the present invention.

[0007]

Specifically, the present invention relates to the following 1) to 20):

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

[0008]



[I]

[0009]

or a pharmacologically acceptable salt or ester thereof,

wherein R_1 and R_2 are the same or different and each represent a substituent selected from the following Substituent Group a1;

m represents an integer of 0 to 3;

n represents an integer of 0 to 2;

X_1 represents i) a single bond, ii)

[0010]

$-C\equiv C-$

[0011]

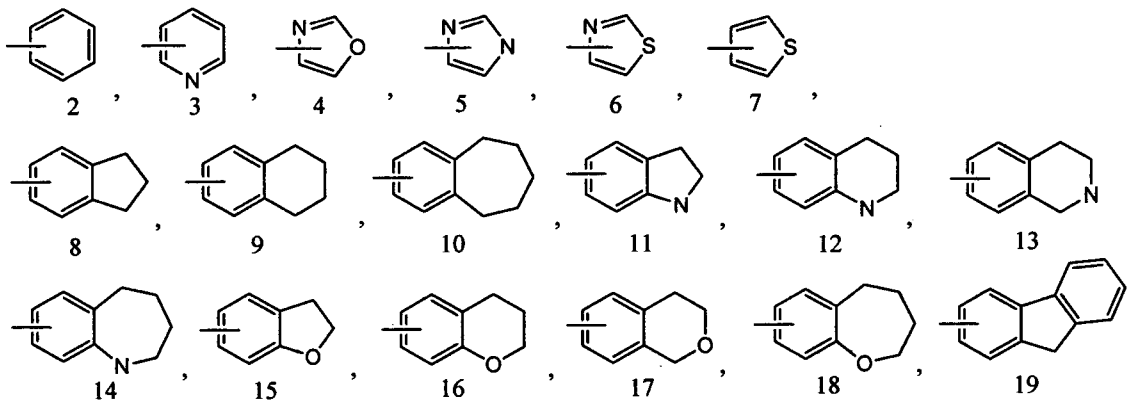
or iii) $-CR_3=CR_4-$ (wherein R_3 and R_4 are the same or different and each represent (1) a hydrogen atom, (2) a C1-6 alkyl group or (3) a halogen atom);

X_2 represents i) a single bond, ii) a C1-6 alkylene group or iii) $-X_3-$ (wherein X_3 represents $-NR_5-$, -O-, -C(O)-, -S-, -S(O)- or $-S(O)_2-$ and R_5 represents a hydrogen atom, a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkanoyl group or a C1-6 alkylsulfonyl group);

Ring A represents i) a five-membered aromatic heterocyclic group or ii) a five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group, which contains two or more nitrogen atoms and may have 1 to 3 substituents selected from the following Substituent Group b1 (wherein the non-aromatic ring group may have a crosslinked structure or a spiro ring system); and

Ring B represents a monocyclic or fused cyclic aromatic ring group selected from the group consisting of the formulas [2] to [19]:

[0012]



[0013]

each of which may have 1 to 3 substituents selected from the following Substituent Group c1,

Substituent Group a1: a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkenyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, an amino group (wherein the amino group may have one C2-6 alkanoyl group or C1-6 alkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group and a nitro group;

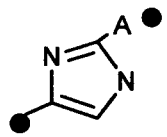
Substituent Group b1: a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C2-6 alkenyl group, a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C4-9 cycloalkylcarbonyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C2-6 alkenylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a C1-6 alkylthio group, a C2-6 alkenylthio group, a C3-8 cycloalkylthio group, an aminosulfonyl group (wherein the aminosulfonyl group may have 1 to 2 C1-6 alkyl groups, C2-6 alkenyl groups or C3-8 cycloalkyl groups), an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group, a nitro group, an oxo group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 1-homopiperidinyl group, an indolin-1-yl group, a 1,2,3,4-tetrahydroquinolin-1-yl group and a 4-morpholinyl group;

Substituent Group c1: i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C2-6 alkenyl group, v)-iii) a C2-6 alkynyl group, v)-iv) a C1-6 alkoxy group, v)-v) a C1-6 alkylthio group, v)-vi) a C1-6 alkylaminocarbonyl group, v)-vii) a

C1-6 alkylsulfonyl group, v)-viii) a C1-6 alkylaminosulfonyl group, v)-ix) a C2-6 alkanoyl group, v)-x) a phenyl group, v)-xi) a pyridyl group, v)-xii) a pyridazinyl group, v)-xiii) a pyrimidinyl group, v)-xiv) a 1-pyrrolidinyl group, v)-xv) a 1-piperidinyl group, v)-xvi) a 1-homopiperidinyl group and v)-xvii) a 4-morpholinyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom;

2) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein Ring A is a five-membered aromatic heterocyclic group selected from the group consisting of the formulas [20] to [26]:

[0014]



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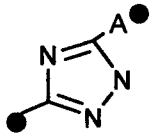

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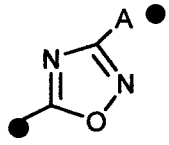

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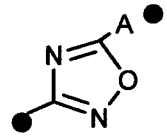

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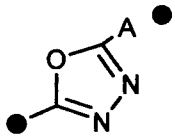

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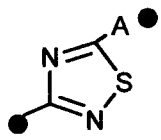

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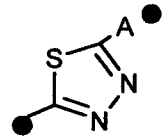
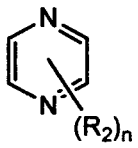


26

[0015]

wherein • represents a bonding site to the formula [27]:

[0016]

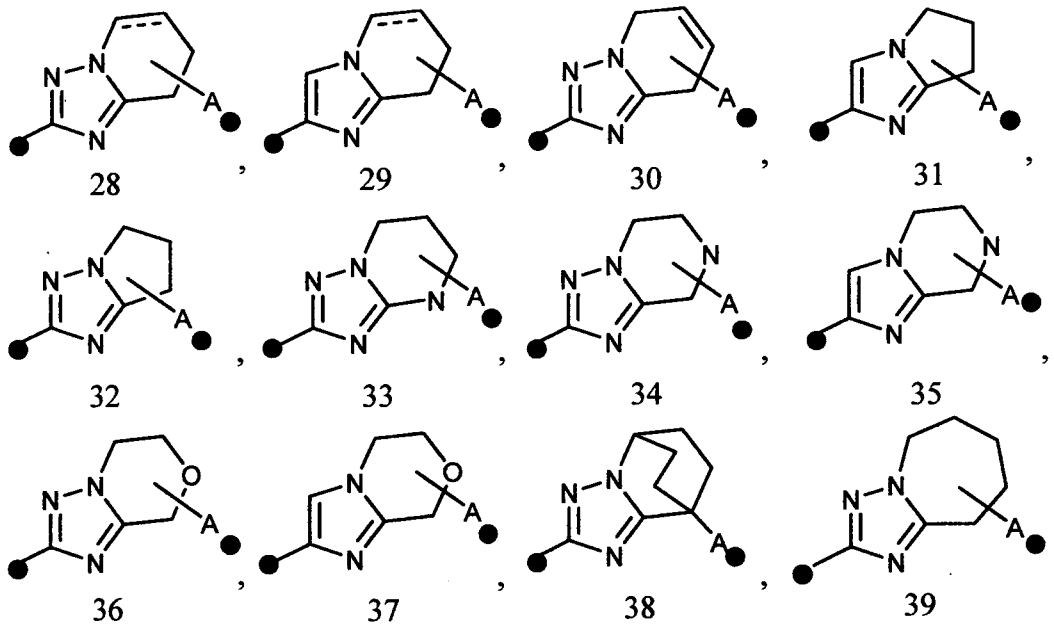


and

[0017]

A• represents a bonding site to X_2, or any one ring selected from the group consisting of the formulas [28] to [39]:

[0018]



[0019]

wherein • and A• are as defined above and the partial structure:

[0020]

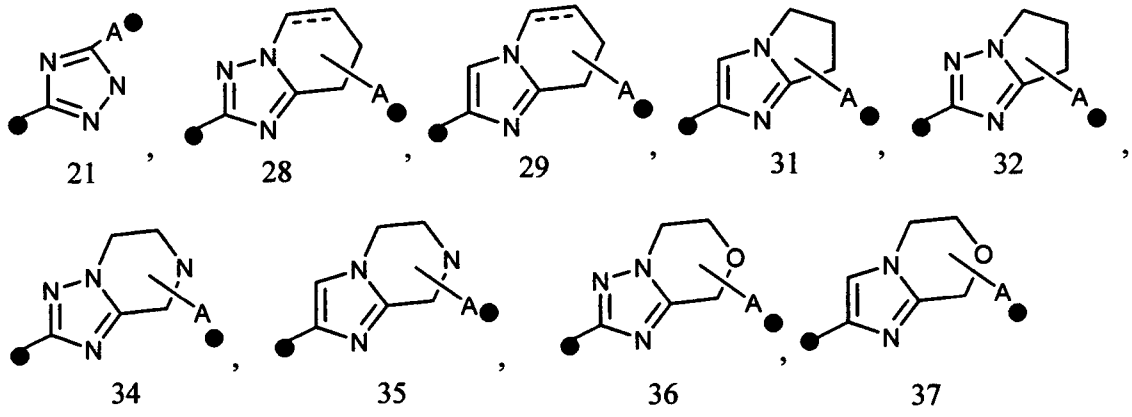
[0021]

represents a single bond or a double bond,

each of which may have 1 to 3 substituents selected from Substituent Group b1;

3) The compound or pharmacologically acceptable salt or ester thereof according to 2) above, wherein Ring A is any one ring selected from the group consisting of the formulas [21], [28], [29], [31], [32] and [34] to [37]:

[0022]



wherein •, A• and the partial structure:

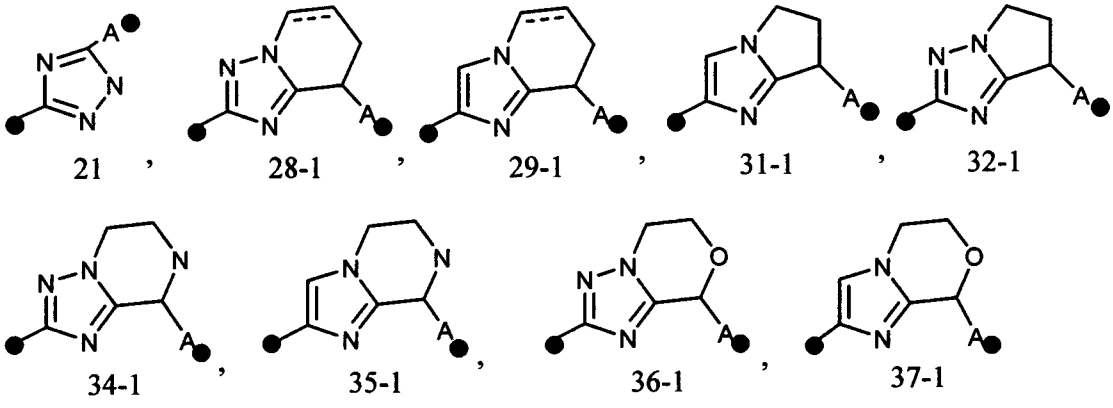
[0023]

[0024]

are as defined above;

4) The compound or pharmacologically acceptable salt or ester thereof according to 2) above, wherein Ring A is any one ring selected from the group consisting of the formulas [21], [28-1], [29-1], [31-1], [32-1] and [34-1] to [37-1]:

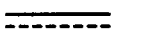
[0025]



[0026]

wherein •, A• and the partial structure:

[0027]

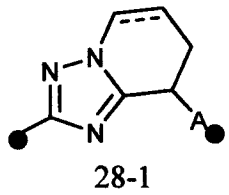


[0028]

are as defined above;

5) The compound or pharmacologically acceptable salt or ester thereof according to 2) above, wherein Ring A is a ring of the formula [28-1]:

[0029]



[0030]

wherein •, A• and the partial structure:

[0031]

[0032]

are as defined above;

6) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein Ring B is a phenyl group, a pyridyl group, an oxazolyl group, an imidazolyl group, a thiazolyl group, a dihydrobenzofuranyl group or a thienyl group;

7) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein X_1 is i) a single bond or ii) $-CR_3=CR_4-$;

8) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein X_1 is a single bond;

9) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein X_1 is $-CR_3=CR_4-$;

10) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein X_2 is i) a single bond or ii) a C1-6 alkylene group;

11) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein X_2 is a single bond;

12) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein R_1 is a C1-6 alkyl group or a halogen atom and m is 1 to 2;

13) The compound or pharmacologically acceptable salt or ester thereof according to 1) above, wherein R_2 is a C1-6 alkoxy group and n is 1;

14) The compound or pharmacologically acceptable salt or ester thereof according to 9) above, wherein R_3 and R_4 are the same or different and are each (1) a hydrogen atom or (2) a halogen atom;

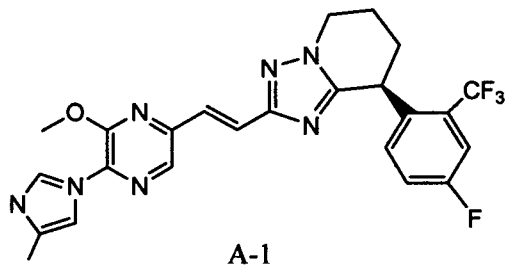
15) The compound or pharmacologically acceptable salt or ester thereof according to 9) above, wherein R_3 and R_4 are each a hydrogen atom;

16) The compound or pharmacologically acceptable salt or ester thereof according to 1), wherein the substituent for Ring A is a substituent selected from the group consisting of: a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a cyano group, a formyl group, a halogen atom, a hydroxyl group and an oxo group;

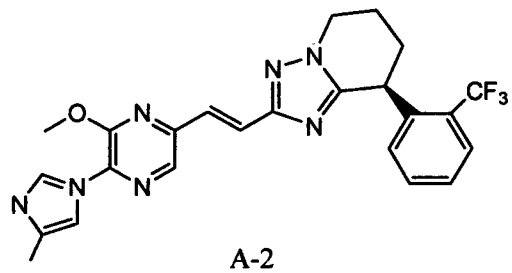
17) The compound or pharmacologically acceptable salt or ester thereof according to 1), wherein the substituent for Ring B is a substituent selected from the group consisting of: i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C1-6 alkoxy group, v)-iii) a C1-6 alkylthio group and v)-iv) a phenyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom;

18) One compound selected from the group consisting of the following formulas [A-1] to [A-7]:

[0033]



A-1



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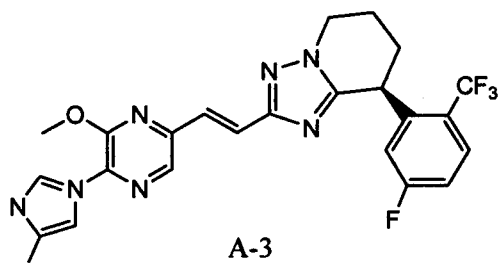

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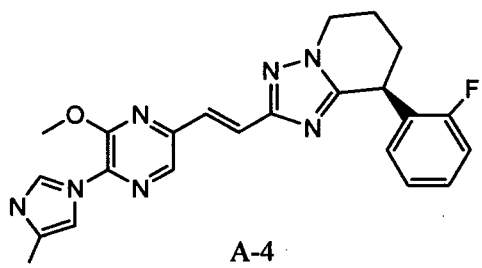
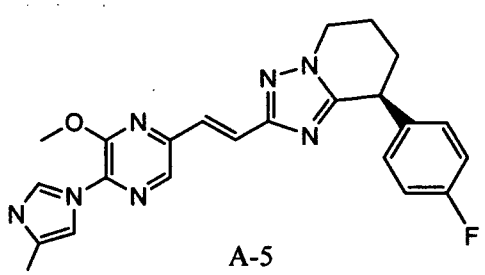
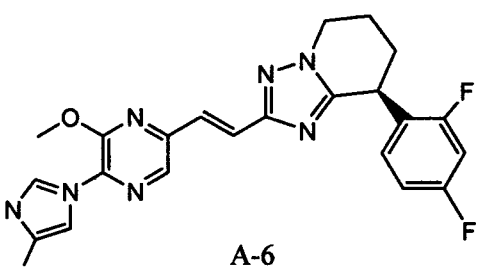


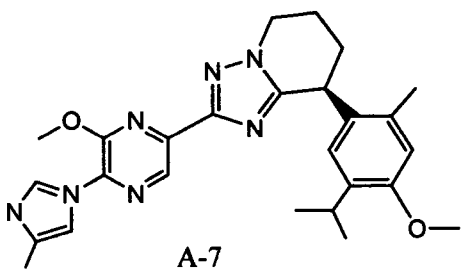
A-4



A-5



A-6



A-7

[0034]

or a pharmacologically acceptable salt or ester thereof;

19) A medicine comprising the compound or pharmacologically acceptable salt or ester thereof according to any one of 1) to 18) above as an active ingredient; and

20) The medicine according to 19) above for the treatment of a disease selected from Alzheimer's disease, dementia, Down's syndrome and amyloidosis.

MODE FOR CARRYING OUT THE INVENTION

[0035]

The compound of the general formula (I) or pharmacologically acceptable salt or ester thereof according to the present invention and the therapeutic agent for a disease caused by Aβ according to the present invention are novel inventions that have not yet been described in any documents.

The compound of the present invention can be converted to a chemical probe for capturing a target protein in a bioactive low-molecular compound. Specifically, the compound of the present invention can be converted to an affinity chromatography probe, a photoaffinity probe or the like by introducing a labeling group, a linker or the like into a moiety differing from a structural moiety essential for expression of activity of the compound by a technique described in J. Mass Spectrum. Soc. Jpn. Vol. 51, No. 5, 2003, p. 492-498 or WO 2007/139149, for example.

Examples of the labeling group, the linker or the like used for the chemical probe include groups shown in the following group consisting of (1) to (5):

(1) protein labeling groups such as photoaffinity labeling groups (such as a benzoyl group, a benzophenone group, an azido group, a carbonylazido group, a diaziridine group, an enone group, a diazo group and a nitro group) and chemical affinity groups (such as a ketone group substituted at the α-carbon atom with a halogen atom, a carbamoyl group, an ester group, an alkylthio group, Michael acceptors such as α,β-unsaturated ketones and esters, and an oxirane group),

(2) cleavable linkers such as -S-S-, -O-Si-O-, monosaccharides (such as a glucose group and a galactose group) and disaccharides (such as lactose), and enzymatically cleavable oligopeptide linkers,

(3) fishing tag groups such as biotin and 3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacen-3-yl)propionyl,

(4) detectable markers such as radioactive labeling groups such as ^{125}I, ^{32}P, ^{3}H and

^{14}C; fluorescence labeling groups such as fluorescein, rhodamine, dansyl, umbelliferone, 7-nitrofurazanyl and 3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacen-3-yl)propionyl; chemiluminescent groups such as luciferin and luminol; and heavy metal ions such as lanthanoid metal ions and radium ions, and

(5) groups bound to solid-phase carriers such as glass beads, glass beds, microtiter plates, agarose beads, agarose beds, polystyrene beads, polystyrene beds, nylon beads and nylon beds.

When a probe is prepared by introducing a labeling group or the like selected from the group consisting of (1) to (5) above into the compound of the present invention in accordance with a method described in the above documents or the like, the probe can be used as a chemical probe for identification of labeled proteins useful for searching for novel drug targets, for example.

[0036]

Meanings of symbols, terms and the like used in the present specification will be explained and the present invention will be described in detail below.

[0037]

In the present specification, a structural formula of a compound may represent a certain isomer for convenience. However, the present invention includes all isomers and isomer mixtures such as geometric isomers which can be generated from the structure of a compound, optical isomers based on asymmetric carbon, stereoisomers and tautomers. The present invention is not limited to the description of a chemical formula for convenience and may include any one of the isomers or mixtures thereof. Accordingly, the compound of the present invention may have an asymmetric carbon atom in the molecule and exist as an optically active compound or racemate, and the present invention includes each of the optically active compound and the racemate without limitations. Although crystal polymorphs of the compound may be present, the compound is not limited thereto as well and may be present as a single crystal form or a mixture of single crystal forms. The compound may be an anhydride or hydrate.

The present invention also includes isotopically-labelled compounds, which are identical to the compounds of formula (I), except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number uusually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{35}S, ^{123}I and ^{125}I.

Compounds of the present invention and pharmaceutically acceptable derivatives (e.g. salts) of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically–labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and/or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. ^{3}H and ^{14}C are considered useful due to their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are considered useful in PET (positron emission tomography), and ^{125}I isotopes are considered useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Substitution with heavier isotopes such as 2H can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, are considered useful in some circumstances. Isotopically labelled compounds of formula (I) of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0038]

The term "diseases attributable to Aβ" includes a wide variety of conditions such as Alzheimer's disease (for example, refer to, Klein WL, and 7 others, Alzheimer's disease-affected brain: Presence of oligomeric Aβ ligands (ADDLs) suggests a molecular basis for reversible memory loss, Proceeding National Academy of Science USA, 2003, Sep 2, 100 (18), p. 10417-10422; Nitsch RM, and 16 others, Antibodies against β-amyloid slow cognitive decline in Alzheimer's disease, Neuron, 2003, May 22, 38 (4), p. 547-554: Jarrett JT, and 2 others, The carboxy terminus of the β amyloid protein is critical for the seeding of amyloid formation: Implications for the pathogenesis of Alzheimer's disease, Biochemistry, 1993, May 11, 32 (18), p. 4693-4697; Glenner GG, and another, Alzheimer's disease; initial report of the purification and characterization of a novel cerebrovascular amyloid protein, Biochemical and biophysical research communications, 1984, May 16, 120 (3), p. 885-890; Masters CL, and 6 others, Amyloid plaque core protein in Alzheimer disease and Down syndrome, Proceeding National Academy of Science USA, 1985, June, 82 (12), p. 4245-4249; Gouras GK, and 11 others, Intraneuronal Aβ42 accumulation in human brain, American journal of pathology, 2000, Jan, 156 (1), p. 15-20; Scheuner D, and 20 others, Secreted amyloid β-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease, Nature Medicine, 1996, Aug, 2 (8), p. 864-870; Forman MS, and 4 others, Differential effects of the Swedish mutant amyloid precursor protein on β-

amyloid accumulation and secretion in neurons and nonneuronal cells, The journal of biological chemistry, 1997, Dec 19, 272 (51), p. 32247-32253), senile dementia (for example, refer to, Blass JP, Brain metabolism and brain disease: Is metabolic deficiency the proximate cause of Alzheimer dementia? Journal of Neuroscience Research, 2001, Dec 1, 66 (5), p. 851-856), frontotemporal dementia (for example, refer to, Evin G, and 11 others, Alternative transcripts of presenilin-1 associated with frontotemporal dementia, Neuroreport, 2002, Apr 16, 13 (5), p. 719-723), Pick disease (for example, refer to, Yasuhara O, and 3 others, Accumulation of amyloid precursor protein in brain lesions of patients with Pick disease, Neuroscience Letters, 1994, Apr 25, 171 (1-2), p. 63-66), Down's syndrome (for example, refer to, Teller JK, and 10 others, Presence of soluble amyloid β-peptide precedes amyloid plaque formation in Down's syndrome, Nature Medicine, 1996, Jan, 2 (1), p. 93-95; Tokuda T, and 6 others, Plasma levels of amyloid β proteins Aβ1-40 and Aβ1-42 (43) are elevated in Down's syndrome, Annals of Neurology, 1997, Feb, 41 (2), p. 271-273), cerebrovascular angiopathy (for example, refer to, Hayashi Y, and 9 others, Evidence for presenilin-1 involvement in amyloid angiopathy in the Alzheimer's disease-affected brain, Brain Research, 1998, Apr 13, 789 (2), p. 307-314; Barelli H, and 15 others, Characterization of new polyclonal antibodies specific for 40 and 42 amino acid-long amyloid β peptides: their use to examine the cell biology of presenilins and the immunohistochemistry of sporadic Alzheimer's disease and cerebral amyloid angiopathy cases, Molecular Medicine, 1997, Oct, 3 (10), p. 695-707; Calhoun ME, and 10 others, Neuronal overexpression of mutant amyloid precursor protein results in prominent deposition of cerebrovascular amyloid, Proceeding National Academy of Science USA, 1999, Nov 23, 96 (24), p. 14088-14093; Dermaut B, and 10 others, Cerebral amyloid angiopathy is a pathogenic lesion in Alzheimer's Disease due to a novel presenilin-1 mutation, Brain, 2001, Dec, 124 (12), p. 2383-2392), hereditary cerebral hemorrhage with amyloidosis (Dutch type) (for example, refer to, Cras P, and 9 others, Presenile Alzheimer dementia characterized by amyloid angiopathy and large amyloid core type senile plaques in the APP 692Ala --> Gly mutation, Acta Neuropathologica (Berl), 1998, Sep, 96 (3), p. 253-260; Herzig MC, and 14 others, Aβ is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis, Nature Neuroscience, 2004, Sep, 7 (9), p. 954-960; van Duinen SG, and 5 others, Hereditary cerebral hemorrhage with amyloidosis in patients of Dutch origin is related to Alzheimer disease, Proceeding National Academy of Science USA, 1987, Aug, 84 (16), p. 5991-5994; Levy E, and 8 others, Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type, Science, 1990, Jun 1, 248 (4959), p. 1124-1126), cognitive impairment (for example, refer to, Laws SM, and 7 others, Association between the presenilin-1 mutation Glu318Gly and complaints of memory impairment,

Neurobiology of Aging, 2002, Jan-Feb, 23 (1), p. 55-58), memory disturbance/learning disturbance (for example, refer to, Vaucher E, and 5 others, Object recognition memory and cholinergic parameters in mice expressing human presenilin 1 transgenes, Experimental Neurology, 2002 Jun, 175 (2), p. 398-406; Morgan D, and 14 others, Aβ peptide vaccination prevents memory loss in an animal model of Alzheimer's disease, Nature, 2000 Dec 21-28, 408 (6815), p. 982-985; Moran PM, and 3 others, Age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid precursor protein, Proceeding National Academy of Science USA, 1995, June 6, 92 (12), p. 5341-5345), amyloidosis, cerebral ischemia (for example, refer to, Laws SM, and 7 others, Association between the presenilin-1 mutation Glu318Gly and complaints of memory impairment, Neurobiology of Aging, 2002, Jan-Feb, 23 (1), p. 55-58; Koistinaho M, and 10 others, β-amyloid precursor protein transgenic mice that harbor diffuse Aβ deposits but do not form plaques show increased ischemic vulnerability: Role of inflammation, Proceeding National Academy of Science USA, 2002, Feb 5, 99 (3), p. 1610-1615; Zhang F, and 4 others, Increased susceptibility to ischemic brain damage in transgenic mice overexpressing the amyloid precursor protein, The journal of neuroscience, 1997, Oct 15, 17 (20), p. 7655-7661), cerebrovascular dementia (for example, refer to, Sadowski M, and 6 others, Links between the pathology of Alzheimer's disease and vascular dementia, Neurochemical Research, 2004, Jun, 29 (6), p. 1257-1266), ophthalmoplegia (for example, refer to, O'Riordan S, and 7 others, Presenilin-1 mutation (E280G), spastic paraparesis, and cranial MRI white-matter abnormalities, Neurology, 2002, Oct 8, 59 (7), p. 1108-1110), multiple sclerosis (for example, refer to, Gehrmann J, and 4 others, Amyloid precursor protein (APP) expression in multiple sclerosis lesions, Glia, 1995, Oct, 15 (2), p. 141-51; Reynolds WF, and 6 others, Myeloperoxidase polymorphism is associated with gender specific risk for Alzheimer's disease, Experimental Neurology, 1999, Jan, 155 (1), p. 31-41), head injury, skull damage (for example, refer to, Smith DH, and 4 others, Protein accumulation in traumatic brain injury, NeuroMolecular Medicine, 2003, 4 (1-2), p. 59-72), apraxia (for example, refer to, Matsubara-Tsutsui M, and 7 others, Molecular evidence of presenilin 1 mutation in familial early onset dementia, American journal of Medical Genetics, 2002, Apr 8, 114 (3), p. 292-298), prion disease, familial amyloid neuropathy, triplet repeat disease (for example, refer to, Kirkitadze MD, and 2 others, Paradigm shifts in Alzheimer's disease and other neurodegenerative disorders: the emerging role of oligomeric assemblies, Journal of Neuroscience Research, 2002, Sep 1, 69 (5), p. 567-577; Evert BO, and 8 others, Inflammatory genes are upreglulated in expanded ataxin-3-expressing cell lines and spinocerebellar ataxia type 3 brains, The Journal of Neuroscience, 2001, Aug 1, 21 (15), p. 5389-5396; Mann DM, and another, Deposition of

amyloid (A4) protein within the brains of persons with dementing disorders other than Alzheimer's disease and Down's syndrome, Neuroscience Letters, 1990, Feb 5, 109 (1-2), p. 68-75), Parkinson's disease (for example, refer to, Primavera J, and 4 others, Brain accumulation of amyloid-β in Non-Alzheimer Neurodegeneration, Journal of Alzheimer's Disease, 1999, Oct, 1 (3), p. 183-193), Dementia with Lewy bodies (for example, refer to, Giasson BI, and 2 others, Interactions of amyloidogenic proteins. NeuroMolecular Medicine, 2003, 4 (1-2), p. 49-58; Masliah E, and 6 others, β-amyloid peptides enhance α-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease, Proceeding National Academy of Science USA, 2001, Oct 9, 98 (21), p. 12245-12250; Barrachina M, and 6 others, Amyloid-β deposition in the cerebral cortex in Dementia with Lewy bodies is accompanied by a relative increase in AβPP mRNA isoforms containing the Kunitz protease inhibitor, Neurochemistry International, 2005, Feb, 46 (3), p. 253-260; Primavera J, and 4 others, Brain accumulation of amyloid-β in Non-Alzheimer Neurodegeneration, Journal of Alzheimer's Disease, 1999, Oct, 1 (3), p. 183-193), Parkinsonism-dementia complex (for example, refer to, Schmidt ML, and 6 others, Amyloid plaques in Guam amyotrophic lateral sclerosis/ parkinsonism-dementia complex contain species of Aβ similar to those found in the amyloid plaques of Alzheimer's disease and pathological aging, Acta Neuropathologica (Berl), 1998, Feb, 95 (2), p. 117-122; Ito H, and 3 others, Demonstration of β amyloid protein-containing neurofibrillary tangles in parkinsonism-dementia complex on Guam, Neuropathology and applied neurobiology, 1991, Oct, 17 (5), p. 365-373), frontotemporal dementia and Parkinsonism linked to chromosome 17 (for example, refer to, Rosso SM, and 3 others, Coexistent tau andamyloid pathology in hereditary frontotemporal dementia with tau mutations, Annals of the New York academy of sciences, 2000, 920, p. 115-119), Dementia with argyrophilic grains (for example, refer to, Tolnay M, and 4 others, Low amyloid (Aβ) plaque load and relative predominance of diffuse plaques distinguish argyrophilic grain disease from Alzheimer's disease, Neuropathology and applied neurobiology, 1999, Aug, 25 (4), p. 295-305), Niemann-Pick disease (for example, refer to, Jin LW, and 3 others, Intracellular accumulation of amyloidogenic fragments of amyloid-β precursor protein in neurons with Niemann-Pick type C defects is associated with endosomal abnormalities, American Journal of Pathology, 2004, Mar, 164 (3), p. 975-985), amyotrophic lateral sclerosis (for example, refer to, Sasaki S, and another, Immunoreactivity of β-amyloid precursor protein in amyotrophic lateral sclerosis, Acta Neuropathologica (Berl), 1999, May, 97 (5), p. 463-468; Tamaoka A, and 4 others, Increased amyloid β protein in the skin of patients with amyotrophic lateral sclerosis, Journal of neurology,

2000, Aug, 247 (8), p. 633-635; Hamilton RL, and another, Alzheimer disease pathology in amyotrophic lateral sclerosis, Acta Neuropathologica, 2004, Jun, 107 (6), p. 515-522; Turner BJ, and 6 others, Brain β-amyloidaccumulation in transgenic mice expressing mutant superoxide dismutase 1, Neurochemical Research, 2004, Dec, 29 (12), p. 2281-2286), hydrocephalus (for example, refer to, Weller RO, Pathology of cerebrospinal fluid and interstitial fluid of the CNS: Significance for Alzheimer's disease, prion disorders and multiple sclerosis, Journal of Neuropathology and Experimental Neurology, 1998, Oct, 57 (10), p. 885-894; Silverberg GD, and 4 others, Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis, Lancet neurology, 2003, Aug, 2 (8), p. 506-511; Weller RO, and 3 others, Cerebral amyloid angiopathy: Accumulation of Aβ in interstitial fluid drainage pathways in Alzheimer's disease, Annals of the New York academy of sciences, 2000, Apr, 903, p. 110-117; Yow HY, and another, A role for cerebrovascular disease in determining the pattern of β-amyloid deposition in Alzheimer's disease, Neurology and applied neurobiology, 2002, 28, p. 149; Weller RO, and 4 others, Cerebrovascular disease is a major factor in the failure of elimination of Aβ from the aging human brain, Annals of the New York academy of sciences, 2002, Nov, 977, p. 162-168), paraparesis (for example, refer to, O'Riordan S, and 7 others, Presenilin-1 mutation (E280G), spastic paraparesis, and cranial MRI white-matter abnormalities, Neurology, 2002, Oct 8, 59 (7), p. 1108-1110; Matsubara-Tsutsui M, and 7 others, Molecular evidence of presenilin 1 mutation in familial early onset dementia, American journal of Medical Genetics, 2002, Apr 8, 114 (3), p. 292-298; Smith MJ, and 11 others, Variable phenotype of Alzheimer's disease with spastic paraparesis, Annals of Neurology, 2001, 49 (1), p. 125-129; Crook R, and 17 others, A variant of Alzheimer's disease with spastic pararesis and unusual plaques due to deletion of exon 9 of presenilin 1, Nature Medicine, 1998, Apr;4 (4), p. 452-455), progressive supranuclear palsy (for example, refer to, Barrachina M, and 6 others, Amyloid-β deposition in the cerebral cortex in Dementia with Lewy bodies is accompanied by a relative increase in AβPP mRNA isoforms containing the Kunitz protease inhibitor, Neurochemistry International, 2005, Feb, 46 (3), p. 253-260; Primavera J, and 4 others, Brain accumulation of amyloid-β in Non-Alzheimer Neurodegeneration, Journal of Alzheimer's Disease, 1999, Oct, 1 (3), p. 183-193), cerebral hemorrhage (for example, refer to, Atwood CS, and 3 others, Cerebrovascular requirement for sealant, anti-coagulant and remodeling molecules that allow for the maintenance of vascular integrity and blood supply, Brain Research Reviews, 2003, Sep, 43 (1), p. 164-78; Lowenson JD, and 2 others, Protein aging: Extracellular amyloid formation and intracellular repair, Trends in cardiovascular medicine, 1994, 4 (1), p. 3-8), spasm (for example,

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[0039]

Various definitions in the present specification will be described below.

[0040]

R_1 and R_2 are the same or different and each represent a substituent selected from the following Substituent Group a1.

[0041]

The "Substituent Group a1" refers to a group consisting of a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkenyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, an amino group (wherein the amino group may have one C2-6 acyl group or C1-6 alkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group and a nitro group. Among these, a C1-6 alkyl group, a C3-8 cycloalkyl group, a halogen atom, a C1-6 alkoxy group and a C3-8 cycloalkyloxy group are preferable, and a C1-6 alkyl group, a halogen atom and a C1-6 alkoxy group are particularly preferable.

[0042]

m represents an integer of 0 to 3 and is preferably 0 to 2, and particularly preferably 1 to 2.

[0043]

n represents an integer of 0 to 2 and is preferably 0 to 1, and particularly preferably 1.

[0044]

X_1 represents i) a single bond, ii)

[0045]

—C≡C—

[0046]

or iii) $-CR_3=CR_4-$ (wherein R_3 and R_4 are the same or different and each represent (1) a hydrogen atom, (2) a C1-6 alkyl group or (3) a halogen atom).

X_2 represents i) a single bond, ii) a C1-6 alkylene group or iii) $-X_3-$ (wherein X_3 represents $-NR_5-$, -O-, -C(O)-, -S-, -S(O)- or $-S(O)_2-$ and R_5 represents a hydrogen atom, a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkanoyl group or a C1-6 alkylsulfonyl group), and is preferably i) a single bond or ii) $-CR_3=CR_4-$.

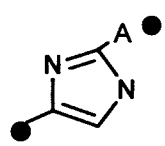
[0047]

Ring A represents i) a five-membered aromatic heterocyclic group or ii) a five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group, which contains two or more nitrogen atoms and may have 1 to 3 substituents selected from the following Substituent Group b1 (wherein the non-aromatic ring group may have a crosslinked structure or a spiro ring system).

[0048]

The "five-membered aromatic heterocyclic group" is not particularly limited insofar as it is a five-membered aromatic heterocyclic group containing two or more nitrogen atoms. The group preferably refers to a five-membered aromatic heterocyclic group selected from the group consisting of the formulas [20] to [26]:

[0049]



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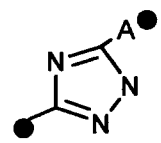

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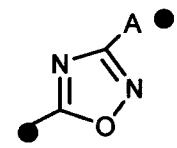

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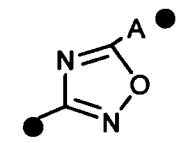

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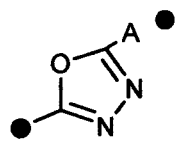

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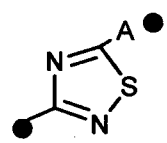

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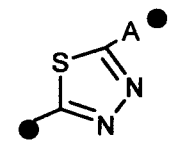
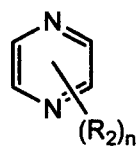


26

[0050]

wherein • represents a bonding site to the formula [27]:

[0051]

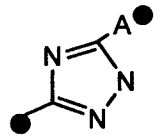


27 and

[0052]

A• represents a bonding site to X_2, and more preferably refers to a ring of the formula [21]:

[0053]



21

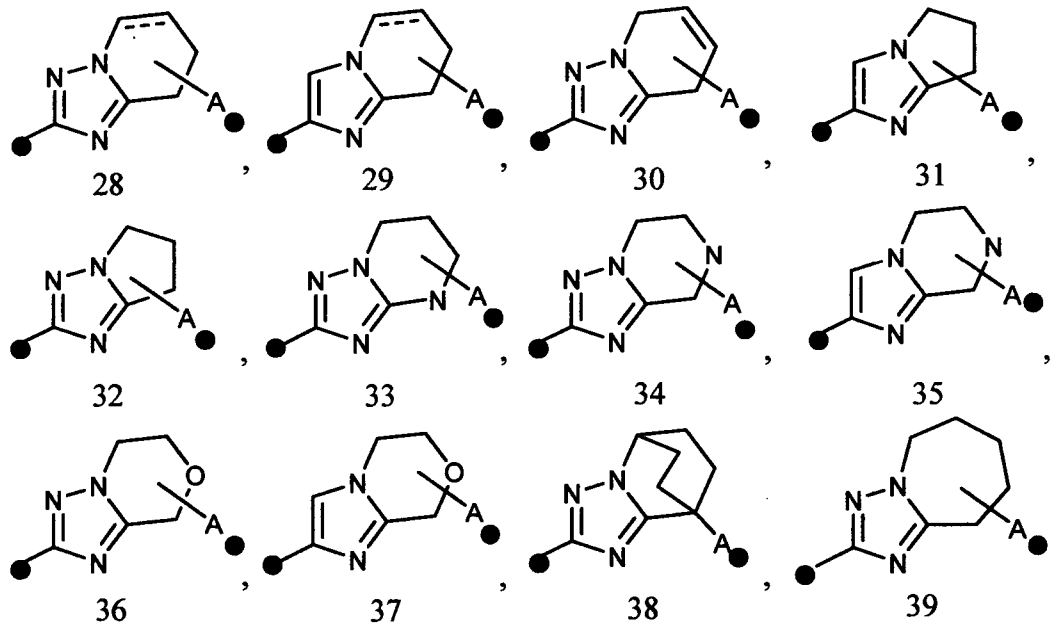
[0054]

The group may have 1 to 3 substituents selected from the following Substituent Group b1.

[0055]

The "five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group (wherein the non-aromatic ring group may have a crosslinked structure or a spiro ring system)" is not particularly limited insofar as it is a five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group which contains two or more nitrogen atoms (wherein non-aromatic ring group may have a crosslinked structure or a spiro ring system). The group is preferably any one ring selected from the group consisting of the formulas [28] to [39]:

[0056]



28, 29, 30, 31

32, 33, 34, 35

36, 37, 38, 39

[0057]

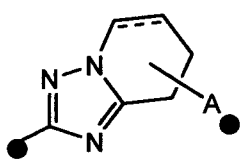
wherein • and A• are as defined above and the partial structure:

[0058]

[0059]

represents a single bond or a double bond, more preferably a ring selected from the group consisting of:

[0060]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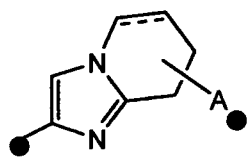
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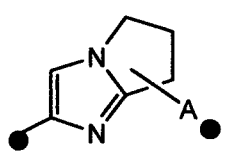
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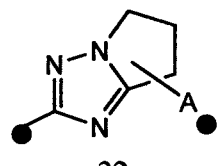
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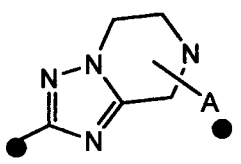
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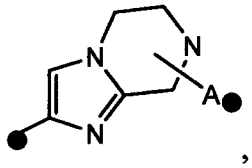
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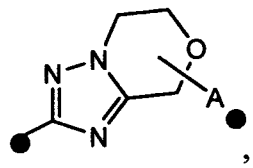
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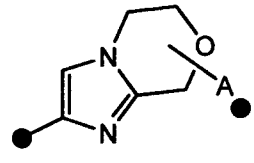

37

[0061]

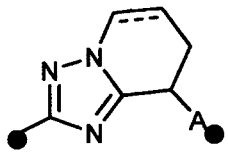
wherein •, A• and the partial structure:

[0062]

[0063]

are as defined above, and particularly preferably a ring selected from the group consisting of the formula [28-1]:

[0064]


28-1

[0065]

wherein •, A• and the partial structure:

[0066]

[0067]

are as defined above. The group may have 1 to 3 substituents selected from the following Substituent Group b1. The phrase "may have a crosslinked structure or a spiro ring system"

refers to the fact that two carbon atoms on the non-aromatic ring group together may form a crosslinked structure, or the fact that a carbon atom on the non-aromatic ring group may form a spiro ring system.

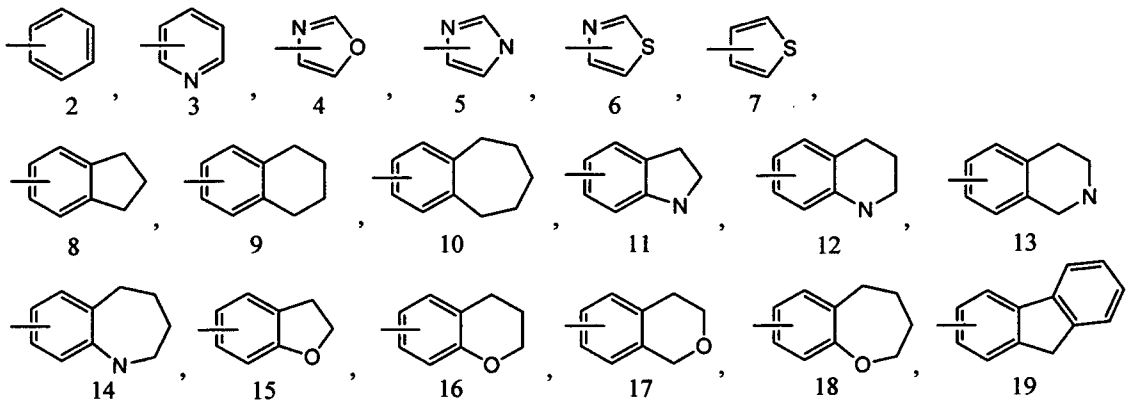
[0068]

The "Substituent Group b1" refers to a group consisting of a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C2-6 alkenyl group, a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C4-9 cycloalkylcarbonyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C2-6 alkenylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a C1-6 alkylthio group, a C2-6 alkenylthio group, a C3-8 cycloalkylthio group, an aminosulfonyl group (wherein the aminosulfonyl group may have 1 to 2 C1-6 alkyl groups, C2-6 alkenyl groups or C3-8 cycloalkyl groups), an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group, a nitro group, an oxo group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 1-homopiperidinyl group, an indolin-1-yl group, a 1,2,3,4-tetrahydroquinolin-1-yl group and a 4-morpholinyl group. Preferable among these is a substituent selected from the group consisting of a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a cyano group, a formyl group, a halogen atom, a hydroxyl group and an oxo group. Particularly preferable are a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C3-8 cycloalkyloxy group and a halogen atom.

[0069]

Ring B represents, for example, a monocyclic or fused cyclic aromatic ring group selected from the group consisting of the formulas [2] to [19]:

[0070]



[0071]

and is preferably a phenyl group, a pyridyl group, an oxazolyl group, an imidazolyl group, a thiazolyl group, a dihydrobenzofuranyl group or a thienyl group, and particularly preferably a phenyl group or a pyridyl group. Ring B may have 1 to 3 substituents selected from the following Substituent Group c1.

[0072]

The "Substituent Group c1" refers to a group consisting of i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C2-6 alkenyl group, v)-iii) a C2-6 alkynyl group, v)-iv) a C1-6 alkoxy group, v)-v) a C1-6 alkylthio group, v)-vi) a C1-6 alkylaminocarbonyl group, v)-vii) a C1-6 alkylsulfonyl group, v)-viii) a C1-6 alkylaminosulfonyl group, v)-ix) a C2-6 alkanoyl group, v)-x) a phenyl group, v)-xi) a pyridyl group, v)-xii) a pyridazinyl group, v)-xiii) a pyrimidinyl group, v)-xiv) a 1-pyrrolidinyl group, v)-xv) a 1-piperidinyl group, v)-xvi) a 1-homopiperidinyl group and v)-xvii) a 4-morpholinyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom. Preferable among these is a substituent selected from the group consisting of i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C1-6 alkoxy group, v)-iii) a C1-6 alkylthio group and v)-iv) a phenyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom. Particularly preferable is a substituent selected from the group consisting of i) a halogen atom and ii) ii)-i) a C1-6 alkyl group and ii)-ii) a C1-6 alkoxy group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl

group and a halogen atom.

[0073]

The "C1-6 alkyl group" refers to an alkyl group having 1 to 6 carbon atoms. Preferable examples of the group include linear or branched alkyl groups such as a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, a tertiary butyl group, an n-pentyl group, an isopentyl group, a neopentyl group, an n-hexyl group, a 1-methylpropyl group, an 1,2-dimethylpropyl group, a 1-ethylpropyl group, a 1-methyl-2-ethylpropyl group, a 1-ethyl-2-methylpropyl group, a 1,1,2-trimethylpropyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 2-ethylbutyl group, a 1,3-dimethylbutyl group, a 2-methylpentyl group and a 3-methylpentyl group.

[0074]

The "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or the like and is preferably a fluorine atom, a chlorine atom or a bromine atom.

[0075]

The "C1-6 alkylene group" refers to an alkylene group having 1 to 6 carbon atoms. Preferable examples of the group include linear or branched alkyl groups such as a methylene group, an ethylene group, a methylmethylene group, a propylene group, a methylethylene group, an ethylmethylene group, a dimethylmethylene group, a butylene group, a methylpropylene group, an ethylethylene group, a dimethylethylene group, a propylmethylene group, a pentylene group and a hexylene group. Among these, a methylene group, an ethylene group, a methylmethylene group, a propylene group, a methylethylene group, an ethylmethylene group and a dimethylmethylene group are preferable, for example.

[0076]

The "C3-8 cycloalkyl group" refers to a cyclic alkyl group having 3 to 8 carbon atoms. Preferable examples of the group include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group and a cycloheptyl group.

[0077]

The "C2-6 alkanoyl group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is substituted with a carbonyl group. Preferable examples of the group include an acetyl group, a propionyl group and a butyryl group.

[0078]

The "C1-6 alkylsulfonyl group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the

group include a methanesulfonyl group and an ethanesulfonyl group.

[0079]

The "C2-6 alkenyl group" refers to an alkenyl group having 2 to 6 carbon atoms. Preferable examples of the group include linear or branched alkenyl groups such as a vinyl group, an allyl group, a 1-propenyl group, an isopropenyl group, a 1-buten-1-yl group, a 1-buten-2-yl group, a 1-buten-3-yl group, a 2-buten-1-yl group and a 2-buten-2-yl group.

[0080]

The "C1-6 alkoxy group" refers to an alkyl group having 1 to 6 carbon atoms in which a hydrogen atom is replaced by an oxygen atom. Preferable examples of the group include a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a sec-butoxy group, a tertiary butoxy group, an n-pentoxy group, an isopentoxy group, a sec-pentoxy group, a tertiary pentoxy group, an n-hexoxy group, an isohexoxy group, a 1,2-dimethylpropoxy group, a 2-ethylpropoxy group, a 1-methyl-2-ethylpropoxy group, a 1-ethyl-2-methylpropoxy group, a 1,1,2-trimethylpropoxy group, a 1,1,2-trimethylpropoxy group, a 1,1-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 2-ethylbutoxy group, a 1,3-dimethylbutoxy group, a 2-methylpentoxy group and a 3-methylpentoxy group.

[0081]

The "C2-6 alkenyloxy group" refers to an alkenyl group having 2 to 6 carbon atoms in which one hydrogen atom is replaced by an oxygen atom. Preferable examples of the group include linear or branched alkenyloxy groups such as a vinyloxy group, an allyloxy group, a 1-propenyloxy group, an isopropenyloxy group, a 1-buten-1-yloxy group, a 1-buten-2-yloxy group, a 1-buten-3-yloxy group, a 2-buten-1-yloxy group and a 2-buten-2-yloxy group.

[0082]

The "C3-8 cycloalkyloxy group" refers to a cyclic alkyl group having 3 to 8 carbon atoms in which one hydrogen atom is replaced by an oxygen atom. Preferable examples of the group include a cyclopropoxy group, a cyclobutoxy group, a cyclopentoxy group, a cyclohexoxy group and a cycloheptyloxy group.

[0083]

The "C6-14 aryl group" refers to an aromatic hydrocarbon group having 6 to 14 carbon atoms. Preferable examples of the group include a phenyl group, a naphthyl group, an anthryl group and a phenanthryl group.

[0084]

The "C6-14 aryl-C1-6 alkyl group" refers to an alkyl group having 1 to 6 carbon

atoms in which one hydrogen atom is replaced by the aforementioned "C6-14 aryl group". Preferable examples of the group include a benzyl group, a phenethyl group, a phenylpropyl group, a naphthylmethyl group, a naphthylethyl group and a naphthylpropyl group.

[0085]

The "C4-9 cycloalkylcarbonyl group" refers to a cyclic alkyl group having 3 to 8 carbon atoms substituted with a carbonyl group. Preferable examples of the group include a cyclopropylcarbonyl group, a cyclobutylcarbonyl group, a cyclopentylcarbonyl group, a cyclohexylcarbonyl group and a cycloheptylcarbonyl group.

[0086]

The "C7-15 aroyl group" refers to the aforementioned "C6-14 aryl group" substituted with a carbonyl group. Preferable examples of the group include a benzoyl group, a naphthylcarbonyl group and an anthrylcarbonyl group.

[0087]

The "C2-6 alkenylsulfonyl group" refers to an alkenyl group having 2 to 6 carbon atoms in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the group include linear or branched alkenylsulfonyl groups such as a vinylsulfonyl group, an allylsulfonyl group, a 1-propenylsulfonyl group, an isopropenylsulfonyl group, a 1-buten-1-ylsulfonyl group, a 1-buten-2-ylsulfonyl group, a 1-buten-3-ylsulfonyl group, a 2-buten-1-ylsulfonyl group and a 2-buten-2-ylsulfonyl group.

[0088]

The "C3-8 cycloalkylsulfonyl group" refers to a cyclic alkyl group having 3 to 8 carbon atoms in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the group include a cyclopropylsulfonyl group, a cyclobutylsulfonyl group, a cyclopentylsulfonyl group, a cyclohexylsulfonyl group and a cycloheptylsulfonyl group.

[0089]

The "C6-14 arylsulfonyl group" refers to an aromatic hydrocarbon group having 6 to 14 carbon atoms in which one hydrogen atom is replaced by a sulfonyl group. Preferable examples of the group include a phenylsulfonyl group, a naphthylsulfonyl group and an anthrylsulfonyl group.

[0090]

The "C1-6 alkylthio group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is replaced by a sulfur atom. Preferable examples of the group include a methylthio group, an ethylthio group, an n-propylthio group, an isopropylthio group, an n-butylthio group, an isobutylthio group, a tert-butylthio group, an n-pentylthio group, an

isopentylthio group, a neopentylthio group, an n-hexylthio group and a 1-methylpropylthio group.

[0091]

The "C2-6 alkenylthio group" refers to an alkenylthio group having 2 to 6 carbon atoms. Preferable examples of the group include linear or branched alkenylthio groups such as a vinylthio group, an allylthio group, a 1-propenylthio group, an isopropenylthio group, a 1-buten-1-ylthio group, a 1-buten-2-ylthio group, a 1-buten-3-ylthio group, a 2-buten-1-ylthio group and a 2-buten-2-ylthio group.

[0092]

The "C3-8 cycloalkylthio group" refers to a cyclic alkyl group having 3 to 8 carbon atoms in which one hydrogen atom is replaced by a sulfur atom. Preferable examples of the group include a cyclopropylthio group, a cyclobutylthio group, a cyclopentylthio group, a cyclohexylthio group and a cycloheptylthio group.

[0093]

Examples of the "aminosulfonyl group which may have 1 to 2 C1-6 alkyl groups, C2-6 alkenyl groups or C3-8 cycloalkyl groups" include an aminosulfonyl group as well as a methylaminosulfonyl group, an ethylaminosulfonyl group, a dimethylaminosulfonyl group, a diethylaminosulfonyl group, a vinylaminosulfonyl group, an allylaminosulfonyl group, a cyclopropylaminosulfonyl group, a cyclobutylaminosulfonyl group and a cyclohexylaminosulfonyl group.

[0094]

Examples of the "amino group which may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups" include an amino group as well as an acetylamino group, an propionylamino group, a methanesulfonylamino group, an ethanesulfonylamino group, a pentanesulfonylamino group, a methylamino group, a dimethylamino group, an ethylamino group, a diethylamino group, a cyclopropylamino group, a cyclobutylamino group and a cyclohexylamino group.

[0095]

The "C1-6 alkylaminocarbonyl group" refers to an alkyl group having 1 to 6 carbon atoms in which one hydrogen atom is replaced by an aminocarbonyl group. Preferable examples of the group include a methylaminocarbonyl group, an ethylaminocarbonyl group, a propylaminocarbonyl group, a butylaminocarbonyl group and a hexylaminocarbonyl group.

[0096]

The "C1-6 alkylaminosulfonyl group" refers to an alkyl group having 1 to 6

carbon atoms in which one hydrogen atom is replaced by an aminosulfonyl group. Preferable examples of the group include a methylaminosulfonyl group, an ethylaminosulfonyl group, a propylaminosulfonyl group, a butylaminosulfonyl group and a hexylaminosulfonyl group.

[0097]

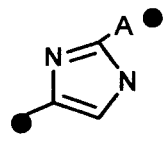
In the present invention, the "pharmacologically acceptable salt" is not particularly limited insofar as it is a pharmacologically acceptable salt formed with the compound of the general formula (I) which is a therapeutic agent for a disease caused by Aβ. Preferable specific examples of the salt include hydrohalides (such as hydrofluorides, hydrochlorides, hydrobromides and hydroiodides), inorganic acid salts (such as sulfates, nitrates, perchlorates, phosphates, carbonates and bicarbonates), organic carboxylates (such as acetates, oxalates, maleates, tartrates, fumarates and citrates), organic sulfonates (such as methanesulfonates, trifluoromethanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates and camphorsulfonates), amino acid salts (such as aspartates and glutamates), quaternary amine salts, alkali metal salts (such as sodium salts and potassium salts) and alkali earth metal salts (such as magnesium salts and calcium salts).

[0098]

Next, the compound of the formula (I) according to the present invention will be described.

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, Ring A is preferably a five-membered aromatic heterocyclic group selected from the group consisting of the formulas [20] to [26]:

[0099]



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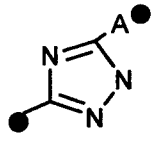

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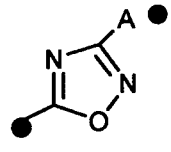

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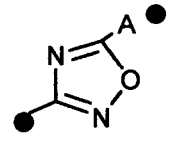

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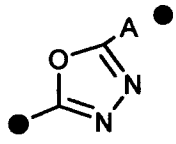

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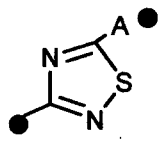

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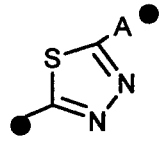
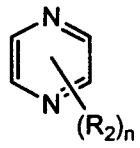


26

[0100]

wherein • represents a bonding site to the formula [27]:

[0101]

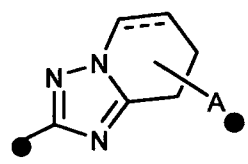


27 and

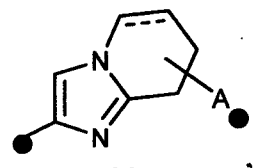
[0102]

A• represents a bonding site to X_2, or any one ring selected from the group consisting of the formulas [28] to [39]:

[0103]



28



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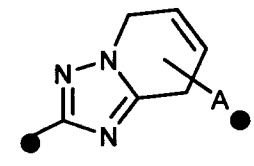

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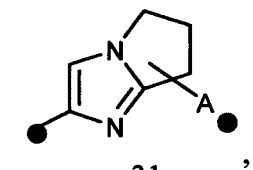

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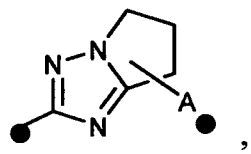

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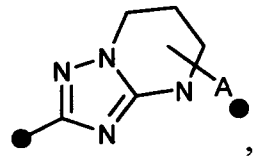

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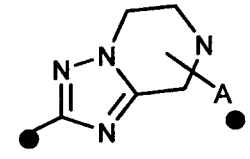

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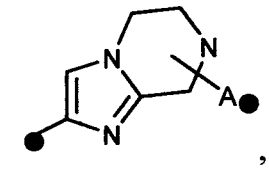

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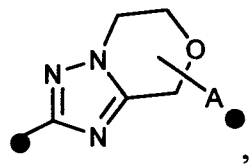

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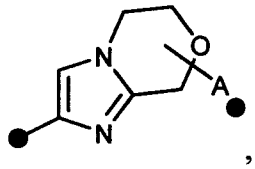

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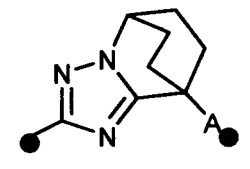

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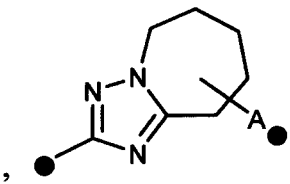


39

[0104]

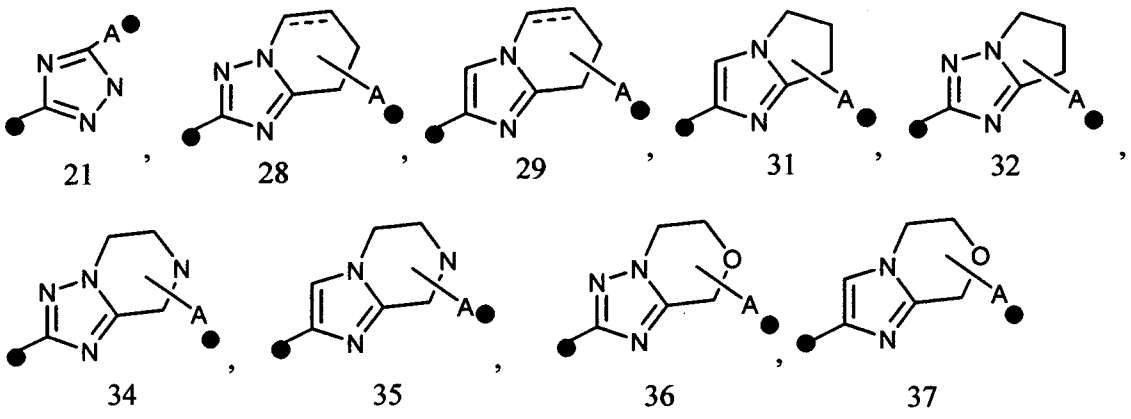
wherein • and A• are as defined above and the partial structure:

[0105]

[0106]

represents a single bond or a double bond, each of which may have 1 to 3 substituents selected from Substituent Group b1. Ring A is more preferably any one ring selected from the group consisting of the formulas [21], [28], [29], [31], [32] and [34] to [37]:

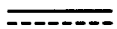
[0107]



[0108]

wherein •, A• and the partial structure:

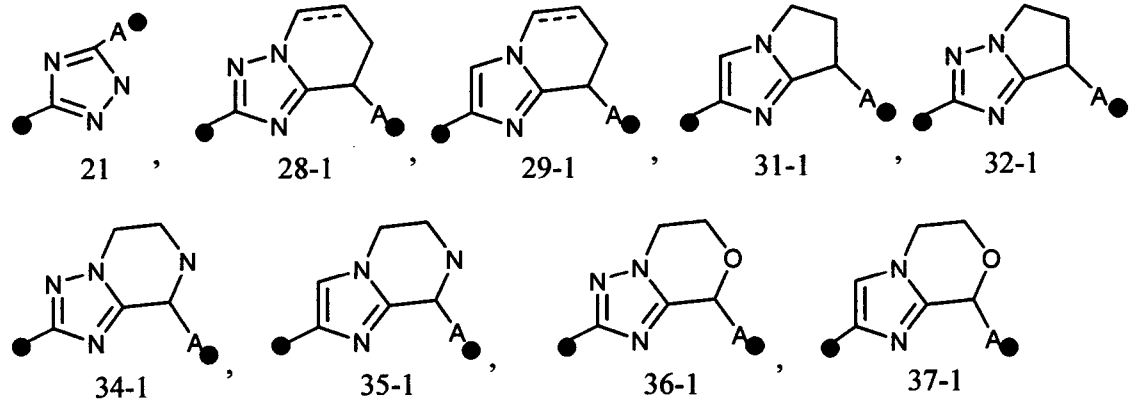
[0109]



[0110]

are as defined above. Ring A is particularly preferably any one ring selected from the group consisting of the formulas [21], [28-1], [29-1], [31-1], [32-1] and [34-1] to [37-1]:

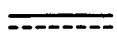
[0111]



[0112]

wherein •, A• and the partial structure:

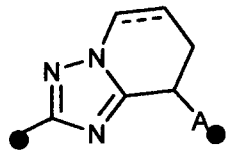
[0113]



[0114]

are as defined above. Ring A is most preferably a ring of the formula [28-1]:

[0115]



28-1

[0116]

wherein •, A• and the partial structure:

[0117]

[0118]

are as defined above.

[0119]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, Ring B is preferably a phenyl group, a pyridyl group, an oxazolyl group, an imidazolyl group, a thiazolyl group, a dihydrobenzofuranyl group or a thienyl group, and more preferably a phenyl group.

[0120]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, X_1 is preferably i) a single bond or ii) $-CR_3=CR_4-$.

[0121]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, X_2 is preferably i) a single bond or ii) a C1-6 alkylene group, and X_2 is more preferably a single bond.

[0122]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, preferably, R_1 is a C1-6 alkyl group or a halogen atom and m is 1 to 2.

[0123]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, preferably, R_2 is a C1-6 alkoxy group and n is 1.

[0124]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, preferably, R_3 and R_4 are the same or different and are each (1) a hydrogen atom or (2) a halogen atom. More preferably, R_3 and R_4 are both hydrogen atoms.

[0125]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, the substituent for Ring A is preferably a substituent selected from the group consisting of a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a cyano group, a formyl group, a halogen atom, a hydroxyl group and an oxo group.

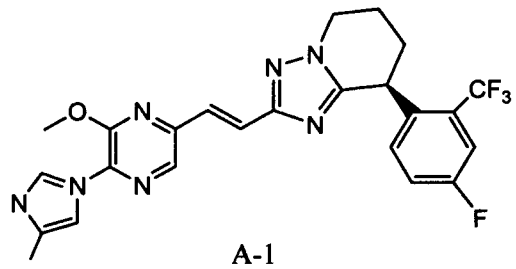
[0126]

In the compound of the formula (I) or pharmacologically acceptable salt or ester thereof, the substituent for Ring B is preferably a substituent selected from the group consisting of i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C1-6 alkoxy group, v)-iii) a C1-6 alkylthio group and v)-iv) a phenyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom.

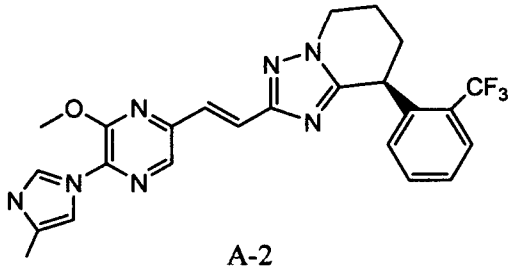
[0127]

At least one compound selected from the group consisting of the following formulas [A-1] to [A-7]:

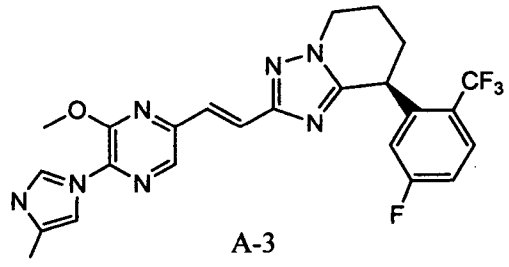
[0128]



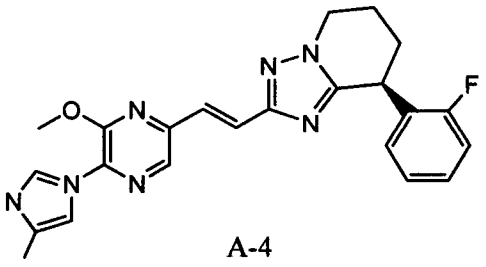
A-1



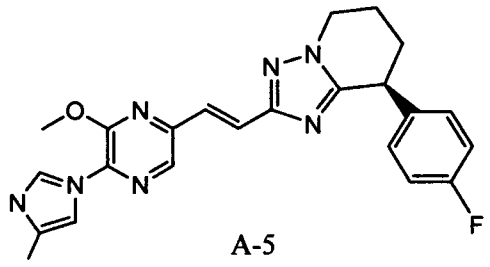
A-2



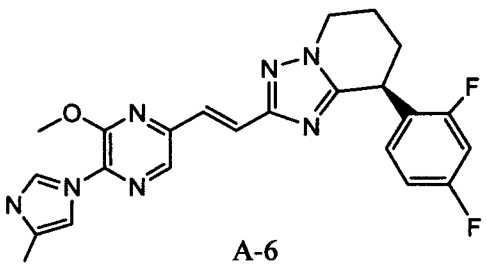
A-3



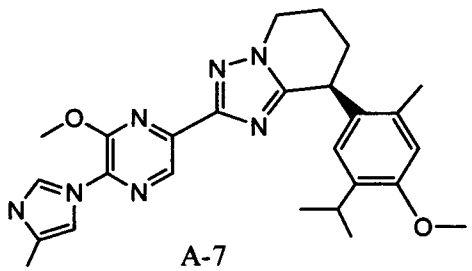
A-4



A-5



A-6



A-7

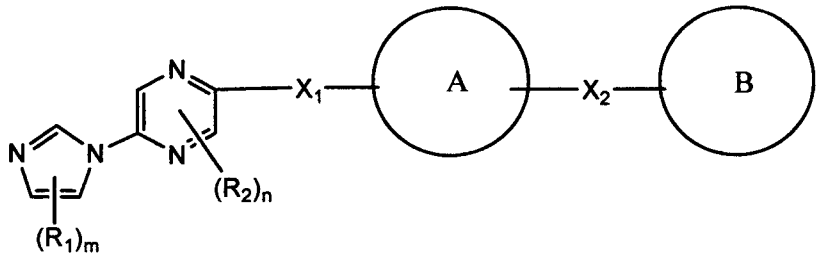
or a pharmacologically acceptable salt thereof is particularly suitable, for example, and is useful as a therapeutic agent for a disease caused by amyloid-β such as Alzheimer's disease, senile dementia, Down's syndrome or amyloidosis.

[0129]

Methods for preparing the compound of the general formula (I) according to the present invention will be described below.

The compound represented by the general formula [I]:

[0130]



[I]

[0131]

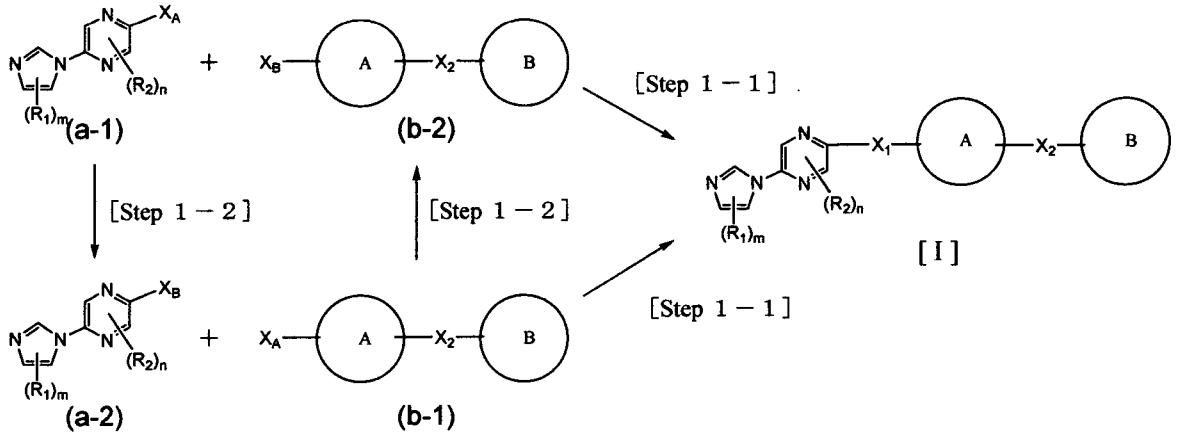
wherein R_1, R_2, X_1, X_2, m, n, Ring A and Ring B are as defined above, is synthesized according to a method such as the following General Preparation Method 1 and General Preparation Method 2, for example. It is obvious that, in order to prepare the compound of the present invention conveniently, the method comprises a protection reaction step and a deprotection reaction step appropriately, using a protecting group known to a person skilled in the art which is suitably selected for each step (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981). It is obvious that, in order to prepare the compound of the present invention conveniently, the method comprises substituent conversion, substituent introduction and the like suitable for each step and known to a person skilled in the art. It is also obvious that, in order to prepare the compound of the present invention conveniently, all isomers and isomer mixtures such as geometric isomers which can be generated from the structure of the compound, optical isomers based on asymmetric carbon, stereoisomers, and tautomers can be prepared as a single compound by a technique known to a person skilled in the art which is suitable for each step such as fractional crystallization or column chromatography.

[0132]

General Preparation Method 1

Typically used General Preparation Method 1 for the compound of the general formula [I] according to the present invention will be described below.

[0133]



[0134]

In the formula, R_1, R_2, X_1, X_2, m, n, Ring A and Ring B are as defined above; X_A represents a halogen atom such as a chlorine atom, a bromine atom or an iodine atom or a sulfonate group such as a methanesulfonate group, a p-toluenesulfonate group or a trifluoromethanesulfonate group; and X_B represents a trialkylstannyl group, a boronic acid group, a boronate group such as a pinacol boronate group, alkylboronalkenyl group, a C2-6 alkenyl group or a C2-6 alkynyl group.

[0135]

The above General Preparation Method 1 is a method for preparing the compound of the general formula [I] by subjecting to coupling reaction in Step 1-1 a compound of the general formula (a-1) and a compound of the general formula (b-2) or a method for preparing the compound of the general formula [I] by subjecting to coupling reaction in Step 1-1 a compound of the general formula (a-2) and a compound of the general formula (b-1) in which the substituents X_A and X_B are replaced by each other.

The coupling reaction in Step 1-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include Mizoroki-Heck reaction (see R.F. Heck, "Org. Reactions.", 1982, vol. 27, p. 345, for example), Suzuki-Miyaura reaction (see A. Suzuki, "Chem. Rev.", 1995, vol. 95, p. 2457, for example), Sonogashira reaction (see K. Sonogashira, "Comprehensive Organic Synthesis", 1991, vol. 3, p. 521, for example) and Stille coupling reaction (see J.K. Stille, "Angew. Chem. Int. Ed. Engl.", 1986, vol. 25, p. 508, for example).

[0136]

In Mizoroki-Heck reaction, a halogen compound or trifluoromethanesulfonate

group compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a compound of the general formula (b-2) (wherein X_B is preferably a C2-6 alkenyl group) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring efficiency. The solvent used varies according to the starting material and the transition metal catalyst used, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone and N,N-dimethylformamide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. The transition metal catalyst is preferably a palladium complex, for example, and more preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). It is also preferable to appropriately add a phosphine ligand (preferably triphenylphosphine, tri-o-tolylphosphine, tri-tert-butylphosphine or 2-(di-tert-butylphosphino)biphenyl, for example) in order to make the reaction efficiently proceed. A preferable result may be achieved in the presence of a base. The base used is not particularly limited insofar as it is used in a coupling reaction similar to this reaction. Preferable examples of the base include triethylamine, N,N-diisopropylethylamine, N,N-dicyclohexylmethylamine and tetrabutylammonium chloride. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0137]

In Suzuki-Miyaura reaction, a halogen compound or trifluoromethanesulfonate compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a compound of the general formula (b-2) (wherein X_B is preferably a boronic acid group, a boronate group such as a pinacol boronate group, an alkylboronalkenyl group or the like) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.5 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring efficiency. The solvent used varies according to the starting

material and the transition metal catalyst used, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone, N,N-dimethylformamide, water and a mixed solvent thereof. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 200°C. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. The transition metal catalyst is preferably a known palladium complex, and more preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). A phosphorus ligand (preferably triphenylphosphine, tri-o-tolylphosphine, tricyclohexylphosphine or tri-tert-butylphosphine, for example) may be appropriately added in order to make the reaction efficiently proceed. A quaternary ammonium salt, preferably tetrabutylammonium chloride or tetrabutylammonium bromide, for example, may also be appropriately added in order to make the reaction efficiently proceed. In this reaction, a preferable result may be achieved in the presence of a base. The base used at this time varies according to the starting material, the solvent used and the like, and is not particularly limited. Preferable examples of the base include sodium hydroxide, barium hydroxide, potassium fluoride, cesium fluoride, sodium carbonate, potassium carbonate, cesium carbonate and potassium phosphate. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0138]

The Sonogashira reaction vary according to the starting material, the solvent and the transition metal catalyst, and are not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferably, a compound of the general formula (a-1) is coupled with 1.0 to 5.0 equivalents of a compound of the general formula (b-2) (wherein X_B is preferably a C2-6 alkynyl group) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. Preferable examples of the solvent used include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone, N,N-dimethylformamide and dimethyl sulfoxide. More preferable examples of the solvent include

tetrahydrofuran, 1,4-dioxane, 1-methyl-2-pyrrolidone and N,N-dimethylformamide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. The transition metal catalyst is, for example, a known palladium complex, and more preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). A phosphorus ligand (preferably triphenylphosphine, tri-o-tolylphosphine or tri-tert-butylphosphine, for example) may be appropriately added, for example, in order to make the reaction efficiently proceed. In the reaction, it is possible to add a metal halide or a quaternary ammonium salt, preferably copper (I) iodide, lithium chloride, tetrabutylammonium fluoride or silver (I) oxide, for example. A preferable result may be achieved in the presence of a base. The base used here is not particularly limited insofar as it is used in a coupling reaction similar to this reaction. Preferable examples of the base include basic solvents such as diethylamine, triethylamine, N,N-diisopropylethylamine, piperidine and pyridine.

[0139]

In Stille coupling reaction, a halogen compound or trifluoromethanesulfonate group compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a compound of the general formula (b-2) (wherein X_B is preferably a trialkylstannyl group) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. It is preferable to appropriately use in this reaction 0.1 to 5.0 equivalents of copper (I) halide or/and lithium chloride in order to make the reaction efficiently proceed. Preferable examples of the solvent used in this reaction include toluene, xylene, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and dimethyl sulfoxide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. The preferable transition metal catalyst is a palladium complex, preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0), for example, and more preferably palladium (II) acetate, tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0), for example. A phosphorus ligand (preferably triphenylphosphine, tri-o-tolylphosphine, 1,3-

bis(diphenylphosphino)propane or tri-tert-butylphosphine, for example) may be appropriately added, for example, in order to make the reaction efficiently proceed. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0140]

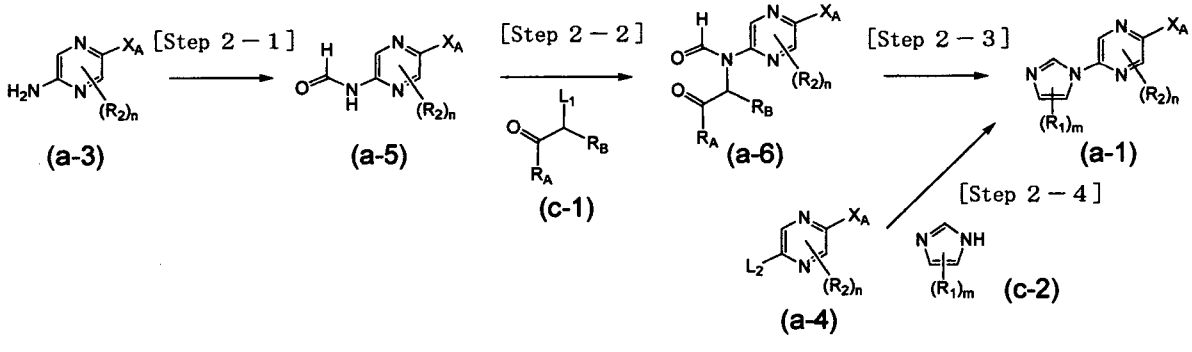
Step 1-2 is an example of a method for preparing a compound of the general formula (a-2) and a compound of the general formula (b-2) in which the substituents X_A and X_B are replaced by each other. This step varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. The same method as in Step 1-1 may be preferably used such as Mizoroki-Heck reaction (see R.F. Heck, "Org. Reactions.", 1982, vol. 27, p. 345, for example), Suzuki-Miyaura reaction (see A. Suzuki, "Chem. Rev.", 1995, vol. 95, p. 2457, for example), Sonogashira reaction (see K. Sonogashira, "Comprehensive Organic Synthesis", 1991, vol. 3, p. 521, for example) or Stille coupling reaction (see J.K. Stille, "Angew. Chem. Int. Ed. Engl.", 1986, vol. 25, p. 508, for example).

The compound of the formula (a-1), the compound of the formula (a-2), the compound of the formula (b-1) and the compound of the formula (b-2) are known or commercially available compounds or are compounds that can be prepared from these compounds by a conventional method.

[0141]

Preparation of compound of general formula (a-1)

[0142]



[0143]

In the formula, R_1, R_2, m, n and X_A are as defined above; R_A and R_B are as defined for R_1 above; L_1 represents a halogen atom such as a chlorine atom, a bromine atom or an iodine atom or a sulfonate group such as a methanesulfonate group, a p-toluenesulfonate group or a trifluoromethanesulfonate group; and L_2 represents a halogen atom such as a chlorine

atom, a bromine atom or an iodine atom, a sulfonate group such as a methanesulfonate group, a p-toluenesulfonate group or a trifluoromethanesulfonate group or a boronic acid group.

[0144]

The compound of the general formula (a-1) can be prepared from an amine compound (a-3) as a starting material through formylation in Step 2-1, coupling reaction in Step 2-2 and formation of an imidazole ring in Step 2-3, or can be prepared from a compound of the general formula (a-4) as a starting material by coupling reaction in Step 2-4.

[0145]

Step 2-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used.

[0146]

Step 2-2 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of stirring a compound of the general formula (a-5) and 1.0 to 10.0 equivalents of a compound of the general formula (c-1) with respect to the compound of the general formula (a-5) in a solvent in the presence of 1.0 to 10.0 equivalents of a base with respect to the compound of the general formula (a-5). The base used varies according to the starting material and is not particularly limited. Preferable examples of the base include alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate) and metal alkoxides (such as sodium methoxide and potassium tert-butoxide). The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixtures thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably 0°C to 200°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product

can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0147]

Step 2-3 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemistry of Heterocyclic Compounds. Imidazole and Derivatives, Part I, p. 33, Inters. Publish. 1953) may be used. Preferable examples of the method include a method for preparing the compound of the general formula (a-1) by forming an imidazole ring from a compound of the general formula (a-6) and ammonia, ammonium salt, formamide or the like as a nitrogen source. The solvent used is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include non-polar solvents such as toluene and benzene; alcohol solvents such as methanol and ethanol; organic acids such as acetic acid or trifluoroacetic acid, sulfonic acids such as p-toluenesulfonic acid and trifluoromethanesulfonic acid; water; and mixtures thereof. Formamide may optionally be used as a nitrogen atom source and as a solvent. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 250°C, for example. The yield may be improved when the reaction is performed using a tight container. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0148]

The coupling reaction in Step 2-4 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in D.D. Davey et al., "J. Med. Chem.", 1991, vol. 34, p. 2671-2677) may be used. Examples of the method include a method of stirring a compound of the general formula (a-4) and 1.0 to 5.0 equivalents of an imidazole compound (c-2) with respect to the compound of the general formula (a-4) in a solvent in the presence or absence of 1.0 to 5.0 equivalents of a base with respect to the compound of the general formula (a-4). Preferable examples of the base used include sodium hydride, sodium hydroxide, potassium hydroxide,

potassium carbonate, sodium carbonate, cesium carbonate, barium carbonate, pyridine, lutidine and triethylamine. The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, dimethyl sulfoxide, N,N-dimethylformamide and N-methylpyrrolidine. The base may optionally be used as a solvent. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 150°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique or/and crystallization.

Examples of the coupling reaction in Step 2-4 include a method of stirring a compound of the general formula (a-4) (wherein L_2 is preferably a boronic acid group or the like) in a solvent in the presence of a copper catalyst (such as described in J.P. Collman et al., "Org. Letters.", 2000, vol. 2, p. 1233-1236). Preferable examples of the method include a method of stirring a compound of the general formula (a-4) and 0.1 to 10.0 equivalents of an imidazole compound (c-2) with respect to the compound of the general formula (a-4) in a solvent in the presence of 0.01 to 1.0 equivalent of a copper reagent such as copper, copper bromide or copper iodide with respect to the compound of the general formula (a-4). The copper reagent used varies according to the starting material and is not particularly limited. Preferable examples of the copper reagent include copper (I) halide, copper (II) acetate, copper (II) nitrate and di-μ-hydroxo-bis[(N,N,N',N'-tetramethylethylenediamine)copper (II)] chloride. The solvent used varies according to the starting material, the reagent and the like, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as ethyl acetate, N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene, benzene and dichlorobenzene; and mixtures thereof. A base may be used depending on the starting material, the reagent and the like. Preferable examples of the base include organic bases such as triethylamine, pyridine and tetramethylethylenediamine; alkali metal salts such as potassium carbonate, sodium carbonate, potassium acetate, sodium acetate and cesium carbonate; and metal alkoxides such as sodium methoxide and potassium tert-butoxide. The reaction temperature

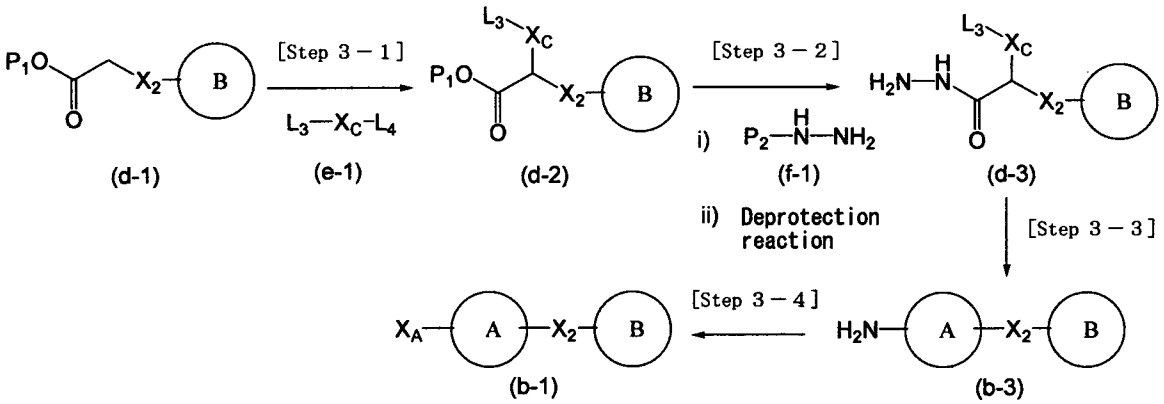
must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 200°C, for example. Good results such as reduction in the reaction time and improvement of the yield can be achieved when the reaction is performed in an oxygen atmosphere or air stream. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

The compound of the formula (a-3), the compound of the formula (a-4), the compound of the formula (c-1) and the compound of the formula (c-2) are known or commercially available compounds or are compounds that can be prepared from these compounds by a conventional method.

[0149]

Preparation of compound of general formula (b-1)

[0150]



[0151]

In the formula, X_2, X_A, Ring A and Ring B are as defined above; L_3 and L_4 are as defined for L_1 above; X_C represents a C2-4 alkylene group, or a C2-3 alkylene group in which one methylene group is replaced by an oxygen atom or a nitrogen atom (wherein the nitrogen atom may have a substituent such as a C1-6 alkyl group or a benzyl group); P_1 represents a carboxyl-protecting group such as a methyl group, an ethyl group, a benzyl group, an allyl group, a triphenylmethyl group, a tert-butyl group or a tert-butyldimethylsilyl group, or a hydrogen atom; and P_2 represents a nitrogen-protecting group such as a tert-butoxycarbonyl group or a benzyloxycarbonyl group.

[0152]

The compound of the general formula (b-1) can be prepared from a compound of

the general formula (d-1) as a starting material through alkylation in Step 3-1, hydrazidation and deprotection reaction in Step 3-2, formation of Ring A in Step 3-3 and Sandmeyer reaction in Step 3-4.

[0153]

Step 3-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of stirring a compound of the general formula (d-1) and 1.0 to 10.0 equivalents of a compound of the general formula (e-1) with respect to the compound of the general formula (d-1) in a solvent in the presence of 1.0 to 10.0 equivalents of a base with respect to the compound of the general formula (d-1). The base used varies according to the starting material and is not particularly limited. Preferable examples of the base include alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate), metal alkoxides (such as sodium methoxide and potassium tert-butoxide) and organometallic bases (such as butyllithium, lithium diisopropylamide and lithium bistrimethylsilylamide). The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixtures thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably -100°C to 100°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0154]

The hydrazidation reaction as the first stage of Step 3-2 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. An amidation reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 137-144)

may be used. The deprotection reaction as the second stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A deprotection reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used.

[0155]

The Ring A formation reaction in Step 3-3 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of heating a compound of the general formula (d-3) and 1.0 to 10.0 equivalents of aminoguanidine, isothiourea, cyanamide or the like with respect to the compound of the general formula (d-3) in a solvent under basic or acidic conditions. The base or acid used varies according to the starting material and is not particularly limited. Examples of the base or acid include bases such as alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate), metal alkoxides (such as sodium methoxide and potassium tert-butoxide) and organic bases (such as triethylamine, pyridine and 1,8-diazabicyclo[5.4.0]undec-7-ene); and acids such as hydrochloric acid, sulfuric acid, p-toluenesulfonic acid and camphorsulfonic acid. The solvent used varies according to the starting material, and is not particularly limited insofar as the solvent does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include alcohol solvents such as methanol, ethanol and tert-butanol; ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as acetonitrile, N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as xylene, toluene and benzene; and mixtures thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably -100°C to 100°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 48 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0156]

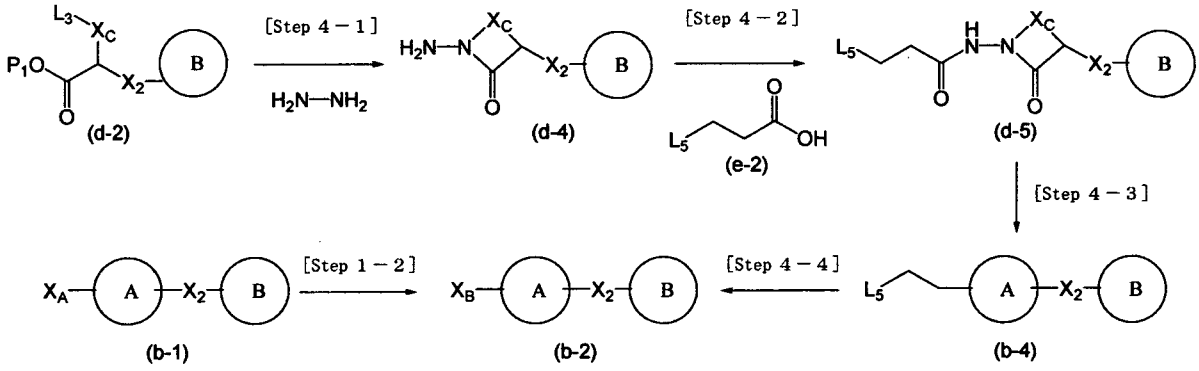
The Sandmeyer reaction in Step 3-4 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 19) Yuki Gosei (Organic Synthesis) [I], Maruzen Co., Ltd., November 1992, p. 450-453) may be used.

[0157]

Preparation of compound of general formula (b-2)

The following formula shows an example of preparation of the compound of the general formula (b-2).

[0158]



[0159]

In the formula, X_2, X_A, X_C, P_1, L_3, Ring A and Ring B are as defined above, wherein X_B represents a C2-6 alkenyl group and L_5 represents a leaving group such as a phenylthio group or a p-tolylsulfanyl group.

[0160]

The compound of the general formula (b-2) can be prepared from a compound of the general formula (b-1) as a starting material in Step 1-2 as described above. Alternatively, the compound can be prepared from a compound of the general formula (d-2) as a starting material through hydrazidation in Step 4-1, acylation in Step 4-2, formation of Ring A in Step 4-3 and thermal decomposition reaction in Step 4-4.

[0161]

Step 4-1 may employ the same amidation reaction as in the aforementioned Step 3-2. Preferable examples of the method include a method of stirring a compound of the general formula (d-2) and 1.0 to 10.0 equivalents of hydrazine with respect to the compound of the general formula (d-1) in a solvent. Neutral reaction conditions are preferred in order to make

the reaction conveniently proceed. The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include ether solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixtures thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 100°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

[0162]

Step 4-2 may employ the same amidation reaction as in the aforementioned Step 3-2. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 137-144) may be used.

[0163]

Step 4-3 may employ the same cyclization conditions as in the aforementioned Step 2-3. More preferably, a compound of the general formula (b-4) can be conveniently prepared by heating with stirring a compound of the general formula (d-5) and 1.0 to 10 equivalents of phosphorus oxychloride with respect to the compound of the general formula (d-5) and then heating the resulting compound and 1.0 to 10 equivalents of ammonium acetate with respect to the compound of the general formula (d-5) in an acetic acid solvent, for example.

[0164]

The thermal decomposition reaction in Step 4-4 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in W. Carrutthers, "Some modern methods of organic synthesis, Third Edition" (Cambridge University Press, 1986, p. 120-121)) may be used. More preferably, the compound of the general formula (b-2) can be conveniently prepared by subjecting the compound of the general formula (b-4) to an oxidation

reaction known to a person skilled in the art and heating the compound, for example.

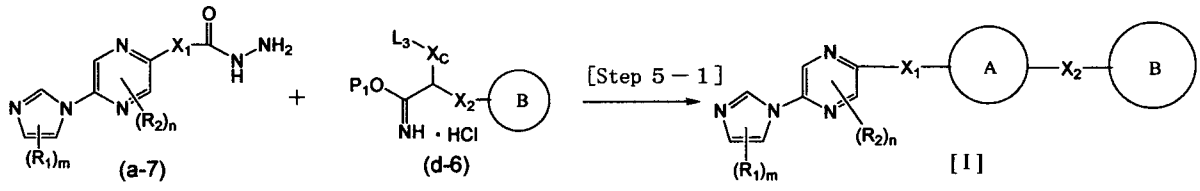
The compound of the formula (d-1), the compound of the formula (e-1), the compound of the formula (e-2) and the compound of the formula (f-1) are known or commercially available compounds or are compounds that can be prepared from these compounds by a conventional method.

[0165]

General Preparation Method 2

Typically used General Preparation Method 2 for the compound of the general formula [I] according to the present invention will be described below.

[0166]



[0167]

In the formula, R_1, R_2, X_1, X_2, X_C, P_1, L_3, m, n, Ring A and Ring B are as defined above.

The above General Preparation Method 2 shows an example describing preparation of the compound of the general formula [I] by subjecting a compound of the general formula (a-7) and a compound of the general formula (d-6) to cyclization reaction in Step 5-1.

[0168]

The Ring A formation reaction in Step 5-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of stirring a compound of the general formula (a-7) and 1.0 to 5.0 equivalents of a compound of the general formula (d-6) with respect to the compound of the general formula (a-7) in a solvent in the presence of 1.0 to 10.0 equivalents of a base with respect to the compound of the general formula (a-7). This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring efficiency. The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include alcohol solvents such as methanol, ethanol and tert-butanol; ether solvents such as tetrahydrofuran, 1,4-

dioxane and diethyl ether; halogenated solvents such as methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as acetonitrile, propionitrile, N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixtures thereof. The base used varies according to the starting material and is not particularly limited. Preferable examples of the base include alkali metal hydrides (such as sodium hydride and lithium hydride), alkali metal salts (such as potassium carbonate, sodium carbonate and cesium carbonate), metal alkoxides (such as sodium methoxide and potassium tert-butoxide) and organic bases (such as triethylamine, N,N-diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene and imidazole). The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably room temperature to 200°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 7 days, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

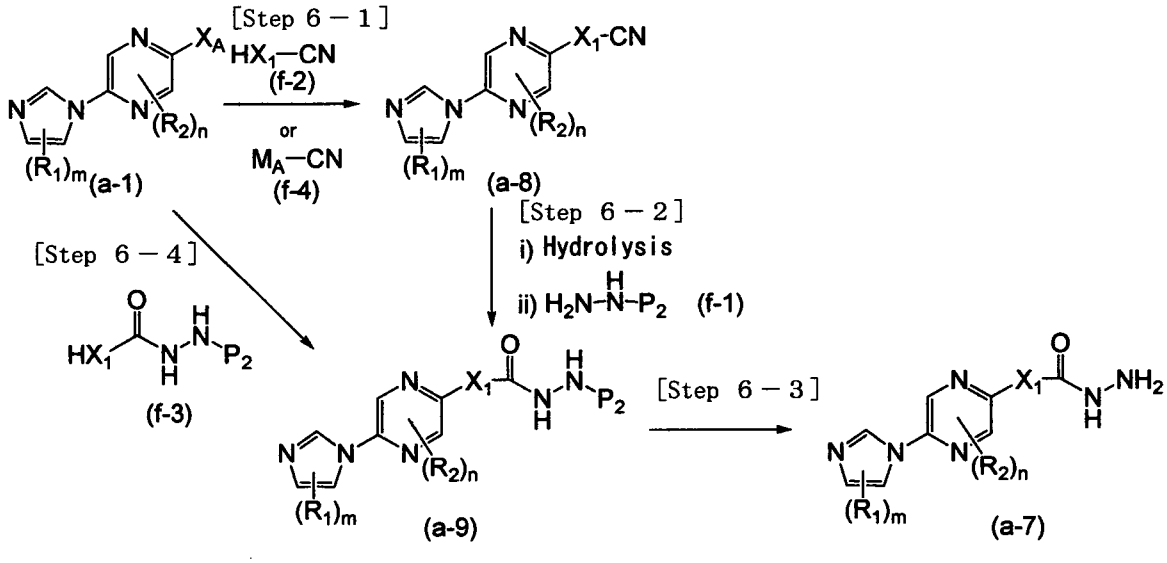
The compound of the formula (d-6) is a known or commercially available compound or is a compound that can be prepared from such a compound by a conventional method.

[0169]

Preparation of compound of general formula (a-7)

The following formula shows an example of preparation of the compound of the general formula (a-7).

[0170]



[0171]

In the formula, R_1, R_2, m, n, X_A and P_2 are as defined above; and M_A represents a metal such as zinc or copper.

The compound of the general formula (a-7) can be prepared from a compound of the general formula (a-1) as a starting material through coupling reaction in Step 6-1, hydrolysis reaction and hydrazidation in Step 6-2 and deprotection reaction in Step 6-3. Alternatively, the compound can be prepared from a compound of the general formula (a-1) as a starting material through coupling reaction in Step 6-4 and deprotection reaction in Step 6-3.

Step 6-1 and Step 6-4 vary according to the starting material and are not particularly limited insofar as the conditions are similar to those in these reactions. A method known to a person skilled in the art may be used for the reactions. Mizoroki-Heck reaction (see R.F. Heck, "Org. Reactions.", 1982, vol. 27, p. 345, for example), Sonogashira reaction (see K. Sonogashira, "Comprehensive Organic Synthesis", 1991, vol. 3, p. 521, for example) or the like is preferable.

[0172]

In Mizoroki-Heck reaction, a halogen compound or trifluoromethanesulfonate compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a compound of the general formula (f-2) or a compound of the general formula (f-3) (wherein X_1 is preferably $-CR_3=CR_4-$) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring efficiency. The solvent used varies according to the starting material and the transition metal catalyst used, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone and N,N-dimethylformamide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. The transition metal catalyst is preferably a palladium complex, for example, and more preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). It is also preferable to appropriately add a phosphorus ligand (preferably triphenylphosphine, tri-o-tolylphosphine, tri-tert-butylphosphine

or 2-(di-tert-butylphosphino)biphenyl, for example) in order to make the reaction efficiently proceed. A preferable result may be achieved in the presence of a base. The base used is not particularly limited insofar as it is used in a coupling reaction similar to this reaction. Preferable examples of the base include triethylamine, N,N-diisopropylethylamine, N,N-dicyclohexylmethylamine and tetrabutylammonium chloride. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0173]

The Sonogashira reaction vary according to the starting material, the solvent and the transition metal catalyst, and are not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferably, a compound of the general formula (a-1) is coupled with 1.0 to 5.0 equivalents of a compound of the general formula (f-2) or a compound of the general formula (f-3), wherein X_1 is preferably

[0174]

$-C\equiv C-$

[0175]

with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. Preferable examples of the solvent used include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone, N,N-dimethylformamide and dimethyl sulfoxide. More preferable examples of the solvent include tetrahydrofuran, 1,4-dioxane, 1-methyl-2-pyrrolidone and N,N-dimethylformamide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique. The transition metal catalyst is, for example, a known palladium complex, and more preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). A phosphorus ligand (preferably triphenylphosphine, tri-o-tolylphosphine or tritert-butylphosphine, for example) may be appropriately added, for example, in order to make the reaction efficiently proceed. In the reaction, it is possible to add a metal halide or a quaternary ammonium salt,

preferably copper (I) iodide, lithium chloride, tetrabutylammonium fluoride or silver (I) oxide, for example. A preferable result may be achieved in the presence of a base. The base used here is not particularly limited insofar as it is used in a coupling reaction similar to this reaction. Preferable examples of the base include organic bases such as diethylamine, triethylamine, N,N-diisopropylethylamine, piperidine and pyridine.

[0176]

The coupling reaction in Step 6-1 may also employ a compound of the general formula (f-4) (wherein X_1 is preferably a single bond). A halogen compound or trifluoromethanesulfonate group compound of the general formula (a-1) is preferably coupled with 1.0 to 5.0 equivalents of a compound of the general formula (f-4) (wherein X_1 is preferably a single bond) with respect to the compound of the general formula (a-1) in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst with respect to the compound of the general formula (a-1), for example. This reaction is preferably performed in the presence of a solvent from the viewpoint of handleability and stirring efficiency. The solvent used varies according to the starting material and the transition metal catalyst used, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone and N,N-dimethylformamide. The reaction temperature must be a temperature that can complete the coupling reaction, and is preferably room temperature to 150°C. This reaction is performed preferably in an inert gas atmosphere, and more preferably in a nitrogen or argon atmosphere. The transition metal catalyst is preferably a palladium complex, for example, and more preferably a known palladium complex such as palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). It is also preferable to appropriately add a phosphorus ligand (preferably triphenylphosphine, tri-o-tolylphosphine, tri-tert-butylphosphine or 2-(di-tert-butylphosphino)biphenyl, for example) in order to make the reaction efficiently proceed. A preferable result may be achieved in the presence of a base. The base used is not particularly limited insofar as it is used in a coupling reaction similar to this reaction. Preferable examples of the base include triethylamine, N,N-diisopropylethylamine, N,N-dicyclohexylmethylamine and tetrabutylammonium chloride. Under preferable reaction conditions, the reaction is completed in 1 to 24 hours, and the progress of the reaction can be monitored by a known chromatography technique.

[0177]

The hydrolysis reaction as the first stage of Step 6-2 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. A method reported in many documents (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 12-13) may be used. The hydrazidation reaction as the second stage varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. An amidation reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (such as described in The Chemical Society of Japan (ed.), Jikken Kagaku Koza (Courses in Experimental Chemistry), 4th edition (vol. 22) Yuki Gosei (Organic Synthesis) [IV], Maruzen Co., Ltd., November 1992, p. 137-144) may be used.

[0178]

The deprotection reaction in Step 6-3 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A deprotection reaction known to a person skilled in the art may be used for the reaction. A method reported in many documents or the like (see T. Greene et al., "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, for example) may be used.

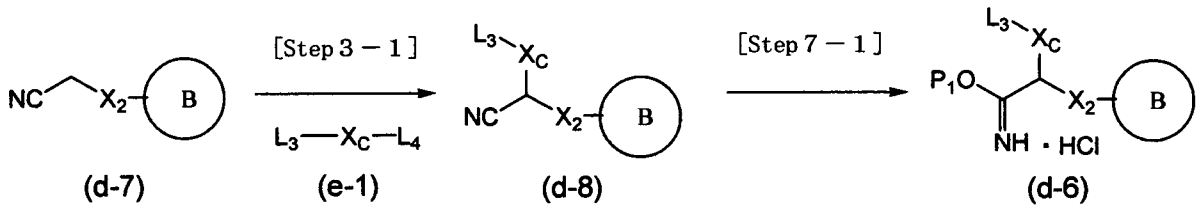
The compound of the formula (f-2), the compound of the formula (f-3) and the compound of the formula (f-4) are known or commercially available compounds or are compounds that can be prepared from these compounds by a conventional method.

[0179]

Preparation of compound of general formula (d-6)

The following formula shows an example of preparation of the compound of the general formula (d-6).

[0180]



(d-7) (e-1) (d-8) (d-6)

[0181]

In the formula, X_2, X_C, Ring B, P_1, L_3 and L_4 are as defined above.

The compound of the general formula (d-6) can be prepared from a compound of

the general formula (d-7) as a starting material through alkylation reaction in Step 3-1 and imidation in Step 7-1.

Step 3-1 is performed by the same method as described above and can prepare a compound of the general formula (d-8) from a compound of the general formula (d-7).

[0182]

Step 7-1 varies according to the starting material and is not particularly limited insofar as the conditions are similar to those in this reaction. A method known to a person skilled in the art may be used for the reaction. Preferable examples of the method include a method of stirring the compound of the general formula (d-8) in an alcohol solvent in the presence of 5.0 to 100.0 equivalents of an acid with respect to the compound of the general formula (d-8). The acid used varies according to the starting material and is not particularly limited. Preferable examples of the acid include hydrogen chloride gas and acetyl chloride. The solvent used varies according to the starting material, and is not particularly limited insofar as it does not inhibit the reaction and allows the starting material to be dissolved therein to a certain extent. Preferable examples of the solvent include alcoholic solvents such as methanol, ethanol and tert-butanol. Preferable examples of the solvent also include halogenated solvents such as a methylene chloride, 1,2-dichloroethane and chloroform; polar solvents such as N,N-dimethylformamide and N-methylpyrrolidone; non-polar solvents such as toluene and benzene; and mixed solvents thereof. The reaction temperature must be a temperature that can complete the reaction without promoting formation of an undesirable by-product, and is preferably 0°C to 100°C, for example. Under preferable reaction conditions, the reaction is completed in 1 to 7 days, and the progress of the reaction can be monitored by a known chromatography technique. An undesirable by-product can be removed by a technique known to a person skilled in the art such as a conventional chromatography technique, extraction or/and crystallization.

The compound of the formula (d-7) and the compound of the formula (e-1) are known or commercially available compounds or are compounds that can be prepared from these compounds by a conventional method.

[0183]

The compound of the general formula (I) or pharmacologically acceptable salt thereof according to the present invention is effective for the treatment of a disease caused by Aβ and is excellent in terms of pharmacokinetics, toxicity, stability, absorption and the like.

A therapeutic agent for a disease caused by Aβ comprising the compound of the formula (I) or pharmacologically acceptable salt thereof according to the present invention as an active ingredient can be prepared by a conventional method. Preferable examples of the dosage

form include tablets, powders, fine granules, granules, coated tablets, capsules, syrups, troches, inhalants, suppositories, injections, ointments, ophthalmic solutions, ophthalmic ointments, nasal drops, ear drops, cataplasms and lotions. The agent can be prepared by using ingredients typically used such as an excipient, a binder, a lubricant, a colorant and a corrective, and ingredients used where necessary such as a stabilizer, an emulsifier, an absorbefacient, a surfactant, a pH adjuster, a preservative and an antioxidant, and can be prepared by blending ingredients generally used as materials for a pharmaceutical preparation. Examples of such ingredients include animal and vegetable oils such as soybean oil, beef tallow and synthetic glyceride; hydrocarbons such as liquid paraffin, squalane and solid paraffin; ester oils such as octyldodecyl myristate and isopropyl myristate; higher alcohols such as cetostearyl alcohol and behenyl alcohol; a silicone resin; silicone oil; surfactants such as polyoxyethylene fatty acid ester, sorbitan fatty acid ester, glycerin fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil and a polyoxyethylene-polyoxypropylene block copolymer; water-soluble polymers such as hydroxyethylcellulose, polyacrylic acid, a carboxyvinyl polymer, polyethylene glycol, polyvinylpyrrolidone and methylcellulose; lower alcohols such as ethanol and isopropanol; polyhydric alcohols such as glycerin, propylene glycol, dipropylene glycol and sorbitol; sugars such as glucose and sucrose; inorganic powders such as silicic anhydride, magnesium aluminum silicate and aluminum silicate; and purified water. Examples of the excipient used include lactose, corn starch, saccharose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide. Examples of the binder used include polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, a polypropylene glycol-polyoxyethylene block copolymer and meglumine. Examples of the disintegrant used include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectin and carboxymethylcellulose calcium. Examples of the lubricant used include magnesium stearate, talc, polyethylene glycol, silica and hydrogenated vegetable oil. Examples of the colorant used include those permitted to be added to pharmaceuticals. Examples of the corrective used include cocoa powder, menthol, empasm, mentha oil, borneol and cinnamon powder.

[0184]

For example, an oral preparation is prepared by adding an active ingredient compound or a salt thereof or a hydrate of the compound or salt, an excipient, and, where necessary, a binder, a disintegrant, a lubricant, a colorant and a corrective, for example, and then forming the mixture into powder, fine granules, granules, tablets, coated tablets or capsules, for

example, by a conventional method. It is obvious that tablets or granules may be appropriately coated, for example, sugar coated, where necessary. A syrup or an injection preparation is prepared by adding a pH adjuster, a solubilizer and an isotonizing agent, for example, and a solubilizing agent, a stabilizer and the like where necessary by a conventional method. An external preparation may be prepared by any conventional method without specific limitations. As a base material, any of various materials usually used for a pharmaceutical, a quasi drug, a cosmetic or the like can be used. Examples of the base material include materials such as animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals and purified water. A pH adjuster, an antioxidant, a chelator, a preservative and fungicide, a colorant, a flavor or the like may be added where necessary. Further, an ingredient having a differentiation inducing effect such as a blood flow enhancer, a bactericide, an antiphlogistic, a cell activator, vitamin, amino acid, a humectant or a keratolytic agent may be blended where necessary.

[0185]

The dose of the therapeutic agent according to the present invention varies according to the degree of symptoms, age, sex, body weight, mode of administration, type of salt and specific type of disease, for example. Typically, the compound of the formula (I) or pharmacologically acceptable salt thereof is orally administered to an adult at about 30 μg to 10 g, preferably 100 μg to 5 g, and more preferably 100 μg to 100 mg per day, or is administered to an adult by injection at about 30 μg to 1 g, preferably 100 μg to 500 mg, and more preferably 100 μg to 30 mg per day, in a single dose or several divided doses, respectively.

[0186]

To treat a disease caused by amyloid-β such as Alzheimer's disease, senile dementia, Down's syndrome or amyloidosis, the compound of the formula (I) or pharmacologically acceptable salt thereof according to the present invention may be used in combination with compounds having the following mechanisms.

For example, the compounds usable in combination include cholinesterase inhibitors (e.g., donepezil, huperzine A, tacrine, rivastigmine, galantamine); AMPA receptor antagonists (e.g., 1,2-dihydropyridine compounds such as 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one); NMDA receptor antagonists (e.g., memantine); acetylcholine releasing stimulants (e.g., pramiracetam; aniracetam); calcium channel agonists (e.g., nefiracetam); free radical scavengers (e.g., EGb 761); platelet activating factor antagonists (e.g., EGb 761); platelet aggregation antagonists (e.g., EGb 761, triflusal); insulin sensitizers (e.g.,

rosiglitazone); peroxisome proliferator-activated receptor agonists (e.g., rosiglitazone); peroxisome proliferator-activated receptor gamma agonists (e.g., rosiglitazone); monoamine oxidase B inhibitors (e.g., rasagiline, selegiline, procaine); carnitine acetyltransferase stimulants (e.g., levacecarnine); NSAIDs (e.g., triflusal, cyclooxygenase-2 inhibitors, such as celecoxib); nerve growth factor agonists (e.g., xaliproden, FPF 1070); beta-amyloid inhibitors (e.g., tarenflurbil, tramiprosate, leuprorelin-D); immunomodulators (e.g., tarenflurbil, immune globulin, icosapentethyl ester); NF-kappa B inhibitors (e.g., tarenflurbil); thyrotropin releasing hormone (e.g., taltirelin); dopamine D2 receptor antagonists (e.g., risperidone); serotonin 2 receptor antagonists (e.g., risperidone); muscarinic M1 receptor agonists (e.g., cevimeline); alpha 1 adrenoceptor agonists (e.g., modafinil); serotonin 3 receptor antagonists (e.g., alosetron); dopamine D2 receptor agonists (e.g., aripiprazole); dopamine D2 receptor antagonists(e.g., aripiprazole); serotonin 1A receptor agonists (e.g., aripiprazole); serotonin 2A receptor antagonists (e.g., aripiprazole); glucocorticoid antagonists (e.g., mifepristone); progesterone antagonists (e.g., mifepristone); HMG-CoA reductase inhibitors (e.g., atorvastatin, simvastatin); adenosine uptake inhibitors (e.g., propentofylline); phosphodiesterase inhibitors (e.g., propentofylline); acetylcholine receptor agonists (e.g., choline alfoscerate); membrane permeability enhancers (e.g., choline alfoscerate); cannabinoid 1 receptor antagonists (e.g., rimonabant); cannabinoid receptor agonists (e.g,. dronabinol); angiogenesis inhibitors (e.g., paclitaxel); immunosuppressants (e.g., paclitaxel); tubulin antagonists (e.g., paclitaxel); thromboxane A synthase inhibitors (e.g., triflusal); antioxidants (e.g., idebenone); alpha adrenoreceptor antagonists (e.g., nicergoline); estrogen antagonists (e.g., conjugated estrogens, trilostane); 3-beta hydroxysteroid dehydrogenase inhibitors (e.g., trilostane); signal transduction pathway inhibitors (e.g., trilostane); melatonin receptor agonists (e.g., ramelteon); immunostimulants (e.g., immune globulin, icosapentethyl ester, procaine); HIV entry inhibitors (e.g., procaine); sodium channel antagonists (e.g., procaine); microtubule inhibitor (e.g., CPH 82); glycine NMDA agonists (e.g., cycloserine); adenosine A1 receptor antagonists (e.g., KW 3902); ATPase stimulants (e.g., triacetyluridine); mitochondrial function enhancers (e.g, triacetyluridine); growth hormone releasing factor agonists (e.g., tesamorelin);. butylcholine esterase inhibitor (e.g., bisnorcymserine); alpha adrenergic receptor antagonists (e.g., nicergoline); NO synthase type II inhibitors (e.g., arundic acid); chelating agents (e.g., PBT 2); amyloid fibrillogenesis inhibitors (e.g., TTP488, PF 4494700); serotonin 4 receptor agonists (e.g., PRX 03140); serotonin 6 receptor antagonists (e.g., SB 742457); benzodiazepine receptor inverse agonists (e.g., radequinil); Ca channel antagonists (e.g., safinamide); nicotinic receptor agonists (e.g., ispronicline); and BACE inhibitor (e.g., CTS 21166).

[0187]

Further, the above compounds include, for example, donepezil, huperzine A, tacrine, rivastigmine, galantamine, pramiracetam, aniracetam, nefiracetam, EGb 761, rosiglitazone, rasagiline, levacecarnine, celecoxib, 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one, talampanel, becampanel, memantine, xaliproden, tarenflurbil, tramiprosate, leuprorelin-D, taltirelin, risperidone, cevimeline, modafinil, alosetron, aripiprazole, mifepristone, atorvastatin, propentofylline, choline alfoscerate, FPF 1070 (CAS Number 143637-01-8), rimonabant, dronabinol, docosahexaenoic acid, paclitaxel, triflusal, idebenone, nicergoline, conjugated estrogens, trilostane, simvastatin, selegiline, ramelteon, immune globulin, icosapentethyl ester, procaine, CPH 82, cycloserine, KW 3902 (CAS Number 136199-02-5), triacetyluridine, estrogen dementia therapeutics (e.g., MIGENIX, Vancouver, Canada), tesamorelin, bisnorcymserine, nicergoline, arundic acid, PBT 2, TTP488, PF 4494700, PRX 03140, SB 742457, radequinil, safinamide, ispronicline, CTS 21166, Bapineuzumab, NP 031112, (2S,3aS,7aS)-1{[(R,R)-2-Phenylcyclopropyl]carbonyl}-2-[(thiazolidin-3-yl)carbonyl]octahydro-1H-indole, citalopram, venlafaxine, levprorelin, prasterone, peptide T (CAS Number 53-43-0), besipiridine, lexipafant, stacofylline, SGS 742 (CAS Number 123690-78-8), T 588 (CAS Number 142935-03-3), nerispiridine, dexanabinol, sabcomeline, GTS 21 (CAS Number 156223-05-1), CX 516 (CAS Number 154235-83-3), ABT 089 (CAS Number 161417-03-4), anapsos, tesofensine, SIB 1553A (i.e., 4-[[2-(1-methyl-2-pyrrolidinyl)ethyl]thio]phenol), ladostigil, radequinil, GPI 1485, ispronicline, arundic acid, MEM 1003 (i.e., 3-Isopropyl 5-(2-methoxyl) 4-(2-chloro-3-cyanophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate), V 3381 (i.e., 2-(2,3-Dihydro-1H-inden-3-ylamino)acetamide hydrochloride), farampator, paliroden, prasterone-paladin, urocortin, DP b99 (i.e., 2,2'-(Ethylenedioxy)bis(2,1-phenylene)bis[N-[2-[2-(octyloxy)ethoxy]-2-oxoethyl]imino]bis(acetic acid)), capserod, DU 125530, bapineuzumab, AL 108 (i.e., L-Asparaginyl-L-alanyl-L-prolyl-L-valyl-L-seryl-L-isoleucyl-L-prolyl-L-glutamine), DAS 431, DEBIO 9902, DAR 100, mitoquinone, IPL 455903 (i.e., 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one), E2CDS, PYM 50028, PBT 2, lecozotan, SB 742457, CX 717, AVE 1625 (i.e., 1-(bis(4-chlorophenyl)methyl)-3-((3,5-difluorophenyl)(methylsulfonyl)methylene)azetidine), LY 450139 (i.e., N2-[2(s)-Hydroxy-3-methylbutyryl]-N1-[3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepin-1(S)-yl]-L-alaninamide), EM 1421 (i.e., 4,4'-[(2R,3S)-2,3-Dimethylbutane-1,4-diyl]bis(1,2-dimethoxybenzene), SRN 001, TTP 488, PRX 03140, dimebolin, glycine-proline-glutamate, C105, AL 208, MEM 3454, AC 1202, L 830982, LY 451395 (i.e., (R)-N-[2-[4'-(methylsulfonamidomethyl)biphenyl-4-yl]propyl]propane-2-sulfonamide), MK 0249, LY

2062430, diethylnorspermine, neboglamine, S 18986, SA 4503 (CAS Number 165377-44-6), GRI 1, S 17092 (i.e., (2S,3aS,7aS)-1{[(R, R)-2-Phenylcyclopropyl]carbonyl}-2-[(thiazolidin-3-yl)carbonyl]octahydro-1H-indole), SL 251188, EUK 189, R 1450, 6,6-dimethyl-3-(2-hydroxyethyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one, CERE 110, dexefaroxan, CAD 106, HF 0220, HF 0420, EHT 0202, VP 025, MEM 1414, BGC 201259 (i.e., N,N-Dimethylcarbamic acid, 4-[1(S)-(methylamino)-3-(4-nitrophenoxy)propyl]phenyl ester), EN 100, ABT 834, ABT 239 (i.e., 4-[2-[2-[(2R)-2-Methylpyrrolidinyl]ethyl]-benzofuran-5-yl]benzonitrile), SGS 518, R 1500, C 9138, SSR 180711, alfatradiol, R 1577, T 817MA (i.e., 1-[3-[2-(1-Benzothien-5-yl)ethoxy]propyl]azetidin-3-olmaleate), CNP 1061 (i.e., 4-Methyl-5-(2-nitrooxyethyl)thiazole), KTX 0101 (i.e., sodium beta-hydroxybutyrate), GSK 189254 (i.e., 6-[3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy]-N-methylnicotinamide), AZD 1080, ACC 001, PRX 07034, midazolam, R-phenserine, AZD 103 (CAS Number 488-59-5), SN 522, NGX 267 (CAS Number 503431-81-0), N-PEP-12, RN 1219, FGLL, AVE 8112, EVT 101, NP 031112, MK 0752, MK 0952, LX 6171, PAZ 417, AV 965, PF 3084014, SYN 114, GSI 953, SAM 315, SAM 531, D-serine, leteprinim potassium, BR 16A (CAS Number 149175-77-9), RPR 107393 (CAS Number 190841-57-7), NXD 2858, REN 1654, CDD 0102, NC 1900 (CAS Number 132925-74-7), ciclosporin, NCX 2216 (i.e., (E)-4-(Nitrooxy)butyl 3-[4-[2-(2-fluorobiphenyl-4-yl)propanoyloxy]-3-methoxyphenyl]acrylate), NXD 3109, NXD 1191, ZSET 845 (i.e., 3,3-diphenylimidazo[1,2-a]pyridin-2-(3H)-one), ET 002, NT 13, RO 638695 (i.e., [1,6-(1,6-dioxohexyl)]dipyrrolidine-(2R)-carboxylic acid), bisnorcymserine, BA 1016, XD 4241, EUK 207 (i.e., (SP-5-13)-(acetato-κO)[13,16,19,22-tetraoxa-3,6-diazatricyclo[21.3.18,12]octacosa-1(27),2,6,8,10,12(28),23,25-octaene-27,28-diolato(2-)-κN3,κN6,κO27,κO28]manganese), LG 617 inhibitors, ZSET 1446, PAN 811, F 14413 (i.e., 2-[5-fluoro-2(S)-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]-4,5-dihydro-1H-imidazole), FP 7832 (i.e., N-[2-(5-methoxy-1-nitroso-1H-indol-3-yl)ethyl]acetamide), ARA 014418 (i.e., N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea), AZD 3102, KP 544 (i.e., 2-amino-5-(4-chlorophenylethynyl)-4-(4-trans-hydroxycyclohexylamino)pyrimidine), DP 155, 5-chloro-N-[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]naphthalene-2-sulfonamide, TAK 070, huperzine, N-[2-(3,5-dimethyladamant-1-yl)ethyl]acetamidine hydrochloride, 6-[4-[(dimethylamino)methyl]-5-ethyl-2-methoxyphenyl]pyridin-2-amine, 4,6-diphenyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine, N-[(1S,2R)-3-(3,5-difluorophenyl)-1-hydroxy-1-[(5S,6R)-5-methyl-6-(neopentyloxy)morpholin-3-yl]propan-2-yl]acetamide hydrochloride, N-[(1R,2S)-3-(3,5-difluorophenyl)-1-hydroxy-1-[(2R,4R)-4-phenoxypyrrolidin-2-yl]propan-2-yl]-3-[(R)-2-(methoxymethyl)pyrrolidine-1-carbonyl]-5-methylbenzamide, R 1589, midafotel, phenserine,

coluracetam, physostigmine, cipralisant, nitroflurbiprofen, PPI 1019 (i.e., (3α, 5β, 7α, 12α)-trihydroxycholan-24-oyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-alanine), dapsone, MDL 100453 (CAS Number 129938-34-7), NS 377, midaxifylline, propofol phosphate, metrifonate, ceronapril, tenilsetam, sufoxazine, seglitide, ebiratide, nebracetam, milacemide, iododoxorubicin, SM 10888 (CAS Number 129297-21-8), U 80816 (CAS Number 138554-11-7), YM 954 (CAS Number 132041-85-1), SUT 8701 (CAS Number 123577-73-1), apovincamine, FR 121196 (CAS Number 133920-65-7), LY 274614 (CAS Number 136109-04-1), CL 275838 (CAS Number 115931-65-2), igmesine, K 7259 (CAS Number 133667-88-6), vinconate, itasetron, CL 287663 (CAS Number 125109-98-0), WAY 100289 (CAS Number 136013-69-9), SR 46559A (CAS Number 137733-33-6), GYKI 46903 (CAS Number 142999-59-5), L 670548 (CAS Number 121564-89-4), Y 29794 (CAS Number 129184-48-1), AF 125 (CAS Number 7631-86-9), KFM 19 (CAS Number 133058-72-7), ST 796 (i.e., (S)-3-[3-(trifluoromethyl)benzoyl)amino]hexahydroazepin-2-one), RU 33965 (CAS Number 122321-05-5), SDZ 210086 (i.e., (-)-1',2(S)-Dimethylspiro[1,3-dioxane-4,4'-piperidine]), L 689660 (CAS Number 144860-79-7), L 689560 (CAS Number 139051-78-8), ST 618 (i.e., 1-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-naphthyl)-4-hydroxy pyrrolidin-2-one), U 74500A (CAS Number 110101-65-0), GEA 857 (CAS Number 120493-42-7), BIBN 99 (CAS Number 145301-48-0), DX 9366, ONO 1603 (CAS Number 114668-76-7), MDL 102234 (CAS Number 137766-81-5), P 9939 (CAS Number 157971-37-4), PD 140532 (CAS Number 157971-39-6), azetirelin, MR 16728 (CAS Number 147614-21-9), dabelotine, MDL 102503 (i.e., 8-[1(R)-methyl-2-phenylethyl]-1,3-dipropyl-7H-xanthine), PD 141606 (i.e., (±)-(Z)-3-(3-Phenyl-2-propynyloxyimino)-1-azabicyclo[2.2.1]heptane), SNK 882 (CAS Number 152221-12-0), L 696986 (CAS Number 141553-45-9), tazomeline, LY 235959 (CAS Number 137433-06-8), 2-(2-thiooxopyrrolidin-1-yl)acetamide, AK 30 NGF, ABT 418 (CAS Number 147402-53-7), itameline, HUP 13, sibopirdine, KST 5452 (CAS Number 157998-88-4), TJ 54, U 92798 (i.e., 7-[4-[Bis(4-fluorophenyl)methyl]perhydro-1,4-diazepin-1-ylmethyl]-4-isopropyl-2-methoxy-2,4,6-cycloheptatrien-1-one), U 92032 (CAS Number 142223-92-5), 3-(sulfamoyloxy)estra-1,3,5(10)-trien-17-one, P 11012 (CAS Number 164723-36-8), A 82695 (CAS Number 147388-86-1), FR 76659 (CAS Number 116904-25-7), apaxifylline, CX 417, 7 MEOTA (CAS Number 5778-80-3), BU 4514N (CAS Number 151013-39-7), pregnenolone, mexidol, ST 857 (CAS Number 154755-63-2), RU 49041 (CAS Number 123828-80-8), RU 35929 (CAS Number 111711-47-8), P 878184, P 128 (CAS Number 157716-52-4), eurystatin A, eurystatin B, LK 12, NBI 108, NBI 107, NBI 117, L 705106, bacoside A+B, clausenamide, SM 21 (CAS Number 155156-22-2),

alaptide, RS 17017 (i.e., 1-(4-Amino-5-chloro-2-methoxyphenyl)-5-(1-piperidinyl)-1-pentanone hydrochloride), AF 150(S) (i.e., (S)-[1-Methyl-piperidine-4-spiro-(2'-methylthiazoline)]), RO 153505 (CAS Number 78771-13-8), PV 113 (i.e., 1,2,3,4-Tetrahydropyrrole-[1,2-a]-pyrazine), arisugacin, A 98284 (i.e., 2(R)-(3-Methyloxazol-5-yl) quinuclidine), AP 5 (CAS Number 136941-85-0), BD 1054, SDZ NDD 094 (i.e., bis-(2-(2-methylimidazol-1-yl]methyl)-pyridine-tris(hydrogen-fumarate), AZ 36041 (CAS Number 173324-76-0), quilostigmine, A 84543 (i.e., 3-[1-Methylpyrrolidin-2-(S)-ylmethoxy]pyridine fumarate), BTG 4247 (i.e., (2-[2-Chloroethoxy[4-(dimethylamino)phenyl]phosphoryl]-acetohydrazine), CGP 50068 (CAS Number 158647-49-5), cerebrocrast, desferri-nordanoxamine, isolichenan, MHP 133 (i.e., 3-(N,N-dimethylcarbamoyloxy)-1-methyl-2-(4-phenyl-semicarbazonomethyl)pyridium chloride), FR 152558 (CAS Number 151098-08-7), GVS 111 (CAS Number 157115-85-0), P 11149 (CAS Number 164724-79-2), PDC 008004, KST 2818 (CAS Number 158623-26-8), KST 5410 (CAS Number 158623-27-9), RU 52583 (CAS Number 123829-33-4), PD 151832 (CAS Number 149929-39-5), UCL 1199 (i.e., 4-[2-[(5-Nitropyridin-2-ylsulfanyl)ethyl]-1H-imidazole), isovanihuperzine A, SIB 1765F (CAS Number 179120-52-6), JWS USC 751X (i.e., 3-[[[2-[[(5-dimethylaminoethyl)-2-furanyl]methyl]thio]ethyl]amino]-4-nitropyridazine), GR 175737 (i.e., 3-(4-Chlorobenzyl)-5-[2-(1H-imidazol-4-yl)ethyl]-1,2,4-oxadiazole), KS 505A (CAS Number 131774-53-3), ZTTA 1 (i.e., N-benzyloxycarbonyl-thiopropyl-thiopropynal-dimethylacetal), AGN 190837 (CAS Number 136527-40-7), P 10358 (188240-59-7), WAY 131256 (CAS Number 174001-71-9), DBO 83 (i.e., 3-(6-chloropyrazin-3-yl)-diazabicyclo[3.2.1]octane dihydrochloride monohydrate), FUB 181 (CAS Number 152029-80-6), RJR 2557, WSU 2088, LVV-haemorphin-7, M 40 (i.e., galanin[1-12]-Pro3-(Ala-Leu)$_2$-Ala-NH$_2$), SIB 1757, SKF 74652 (i.e., [5-chloro-2-(4-methoxy phenyl)-3-benzofuranyl][4-[3-(dimethylamino)-propoxy]phenyl]methanone), CGP 71982, SCH 57790 (i.e., 4-cyclohexyl-alpha-[4-[[4-methoxyphenyl]sulfinyl]phenyl]-1-piperazineacetonitrile), Putrescine-D-YiAbetal1, DU 14 (i.e., p-O-(sulfamoyl)-N-tetradecanoyl tyramine), CLZ 4, SL 340026, PPRT 424, ciproxifan, UR 1827 (i.e., 2-(1-benzylpiperidin-4-yl)-1-[4-(5-methylpyrimidin-4-ylamino)phenyl]-1-ethanone), caproctamine, TGS 20 (i.e., L-pyroglutamil-D-alanine amide), PG 9 (i.e., alpha-tropanyl 2-[(4-bromo)phenyl]propionate), TEI 3356 (i.e., (16S)-15-Deoxy-16-hydroxy-16-methyl-9-(O)-methano-DELTA6(9alpha)-prostaglandin I1), LY 392098 (i.e., Thiophene, 3-[(2-methylethyl-2)sulphonylaminopropyl-2]phenyl-4-yl-), PG 1000, DM 232, NEPP 11 (i.e., 12-iso-15-Deoxy-18-(4-methyl)phenyl-13,14-dihydro-delta7-prostaglandinA1 methyl ester), VA 100 (i.e., (2,3-Dihydro-2-[[(4-fluorobenzoyl)amino]ethyl]-1-methyl-5-phenyl-1H-1,4-benzodiazepine), VA 101 (i.e., (2,3-dihydro-2-[[(2-thienylcarbonyl)amino]ethyl]-1-methyl-5-phenyl-1H-1,4-

benzodiazepine), NC 111585 (i.e., (3S)-1,3-Bis-[3-[(3-azabicylo[2.2.2]octanyl)-1,2,5-thiadiazol-4-yloxy]-1-propyn-1-yl]benzene, 2L-(+)-tartate), IN 201, imoproxifan, kanokodiol, picroside I, picroside II, DM 235 (i.e., 1-(4-Benzoylpiperazin-1-yl)propan-1-one), monoclonal antibody 10D5, JLK2, JLK 6, JLK 7, DAPT (i.e., N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester), huperine X, SGS 111 (i.e., (S)-ethyl 2-[1-(2-phenylacetyl)pyrrolidine-2-carboxamido]acetate), NP 7557, C 9136, C 7617, R 1485, rofecoxib, velnacrine, montirelin, lazabemide, ORG 2766 (CAS Number 50913-82-1), sabeluzole, adafenoxate, CAS Number 9061-61-4, ipidacrine, bemesetron, idazoxan, linopirdine, selfotel, suritozole, milameline, xanomeline, TJ 960, fasoracetam, eptastigmine, ensaculin, zanapezil, posatirelin, zacopride, RS 86 (CAS Number 3576-73-6), ORG 5667 (CAS Number 37552-33-3), RX 77368 (CAS Number 76820-40-1), BMS 181168 (CAS Number 123259-91-6), BY 1949 (CAS Number 90158-59-1), AWD 5239 (CAS Number 109002-93-9), YM 796 (171252-79-2), aloracetam, CI 933 (CAS Number 91829-95-7), ST 793 (CAS Number 99306-37-3), cebaracetam, zifrosilone, talsaclidine, alvameline, JTP 2942 (148152-77-6), OPC 14117 (CAS Number 103233-65-4), elziverine, AP 521 (i.e., N-(1,3-Benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro[1]benzothieno[2,3-c]pyridine-3(R)-carboxamide hydrochloride), S 8510 (CAS Number 151466-23-8), JTP 4819 (CAS Number 162203-65-8), icopezil, SC 110, FK 960 (CAS Number 133920-70-4), DMP 543 (CAS Number 160588-45-4), ganstigmine, CI 1017 (i.e., (R)-(-)-(Z)-1-Azabicyclo[2.2.1]heptan-3-one, O-(3-(3'-methoxyphenyl)-2-propionyl)-oxime maleate), T 82 (i.e., 2-[2-(1-Benzylpiperidin-4-yl)ethyl]-2,3-dihydro-9-methoxy-1H-pyrrolo[3,4-b]quinolin-1-one hemifumarate), NGD 971, vaccine of Aspartyl-alanyl-glutamyl-phenylalanyl-arginyl-histidyl-aspartyl-seryl-glycyl-tyrosyl-glutamyl-valyl-histidyl- histidyl-glutaminyl-lysyl-leucyl-valyl-phenylalanyl-phenylalanyl-alanyl-glutamyl-aspartyl-valyl-glycyl-seryl-asparaginyl-lysyl-glycyl- alanyl-isoleucyl-isoleucyl-glycyl-leucyl-methionyl-valyl-glycyl-glycyl-valyl-valyl-isoleucyl-alanine, PBT 1 (CAS Number 130-26-7), TCH 346, FK 962 (i.e., N-(1-acetylpiperidin-4-yl)-4-fluorobenzamide), voxergolide, KW 6055 (CAS Number 63233-46-5), thiopilocarpine, ZK 93426 (CAS Number 89592-45-0), SDZ NVI 085 (CAS Number 104195-17-7), CI 1002 (CAS Number 149028-28-4), Z 321 (CAS Number 130849-58-0), mirisetron, CHF 2060 (i.e., N-Heptylcarbamic acid 2,4a,9-trimethyl-2,3,4,4a,9,9a-hexahydro-1,2-oxazino[6,5-b]indol-6-yl ester-L-tartrate), gedocarnil, terbequinil, HOE 065 (CAS Number 123060-44-6), SL 650102, GR 253035, ALE 26015, SB 271046 (i.e., 5-Chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide), iAbeta5, SCH 211803 (i.e., Piperidine, 1-[1-(3-methyl-2-aminophenyl)carbonylpiperidin-4-yl]-4-[(3-chlorophenyl)sulphonylphenyl-4]methyl-), EVT 301, alpha-Linolenic acid/linoleic acid, Kamikihi-To, siagoside, FG 7142 (CAS Number 78538-74-6),

RU 47067 (CAS Number 111711-92-3), RU 35963 (CAS Number 139886-03-6), FG 7080 (CAS Number 100332-18-1), E 2030 (CAS Number 142007-70-3), transforming growth factor beta-1, A 72055 (i.e., 2',1-Dimethylspiro[piperidine-4,5'oxazolidine]-3'-carboxaldehyde), NS 626, dimiracetam, GT 3001, GT 2501, GT 2342, GT 2016 (CAS Number 152241-24-2), ORG 20091 (CAS Number 141545-50-8), BCE 001 (CAS Number 95678-81-2), CGP 35348 (CAS Number 123690-79-9), WAY 100635 (CAS Number 146714-97-8), E 4804 (CAS Number 162559-34-4), LIGA 20 (CAS Number 126586-85-4), NG 121 (i.e., 2-[4,8-Dimethyl-3(E),7(E)-monoadienyl]-3,5-dihydroxy-2-methyl-3,4,7,9-tetrahydro-2H-fluoro[3,4-h]-1-benzopyran-7-one), MF 247 (i.e., N-[10-(Diethylamino)decyl]carbamic acid (3aS,8aR)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-yl ester), JTP 3399 (i.e., N-Benzyl-2(S)-[2(S)-(phenoxyacetyl)pyrrolidin-1-ylcarbonyl]pyrrolidine-1-carboxamide), KF 17329, thioperamide, F 3796 (i.e., 1-[2-(1-Benzylpiperidin-4-yl)ethyl]-3-[3,4-(methylene-dioxy)benzoyl]thiourea), GT 4001, GT 4002, FPL 14995 (CAS Number 123319-03-9), RU 34332 (CAS Number 137157-58-5), SR 96777A (CAS Number 115767-94-7), SIB T1980, NS 649 (CAS Number 146828-02-6), PD 142505 (CAS Number 149929-08-8), GYKI 52466 (CAS Number 102771-26-6), RO 246173 (CAS Number 159723-57-6), SCH 50911 (CAS Number 160415-07-6), Z 4105 (CAS Number 119737-52-9), RS 67333 (CAS Number 168986-60-5), NS 1546, ZM 241385 (CAS Number 139180-30-6), RO 249975 (i.e., [1S,3S(2'S),5R]-3-(1-Benzyl-5-oxopyrrolidin-2-ylmethyl)-5-(1H-imidazol-5-ylmethyl)cyclohexane-1-acetamide), AF 185 (i.e., 8-Methyl-3-(2-propynyl)-1,3,8-triazaspiro[4,5]decane-2,4-dione), CEP 427, CX 423, CX 438, CX 480, CDP-ethanolamine, GT 4003, GT 4011, GT 5011, MS 430 (CAS Number 122113-44-4), MBF 379 (i.e., [3,3-Bis(hydroxymethyl)-8-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-5-yl][3',5'-dihydroxy-4'-(2-oxo-2-phenylethoxy)phenyl]methanone), NGD 187 (CAS Number 163565-48-8), DUP 856, MR 3066, MF 8615 (i.e., 5-Amino-6-chloro-4-hydroxy-3,4-dihydro-1H-thiopyrano-[3,4-b]quinolinone), himbacine, ABS 300, RJR 2403 (CAS Number 538-79-4), MF 268 (CAS Number 174721-00-7), RO 465934 (i.e., N,N-Dimethylcarbamic acid 3-(2-cyclohexyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indol-6-yl ester), NS 393, RGH 2716 (CAS Number 134069-68-4), WIN 678702 (12,12-Bis(3-furyl)-6,11-dihydro-6,11-ethanobenzo[b]quinolizinium chloride), RS 66252 (i.e., 1-Butyl-2-[(2'-(2H-tetrazol-5-yl)-biphenyl-4-yl)methyl]-1H-indole-3-carboxylic acid), AIT 034 (CAS Number 138117-48-3), NG 012 (CAS Number 131774-53-3), PD 142012 (CAS Number 5778-84-7), GT 4054, GT 4077, GT 4035, P 26 (CAS Number 152191-74-7), RGH 5279 (i.e., (-)-(13aR,13bS)-13a-Ethyl-2,3,5,6,13a,13b-hexahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine-12-carboxylic acid 2-acetoxyethyl ester), AIT 083, CeNeS, estradiol (i.e.,

1,3,5(10)-Estratriene-3,17beta-diol), WAY 132983 ((3R,4R)-3-(3-hexasulfanylpyrazin-2-yloxy)-1-azabicyclo[2.2.1]heptane hydrochloride), ABS 205, ABS 401, SX 3507 (i.e., 3-(3-Propyl-1,2,4-oxadiazol-5-yl)quinoxaline-2(1H)-one), ARR 17779 (i.e., (-)-Spiro[1-azabicyclo[2.2.2]octaene-3,5-oxazolidine]-2-one), XE 991 (i.e., 10,10-bis(4-Pyridylmethyl)anthracen-10(9H)-one), phenethylnorcymserine, RO 657199, RJR 1781 (i.e., R(+)-2-(3-pyridyl)-1-azabicyclo[2.2.2.]octane), RJR 1782 (i.e., S(-)-2-(3-pyridyl)-1-azabicyclo[2.2.2.]octane), gilatide, tolserine, TC 2559 (i.e., (E)-N-Methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine), ER 127528 (i.e., 1-(3-Fluorobenzyl)-4-[(2-fluoro-5,6-dimethoxy-1-indanone-2-yl)methyl]piperidine hydrochloride), thiatolserine, targacept, axonyx, cymserine, thiacymserine, monoclonal antibody 266, Apan-CH, DP 103, SPI 339 (i.e., 4-[3-(4-Oxo-4,5,6,7-tetrahydroindol-1-yl)propionylamino]benzoic acid ethyl ester), S 37245 (i.e., 4-(1,4-Benzodioxan-5-yl)-1-[3(S)-hydroxy-5-nitro-indan-2-yl]-piperazine), LLG 88, AZD 2858, trometamol, AN 240, NG 002 (i.e., 5-Hydroxy-5-(2-hydroxy-1-methylethyl)-4-methoxyfuran-2(5H)-one), UCB 29427 (i.e., 2-Cyclopropyl-4-(cyclopropylamino)-6-(morpholino)-1,3,5-triazine), TRH-SR, RO 401641 (CAS Number 122199-02-4), MPV 1743AIII (CAS Number 150586-64-4), IDRA 21 (CAS Number 22503-72-6), CEP 431, ACPD (CAS Number 67684-64-4), CT 3577 (i.e., 3,7-Dimethyl-1-[11-(3,4,5-trimethoxybenzylamino)-11-oxoundecyl]xanthine), CT 2583, NXD 9062, Desferri-nordanoxamine, DP b99, PBT 1, T 817MA, Alfatradiol (CAS No. 57-91-0), AL 108, SL 650102, RS 67333 (CAS No. 168986-60-5), RS 17017, SGS 518, SYN 114, SB 271046, RO 657199, PRX 07034, Suritozole (CAS No. 110623-33-19), Terbequinil (CAS No. 113079-82-6), FG 7142 (CAS No. 78538-74-6). RU 34332 (CAS No. 137157-58-5), SX 3507, RO 153505 (CAS No. 78771-13-8), RU 33965 (CAS No. 122321-05-5), S 8510 (CAS No. 151466-23-8), Sabeluzole (CAS No. 104383-17-7), Cerebrocrast (CAS No. 118790-71-9), NS 626, NS 649 (CAS No. 146828-02-6), U 92032 (CAS No. 142223-92-5), MEM 1003, U 92798, RGH 2716 (CAS No. 134069-68-4), Safinamide (CAS No. 133865-89-1), AZD 0328, MEM 63908, ABT 418 (CAS No. 147402-53-7), ARR 17779, RJR 2403 (CAS No. 538-79-4), TC 2559, A 82695 (CAS No. 147388-86-1), A 84543, A 98284, DBO 83, RJR 2557, SIB 1765F (CAS No. 179120-52-6), GTS 21 (CAS No. 156223-05-1), MEM 3454, SIB 1553A, EVP 6124, SSR 180711, ABT 089 (CAS No. 161417-03-4), ABT 107, ABT 560, TC 5619, TAK 070, N-[(1S,2R)-3-(3,5-Difluorophenyl)-1-hydroxy-1-[(5S,6R)-5-methyl-6-(neopentyloxy)morpholin-3-yl]propan-2-yl]acetamide hydrochloride, 6-Fluoro-5-(2-fluoro-5-methylphenyl)-3,4-dihydropyridine, 2-Amino-6-[2-(3'-methoxybiphenyl-3-yl)ethyl]-3,6-dimethyl-5,6-hydroxypyrimidin-4(3H)-one, AZD 1080, ARA 014418, XD 4241, Z 321 (CAS No. 130849-58-0), ONO 1603 (CAS No. 114668-76-7), JTP 3399, Eurystatin A (CAS No. 137563-63-4),

Eurystatin B (CAS No. 137563-64-5), P 128 (CAS No. 157716-52-4), Y 29794(CAS No. 129184-48-1), ZTTA 1, JTP 4819 (CAS No. 162203-65-8), Monoclonal antibody 266, duloxetine, escitalopram oxalate, fluoxetine, fluvoxamine maleate, paroxetine, sertraline, dapoxetine, desvenlafaxine, sibutramine, nefazodone, milnacipran, desipramine, duloxetine, and bicifadine.

[0188]

The present invention will now be described in detail with reference to examples; however, the examples are provided only for illustration purposes. The therapeutic agent for a disease caused by Aβ according to the present invention is not limited to the following specific examples in any cases. A person skilled in the art can fully implement the present invention by making various modifications to not only the following reference examples and examples but also the claims of the present specification, and such modifications are within the scope of the claims of the present specification.

When example compounds have stereoisomers, the names of compounds with optical rotation may not necessarily correspond to the structural formulas sequentially in the following examples, if the absolute configuration is not determined.

[0189]

The following abbreviations are used in the following examples.

DMF: N,N-Dimethylformamide

THF: Tetrahydrofuran

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

HOBT: 1-Hydroxybenzotriazole

IPEA: Diisopropylethylamine

TEA: Triethylamine

BOPCl: Bis(2-oxo-3-oxazolidinyl)phosphonic chloride

Chromatography was performed using BW-300 manufactured by Fuji Silysia Chemical Ltd. as a carrier unless otherwise specified.

EXAMPLES

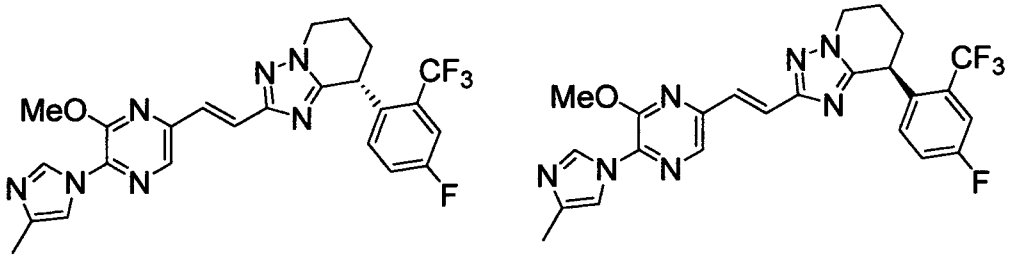
[0190]

Examples 1 and 2

(+)-8-(4-Fluoro-2-trifluoromethylphenyl)-2-{(E)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]vinyl}-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(4-fluoro-2-trifluoromethylphenyl)-2-{(E)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]vinyl}-

5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine

[0191]



[0192]

(E)-3-[6-Methoxy-5-(4-methyl-1H-imidazol-1-yl)-pyrazin-2-yl]acrylic acid hydrazide trihydrochloride obtained in Reference Example 2 (4.7 g) and imidazole (10 g) were added to a solution of ethyl 5-chloro-2-(4-fluoro-2-trifluoromethylphenyl)pentanimidate hydrochloride obtained in Reference Example 4 (5.2 g) in methanol (228 mL), followed by stirring at room temperature for seven days. Then, the reaction solution was stirred at 50°C for 28 hours. Ethyl acetate (200 mL), 10% saline (100 ml), 5 N hydrochloric acid (20 mL) and water (300 mL) were sequentially added to the reaction solution, and then the organic layer was separated. The aqueous layer was reextracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 5.7 g of a racemate of the title compound. The resulting racemate was separated by CHIRALPAK™ IC manufactured by Daicel Chemical Industries, Ltd. (2 cm × 25 cm; mobile phase: acetonitrile:methanol = 3:7, flow rate: 15 mL/min) to obtain the title optically active compound with a retention time of 10.1 minutes resulting from analysis by CHIRALPAK™ IB manufactured by Daicel Chemical Industries, Ltd. (4.6 mm × 150 mm, mobile phase: hexane:ethanol = 85:15, flow rate: 1.0 mL/min, 40°C) and positive optical rotation (1.21 g, 94% ee) and the title optically active compound with a retention time of 9.25 minutes resulting from the same analysis and negative optical rotation (1.09 g, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 500 [M^++H].

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.96 (m, 1H), 2.13-2.29 (m, 2H), 2.29 (s, 3H), 2.42-2.48 (m, 1H), 4.14 (s, 3H), 4.27-4.41 (m, 2H), 4.64 (dd, J = 5.6, 8.8 Hz, 1H), 7.03 (dd, J = 5.2, 8.8 Hz, 1H), 7.17-7.22 (m, 1H), 7.44 (dd, J = 2.8, 9.2 Hz, 1H), 7.45 (d, J = 15.6 Hz, 1H), 7.58 (m, 1H), 7.61 (d, J = 15.6 Hz, 1H), 7.93 (s, 1H), 8.44 (d, J = 1.6 Hz, 1H).

The property values of the title optically active compound with negative optical

rotation are as follows. ESI-MS; m/z 500 [M^++H].

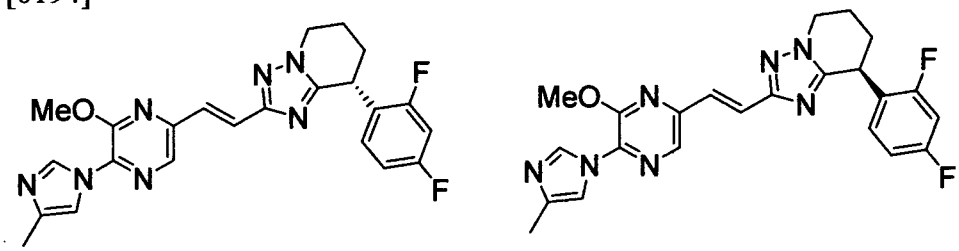
^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.96 (m, 1H), 2.12-2.31 (m, 2H), 2.29 (s, 3H), 2.42-2.48 (m, 1H), 4.14 (s, 3H), 4.27-4.41 (m, 2H), 4.64 (dd, J = 5.6, 8.8 Hz, 1H), 7.03 (dd, J = 5.2, 8.8 Hz, 1H), 7.17-7.22 (m, 1H), 7.44 (dd, J = 2.8, 9.2 Hz, 1H), 7.45 (d, J = 15.6 Hz, 1H), 7.58 (m, 1H), 7.61 (d, J = 15.6 Hz, 1H), 7.93 (s, 1H), 8.44 (d, J = 1.6 Hz, 1H).

[0193]

Examples 3 and 4

(+)-8-(2,4-Difluorophenyl)-2-{(E)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]vinyl}-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine and (-)-8-(2,4-difluorophenyl)-2-{(E)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]vinyl}-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine

[0194]



[0195]

Tris(dibenzylieneacetone)dipalladium (140 mg), tri(o-tolyl)phosphine (93.1 mg) and TEA (358 uL) were added to a suspension of 8-(2,4-difluoro-phenyl)-2-vinyl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Reference Example 5 (200 mg) and 5-bromo-3-methoxy-2-(4-methyl-1H-imidazol-1-yl)pyrazine obtained in Reference Example 1 (226 mg) in toluene (13.3 mL), followed by stirring at 110°C for 18 hours. The solid in the reaction solution was removed by filtration through celite, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Chromatorex™ NH manufactured by Fuji Silysia Chemical Ltd.(hereinafter abbreviated as "NH silica gel")) to obtain 124 mg of a racemate of the title compound. The resulting racemate was separated by CHIRALPAK™ IC manufactured by Daicel Chemical Industries, Ltd. (2 cm × 25 cm; mobile phase: acetonitrile:methanol = 3:7, flow rate: 13 mL/min) to obtain the title optically active compound with a retention time of 4.5 minutes resulting from analysis by CHIRALPAK™ IC manufactured by Daicel Chemical Industries, Ltd. (4.6 mm × 150 mm, mobile phase: acetonitrile:methanol = 3:7, flow rate: 1.0 mL/min, 40°C) (36.3 mg, >99% ee) and the title optically active compound with a retention time of 8.9 minutes resulting from the same analysis (49.4 mg, >99% ee).

The property values of the title optically active compound with a retention time of 4.5 minutes are as follows.

ESI-MS; m/z 450 [M^++H].

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.00-2.20 (m, 3H), 2.29 (s, 3H), 2.35-2.38 (m, 1H), 4.16 (s, 3H), 4.31 (m, 2H), 4.54 (m, 1H), 6.85-6.88 (m, 2H), 6.96 (m, 1H), 7.48 (d, J = 15.6 Hz, 1H), 7.69-7.65 (m, 2H), 7.94 (s, 1H), 8.45 (s, 1H).

The property values of the title optically active compound with a retention time of 8.9 minutes are as follows.

ESI-MS; m/z 450 [M^++H].

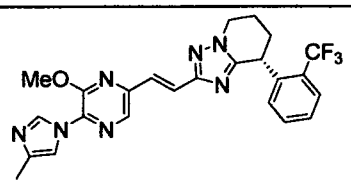
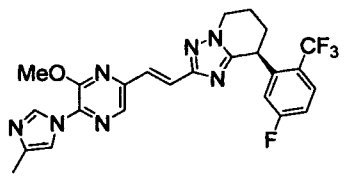
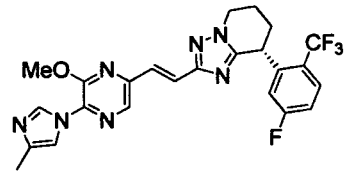
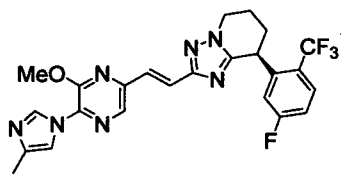
^{1}H-NMR ($CDCl_3$) δ (ppm): 2.00-2.26 (m, 3H), 2.29 (s, 3H), 2.33-2.40 (m, 1H), 4.16 (s, 3H), 4.30-4.32 (m, 2H), 4.54 (m, 1H), 6.82-6.89 (m, 2H), 6.96 (m, 1H), 7.48 (d, J = 15.6 Hz, 1H), 7.59-7.65 (m, 2H), 7.94 (s, 1H), 8.45 (s, 1H).

[0196]

The compounds of Examples 5 to 12 were obtained by the same method as in Examples 3 and 4 (Tables 1 and 2).

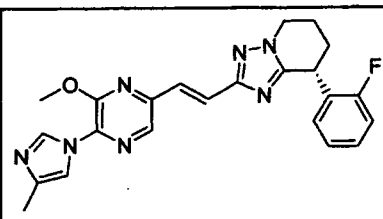
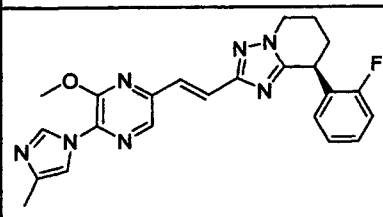
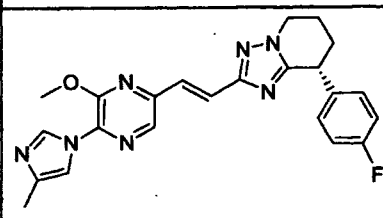
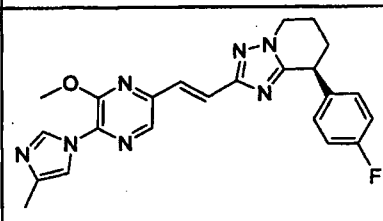
[0197]

Table 1

Example No.	Structural formula	^{1}H−NMR
Example 5		(CDCl$_3$) δ (ppm) : 1.92−1.99 (m, 1H), 2.17−2.29 (m, 2H), 2.29 (s, 3H), 2.45−2.49 (m, 1H), 4.14 (s, 3H), 4.29−4.39 (m, 2H), 4.70 (m, 1H), 7.02 (d, J=7.6Hz, 1H), 7.38−7.51 (m, 3H), 7.58−7.64 (m, 2H), 7.73 (d, J=8.0Hz, 1H), 7.93 (s, 1H), 8.44 (s, 1H).
Example 6		(CDCl$_3$) δ (ppm) : 1.94−1.97 (m, 1H), 2.13−2.29 (m, 2H), 2.29 (s, 3H), 2.44−2.49 (m, 1H), 4.14 (s, 3H), 4.33−4.37 (m, 2H), 4.70 (dd, J=6.0, 8.8Hz, 1H), 7.02 (d, J=7.6Hz, 1H), 7.38−7.51 (m, 3H), 7.58−7.64 (m, 2H), 7.73 (d, J=8.0Hz, 1H), 7.93 (s, 1H), 8.44 (s, 1H).
Example 7		(CDCl$_3$) δ (ppm) : 1.89−1.98 (m, 1H), 2.13−2.30 (m, 2H), 2.29 (s, 3H), 2.45−2.52 (m, 1H), 4.15 (s, 3H), 4.30−4.40 (m, 2H), 4.69 (dd, J=6.4, 8.4Hz, 1H), 6.73 (dd, J=2.4, 9.6Hz, 1H), 7.09 (m, 1H), 7.47 (d, J=16.0Hz, 1H), 7.58 (m, 1H), 7.62 (d, J=15.6Hz, 1H), 7.74 (dd, J=5.6, 8.8Hz, 1H), 7.94 (s, 1H), 8.45 (d, J=1.6Hz, 1H).
Example 8		(CDCl$_3$) δ (ppm) : 1.90−1.98 (m, 1H), 2.15−2.30 (m, 2H), 2.29 (s, 3H), 2.46−2.50 (m, 1H), 4.15 (s, 3H), 4.29−4.41 (m, 2H), 4.69 (dd, J=6.4, 8.4Hz, 1H), 6.73 (dd, J=2.4, 9.6Hz, 1H), 7.09 (m, 1H), 7.47 (d, J=16.0Hz, 1H), 7.58 (m, 1H), 7.62 (d, J=15.6Hz, 1H), 7.74 (dd, J=5.6, 8.8Hz, 1H), 7.94 (s, 1H), 8.45 (d, J=1.6Hz, 1H).

[0198]

Table 2

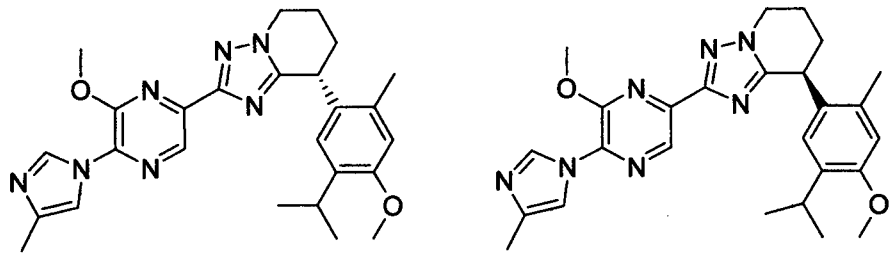
Example 9		(CD_3OD) δ (ppm) : 2.03-2.27 (m, 3H), 2.24 (s, 3H), 2.34-2.40 (m, 1H), 4.19 (s, 3H), 4.27-4.34 (m, 2H), 4.55 (m, 1H), 7.11-7.18 (m, 3H), 7.31-7.36 (m, 1H), 7.44 (d, J=15.6Hz, 1H), 7.54 (d, J=16.0Hz, 1H), 7.67 (s, 1H), 8.03 (s, 1H), 8.45 (d, J=1.2Hz, 1H).
Example 10		(CD_3OD) δ (ppm) : 2.03-2.27 (m, 3H), 2.24 (s, 3H), 2.34-2.40 (m, 1H), 4.19 (s, 3H), 4.27-4.34 (m, 2H), 4.55 (m, 1H), 7.11-7.18 (m, 3H), 7.31-7.36 (m, 1H), 7.44 (d, J=15.6Hz, 1H), 7.54 (d, J=16.0Hz, 1H), 7.67 (s, 1H), 8.03 (s, 1H), 8.45 (d, J=1.2Hz, 1H).
Example 11		(CD_3OD) δ (ppm) : 2.00-2.21 (m, 3H), 2.25 (s, 3H), 2.34-2.40 (m, 1H), 4.20 (s, 3H), 4.29-4.38 (m, 3H), 7.06-7.11 (m, 2H), 7.20-7.23 (m, 2H), 7.46 (d, J=15.6Hz, 1H), 7.56 (d, J=15.6Hz, 1H), 7.68 (m, 1H), 8.05 (s, 1H), 8.48 (d, J=1.6Hz, 1H).
Example 12		(CD_3OD) δ (ppm) : 2.01-2.23 (m, 3H), 2.25 (s, 3H), 2.33-2.38 (m, 1H), 4.20 (s, 3H), 4.29-4.38 (m, 3H), 7.06-7.11 (m, 2H), 7.20-7.23 (m, 2H), 7.46 (d, J=15.6Hz, 1H), 7.56 (d, J=15.6Hz, 1H), 7.68 (m, 1H), 8.05 (s, 1H), 8.48 (d, J=1.6Hz, 1H).

[0199]

Examples 13 and 14

Synthesis of (+) and (-)-8-(5-isopropyl-4-methoxy-2-methylphenyl)-2-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0200]



[0201]

A mixture of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine obtained in Reference Example 6 (120 mg), 3-methoxy-2-(4-methyl-1H-imidazol-1-yl)-5-tributylstannylpyrazine obtained by Reference Example 3 (270 mg), palladium (II) acetate (14.8 mg), 1,3-bis(diphenylphosphino)propane (54.3 mg), cuprous (I) oxide (94.2 mg) and 1-methyl-2-pyrrolidone (4 ml) was heated with stirring at 120°C in a nitrogen atmosphere for two hours. The reaction mixture was brought back to room temperature, diluted with ethyl acetate and then filtered through celite. Water and brine were added to the filtrate, and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (carrier: Chromatorex^{TM} NH) to obtain the racemic title compound. The racemic title compound was separated by CHIRALPAK^{TM} IC manufactured by Daicel Chemical Industries, Ltd. (2 cm × 25 cm; mobile phase: acetonitrile:methanol = 20:80, flow rate: 12 mL/min) to obtain the title optically active compound with a retention time of 9.8 minutes and positive optical rotation (13.9 mg, >99% ee) and the title optically active compound with a retention time of 10.8 minutes and negative optical rotation (12.7 mg, >99% ee).

The property values of the title optically active compound with positive optical rotation are as follows.

ESI-MS; m/z 474 [M^++H].

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.06 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.95-2.03 (m, 1H), 2.05-2.15 (m, 1H), 2.20-2.38 (m, 2H), 2.30 (d, J = 0.8 Hz, 3H), 2.35 (s, 3H), 3.19 (qq, J = 6.8, 6.8 Hz, 1H), 3.82 (s, 3H), 4.26 (s, 3H), 4.39-4.44 (m, 2H), 4.49 - 4.51 (m, 1H), 6.58 (s, 1H), 6.69 (s, 1H), 7.64 (dd, J = 1.2, 0.8 Hz, 1H), 8.49 (d, J = 1.2 Hz, 1H), 8.73 (s, 1H).

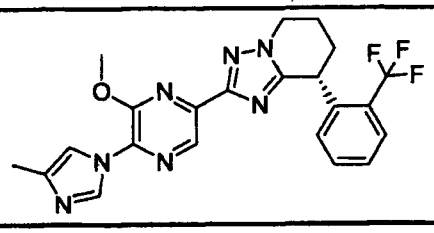
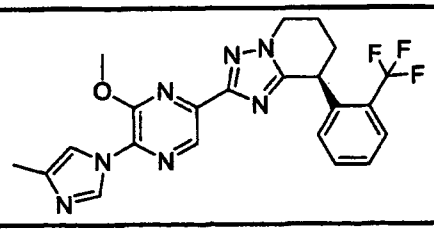
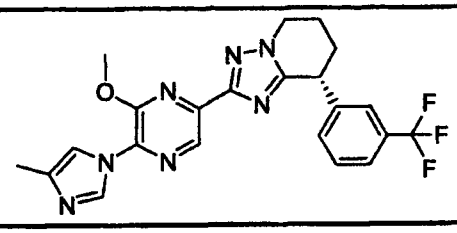
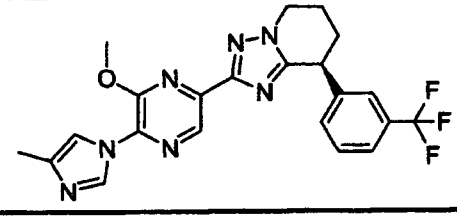
The property values of the title optically active compound with negative optical rotation coincided with those of the (+)-isomer.

[0202]

The compounds of Examples 15 to 18 were obtained by the same method as in Examples 13 and 14 (Table 3).

[0203]

Table 3

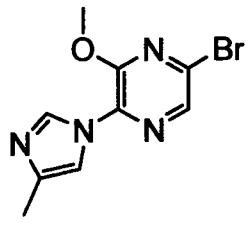
Example No.	Structural formula
Example 15	
Example 16	
Example 17	
Example 18	

[0204]

Reference Example 1

Synthesis of 5-bromo-3-methoxy-2-(4-methyl-1H-imidazol-1-yl)pyrazine

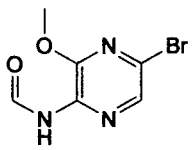
[0205]



[0206]

Synthesis of N-(5-bromo-3-methoxypyrazin-2-yl)formamide

[0207]



[0208]

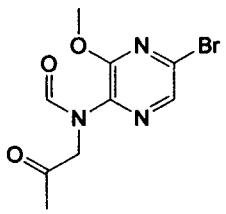
Acetic anhydride (150 ml) was added dropwise to formic acid (150 ml) under ice-cooling, followed by stirring at the same temperature for 25 minutes. A solution of 5-bromo-3-methoxypyrazin-2-ylamine (CAS #5900-13-0, 38.7 g) in THF (200 ml) was added dropwise to the reaction mixture over 10 minutes, and then the reaction solution was stirred at room temperature for one hour. Ice water was added to the reaction solution, and the precipitated powder was collected by filtration. The resulting powder was washed with water and then air-dried overnight to obtain 41.2 g of the title compound. The property values of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 4.06 (s, 3H), 7.87 (s, 1H), 7.87 (brd, J = 11.0 Hz, 1H), 9.37 (d, J = 11.0 Hz, 1H).

[0209]

Synthesis of N-(5-bromo-3-methoxypyrazin-2-yl)-N-(2-oxopropyl)formamide

[0210]



[0211]

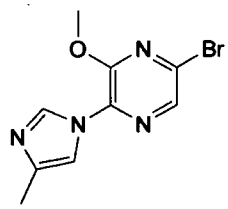
Chloroacetone (21.2 ml) was added dropwise to a suspension heated to 50°C of N-(5-bromo-3-methoxypyrazin-2-yl)formamide (41.2 g), cesium carbonate (92.7 g) and potassium iodide (3.09 g) in DMF (412 ml). Then, the reaction solution was stirred for 1.5 hours. The reaction solution was introduced into stirred ice water (3 L), and the precipitated powder was collected by filtration. The resulting powder was washed with water and then air-dried for three hours. Thereafter, 41.3 g of the title compound was obtained by drying under reduced pressure at room temperature. The property values of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.23 (s, 3H), 4.06 (s, 3H), 4.75 (s, 2H), 8.00 (s, 1H), 9.18 (s, 1H).

[0212]

Synthesis of 5-bromo-3-methoxy-2-(4-methyl-1H-imidazol-1-yl)pyrazine

[0213]



[0214]

A mixture of ammonium acetate (16.6 g), N-(5-bromo-3-methoxypyrazin-2-yl)-N-(2-oxopropyl)formamide (41.3 g), trifluoroacetic acid (16.6 ml) and toluene (268 ml) was heated under reflux for two hours while removing the moisture using a Dean-Stark apparatus. The reaction solution was brought back to room temperature. Ethyl acetate and ice water were added to the reaction solution, and the mixture was ice-cooled. Then, the reaction solution was made alkaline with concentrated aqueous ammonia, and then the organic layer was separated. The resulting organic layer was washed with brine and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and the eluted fraction was concentrated under reduced pressure. The resulting residue was solidified with tert-butyl methyl ether, and the solid was collected by filtration. The solid was washed with ether tert-butyl methyl ether-heptane (2:1) and air-dried to obtain 20.4 g of the title compound. The property values of the compound are as follows.

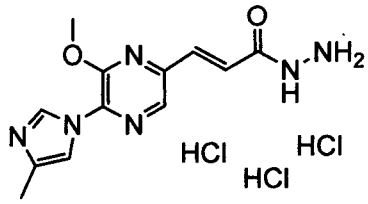
^{1}H-NMR ($CDCl_3$) δ (ppm): 2.29 (d, J = 1.2 Hz, 3H), 4.15 (s, 3H), 7.55 (dd, J = 1.2, 1.2 Hz, 1H), 8.09 (s, 1H), 8.40 (d, J = 1.2 Hz, 1H).

[0215]

Reference Example 2

Synthesis of (E)-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]acrylohydrazide trihydrochloride

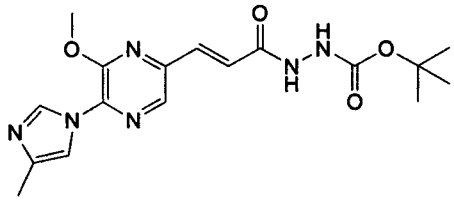
[0216]



[0217]

Synthesis of t-butyl 2-{(E)-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]acryloyl}hydrazinecarboxylate

[0218]



[0219]

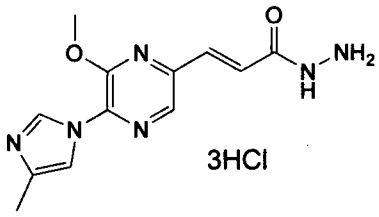
A mixture of 5-bromo-3-methoxy-2-(4-methyl-1H-imidazol-1-yl)pyrazine obtained in Reference Example 1 (15 g), t-butyl 2-acryloylhydrazinecarboxylate (CAS #28689-14-7, 11.5 g), tri-o-tolylphosphine (3.4 g), tris(dibenzylieneacetone)dipalladium (0) (5.14 g), IPEA (14.4 ml) and DMF (90.9 ml) was stirred at 100°C for two hours. The reaction solution was cooled to room temperature. Then, ethyl acetate (50 ml) and tert-butyl methyl ether (50 ml) were added to the reaction solution, followed by ice-cooling. The precipitated solid was collected by filtration. The resulting powder was washed with tert-butyl methyl ether-ethyl acetate (1:1) and then air-dried overnight to obtain 22.8 g of the title compound. The property values of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.51 (s, 9H), 2.30 (s, 3H), 4.17 (s, 3H), 6.96 (d, J = 15.2 Hz, 1H), 7.62 (brs, 1H), 7.67 (d, J = 15.2 Hz, 1H), 8.03 (s, 1H), 8.50 (brs, 1H).

[0220]

Synthesis of (E)-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]acrylohydrazide trihydrochloride

[0221]



[0222]

Concentrated hydrochloric acid (110 ml) was added to a suspension of t-butyl 2-{(E)-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrazin-2-yl]acryloyl}hydrazinecarboxylate (22.8 g) in methanol (110 ml), followed by stirring at room temperature for 4.5 hours. The reaction solution was filtered through celite. The filtrate was concentrated under reduced pressure. The residue was diluted with toluene and then concentrated under reduced pressure. Again, the residue was diluted with toluene and then concentrated under reduced pressure. The residue was diluted with THF and then the precipitated solid was collected by filtration. The solid was washed with THF and then dried under reduced pressure at room temperature to obtain 16.1 g of the title compound. The property values of the compound are as follows.

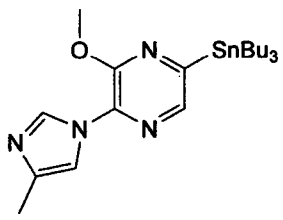
^{1}H-NMR (CD_3OD) δ (ppm): 2.46 (d, J = 1.2 Hz, 3H), 4.28 (s, 3H), 7.27 (d, J = 15.2 Hz, 1H), 7.84 (d, J = 15.2 Hz, 1H), 8.17 (dd, J = 1.6, 1.2 Hz, 1H), 8.38 (s, 1H), 9.72 (d, J = 1.6 Hz, 1H).

[0223]

Reference Example 3

Synthesis of 3-methoxy-2-(4-methyl-1H-imidazol-1-yl)-5-tributylstannylpyrazine

[0224]



[0225]

A mixture of 5-bromo-3-methoxy-2-(4-methyl-1H-imidazol-1-yl)pyrazine obtained in Reference Example 1 (500 mg), hexa-n-butylditin (1.48 ml), tetrakis(triphenylphosphine)dipalladium (0) (215 mg) and xylene (20 ml) was heated under reflux for one hour. The reaction solution was cooled to room temperature and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 270 mg of the title compound as an oil. The property values of the

compound are as follows.

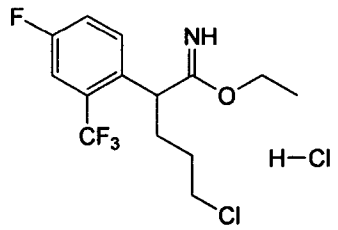
^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 - 0.94 (m, 9H), 1.31 - 1.56 (m, 12H), 1.62 - 1.66 (m, 6H), 2.30 (d, J = 0.8 Hz, 3H), 4.12 (s, 3H), 7.60 (dd, J = 1.2, 0.8 Hz, 1H), 7.98 (s, 1H), 8.45 (d, J = 1.2 Hz, 1H).

[0226]

Reference Example 4

Synthesis of ethyl 5-chloro-2-(4-fluoro-2-trifluoromethylphenyl)pentanimidate hydrochloride

[0227]



[0228]

Potassium tert-butoxide (9.58 g) was added to a solution of 4-fluoro-2-(trifluoromethyl)phenylacetonitrile (15.08 g) in THF (400 mL) under ice-cooling in a nitrogen atmosphere, and the mixture was stirred at the same temperature for 20 minutes. 1-Bromo-3-chloropropane (8.07 mL) was added to the reaction solution, followed by stirring for three hours. A saturated ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain crude 5-chloro-2-(4-fluoro-2-trifluoromethylphenyl)pentanenitrile.

A solution of the crude 5-chloro-2-(4-fluoro-2-trifluoromethylphenyl)pentanenitrile in ethanol (800 mL) was bubbled with hydrogen chloride gas under ice-cooling for one hour. Then, the reaction solution was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure. A solution of the residue in ethanol (800 mL) was bubbled again with hydrogen chloride gas under ice-cooling for one hour. Then, the reaction solution was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure. tert-Butyl methyl ether was added to the resulting residue. Trituration gave 13.4 g of the title compound. The property values of the compound are as follows.

ESI-MS; m/z 326 [M^++H].

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.41 (t, J = 7.2 Hz, 3H), 1.69-1.94 (m, 2H), 2.37 (m, 1H), 2.58 (m, 1H), 3.55-3.62 (m, 2H), 4.46 (dd, J = 7.2, 8.4 Hz, 1H), 4.64 (q, J = 7.2 Hz, 2H), 7.38 (m, 1H),

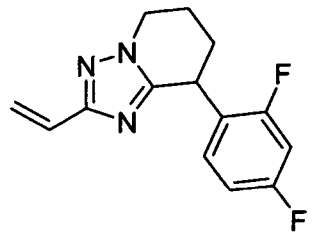
7.43 (dd, J = 2.8, 8.8 Hz, 1H), 7.90 (dd, J = 4.8, 13.6 Hz, 1H).

[0229]

Reference Example 5

Synthesis of 8-(2,4-difluorophenyl)-2-vinyl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

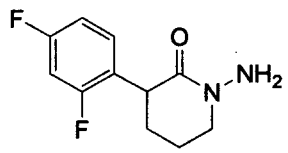
[0230]



[0231]

Synthesis of 1-amino-3-(2,4-difluorophenyl)piperidin-2-one

[0232]



[0233]

Thionyl chloride (7 mL) was added dropwise to a solution of 2,4-difluorophenylacetic acid (4 g) in methanol (80 mL) under ice-cooling, and then the reaction solution was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure. The resulting residue was allowed to pass through a short column to obtain a crude product of methyl (2,4-difluorophenyl)acetate.

Sodium hydride (containing 60% mineral oil, 976 mg) was added to a solution of the crude methyl (2,4-difluorophenyl)acetate in DMF (60 mL) under ice-cooling, followed by stirring at room temperature for 1.5 hours. The reaction solution was ice-cooled and 1-chloro-3-iodopropane (2.57 mL) was added dropwise. Then, the reaction solution was stirred at room temperature for three hours. A saturated ammonium chloride solution and ethyl acetate were added to the reaction solution, and the organic layer was separated. The resulting organic layer was sequentially washed with water and brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resulting residue was allowed to pass through a short column to obtain a crude product of methyl 5-chloro-2-(2,4-difluorophenyl)pentanoate.

Hydrazine monohydrate (11.3 mL) was added to a solution of the crude methyl 5-

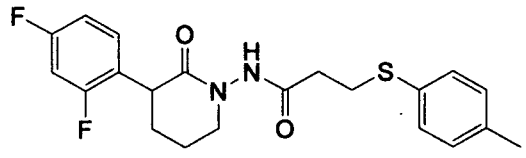
chloro-2-(2,4-difluorophenyl)pentanoate in ethanol (60 mL). The mixture was stirred at room temperature for 14 hours and then heated under reflux for 11 hours. The reaction solution was concentrated under reduced pressure. Ethyl acetate and a saturated sodium bicarbonate solution were added to the resulting residue, and the organic layer was separated. The resulting organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (carrier: Chromatorex™ NH) to obtain 2.97 g of the title compound. The property values of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.89-2.16 (m, 4H), 3.56-1.89-2.16 (m, 2H), 3.83 (m, 1H), 4, 58 (brs, 2H), 6.78-6.86 (m, 2H), 7.11 (m, 1H).

[0234]

Synthesis of N-[3-(2,4-difluorophenyl)-2-oxopiperidin-1-yl]-3-p-tolylsulfanylpropionamide

[0235]



[0236]

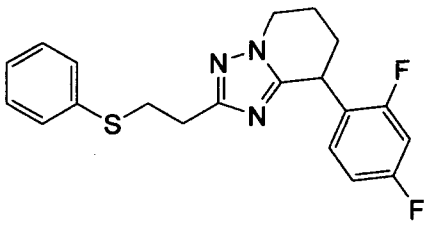
EDC (3.77 g), HOBT (2.66 g) and IPEA (9.13 mL) were sequentially added to a solution of 1-amino-3-(2,4-difluorophenyl)piperidine-2-one (2.97 g) and 3-[(4-methylphenyl)thio]propanoic acid (2.7 g) in DMF (90 mL), followed by stirring at room temperature for 27 hours. Ethyl acetate and water were added to the reaction solution, and the organic layer was separated. The resulting organic layer was dried over anhydrous magnesium sulfate, filtered through a silica pad and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain 3.66 g of the title compound. The property values of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.96-2.03 (m, 3H), 2.14 (m, 1H), 2.32 (s, 3H), 2.52 (m, 2H), 3.18 (m, 2H) 3.60-3.78 (m, 2H), 3.93 (m, 1H), 6.77-6.87 (m, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.22-7.30 (m, 4H), 7.84 (brs, 1H).

[0237]

Synthesis of 8-(2,4-difluorophenyl)-2-(2-p-tolylsulfanylethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine

[0238]



[0239]

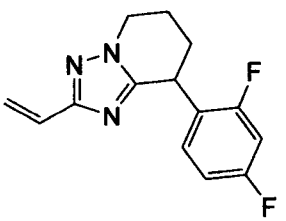
Phosphorus oxychloride (75.6 mL) was added to N-[3-(2,4-difluorophenyl)-2-oxopiperidin-1-yl]-3-p-tolylsulfanylpropionamide (3.66 g), followed by stirring at 120°C for one hour. Then, the reaction solution was concentrated under reduced pressure. Ammonium acetate (6.66 g) and acetic acid (90 mL) were sequentially added to the resulting residue, and the reaction mixture was stirred at 150°C for 2.5 hours. The reaction solution was concentrated under reduced pressure. Ethyl acetate and aqueous ammonia were added to the resulting residue, and the organic layer was separated. The resulting organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (carrier: Chromatorex^{TM} NH) to obtain 1.4 g of the title compound. The property values of the compound are as follows.

ESI-MS; m/z 386 [M^++H].

[0240]

Synthesis of 8-(2,4-difluorophenyl)-2-vinyl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0241]



[0242]

Sodium periodate (1.16 g) was added to a mixed solution of 8-(2,4-difluorophenyl)-2-(2-p-tolylsulfanylethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine (1.4 g) in Methanol (135 mL) and water (67.4 mL), followed by stirring at room temperature for 19 hours. The reaction solution was concentrated under reduced pressure. Then, ethyl acetate and water were added to the residue, and the organic layer was separated. The resulting organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. A solution of the resulting residue in toluene was heated under reflux for three days. The reaction

solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography. Then, the resulting product was allowed to pass through an NH silica pad to obtain 744 mg of the title compound. The property values of the compound are as follows.

ESI-MS; m/z 262 [M^++H].

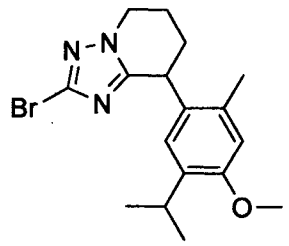
^{1}H-NMR ($CDCl_3$) δ (ppm): 1.96-2.19 (m, 3H), 2.32 (m, 1H), 4.25 (m, 2H), 4.52 (dd, J = 6.0, 7.22 Hz, 1H), 5.45 (dd, J = 1.6, 10.8 Hz, 1H), 6.15 (dd, J = 1.6, 17.6 Hz, 1H), 6.67 (dd, J = 10.8, 17.6 Hz, 1H), 6.79-6.92 (m, 3H).

[0243]

Reference Example 6

Synthesis of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

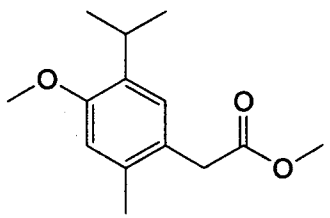
[0244]



[0245]

Synthesis of methyl (5-isopropyl-4-methoxy-2-methylphenyl)acetate

[0246]



[0247]

Thionyl chloride (3.5 ml) was added dropwise to a solution of (5-isopropyl-4-methoxy-2-methylphenyl)acetic acid (CAS No, 81354-65-6, 5.5 g) in methanol (50 ml) under ice-cooling. Then, the reaction solution was brought back to room temperature and stirred for two hours. The reaction solution was concentrated under reduced pressure. A saturated sodium bicarbonate solution and tert-butyl methyl ether were added to the residue, and the organic layer was separated. The resulting organic layer was washed with brine and then dried

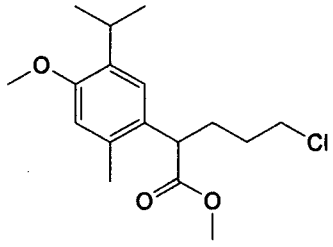
over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (5.0 g). The property values of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.19 (d, J = 7.2 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H), 2.28 (s, 3H), 3.25 (qq, J = 7.2, 7.2 Hz, 1H), 3.58 (s, 2H), 3.68 (s, 3H), 3.80 (s, 3H), 6.66 (s, 1H), 7.00 (s, 1H).

[0248]

Synthesis of methyl 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoate

[0249]



[0250]

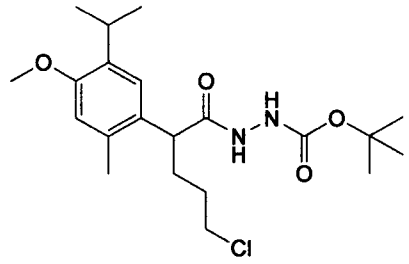
A solution of methyl (5-isopropyl-4-methoxy-2-methylphenyl)acetate (5 g) in anhydrous DMF (30 ml) was added to a suspension of 60% sodium hydride (928 mg) in anhydrous DMF (50 ml) at an internal temperature of 4 to 6°C in a nitrogen atmosphere, followed by stirring at the same temperature for five minutes. Then, 1-chloro-3-iodopropane (4.5 ml) was added to the reaction solution at internal temperature of 4 to 6°C. Thereafter, the reaction solution was brought back to room temperature and stirred for four hours. Ethyl acetate was added to the reaction solution, followed by washing with water. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (7.7 g). The property values of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.17 (d, J = 7.2 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H), 1.64-1.97 (m, 3H), 2.14-2.25 (m, 1H), 2.35 (s, 3H), 3.24 (qq, J = 7.2, 7.2 Hz, 1H), 3.48-3.56 (m, 2H), 3.64 (s, 3H), 3.77 (t, 7.6 Hz, 1H), 3.08 (s, 3H), 6.64 (s, 1H), 7.08 (s, 1H).

[0251]

Synthesis of tert-butyl N'-[5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoyl]hydrazinecarboxylate

[0252]



[0253]

A 5 N sodium hydroxide solution (22 ml) was added to a mixed solution of methyl 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoate (7.7 g) in methanol (25 ml)-THF (25 ml), followed by stirring at room temperature for four hours. The reaction solution was concentrated under reduced pressure. Water was added to the residue, followed by washing with heptane. The aqueous layer was made acidic with 5 N hydrochloric acid, followed by extraction with tert-butyl methyl ether. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration and the organic layer was concentrated under reduced pressure to obtain 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid (6.2 g).

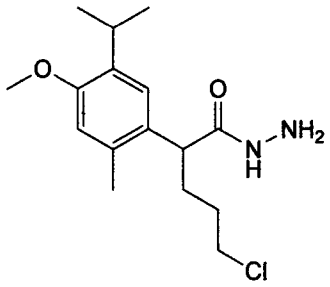
BOPCl (7.9 g) was added to a solution of 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid (6.2 g), tert-butyl carbazate (4.1 g) and IPEA (10.8 ml) in dichloromethane (120 ml) under ice-cooling. Then, the reaction solution was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure. A sodium bicarbonate solution and tert-butyl methyl ether were added to the residue, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (6.1 g). The property values of the compound are as follows.

ESI-MS; m/z 435 [M^++Na].

[0254]

Synthesis of 5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid hydrazide

[0255]



[0256]

A 4 N hydrogen chloride-ethyl acetate solution (50 ml) was added to a solution of tert-butyl N'-[5-chloro-2-(5-isopropyl-4-methoxy-2-methylphenyl)pentanoyl]hydrazinecarboxylate (6.1 g) was dissolved in ethyl acetate (50 ml), followed by stirring at room temperature for 3.5 hours. The reaction solution was made alkaline with a 5 N sodium hydroxide solution under ice-cooling, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (4.4 g). The property values of the compound are as follows.

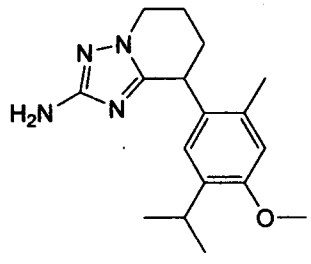
ESI-MS; m/z 313 [M^++H].

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.186 (d, J = 6.8 Hz, 3H), 1.190 (d, J = 7.2 Hz, 3H), 1.61-1.85 (m, 2H), 1.93-2.04 (m, 1H), 2.26-2.88 (m, 1H), 2.27 (s, 3H), 3.25 (qq, J = 7.2, 6.8 Hz, 1H), 3.48-3.59 (m, 3H), 3.75-3.89 (m, 5H), 6.49 (br s, 1H), 6.65 (s, 1H), 7.08 (s, 1H).

[0257]

Synthesis of 8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-2-ylamine

[0258]



[0259]

p-Toluenesulfonic acid monohydrate (4 g) was added to a solution of 5-chloro-2-

(5-isopropyl-4-methoxy-2-methylphenyl)pentanoic acid hydrazide (4.4 g) and cyanamide (3.6 g) in ethanol (150 ml), and the mixture was heated under reflux at 80°C for two hours. After cooling to room temperature, TEA (9.8 ml) was added to the reaction solution, and the mixture was further heated under reflux at 80°C for three days. The reaction solution was concentrated under reduced pressure. A sodium bicarbonate solution and ethyl acetate were added to the residue, and the organic layer was separated. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (2.4 g). The property values of the compound are as follows.

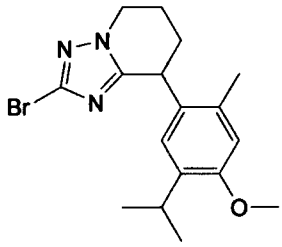
ESI-MS; m/z 301 [M^++H].

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.12 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.86-2.26 (m, 4H), 2.27 (s, 3H), 3.19 (qq, J = 6.8, 6.8 Hz 1H), 3.79 (s, 3H), 4.02 (br s, 2H), 4.06-4.12 (m, 2H), 4.19-4.24 (m, 1H), 6.64 (s, 1H), 6.69 (s, 1H).

[0260]

Synthesis of 2-bromo-8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridine

[0261]



[0262]

Isoamyl nitrite (1 mL) was added to a solution of 8-(5-isopropyl-4-methoxy-2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-a]pyridin-2-ylamine (1.5 g) and copper (II) bromide (1.7 g) in acetonitrile (50 mL), and the mixture was heated with stirring at 70°C for 45 minutes. Ethyl acetate was added to the reaction solution, followed by washing with aqueous ammonia. The resulting organic layer was washed with brine and then dried over anhydrous sodium sulfate. The drying agent was separated by filtration, and then the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain the title compound (1.4 g). The property values of the compound are as follows.

ESI-MS; m/z 364 [M^++H].

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.11 (d, J = 7.2 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 1.90-2.30 (m, 4H), 2.26 (s, 3H), 3.19 (qq, J = 7.2, 7.2 Hz, 1H), 3.80 (s, 3H), 4.24-4.29 (m, 2H), 4.30-4.36 (m, 1H), 6.59 (s, 1H), 6.65 (s, 1H).

[0263]

Test Example 1

Quantification of Aβ peptide in culture of neurons from rat fetus brain

The present inventors performed the following tests in order to exhibit utility of the compound of the general formula (I) according to the present invention.

[0264]

(1) Rat primary neuronal culture

Primary neuronal cultures were prepared from the cerebral cortex of embryonic day 18 Wistar rats (Charles River Japan, Yokohama, Japan). Specifically, the embryos were aseptically removed from pregnant rats under ether anesthesia. The brain was isolated from the embryo and immersed in an ice-cold L-15 medium (Invitrogen Corp. Cat #11415-064, Carlsbad, CA, USA, or SIGMA L1518, for example). The cerebral cortex was collected from the isolated brain under a stereoscopic microscope. The cerebral cortex fragments collected were enzymatically treated in an enzyme solution containing 0.25% trypsin (Invitrogen Corp. Cat #15050-065, Carlsbad, CA, USA) and 0.01% DNase (Sigma D5025, St. Louis, MO, USA) at 37°C for 30 minutes to disperse the cells. Here, the enzymatic reaction was stopped by adding inactivated horse serum to the solution. The enzymatically treated solution was centrifuged at 1,500 rpm for five minutes to remove the supernatant. 5 to 10 ml of a medium was added to the resulting cell mass. Neurobasal medium (Invitrogen Corp. Cat #21103-049, Carlsbad, CA, USA) supplemented with 2% B27 supplement (Invitrogen Corp. Cat #17504-044, Carlsbad, CA, USA), 25 μM 2-mercaptoethanol (2-ME, WAKO Cat #139-06861, Osaka, Japan), 0.5 mM L-glutamine (Invitrogen Corp. Cat #25030-081, Carlsbad, CA, USA), and Antibiotics-Antimycotics (Invitrogen Corp. Cat #15240-062, Carlsbad, CA, USA) was used as the medium (Neurobasal/B27/2-ME). However, the above Neurobasal medium not supplemented with 2-ME (Neurobasal/B27) was used for the assay. The cells were redispersed by mild pipetting of the cell mass to which the medium was added. The cell dispersion was filtered through a 40-μm nylon mesh (Cell Strainer, Cat #35-2340, Becton Dickinson Labware, Franklin Lakes, NJ, USA) to remove the remaining cell mass, and thus a neuronal cell suspension was obtained. The neuronal cell suspension was diluted with the medium and then plated in a volume of 100 μl/well at an initial cell density of 5×10^5 cells/cm^2 in a 96-well polystyrene culture plate pre-

coated with poly-L or D-lysine (Falcon Cat #35-3075, Becton Dickinson Labware, Franklin Lakes, NJ, USA coated with poly-L-lysine using the method shown below, or BIOCOAT™ cell environments Poly-D-lysine cell ware 96-well plate, Cat #35-6461, Becton Dickinson Labware, Franklin Lakes, NJ, USA). Poly-L-lysine coating was carried out as follows. 100 μg/ml of a poly-L-lysine (SIGMA P2636, St. Louis, MO, USA) solution was aseptically prepared with a 0.15 M borate buffer (pH 8.5). 100 μg/well of the solution was added to the 96-well polystyrene culture plate and incubated at room temperature for one or more hours or at 4°C overnight or longer. Thereafter, the coated 96-well polystyrene culture plate was washed with sterile water four or more times, and then dried or rinsed with sterile PBS or medium, and used for cell plating. The plated cells were cultured in the culture plate at 37°C in 5% CO_2-95% air for one day. Then, the total amount of the medium was replaced with a fresh Neurobasal/B27/2-ME medium, and then the cells were cultured for further three days.

[0265]

Addition of compounds

The drug was added to the culture plate on Day 4 of culture as follows. The total amount of the medium was removed from the wells, and 180 μl/well of Neurobasal medium not containing 2-ME and containing 2% B-27 (Neurobasal/B27) was added thereto. A solution of the test compound in dimethyl sulfoxide (hereinafter abbreviated as DMSO) was diluted with Neurobasal/B27 to a concentration 10-fold higher than the final concentration. 20 μl/well of the dilution was added to and sufficiently mixed with the medium. The final DMSO concentration was 1% or less. Only DMSO was added to the control group.

[0266]

Sampling

The cells were cultured for three days after addition of the compound, and the total amount of the medium was collected. The resulting medium was used as an ELISA sample.

[0267]

Evaluation of cell survival

Cell survival was evaluated by an MTT assay according to the following procedure. After collecting the medium, 100 μl/well of a pre-warmed medium was added to the wells. Further, 8 μl/well of a solution of 8 mg/ml of MTT (SIGMA M2128, St. Louis, MO, USA) in D-PBS(-) (Dulbecco's phosphate buffered Saline, SIGMA D8537, St. Louis, MO, USA) was added to the wells. The 96-well polystyrene culture plate was incubated in an incubator at

37°C in 5% CO_2 -95% air for 20 minutes. 100 μl/well of an MTT lysis buffer was added thereto, and MTT formazan crystals were sufficiently dissolved in the buffer in the incubator at 37°C in 5% CO_2 -95% air. Then, the absorbance at 550 nm in each well was measured. The MTT lysis buffer was prepared as follows. 100 g of SDS (sodium dodecyl sulfate (sodium lauryl sulfate), WAKO 191-07145, Osaka, Japan) was dissolved in a mixed solution of 250 mL of N,N-dimethylformamide (WAKO 045-02916, Osaka, Japan) with 250 mL of distilled water. 350 μl each of concentrated hydrochloric acid and acetic acid were further added to the solution to allow the solution to have a final pH of about 4.7.

Upon measurement, wells having no cells plated and containing only the medium and MTT solution were set as background (bkg). The measured values were respectively applied to the following formula including subtracting bkg values from them. Thus, the proportion against the control group (group not treated with the drug, CTRL) (% of CTRL) was calculated to compare and evaluate cell survival activities.

$$\%\ \text{of CTRL} = ((A550\_\text{sample} - A550\_\text{bkg})/(A550\_\text{CTRL} - \text{bkg})) \times 100$$

(A550_sample: absorbance at 550 nm of sample well, A550_bkg: absorbance at 550 nm of background well, A550_CTRL: absorbance at 550 nm of control group well)

[0268]

Aβ ELISA

For Aβ ELISA, Human/Rat β Amyloid (42) ELISA Kit Wako (#290-62601) from Wako Pure Chemical Industries, Ltd. or Human Amyloid beta (1-42) Assay Kit (#27711) from IBL Co., Ltd. was used. Aβ ELISA was carried out according to the protocols recommended by the manufacturers (methods described in the attached documents). However, the Aβ calibration curve was created using beta-amyloid peptide 1-42, rat (Calbiochem, #171596 [$A\beta_{42}$]). The results are shown in Table 1 as percentage to the Aβ concentration in the medium of the control group (% of CTRL).

[0269]

From the results of Aβ concentrations, the concentration of each compound that decreases Aβ concentration by 50% of control (IC50) was calculated. Those data are shown in Table 4.

[0270]

Table 4

Test compound	Aβ42 production reducing effect IC50 (nM)
Example 2	41
Example 6	18
Example 8	39
Example 10	72
Example 12	81
Example 14	8

[0271]

As is clear from the results of Table 4, the compound of the present invention was proved to have an Aβ42 production reducing effect.

[0272]

Accordingly, the compound of the general formula (I) or pharmacologically acceptable salt thereof according to the present invention have an Aβ42 production reducing effect. Thus, the present invention can particularly provide a therapeutic agent for a neurodegenerative disease caused by Aβ such as Alzheimer's disease or Down's syndrome.

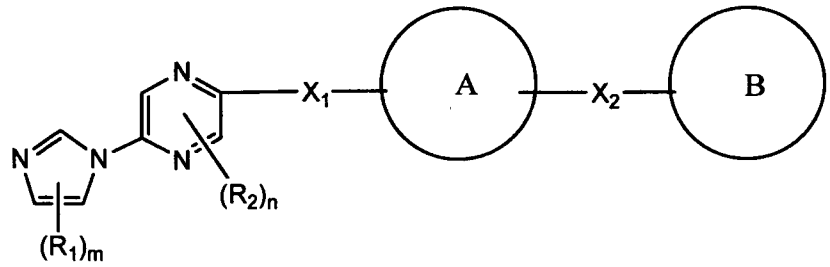
INDUSTRIAL APPLICABILITY

[0273]

The compound of the general formula (I) according to the present invention has an Aβ production reducing effect, and thus is particularly useful as a therapeutic agent for a neurodegenerative disease caused by Aβ such as Alzheimer's disease or Down's syndrome.

CLAIMS

1. A compound represented by the formula [I]:



[I]

or a pharmacologically acceptable salt or ester thereof,

wherein R_1 and R_2 are the same or different and each represent a substituent selected from the following Substituent Group a1;

m represents an integer of 0 to 3;

n represents an integer of 0 to 2;

X_1 represents i) a single bond, ii)

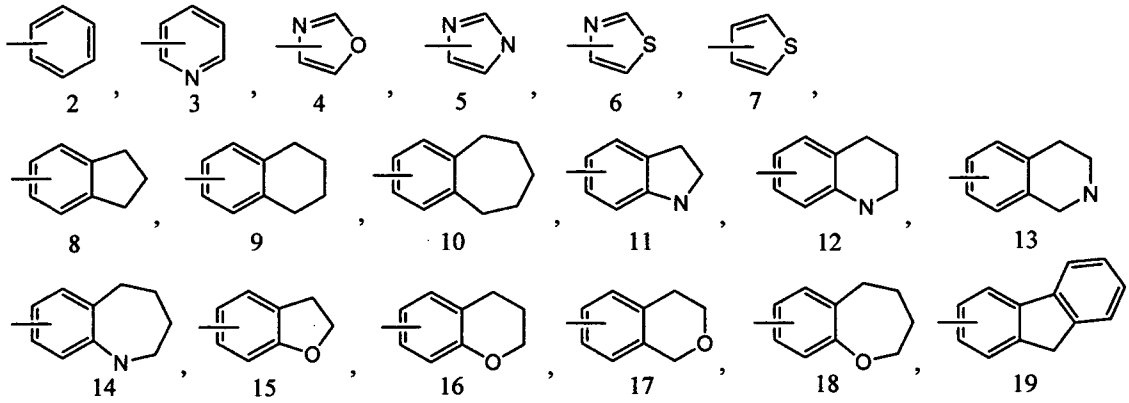
—C≡C—

or iii) $-CR_3=CR_4-$ (wherein R_3 and R_4 are the same or different and each represent (1) a hydrogen atom, (2) a C1-6 alkyl group or (3) a halogen atom);

X_2 represents i) a single bond, ii) a C1-6 alkylene group or iii) $-X_3-$ (wherein X_3 represents $-NR_5-$, -O-, -C(O)-, -S-, -S(O)- or $-S(O)_2-$ and R_5 represents a hydrogen atom, a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkanoyl group or a C1-6 alkylsulfonyl group);

Ring A represents i) a five-membered aromatic heterocyclic group or ii) a five-membered aromatic heterocyclic group fused with a 5- to 14-membered non-aromatic ring group, which contains two or more nitrogen atoms and may have 1 to 3 substituents selected from the following Substituent Group b1 (wherein the non-aromatic ring group may have a crosslinked structure or a spiro ring system); and

Ring B represents a monocyclic or fused cyclic aromatic ring group selected from the group consisting of the formulas [2] to [19]:



each of which may have 1 to 3 substituents selected from the following Substituent Group c1,

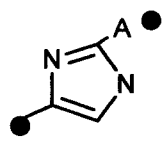
Substituent Group a1: a C1-6 alkyl group, a C3-8 cycloalkyl group, a C2-6 alkenyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, an amino group (wherein the amino group may have one C2-6 alkanoyl group or C1-6 alkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group and a nitro group;

Substituent Group b1: a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C2-6 alkenyl group, a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C2-6 alkenyloxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C4-9 cycloalkylcarbonyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C2-6 alkenylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a C1-6 alkylthio group, a C2-6 alkenylthio group, a C3-8 cycloalkylthio group, an aminosulfonyl group (wherein the aminosulfonyl group may have 1 to 2 C1-6 alkyl groups, C2-6 alkenyl groups or C3-8 cycloalkyl groups), an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), a cyano group, a formyl group, a halogen atom, a hydroxyl group, a nitro group, an oxo group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 1-homopiperidinyl group, an indolin-1-yl group, a 1,2,3,4-tetrahydroquinolin-1-yl group and a 4-morpholinyl group;

Substituent Group c1: i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C2-6 alkenyl group, v)-iii) a C2-6 alkynyl group, v)-iv) a C1-6 alkoxy group, v)-v) a C1-6 alkylthio group, v)-vi) a C1-6 alkylaminocarbonyl

group, v)-vii) a C1-6 alkylsulfonyl group, v)-viii) a C1-6 alkylaminosulfonyl group, v)-ix) a C2-6 alkanoyl group, v)-x) a phenyl group, v)-xi) a pyridyl group, v)-xii) a pyridazinyl group, v)-xiii) a pyrimidinyl group, v)-xiv) a 1-pyrrolidinyl group, v)-xv) a 1-piperidinyl group, v)-xvi) a 1-homopiperidinyl group and v)-xvii) a 4-morpholinyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom.

2. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein Ring A is a five-membered aromatic heterocyclic group selected from the group consisting of the formulas [20] to [26]:



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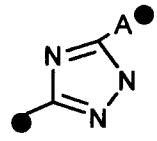

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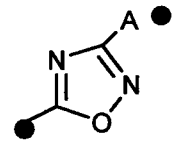

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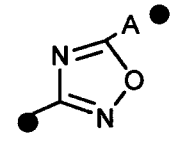

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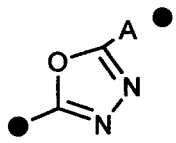

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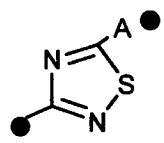

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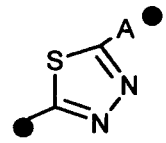

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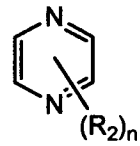
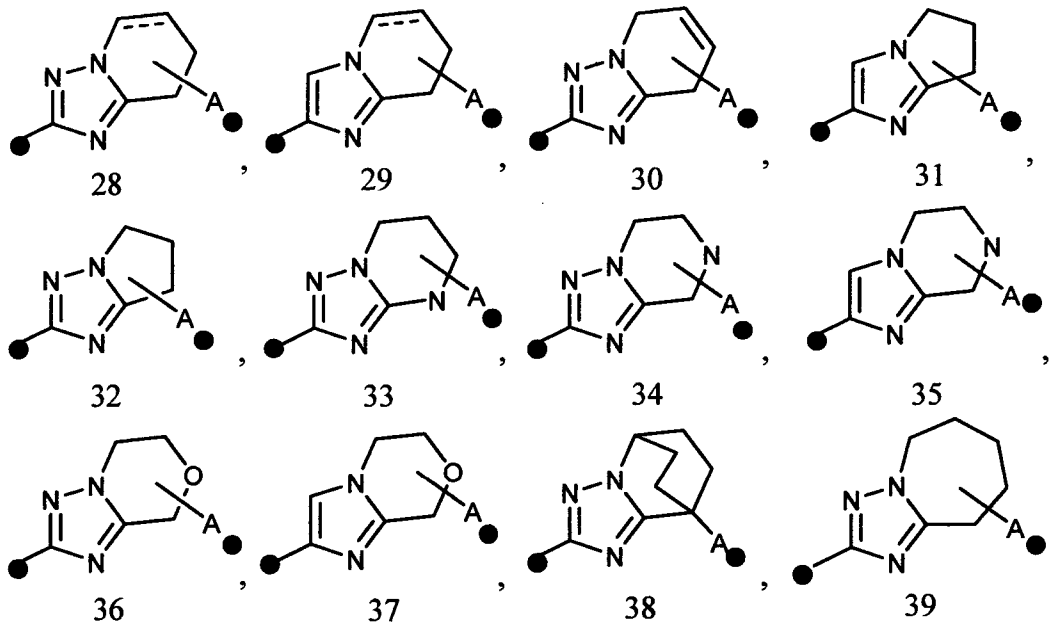
26

wherein • represents a bonding site to the formula [27]:

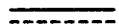


27 and

A• represents a bonding site to X_2, or any one ring selected from the group consisting of the formulas [28] to [39]:



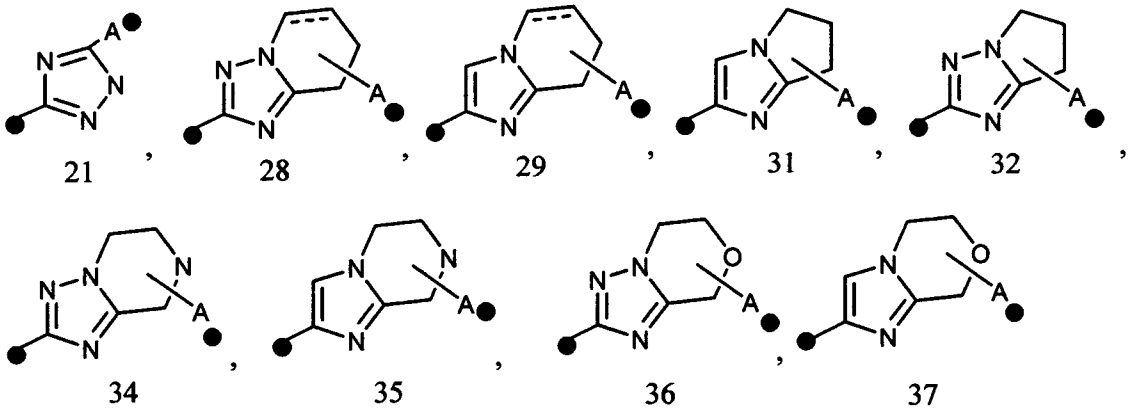
wherein • and A• are as defined above and the partial structure:



represents a single bond or a double bond,

each of which may have 1 to 3 substituents selected from Substituent Group b1.

3. The compound or pharmacologically acceptable salt or ester thereof according to claim 2, wherein Ring A is any one ring selected from the group consisting of the formulas [21], [28], [29], [31], [32] and [34] to [37]:

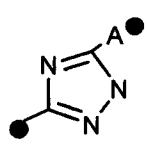


wherein •, A• and the partial structure:

are as defined above.

4. The compound or pharmacologically acceptable salt or ester thereof according to claim 2, wherein Ring A is any one ring selected from the group consisting of the formulas [21],

[28-1], [29-1], [31-1], [32-1] and [34-1] to [37-1]: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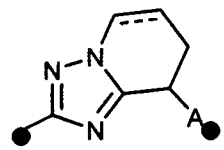
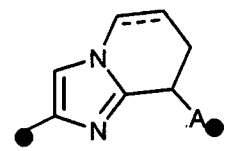

28-1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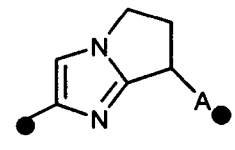
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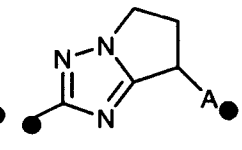
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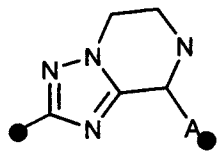
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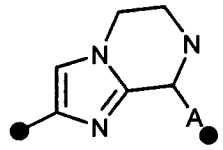
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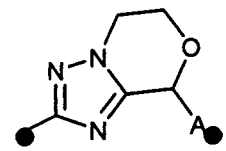
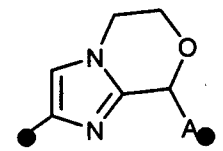
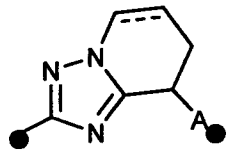

36-1


37-1

wherein •, A• and the partial structure:

are as defined above.

5. The compound or pharmacologically acceptable salt or ester thereof according to claim 2, wherein Ring A is a ring of the formula [28-1]:


28-1

wherein •, A• and the partial structure:

are as defined above.

6. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein Ring B is a phenyl group, a pyridyl group, an oxazolyl group, an imidazolyl group, an thiazolyl group, a dihydrobenzofuranyl group or a thienyl group.

7. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein X_1 is i) a single bond or ii) $-CR_3=CR_4-$.

8. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein X_1 is a single bond.

9. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein X_1 is $-CR_3=CR_4-$.

10. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein X_2 is i) a single bond or ii) a C1-6 alkylene group.

11. The compound or pharmacologically acceptable salt or ester thereof according to

claim 1, wherein X_2 is a single bond.

12. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein R_1 is a C1-6 alkyl group or a halogen atom and m is 1 to 2.

13. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein R_2 is a C1-6 alkoxy group and n is 1.

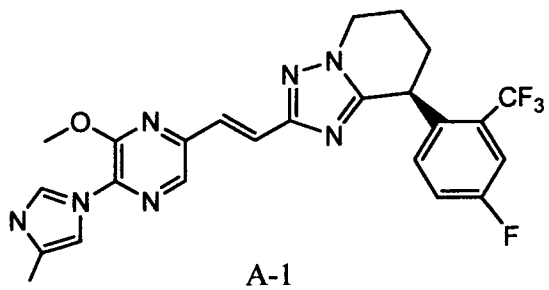
14. The compound or pharmacologically acceptable salt or ester thereof according to claim 9, wherein R_3 and R_4 are the same or different and are each (1) a hydrogen atom or (2) a halogen atom.

15. The compound or pharmacologically acceptable salt or ester thereof according to claim 9, wherein R_3 and R_4 are each a hydrogen atom.

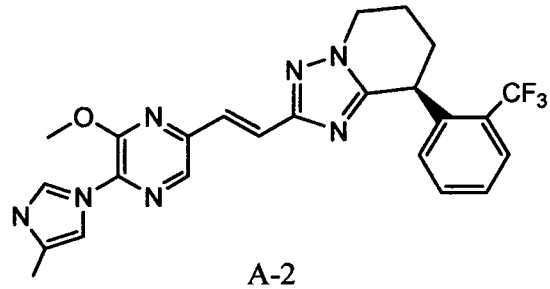
16. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein the substituent for Ring A is a substituent selected from the group consisting of: a C1-6 alkyl group (wherein the alkyl group may be substituted with 1 to 3 halogen atoms), a C3-8 cycloalkyl group, a C6-14 aryl group, a C6-14 aryl-C1-6 alkyl group, a C1-6 alkoxy group, a C3-8 cycloalkyloxy group, a C2-6 alkanoyl group, a C7-15 aroyl group, a C1-6 alkylsulfonyl group, a C3-8 cycloalkylsulfonyl group, a C6-14 arylsulfonyl group, a cyano group, a formyl group, a halogen atom, a hydroxyl group and an oxo group.

17. The compound or pharmacologically acceptable salt or ester thereof according to claim 1, wherein the substituent for Ring B is a substituent selected from the group consisting of: i) an amino group (wherein the amino group may have one C2-6 alkanoyl group, C1-6 alkylsulfonyl group or C3-8 cycloalkylsulfonyl group or 1 to 2 C1-6 alkyl groups or C3-8 cycloalkyl groups), ii) a cyano group, iii) a halogen atom, iv) a hydroxyl group and v) v)-i) a C1-6 alkyl group, v)-ii) a C1-6 alkoxy group, v)-iii) a C1-6 alkylthio group and v)-iv) a phenyl group, each of which may have 1 to 3 substituents selected from the group consisting of a C1-6 alkyl group and a halogen atom.

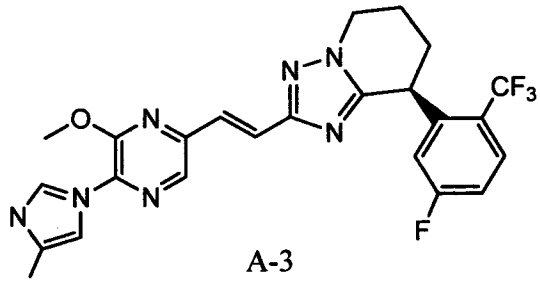
18. One compound selected from the group consisting of the formulas [A-1] to [A-7]:



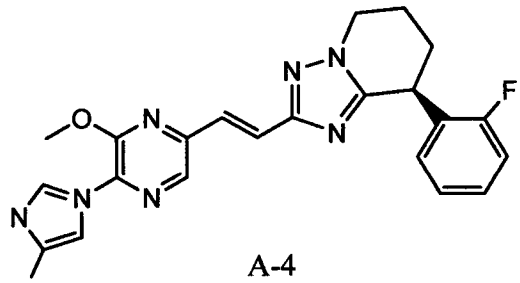
A-1



A-2



A-3



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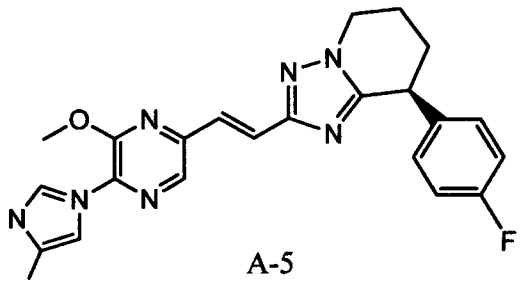

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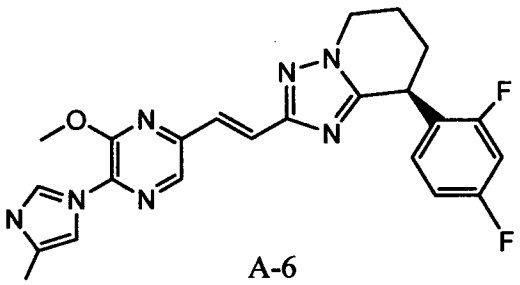

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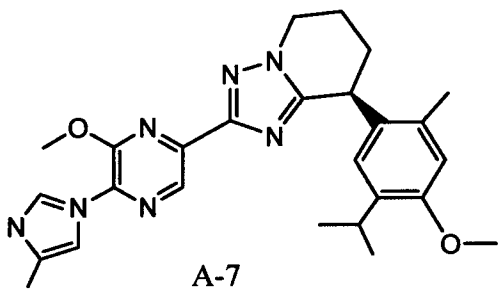

A-7

or a pharmacologically acceptable salt or ester thereof.

19. A medicine comprising the compound or pharmacologically acceptable salt or ester thereof according to any one of claims 1 to 18 as an active ingredient.

20. The medicine according to claim 19 for the treatment of a disease selected from Alzheimer's disease, dementia, Down's syndrome and amyloidosis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2010/053378

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/498 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/110350 A2 (NEUROGENETICS INC [US]; CHENG SOAN [US]; COMER DANIEL D [US]; MAO LONG) 23 December 2004 (2004-12-23) the whole document	1,2, 6-17,20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 May 2010	07/06/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Diederen, Jeroen

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2010/053378

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004110350 A2	23-12-2004	AU 2004247013 A1	23-12-2004
		BR PI0410348 A	30-05-2006
		CA 2525547 A1	23-12-2004
		EP 1628666 A2	01-03-2006
		JP 2007504282 T	01-03-2007
		KR 20060023529 A	14-03-2006
		MX PA05012281 A	19-05-2006