DESCRIPTION

CINNAMIDE COMPOUND

Technical Field

[0001]

The present invention relates to a pharmaceutical agent, particularly an agent of reducing amyloid beta (hereinafter referred to as Aβ) production, which is effective in the treatment of neurodegenerative diseases caused by Aβ, such as Alzheimer's disease and Down syndrome.

Background Art

[0002]

Alzheimer's disease is a disease characterized by degeneration and loss of neurons and also by the formation of senile plaques and neurofibrillary change. Presently, treatment of Alzheimer's disease is limited to symptomatic therapies with a symptom-improving agent represented by an acetylcholinesterase inhibitor, and the basic remedy which prevents progress of the disease has not been developed. A method of controlling the cause of onset of pathologic conditions needs to be developed for creation of the basic remedy of Alzheimer's disease.

Aβ protein, which is a metabolite of amyloid precursor protein (hereinafter referred to as APP), is

considered to be greatly involved in degeneration and loss of neurons as well as onset of demential conditions (for example, see Non-Patent Document 1 and Non-Patent Document 2). The main components of Aβ protein are Aβ40 consisting of 40 amino acids and Aβ42 having two additional amino acids at the C-terminal. The Aβ40 and Aβ42 tend to aggregate (for example, see Non-Patent Document 3) and constitute main components of senile plaques (for example, Non-Patent Document 3, Non-Patent Document 4 and Non-Patent Document 5), and furthermore, it is known that mutations of APP and presenelin genes, which is observed in familial Alzheimer's disease, increase production of Aβ40 and Aβ42 (for example, see Non-Patent Document 6, Non-Patent Document 7 and Non-Patent Document 8). Therefore, compounds which reduce production of Aβ40 and Aβ42 are expected as an agent for controlling progress of Alzheimer's disease or for preventing the disease.

These Aβs are produced when APP is cleaved by beta secretase and subsequently clipped by gamma secretase. In consideration of this, creation of inhibitors of γ secretase and β secretase has been attempted for the purpose of reducing production of Aβs. Many of these secretase inhibitors already known are peptides or peptidomimetics such as L-685,458 (for example, see Non-Patent Document 9) and LY-411575 (for example, see Non-Patent Document 10, Non-Patent

Document 11 and Non-Patent Document 12).

Non-Patent Document 1: Klein WL, and seven others, Related Articles, Links 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;

Non-Patent Document 2: 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;

Non-Patent Document 3: 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;

Non-Patent Document 4: 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;

Non-Patent Document 5: Masters CL, and six others, Amyloid plaque core protein in Alzheimer disease and Down syndrome, Proceeding 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 4 others, Differential effects of the swedish mutant amyloid precursor protein on β-amyloid accumulation and secretion in neurons and nonneuronal cells, 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 cleavages, 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), 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, Journal of Biological Chemistry, 2004, Mar 26, 279(13), p. 12876-12882.

Disclosure of the Invention

Problems to be Solved by the Invention

[0003]

As mentioned above, compounds which prevent production of Aβ40 and Aβ42 from APP are expected as an preventive or therapeutic agent for diseases caused by Aβ represented by Alzheimer's disease. However, non-peptide compounds which prevent production of Aβ40 and Aβ42 and have an excellent medicinal effect have not been known. Therefore, a novel low molecular compound that inhibits production of Aβ40 and Aβ42 is demanded.

Means for Solving the Problems

[0004]

The present inventors have conducted intensive studies and first discovered non-peptidic

cinnamide compounds which inhibit production of Aβ40 and Aβ42 from APP and discovered preventive or therapeutic agents for diseases caused by Aβ, represented by Alzheimer's disease, thereby completed the present invention.

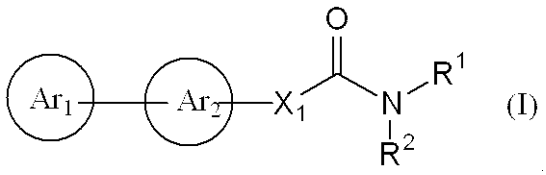
[0005]

That is, the present invention relates to the followings:

1) A compound or a pharmacologically acceptable salt thereof represented by Formula (I):

[0006]

[Formula 1]



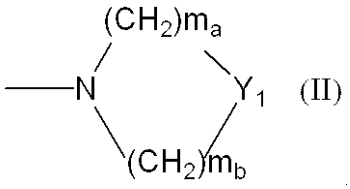
(wherein Ar_1 represents an imidazolyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A1 shown below; Ar_2 represents a pyridinyl group, a pyrimidinyl group, or a phenyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A2 shown below; X_1 represents (1) $-C\equiv C-$ or (2) $-CR^3=CR^4-$ (wherein R^3 and R^4 represents a substituent selected from Substituent Group A3 shown below); and

(1) R^1 and R^2 represent groups selected from Substituent Group A4 shown below or

R^1 and R^2, together with a nitrogen atom to which they bind, form one of the following groups:

(2-1) a 5- to 11-membered non-aromatic heterocyclic group represented by Formula (II):

[Formula 2]



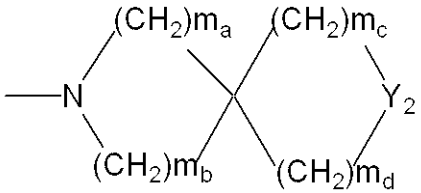
(II)

(wherein Y_1 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO-, (10) $-CR^5=CR^6-$ (wherein R^5 and R^6 represent substituents selected from Substituent Group A4 shown below), (11) a single bond or (12) $>C=CR^{13}R^{14}$ (wherein R^{13} and R^{14} represent substituents selected from Substituent Group A4 shown below); and

m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(2-2) a 6- to 20-membered non-aromatic heterocyclic group represented by Formula (III):

[Formula 3]



(III)

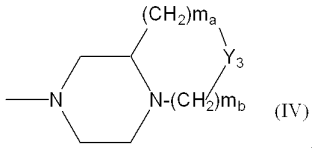
(wherein Y_2 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9)

–NHCO–, (10) $-CR^5=CR^6-$ (wherein R^5 and R^6 represent substituents selected from Substituent Group A4 shown below or R^5 and R^6, together with a carbon atom to which they bind, form a 6- to 14-membered aromatic hydrocarbon ring group or a 6- to 14-membered non-aromatic hydrocarbon ring group) or (11) a single bond; and

m_a, m_b, m_c and m_d represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(2-3) a 9- to 16-membered non-aromatic heterocyclic group represented by Formula (IV):

[Formula 4]



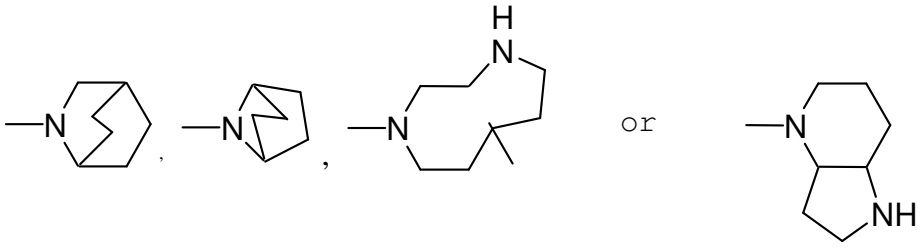
(IV)

(wherein Y_3 represents (1) –NH–, (2) –O–, (3) –S–, (4) –SO–, (5) $-SO_2-$, (6) $-CH_2-$, (7) –CO–, (8) –CONH–, (9) –NHCO– or (10) a single bond; and

m_a and m_b are the same as defined above) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(2-4) a group represented by the following formula:

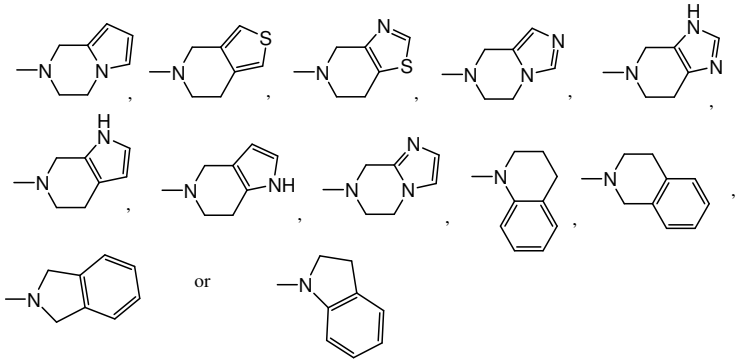
[Formula 5]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below;

(2-5) a group represented by the following formula:

[Formula 6]

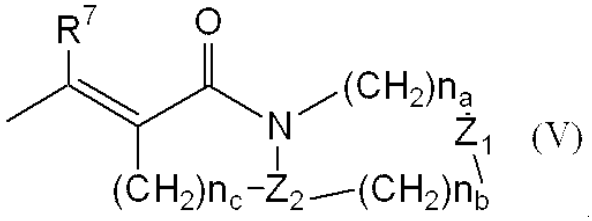


which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below; or

R^1 and R^2, together with $-X_1-CO-N-$, form one of the following ring structures:

(3-1) a cyclic group represented by Formula (V):

[Formula 7]



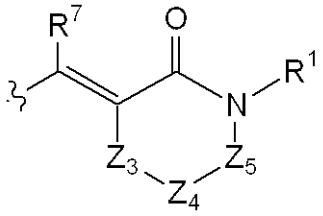
(V)

(wherein Z_1 represents (1) -NH-, (2) -O-, (3) -S-, (4)

-SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO- or (10) a single bond; Z_2 represents (1) a methine group or (2) a nitrogen atom; R^7 represents a substituent selected from Substituent Group A3 shown below; and n_a, n_b and n_c represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(3-2) a cyclic group represented by Formula (VI):

[Formula 8]



(VI)

(wherein Z_3 represents (1) a single bond, (2) -CO-, (3) $-(CH_2)n_d-$ (wherein n_d represents an integer of 1 to 3) or (4) $-CR^8R^9-$ (wherein R^8 and R^9 represent a substituent selected from Substituent Group A4 shown below;

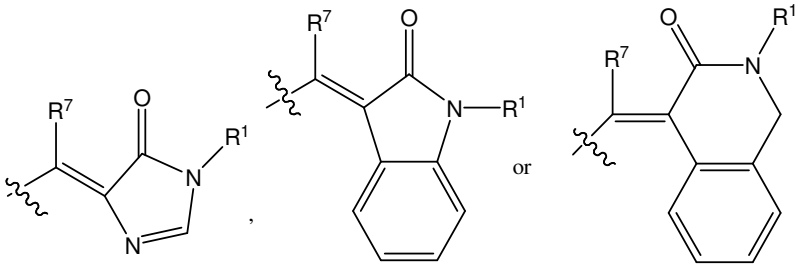
Z_4 represents (1) a single bond, (2) -O-, (3) -NRCO-, (4) -CONR-, (5) -CSNR- (6)-NRCS-(wherein R represents a substituent selected from Substituent Group A4 shown below) or (7) -S-;

Z_5 represents (1) a single bond, (2) an imino group which may be substituted with a substituent selected from Substituent Group A4 shown below, (3) $-(CH_2)n_e-$ (wherein n_e represents an integer of 1 to 3), (4) $-CR^8R^9-$ (wherein R^8 and R^9 are the same as defined above) or (5) -O-; and

R^1 and R^7 are the same as defined above);or

(3-3) a cyclic group represented by the following formula:

[Formula 9]



(wherein R^1 and R^7 are the same as defined above) which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below.

Substituent Group A1: (1) a hydrogen atom, (2) a halogen atom, (3) a cyano group, (4) a nitro group, (5) a C3-8 cycloalkyl group, (6) a C2-6 alkenyl group, (7) a C2-6 alkynyl group, (8) a C1-6 alkoxy group, (9) a C3-8 cycloalkoxy group, (10) a formyl group, (11) a C1-6 alkylcarbonyl group, and (12) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C1-6 alkoxy group, a C3-8 cycloalkyl group and a C1-6 alkylcarbonyl group).

Substituent Group A2: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a cyano group, a C1-6 alkoxy group, a C2-6 alkeny group, a C2-6

alkyny group and a C3-8 cycloalkyl group), (6) a C3-8 cycloalkoxy group, (7) a C2-6 alkenyloxy group and (8) a C2-6 alkynyloxy group.

Substituent Group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2-6 alkenyl group, a C2-6 alkynyl group, a C3-8 cycloalkyl group, a C1-6 alkoxy group, a C1-6 alkylthio group, a C1-6 alkylsulfinyl group, a C1-6 alkylsulfonyl group, a C1-6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a

5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4) and (6) a C1-6 alkoxyl group.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered

aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

2) The compound or pharmacologically acceptable salt thereof according to above 1) wherein Ar_1 is an imidazolyl group which may be substituted with 1 to 2 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group, (4) a C2-6 alkeny group, (5) a C2-6 alkyny group, (6) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 halogen atoms).

3) The compound or pharmacologically acceptable

salt thereof according to above 1) wherein Ar_2 is a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (6) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 3 substituents selected from a C2–6 alkenyl group, a C2–6 alkyny group and a C3–8 cycloalkyl group), (7) a C2–6 alkenyloxy group and (8) a C2–6 alkynyloxy group.

4) The compound or pharmacologically acceptable salt thereof according to above 2) wherein Ar_1 is an imidazolyl group which may be substituted with 1 to 2 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a C3–8 cycloalkyl group and (4) a C1–6 alkyl group.

5) The compound or pharmacologically acceptable salt thereof according to above 3) wherein Ar_2 is a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a cyano group and (4) a C1–6 alkoxy group.

6) The compound or pharmacologically acceptable salt thereof according to above 1) wherein X_1 is –C≡C–.

7) The compound or pharmacologically acceptable salt thereof according to above 1) wherein X_1 is $-CR^3=CR^4-$ (wherein R^3 and R^4 represent substituents selected from Substituent Group A3 shown below).

Substituent Group A3: (1) a hydrogen atom, (2) a

halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2-6 alkenyl group, a C2-6 alkynyl group, a C3-8 cycloalkyl group, a C1-6 alkoxy group, a C1-6 alkylthio group, a C1-6 alkylsulfinyl group, a C1-6 alkylsulfonyl group, a C1-6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents

a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4) and (6) a C1-6 alkoxy group.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1

to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

8) The compound or pharmacologically acceptable salt thereof according to above 7) wherein X_1 is $-CR^{31}=CR^{41}-$ (wherein R^{31} is a group selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a C1-6 alkyl group and (4) a C1-6 alkoxy group; and R^{41} represents a group selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 and (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with

1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C1-6 alkyl group, a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 and -O-A^1 (wherein A^1 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5))).

Substituent Group A5: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 halogen atoms), (8) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms) and (9) an amino group (wherein said amino group may be

substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms).

9) The compound or pharmacologically acceptable salt thereof according to above 8) wherein X_1 is $-CR^{32}=CR^{42}-$ (wherein R^{32} represents a hydrogen atom or a halogen atom, and R^{42} represents a substituent selected from the group consisting of a hydrogen atom, a halogen atom, a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with a C3–8 cycloalkyl group or a phenyl group) and a phenyl group).

10) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2 are groups selected from substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2

substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

11) The compound or pharmacologically acceptable salt thereof according to above 10) wherein R^1 is a group selected from Substituent Group A8 shown below and R^2 is a group selected from Substituent Group A6

shown below.

Substituent Group A6: (1) a hydrogen atom, (2) a C3-8 cycloalkyl group, (3) a C3-8 cycloalkoxy group, (4) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkylthio group, a hydroxyimino group, a C1-6 alkoxyimino group, a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below and $-O-A^2$ (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below)) and (5) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with

1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkylthio group, a hydroxyimino group, a C1–6 alkoxyimino group, a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14–membered non–aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below and –O–A^2 (wherein A^2 is the same as defined above)).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3–8 cycloalkyl group, (6) a C3–8 cycloalkoxy group, (7) a C1–6 alkylcarbonyl group, (8) a C1–6 alkylthio group, (9) a C1–6 alkylsulfinyl group, (10) a C1–6 alkylsulfonyl group, (11) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group, a 6- to 14–membered aromatic hydrocarbon ring group, a 5- to 14–membered aromatic heterocyclic group and –O–A^3 (wherein

A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group)), (12) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

Substituent Group A8: (1) a hydrogen atom, (2) C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group

(wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A7, a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5– to 14–membered non–aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and $-X-A^2$ (wherein X represents an imino group, –O– or –S– and A^2 represents a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A7 or a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7)), (3) a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (4) a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (5) $-X-A^2$ (wherein X and A^2 are the same as defined above).

12) The compound or pharmacologically acceptable salt thereof according to above 11) wherein R^1 is a C1–6

alkyl group (wherein said C1–6 alkyl group is a hydrogen atom, a C3–8 cycloalkoxy group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and –O–A^4 (A^4 represents a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 or a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9)), and R^2 is (1) a hydrogen atom or (2) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a C1–6 alkylthio group, an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), a 6– to 14–membered aromatic hydrocarbon ring group which may be

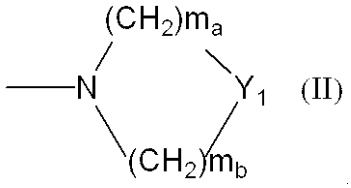
substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9).

Substituent Group A9: (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group, (4) a C3-8 cycloalkoxy group, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1-6 alkyl group), (6) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (7) an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents

selected from Substituent Group A9.

13) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a 5- to 11-membered heterocyclic group represented by Formula (II):

[Formula 10]



(wherein Y_1 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO-, (10) $-CR^5=CR^6-$ (wherein R^5 and R^6 represent groups selected from Substituent Group A4 shown below), (11) a single bond or (12) $>C=CR^{13}R^{14}$ (wherein R^{13} and R^{14} represent substituents selected from Substituent Group A4 shown below); and; m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl

group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from

Substituent Group A4), (31) –CO–A (wherein A is the same as defined above) and (32) =CH–A (wherein A is the same as defined above).

14) The compound or pharmacologically acceptable salt thereof according to above 13) wherein a 5- to 11-membered heterocyclic group is a piperidinyl group, a pyrrolidinyl group, an azepinyl group, an azocanyl group, a piperazinyl group, a 1,4-diazepanyl group, a morpholinyl group or a thiomorpholinyl group.

15) The compound or pharmacologically acceptable salt thereof according to above 14) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a piperidinyl group, a pyrrolidinyl group, an azepinyl group, an azocanyl group, a piperazinyl group, a 1,4-diazepanyl group, a morpholinyl group or a thiomorpholinyl group which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a formyl group, (5) a hydroxyimino group, (6) a C1–6 alkoxyimino group, (7) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 hydroxyl groups or 1 to 3 substituents selected from the group consisting of a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent

Group A7 shown below), (8) 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from substituents of A7 shown below, (9) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, (10) $-O-A^2$ (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below), (11) $-CO-A^2$ (wherein A^2 is the same as defined above) and (12) $=CH-A^2$ (wherein A^2 is the same as defined above).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkylcarbonyl group, (8) a C1-6 alkylthio group, (9) a C1-6 alkylsulfinyl group, (10) a C1-6 alkylsulfonyl group, (11) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1-6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic

group)), (12) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

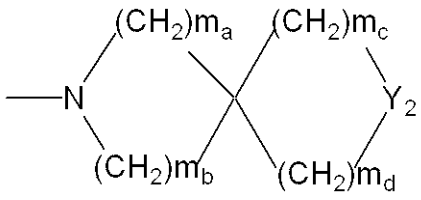
16) The compound or pharmacologically acceptable salt thereof according to above 15) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a piperidinyl group, a pyrrolidinyl group, an azepinyl group, an azocanyl group, a piperazinyl group, a 1,4-diazepanyl group, a morpholinyl group or a thiomorpholinyl group which may be substituted with 1 to 4 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 hydroxyl groups or 1 to 3 substituents selected from the group consisting

of a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A10 shown below), (5) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from substituents of A10 shown below, (6) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A10 shown below, (7) $-O-A^6$ (wherein A^6 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A10 shown below), (8) $=CH-A^6$ (wherein A^6 has the same above).

Substituent Group A10: (1) a hydrogen atom, (2) a halogen atom, (3) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 halogen atoms), (4) a C1-6 alkoxy group and (5) a 6- to 14-membered aromatic hydrocarbon ring group.

17) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a 6- to 20-membered non-aromatic heterocyclic group represented by Formula (III):

[Formula 11]



(III)

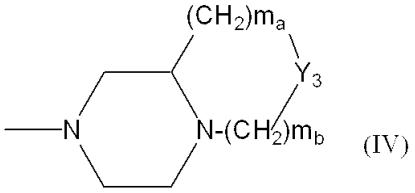
(wherein Y_2 represents (1) –NH–, (2) –O–, (3) –S–, (4) –SO–, (5) $–SO_2–$, (6) $–CH_2–$, (7) –CO–, (8) –CONH–, (9) –NHCO–, (10) $–CR^5= CR^6–$ (wherein R^5 and R^6 represent groups selected from Substituent Group A4 shown below or R^5 and R^6, together with a nitrogen atom to which they bind, form a 6- to 14-membered aromatic hydrocarbon ring group or a 6- to 14-membered non-aromatic hydrocarbon ring group) or (11) a single bond; and m_a, m_b, m_c and m_d represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a

6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

18) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a 9- to 16-membered non-aromatic heterocyclic group represented by Formula (IV):

[Formula 12]



(IV)

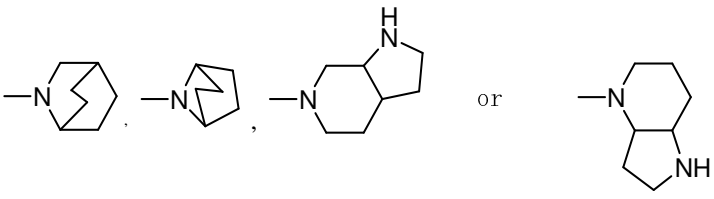
(wherein Y_3 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO- or (10) a single bond; and m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which

may be substituted with 1 to 3 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

19) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a group represented by the following formula:

[Formula 13]



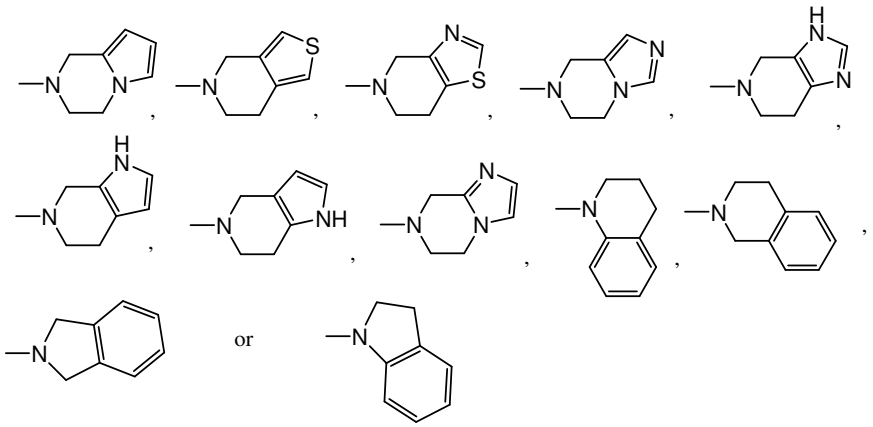
which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and (25) a 5- to 14-membered non-aromatic heterocyclic

group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

20) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a group represented by the following formula:

[Formula 14]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

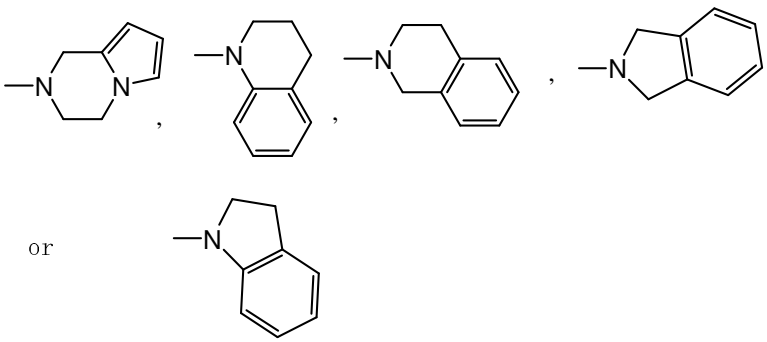
Substituent Group A4: (1) a hydrogen atom, (2) a

halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2–6 alkenyloxy group, (27) a C2–6 alkynyloxy group, (28) a

C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

21) The compound or pharmacologically acceptable salt thereof according to above 20) wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a group represented by the following formula:

[Formula 15]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group,

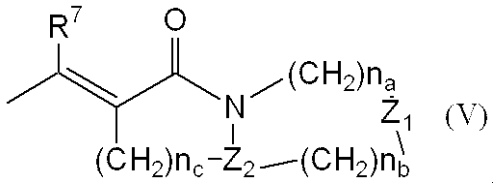
(11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or

5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

22) The compound or pharmacologically acceptable salt thereof according to above 21) wherein the group formed by R^1 and R^2, together with a nitrogen atom to which they bind, may be substituted with 1 to 4 fluorine atoms.

23) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with $-X_1-CO-N-$, form a cyclic group represented by Formula (V):

[Formula 16]



(V)

(wherein Z_1 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO- or (10) a single bond; Z_2 represents (1) a methine group or (2) a nitrogen atom; R^7 represents a substituent selected from Substituent Group A3 shown below; and n_a, n_b and n_c represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A3: (1) a hydrogen atom, (2) a

halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2-6 alkenyl group, a C2-6 alkynyl group, a C3-8 cycloalkyl group, a C1-6 alkoxy group, a C1-6 alkylthio group, a C1-6 alkylsulfinyl group, a C1-6 alkylsulfonyl group, a C1-6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents

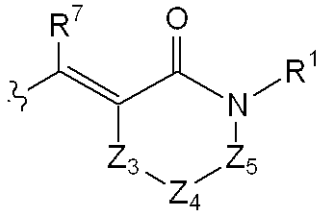
a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) and (6) a C1-6 alkoxy group.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1

to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

24) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with $-X_1-CO-N-$, form a cyclic group represented by Formula (VI):

[Formula 17]



(VI)

(wherein Z_3 represents (1) a single bond, (2) -CO-, (3) $-(CH_2)n_d-$ (wherein n_d represents an integer of 1 to 3) or (4) $-CR^8R^9-$ (wherein R^8 and R^9 represent a substituent selected from Substituent Group A4 shown below;

Z_4 represents (1) a single bond, (2) -O-, (3) -NRCO-,

(4) –CONR–, (5) –CSNR–, (6)–NRCS–(wherein R represents a substituent selected from Substituent Group A4 shown below) or (7) –S–;

Z_5 represents (1) a single bond, (2) an imino group which may be substituted with a substituent selected from Substituent Group A4 shown below, (3) $-(CH_2)n_e-$ (wherein n_e represents an integer of 1 to 3), (4) $-CR^8R^9-$ (wherein R^8 and R^9 are the same as defined above) or (5) –O–; and R^1 represents a substituent selected from Substituent Group A4 and R^7 represents a substituent selected from Substituent Group A3) which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2–6 alkenyl group, a C2–6 alkynyl group, a C3–8 cycloalkyl group, a C1–6 alkoxy group, a C1–6 alkylthio group, a C1–6 alkylsulfinyl group, a C1–6 alkylsulfonyl group, a C1–6 alkylcarbonyl

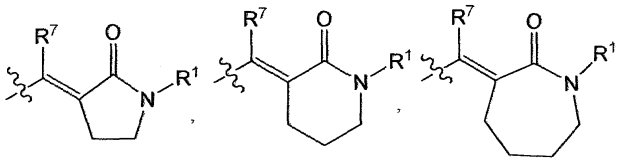
group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and –X–A (wherein X represents an imino group, –O– or –S– and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) and (6) a C1–6 alkoxy group.

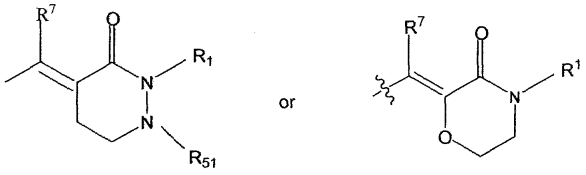
Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3

substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group, which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

25) The compound or pharmacologically acceptable salt thereof according to above 24) wherein Formula (VI) is a cyclic group:

[Formula 18]





(wherein R^1 and R_{51} represents a substituent selected from Substituent Group A4 and R^7 represents a substituent selected from Substituent Group A3) which may be substituted with 1 to 4 substituents selected from Substituent Group A7.

Substituent Group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a

hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2–6 alkenyl group, a C2–6 alkynyl group, a C3–8 cycloalkyl group, a C1–6 alkoxy group, a C1–6 alkylthio group, a C1–6 alkylsulfinyl group, a C1–6 alkylsulfonyl group, a C1–6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14–membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14–membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and –X–A (wherein X represents an imino group, –O– or –S– and A represents a 6- to 14–membered aromatic hydrocarbon ring group or 5- to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) and (6) a C1–6 alkoxy group.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group,

(11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or

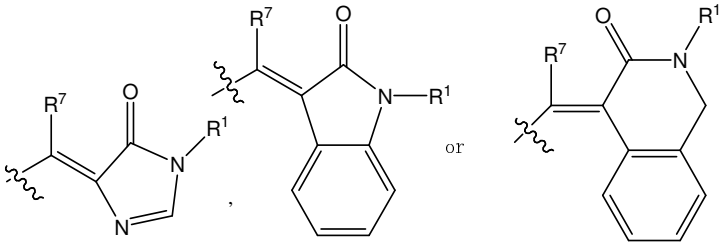
5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) –CO–A (wherein A is the same as defined above) and (32) =CH–A (wherein A is the same as defined above).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3–8 cycloalkyl group, (6) a C3–8 cycloalkoxy group, (7) a C1–6 alkylcarbonyl group, (8) a C1–6 alkylthio group, (9) a C1–6 alkylsulfinyl group, (10) a C1–6 alkylsulfonyl group, (11) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group)), (12) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group

which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

26) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 and R^2, together with $-X_1-CO-N-$, form a cyclic group represented by the following formula:

[Formula 19]



(wherein R^1 and R^7 are the same as defined above) which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a

hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the

same as defined above) and (32) =CH-A (wherein A is the same as defined above).

27) The compound or pharmacologically acceptable salt thereof according to any one of above 24) and 26) wherein R^1 is a substituent selected from Substituent Group A8.

Substituent Group A8: (1) a hydrogen atom, (2) C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected

from Substituent Group A7 and $-X-A^2$ (wherein X represents an imino group, -O- or -S- and A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7)), (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (5) $-X-A^2$ (wherein X and A^2 are the same as defined above).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkylcarbonyl group, (8) a C1-6 alkylthio group, (9) a C1-6 alkylsulfinyl group, (10) a C1-6 alkylsulfonyl group, (11) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1-6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group), (12) a C1-6 alkoxy group (wherein said C1-6

alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

28) The compound or pharmacologically acceptable salt thereof according to above 27) wherein R^1 is a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen

atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and $-X-A^4$ (wherein X represents an imino group, –O– or –S– and A^4 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9)).

Substituent Group A9: (1) a hydrogen atom, (2) a halogen atom, (3) a C3–8 cycloalkyl group, (4) a C3–8 cycloalkoxy group, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1–6 alkyl group), (6) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (7) an amino group

(wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

29) The compound or pharmacologically acceptable salt thereof according to any one of above 10), 24) and 26) wherein R^1 is $-X_{21}-X_{22}-Ar_3$ (wherein X_{21} represents 1) a C1-6 alkylene group (wherein said C1-6 alkylene group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with

a C1–6 alkyl), a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7) or 2) a single bond, and X_{22} represents a single bond, an imino group which may be substituted with a substituent selected from Substituent Group A7, –O– or –S– and Ar_3 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3–8 cycloalkyl group, (6) a C3–8 cycloalkoxy group, (7) a C1–6 alkylcarbonyl group, (8) a C1–6 alkylthio group, (9) a C1–6 alkylsulfinyl group, (10) a C1–6 alkylsulfonyl group, (11) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group), (12) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said

adjacent C1-6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

30) The compound or pharmacologically acceptable salt thereof according to above 29) wherein R^1 is $-X_{21a}-X_{22a}-Ar_{3a}$ (wherein X_{21a} represents a C1-6 alkylene group (wherein said C1-6 alkylene group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, an amino group (wherein

said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9), and X_{22a} represents a single bond or an oxygen atom and Ar_{3a} represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9).

Substituent Group A9: (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group, (4) a C3-8 cycloalkoxy group, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1-6 alkyl group), (6) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (7) an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic

hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

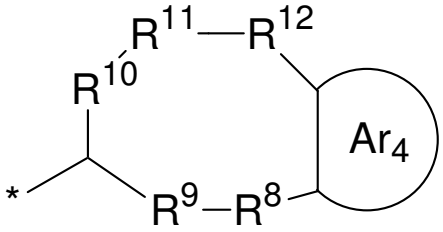
31) The compound or pharmacologically acceptable salt thereof according to above 30) wherein Ar_{3a} is a 6- to 14-membered aromatic hydrocarbon ring group selected from the group consisting of a phenyl group, a naphthyl group and a fluorenyl group or a 5- to 14-membered aromatic heterocyclic group selected from the group consisting of a thienyl group, a pyridyl group, a quinolyl group, an isoquinolyl group, an indolyl group, a benzothiazolyl group, a benzoxazolyl group and a furyl group, which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

Substituent Group A9: (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group, (4) a C3-8 cycloalkoxy group, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1-6 alkyl group), (6) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (7) an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms),

(8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

32) The compound or pharmacologically acceptable salt thereof according to above 1) wherein R^1 is a 6- to 14-membered non-aromatic hydrocarbon ring group or a 5- to 14-membered non-aromatic heterocyclic group represented by Formula (VII):

[Formula 20]



(VII)

(wherein R^8 to R^{12} represent 1) a single bond, 2) -CO-, 3) a methylene group which may be substituted with 1 or 2 substituents selected from Substituent Group A4, 4) -O-, 5) an imino group which may have a substituent selected from Substituent Group A4 or 6) -S-, and Ar_4 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3

substituents selected from Substituent Group A4 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 shown below).

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1

to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

33) The compound or pharmacologically acceptable salt thereof according to above 32) wherein Ar_4 represents a phenyl group or a 5- to 14-membered aromatic heterocyclic group selected from the group consisting of a pyridinyl group, a pyrimidinyl group, a pyrazinyl group, a thienyl group, an oxazolyl group, a pyrrolyl group, a thiazolyl group and a furyl group, which may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom and a C1-6 alkyl group), a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 halogen atoms), an

amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and –CO–A^2 (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3–8 cycloalkyl group, (6) a C3–8 cycloalkoxy group, (7) a C1–6 alkylcarbonyl group, (8) a C1–6 alkylthio group, (9) a C1–6 alkylsulfinyl group, (10) a C1–6 alkylsulfonyl group, (11) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and –O–A^3 (wherein

A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group), (12) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

34) The compound or pharmacologically acceptable salt thereof according to above 33) wherein R^1 is an indanyl group, an azaindanyl group, a tetrahydronaphthyl group, an azatetrahydronaphthyl group, a chromanyl group, an azachromanyl group, a tetrahydrobenzofuranyl group or a tetrahydrobenzothienyl group, which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a halogen atom, (2) a hydroxyl group, (3) a cyano group, (4) a C3-8 cycloalkyl group, (5) a

C3-8 cycloalkoxy group, (6) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 halogen atoms or C1-6 alkyl groups), (7) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 halogen atoms), (8) an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), and (9) a 5- to 14-membered non-aromatic heterocyclic group.

35) The compound or pharmacologically acceptable salt thereof according to above 1) selected from the following group:

1) (E)-N-biphenyl-3-ylmethyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide,

2) (E)-N-((1S)-indan-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylamide,

3) (E)-N-(chroman-4-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylamide,

4) (E)-1-(3,4-difluorobenzyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

5) (E)-1-indan-2-yl-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

6) (E)-1-(chroman-4-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

7) (E)-1-((1S)-1-(4-fluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

8) (E)-1-((6-chloropyridin-2-yl)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

9) (E)-1-(4-tert-butylbenzyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

10) (E)-1-(3,4-difluorobenzyl)-3-((5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl) methylene) piperidin-2-one,

11) (E)-1-((1H-indol-3-yl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

12) (E)-1-(5-fluoroindan-2-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

13) (E)-1-(7-fluorochroman-4-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

14) (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(1,2,3,4-tetrahydronaphthalen-2-yl) piperidin-2-one and

15) (E)-1-((2,4-difluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one.

36) A preventive or therapeutic agent for a disease resulting from amyloid betas comprising a compound represented by general formula (I) or pharmacologically acceptable salt thereof as an active ingredient.

37) The preventive or therapeutic agent according to above 36) wherein the disease resulting from amyloid betas is Alzheimer's disease, senile dementia, Down syndrome or amyloidosis.

The compound of the general formula (I) of the present invention or pharmacologically acceptable salt thereof and preventive or therapeutic agent of

diseases caused by Aβs are new inventions not described in documents.

[0007]

Hereinbelow, symbols, terms and the like used in the present specification are explained and the present invention is described in detail.

[0008]

Although a structural formula of a compound may express a certain isomer for the sake of convenience in the present specification, the present invention encompasses all the isomers such as geometric isomers which can be generated from the structure of a compound, optical isomers based on chiral carbon(s), stereoisomers and tautomers and a mixture of isomers and the invention is not limited to the formula described for the sake of convenience and may be either one of isomers or mixtures thereof. Therefore, although some molecules may have a chiral carbon atom therein and there may be an optically-active substance and racemate, the present invention is not limited to a certain one of them and includes either one of them. Furthermore, crystal polymorphs, which may exist, are not limited, and may be either one of single crystal type thereof or a mixture thereof, and may be hydrate or may be an anhydride.

[0009]

The term "disease(s) caused by Aβ" encompasses a wide variety of diseases includeing

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Glenner GG, and another, Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein, Biochem Biophys Res Commun, 1984, May 16, 120(3), p. 885-890;

Masters CL, and six others, Amyloid plaque core protein in Alzheimer disease and Down syndrome, Proceeding National Academy of Science USA, 1985, Jun, 82(12), p. 4245-4249;

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

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; and

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, Journal of Biological Chemistry, 1997, Dec 19, 272(51), p. 32247-32253.), senile dementia (for example, see 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. 851-6.), frontotemporal dementia (for example, see Evin G, and eleven others, Alternative transcripts of presenilin-1 associated with frontotemporal dementia, Neuroreport, 2002, Apr 16, 13(5), p. 719-723.), Pick disease (for example, see Yasuhara O, and three 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 syndrome (for example, see Teller JK, and ten others, Presence of soluble amyloid β-peptide precedes amyloid plaque formation in Down's syndrome, Nature Medicine, 1996, Jan, 2(1), p. 93-95; and

Tokuda T, and six 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.), cerebral amyloid angiopathy (for example,

see Hayashi Y, and nine 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 fifteen 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 ten 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; and

Dermaut B, and ten others, Cerebral amyloid angiopathy is a pathogenic lesion in Alzheimer's disease due to a novel presenilin 1 mutation, Brain, 2001, Dec, 124(Pt 12), p. 2383-2392.), hereditary cerebral hemorrhage with amyloidosis-Dutch type (for example, see Cras P, and nine 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;

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[0010]

The "6- to 14-membered aromatic hydrocarbon ring group," "5- to 14-membered aromatic heterocyclic group," "6- to 14-membered non-aromatic hydrocarbon ring group" and "5- to 14-membered non-aromatic heterocyclic group" in the above-mentioned formula (I) contained in the therapeutic or preventive agent of diseases caused by Aβs according to the present invention have the following meanings.

[0011]

The "6- to 14-membered aromatic hydrocarbon ring group" means a monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring group having 6 to 14 carbon atoms and preferable groups include a monocyclic, bicyclic or tricyclic 6- to 14-membered aromatic hydrocarbon ring group, for example, a phenyl group, an indenyl group, a naphthyl group, an azulenyl group, a heptalenyl group, a biphenyl group, a fluorenyl group, a phenalenyl group, a phenanthrenyl group, an anthracenyl group, etc.

[0012]

The "5- to 14-membered aromatic heterocyclic group" refers to a monocyclic, bicyclic or tricyclic aromatic heterocyclic group having 5 to 14 atoms and preferable groups include, for example, (1) nitrogen-containing aromatic heterocyclic groups such as a pyrrolyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a pyrazolinyl group, an imidazolyl group, an indolyl group, an isoindolyl group, an indolizinyl group, a purinyl group, an indazolyl group, a quinolyl group, an isoquinolyl group, a quinolizinyl group, a phthalazinyl group, a naphthylizinyl group, a quinoxalinyl group, a quinazolinyl group, a cinnolinyl group, a pteridinyl group, an imidazotriazinyl group, a pyrazinopyridazinyl group, an acridinyl group, a phenantholizinyl group, a carbazolyl group, a perimidinyl group, a

phenanthrolinyl group and a phenacyl group; (2) sulfur-containing aromatic heterocyclic groups such as a thienyl group and a benzothienyl group; (3) oxygen-containing aromatic heterocyclic groups such as a furyl group, a pyranyl group, a cyclopentapyranyl group, a benzofuranyl group and an isobenzofuranyl group; (4) aromatic heterocyclic groups containing two or more hetero atoms selected from the group consisting of a nitrogen atom, a sulfur atom, and an oxygen atom such as a thiazolyl group, an isothiazolyl group, a benzothiazolyl group, a benzothiadiazolyl group, a phenothiazinyl group, an isoxazolyl group, a furazanyl group, a phenoxazinyl group, a pyrazoloxazolyl group, imidazothiazolyl group, a thienofuryl group, a furopyrrolyl group, a pyridoxazinyl group, etc.

[0013]

The "6- to 14-membered non-aromatic hydrocarbon ring group" refers to a cyclic, aliphatic hydrocarbon group having 6 to 14 carbon atoms, and means, for example, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, a spiro[3.4]octanyl group, a decanyl group, an indanyl group, 1-acenaphthenyl group, a cyclopentacyclooctenyl group, a benzocyclooctenyl group, an indenyl group, a tetrahydronaphthyl group, a 6,7,8,9-tetrahydro-5H-benzocycloheptenyl group, 1,4-dihydronaphthalenyl group and the other cyclic, aliphatic hydrocarbon groups

having 6 to 14 carbon atoms.

[0014]

The "5- to 14-membered non-aromatic heterocyclic group" means not only a 5- to 14-membered non-aromatic hetero monocyclic group but also a saturated heterocyclic group condensed with aromatic hydrocarbon ring groups, or a saturated hydrocarbon ring group or a saturated heterocyclic group condensed with aromatic heterocyclic group(s), which 1) has 5 to 14 ring-constituting atoms, 2) contains 1 to 5 hetero atoms such as a nitrogen atom, -O- or -S- in the ring-constituting atoms and 3) may contain one or more carbonyl groups, double bonds, or triple bonds in the ring. Specific examples of 5- to 14-membered non-aromatic heterocyclic group include an azetidinyl ring, a pyrrolidinyl ring, a piperidinyl ring, an azepanyl ring, an azocanyl ring, a tetrahydrofuranyl ring, a tetrahydropyranyl ring, a morpholinyl ring, a thiomorpholinyl ring, a piperazinyl ring, a thiadiazolidinyl ring, a dioxanyl ring, an imidazolinyl ring, a thiadiazolinyl ring, 1,2-benzopyranyl ring, an isochromanyl ring, a chromanyl ring, an indolinyl ring, an isoindolinyl ring, an azaindanyl group, an azatetrahydronaphthyl group, an azachromanyl group, a tetrahydrobenzofuranyl group, a tetrahydrobenzothienyl group, a 2,3,4,5- tetrahydrobenzo[b]thienyl group, a 3,4-dihydro-2H-benzo[b] [1,4] dioxepinyl group, an indan-1-onyl group, a 6,7-dihydro-5H-

cyclopentapyrazinyl group, a 6,7-dihydro-5H-[1]-pyridinyl group, a 6,7-dihydro-5H-[1]-pyridinyl group, a 5,6-dihydro-4H-cyclopenta[b]thienyl group, a 4,5,6,7-tetrahydro-benzo[b]thienyl group, a 3,4-dihydro-2H-naphthale-1-onyl group, a 2,3-dihydro-isoindol-1-onyl group, a 3,4-dihydro-2H-isoquinoline-1-onyl group, a 3,4-dihydro-2H-benzo[1,4]oxapinyl group, etc.

[0015]

The substituent group A1, substituent group A2, substituent group A3, substituent group A4, substituent group A5, substituent group A6, substituent group A7, substituent group A8, substituent group A9 and substituent group A10 represent the following groups.

Substituent Group A1 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a cyano group, (4) a nitro group, (5) a C3-8 cycloalkyl group, (6) a C2-6 alkenyl group, (7) a C2-6 alkynyl group, (8) a C1-6 alkoxy group, (9) a C3-8 cycloalkoxy group, (10) a formyl group, (11) a C1-6 alkylcarbonyl group, or (12) a C1-6 alkyl group (wherein the above described C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C1-6 alkoxy group, a C3-8 cycloalkyl group and a C1-6 alkylcarbonyl group).

Substituent Group A2 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C1-6 alkoxy group (wherein the C1-6

alkoxy group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a cyano group, a C1-6 alkoxy group, a C2-6 alkeny group, a C2-6 alkyny group and a C3-8 cycloalkyl group), (6) a C3-8 cycloalkoxy group, (7) a C2-6 alkenyloxy group or (8) a C2-6 alkynyloxy group.

Substituent Group A3 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2-6 alkenyl group, a C2-6 alkynyl group, a C3-8 cycloalkyl group, a C1-6 alkoxy group, a C1-6 alkylthio group, a C1-6 alkylsulfinyl group, a C1-6 alkylsulfonyl group, a C1-6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from

Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) or (6) a C1-6 alkoxy group.

Substituent Group A4 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected

from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) or (32) =CH-A (wherein A is the same as defined above).

Substituent Group A5 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 halogen atoms) (8) a C1-6 alkoxy group (wherein said alkoxy

group may be substituted with 1 to 5 halogen atoms) or (9) an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms).

Substituent Group A6 refers to (1) a hydrogen atom, (2) a C3–8 cycloalkyl group, (3) a C3–8 cycloalkoxy group, (4) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkylthio group, a hydroxyimino group, a C1–6 alkoxyimino group, a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below and $-O-A^2$ (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic

group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below)) or (5) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkylthio group, a hydroxyimino group, a C1–6 alkoxyimino group, a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below and $-O-A^2$ (wherein A^2 is the same as defined above)).

Substituent Group A7 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3–8 cycloalkyl group, (6) a C3–8 cycloalkoxy group, (7) a C1–6 alkylcarbonyl group, (8) a C1–6 alkylthio group, (9) a C1–6 alkylsulfinyl group, (10) a C1–6 alkylsulfonyl group, (11) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted

with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group)), (12) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 or (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

Substituent Group A8 refers to (1) a hydrogen atom, (2) C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl

group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and $-X-A^2$ (wherein X represents an imino group, -O- or -S- and A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7)), (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 or (5) $-X-A^2$ (wherein X and A^2 are the same as defined above).

Substituent Group A9 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a C3–8 cycloalkyl group, (4) a C3–8 cycloalkoxy group, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1–6 alkyl group), (6) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (7) an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 or (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

Substituent Group A10 refers to (1) a hydrogen atom, (2) a halogen atom, (3) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 halogen atoms), (4) a C1–6 alkoxy group and (5) a 6- to 14-membered aromatic hydrocarbon ring group.

[0016]

The term "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, etc., and preferably a fluorine atom, a chlorine atom and a bromine atom.

[0017]

The term "C1-6 alkyl group" refers to an alkyl group having 1 to 6 carbon atoms and preferable groups include linear or branched alkyl groups, for example, methyl group, ethyl group, n-propyl group, iso-propyl group, n-butyl group, iso-butyl group, tert-butyl group, n-pentyl group, iso-pentyl group, neopentyl group, n-hexyl group, 1-methylpropyl group, 1,2-dimethylpropyl group, 1-ethylpropyl group, 1-methyl-2-ethylpropyl group, 1-ethyl-2-methylpropyl group, 1,1,2-trimethylpropyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylbutyl group, 2,2-dimethylbutyl group, 2-ethylbutyl group, 1,3-dimethylbutyl group, 2-methylpentyl group, 3-methylpentyl group, etc.

[0018]

The term "C1-6 alkoxy group" refers to a group in which a hydrogen atom has been substituted with an oxygen atom in an alkyl group having 1 to 6 carbon atoms and preferable groups include, for example, methoxy group, ethoxy group, n-propoxy group, an i-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group, tert-butoxy group, n-pentoxy group,

i-pentoxy group, sec-pentoxy group, tert-pentoxy group, n-hexoxy group, i-hexoxy group, 1,2-dimethylpropoxy group, 2-ethylpropoxy group, 1-methyl-2-ethylpropoxy group, 1-ethyl-2-methylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1-dimethylbutoxy group, 2,2-dimethylbutoxy group, 2-ethylbutoxy group, 1,3-dimethylbutoxy group, 2-methylpentoxy group, 3-methylpentoxy group, a hexyloxy group, etc.

[0019]

The term "C1-6 alkylsulfonyl group" refers to a group in which a hydrogen atom has been substituted with a sulfonyl group in an alkyl group having 1 to 6 carbon atoms and preferable groups include, for example, methanesulfonyl group, ethanesulfonyl group, etc.

[0020]

The term "amino group which may be substituted with C1-6 alkyl groups" refers to an amino group which may be substituted with alkyl groups having 1 to 6 carbon atoms and preferable groups include, for example, amino group, methylamino group, ethylamino group, propylamino group, dimethylamino group, etc.

[0021]

The term "C2-6 alkenyl group" refers to an alkenyl group having 2 to 6 carbon atoms and preferable groups include linear or branched alkenyl groups, for example, vinyl group, allyl group, 1-propenyl group,

isopropenyl group, 1-buten-1-yl group, 1-buten-2-yl group, 1-buten-3-yl group, 2-buten-1-yl group, 2-buten-2-yl group, etc.

[0022]

The term "C2-6 alkynyl group" refers to an alkynyl group having 2 to 6 carbon atoms and preferable groups include linear or branched alkynyl groups, for example, ethynyl group, 1-propynyl group, 2-propynyl group, butynyl group, pentynyl group, hexynyl group, etc.

[0023]

The term "C3-8 cycloalkyl group" refers to a cyclic alkyl group having 3 to 8 carbon atoms and preferable groups include, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, etc.

[0024]

The term "C1-6 alkylthio group" refers to a group in which a hydrogen atom has been substituted with a sulfur atom in an alkyl group having 1 to 6 carbon atoms and preferable groups include, for example, methylthio group, ethylthio group, n-propylthio group, i-propylthio group, n-butylthio group, i-butylthio group, tert-butylthio group, n-pentylthio group, i-pentylthio group, neopentylthio group, n-hexylthio group, 1-methylpropylthio group, etc.

[0025]

The term "C1-6 alkylsulfinyl group" refers to a group in which a hydrogen atom has been substituted with a sulfinyl group in an alkyl group having 1 to 6 carbon atoms and preferable groups include, for example, methylsulfinyl group, ethyl methylsulfinyl group, n-propylsulfinyl group, i-propylsulfinyl group, n-butylsulfinyl group, i-butylsulfinyl group, tert-butylsulfinyl group, n-pentylsulfinyl group, i-pentylsulfinyl group, neopentylsulfinyl group, n-hexylsulfinyl group, 1-methyl propyl sulfinyl group, etc.

[0026]

The term "C1-6 alkylcarbonyl group" refers to a group in which a hydrogen atom has been substituted with a carbonyl group in an alkyl group having 1 to 6 carbon atoms and preferable groups include, for example, acetyl group, propionyl group, butyryl group, etc.

[0027]

The term "C3-8 cycloalkoxy group" refers to a group in which a hydrogen atom has been substituted with an oxygen atom in a cyclic alkyl group having 3 to 8 carbon atoms and preferable groups include, for example, cyclopropoxy group, cyclobutoxy group, cyclopentoxy group, cyclohexoxy group, cycloheptyloxy group, cyclooctyloxy group, etc.

[0028]

The term "C3-8 cycloalkylthio group" refers

to a group in which a hydrogen atom has been substituted with a sulfur atom in a cyclic alkyl group having 3 to 8 carbon atoms and preferable groups include, for example, cyclopropylthio group, cyclobutylthio group, cyclopentylthio group, cyclohexylthio group, cycloheptylthio group, cyclooctylthio group, etc.

[0029]

The term "C1-6 alkoxyimino group" refers to a group in which a hydrogen atom has been substituted with a C1-6 alkoxy group in an imino group and preferable groups include, for example, methoxyimino group, ethoxyimino group, etc.

[0030]

The term "C2-6 alkenyloxy group" refers to a group in which a hydrogen atom has been substituted with an oxygen atom in an alkenyl group having 2 to 6 carbon atoms and preferable groups include linear or branched alkenyloxy groups, for example, vinyloxy group, allyloxy group, 1-propenyloxy group, isopropenyloxy group, 1-buten-1-yloxy group, 1-buten-2-yloxy group, 1-buten-3-yloxy group, 2-buten-1-yloxy group, 2-buten-2-yloxy group.

[0031]

The term "C2-6 alkynyloxy group" refers to a group in which a hydrogen atom has been substituted with an oxygen atom in an alkynyl group having 2 to 6 carbon atoms and preferable groups include linear or

branched alkynyloxy groups, for example, ethynyloxy group, 1-propynyloxy group, 2-propynyloxy group, butynyloxy group, pentynyloxy group, hexynyloxy group, etc.

[0032]

The term "C3-8 cycloalkylsulfinyl group" refers to a group in which a hydrogen atom has been substituted with a sulfinyl group in a cyclic alkyl group having 3 to 8 carbon atoms and preferable groups include, for example, cyclopropylsulfinyl group, cyclobutylsulfinyl group, cyclopentylsulfinyl group, cyclohexylsulfinyl group, cycloheptylsulfinyl group, cyclooctylsulfinyl group, etc.

[0033]

The term "C3-8 cycloalkylsulfonyl group" refers to a group in which a hydrogen atom has been substituted with a sulfonyl group in a cyclic alkyl group having 3 to 8 carbon atoms and preferable groups include, for example, cyclopropylsulfonyl group, cyclobutylsulfonyl group, cyclopentylsulfonyl group, cyclohexylsulfonyl group, cycloheptylsulfonyl group, cyclooctylsulfonyl group, etc.

[0034]

Preferable examples of "hydroxyl group having a protecting group" include methoxymethyl ether group, tetrahydropyranyl ether group, tert-butyl ether group, allyl ether group, benzoate group, acetate group, formate group, crotonate group, p-phenylbenzoate group

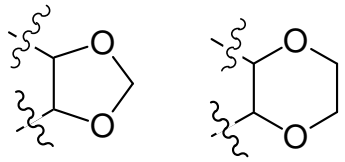
or pivaloate group, tert-butydimethyl silyl group, tert-butyldiphenyl silyl group, trityl group, benzyl group, etc.

[0035]

Preferable examples of C1-6 alkoxy group in "C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group)" include a C1-6 alkoxy group substituted with 1 to 5 halogen atoms or a cyclic group can be formed together with a carbon atom to which said adjacent C1-6 alkoxy groups bind. The expression "a cyclic group can be formed together with a carbon atom to which said adjacent C1-6 alkoxy groups bind" means, for example, a methylenedioxy group, ethylenedioxy group, etc. and it can be specifically illustrated by, for example, a formula:

[0036]

[Formula 21]



and the like.

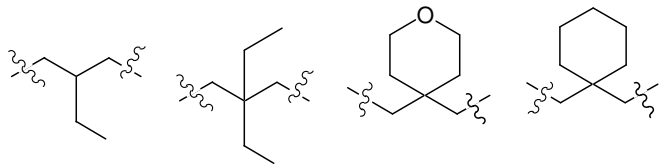
[0037]

The substituent in a "C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the

carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom))" can be specifically illustrated by, for example, a formula:

[0038]

[Formula 22]



and the like.

[0039]

Next, the compound of Formula (I) of the present invention is described.

Among the compounds represented by Formula (I), preferred is a compound or a pharmacologically acceptable salt thereof in which Ar_1 is an imidazolyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A1;

more preferred is a compound or a pharmacologically acceptable salt thereof in which Ar_1 is an imidazolyl group which may be substituted with 1 to 2 substituents selected from a hydrogen atom, a halogen atom, a C3-8 cycloalkyl group, a C2-6 alkeny group, a C2-6 alkyny group and a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 halogen atoms); and

the most preferred is a compound or a pharmacologically

acceptable salt thereof in which Ar_1 is an imidazolyl group which may be substituted with 1 to 2 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a C3–8 cycloalkyl group and a C1–6 alkyl group.

[0040]

Among the compounds represented by Formula (I), preferred is a compound or a pharmacologically acceptable salt thereof in which Ar_2 is a pyridinyl group, a pyrimidinyl group, or a phenyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A2;

more preferred is a compound or a pharmacologically acceptable salt thereof in which Ar_2 is a pyridinyl group, a pyrimidinyl group or a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 3 substituents selected from a C2–6 alkeny group, a C2–6 alkyny group and a C3–8 cycloalkyl group), a C2–6 alkenyloxy group and a C2–6 alkynyloxy group; and

the most preferred is a compound or a pharmacologically acceptable salt thereof in which Ar_2 is a pyridinyl group, a pyrimidinyl group or a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a hydrogen atom, (2) a

halogen atom, (3) a cyano group and (4) a C1–6 alkoxy group.

[0041]

Among the compounds represented by Formula (I), preferred is a compound or a pharmacologically acceptable salt thereof in which X_1 represents (1) –C≡C– or (2) $-CR^3=CR^4-$ (wherein R^3 and R^4 represents a substituent selected from Substituent Group A3; more preferred is a compound or a pharmacologically acceptable salt thereof in which X_1 is $-CR^{31}=CR^{41}-$ (wherein R^{31} is a group selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a C1–6 alkyl group and (4) a C1–6 alkoxyl group; and R^{41} represents a group selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 and (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a cyano group, a C3–8 cycloalkyl group, a C1–6 alkyl group, a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered

aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 and $-O-A^1$ (wherein A^1 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5))); and

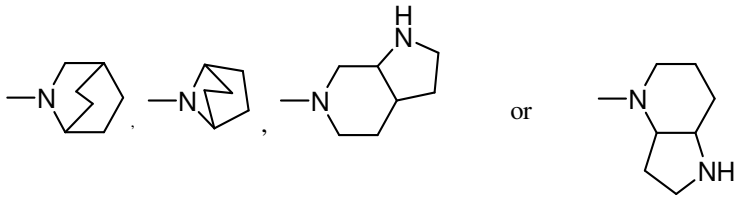
the most preferred is a compound or a pharmacologically acceptable salt thereof in which X_1 is $-CR^{32}=CR^{42}-$ (wherein R^{32} represents a hydrogen atom or a halogen atom, and R^{42} represents a substituent selected from the group consisting of a hydrogen atom, a halogen atom and a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with a C3-8 cycloalkyl group or a phenyl group) and a phenyl group).

[0042]

Among the compounds represented by Formula (I), a compound or a pharmacologically acceptable salt thereof in which R^1 and R^2 represent groups selected from Substituent Group A4 or the group formed by R^1 and R^2, together with a nitrogen atom is a 5- to 11-membered

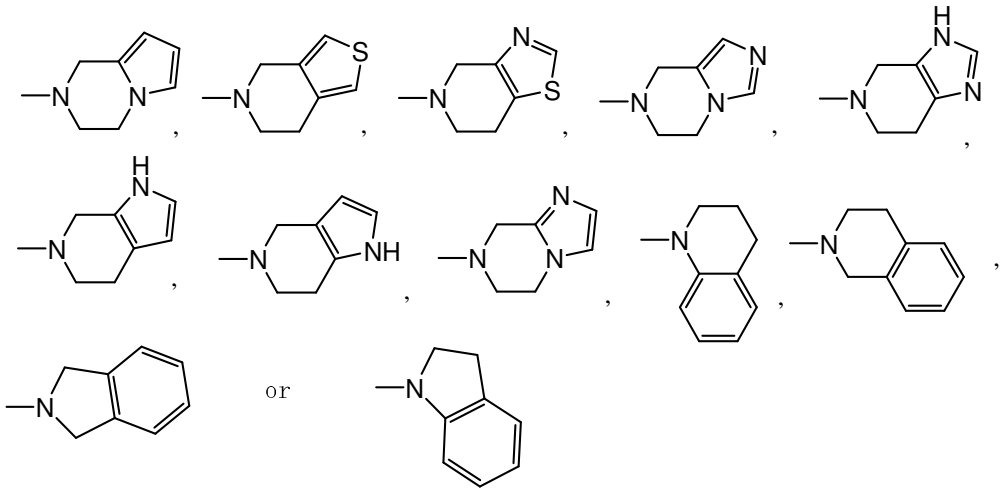
heterocyclic group represented by Formula (II) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;, a 6- to 20-membered non-aromatic heterocyclic group represented by Formula (III) which may be substituted with 1 to 4 substituents selected from Substituent Group A4, a 9- to 16-membered non-aromatic heterocyclic group represented by Formula (IV) which may be substituted with 1 to 4 substituents selected from Substituent Group A4, a group represented by the following formula:

[Formula 23]



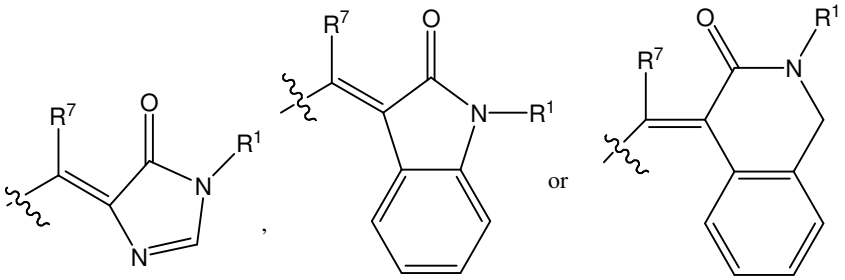
which may be substituted with 1 to 4 substituents selected from Substituent Group A4, a group represented by the following formula:

[Formula 24]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4, a cyclic group represented by Formula (V) which may be substituted with 1 to 4 substituents selected from Substituent Group A4, a cyclic group represented by Formula (VI) which may be substituted with 1 to 4 substituents selected from Substituent Group A4 and a cyclic group represented by the following formula:

[Formula 25]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4 can be exemplified as a preferable compound.

[0043]

Among the compounds represented by Formula (I), preferred is a compound or a pharmacologically acceptable salt thereof in which R^1 and R^2 are groups selected from Substituent Group A4;

more preferred is a compound or a pharmacologically acceptable salt thereof in which R^1 is a group selected from Substituent Group A8 and R^2 is a group selected from Substituent Group A6; and

the most preferred is a compound or a pharmacologically acceptable salt thereof in which R^1 is a C1-6 alkyl

group (wherein said C1–6 alkyl group is a hydrogen atom, a C3–8 cycloalkoxy group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and –O–A^4 (A^4 represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9)), and R^2 is (1) a hydrogen atom or (2) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a C1–6 alkylthio group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14-membered

aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9).

[0044]

Among the compounds represented by Formula (I), a 5- to 11-membered heterocyclic group represented by Formula (II) formed by R^1 and R^2, together with a nitrogen atom to which they bind, refers to a hetero atom containing cyclic group having 5 to 11 total members and preferable examples include a piperidinyl group, a pyrrolidinyl group, an azepinyl group, an azocanyl group, a piperazinyl group, a 1,4-diazepanyl group, a morpholinyl group or a thiomorpholinyl group.

Among the compounds represented by Formula (I), preferred is a compound or a pharmacologically acceptable salt thereof in which R^1 and R^2 form a 5- to 11-membered heterocyclic group represented by Formula (II), together with a nitrogen atom to which they bind, which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

more preferred is a compound or a pharmacologically acceptable salt thereof in which R^1 and R^2 form a 5- to 11-membered heterocyclic group represented by Formula (II), together with a nitrogen atom to which they bind, which may be substituted with 1 to 4 substituents selected from the group consisting of a hydrogen atom,

a halogen atom, a hydroxyl group, a formyl group, a hydroxyimino group, a C1–6 alkoxyimino group, a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below), 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from substituents of A7 shown below, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, $-O-A^2$ (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below), $-CO-A^2$ (wherein A^2 is the same as defined above) and $=CH-A^2$ (wherein A^2 is the same as defined above); and

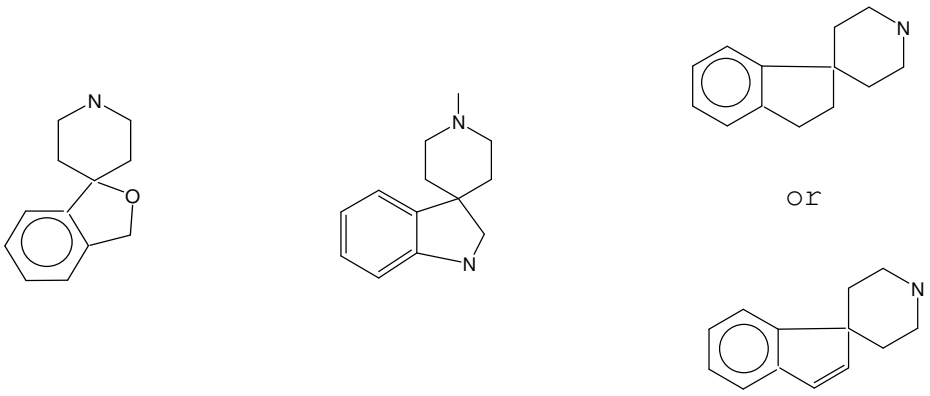
the most preferred is a compound or a pharmacologically acceptable salt thereof in which R^1 and R^2 form a 5- to 11-membered heterocyclic group represented by Formula

(II), together with a nitrogen atom to which they bind, which may be substituted with 1 to 4 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group or a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A10), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from substituents of A10, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A10, $-O-A^6$ (wherein A^6 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A10 shown below) and $=CH-A^6$ (wherein A^6 is the same as defined above).

[0045]

Among the compounds represented by Formula (I), the "6- to 20-membered non-aromatic heterocyclic group" represented by Formula (III) formed by R^1 and $R^{2'}$ together with a nitrogen atom to which they bind, refers to a hetero atom containing spiro cyclic group having 6 to 20 total members and preferable examples include

[Formula 26]



and the like.

In addition, among the compounds represented by Formula (I), preferred is a compound or a pharmacologically acceptable salt thereof in which R^1 and R^2 form a 6- to 20-membered non-aromatic heterocyclic group represented by Formula (III), together with a nitrogen atom to which they bind, which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

[0046]

Among the compounds represented by Formula (I), preferred is a compound in which the group formed by R^1 and R^2, together with a nitrogen atom to which they bind is a 9- to 16-membered non-aromatic heterocyclic group represented by Formula (IV) which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

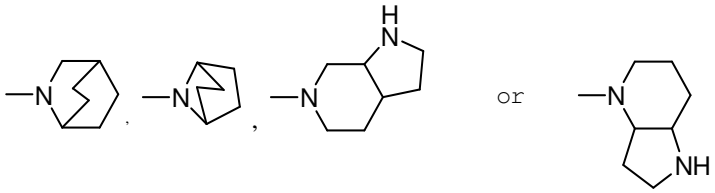
The "9- to 16-membered non-aromatic heterocyclic group" represented by Formula (IV) refers

to a hetero atom containing cyclic group having 9 to 16 members in total.

[0047]

Among the compounds represented by Formula (I), preferred is a compound in which the group formed by R^1 and R^2, together with a nitrogen atom to which they bind, is a group represented by the following formula:

[Formula 27]

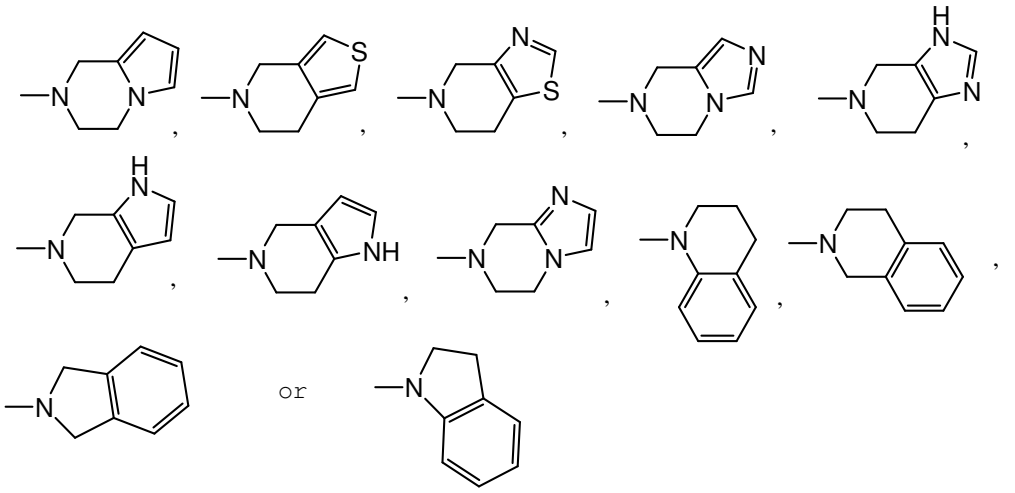


which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

[0048]

Among the compounds represented by Formula (I), preferred is a compound in which the group formed by R^1 and R^2, together with a nitrogen atom to which they bind, is a group represented by the following formula:

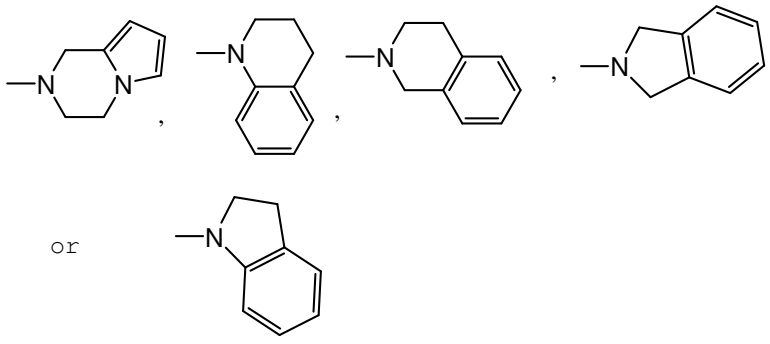
[Formula 28]



which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), more preferred is a compound in which R^1 and R^2, together with a nitrogen atom to which they bind, form a group represented by the following formula:

[Formula 29]



which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), preferred is a compound in which the group formed

by R^1 and R^2, together with a nitrogen atom to which they bind, may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), more preferred is a compound in which the group formed by R^1 and R^2, together with a nitrogen atom to which they bind, may be substituted with 1 to 4 fluorine atoms and the like or a pharmaceutically acceptable salt thereof.

[0049]

Among the compounds represented by Formula (I), preferred is a compound in which the group formed by R^1 and R^2, together with $-X_1-CO-N$, is a cyclic group (wherein R^7 represents a substituent selected from substituent Group A3) represented by Formula (V) in which may be substituted with 1 to 4 substituents selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

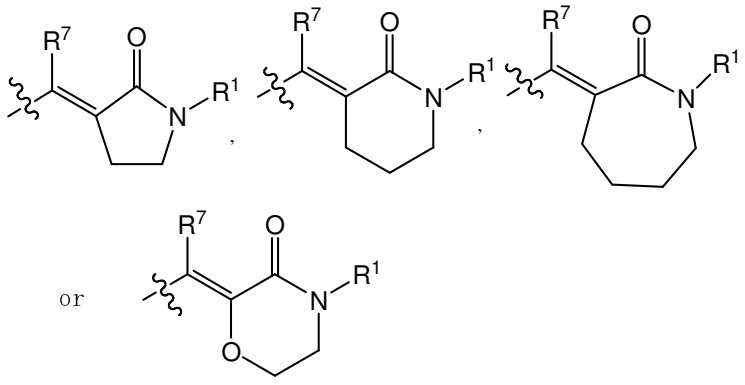
[0050]

Among the compounds represented by Formula (I), preferred is a compound in which the group formed by R^1 and R^2, together with $-X_1-CO-N$, is a cyclic group represented by Formula (VI) in which may be substituted with 1 to 4 substituents selected from Substituent Group A4 (wherein R1 represents a substituent selected from Substituent Group A4, and R^7 represents a substituent selected from Substituent Group A3) or a

pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), more preferred is a compound in which the group formed by R^1 and R^2, together with $-X_1-CO-N$, is a cyclic group represented by the following formula:

[Formula 30]



which may be substituted with 1 to 4 substituent groups selected from Substituent Group A7 (wherein, R1 represents a substituent selected from Substituent Group A4, and R7 represents Substituent Group A3) or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), preferred is a compound in which R^1 in the above described cyclic group is a substituent selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), more preferred is a compound in which R^1 in the above described cyclic group is a substituent selected from Substituent Group A8 or a pharmaceutically

acceptable salt thereof.

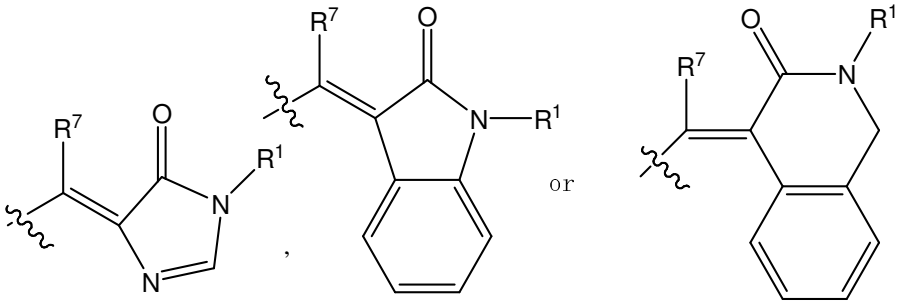
Among the compounds represented by Formula (I), the most preferred is a compound in which R^1 in the above described cyclic group is a substituent selected from the group consisting of a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituent groups selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9, a 5- to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9, a 5- to 14–membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9 and –X–A^4 (wherein X represents an imino group, –O– or –S– and A^4 represents

a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9 or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9)) or a pharmaceutically acceptable salt thereof.

[0051]

Among the compounds represented by Formula (I), preferred is a compound in which the group formed by R^1 and R^2, together with $-X_1-CO-N$, is a cyclic group represented by the following formula:

[Formula 31]



which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), preferred is a compound in which R^1 in the above described cyclic group is a substituent selected from Substituent Group A4 or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula

(I), more preferred is a compound in which R^1 in the above described cyclic group is a substituent selected from Substituent Group A8 or a pharmaceutically acceptable salt thereof.

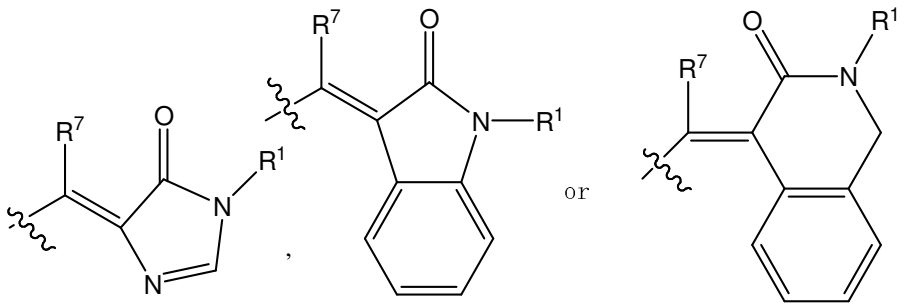
Among the compounds represented by Formula (I), the most preferred is a compound in which R^1 in the above described cyclic group is a substituent selected from the group consisting of a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituent groups selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9, a 5- to 14-membered non-aromatic heterocyclic group

which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9 and $-X-A^4$ (wherein X represents an imino group, -O- or -S- and A^4 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9 or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9)) or a pharmaceutically acceptable salt thereof.

[0052]

Among the compounds represented by Formula (I), preferred is a compound in which R^1 in Formula (I), R^1 in Formula (VI) and R^1 in the cyclic group represented by the following formula:

[Formula 32]



is $-X_{21}-X_{22}-Ar_3$

wherein X_{21} represents a C1-6 alkylene group (wherein said C1-6 alkylene group may be substituted with 1 to 3 substituent groups selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8

cycloalkoxy group, a formyl group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl), a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A7) or a single bond, and X_{22} represents a single bond, an imino group which may be substituted with a substituent selected from Substituent Group A7, –O– or –S– and Ar_3 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A7 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A7 or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), more preferred is a compound in which R^1 is $-X_{21a}-X_{22a}-Ar_{3a}$ wherein X_{21a} represents a C1–6 alkylene group (wherein said C1–6 alkylene group may be substituted with 1 to 3 substituent groups selected from the group consisting of a hydrogen atom, a halogen

atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl having 1 to 5 halogen atoms), a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9), and X_{22a} represents a single bond or an oxygen atom and Ar_{3a} represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A9 or a pharmaceutically acceptable salt thereof.

Furthermore, Ar_{3a} in "$-X_{21a}-X_{22a}-Ar_{3a}$" represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group and preferably a group selected from a phenyl group, a naphthyl group and a fluorenyl group or a group selected from a thienyl group, a pyridinyl group, a

quinolinyl group, an isoquinolinyl group, an indolyl group, a benzothiazolyl group, a benzoxazolyl group and a furyl group.

[0053]

Among the compounds represented by Formula (I), preferred is a compound in which R^1 is a 6- to 14-membered non-aromatic hydrocarbon ring group or a 5- to 14-membered non-aromatic heterocyclic group represented by Formula (VII) or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), preferred is a compound in which R^1 is represented by Formula (VII) wherein Ar_4 represents a phenyl group, a pyridinyl group, a pyrimidinyl group, a pyrazinyl group, a thienyl group, an oxazolyl group, a pyrrolyl group, a thiazolyl group and a furyl group, which may be substituted with 1 to 3 substituent groups selected from the group consisting of a halogen atom, a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituent groups selected from the group consisting of a halogen atom and a C1-6 alkyl group), a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 halogen atoms), an amino group (wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group

A7, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A7, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A7 and $-CO-A^2$ (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A7 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A7) or a pharmaceutically acceptable salt thereof.

Among the compounds represented by Formula (I), the most preferred is a compound in which R^1 is represented by Formula (VII) wherein R^1 is an indanyl group, an azaindanyl group, a tetrahydronaphthyl group, an azatetrahydronaphthyl group, a chromanyl group, an azachromanyl group, a tetrahydrobenzofuranyl group or a tetrahydrobenzothienyl group, which may be substituted with 1 to 3 substituent groups selected from the group consisting of, for example, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 halogen atoms or C1-6 alkyl groups), a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 halogen atoms), an amino group (wherein said

amino group may be substituted with a C1-6 alkyl having 1 to 5 halogen atoms), and a 5- to 14-membered non-aromatic heterocyclic group or a pharmaceutically acceptable salt thereof.

[0054]

Particularly, preferred are compounds selected from the following group, for example, or a pharmaceutically acceptable salt thereof, which are useful as a preventive or therapeutic agent for diseases caused by amyloid beta, for example, Alzheimer's disease, senile dementia, Down syndrome, amyloidosis, etc.

1) (E)-N-Biphenyl-3-ylmethyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide,

2) (E)-N-((1S)-Indan-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide,

3) (E)-N-(Chroman-4-yl)-3[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide,

4) (E)-1-(3,4-Difluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

5) (E)-1-Indan-2-yl-3[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

6) (E)-1-(Chroman-4-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

7) (E)-1-[(1S)-1-(4-Fluorophenyl)ethyl]-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

8) (E)-1-[(6-Chloropyridin-2-yl)methyl]-3-[3-methoxy-

4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

9) (E)-1-(4-Tert-butylbenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

10) (E)-1-(3,4-Difluorobenzyl)-3-{[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl]methylene}piperidin-2-one,

11) (E)-1-[(1H-Indole-3-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

12) (E)-1-(5-Fluoroindan-2-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

13) (E)-1-(7-Fluorochroman-4-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one,

14) (E)-3-[3-Methoxy-4-(4-methyl-1H-imidazol-1-yl)benzyliden]-1-(1,2,3,4-tetrahydronaphthalen-2-yl)piperidin-2-one and,

15) (E)-1-[(2,4-Difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one.

[0055]

Although the above are preferable embodiments of the compound of the above-mentioned general formula (I), the active ingredient of a pharmaceutical agent according to the present invention is not limited to a specific compound described in this specification, and any embodiment can be selected from the full extent contained in the range of the compound of general formula (I).

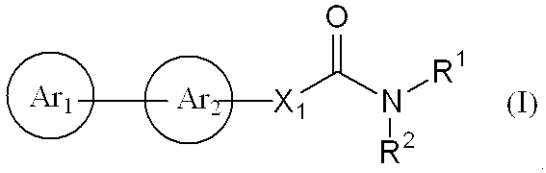
[0056]

The production process of the compound of the general formula (I) of the present invention is described below.

The compound represented by the general formula (I)

[0057]

[Formula 33]



(I)

(wherein Ar_1, Ar_2, X_1, R^1 and R^2 have the same meanings as above and if necessary, Ar_1 and Ar_2 may contain protecting group(s) for functional groups such as hydroxy group(s), amino group(s) or carboxylic acid group(s).) can be synthesized according to the following General Production Processes 1 to 5.

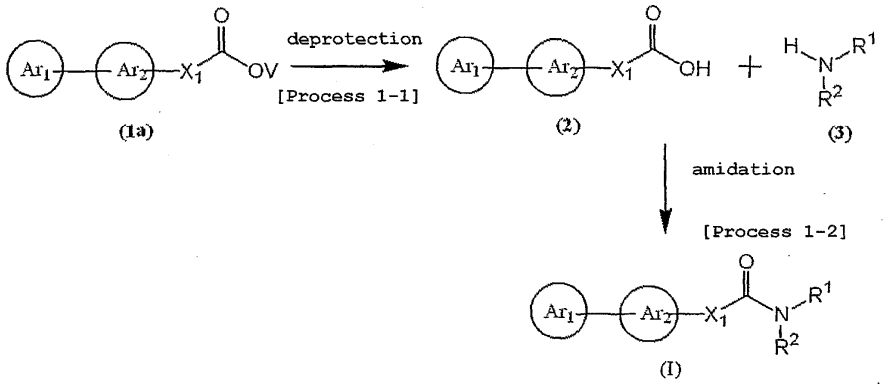
[0058]

(General Production Process 1)

A typical production process (General Production Process 1) of the compound of the general formula (I) according to the present invention is described below.

[0059]

[Formula 34]



(wherein Ar_1, Ar_2 and X_1 is the same as defined above; V represents a protecting group for carboxyl group such as a methyl group, an ethyl group, a benzyl group, an allyl group, a triphenylmethyl group, a tert-butyl group, a methoxymethyl group or a tert-butyldimethylsilyl group, and

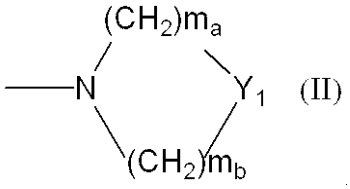
(1) R^1 and R^2 represent groups selected from Substituent Group A4 shown below or

R^1 and R^2, together with a nitrogen atom to which they bind, form one of the following groups:

(2-1) a 5- to 11-membered non-aromatic heterocyclic group represented by Formula (II):

[0060]

[Formula 35]



(II)

(wherein Y_1 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9)

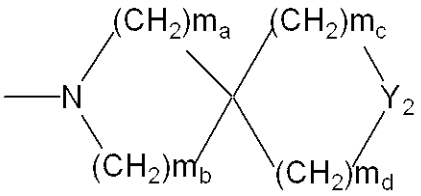
-NHCO-, (10) $-CR^5=CR^6-$ (wherein R^5 and R^6 represent groups selected from Substituent Group A4 shown below), (11) a single bond or (12) $>C=CR^{13}R^{14}$ (wherein R^{13} and R^{14} represent groups selected from Substituent Group A4 shown below); and

m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4;

(2-2) a 6- to 20-membered non-aromatic heterocyclic group represented by Formula (III):

[0061]

[Formula 36]



(III)

(wherein Y_2 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO-, (10) $-CR^5= CR^6-$ (wherein R^5 and R^6 represent groups selected from Substituent Group A4 shown below or R^5 and R^6, together with a carbon atom to which they bind, form a 6- to 14-membered aromatic hydrocarbon ring group or a 6- to 14-membered non-aromatic hydrocarbon ring group) or (11) a single bond; and

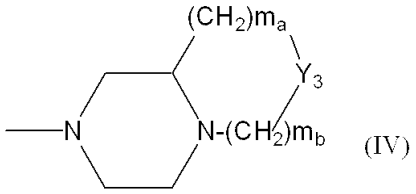
m_a, m_b, m_c and m_d represent an integer of 0 to 4) which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4;

(2-3) a 9- to 16-membered non-aromatic heterocyclic

group represented by Formula (IV):

[0062]

[Formula 37]



(IV)

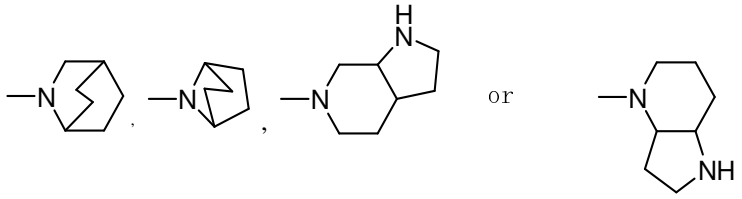
(wherein Y_3 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO- or (10) a single bond; and

m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4;

(2-4) a group represented by the following formula:

[0063]

[Formula 38]

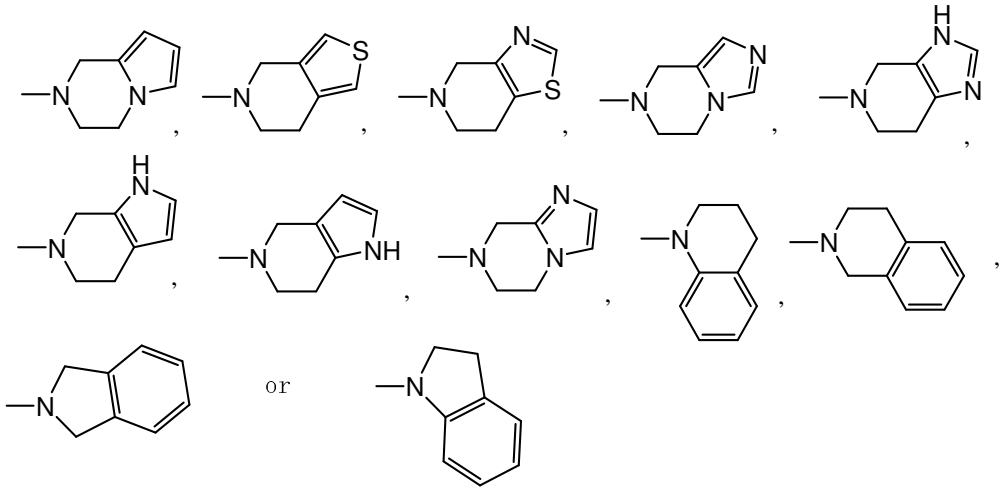


which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4;

(2-5) a group represented by the following formula:

[0064]

[Formula 39]



which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 shown below.

Substituent group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituent groups selected from Substituent Group A4, (21) a carbamoyl group which may

be substituted with 1 to 2 substituent groups selected from Substituent Group A4, (22) 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituent groups selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[0065]

The above described "General Production Process 1" is an example of production process of the compound of the general formula (I) in which an ester

compound (1a) is subjected to deprotection reaction in "step 1-1" to be converted into a carboxylic acid compound (2) and subsequently the carboxylic acid compound (2) is subjected to amidation reaction together with an amine compound (3).

[0066]

(Preparation of carboxylic acid compound (2))

The carboxylic acid compound (2) can be prepared, for example, by subjecting an ester compound (1a) to the "step 1-1". That is, although the deprotection reaction in "step 1-1" may vary depending on the starting material, no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction by methods known in the art (for example, methods as described in T.W. Green. "Protective Groups in Organic Synthesis" John Wiley & Sons. Inc., 1981, p154-186) can be employed. Preferably, it is a hydrolysis reaction of an ester compound, and techniques described in many known references can be used (for example, such methods are described in "Composition and Reaction of Organic Compound [II]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1978, p.930-943). Preferably, a desired carboxylic acid compound (2) can be obtained by reacting an ester compound (1a) using a water-containing solvent (mixed solvent of water with, for example, methanol, ethanol and/or tetrahydrofuran,

etc.) at room temperature to 100°C in the presence of 1.0 to 5.0 equivalents of metal hydroxide (preferably, for example, sodium hydroxide, potassium hydroxide or lithium hydroxide etc.). Moreover, depending on a corresponding ester compound (1a), a carboxylic acid compound (2) can also be suitably obtained under an acidic condition (preferably with trifluoroacetic acid). Under a preferable reaction condition, the reaction completes in 1 to 24 hours, and the progress of reaction can be monitored by known chromatography technology. Undesirable by-products can be removed by techniques in the art such as conventional chromatography technology, extraction procedure and/or crystallization.

[0067]

(Preparation of compound of general formula (I))

The compound of general formula (I) can be prepared, for example, by subjecting carboxylic acid compound (2) to the "step 1-2". That is, although the amidation reaction of "step 1-2" may vary depending on the starting material, no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction by known techniques described in many references (for example, such methods are described in "Composition and Reaction of Organic Compound [II]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1978,

p.1136-1162) can be employed. Preferable examples include i) a process comprising converting a carboxylic acid compound (2) to an acid halide followed by reacting the acid halide with an amine compound under a basic condition (for example, such a process is described in "Composition and Reaction of Organic Compound [II]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1978, p.1142-1145), ii) a process comprising reacting a carboxylic acid compound (2) and an amine compound using a condensation agent (for example, such a process is described in "Guide to Organic Chemistry Experiment (4)," KagakuDojin, September, 1990, p.27-52), etc.

[0068]

In the case of above i), the base, solvent and reaction temperature to be used may vary depending on the starting material and are not particularly limited, and (i) a technique using, for example, pyridine, lutidine, quinoline, isoquinoline, etc. as a basic solvent; (ii) a technique using, for example, pyridine, triethylamine, N,N-diisopropylethylamine etc. as a base and preferably, for example, tetrahydrofuran, 1,4-dioxane etc. as a solvent which dissolves the starting substance(s) to some extent but does not prevent the reaction or a mixed solvent thereof; or (iii) a technique using a two-layer distribution system comprising of an alkali solution, preferably, for

example, an aqueous solution of a base, such as sodium hydroxide, potassium hydroxide, etc., and a halogenated solvent preferably, for example, methylene chloride, 1,2-dichloroethane, etc. can be used. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and is preferably an ice-cooling temperature to 100°C. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technology. Although the technique of converting the carboxylic acid compound (2) to an acid halide may vary depending on the starting material, no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction by methods known in the art can be used. Preferably, a chlorination agent such as thionyl chloride and oxalyl chloride can be used in an inert solvent such as methylene chloride, toluene and tetrahydrofuran. A catalytic amount of N,N-dimethylformamide, etc. may be suitably added to advance the reaction. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and is an ice-cooling temperature to 100°C preferably.

[0069]

In the case of above ii), the condensation

agent to be used may vary depending on the starting material and is not particularly limited, and it is preferable to use suitably 1.0 equivalent to 2.0 equivalents of 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate etc., for example, to the carboxylic acid compound (2). In order to advance the reaction efficiently, 1.0 equivalents to 2.0 equivalents of N-hydroxysuccinimide, N-hydroxybenzotriazol, etc., for example, may be added. It is preferable from a viewpoint of operativity and stirring efficiency to perform this reaction in the presence of a solvent, and although the solvent to be used may vary depending on the starting material and the condensation agent to be used and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, a halogen solvent such as methylene chloride and 1,2-dichloroethane, or a polar solvent such as tetrahydrofuran and N,N-dimethylformamide are preferable. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and is an ice-cooling temperature to 100°C preferably. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by

known chromatography technique. Undesirable by-products can be removed by any technique known in the art, such as conventional chromatography technique and/or crystallization. It is also possible to obtain a desired compound of the general formula (I) by forming an amide bond and subsequently converting R^1 and R^2 by a usual method using a technique known and it is also possible to obtain a desired compound of the general formula (I) by suitably modifying the substituent groups of Ar_1, Ar_2 and X_1.

[0070]

(Preparation of amine compound (3))

The amine compound (3) is commercially available or can be obtained by a technique known in the art. Preferable examples thereof include i) a method of converting a corresponding alcohol compound or alkyl halide compound to the amine compound by a known technique; ii) a method of converting a corresponding nitro compound, nitrile compound, oxime compound, azide compound or acid amide compound by a known reduction reaction, iii) a method of converting a corresponding carbonyl compound by a known reductive amidation reaction, iv) a method of obtaining amine compound by subjecting the nitrogen atom protected by a protecting group to deprotection reaction, etc.

[0071]

In the case of above i), conversion can be effected by methods described in many known references,

and for example, methods of obtaining the amine compound from a corresponding alcohol compound by Mitsunobu method (see, for example, O. Mitsunobu, "Synthesis," p.1, 1981) or from a alkyl halide compound by Gabriel method (see, for example, M.M.S. Gibson et al., "Angew. Chem.," vol. 80, p.986, 1968) are preferable. In the case of Mitsunobu method, the desired amine compound can be efficiently obtained preferably by a two-step reaction comprising condensing a corresponding alcohol compound with an imide compound using 1.0 to 3.0 equivalents of diethyl azodicarboxylate under the coexistence of 1.0 to 3.0 equivalents of triphenylphosphine and treating a product obtained from the first step with 1.0 to 3.0 equivalents of hydrazine, for example. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and it is preferably an ice-cooling temperature to 100°C for the condensation reaction with an imide compound at the first step and 50°C to 100°C for the hydrazine treatment at the second step. Although the solvent to be used in this reaction may vary depending on the starting material and the condensation agent to be used and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, diethyl ether, tetrahydrofuran, etc., for example, are preferable for the reaction of the first

step and methanol, ethanol, etc., for example, are preferable for the reaction of the second step. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization. In the case of Gabriel method, the desired amine compound can be efficiently obtained preferably by a two-step reaction comprising condensing a corresponding alkyl halide compound with an imide compound by any technique known in the art and treating a product obtained from the first step with 1.0 to 3.0 equivalents of hydrazine for example. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and it is preferably an ice-cooling temperature to 100°C for the condensation reaction with an imide compound in the first step and 50°C to 100°C for the hydrazine treatment in the second step. Although the solvent to be used in this reaction may vary depending on the starting material and the condensation agent to be used and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, etc., for example, are preferable

for the reaction of the first step and methanol, ethanol, etc., for example, are preferable for the reaction of the second step. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0072]

In the case of above ii), reduction processes described in many known references can be used (for example, such a process is described in "Composition and Reaction of Organic Compound [III]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1978, p.1333-1341), and the desired amine compound can be efficiently obtained by catalytic hydrogenation method which preferably uses, for example, a metal catalyst, a reduction method using a metal hydride, etc. The catalytic hydrogenation method is preferably conducted at ordinary pressure to 100 atm under hydrogen atmosphere. The metal catalysts usable in this reaction are preferably, for example, platinum, platinum oxide, platinum black, Raney nickel, palladium-carbon, etc. Although the solvent to be used in this reaction may vary depending on the starting material and is not particularly limited as long as it

dissolves the starting substance(s) to some extent but does not prevent the reaction, methanol, ethanol, diethyl ether, tetrahydrofuran, methylene chloride, chloroform, ethyl acetate, etc., for example, are preferable. In order to advance the reaction efficiently, acidic substances such as acetic acid or hydrochloric acid may be added. As for the reduction method using a metal hydride, the desired amine compound (3) will be obtained efficiently by preferably using lithium aluminum hydride or diborane. The solvent to be used in this reaction may vary depending on the starting material and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, diethyl ether, tetrahydrofuran, etc. are preferable, for example. The temperature for the reduction reaction of ii) should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products, and it is preferably an ice-cooling temperature to 100°C. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0073]

In the case of above iii), reductive

amination reaction known in the art (for example, such a process is described in "Composition and Reaction of Organic Compound [III]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1978, p.1380-1384) can be used, and a preferable process comprises obtaining an imine compound by dehydration reaction from a corresponding carbonyl compound and an amine compound by heat-refluxing in the presence of an acid catalyst (preferably, for example, an inorganic acid such as hydrochloric acid or sulfuric acid, an organic acid such as methanesulfonic acid, p-toluenesulfonic acid, and camphorsulfonic acid or an organic acid salt such as pyridinium p-toluenesulfonate) and reducing the imine compound with a metal hydride such as lithium aluminum hydride, sodium borohydride, etc. to obtain a desired amine compound. Alternatively, a process comprising treating an imine compound in an inert solvent such as tetrahydrofuran in the presence of a Lewis acid catalyst (preferably titanium (IV) isopropoxide) and reducing the imine compound with a metal hydride such as sodium borohydride is also preferable. Alternatively, for example, a technique of reducing a carbonyl compound and 0.5 to 5.0 equivalents of an amine compound with a metal hydride such as sodium triacetoxy borohydride and sodium cyano borohydride in an inert solvent such as methylene chloride, 1,2-dichloroethane, tetrahydrofuran, methanol

and ethanol to obtain a desired amine compound is also preferable. It is preferable to suitably add an acidic substance such as acetic acid or hydrochloric acid in order to advance the reaction efficiently. The progress of the reductive amination reaction iii) can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0074]

In the case of above iv), deprotection reactions described in many known references can be used (see, for example, T.W. Green, "Protective Groups in Organic Synthesis," John Wiley & Sons. Inc., 1981), and a method of obtaining a desired amine compound from a corresponding carbamate compound (preferably, for example, a tert-butylcarbamate compound, a benzylcarbamate compound, a 9-fluorenylmethylcarbamate compound etc.), or a method of obtaining such a desired amine compound from a corresponding amide compound (preferably, for example, a formamide compound, an acetamide compound, a trifluoroacetamide compound, etc.) are preferable. Alternatively, a method of deprotecting a corresponding imide compound according to the above described Gabriel method to obtain a desired amine compound is also preferable. Although the conditions of deprotecting reaction may vary depending on the starting material and no particular

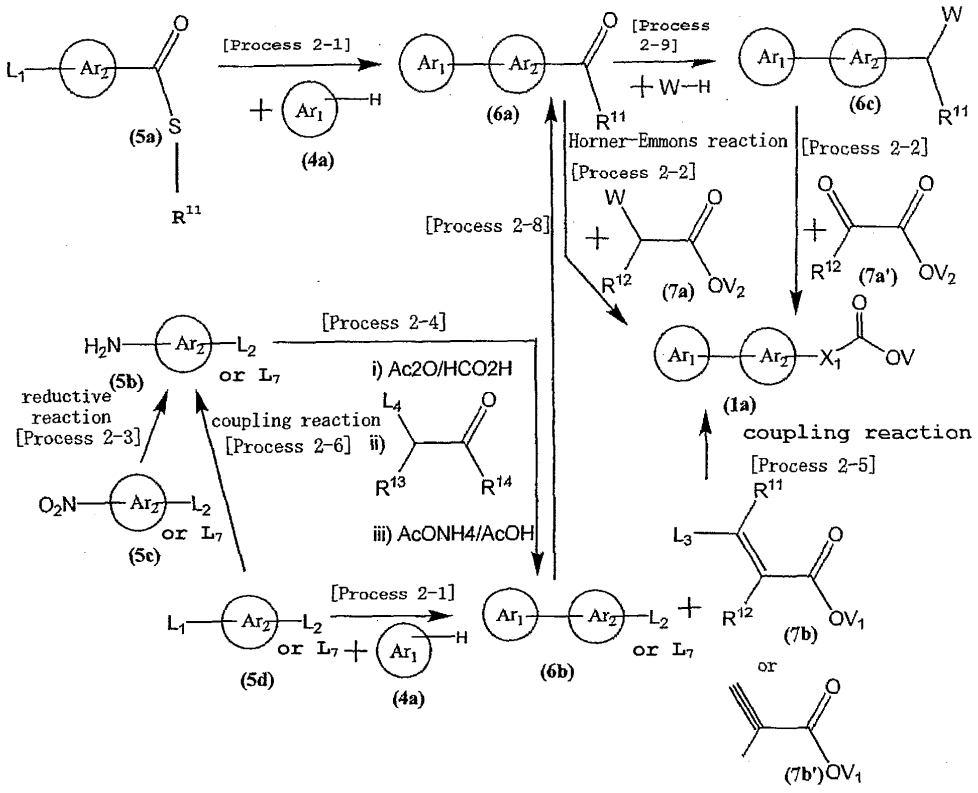
limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction and any known method can be used. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0075]

(Preparation-1 of an ester compound (1a))

[0076]

[Formula 40]



(wherein Ar_1, Ar_2, X_1 and V represent the same meaning as above;

V, V_1 and V_2 are the same or different and represent protecting groups for a carboxyl 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;

L_1, L_2, L_3 and L_4 represent leaving groups such as a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a sulfonate such as triflate, a trialkyltin group, boronic acid or boronic acid ester ($B(OV_1)_2$);

L_7 represents ester groups such as methylester, ethylester or benzylester, or cyano group;

W represents a diethylphosphonyl group, a diphenyl phosphonyl group or a bis(2,2,2-trifluoroethyl)phosphonyl group;

R^{13} and R^{14} represent groups selected from Substituent Group A1 shown below; and

R^{11} and R^{12} represent groups selected from Substituent Group A3 shown below.

Substituent group A1: (1) a hydrogen atom, (2) a halogen atom, (3) a cyano group, (4) a nitro group, (5) a C3-8 cycloalkyl group, (6) a C2-6 alkenyl group, (7) a C2-6 alkynyl group, (8) a C1-6 alkoxy group, (9) a C3-8 cycloalkoxy group, (10) a formyl group, (11) a C1-6 alkylcarbonyl group, and (12) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with

1 to 3 substituent groups selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C1–6 alkoxy group, a C3–8 cycloalkyl group and a C1–6 alkylcarbonyl group).

Substituent group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituent groups selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2–6 alkenyl group, a C2–6 alkynyl group, a C3–8 cycloalkyl group, a C1–6 alkoxy group, a C1–6 alkylthio group, a C1–6 alkylsulfinyl group, a C1–6 alkylsulfonyl group, a C1–6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be

substituted with 1 to 3 substituent groups selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted group with 1 to 3 substituted groups selected from Substituent Group A4) and (6) a C1-6 alkoxyl group.

[0077]

Although the ester compound (1a) may vary depending on the starting material, it can be obtained by a technique known in the art. Preferably, for example, the ester compound (1a) can be prepared as shown in the above-mentioned reaction formula, but the preparation is not limited thereto. That is, the ester compound (1a) can be prepared, for example, by reacting a compound (4a) and a compound (5a) at "Step 2-1" to obtain a carbonyl compound (6a), and subjecting the carbonyl compound to Horner-Emmons reaction at "Step 2-2" to yield the ester compound (1a). Alternatively, starting from a carbonyl compound (6a) through "step 2-9" to obtain a compound (6c), and subjecting the compound (6c) to Horner-Emmons reaction with a compound (7a') at "Step 2-2" to yield the ester compound (1a). Alternatively, the ester compound (1a) can be also

prepared through a three-step reaction of "step 2-4" using an amino compound (5b) as the starting material to build Ar_1 of a compound (6b) followed by a coupling reaction with a compound (7b) or (7b') according to "step 2-5". The ester compound (1a) can be also prepared by using a compound (5d) as the starting material and converting it into a compound (6b) according to "Step 2-1" to yield an ester compound (1a) at "Step 2-5".

[0078]

(Preparation of carbonyl compound (6a))

The carbonyl compound (6a) is commercially available or can be acquired with technique known in the art. When not marketed, the carbonyl compound (6a) can be prepared according to "Step 2-1" by using a compound (5a), for example, as the starting material. That is, the reaction of "Step 2-1" may vary depending on the starting material and no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction and any method known in the art can be used. For example, it is preferable to conduct a coupling reaction of a compound (4a) and a compound (5a) under neutral or basic conditions (see, for example, D.D. Davey et al., "J. Med. Chem.," vol. 39, p.2671-2677, 1991). That is, it is preferable to use 1.0 to 5.0 equivalents of compound (4a) to compound (5a). In order to perform the reaction efficiently, the base is preferably used

in 1.0 to 5.0 equivalents, and preferable examples include sodium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, cesium carbonate, barium carbonate, etc. The solvent to be used in this reaction may vary depending on the starting material and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, acetonitrile, tetrahydrofuran, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidine, etc. are preferable, for example. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and it is preferably 50°C to 200°C. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0079]

The carbonyl compound (6a) can be prepared according to "Step 2-8" by using a compound (6b) as the starting material. That is, the reaction of "Step 2-8" may vary depending on the starting material and no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction and any method known in the art can be

used. For example, a two-step technique comprising subjecting a compound (6b) (wherein L_2 is preferably a chlorine atom, a bromine atom, an iodine atom, and a sulfonate such as triflate) and a vinyl tin compound to Stille coupling reaction to convert the former to a vinyl compound and subjecting the vinyl compound to ozone oxidation reaction (see, for example, S.S. Chandran et al., "Bioorg. Med. Chem. Lett.," vol. 11, p.1493-1496, 2001) can also be used. Alternatively, carbon monoxide insertion reaction (see, for example, T. Okano et al., "Bull. Chem. Soc. Jpn.," vol. 67, p.2329-2332, 1994) using a transition metal catalyst can also be used.

Additionally, for example, in case the carbonyl compound (6b) has L7 group, the compound 6a can be prepared by reductive reaction which methods are known in the art.

[0080]

(Preparation of a compound (5a))

The compound (5a) used in this step is commercially available, or can be obtained by a technique known in the art. When not marketed, a preferable compound (5a) (wherein, L_1 represents a fluorine atom, a chlorine atom or a bromine atom) can be obtained as a corresponding alcohol by an oxidation reaction known in the art, and an ester can be subjected to a known reduction reaction to yield a carbonyl compound.

[0081]

(Preparation of a compound (4a))

The compound (4a) used at this step is commercially available, or can be obtained by a technique known in the art (see, for example, M. Komoto et al., "Agr. Biol. Chem.," vol. 32, p.983-987, 1968 or J.M. Kokosa et al., "J. Org. Chem.," vol. 48, p.3605-3607, 1983).

[0082]

(Conversion of carbonyl compound (6a) to ester compound (1a))

Although the conversion of the carbonyl compound (6a) to an ester compound (1a) may vary depending on the starting material, known technique described in many references can be used (such a process is described, for example, in H.O. House, "Modern synthetic reactions," W.A. Benjamin Inc., p629-733, 1972, or W. Carrthers, "Some modern methods of organic synthesis," Cambridge University press, p.125-144, 1986). For example, an ester compound (1a) can be prepared by converting a carbonyl compound (6a) according to "Step 2-2". That is, although the Horner-Emmons reaction of "Step 2-2" may vary depending on the starting material, no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction and methods known in the art (see, for example, W.S. Wadsworth, Jr. "Org. Reactions.," vol. 25, p.73, 1997)

can be used. That is, the carbonyl compound (6a) and the phosphonic acid ester compound (7a) can be subjected to a reaction condensation and converted into a corresponding ester compound (1a) under basic conditions. The base is preferably used in 1.0 to 2.0 equivalents to carbonyl compound (6a), and preferable examples include sodium hydride, sodium hydroxide, potassium hydroxide, lithium hydroxide, n-butyl lithium, lithium diisopropyl amide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, triethylamine, diisopropylethylamine, etc. The solvent to be used in this reaction may vary depending on the starting material and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, diethyl ether, tetrahydrofuran, dimethylsulfoxide, toluene, benzene, ethanol, methanol, etc. are preferable, for example. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and it is preferably -78°C to 100°C, and more preferably -78°C to room temperature. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. As for the geometric isomers formed during this reaction, the desired geometric isomer can be selectively prepared by a suitable

selection of a phosphonic acid ester compound (7a), base, reaction temperature and/or solvent, and undesirable by-products and geometric isomers can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0083]

For example, conversion of a carbonyl compound (6a) to an ester compound (1a) can be effected through a compound (6c) by subjecting the compound (7a') to Horner-Emmons reaction of "Step 2-2" to yield an ester compound (1a). For example, well-known technique described in many references can be used in the "Step 2-9" to prepare the compound (6c) (for example, as described in O. Pamies et al., J. Org. Chem., p.4815-4818, 2003, etc.). That is, it is preferable to use a carbonyl compound (6a) and a phosphate compound such as diethyl phosphite, etc. under basic conditions. As a base, it is preferable to use 1.0 to 2.0 equivalent to the carbonyl compound (6a), preferable examples of which include 1,8-diazabicyclo[5.4.0]undec-7-ene, triethylamine, piridine, sodium methoxide, etc. The solvent used for this reaction may vary depending on the starting material, and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction. Preferable examples include diethyl ether, tetrahydrofuran,

dimethylsulfoxide, toluene, benzene, ethanol, methanol, etc. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-product and it is preferably -78°C to 100°C, and more preferably -78°C to room temperature. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products formed in this reaction can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization. Moreover, the prepared compound (6c) can be modified by a technology well-known to those skilled in the art into a desired compound (for example, as described in T.-J.Tsai. Tetrahedron Letters, vol. 37, No. 5, p.629-632, 1996).

[0084]

(Preparation of compound (7a'))

The compound (7a') used at this step is commercially available, or can be obtained by a technique known in the art. When not marketed, a preferable compound (7a') can be obtained by subjecting a corresponding alcohol to an oxidation reaction well-known to those skilled in the art or by subjecting a corresponding ester to well-known oxidation reaction to obtain an α-ketoester compound.

[0085]

(Preparation of amine compound (5b))

The amine compound (5b) is commercially available, or can be obtained by a technique known in the art. Preferably, it can be prepared according to "Step 2-3" using a nitro compound (5c) as the starting material. That is, although the reduction reaction of "Step 2-3" may vary depending on the starting material, no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction and methods known in the art (for example, such a process is described in "Composition and Reaction of Organic Compound [III]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1978, p.1333-1341) can be used. Preferably, they are catalytic hydrogenation method which preferably uses, for example, a metal catalyst, or a reduction method using a metal, etc. The catalytic hydrogenation method is preferably conducted at ordinary pressure to 100 atm under hydrogen atmosphere. The metal catalysts usable in this reaction are preferably, for example, platinum, platinum oxide, platinum black, Raney nickel, palladium-carbon, etc. Although the solvent to be used in this reaction may vary depending on the starting material and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, methanol, ethanol, diethyl ether, tetrahydrofuran, methylene chloride, chloroform, ethyl acetate, etc., for example, are

preferable. In order to advance the reaction efficiently, acidic substances such as acetic acid or hydrochloric acid may be added. As for the reduction method using a metal, it is preferable to use zinc, iron, tin, etc. and to carry out under acidic conditions using, for example, hydrochloric acid, acetic acid, and ammonium chloride, preferably. Although the solvent to be used in this reaction may vary depending on the starting material and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, methanol, ethanol, 2-propanol, etc. are preferable, for example. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and it is preferably room temperature to 100°C. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0086]

The preferable amine compound (5b) can also be prepared according to the coupling reaction in "Step 2-6" by using as a starting material the compound (5d) which is commercially available or can be obtained by a

technique known in the art. That is, although the coupling reaction of "Step 2-6" may vary depending on the starting material, no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction and methods known in the art can be used. Preferably, two-step technique of carrying out known de-benzophenone reaction processing after coupling reaction of benzophenone imine using a transition metal catalyst can be used (see, for example, S.L. Buchwald et al., "Tetrahedron Lett.," vol. 38, p.6367-6370, 1997 or J.F. Hartwig et al., " J. Am. Chem. Soc.," vol. 120, p.827-828, 1998). In the coupling reaction of benzophenone imine, a catalytic amount (0.01 to 0.2 equivalents to compound (5d)) of a conventional palladium catalyst such as palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0) or tris(dibenzylideneacetone)dipalladium(0), or a conventional nickel catalyst such as (1,5-cyclooctadien) nickel (0), etc. can be preferably used as a catalyst. In addition, it is also preferable to suitably add a phosphorus ligand (preferably, for example, triphenylphosphine, tri-o-tolylphosphine, tri-tert-butylphosphine, 2-(di-tert-butylphosphino)-biphenyl, 2,2'- bis(diphenylphosphino)-1,1'-binaphthyl, 1,2- bis(diphenylphosphino)ethane, or 1,1'-bis(diphenylphosphino) ferrocene, etc. in order to

advance the reaction efficiently. Moreover, the reaction may give a preferable result in the presence of a base, and although the base to be used is not particularly limited as long as it can be used in a similar coupling reactions as this reaction, and preferable examples include sodium hydroxide, barium hydroxide, potassium fluoride, cesium fluoride, sodium carbonate, potassium carbonate, cesium carbonate, potassium phosphate, sodium tert-butoxide, etc. This reaction is preferably conducted in the presence of a solvent from a viewpoint of operativity and stirring efficiency, and although the solvent to be used in this reaction may vary depending on the starting material and the transition metal catalyst to be used and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone, N,N-dimethylformamide etc. are preferable, for example. The reaction temperature should be a temperature which is sufficient for completing the coupling reaction and it is preferably room temperature to 100°C. It is preferable to carry out this reaction under an inactive gas atmosphere, and more preferably under nitrogen or argon atmosphere. Post-processing of the second step can use a technique known in the art (see, for example, T.W. Green. "Protective Groups in Organic Synthesis" John

Wiley & Sons. Inc., 1981). Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0087]

As for the preferable amine compound (5b), L_2 can be modified by a technique known in the art, and preferably conversion from a hydrogen atom to a halogen substituent group is possible at L_2 (for example, as described in "Composition and Reaction of Organic Compound [I]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., November, 1977, p. 354-360).

[0088]

(Preparation of nitro compound (5c))

The nitro compound (5c) used at this step is commercially available, or can be obtained by a technique known in the art. When not marketed, a preferable compound (5c) (wherein L_2 represents a fluorine atom, a chlorine atom, a bromine atom, or iodine) can be efficiently obtained by subjecting a corresponding precursor to a nitration known to those skilled in the art (for example, as described in "Composition and Reaction of Organic Compound [III]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1978, p. 1261-1300).

[0089]

(Preparation of a compound (6b))

A compound (6b) can be obtained by a technique known in the art. It is preferably prepared through the above "Step 2-1," using a compound (5d) as the starting material, or it can also be prepared according to "step 2-4" using an amine compound (5b) as the starting material. For example, the "step 2-4" can be conducted by treating the compound (5b) with a mixed solvent of acetic anhydride and formic acid in the first phase, effecting condensation with an α-haloketone (in which L_4 is a chlorine atom, a bromine atom, or iodine) under a basic condition in the second phase, and heat-treating with ammonium acetate and acetic acid in the third phase to efficiently convert into a compound (6b). It is preferable in the first phase to conduct treatment with a mixed solvent of 2.0 to 10.0 equivalents of acetic anhydride and 10.0 to 20.0 equivalents of formic acid to the compound (5b) at a temperature of ice-cooling temperature to 50°C. The base used in the second phase is preferably used in 1.0 to 5.0 equivalents to the compound (5b), and, for example, sodium hydride, sodium hydroxide, potassium hydroxide, lithium hydroxide, n-butyl lithium, lithium diisopropyl amide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, etc. are preferable. Although the solvent to be used in this reaction may vary depending on the starting material and is not particularly limited as long as it dissolves the

starting substance(s) to some extent but does not prevent the reaction, diethyl ether, tetrahydrofuran, dimethylsulfoxide, N,N-dimethylformamide, etc. are preferable, for example. It is preferable to suitably add, for example, potassium iodide, sodium iodide, etc. in order to advance the reaction efficiently. The reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and it is preferably room temperature to 100°C. It is preferable in the third phase to conduct treatment with a mixed solvent of 5.0 to 10.0 equivalents of ammonium acetate and 10.0 to 20.0 equivalents of acetic acid to the compound (5b) at a temperature of 50°C to 150°C. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique. Undesirable by-products can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0090]

The α-haloketone used in the second phase of this step is commercially available, or can be acquired with technique known in the art. When not marketed, preferable α-haloketone (in which L_4 is a chlorine atom, a bromine atom, or iodine) can be efficiently obtained by subjecting a corresponding precursor to a halogenation reaction known to those skilled in the art

(for example, as described in "Composition and Reaction of Organic Compound [I]," New Experiment Chemistry Series, vol. 14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., February, 1977, p. 307-450).

[0091]

As for the compound (6b), L_2 can be modified by a technique known in the art, and preferably conversion to an iodine group (see, for example, S.L. Buchwald et al. "J. Am. Chem. Soc.," vol. 124, p.14844-14845, 2002), to a lower alkyl tin group (see, for example, J. Marti et al., "Synth. Commun.," vol. 30, p.3023-3030, 2000), and to a boron group (see, for example, N. Miyaura et al., " J. Org. Chem.," vol. 60, p.7508-7510, 1995), etc. is possible.

[0092]

(Conversion from compound (6b) to ester compound (1a))

The conversion from a compound (6b) to an ester compound (1a) can be conducted by using a known technique in the art. For example, an ester compound (1a) can be prepared by subjecting a compound (6b) to "Step 2-5" together with a compound (7b) or a compound (7b'). That is, although the coupling reaction of "Step 2-5" may vary depending on the starting material, no particular limitation is imposed upon it as long as the reaction is conducted under conditions similar to those in this reaction and methods known in the art can be used, and Mizoroki-Heck reaction (see, for example, R.F. Heck, "Org. Reactions.," vol. 27, p.345, 1982),

Suzuki-Miyaura reaction (see, for example, A. Suzuki, "Chem. Rev.," vol. 95, p.2457, 1995), Sonogashira reaction (see, for example, K. Sonogashira, "Comprehensive Organic Synthesis," vol. 3, p.521, 1991), Stille coupling reaction (J.K. Stille, "Angew. Chem. Int. Ed. Engl.," vol. 25, p.508,1986), etc. are preferable.

[0093]

In Mizoroki-Heck reaction preferably performed is a coupling reaction of a halide, a triflate compound (6b) (wherein L_2 represents a chlorine atom, a bromine atom, an iodine atom, or a triflate), with an alkene compound (7b; L_3 is a hydrogen atom) in 1.0 to 5.0 equivalents to the compound (6b) in the presence of 0.01 to 0.2 equivalents of a transition metal catalyst, for example. This reaction is preferably conducted in the presence of a solvent from a viewpoint of operativity and stirring efficiency, and although the solvent to be used in this reaction may vary depending on the starting material and the transition metal catalyst to be used and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction, acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone, N,N-dimethylformamide, etc. are preferable, for example. The reaction temperature should be a temperature which is sufficient

for completing the coupling reaction and it is preferably room temperature to 150°C. It is preferable to carry out this reaction under an inactive gas atmosphere, and more preferably under nitrogen or argon atmosphere. The transition metal catalyst is preferably a palladium complex, for example, and more preferably includes a conventional palladium complex such as palladium(II) acetate, dichlorobis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0) or tris(dibenzylideneacetone)dipalladium(0). In addition, it is also preferable to suitably add a phosphorus ligand (preferably, for example, triphenylphosphine, tri-o-tolylphosphine, tri-tert-butylphosphine, 2-(di-tert-butylphosphino)biphenyl, etc.) in order to advance the reaction efficiently. Moreover, the reaction may give a preferable result in the presence of a base, and although the base to be used is not particularly limited as long as it can be used in a similar coupling reactions as this reaction, and preferable examples include triethylamine, N,N-diisopropylethylamine, N,N-dicyclohexylmethylamine, tetrabutylammonium chloride, etc. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique.

[0094]

Suzuki-Miyaura reaction is preferably carried

out by coupling, for example, a halide or a triflate compound (6b), wherein L_2 represents a chlorine atom, a bromine atom, an iodine atom or a triflate, with, for example, a boronic acid compound or a boronic ester compound (7b), wherein L_3 represents $B(OH)_2$ or $B(OV_1)_2$, in the presence of 0.01 to 0.5 equivalent of a transition metal catalyst based on the triflate compound. This reaction is preferably carried out in the presence of a solvent in order to achieve easy operation and stirring. The solvent used differs according to the starting material and the transition metal catalyst used, and is not specifically limited insofar as the solvent does not inhibit the reaction and allows the starting material to be solved therein to a certain extent. Preferable examples include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone and N,N-dimethylformamide, and mixtures of water with these solvents. The reaction temperature should be a temperature that can complete the coupling reaction, and is preferably room temperature to 200°C. The reaction is carried out 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 using a known chromatography technology. The transition metal catalyst is preferably a known palladium catalyst, and

more preferably a known palladium catalyst such as, for example, palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). In order to proceed the reaction efficiently, a phosphorus ligand (preferably, for example, triphenylphosphine, tri-o-tolylphosphine, tricyclohexylphosphine or tri-tert-butylphosphine) or the like may be appropriately added. Further, in order to proceed the reaction efficiently, a quaternary ammonium salt, preferably, for example, tetrabutylammonium chloride or tetrabutylammonium bromide may be appropriately added. This reaction can bring about preferable results in the presence of a base. The base used in this case differs according to the starting material, the solvent used, and the like, and is not specifically limited. Preferable examples 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 using a known chromatography technology. In this reaction, even if the compound (7b) is, for example, a halide or a triflate compound (7b), wherein L_3 represents a chlorine atom, a bromine atom, an iodine atom or a triflate, and the compound (6b) is, for example, a boronic acid compound or a

boronic ester compound (6b), wherein L_2 represents $B(OH)_2$ or $B(OV_1)_2$, a desired coupling product (1a) can be efficiently obtained.

[0095]

The reaction conditions for Sonogashira reaction differ according to the starting material, the solvent and the transition metal catalyst, but are not specifically limited insofar as the reaction conditions are those used in a reaction like this reaction. A technique known to a person skilled in the art may be used for the reaction. As the starting material, an alkyne compound (7b') is preferably used. Examples of preferable solvents include acetonitrile, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, benzene, toluene, xylene, 1-methyl-2-pyrrolidone, N,N-dimethylformamide and dimethyl sulfoxide. Examples of more preferable solvents include tetrahydrofuran, 1,4-dioxane, 1-methyl-2-pyrrolidone and N,N-dimethylformamide. The reaction temperature should be a temperature that can complete the coupling reaction, and is preferably room temperature to 100°C. The reaction is carried out 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 using a known chromatography technology. The transition metal catalyst is preferably, for example, a known palladium

catalyst, and more preferably a known palladium catalyst such as, for example, palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). In order to proceed the reaction efficiently, a phosphorus ligand (preferably, for example, triphenylphosphine, tri-o-tolylphosphine or tri-tert-butylphosphine) may be appropriately added, for example. In this reaction, a metal halide, a quaternary ammonium salt, or the like, preferably, for example, copper (I) iodide, lithium chloride, tetrabutylammonium fluoride or silver (I) oxide may be added. The reaction can bring about preferable results in the presence of a base. The base used in this case is not specifically limited insofar as the base can be used in a coupling reaction like this reaction. Preferable examples include basic solvents such as diethylamine, triethylamine, N,N-diisopropylethylamine, piperidine and pyridine.

[0096]

Stille coupling reaction is preferably carried out by reacting 1.0 equivalent or more of a trialkyltin compound (6b), wherein L_2 represents $(V_1)Sn$, with a halide or a triflate compound (7b), wherein L_3 represents a chlorine atom, a bromine atom, an iodine atom or a triflate, in the presence of 0.01 to 0.2 equivalent of a transition metal catalyst. In order to proceed the reaction efficiently, it is preferable to

use 0.1 to 5.0 equivalents of copper (I) halide and/or lithium chloride appropriately. Examples of preferable solvents used in this reaction include toluene, xylene, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and dimethyl sulfoxide. The reaction temperature should be a temperature that can complete the coupling reaction, and is preferably room temperature to 100°C. The transition metal catalyst is preferably a palladium catalyst, more preferably a known palladium catalyst such as, for example, palladium (II) acetate, dichlorobis(triphenylphosphine)palladium (II), tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0), and still more preferably, for example, tetrakis(triphenylphosphine)palladium (0) or tris(dibenzylideneacetone)dipalladium (0). The reaction is carried out 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 using a known chromatography technology.

[0097]

[Preparation of compound (7b) and compound (7b')]

The compound (7b) and the compound (7b') used in this step are commercially available or can be obtained by a technique known to a person skilled in

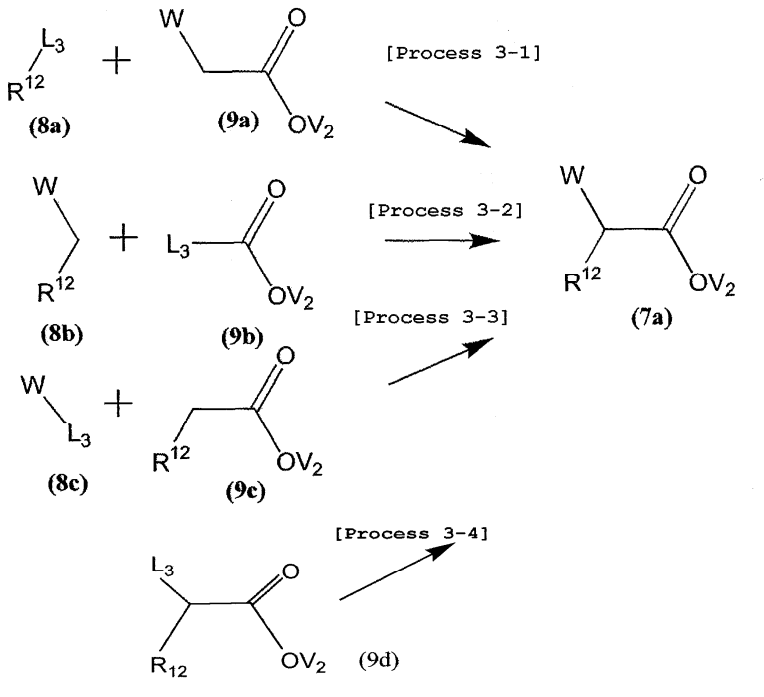
the art. When such a compound is not commercially available, a preferable compound (7b), wherein L_3 represents $B(OH)_2$ or $B(OV_1)_2$, and V_1 represents the same as defined above, can be efficiently obtained, for example, from a corresponding precursor by a coupling reaction known to a person skilled in the art (as described in, for example, C.R. Deloge et al., "Bull. Soc. Chim. Fr.", 1992, vol.129, pp.285-290). Alternatively, a preferable compound (7b), wherein L_3 is a triflate, can be efficiently obtained from, for example, a corresponding precursor by a method known to a person skilled in the art (as described in, for example, B. Dupre et al., "J. Org. Chem.", 1991, vol.56, pp.3197-3198.

[0098]

(Preparation of phosphonic acid ester compound (7a))

[0099]

[Formula 41]



(wherein V_2 and R^{12} is the same as defined above, W represents $(EtO)_2PO$, $(PhO)_2PO$ or $(CF_3CH_2O)_2PO$, and L_3 represents a chlorine atom, a bromine atom or an iodine atom.)

The above-mentioned formula shows an example of the method of preparing a phosphonic acid ester compound (7a). That is, a phosphonic acid ester compound (7a) is commercially available or can be obtained by a method known to those skilled in the art shown above as "Step 3-1" to "Step 3-3" (see, for example, C.Patois et al., Synth.Commun., vol. 22, p.2391, 1991 or J.A.Jackson et al., J.Org.Chem., vol. 20, p.5556, 1989). For example, "Step 3-1" is a process in which a desired phosphonic acid ester compound (7a) is obtained by processing a phosphonic acid ester compound (9a) with an alkyl halide compound (8a) 1.0 to 2.0 equivalent to the phosphonic acid ester compound (9a) under basic conditions and introducing R^{12}. "Step 3-2" is a process in which a desired phosphonic acid ester compound (7a) is obtained by processing a phosphonic acid ester compound (8b) with a halogenated formic acid ester compound (9b) 1.0 to 2.0 equivalent to the phosphonic acid ester compound (8b) under basic conditions. "Step 3-3" is a process in which a desired phosphonic acid ester compound (7a) is obtained by processing a phosphonic acid halide (8c) with an ester compound (9c) 1.0 to 2.0 equivalent to the phosphonic acid halide (8c) under basic conditions.

"Step 3-4" is a process in which a desired phosphonic acid ester compound (7a) is obtained by processing on α-haloester compound (9d) with trialkylphosphite 1.0 to 10.0 equivalent to the α-haloester compound (9d). Although the base compounds used at this step vary depending on the starting materials, it is preferable to use sodium hydride, n-butyl lithium, lithium diisopropyl amide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide etc., in an amount of 1.0 to 1.5 equivalent, for example. Although the trialkyl phosphites used at this step vary depending on the starting materials, it is preferable to use trimethyl phosphite, triethylphosphite etc., in an amount of 1.0 to 10.0 equivalent, for example. The solvent used for this reaction may vary depending on the starting material, and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction. Preferable examples include hexane, toluene, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, hexamethyl phosphoric acid triamide, or a mixed solvent of thereof. Reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and is preferably -78°C to 150°C. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique.

Undesirable by-products formed in this reaction can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization. Moreover, as for the phosphonic acid ester compound (7a), R^{12} can be modified by a technology well-known to those skilled in the art into a desired phosphonic acid ester compound (7a) efficiently.

[0100]

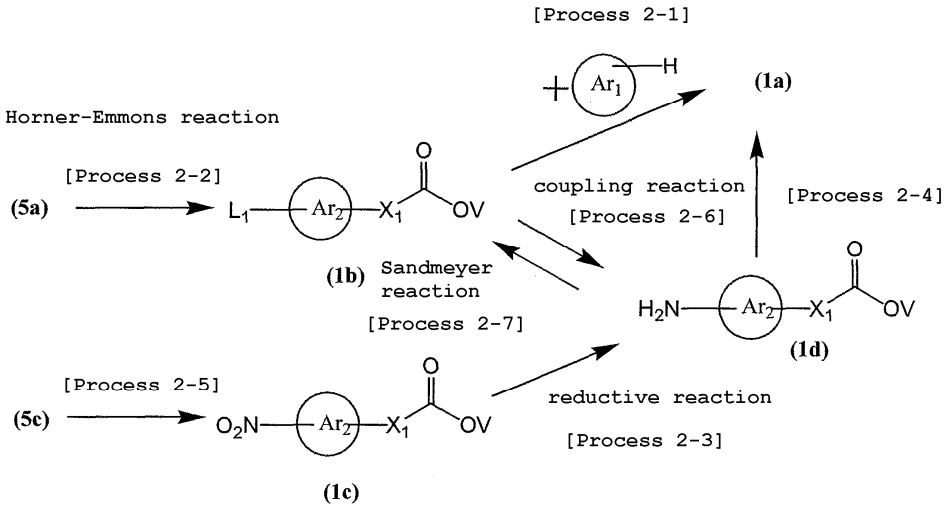
The alkyl halide compound (8a), phosphonic acid ester compound (8b), phosphonic acid halide (8c), phosphonic acid ester compound (9a), halogenated formic acid ester compound (9b) ester compound (9c) and α-habester compound (9d) used at this step are commercially available or can be obtained by a technique known in the art.

[0101]

(Preparation-2 of ester compound (1a))

[0102]

[Formula 42]



(wherein Ar_2, X_1, V and L_1 have the same meaning as in formula (I);

V represents an methyl group, an ethyl group, a benzyl group, an allyl group, a triphenylmethyl group, a tert-butyl group, or a protecting group such as a tert-butyldimethylsilyl group, a methoxymethyl group;

L_1 represents a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, and a triflate such as a sulfonate, a trialkyltin group, boronic acid or boronic acid ester ($B(OV_1)_2$.)

The above described formula shows an example of the method of preparing an ester compound (1a) as an alternative method. That is, it is (i) a process in which the above described compound (5a) is used as a starting material, which is converted to an ester compound (1b) following the above described "Step 2-2" to prepare an ester compound (1a) in the above-mentioned "Step 2-1"; (ii) a process in which an ester compound (1b) is converted to an amine compound (1d) at "Step 2-6" from which an ester compound (1a) is prepared according to the above described "Step 2-4" or (iii) a process in which the above described nitro compound (5c) is used as a starting material, which is subjected to the three of the above "Step 2-5", "Step 2-3" and "Step 2-4" to prepare an ester compound (1a). In addition, it is shown that the amine compound (1d) can be also converted to an ester compound (1b) at the Sandmeyer reaction of "Step 2-7" and then converted to

an ester compound (1a) according to the above "Step 2-1".

[0103]

(Conversion from ester compound (1b) to amine compound (1d))

The conversion to an amine compound (1d) from an ester compound (1b) can be effected using a technique known in the art. Preferably, the same technique as the above "Step 2-6" can be used.

(Conversion from amine compound (1d) to ester compound (1b))

[0104]

The conversion from an amine compound (1d) to an ester compound (1b) may vary depending on the starting material, and is not particularly limited as long as it can be effected under similar conditions as in this process and processes known in the art can be used. Preferably, the Sandmeyer reaction of "Step 2-7" etc. can be used, and a preferable ester compound (1b) can be efficiently obtained by the technique known in the art (for example, as described in "Composition and Reaction of Organic Compound [I]", New Experiment Chemistry Series, vol.14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., November, 1977, p. 383-388)

[0105]

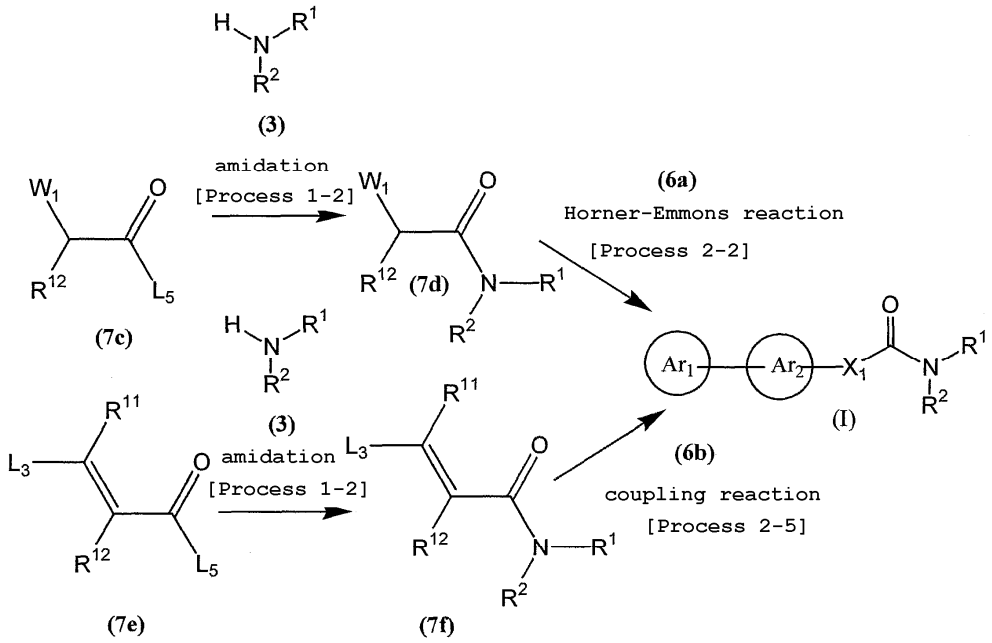
(General preparing process 2)

The "general preparing process 2" for

preparing typical compound of general formula (I) is explained below.

[0106]

[Formula 43]



(wherein Ar_1, Ar_2, X_1, R^1, R^2, R^{11}, R^{12} and L_3 is the same as defined above;

W_1 has the same meaning as W and L_5 represents a hydroxyl group, a chlorine atom and a bromine atom).

The compound of general formula (I) can be prepared by, for example, converting a compound (7c) to a compound (7d) according to the above "Step 1-2", and then performing "Step 2-2" with a carbonyl compound (6a) as described above, or by converting a compound (7e) to a compound (7f) according to the above "Step 1-2", and then performing "Step 2-5" with a carbonyl compound (6b) as described above.

[0107]

(Preparation of compound (7d))

The compound (7d) is commercially available or can be prepared by subjecting a compound (7c) to a similar step as the above "Step 1-2" with an amine compound (3) as described above.

[0108]

(Preparation of compound (7c))

The compound (7c) is commercially available or can be prepared by a technique known in the art. Preferably, compound (7c) can be efficiently obtained by using the above described phosphonic acid ester (7a) as the starting material and subjecting it to a similar deprotection reaction as in above "step 1-1".

[0109]

(Preparation of compound (7f))

The compound (7f) is commercially available or can be prepared by subjecting a compound (7e) to a similar step as in above "Step 1-2" together with an amine compound (3) as described above.

[0110]

(Preparation of compound (7e))

The compound (7e) is commercially available or can be obtained by a technique known in the art. Preferably, compound (7e) can be efficiently obtained by using the above described compound (7b) as the starting material and subjecting it to a similar deprotection reaction as in above "step 1-1".

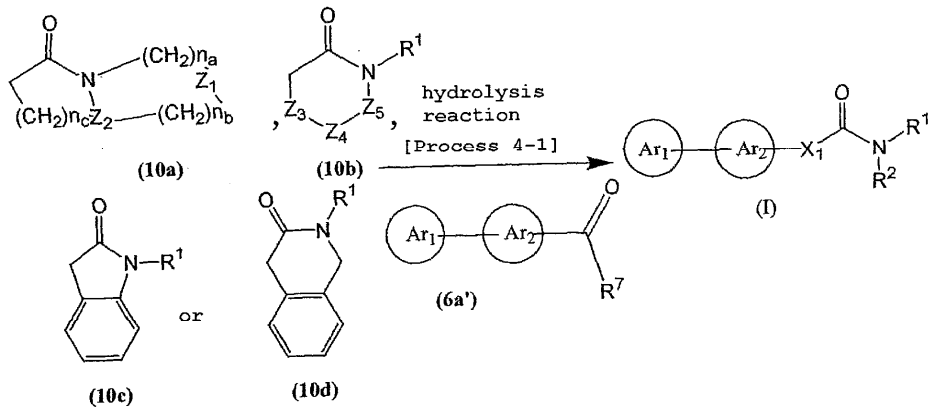
[0111]

(General manufacturing process 3)

The typical (general manufacturing process 3) of the compound of general formula (I) is explained below.

[0112]

[Formula 44]

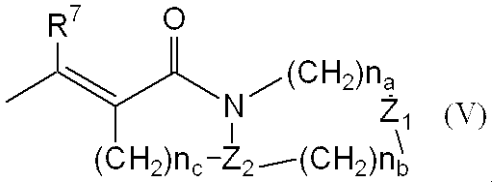


(wherein, Ar_1, Ar2 and X_1 is the same as defined above; R^1 and R^2, together with $-X_1-CO-N-$, form one of the following ring structures:

(3-1) a cyclic group represented by Formula (V):

[0113]

[Formula 45]



(V)

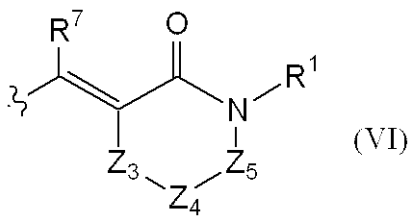
(wherein Z_1 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9)

–NHCO– or (10) a single bond; Z_2 represents (1) a methine group or (2) a nitrogen atom; R^7 represents a substituent selected from Substituent Group A3 shown below; and n_a, n_b and n_c represent an integer of 0 to 4) which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4;

(3-2) a cyclic group represented by Formula (VI):

[0114]

[Formula 46]



(VI)

(wherein Z_3 represents (1) a single bond, (2) –CO–, (3) $-(CH_2)n_d-$ (wherein n_d represents an integer of 1 to 3) or (4) $-CR^8R^9-$ (wherein R^8 and R^9 represent a substituent selected from Substituent Group A4 shown below;

Z_4 represents (1) a single bond, (2) –O–, (3) –NRCO–, (4) –CONR–, (5) –CSNR– or (6)–NRCS–(wherein R represents a substituent selected from Substituent Group A4 shown below) or (7) –S–;

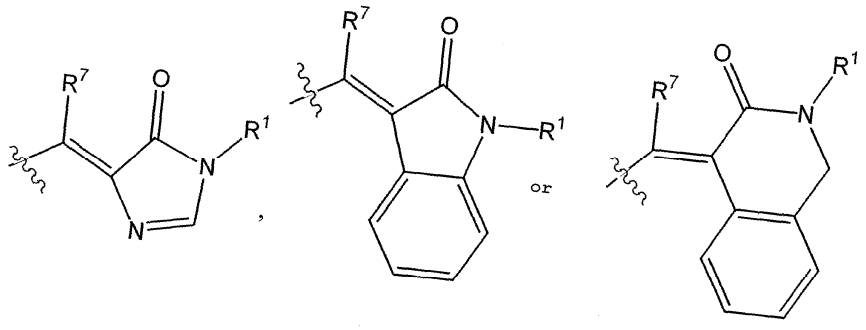
Z_5 represents (1) a single bond, (2) an imino group which may be substituted with a substituent selected from Substituent Group A4 shown below, (3) $-(CH_2)n_e-$ (wherein n_e represents an integer of 1 to 3), (4) $-CR^8R^9-$ (wherein R^8 and R^9 is the same as defined above) or (5) –O–; and

R^1 to R^7 are the same as defined above); or

(3-3) a cyclic group represented by the following formula:

[0115]

[Formula 47]



(wherein R^1 and R^7 are the same as defined above)

which may be substituted with 1 to 4 substituent groups selected from Substituent Group A4 shown below.

Substituent group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituent groups selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2-6 alkenyl group, a C2-6

alkynyl group, a C3–8 cycloalkyl group, a C1–6 alkoxy group, a C1–6 alkylthio group, a C1–6 alkylsulfinyl group, a C1–6 alkylsulfonyl group, a C1–6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with a C1–6 alkyl group optionally having 1 to 5 halogen atoms), a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, a 6– to 14–membered non–aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, a 5– to 14–membered non–aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4 and –X–A (wherein X represents an imino group, –O– or –S– and A represents a 6– to 14–membered aromatic hydrocarbon ring group or 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4) and (6) a C1–6 alkoxyl group.

Substituent group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group,

(11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituent groups selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituent groups selected from Substituent Group A4, (22) 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X

represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituent groups selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

The above-mentioned formula is given to illustrate an example of a process using a compound (10a), a compound (10b), a compound (10c) or a compound (10d) as starting materials, and subjecting them to a dehydration reaction of "Step 4-1" with a carbonyl compound (6a') to prepare the compound of general formula (I). That is, although the dehydration reaction of "Step 4-1" may vary depending on the starting material, and is not particularly limited as long as it can be effected under similar conditions as in this process and processes known in the art can be used (for example, as described in H.O.House."Modern synthetic reactions" W.A.Benjamin, Inc., p.629-653, 1972). Preferably, the compound of Formula (I) can be efficiently obtained by carrying out dehydrating condensation reaction of the acidic hydrogen of a compound (10a), a compound (10b), a compound (10c) or a compound (10d) and the oxygen atom of a carbonyl compound (6a') on basic conditions. Preferable examples of base usable in this reaction include piperidine, pyrrolidine, sodium methoxide, sodium

ethoxide, potassium tert-butoxide, sodium hydride, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, cesium carbonate, n-butyl lithium, lithium diisopropyl amide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, etc. The equivalent of the base may vary depending on the base to be used, starting material and the solvent to be used, and is not limited. The solvent used for this reaction may vary depending on the starting material and base, and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction. Preferable examples include diethyl ether, tetrahydrofuran, benzene, toluene, xylene, methanol, ethanol or tert-butyl alcohol. Reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and is preferably -78°C to 150°C. In preferable reaction conditions, the reaction completes in 1 to 24 hours, and the progress of the reaction can be monitored by known chromatography technique.

[0116]

In addition, the compound of general formula (I) can also be obtained two-step process wherein compounds (10a), (10b), (10c) or (10d) which have been processed under basic conditions and a carbonyl

compound (6a') form an alcohol compound through aldol reaction and then the hydroxyl group thereof is eliminated by a known technique. As a base used at the first step of this technique, sodium hydride, n-butyl lithium, lithium diisopropyl amide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, sodium ethoxide, tert-butoxide, etc. are mentioned preferably. The equivalent of these bases may vary depending on the starting material, and although it is not limited, 1.0 to 2.0 equivalent is preferable. In order to advance the reaction efficiently, titanium (IV) isopropoxide or boron trifluoride may be added, for example. The solvent used for the first step may vary depending on the starting material and base and is not particularly limited as long as it dissolves the starting substance(s) to some extent but does not prevent the reaction. Preferable examples include diethyl ether, tetrahydrofuran, etc. Reaction temperature should be a temperature which is sufficient for completing the reaction without promoting formation of undesired by-products and is preferably -78°C to room temperature. As the second step of this reaction any technique known in the art can be used (for example, as described in "Composition and Reaction of Organic Compound [I]", New Experiment Chemistry Series, vol.14, edited by the Chemical Society of Japan, Maruzen Co., Ltd., November, 1977, p. 115-127). The progress of the reaction can be

monitored by known chromatography technique. Undesirable by-products formed in this reaction can be removed by any technique known in the art such as conventional chromatography technique and/or crystallization.

[0117]

(Preparation of carbonyl compound (6a'))

The carbonyl compound (6a') can be prepared by the same technique as for the above described carbonyl compound (6a), for example.

[0118]

(Preparation of compound (10a), compound (10b), compound (11c) and compound (11d))

The compound (10a), compound (10b), compound (11c) and compound (11d) are commercially available or can be prepared by the technique known in the art. Preferably, they can be prepared efficiently by introducing R^1 group into the secondary amide nitrogen under basic conditions (see J. A.Campbell et al., J. Org. Chem., vol. 60, p.4602-4616, 1995).

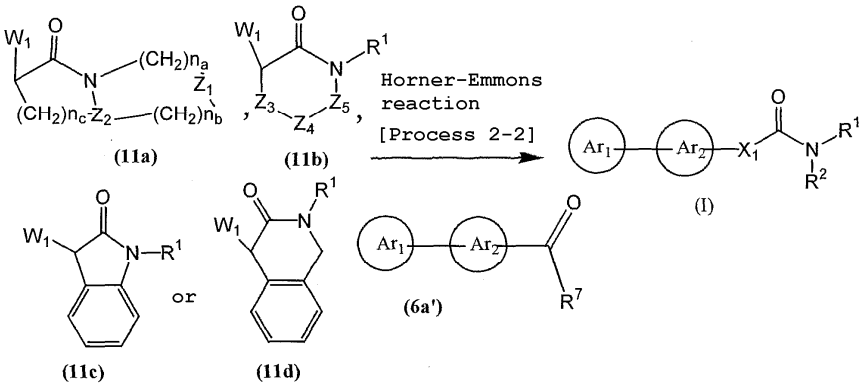
[0119]

(General manufacturing process 4)

The typical (general manufacturing process 4) of the compound of general formula (I) is explained below.

[0120]

[Formula 48]



(wherein, Ar_1, Ar_2, X_1, R^1, R^2, R^7, Z_1, Z_2, Z_3, Z_4, Z_5, n_a, n_b, n_c and W_1 is the same as defined above).

The above described formula illustrates an example of a process using a compound (11a), a compound (11b), a compound (11c) or a compound (11d) as starting materials, and subjecting them to the reaction of "Step 2-2" with a carbonyl compound (6a') to prepare the compound of general formula (I).

[0121]

(Preparation of compound (11a), compound (11b), compound (11c), and compound (11d))

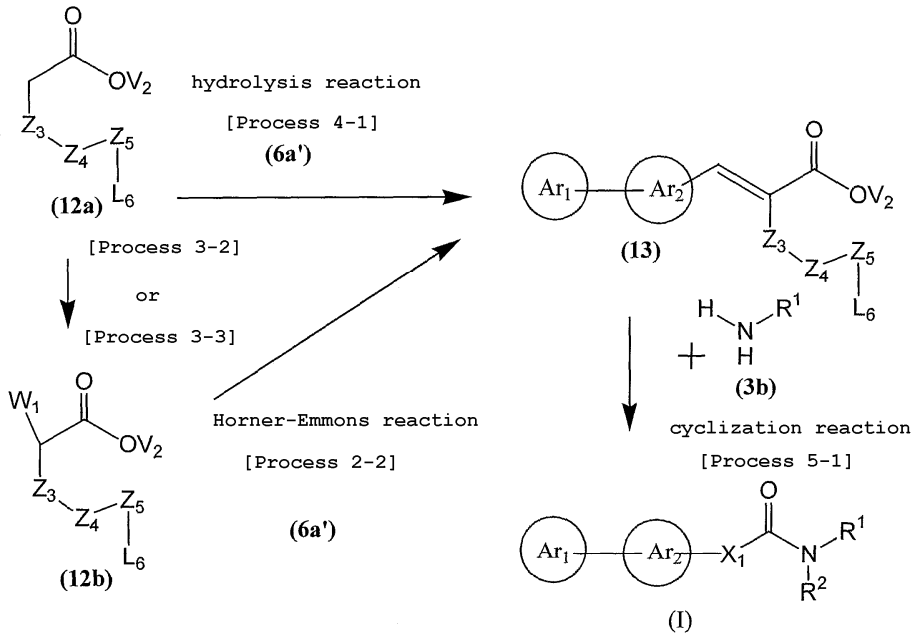
The compound (11a), the compound (11b), the compound (11c), and the compound (11d) are commercially available, or can be prepared by the technique known in the art. Preferably, according to the "Step 3-3" of the above (Preparation of a phosphonic acid ester compound (7a)), they can be prepared efficiently by using a corresponding amide compound as starting materials.

[0122]

(General manufacturing process 5)

The typical (general manufacturing process 5) of the compound of general formula (I) is explained below.

[Formula 49]



(wherein, Ar_1, Ar_2, X_1, R^1, R^2, R^7, Z_3, Z_4, Z_5, W_1 and V_2 is the same as defined above and

L_6 is selected from the above-mentioned substituent group A4).

The above described formula illustrates an example of a process using an ester compound (12a) as the starting material, and subjecting it to the reaction of "Step 4-1" with a carbonyl compound (6a') to convert to a compound (13) which is then converted

to a compound of general formula (I) by cyclization reaction of "Step 5-1" or a process using a compound (12b) as the starting material, and subjecting it to the reaction of "Step 2-2" with a carbonyl compound (6a') to convert to a compound (13) which is then subjected to "Step 5-1". For example, the cyclization of "Step 5-1" may vary depending on the starting material, and is not particularly limited as long as it can be effected under similar conditions as in this process and processes known in the art can be used. For example, cyclization can be effected by (i) reacting the compound (13) with an amine compound (3b) through two of the above "step 1-1" and "Step 1-2" to form an amide bond and cyclize while eliminating the substituent group L_6 or (ii) introducing an amine compound (3b) into the substituent group L_6 and subjecting the product to the above "step 1-1" and 2 of "Step 1-2" to form an intramolecular amide bond to effect cyclization. The substituent groups L_6 or V_2 may be preferably suitably modified using a technique known to those skilled in the art in order to advances the reaction efficiently at each step.

[0123]

(Preparation of compound (12a))

The compound (12a) is commercially available or can be prepared by the technique known in the art. When the carboxylic acid compound is not marketed, a corresponding compound, for example, can be obtained by

subjecting a corresponding carboxylic acid compound to a protection reaction known in the art (see T.W. Green."Protective Groups in Organic Synthesis" John Wiley & Sons. Inc., 1981).

[0124]

(Preparation of the amine compound (3b))

The amine compound (3b) is commercially available or can be prepared by the technique known in the art. Preferably, it can be prepared by the same technique as in the above (Preparation of the amine compound (3)).

[0125]

(Preparation of compound (12b))

The compound (12b) is commercially available or can be prepared by the technique known in the art. Preferably, it can be prepares by the same technique as in the above (phosphonic acid ester compound (7a)).

Effect of the Invention

[0126]

The present inventors performed the following tests in order to demonstrate the usefulness of the compound of the general formula (I) of the present invention.

[0127]

Test Example 1 [Quantification of Aβ Peptide in Neuronal Culture From Rat Fetus Brain]

(1)

Rat Primary Neuronal Culture

Primary neuronal cultures were prepared from cerebral cortices from embryonic day 18 Wistar rat (Charles River Japan, Yokohama, Japan). The embryos were aseptically removed from a pregnant rat under ether anesthesia. The brain was isolated from the embryo, and immersed in ice-cold L-15 medium (for example, Invitrogen Corp. Cat #11415-064, Carlsbad, CA, USA, or SIGMA L1518, St. Louis. MO, USA). The cerebral cortex was collected under a stereoscopic microscope from the brain. The cerebral cortex fragments collected were subjected to enzyme treatment in an enzyme solution containing 0.25% trypsin (for example, Invitrogen Corp., Cat #15050-065, Carlsbad, CA, USA) and 0.01% DNase (for example, Sigma D5025, St. Louis. MO, USA) at 37C for 30 minutes to allow for cell dispersion. The enzyme reaction was terminated by addition of same volume of heat-inactivated horse serum. After centrifugation at 1500 rpm for 5 minutes, the supernatant was removed and 5-10 ml of medium was added to the cell pellet. Neurobasal medium™ (Invitrogen Corp., Carlsbad, CA, USA) supplemented with 2% B-27 supplement (Invitrogen Corp., Carlsbad, CA, USA), 25 μM 2-mercaptoethanol (2-ME, WAKO, 139-06861, Osaka, Japan), 0.5 mM L-glutamine (for example, Invitrogen Corp., Cat # 25030-081, Carlsbad, CA, USA), and 1% antibiotics-antimycotics (Invitrogen Corp., Cat # 15240-062, Carlsbad, CA, USA) was used as the culture

medium (Neurobasal/B27/2-ME). At the compound evaluation, the medium of the same composition not to add 2-ME alone (Neurobasal/B27) was used. The cell pellet was triturated by mild pipetting. Remaining cell pellet was removed by filtering through a 40-μm nylon mesh (Cell Strainer, Cat # 35-2340, Becton Dickinson Labware, Franklin Lakes, NJ, USA) and a neuronal cell suspension was obtained. The neuronal cell suspension was diluted with the Neurobasal/B27/2-ME medium and then plated in a volume of 100 μl/well to obtain an initial cell density of 5×10^5 cells/cm^2 in a 96-well polystyrene plate pre-coated with poly-L or D-lysine (for example, Falcon MICROTEST™ Tissue culture plate 96 well flat bottom with low evaporation lid (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. Poly-L-lysine (SIGMA P2636, St. Louis, MO, USA) solution at 100 μg/ml was prepared aseptically with 0.15 M Borate buffer (pH 8.5). The solution was added to a 96-well polystyrene incubator at 50-100 μl/well and incubated at room temperature for one hour or more, or at 4C overnight or longer. This was rinsed 4 or more times with sterile water, and then dried or rinsed with, for example, sterile PBS or medium, and used for plating

cells. Cells were cultured for one day in an incubator of 5% CO_2–95% air at 37C, the entire amount of the medium was exchanged with fresh Neurobasal/B27/2-ME, and the cells were then cultured for further 3 days.

Addition of Compounds

Drugs were added on day 4 of culture as follows. The entire amount of the medium was removed from culture well, and Neurobasal/B27 medium was added at 180 µl/well. The test compound dimethyl sulfoxide (hereinafter abbreviated as DMSO) solution was diluted with Neurobasal/B27 so than it would be 10-fold of the desired final concentration. A diluent was added at 20 µl/well and mixed well. The final concentration of DMSO was 1 % or less. Only DMSO was added to the control group.

Sampling

After incubation for 3 days, the entire amount of the medium was collected as ELISA sample. This was used without any dilution for Aβx-42 measurement, and diluted to 5-fold with the diluent supplied with ELISA kit for Aβx-40 measurement, before subjecting to respective ELISA assays.

Evaluation of Cell Survival

Cell survival was evaluated by MTT assay. MTT assay was carried out according to the following

protocols. Pre-warmed medium of 100 μl/well was added to the wells after collecting the medium. A solution of 8 mg/ml of MTT (SIGMA M2128, St. Louis, MO, USA) dissolved in D-PBS(-) (Dulbecco's phosphate buffered Saline, SIGMA D8537, ST. Louis, MO, USA) was added at 8 μl/well, and this was incubated in an incubator of 5% CO2-95% air at 37C for 20 minutes. MTT solubilizing buffer was added to this at 100 μl/well, MTT formazan crystals were dissolved well in an incubator of 5% CO_2-95% air at 37C, and absorbance was measured at 550 nm. MTT solubilizing buffer was prepared as follows. N, N'-dimethylformamide (for example, WAKO 045-02916, Osaka, Japan) and distilled water 250 ml each were mixed together. To this 100 g of SDS (sodium dodecyl sulfate (for example, sodium lauryl sulfate, WAKO 191-07145, Osaka, Japan)) was dissolved. Conc. HCl and conc. Acetic acid 350 μl each were added to allow for a final pH of about 4.7.

Upon measurement, wells without plating any cells containing only the medium and MTT solution were set as background (bkg). Individual measured values were subjected to the following formula and calculate the proportion against the control group (group without treatment with drugs, CTRL) (% of CTRL), to compare and evaluate cell survival.

% of CTRL = (A550_sample - A550_bkg) / (A550_CTRL - A550_bkg) × 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)

Aβ ELISA

For Aβ ELISA, Human Amyloid beta (1-42) Assay Kit (#17711 or #27711) and Human Amyloid beta (1-40) Assay Kit (#17713 or #27713) from Immuno-Biological Laboratories, Co., Ltd. (IBL Co., Ltd.) were used. The methods were as described in the protocols recommended by the manufacturer (methods described in the attached document), except that Aβ calibration curve was created using beta-amyloid peptide 1-42, rat and beta-amyloid peptide 1-40, rat (Calbiochem, #171596 [Aβ42], #171593[Aβ40]). The results are shown as percentage to the Aβ concentration in the medium of control group (% of CTRL). The results are shown in Table 1.

(2) Accordingly, the compound of the present invention was proved to have effect to reduce Aβ42 production.

[0128]

Consequently, as the compound of the general formula (I) or a pharmaceutically acceptable salt thereof have effect to reduce Aβ42 production, according to the present an invention, they can provide a preventive or therapeutic agent particularly for neurodegenerative diseases caused by Aβ such as Alzheimer's disease and Down syndrome.

[0129]

[Table 1-1]

Test Compound	Effect to Reduce Aβ42 Production IC50(nM)
Example 153	190
Example 121	70
Example 173	190
Example 175	60
Example 186	190
Example 86	320
Example 122	190
Example 139	200
Example 398	220
Example 96	220
Example 338	330
Example 90	240
Example 402	70
Example 403	90
Example 366	330
Example 353	220

[0130]

[Table 1-2]

Test Compound	Effect to Reduce Aβ42 Production IC_{50}(nM)
Example 414	130
Example 416	100
Example 418	109
Example 420	120
Example 425	80

[0131]

[Table 1-3]

Test Compound	Effect to Reduce Aβ42 Production IC_{50}(nM)
Example 427	780
Example 430	119
Example 611	265
Example 639	56
Example 908	68
Example 976	80
Example 1014	60
Example 1027	71
Example 965	87
Example 991	60
Example 1025	70
Example 621	100

[0132]

"Salt" indicates a pharmaceutically acceptable salt, and is not particularly limited provided that it forms a pharmaceutically acceptable salt with a compound of the general formula (I) which would be a preventive or therapeutic agent for diseases caused by Aβ. Particular examples which can be mentioned are, for example, preferably hydrohalic acid salts (such as for example hydrofluorides, hydrochlorides, hydrobromides, and hydroiodides), inorganic acid salts (such as for example sulfates, nitrates, perchlorates, phosphates, carbonates, and bicarbonates), organic carboxylates (such as for example acetates, oxalates, maleates, tartrates, fumarates, and citrates), organic sulfonates (such as

for example methanesulfonates, trifluoromethanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates, and camphorsulfonates), amino acid salts (such as for example aspartates and glutamates), quaternary amine salts, alkaline metal salts (such as for example sodium salts and potassium salts), alkaline earth metal salts (such as for example magnesium salts and calcium salts) etc.

[0133]

The preventive agent for diseases caused by Aβ according to the present invention can be formulated by customary methods. Preferred dosage forms are, for example, tablets, powders, subtle granules, granules, coated tablets, capsules, syrups, troches, inhalants, suppositories, injections, ointments, ophthalmic solutions, ophthalmic ointments, nasal drops, ear drops, cataplasms, lotions, etc. For formulation, commonly used excipients, such as for example binders, lubricants, colorants, and correctives, and where necessary stabilizers, emulsifiers, absorbefacients, surfactants, pH adjusters, preservatives, and antioxidants, can be used, and components generally used as ingredients for pharmaceuticals can be blended to formulate by customary methods. Such components which can be mentioned are animal and plant oils such as for example soybean oil, beef tallow, and synthetic glycerides; hydrocarbons such as for example liquid

paraffin, squalane, solid paraffin; ester oils such as for example octyldodecyl myristate, isopropyl myristate; higher alcohols such as for example cetostearyl alcohol, behenyl alcohol; silicone resin; for example silicone oil; surfactants such as polyoxyethylene fatty acid ester, sorbitan fatty acid ester, glycerine fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene block copolymer; water-soluble polymers such as for example hydroxyethylcellulose, polyacrylate, carboxyvinyl polymer, polyethyleneglycol, polyvinylpyrrolidone, methylcellulose; lower alcohols such as for example ethanol, isopropanol; polyols such as for example glycerine, propylene glycol, dipropylene glycol, sorbitol; sugars such as glucose, sucrose; inorganic powders such as for example silicic anhydride, aluminium magnesium silicate, aluminium silicate; and purified water, etc. Excipients used are for example lactose, corn starch, white soft sugar, dextrose, mannitol, sorbitol, crystalline cellulose, and silicone dioxide etc. Binders used are for example polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polypropylene glycol/polyoxyethylene block polymer, and meglumine etc. Disintegrators used are for example

starch, agar, gelatin powders, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectin, and carboxymethylcellulose calcium etc. Lubricants used are for example magnesium stearate, talc, polyethyleneglycol, silica, and hydrogenated plant oils etc. As colorants, those approved as additives to pharmaceuticals are used. Correctives used are cocoa powder, peppermint camphor, empasm, mentha oil, borneol, and cinnamon powder etc.

[0134]

Oral formulations, for example, are formulated by adding a compound which is an active ingredient or a salt thereof or a hydrate thereof and excipients, and further for example binders, disintegrators, lubricants, colorants, and correctives etc. as necessary, then by customary methods formulating into for example powders, subtle granules, granules, tablets, coated tablets, and capsules etc. In case of tablets/granules, needless to say, it is acceptable to coat them accordingly as necessary with for example sugar coating. In case of syrups or injection formulation, for example pH adjusters, solubilizers, and tonicity adjusting agents etc., and when necessary solubilization facilitators and stabilizers etc. are added, and formulated by customary methods. In case of external preparations, formulation methods are not particularly limited and can be manufactured by customary methods. As base materials

used, various materials commonly used such as for pharmaceuticals, quasi drugs, and cosmetics can be used. Examples of such which can be mentioned are animal and plant oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyols, water-soluble polymers, clay minerals, and purified water etc., and pH adjuster, antioxidants, chelators, preservatives and fungicides, colorants, and fragrances etc. can also be added as necessary. In addition, ingredients having differentiation inducing effect, such as for example blood flow facilitating agents, bactericides, anti-inflammatory agents, cell stimulants, vitamins, amino acids, humectants, and keratolytic agents can be formulated as necessary. Amount of the therapeutic/preventive agents according to the present invention administered varies according to for example degree of symptoms, age, gender, weight, mode of administration, type of salt, and particular type of disease etc. A typical amount for an adult is about 30 μg to 10 g, preferably 100 μg to 5g, more preferably 100 μg to 3 g per day for oral administration, and about 30 μg to 1 g, preferably 100 μg to 500 mg, more preferably 100 μg to 30 mg for injection administration, which are either administered in a single or multiple dose(s).

Best Mode for Carrying out the Invention

[0135]

The present invention will now be described in further detail with reference to Examples. These are illustrative, and are in no means to limit the preventive or therapeutic agents for diseases caused by Aβ of the present invention to the particular Examples below. Those having ordinary skills in the art are capable of applying different variations to the reference examples and Examples below as well as Claims according to the present invention to carry out the invention to its full. Such variations are within the scope of Claims according to the present invention.

[0136]

The following symbols are used in the following Examples.

DMF: N,N'-dimethylformamide

THF: tetrahydrofuran

LAH: lithium aluminum hydride

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

HOBT: 1-hydroxybenzotriazol

IPEA: diisopropylethylamine

TEA: triethylamine

DPPF: 1,1-bis(diphenylphosphino)ferrocene

CDI: N,N'-carbonyldiimidazole

TBAF: tetrabutylammonium fluoride

PYBOP: benzotriazol-1-yloxytris(pyridino)phosphoniumhexafluorophosphonic acid

ester

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DAST: diethylamino sulfur trifluoride

BOP: benzotriazol-1-yloxy-
tris(dimethylamino)phosphoniumhexafluorophosphate

DIBAL-H: diisobutyl aluminum hydride

Dess-Martin reagent: Dess-Martin Periodinane

Chromatography was conducted using BW-300 (product of Fuji Silysia Chemical Ltd.) as a carrier unless otherwise stated.

LC-MS: High-performance liquid chromatography for preparative isolation of the object compound using mass spectrometry. As an elution solvent, 10 to 99% of linear gradient system of water containing 0.1% trifluoroacetic acid and acetonitrile containing 0.1% trifluoroacetic acid was used.

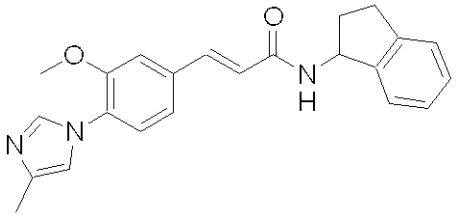
[0137]

Example 1

Synthesis of (E)-N-indan-1-yl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[138]

[Formula 50]



[0139]

Synthesis of 3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzaldehyde and 3-methoxy-4-(5-methyl-1H-imidazol-1-yl)benzaldehyde

To a DMF (50 mL) solution of 4-fluoro-3-methoxybenzaldehyde (3.00 g) and 4-methylimidazole (3.307 g), potassium carbonate (4.05 g) was added and the reaction mixture was agitated at 100°C overnight. The obtained reaction mixture was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: hexane-ethyl acetate system), and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (856 mg) and 3-methoxy-4-(5-methyl-1H-imidazol-1-yl)benzaldehyde (44 mg) were obtained.

The physical properties of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde:

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 3.97 (s, 3H), 7.02 (brs, 1H), 7.44 (d, J=8.0 Hz, 1H), 7.55 (dd, J=1.6 Hz, 8.0 Hz, 1H), 7.58 (d, J=1.6 Hz, 1H), 7.84 (brs, 1H), 10.00 (s, 1H).

The physical properties of 3-methoxy-4-(5-methyl-1H-imidazol-1-yl)benzaldehyde:

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.10 (s, 3H), 3.90 (s, 3H), 6.91 (brs, 1H), 7.40 (d, J=8.0 Hz, 1H), 7.50 (d, J=1.2 Hz, 1H), 7.57-7.59 (m, 1H), 7.84 (s, 1H), 10.05 (s, 1H).

In addition, 3-methoxy-4-(4-methy-1H-limidazol-1-yl)benzaldehyde can be synthesized also in the following alternative method.

[0140]

Synthesis of 3-methoxy-4-nitrobenzoic acid methyl ester

Methyl iodide (463 g) was dropped to a mixture of 3-hydroxy-4-nitrobenzoic acid (199 g) and potassium carbonate (450 g) in DMF (1 L) at room temperature. After agitating the reaction solution at room temperature overnight, methyl iodide (230 g) was further added to the reaction mixture, and the reaction mixture was further agitated at room temperature for 6 hours. The reaction mixture was added to ice water and the deposited solids were obtained by filtration. 178 g of the title compound was obtained by drying the obtained solid at 50°C overnight. The physical properties was in agreement with the reported values (CAS#5081-37-8).

[0141]

Synthesis of 4-amino-3-methoxybenzoic acid methyl ester

To a solution of 3-methoxy-4-nitrobenzoic acid methyl ester (150 g) in methanol (600 mL) and THF (300 mL), 10% palladium-carbon (15 g) was added and the reaction mixture was agitated at 50°C to 64°C under hydrogen pressure of 0.9 MPa(s) for 6.5 hours. After allowing cool the reaction solution to room temperature, 134 g of the title compound was obtained by filtering the reaction solution on celite and

condensing the obtained filtrate under reduced pressure. The physical properties was in agreement with the reported values (CAS#41608-64-4).

[0142]

Synthesis of 4-formylamino-3-methoxybenzoic acid methyl ester

Anhydrous acetic acid (268 mL) was added dropwise to formic acid (401 mL) at room temperature, and the reaction solution was agitated for 40 minutes at room temperature. To this reaction solution, a THF (600 mL) solution of 4-amino-3-methoxybenzoic acid methyl ester (134 g) was added dropwise at room temperature, and the reaction solution was agitated for 1 hour. 3.8 L of iced water was added to the reaction solution, and the deposited solids were separated by filtering, and further washed with water (2 L). 111 g of the title compound was obtained by drying the obtained solid at 50°C overnight. The physical properties was in agreement with the reported values (CAS#700834-18-0).

[0143]

Synthesis of 4-[formyl-(2-oxopropyl)amino]-3-methoxybenzoic acid methyl ester

Chloroacetone (84.5 mL) was added dropwise to the DMF (497 mL) mixture of 4-formylamino-3-methoxybenzoic acid methyl ester (111 g), cesium carbonate (346 g), and potassium iodide (8.78 g) at room temperature, and the reaction mixture was agitated

for 3 hours. Cesium carbonate (173 g) and chloroacetone (42.0 mL) were added to the reaction mixture, and the reaction mixture was agitated at room temperature for 2 hours. Iced water and ethyl acetate were added to the reaction mixture, and the organic layer was partitioned. Ethyl acetate was added to the aqueous layer and the organic layer was partitioned. The organic layers were combined, washed with water and a saturated saline solution in this order, and the obtained organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was diluted with toluene and the solution was concentrated under reduced pressure. Tert-butylmethyl ether and heptane were added to the resulted residue and the deposited solids were separated by filtering and washed with a 50% heptane solution of tert-butylmethyl ether. 118 g of the title compound was obtained by air-drying the obtained solids overnight.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.19 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 4.49 (s, 2H), 7.31 (d, J=8.0 Hz, 1H), 7.63 (d, J=2.0 Hz, 1H), 7.69 (dd, J=8.0, 2.0 Hz, 1H), 8.33 (s, 1H).

[0144]

<u>Synthesis of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzoic acid methyl ester</u>

An acetic acid (255 mL) solution of 4-(formyl-(2-oxopropyl)amino)-3-methoxybenzoic acid

methyl ester (118 g) and ammonium acetate (172 g) was heated under stirring at 140°C for 1 hour. The reaction solution was neutralized with an ammoniac solution under ice-cooling after the reaction completed. Ethyl acetate was added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was filtered with a silica gel pad after dried over anhydrous magnesium sulfate, and the filtrate was concentrated under reduced pressure. Tert-butylmethyl ether and heptane were added to the residue and the deposited solids were separated by filtering and washed with a 50% heptane solution of tert-butylmethyl ether. 68.4 g of the title compound was obtained by air-drying the obtained solids overnight. Furthermore, crystallization mother liquid was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system), and 22.3 g of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.98 (brs, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.71-7.73 (m, 2H), 7.79 (brs, 1H).

[0145]

Synthesis of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde

To a THF (60 mL) solution of sodium bis(2-methoxyethoxy) aluminum hydride (65% toluene solution, 56 mL), a THF (45 mL) solution of pyrrolidine (18 mL)

was added dropwise for 15 minutes at -5°C or less. The reaction solution was agitated at room temperature for 1 hour, a THF (15 mL) suspension of tert-butoxide (2.10 g) was added dropwise to the reaction solution at room temperature and the reaction mixture was agitated for 15 minutes. The reaction mixture was added dropwise to a THF (50 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzoic acid methyl ester (20 g) under ice-cooling for 30 minutes. The reaction mixture was agitated at room temperature for 2 hours and a 5N sodium hydroxide solution (150 mL) was added dropwise to the reaction solution. Ethyl acetate was added to the reaction solution and the organic layer was partitioned. The organic layer was washed with a saturated ammonium chloride solution and a saturated saline solution in this order. The organic layer was dried over anhydrous magnesium sulfate, and the filtrate was concentrated under reduced pressure after filtration with a silica gel pad. The residue was diluted with ethyl acetate and the deposited solids were separated by filtering. 7.10 g of the title compound was obtained by air-drying the obtained solids overnight. Furthermore, crystallization mother liquid was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate-2-propanol system), and 2.65 g of the title compound was obtained.

[0146]

Synthesis of indan-1-ylcarbamoylmethylphosphonic acid diethyl ester

After adding thionyl chloride (6.07 g) to a methylene chloride (20 mL) solution of diethoxyphosphoryl acetic acid (5.00 g), this reaction mixture was agitated at room temperature for 2 hours and the reaction solution was concentrated under reduced pressure. THF (40 mL) solution of the obtained residue was added dropwise to a THF (80 mL) solution of 1-aminoindane (3.40 g) and TEA (3.5 mL) under ice-cooling, and the reaction solution was agitated at the temperature. Water and ethyl acetate were added to this reaction mixture, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: hexane-ethyl acetate system), and 4.2 g of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.31-1.36 (m, 6H), 1.79-1.89 (m, 1H), 2.56-2.63 (m, 1H), 2.83-3.03 (m, 4H), 4.09-4.18 (m, 4H), 5.47 (q, J=7.6 Hz, 1H), 6.83-6.89 (brd, 1H), 7.19-7.32 (m, 4H).

[0147]

Synthesis of (E)-N-indan-1-yl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

Lithium hydroxide monohydrate (9 mg) was

added to a THF (2 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (21 mg) and indan-1-ylcarbamoylmethylphosphonic acid diethyl ester (30 mg) obtained above, and the reaction solution was agitated at room temperature overnight. After the reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: hexane-ethyl acetate system), and 13 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.95 (m, 1H), 2.29 (s, 3H), 2.63-2.72 (m, 1H), 2.88-3.06 (m, 2H), 3.88 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.88 (d, J=8.4 Hz, 1H), 6.41 (d, J=15.4 Hz, 1H), 6.92 (t, J=1.2 Hz, 1H), 7.13-7.35 (m, 7H), 7.67 (d, J=15.4 Hz, 1H), 7.71 (d, J=1.6 Hz, 1H).

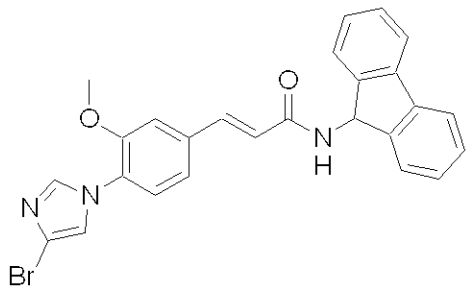
[0148]

Example 1-1

Synthesis of (E)-3-[4-(4-bromo-1H-imidazol-1-yl)-3-methoxyphenyl]-N-(9H-fluoren-9-yl)acrylamide

[0149]

[Formula 51]



Synthesis of 4-(4-bromo-1H-imidazol-1-yl)-3-methoxybenzaldehyde

Potassium carbonate (1.74 g) was added to a DMF solution of 4-fluoro-3-methoxybenzaldehyde (1.94 g) and 4-bromoimidezole(1.85 g), and the reaction solution was agitated at 100°C overnight. The obtained reaction mixture was concentrated under reduced pressure, water and ethyl acetate were added to the obtained residue, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane: ethyl acetate system), and 1.21 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.93 (s, 3H), 7.24 (s, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.52-7.55 (m, 2H), 7.74 (s, 1H), 9.97 (s, 1H).

[0150]

Synthesis of (E)-3-[4-(4-bromo-1H-imidazol-1-yl)-3-methoxyphenyl]-N-(9H-fluoren-9-yl)acrylamide

By the same method as in Example 121, the title compound was synthesized from 3-(4-(4-bromo-1H-imidazol-1-yl)-3-methoxyphenyl)acrylic acid (100 mg) obtained from 4-(4-bromo-1H-imidazol-1-yl)-3-methoxybenzaldehyde and 9-fluoren-9-ylamine hydrochloride (81 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83-1.97 (m, 1H), 2.60-2.74 (m, 1H), 2.84-3.08 (m, 2H), 3.89 (s, 3H), 5.64 (q, J=7.6 Hz, 1H), 6.05 (d, J=8.4 Hz, 1H), 6.46 (d, J=15.2 Hz, 1H), 7.10-7.30 (m, 7H), 7.34 (d, J=6.8 Hz, 1H), 7.61 (d, J=6.0 Hz, 1H), 7.67 (d, J=15.6 Hz, 1H).

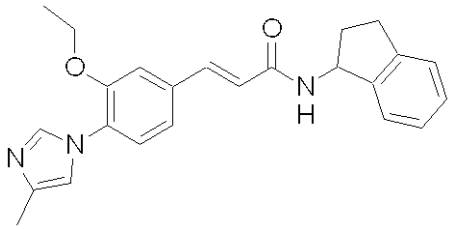
[0151]

Example 2

Synthesis of (E)-3-[3-ethoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

[0152]

[Formula 52]



Synthesis of 4-fluoro-3-hydroxybenzaldehyde

Boron tribromide (1M methylene chloride solution, 100 mL) was gradually added dropwise to a methylene chloride (100 mL) solution of 3-methoxy-4-fluoro benzaldehyde (4.4 g) under ice-cooling. The reaction solution was agitated at room temperature for 2 hours after the dropping ended. The reaction solution was again cooled with ice, iced water was gradually added to the reaction solution to terminate the reaction, and further 5N hydrochloride solution was added until the pH reached 1. After condensing the reaction solution under reduced pressure, water and ethyl acetate were added to the residue, and the

organic layer was separated. The obtained organic layer was washed with a saturated sodium chloride solution, and the solvent was evaporated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane–ethyl acetate 4:1), and 3.18 g (79%) of 4-fluoro-3-hydroxybenzaldehyde was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm):5.70 (s, 1H), 7.24 (dd, J=8.4, 10.0 Hz, 1H), 7.40–7.50 (m, 1H), 7.55 (dd, J=2.0, 8.4 Hz, 1H), 9.91 (s, 1H).

[0153]

Synthesis of 3-ethoxy-4-fluorobenzaldehyde

Sodium hydride (171 mg) was added to a DMF (10 mL) solution of 4-fluoro-3-hydroxybenzaldehyde (300 mg) obtained above at room temperature, and the reaction solution was agitated for 30 minutes. Then, iodoethane (0.26 mL) was added dropwise to the reaction solution, and the reaction mixture was agitated at room temperature for 1 hour. After the reaction ended, water and ethyl acetate were added to the reaction solution under ice-cooling and the organic layer was separated. The obtained organic layer was washed with a saturated sodium chloride solution, and the solvent was evaporated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution

solvent: heptane-ethyl acetate 5:1), and 250 mg (70%) 3-ethoxy-4-fluorobenzaldehyde was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.49 (t, J=6.8 Hz, 3H), 4.19 (q, J=6.8 Hz, 2H), 7.23 (dd, J=8.0, 10.4 Hz, 1H), 7.43 (m, 1H), 7.50 (dd, J=2.0, 8.0 Hz, 1H), 9.91 (s, 1H).

[0154]

Synthesis of 3-ethoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde

4-methylimidazole (244 mg) was added to a DMF (3 mL) solution of 3—ethoxy-4-fluorobenzaldehyde (250 mg) obtained above, and the reaction solution was agitated at 150°C for 4 hours. The reaction solution was concentrated as it was after the reaction ended, water and ethyl acetate were added to the obtained reaction residue, and the organic layer was separated. The obtained organic layer was washed with a saturated sodium chloride solution, and the solvent was evaporated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 1:4), and 60 mg (18%) of 3-ethoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.46 (t, J=8.4 Hz, 3H), 2.31 (s, 3H), 4.20 (q, J=8.4 Hz, 2H), 7.00-7.06 (m, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.53 (dd, J=1.6, 8.0 Hz, 1H), 7.55

(d, J=1.6 Hz, 1H), 7.90 (d, J=1.2 Hz, 1H), 9.99 (s, 1H).

[0155]

Synthesis of (E)-3-[3-ethoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

To a THF (8 mL) solution of 3-ethoxy-4-(4-methyl-1H-imidazole-1-yl)benzaldehyde (60 mg), (indan-1-ylcarbamoylmethyl)phosphonic acid diethyl ester (81 mg) and lithium hydroxide monohydrate (22 mg) were added, and the reaction mixture was agitated at room temperature for 14 hours. Water and ethyl acetate were added to the reaction solution after the reaction ended, and the organic layer was separated. The obtained organic layer was washed with a saturated sodium chloride solution, and the solvent was evaporated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 1:4), and 23 mg (23%) of the title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z388 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.41 (t, J=6.8 Hz, 3H), 1.82-1.97 (m, 1H), 2.30 (s, 3H), 2.60-2.74 (m, 1H), 2.84-3.10 (m, 2H), 4.10 (q, J=6.8 Hz, 2H), 5.64 (q, J=7.6 Hz, 1H), 5.88 (d, J=8.4 Hz, 1H), 6.39 (d, J=15.6 Hz, 1H), 6.95 (s, 1H), 7.10-7.19 (m, 2H), 7.20-7.31 (m, 4H), 7.34 (d, J=6.8 Hz, 1H), 7.66 (d, J=15.6 Hz, 1H), 7.78 (d, J=1.6 Hz, 1H).

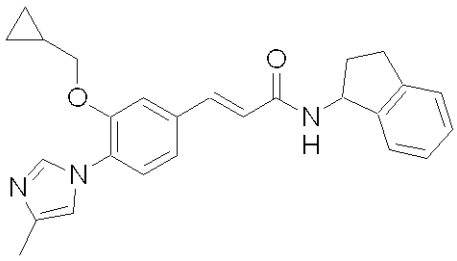
[0156]

Example 3

Synthesis of (E)-3-[3-cyclopropyl methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

[0157]

[Formula 53]



By the same method as in Example 2, 22 mg (3.6%) of the title compound was obtained from 4-fluoro-3-hydroxybenzaldehyde (200 mg). The physical properties of the compound are as follows.

ESI-MS; m/z414 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 0.24-0.38 (m, 2H), 0.56-0.70 (m, 2H), 1.16-1.32 (m, 1H), 1.82-1.98 (m, 1H), 2.30 (s, 3H), 2.60-2.74 (m, 1H), 2.84-3.10 (m, 2H),3.87 (d, J=6.8 Hz, 2H), 5.63 (q, J=7.6 Hz, 1H), 5.93 (d, J=8.4 Hz, 1H), 6.39 (d, J=15.6 Hz, 1H), 6.98 (s, 1H), 7.11 (d, J=1.7 Hz, 1H), 7.16 (dd, J=1.7, 8.4 Hz, 1H), 7.19-7.30 (m, 4H), 7.34 (d, J=6.8 Hz, 1H), 7.65 (d, J=15.2 Hz, 1H), 7.84 (m, 1H).

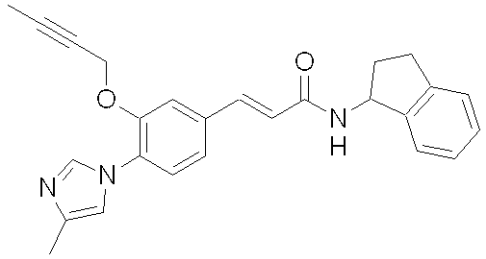
[0158]

Example 4

Synthesis of (E)-3-[3-(2-butynyloxy)-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

[0159]

[Formula 54]



By the same method as in Example 2, 58 mg (7.8%) of the title compound was obtained from 4-fluoro-3-hydroxybenzaldehyde (250 mg). The physical properties of the compound are as follows.

ESI-MS; m/z412 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.85 (t, J=3.0 Hz, 3H), 1.82-1.98 (m, 1H), 2.45 (s, 3H), 2.62-2.74 (m, 1H), 2.86-3.10 (m, 2H), 4.71 (d, J=3.0 Hz, 2H), 5.65 (q, J=7.6 Hz, 1H), 5.93 (d, J=8.0 Hz, 1H), 6.41 (d, J=15.6 Hz, 1H), 6.92-6.97 (m, 1H), 7.18-7.32 (m, 6H), 7.35 (d, J=7.6 Hz, 1H), 7.69 (d, J=15.6 Hz, 1H), 7.74 (d, J=1.6 Hz, 1H).

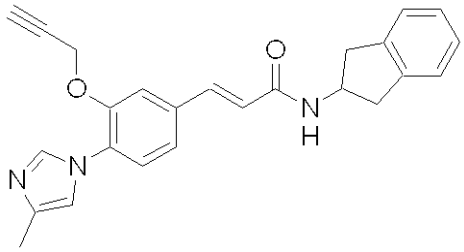
[0160]

Example 5

Synthesis of (E)-N-indan-2-yl-3-[4-(4-methyl-1H-imidazol-1-yl)-3-(2-propynyloxy)phenyl]acrylamide

[0161]

[Formula 55]



[0162]

By the same method as the Example 2, 96 mg (9.5%) of the title compound was obtained from 4-fluoro-3-hydroxybenzaldehyde (350 mg). The physical properties of the compound are as follows.

ESI-MS; m/z398 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.29 (d, J=1.0 Hz, 3H), 2.55 (t, J=2.0 Hz, 1H), 2.99 (dd, J=4.0, 16.4 Hz, 2H), 3.39 (dd, J=6.8, 16.4 Hz, 2H), 4.73 (d, J=2.0 Hz, 2H), 4.85-4.95 (m, 1H), 5.94 (d, J=8.0 Hz, 1H), 6.33 (d, J=15.6 Hz, 1H), 6.91-6.95 (m, 1H), 7.16-7.32 (m, 7H), 7.63 (d, J=15.6 Hz, 1H), 7.71 (d, J=1.6 Hz, 1H).

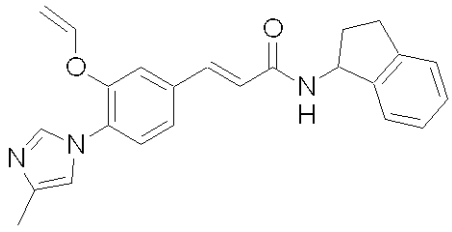
[0163]

Example 6

Synthesis of (E)-N-indan-1-yl-3-[4-(4-methyl-1H-imidazol-1-yl)-3-vinyloxyphenyl]acrylamide

[0164]

[Formula 56]



Synthesis of 3-(2-bromoethoxy)-4-fluoro benzaldehyde

Sodium hydride (1.14 g) was added to a DMF (30 mL) solution of 4-fluoro-3-hydroxybenzaldehyde (2.00 g) at room temperature, and the reaction solution was agitated for 30 minutes. Then, dibromoethane (2.46 mL) was added dropwise to the reaction solution, and the reaction solution was heated at 140°C for 3 hours after the dropping ended. Water and ethyl acetate were added to the reaction solution under ice-cooling, and the organic layer was separated. The obtained organic layer was washed with a saturated sodium chloride solution, and the solvent was evaporated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 6:1), and 606 mg (20%) 3-(2-bromoethoxy)-4-fluoro benzaldehyde was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 3.69 (t, J=6.4 Hz, 2H), 4.42 (t, J=6.4 Hz, 2H), 7.27 (dd, J=8.4, 9.6 Hz, 1H), 7.46-7.56 (m, 2H), 9.92 (s, 1H).

[0165]

Synthesis of 4-fluoro-3-vinyloxybenzaldehyde

A 50% sodium hydroxide solution (5 mL) and tetrabutylammonium hydrogen sulfate (859 mg) were added to the toluene (8 mL) solution of 3-(2-bromoethoxy)-4-fluorobenzaldehyde derivative (606 mg) obtained above, and the reaction solution was agitated at room

temperature for 1 hour. Water and ethyl acetate were added to the reaction solution after the reaction ended, and the organic layer was separated. The obtained organic layer was washed with a saturated sodium chloride solution, and the solvent was evaporated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane–ethyl acetate 6:1), and 200 mg (49%) of 4-fluoro-3-vinyloxybenzaldehyde was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 4.60 (dd, J=2.0, 6.0 Hz, 1H), 4.84 (dd, J=2.0, 13.6 Hz, 1H), 6.67 (dd, J=6.0, 13.6 Hz, 1H), 7.30 (dd, J=8.4, 10.0 Hz, 1H), 7.50–7.70 (m, 2H), 9.93 (s, 1H).

[0166]

Synthesis of 4-(4-methyl-1H-imidazol-1-yl)-3-vinyloxybenzaldehyde

By the same method as in Example 2, 66 mg (24%) of 4-(4-methyl-1H-imidazol-1-yl)-3-vinyloxybenzaldehyde was obtained from 4-fluoro-3-vinyloxybenzaldehyde (200 mg) obtained above. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.31 (s, 3H), 4.64 (dd, J=2.0, 6.0 Hz, 1H), 4.87 (dd, J=2.0, 13.6 Hz, 1H), 6.63 (dd, J=6.0, 13.6 Hz, 1H), 7.03 (s, 1H), 7.50 (d, J=8.4 Hz, 1H), 7.64–7.74 (m, 2H), 7.85 (s, 1H), 10.00 (s, 1H).

[0167]

Synthesis of (E)-N-indan-1-yl-3-[4-(4-methyl-1H-imidazol-1-yl)-3-vinyloxyphenyl]acrylamide

By the same method as in Example 2, 60 mg (54%) of (E)-N-indan-1-yl-3-(4-(4-methyl-1H-imidazol-1-yl)-3-vinyloxyphenyl)acrylamide was obtained from 4-(4-methyl-1H-imidazol-1-yl)-3-vinyloxybenzaldehyde (66 mg) obtained above. The physical properties of the compound are as follows.

ESI-MS; m/z386 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.89-1.98 (m, 1H), 2.30 (s, 3H), 2.60-2.74 (m, 1H), 2.84-3.10 (m, 2H), 4.53 (dd, J=2.8, 5.6 Hz, 1H), 4.76 (dd, J=2.8, 14.0 Hz, 1H), 5.64 (q, J=7.2 Hz, 1H), 5.91 (d, J=8.4 Hz, 1H), 6.41 (d, J=15.6 Hz, 1H), 6.55 (dd, J=6.4, 14.0 Hz, 1H), 6.95 (s, 1H), 7.20-7.37 (m, 6H), 7.34 (d, J=6.8 Hz, 1H), 7.65 (d, J=15.6 Hz, 1H), 7.73 (d, J=1.6 Hz, 1H).

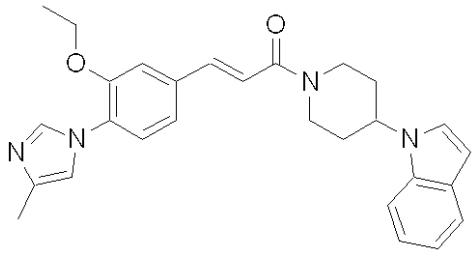
[0168]

Example 7

Synthesis of (E)-3-[3-ethoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(4-indol-1-yl-piperidin-1-yl)propenone

[0169]

[Formula 57]



By the same method as in Example 121, 60 mg

(26%) of the title compound was obtained from (E)-(3-ethoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (140 mg). The physical properties of the compound are as follows.

ESI-MS; m/z477 [M^++Na]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.42 (t, J=6.8 Hz, 3H), 1.90-2.10 (m, 2H), 2.19-2.29 (m, 2H), 2.30 (s, 3H), 2.80-3.06 (m, 1H), 3.25-3.50 (m, 1H), 4.12 (q, J=6.8 Hz, 2H), 4.24-4.40 (m, 1H), 4.46-4.60 (m, 1H), 4.90-5.08 (m, 1H), 6.54 (dd, J=0.8, 3.2 Hz, 1H), 6.92-6.97 (m, 1H), 7.08-7.30 (m, 7H), 7.39 (d, J=8.0 Hz, 1H), 7.64 (d, J=7.6 Hz, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.78 (d, J=1.6 Hz, 1H).

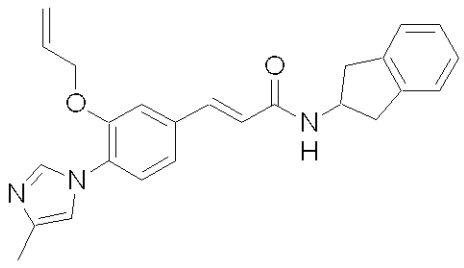
[0170]

Example 8

Synthesis of (E)-3-[3-allyloxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-2-yl-acrylamide

[0171]

[Formula 58]



By the same method as in Example 121, 48 mg (17%) of the title compound was obtained from (E)-(3-allyloxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (512 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ: 2.29 (s, 3H), 2.89 (dd, J=4.0, 16.0 Hz, 2H), 3.38 (dd, J=6.8, 16.0 Hz, 2H), 4.58 (d, J=5.2 Hz, 2H), 4.82-4.98 (m, 1H), 5.27 (dd, J=1.2, 10.8 Hz, 1H), 5.35 (dd, J=1.2, 15.6 Hz, 1H), 5.90-6.10 (m, 1H), 6.04 (d, J=8.0 Hz, 1H), 6.32 (d, J=15.2 Hz, 1H), 6.94 (s, 1H), 7.07-7.17 (m, 2H), 7.18-7.30 (m, 5H), 7.59 (d, J=15.6 Hz, 1H), 7.74 (d, J=0.8 Hz, 1H).

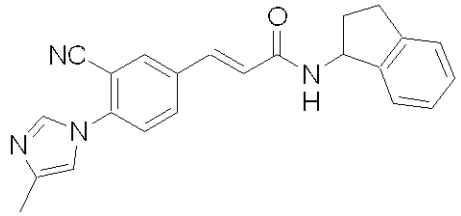
[0172]

Example 9

Synthesis of (E)-3-[3-cyano-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0173]

[Formula 59]



Synthesis of 5-bromo-2-(4-methyl-1H-imidazol-1-yl)benzonitrile and 5-bromo-2-(5-methyl-1H-imidazol-1-yl)benzonitrile

Potassium carbonate (2.07 g) was added to a DMF (20 mL) solution of 5-bromo-2-fluorobenzonitrile (2.00 g) and 4-methylimidazole (1.23 g) and the reaction solution was agitated at 100°C for 4.5 hours. The reaction mixture was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. The

organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: hexane–ethyl acetate system), and 5-bromo-2-(4-methyl-1H-imidazol-1-yl)benzonitrile (962 mg) and 5-bromo-2-(5-methyl-1H-imidazol-1-yl)benzonitrile (60 mg) were obtained.

The physical properties of 5-bromo-2-(4-methyl-1H-imidazol-1-yl)benzonitrile are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.32 (s, 3H), 7.05 (t, J=1.2 Hz, 1H), 7.31 (d, J=8.8 Hz, 1H), 7.74 (d, J=1.2 Hz, 1H), 7.83 (dd, J=2 Hz, 8.8 Hz, 1H), 7.93 (d, J=1.2 Hz, 1H).

The physical properties of 5-bromo-2-(5-methyl-1H-imidazol-1-yl)benzonitrile are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.15 (s, 3H), 6.97 (t, J=1.2 Hz, 1H), 7.28 (d, J=8.4 Hz, 1H), 7.56 (d, J=1.2 Hz, 1H), 7.89 (dd, J=2.4 Hz, 8.4 Hz, 1H), 7.97 (d, J=2.4 Hz, 1H).

[0174]

Synthesis of N-indan-1-yl-acrylamide

A THF (10 mL) solution of acrylic acid chloride (2.04 g) was added dropwise to a THF (30 mL) solution of 1-aminoindane (3.00 g) and TEA (2.28 g) under ice-cooling, and the reaction solution was agitated for 20 minutes at the temperature. Water and ethyl acetate were added to this reaction mixture, and the organic layer was partitioned. The organic layer

was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. 2.23 g of the title compound was obtained by adding ether to the residue and filtering insoluble matter.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81-1.90 (m, 1H), 2.61-2.69 (m, 1H), 2.86-3.05 (m, 2H), 5.58 (q, J=7.6 Hz, 1H), 5.68 (dd, J=1.6 Hz, 10.4 Hz, 1H), 5.70-5.78 (brs, 1H), 6.10 (dd, J=10.4 Hz, 17.2 Hz, 1H), 6.34 (dd, J=1.6 Hz, 17.2 Hz, 1H), 7.20-7.32 (m, 4H).

[0175]

Synthesis of (E)-3-[3-cyano-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

To a DMF (2 mL) solution of 5-bromo-2-(4-methyl-1H-imidazol-1-yl)benzonitrile (50 mg) and N-indan-1-yl-acrylamide (43m g) obtained above, palladium acetate (2.2 mg), ortho-tritolylphosphine (6 mg) and TEA (0.5 mL) were added, and the reaction solution was agitated at 70°C under nitrogen atmosphere overnight. The reaction mixture was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex®NH, elution solvent:hexane-ethyl acetate system), and 31 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86–1.95 (m, 1H), 2.32 (s, 3H), 2.64–2.72 (m, 1H), 2.89–3.08 (m, 2H), 5.64 (q, J=7.6 Hz, 1H), 5.96 (d, J=8.4 Hz, 1H), 6.44 (d, J=16 Hz, 1H), 7.10 (t, J=1.2 Hz, 1H), 7.22–7.30 (m, 3H), 7.34 (d, J=7.6 Hz, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.69 (d, J=16 Hz, 1H), 7.78–7.80 (m, 2H), 7.90 (d, J=2 Hz, 1H).

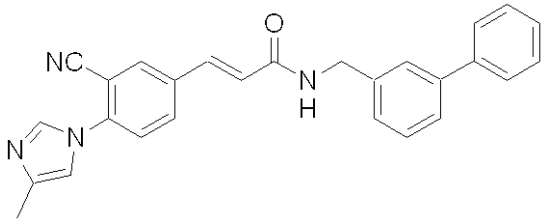
[0176]

Example 10

Synthesis of (E)-N-biphenyl-3-ylmethyl-3-[3-cyano-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0177]

[Formula 60]



Synthesis of (E)-3-[3-cyano-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid

To a DMF (10 mL) solution of 5-bromo-2-(4-methyl-1H-imidazol-1-yl)benzonitrile (700 mg) and acrylic acid ethyl ester (362 mg), palladium acetate (31 mg), tri-ortho-tolylphosphine (85 mg) and TEA (2 mL) were added, and the reaction solution was agitated at 80°C under nitrogen atmosphere overnight. The reaction mixture was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. The

organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: hexane–ethyl acetate system), fractions of the object substance were combined, and concentrated under reduced pressure. The obtained substance was dissolved by 5N sodium hydroxide solution (5 mL) and ethanol (30 mL), and the reaction mixture was agitated at 60°C for 3 hours. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and was made neutral with 5N hydrochloric acid. Insoluble matter consequently deposited was separated by filtering, washed with ether, and 498 mg of the title compound was obtained.

ESI–MS; m/z254 $[M^+ + H]$.

[0178]

Synthesis of (E)–N–biphenyl–3–ylmethyl–3–[3–cyano–4–(4–methyl–1H–imidazol–1–yl)phenyl]acrylamide

To a DMF (0.2 mL) solution of (E)–3–[3–cyano–4–(4–methyl–1H–imidazol–1–yl)phenyl]acrylic acid (15 mg) and 3–phenylbenzylamine monohydrochloride (16 mg), TEA (0.007 mL), HOBT (10 mg) and EDC (14 mg) were added one by one, and the reaction mixture was agitated at room temperature overnight. The reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (Carrier: Chromatorex®NH, elution solvent:hexane–ethyl acetate

system), and 5 mg of the title compound was obtained. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.32 (s, 3H), 4.67 (d, J=6 Hz, 2H), 6.04-6.08 (m, 1H), 6.49 (d, J=15.6 Hz, 1H), 7.09 (s, 1H), 7.32-7.60 (m, 10H), 7.68 (d, J=15.6 Hz, 1H), 7.76-7.79 (m, 2H), 7.89 (d, J=2 Hz, 1H).

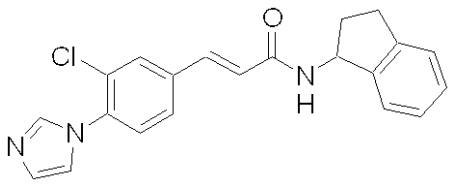
[0179]

Example 11

Synthesis of (E)-3-[3-chloro-4-(1H-imidazol-1-yl-phenyl]-N-indan-1-yl-acrylamide

[0180]

[Formula 61]



Synthesis of 3-chloro-4-(1H-imidazol-1-yl)benzaldehyde

To a DMF (20 mL) solution of 3-chloro-4-fluorobenzaldehyde (500 mg), potassium carbonate (1.20 g) and imidazole (275 mg) were added one by one, and the reaction solution was agitated at 80°C overnight. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : methanol = 10:1), and 548 mg of the title

compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 10.0 (s, 1H), 8.09 (d, J=2.0 Hz, 1H), 7.91 (dd, J=2.0, 8.0 Hz, 1H), 7.80 (s, 1H), 7.54 (d, J=8.0 Hz, 1H), 7.24-7.27 (m, 2H).

[0181]

Synthesis of (E)-3-[3-chloro-4-(1H-imidazol-1-yl-phenyl]acrylic acid

To a THF (13 mL) solution of 3-chloro-4-(1H-imidazol-1-yl)benzaldehyde (545 mg) dimethylphosphonoacetic acid methyl ester (513 μL) and lithium hydroxide monohydrate (133 mg) were added one by one, and the reaction solution was agitated overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 442 mg of crude ester product. 2N sodium hydroxide solution (5.0 mL) was added to the reaction solution obtained by which dissolving the obtained ester product in THF (5.0 mL), and the reaction solution was agitated at room temperature overnight. The reaction solution was cooled to 0°C, 2N hydrochloric acid was added to the reaction solution, and the deposited precipitation was separated by filtering with Kiriyama funnel. The

obtained precipitation was washed with water and ethyl acetate, and 218 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 8.08 (d, J=2.0 Hz, 1H), 7.93 (s, 1H), 7.82 (dd, J=2.0, 8.4 Hz, 1H), 7.61 (d, J=16 Hz, 1H), 7.56 (d, J=8.4 Hz, 1H), 7.48 (s, 1H), 7.11 (s, 1H), 6.70 (d, J=16 Hz, 1H).

[0182]

Synthesis of (E)-3-[3-chloro-4-(1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

17.0 mg of the title compound was obtained from (E)-3-[3-chloro-4-(1H-imidazol-1-yl)phenyl] acrylic acid (20.0 mg) and 1-aminoindan (15.0 μL) by the same method as in Example 324. The physical properties of the compound are as follows.

ESI-MS; m/z364[M^++H].

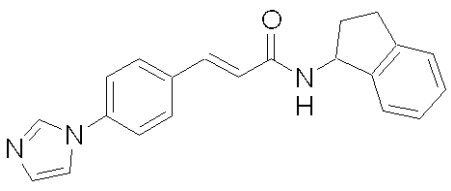
[0183]

Example 12

Synthesis of (E)-3-[4(1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

[0184]

[Formula 62]



Synthesis of (E)-3-[4(1H-imidazol-1-yl)phenyl]acrylic acid

To a THF (3.0 mL) solution of 4-imidazol-1-yl-benzaldehyde (100 mg), dimethylphosphonoacetic acid methyl ester (103 μL) and lithium hydroxide monohydrate (27.0 mg) were added to one by one, and the reaction solution was agitated overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 143 mg of crude ester product. 2N sodium hydroxide solution (2.0 mL) was added to a THF (2.0 mL) solution of the obtained ester product, and the reaction solution was agitated at room temperature overnight. The reaction solution was cooled to 0°C, and 2N hydrochloric acid was added to the reaction solution, and the deposited precipitation was separated by filtering with Kiriyama funnel. The obtained precipitation was washed with water and ethyl acetate, and 98.0 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 8.35 (s, 1H), 7.83 (d, J=8.4 Hz, 2H), 7.82 (s, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.60 (d, J=16 Hz, 1H), 7.11 (s, 1H), 6.58 (d, J=16 Hz, 1H).

[0185]

<u>Synthesis of (E)-3-[4-(1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide</u>

11.0 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)phenyl]acrylic acid (20.0 mg) and 1-aminoindan (17.0 μL) by the same method as in Example 324. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.91 (s, 1H), 7.70 (d, J=16 Hz, 1H), 7.62 (d, J=8.4 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 7.22-7.37 (m, 5H), 7.20 (s, 1H), 6.43 (d, J=16 Hz, 1H), 5.88 (d, J=7.2 Hz, 1H), 5.64 (q, J=7.2 Hz, 1H), 3.03 (ddd, J=4.4, 8.8, 16 Hz, 1H), 2.92 (td, J=8.0, 16 Hz, 1H), 2.64-2.72 (m, 1H), 1.86-1.95 (m, 1H)

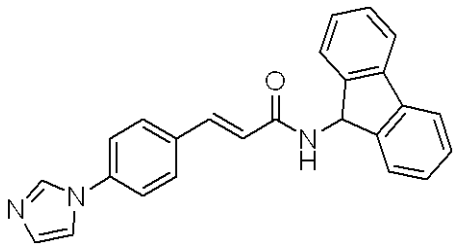
[0186]

Example 12-1

Synthesis of (E)-N-(9H-fluoren-9-yl)-3-[4-(1H-imidazol-1-yl)phenyl]acrylamide

[0187]

[Formula 63]



By the same method as in Example 12, 3.6 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl-phenyl)acrylic acid (13 mg) and 9-aminofluorene hydrochloride (20 mg). The physical properties of the compound are as follows.

ESI-MS; m/z378 [M^++H].

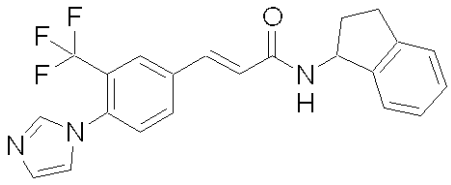
[0188]

Example 13

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-trifluoromethylphenyl]-N-indan-1-yl-acrylamide

[0189]

[Formula 64]



To a DMF (2.0 mL) solution of 4-fluoro-3-trifluoromethylbenzaldehyde (400 mg), potassium carbonate (414 mg) and imidazole (136 mg) were added one by one, and the reaction solution was agitated at 80°C for 6 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane : ethyl acetate 3:1 -> ethyl acetate) and 13.7 mg of 4-(1H-imidazol-1-yl)-3-trifluoromethylbenzaldehyde was obtained. Next, malonic acid (11.0 mg) and piperidine (53.0 mg) were added to an ethanol (1.0 mL) solution of the obtained aldehyde compound (13.0 mg), and the reaction solution was refluxed for 5 hours. Pyridine (2.0 mL) and malonic acid (11.0 mg) were added to the

reaction solution, and the reaction solution was refluxed for one and a half hour. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 15.0 mg of crude carboxylic acid was obtained by condensing under reduced pressure. By the same method as in Example 324, 10.7 mg of the title compound was obtained from the obtained carboxylic acid and 1-aminoindan. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.94 (dd, J=2.0, 8.4 Hz, 1H), 7.76 (d, J=16 Hz, 1H), 7.75-7.78 (m, 1H),7.64 (s, 1H), 7.41 (d, J=8.4 Hz, 1H), 7.34 (d, J=7.2 Hz, 1H), 7.26-7.31 (m, 3H), 7.21 (s, 1H), 7.13 (s, 1H), 6.53 (d, J=16 Hz, 1H), 5.97 (brs, 1H), 5.65 (q, J=7.6 Hz, 1H), 3.04 (ddd, J=4.4, 8.8, 16 Hz, 1H), 2.95 (td, J=8.0, 16 Hz, 1H), 2.69 (dtd, 4.4, 8.0, 13 Hz, 1H), 1.87-1.96 (m, 1H)

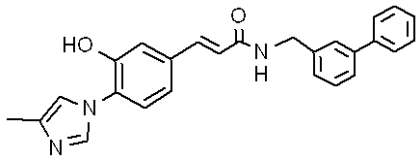
[0190]

Example 14

Synthesis of (E)-N-biphenyl-3-ylmethyl-3-[3-hydroxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

[0191]

[Formula 65]



To a methylene chloride solution (3 mL) of (E)-N-biphenyl-3-ylmethyl-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid amide (100 mg) obtained in Example 121, boron tribromide (1M pentane solution, 1.18 mL) was added dropwise at -78°C and the reaction solution was agitated at room temperature for 6 hours. The reaction solution was diluted with a saturated sodium bicarbonate solution and ethyl acetate, and the organic layer was partitioned. The organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (elution solvent: chloroform-methanol system), and 16.5 mg of the title compound was obtained.

ESI-MS; m/z410 $[M^+ + H]$. ^{1}H-NMR (DMSO-d_6) δ(ppm): 2.15 (s, 3H), 4.49 (d, J=6.0 Hz, 1H), 6.63 (d, J=15.6 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H), 7.19-7.20 (m, 2H), 7.30-7.66 (m, 11H), 7.86 (s, 1H), 8.72 (t, J=6.0 Hz, 1H), 10.43 (s, 1H).

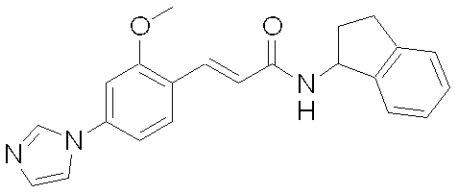
[0192]

Example 15

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-2-methoxyphenyl]-N-indan-1-yl-acrylamide

[0193]

[Formula 66]



Synthesis of 4-(1H-imidazol-1-yl)-2-methoxybenzoic acid methyl ester

To an acetone (10 mL) solution of 4-fluoro-2-hydroxy benzoic acid methyl ester (1.0 g), potassium carbonate (1.2 g) and iodomethane (732 μL) were added one by one, and the reaction solution was concentrated under reduced pressure, after refluxing for 4 hours. Potassium carbonate (1.20 g) and imidazole (479 mg) were added to a DMF (10 mL) solution of the obtained residue (1.08 g) one by one, and the reaction solution was agitated at 80°C overnight. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane : ethyl acetate = 3:1 -> ethyl acetate : methanol = 10:1), and 370 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.92-7.96 (m, 2H), 7.34 (s, 1H), 7.23 (s, 1H), 6.97-7.04 (m, 2H), 3.98 (s, 3H), 3.91 (s, 3H)

[0194]

Synthesis of (E)-3-[4-(1H-imidazol-1-yl-2-methoxyphenyl]-N-indan-1-yl-acrylamide

DIBAL-H (1.0M toluene solution, 3.27 mL) was added to a methylene chloride (5.0 mL) solution of 4-(1H-imidazol-1-yl)-2-methoxybenzoic acid methyl ester (253 mg) at -78°C, and the reaction solution was agitated for 1 hour. Saturated Rochelle salt aqueous solution was added to the reaction solution, and the reaction solution was agitated at room temperature overnight. Ethyl acetate was added to the reaction solution and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 216 mg of crude alcohol compound was obtained by condensing under reduced pressure.

To a methylene chloride (4.0 mL) solution of oxalyl chloride (277 μL), dimethylsulfoxide (451 μL) was added at -78°C and the reaction solution was agitated for 15 minutes. Next, a methylene chloride (3.0 mL) solution of alcohol compound (216 mg) obtained at a precedent step was added to the above-mentioned reaction solution at -78°C, and was agitated for 25 more minutes. Then, TEA (1.0 mL) was added to the reaction solution, heated to 0°C, and agitated for 3 hours.

Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and obtained 214 mg of crude aldehyde compounds by condensing under reduced pressure. To a THF (2.0 mL) solution of the obtained aldehyde (25.5 mg), sodium hydride (8.0 mg) and (indan-1-ylcarbamoylmethyl)phosphonic acid diethyl ester (63.0 mg) obtained in Example 1 were added at 0°C, and the reaction solution was agitated at room temperature for one hour and 40 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane : ethyl acetate = 1:1 -> ethyl acetate -> ethyl acetate : methanol = 10:1), and 28.4 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.89 (d, J=16 Hz, 1H), 7.88 (s, 1H), 7.56 (d, J=8.4 Hz, 1H), 7.35 (d, J=6.4 Hz, 1H), 7.20-7.30 (m, 5H), 6.98 (dd, J=2.0, 8.4 Hz, 1H), 6.89 (d, J=2.0 Hz, 1H), 6.57 (d, J=16 Hz, 1H), 5.93 (brd, J=8.0 Hz, 1H), 5.65 (q, J=8.0 Hz, 1H), 3.94 (s, 3H), 3.02 (ddd, J=4.4, 8.8, 16 Hz, 1H), 2.87-2.96 (m, 1H),

2.67 (dtd, J=4.4, 8.0, 16 Hz, 1H), 1.85-1.95 (m, 1H)

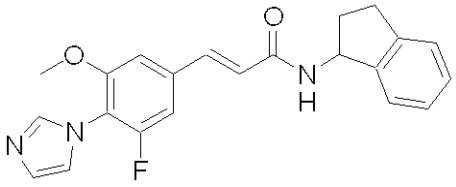
[0195]

Example 16

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)-5-methoxyphenyl]-N-indan-1-yl-acrylamide

[0196]

[Formula 67]



Synthesis of 1-(4-bromo-2-fluoro-6-methoxyphenyl)-1H-imidazole

To an acetone (10 mL) solution of 5-bromo-2,3-difluoro phenol (600 μL), potassium carbonate (1.10 g) and iodomethane (654 μL) were added one by one, and the reaction solution was refluxed for 4 hours. The reaction solution was concentrated under reduced pressure and the crude bromo compound was obtained. Potassium carbonate (1.10 g) and imidazole (429 mg) were added to a DMF (10 mL) solution of the obtained bromo compound (1.17 g) one by one, and the reaction solution was agitated at 80°C overnight. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate

and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane:ethyl acetate= 3:1 -> ethyl acetate:ethanol = 10:1), and 510 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.24 (s, 1H), 7.21 (s, 1H), 7.05-7.08 (m, 2H), 3.98 (s, 3H).

[0197]

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)-5-methoxyphenyl]-N-indan-1-yl-acrylamide

By the same method as in Example 9, 3.80 mg of the title compound was obtained from 1-(4-bromo-2-fluoro-6-methoxyphenyl)-1H-imidazole (86.0 mg) and N-indan-1-yl-acrylamide (90.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.84 (s, 1H), 7.64 (d, J=16 Hz, 1H), 7.34 (d, J=7.2 Hz, 1H), 7.23-7.29 (m, 5H), 7.11 (t, J=8.0 Hz, 1H), 6.40 (d, J=16.0 Hz, 1H), 5.95 (d, J=8.0 Hz, 1H), 5.64 (q, J=8.0 Hz, 1H), 3.98 (s, 3H), 3.04 (ddd, J=4.4, 8.8, 16.0 Hz, 1H), 2.93 (td, J=8.0, 16.0 Hz, 1H), 2.64-2.72 (m, 1H), 1.86-1.95 (m, 1H).

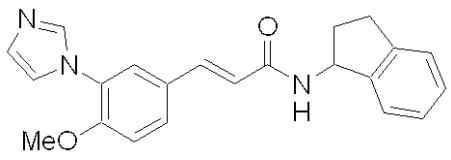
[0198]

Example 17

Synthesis of (E)-3-[3-(1H-imidazol-1-yl)-4-methoxyphenyl]-N-indan-1-yl-acrylamide

[0199]

[Formula 68]



Synthesis of 3-(1H-imidazol-1-yl-4-methoxybenzaldehyde

To an aqueous solution (15 mL) of imidazole (5.69 g), 3-bromo-4-methoxybenzaldehyde (3.00 g) and copper powder (86 mg) were added, and the reaction solution was agitated for three days at 100°C under nitrogen atmosphere. A concentrated ammonia water and ethyl acetate were added to the reaction mixture, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: ethyl acetate), and 321 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.98 (s, 3H), 7.11-7.28 (m, 3H), 7.84-7.93 (m, 3H), 9.94 (s, 1H)

[0200]

Synthesis of (E)-3-[3-(1H-imidazol-1-yl)-4-methoxyphenyl]-N-indan-1-yl-acrylamide

By the same method as in Example 1, 44 mg of the title compound was obtained from 3-imidazol-1-yl-4-methoxybenzaldehyde (33 mg)

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.84-1.93 (m, 1H), 2.60-2.68 (m, 1H), 2.85-3.04 (m, 2H), 3.87 (s, 3H), 5.61 (q, J=7.6 Hz, 1H), 6.28 (d, J=8 Hz, 1H), 6.37 (d, J=15.6 Hz, 1H), 7.03 (d, J=8.8 Hz, 1H), 7.13-7.34 (m, 6H), 7.41 (d, J=2 Hz, 1H), 7.47 (dd, J=2.4 Hz, 8.8 Hz, 1H), 7.64 (d, J=15.6 Hz, 1H), 7.72 (s, 1H).

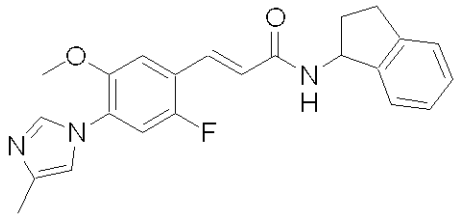
[0201]

Example 18

Synthesis of (E)-3-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

[0202]

[Formula 69]



Synthesis of 4-bromo-5-fluoro-2-methoxyaniline

To a THF (20 mL) solution of 5-fluoro-2-methoxyaniline (1.76 g), a THF (30 mL) solution of pyridinium bromide perbromide (4.36 g) was added dropwise under ice-cooling, and the reaction solution was agitated for 30 minutes at room temperature. The solid which deposited from the reaction mixture was separated by filtering and the solid was washed by THF. After the obtained solid was dissolved with water and ethyl acetate, the aqueous layer was neutralized with a saturated sodium bicarbonate water, and the organic

layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane–ethyl acetate system), and 1.83 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.91 (brs, 2H), 6.50 (d, J=9.6 Hz, 1H), 6.84 (d, J=6.0 Hz, 1H).

[0203]

Synthesis of 1-(4-bromo-5-fluoro-2-methoxyphenyl)-4-methyl-1H-imidazole

By the same method as in Example 23, 326 mg of the title compound was obtained from 4-bromo-5-fluoro-2-methoxyaniline (500 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.29 (s, 3H), 3.85 (s, 3H), 6.89 (s, 1H), 7.09 (d, J=8.4 Hz, 1H), 7.19 (d, J=6.0 Hz, 1H), 7.70 (s, 1H).

[0204]

Synthesis of (E)-3-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

By the same method as in Example 9, 31 mg of the title compound was obtained from 1-(4-bromo-5-fluoro-2-methoxyphenyl)-4-methyl-1H-imidazole (44 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86–1.95 (m, 1H), 2.29 (s, 3H), 2.63–2.72 (m, 1H), 2.88–3.07 (m, 2H), 3.86 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.97 (d, J=8.4 Hz, 1H), 6.57 (d, J=15.6 Hz, 1H), 6.93 (s, 1H), 7.05 (d, J=10.4 Hz,

1H), 7.08 (d, J=6.8 Hz, 1H), 7.21-7.27 (m, 3H), 7.34 (d, J=6.4 Hz, 1H), 7.71 (d, J=15.6 Hz, 1H), 7.76 (s, 1H).

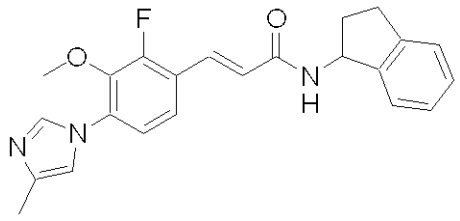
[0205]

Example 19

Synthesis of (E)-3-[2-fluoro-3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

[0206]

[Formula 70]



Synthesis of 2,4-difluoro-3-methoxybenzaldehyde

Lithium diisopropyl amide (1.5M cyclohexane solution, 5.6 mL) was added dropwise to a THF (10 mL) solution of 2,6-difluoroanisole (1.00 g) at -72°C under nitrogen atmosphere, and the reaction solution was agitated for 30 minutes. DMF (2.7 mL) was added to the reaction mixture, the reaction solution was agitated for 30 minutes at -78°C, and then agitated at room temperature for 1 hour. Water and ethyl acetate were added to the reaction mixture, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (elution solvent: hexane-ethyl acetate system) and 433 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 4.05 (s, 3H), 6.99-7.05 (m, 1H), 7.54-7.60 (m, 1H), 10.27 (s, 1H).

[0207]

Synthesis of (E)-3-[2-fluoro-3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide

By the same method as in Example 1, 5 mg of the title compound was obtained from 2,4-difluoro-2-methoxybenzaldehyde (443 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.95 (m, 1H), 2.30 (s, 3H), 2.64-2.73 (m, 1H), 2.89-3.07 (m, 2H), 3.81 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.88 (d, J=8.4 Hz, 1H), 6.54 (d, J=15.6 Hz, 1H), 6.98 (s, 1H), 7.08 (dd, J=2 Hz, 8.4 Hz, 1H), 7.21-7.27 (m, 4H), 7.35 (d, J=7.6 Hz, 1H), 7.76 (d, J=15.6 Hz, 1H), 7.78 (s, 1H).

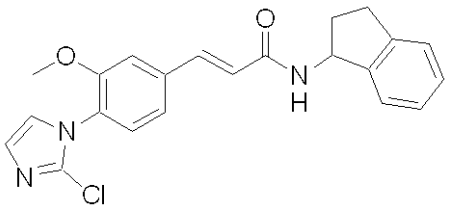
[0208]

Example 20

Synthesis of (E)-3-[4-(2-chloro-1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-ylacrylamide

[0209]

[Formula 71]



Synthesis of 4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde and 4-(5-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde

To a chloroform (3 mL) solution of the 4-(1H-imidazol-1-yl)-3-methoxybenzaldehyde (50 mg) obtained in Example 111, N-chlorosuccinimide (35 mg) was added, and the reaction solution was heated to reflux for 1.5 hours. The reaction mixture was allowed to be cooled and then purified by silica gel column chromatography (elution solvent: hexane-ethyl acetate system), and 4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde (13 mg) and 4-(5-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde (14 mg) were obtained.

The physical properties of 4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.92 (s, 3H), 7.04 (d, J=1.4 Hz, 1H), 7.10 (d, J=1.4 Hz, 1H), 7.48 (d, J=8 Hz, 1H), 7.57-7.59 (m, 2H), 10.6 (s, 1H).

The physical properties of 4-(5-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.92 (s, 3H), 7.10 (s, 1H), 7.47 (d, J=8 Hz, 1H), 7.58-7.60 (m, 3H), 10.6 (s, 1H)

[0210]

Synthesis of (E)-3-[4-(2-chloro-1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-ylacrylamide

By the same method as in Example 1, 18 mg of the title compound was obtained from 4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde (13 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.96 (m, 1H), 2.63-2.72 (m, 1H), 2.88-3.07 (m, 2H), 3.84 (s, 3H), 5.64 (q, J=7.6 Hz, 1H), 5.94 (d, J=8.4 Hz, 1H), 6.46 (d, J=15.4 Hz, 1H), 7.00 (d, J=1.0 Hz, 1H), 7.06 (d, J=1.0 Hz, 1H), 7.14-7.36 (m, 7H), 7.70 (d, J=15.4 Hz, 1H).

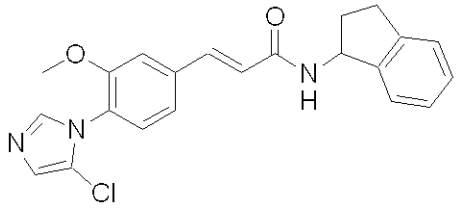
[0211]

Example 21

Synthesis of (E)-3-[4-(5-chloro-1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-ylacrylamide

[0212]

[Formula 72]



By the same method as in Example 1, 19 mg of the title compound was obtained from 4-(5-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde (14 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.96 (m, 1H), 2.63-2.72 (m, 1H), 2.86-3.07 (m, 2H), 3.84 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 6.01 (d, J=8.4 Hz, 1H), 6.47 (d, J=15.4 Hz, 1H), 7.05 (s, 1H), 7.15-7.36 (m, 7H), 7.53 (s, 1H), 7.70 (d, J=15.4 Hz, 1H).

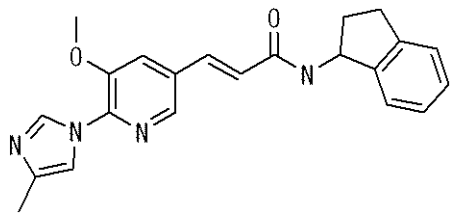
[0213]

Example 22

Synthesis of (E)-N-indan-1-yl-3-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridine-3-yl]acrylamide

[0214]

[Formula 73]



Synthesis of (E)-3-(5-methoxy-6-nitropyridin-3-yl)acrylic acid ethyl ester

To a DMF (20 mL) solution of 5-bromo-3-methoxy-2-nitropyridine (726 mg) synthesized according to the method described in Acta Chemica Scandinavica vol.47, p.805, 1993, ethyl acrylate (0.44 mL), palladium acetate (35 mg), 2-(di-tert-butylphosphino) biphenyl (93 mg) and TEA (0.87 mL) were added, and the reaction solution was agitated at 80°C for 3 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate and a saturated ammonium chloride solution were added to the reaction solution to separate an organic layer. After the obtained organic layer was dried over anhydrous magnesium sulfate, solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 2:1), and 787 mg (69%) of (E)-3-(5-methoxy-6-nitropyridin-3-yl)acrylic acid ethyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.35 (t, J=7.6 Hz, 3H), 4.01 (s, 3H), 4.28 (q, J=7.6 Hz, 2H), 6.58 (d, J=16.4 Hz, 1H), 7.56 (d, J=1.6 Hz, 1H), 7.67 (d, J=16.4 Hz, 1H), 8.20 (d, J=1.6 Hz, 1H).

[0215]

Synthesis of (E)-3-(6-amino-5-methoxypyridin-3-yl)acrylic acid ethyl ester

Iron (1.6 g) and ammonium chloride (3 g) were added to the suspension of (E)-3-(5-methoxy-6-nitropyridin-3-yl)acrylic acid ethyl ester (787 mg) in ethanol (40 mL) and water (8 mL) obtained above, and the reaction solution was heated to reflux for 1 hour. After the reaction solution was allowed to be cooled to room temperature, deposited substance was filtered by celite. Ethyl acetate and saturated sodium bicarbonate water were added to the filtrate, and the organic layer was partitioned. After drying the obtained organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 2:1), and 506 mg (66%) (E)-3-(6-amino-5-methoxypyridin-3-yl)acrylic acid ethyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.33 (t, J=7.2 Hz, 3H), 3.88 (s, 3H), 4.25 (q, J=7.2 Hz, 2H), 5.02 (brs, 2H), 6.23 (d, J=16.0 Hz, 1H), 7.06 (d, J=1.6 Hz, 1H), 7.60 (d, J=16.0 Hz, 1H), 7.78 (d, J=1.6 Hz, 1H).

[0216]

Synthesis of (E)-3-(6-chloro-5-methoxypyridin-3-yl)acrylic acid ethyl ester

Sodium nitrite (124 mg) was added to a concentrated hydrochloric acid (10 mL) solution of (E)-3-(6-chloro-5-methoxypyridin-3-yl)acrylic acid ethyl ester (200 mg) obtained above at 0°C. The reaction solution was agitated for 1 hour and 30 minutes at 0°C and further for 1 hour and 30 minutes at room temperature. Then, the reaction solution was neutralized with 8N sodium hydroxide solution, and extracted with ethyl acetate. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 2:1), and 57 mg (26%) (E)-3-(6-chloro-5-methoxypyridin-3-yl)acrylic acid ethyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.35 (t, J=7.2 Hz, 3H), 3.96 (s, 3H), 4.28 (q, J=7.2 Hz, 2H), 6.48 (d, J=16.4 Hz, 1H), 7.29 (d, J=1.6 Hz, 1H), 7.64 (d, J=16.4 Hz, 1H), 8.11 (d, J=1.6 Hz, 1H).

[0217]

Synthesis of (E)-3-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridine-3-yl]acrylic acid ethyl ester

4-methylimidazole (39 mg) and potassium carbonate (65 mg) were added to a DMF (5 mL) solution

of (E)-3-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl]acrylic acid ethyl ester (57 mg) obtained above, and agitated at 120°C for 32 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate was added to the reaction solution and the organic layer was washed with a saturated sodium bicarbonate water. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: ethyl acetate), and 12 mg (18%) (E)-3-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridine-3-yl]acrylic acid ethyl ester was obtained. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.35 (t, J=7.2 Hz, 3H), 2.29 (s, 3H), 4.04 (s, 3H), 4.29 (q, J=7.2 Hz, 2H), 6.48 (d, J=15.6 Hz, 1H), 7.45 (d, J=1.6 Hz, 1H), 7.56 (s, 1H), 7.67 (d, J=15.6 Hz, 1H), 8.18 (d, J=1.6 Hz, 1H), 8.39 (s, 1H).

[0218]

Synthesis of (E)-N-indan-1-yl-3-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridine-3-yl]acrylamide

1N sodium hydroxide solution (0.2 mL) was added to a methanol (0.5 mL) solution of (E)-3-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridine-3-yl]acrylic acid ethyl ester (12 mg) obtained above, and agitated at room temperature for 12 hours. After adding 1N hydrochloric acid water (0.2 mL) to the

reaction solution for neutralizing the reaction solution, it was extracted with ethyl acetate, the organic layer was dried over anhydrous magnesium sulfate, and 11 mg (100%) of (E)-3-[5-methoxy-6-(4-methy-1H-limidazol-1-yl)pyridine-3-yl]acrylic acid was obtained for by evaporating the solvent under reduced pressure. 4 mg (23%) of the title compound was obtained for by condensing 1-aminoindane (7.5 mg) with an acrylic acid compound obtained by the same method as in Example 121. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.97 (m, 1H), 2.29 (s, 3H), 2.63-2.74 (m, 1H), 2.88-3.09 (m, 2H), 3.99 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.87 (brd, J=7.6 Hz, 1H), 6.46 (d, J=15.6 Hz, 1H), 7.20-7.35 (m, 4H), 7.42 (d, J=1.6 Hz, 1H), 7.56 (s, 1H), 7.68 (d, J=15.6 Hz, 1H), 8.20 (d, J=1.6 Hz, 1H), 8.39 (s, 1H).

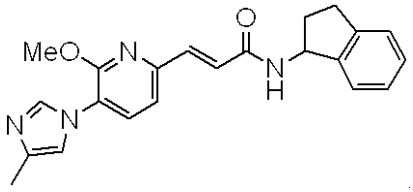
[0219]

Example 23

Synthesis of (E)-N-indan-1-yl-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylamide

[0220]

[Formula 74]



Synthesis of 6-chloro-2-methoxy-3-nitropyridine

Sodium methoxide (1.40 g) was gradually added to a THF (50 mL) solution of 2,6-dichloro-3-nitropyridine (5.00 g) over 30 minutes under ice-cooling. Then, the reaction solution was agitated at 0°C for 1 hour, and agitated at room temperature for further 12 hours. The reaction solution was poured into a saturated ammonium chloride solution (50 mL), and extracted with ethyl acetate. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 2:1), and 2.90 g (58%) of 6-chloro-2-methoxy-3-nitropyridine was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 4.16 (s, 3H), 7.03 (d, J=8.8 Hz, 1H), 8.25 (d, J=8.8 Hz, 1H).

[0221]

Synthesis of (E)-3-(6-methoxy-5-nitropyridin-2-yl)acrylic acid tert-butyl ester

To a DMF (10 mL) solution of 6-chloro-2-methoxy-3-nitropyridine (440 mg) obtained above, acrylic acid tert-butyl ester (0.44 mL), palladium acetate (26 mg), 2-(di-tert-butylphosphino)biphenyl (70 mg) and TEA (0.65 mL) were added, and the reaction solution was agitated at 120°C for 3 hours. After the reaction solution was allowed to be cooled to room

temperature, ethyl acetate and a saturated ammonium chloride solution were added and the reaction solution was partitioned. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane–ethyl acetate 2:1), and 491 mg (75%) (E)-3-(6-methoxy-5-nitropyridin-2-yl)acrylic acid tert-butyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (s, 9H), 4.16 (s, 3H), 6.93 (d, J=15.6 Hz, 1H), 7.08 (d, J=8.8 Hz, 1H), 7.47 (d, J=15.6 Hz, 1H), 8.29 (d, J=8.8 Hz, 1H).

[0222]

Synthesis of (E)-3-(5-amino-6-methoxypyridin-2-yl)acrylic acid tert-butyl ester

Iron (780 mg) and ammonium chloride (1.5 g) were added to a suspension of (E)-3-(5-amino-6-methoxypyridin-2-yl)acrylic acid tert-butyl ester (491 mg) obtained above in ethanol (40 mL) and water (8 mL), and heating refluxing of the reaction solution was carried out for 7 hours. After the reaction solution was allowed to be cooled to room temperature, deposited substance was filtered by celite. Ethyl acetate and saturated sodium bicarbonate water were added to the filtrate and the organic layer was partitioned. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced

pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 2:1), and 340 mg (78%) (E)-3-(5-amino-6-methoxypyridin-2-yl)acrylic acid tert-butyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (s, 9H), 4.01 (s, 3H), 4.03 (brs, 2H), 6.63 (d, J=15.6 Hz, 1H), 6.77 (d, J=8.8 Hz, 1H), 6.81 (d, J=8.8 Hz, 1H), 7.40 (d, J=15.6 Hz, 1H).

[0223]

Synthesis of (E)-3-(5-formylamino-6-methoxypyridin-2-yl)acrylic acid tert-butyl ester

A methylene chloride (3 mL) solution of (E)-3-(5-formylamino-6-methoxypyridin-2-yl)acrylic acid tert-butyl ester (136 mg) obtained above was added dropwise to a mixed solution of acetic anhydride (0.2 mL) and formic acid (0.4 mL) agitated at room temperature for 10 minutes. After agitating reaction solution at room temperature for 20 minutes, ethyl acetate and a saturated sodium bicarbonate water were added to the reaction solution and the organic layer was partitioned. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 1:1), and 151 mg (69%) (E)-3-(5-formylamino-6-methoxypyridin-2-yl)acrylic acid tert-butyl ester was obtained. The physical properties

of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.54 (s, 9H), 4.06 (s, 3H), 6.76 (d, J=15.6 Hz, 1H), 6.99 (d, J=8.8 Hz, 1H), 7.45 (d, J=15.6 Hz, 1H), 7.79 (brs, 1H), 8.50 (s, 1H), 8.57 (d, J=8.8 Hz, 1H).

[0224]

Synthesis of (E)-3-{5-[formyl(2-oxopropyl)amino]-6-methoxypyridin-2-yl}acrylic acid tert-butyl ester

Cesium carbonate (490 mg), potassium iodide (13 mg) and chloroacetone (0.12 mL) were added to a DMF (2 mL) solution of (E)-3-{5-formyl(2-oxopropyl)amino]-6-methoxypyridin-2-yl}acrylic acid tert-butyl ester (104 mg) obtained above, and the reaction solution was agitated at room temperature for 10 hours. Then, ethyl acetate and saturated sodium bicarbonate water were added to the reaction solution and the organic layer was partitioned, and the solvent was evaporated under reduced pressure after the organic layer was dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate = 1:1), and 116 mg (93%) of (E)-3-{5-[formyl(2-oxopropyl)amino]-6-methoxypyridin-2-yl}acrylic acid tert-butyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.53 (s, 9H), 2.16 (s, 3H), 4.00 (s, 3H), 4.50 (s, 2H), 6.81 (d, J=15.6 Hz, 1H), 7.00 (d, J=8.8 Hz, 1H), 7.43 (d, J=15.6 Hz, 1H), 7.55 (d,

J=8.8 Hz, 1H), 8.28 (s, 1H).

[0225]

Synthesis of (E)-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylic acid tert-butyl ester

Ammonium acetate (130 mg) was added to an acetic acid (2 mL) solution of (E)-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylic acid tert-butyl ester (116 mg) obtained above, and the reaction solution was agitated at 120°C for 3 hours. Then, after the reaction solution was allowed to be cooled to room temperature, the reaction solution was diluted with ethyl acetate and the resultant mixture was neutralized with a saturated sodium bicarbonate water. After separating and drying the organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: ethyl acetate), and 40 mg (37%) (E)-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylic acid tert-butyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (s, 9H), 2.30 (s, 3H), 4.06 (s, 3H), 6.86 (d, J=15.6 Hz, 1H), 6.99 (s, 1H), 7.05 (d, J=8.8 Hz, 1H), 7.48 (d, J=15.6 Hz, 1H), 7.52 (d, J=8.8 Hz, 1H), 7.82 (s, 1H).

[0226]

Synthesis of (E)-N-indan-1-yl-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylamide

An ethyl acetate solution (3 mL) of 4N hydrochloric acid was added to (E)-N-indan-1-yl-3-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylamide (20 mg) obtained above, and the reaction solution was agitated at room temperature for 3 hours. Then, the reaction solution was concentrated under reduced pressure. 20 mg (69%) of the title compound was obtained by condensing the obtained crude acrylic acid compound with 1-aminoindane (0.015 mL) by the same method as in Example 121. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.97 (m, 1H), 2.30 (s, 3H), 2.64-2.74 (m, 1H), 2.88-3.09 (m, 2H), 4.04 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.95 (brd, J=7.6 Hz, 1H), 6.95 (d, J=15.6 Hz, 1H), 6.98 (brs, 1H), 7.06 (d, J=8.8 Hz, 1H), 7.20-7.39 (m, 4H), 7.56 (d, J=8.8 Hz, 1H), 7.60 (d, J=15.6 Hz, 1H), 7.81 (brs, 1H).

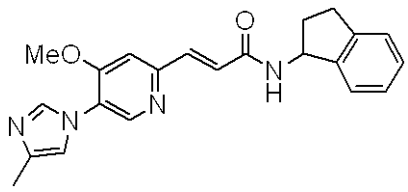
[0227]

Example 24

Synthesis of (E)-N-indan-1-yl-3-[4-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylamide

[0228]

[Formula 75]



Synthesis of 5-bromo-4-methoxypyridine-2-carbaldehyde

Dess-Martin reagent (1.14 g) was added at 0°C to a methylene chloride (5 mL) solution of (5-bromo-4-methoxypyridin-2-yl)methanol (450 mg) synthesized by the method described in Organic Process Research & Development 2000 4,473. The reaction solution was agitated at 0°C for 1 hour and further agitated at room temperature for 1 hour. 1N sodium hydroxide solution was added to the reaction solution, the organic layer was separated, and washed with a saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 1:1), and 300 mg (67%) 5-bromo-4-methoxypyridine-2-carbaldehyde was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 4.04 (s, 3H), 7.48 (s, 1H), 8.75 (s, 1H), 10.1 (s, 1H).

[0229]

Synthesis of (E)-3-(5-bromo-4-methoxypyridin-2-yl)acrylic acid tert-butyl ester

Diethylphosphonoacetic acid tert-butyl ester (0.26 mL) was added to a THF (4 mL) suspension of sodium hydride (45 mg), and the reaction solution was agitated at room temperature for 1 hour. Then, the reaction solution was cooled to 0°C, and a THF (1 mL)

solution of 5-bromo-4-methoxypyridine-2-carbaldehyde (200 mg) obtained above was added dropwise to the reaction solution. The reaction solution was agitated for 1h at 0°C and further agitated for 12h at room temperature. A saturated ammonium chloride solution was added to the reaction solution after the reaction ended, and the reaction solution was extracted with ethyl acetate to separate an organic layer. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate 2:1), and 116 mg (40%) (E)-3-(5-bromo-4-methoxypyridin-2-yl)acrylic acid tert-butyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.53 (s, 9H), 3.98 (s, 3H), 6.82 (d, J=15.6 Hz, 1H), 6.92 (s, 1H), 7.49 (d, J=15.6 Hz, 1H), 8.56 (s, 1H).

[0230]

Synthesis of (E)-3-(5-amino-4-methoxypyridin-2-yl)acrylic acid tert-butyl ester

Benzophenone imine (0.04 mL), sodium tert-butoxide (26 mg) and DPPF (13 mg), and bis(1,5-cyclooctadiene) nickel (0) were added to a toluene (3 mL) solution of (E)-3-(5-bromo-4-methoxypyridin-2-yl)acrylic acid tert-butyl ester (70 mg) obtained above, and heating refluxing of the solution was

carried out for 14 hours. After the reaction solution was allowed to be cooled to room temperature, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane–ethyl acetate 3:1), and 45 mg of (49%) imine compound was obtained. Hydroxylamine hydrochloride (15 mg) and sodium acetate (30 mg) were added to a methanol (3 mL) solution of the obtained imine compound, and the reaction solution was agitated at room temperature for 1 hour. A saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution after the reaction ended, and the organic layer was separated. After drying the organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane–ethyl acetate = 1:2), and 20 mg (73%) (E)-3-(5-amino-4-methoxypyridin-2-yl)acrylic acid tert-butyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (s, 9H), 3.91 (s, 3H), 3.93 (brs, 2H), 6.54 (d, J=15.6 Hz, 1H), 6.88 (s, 1H), 7.49 (d, J=15.6 Hz, 1H), 8.00 (s, 1H).

[0231]

Synthesis of (E)-3-[4-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylic acid tert-butyl ester

By the same method as in Example 23, 15 mg

(60%) of (E)-3-(4-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl)acrylic acid tert-butyl ester was obtained from (E)-3-(5-amino-4-methoxypyridin-2-yl)acrylic acid tert-butyl ester (20 mg) obtained above. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ: 1.54 (s, 9H), 2.31 (s, 3H), 3.97 (s, 3H), 6.83 (d, J=15.6 Hz, 1H), 6.93 (s, 1H), 7.07 (s, 1H), 7.55 (d, J=15.6 Hz, 1H), 7.74 (s, 1H), 8.45 (s, 1H).

[0232]

Synthesis of (E)-N-indan-1-yl-3-[4-methoxy-5-[4-methyl-1H-imidazol-1-yl)pyridin-2-yl]acrylamide

By the same method as in Example 23, 4 mg (27%) (E)-N-indan-1-yl-3-[4-methoxy-5-(4-methylimidazol-1-yl)pyridin-2-yl)acrylamide was obtained from (E)-3-(4-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl)acrylic acid tert-butyl ester (15 mg) obtained above and 1-aminoindan. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.84-1.96 (m, 1H), 2.30 (s, 3H), 2.65-2.74 (m, 1H), 2.88-3.08 (m, 2H), 3.98 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 6.00 (brd, J=7.6 Hz, 1H), 6.93 (s, 1H), 7.01 (d, J=15.6 Hz, 1H), 7.05 (s, 1H), 7.21-7.37 (m, 4H), 7.66 (d, J=15.6 Hz, 1H), 7.72 (s, 1H), 8.43 (s, 1H).

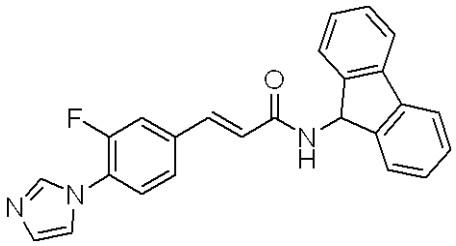
[0233]

Example 24-1

Synthesis of (E)-N-(9H-fluoren-9-yl)-3-(3-fluoro-4-(1H-imidazol-1-yl)phenyl]acrylamide

[0234]

[Formula 76]



By the same method as in Example 12, 7.6 mg of the title compound was obtained from (E)-3-(3-fluoro-4-(1H-imidazol-1-yl)phenyl]acrylic acid (14 mg) and 9-aminofluorene hydrochloride (20 mg). The physical properties of the compound are as follows.

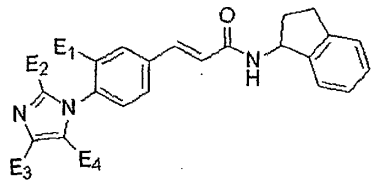
ESI-MS; m/z396 [M^++H]

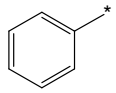
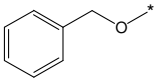
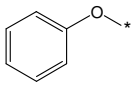
[0235]

According to the Example 1, the combination of an imidazole derivative and a benzaldehyde derivative was changed, and the compounds shown in Table 2 were synthesized. The structural formulae and physicochemical properties are shown in Table 2, respectively.

[0236]

[Table 2-1]

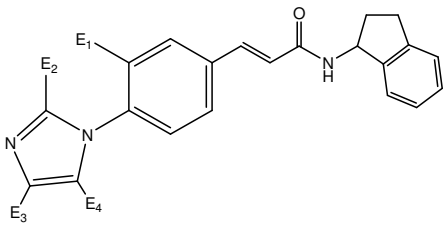


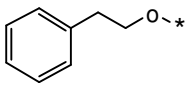
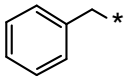
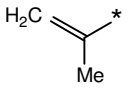
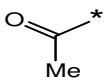
Example	E_1	E_2	E_3	E_4	Data:MS m/z
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26	F	Me	H	H	M^++H:362 (ESI)
27	F	H	Me	H	M^++H:362 (ESI)
28	F	H		H	M^++H:424 (ESI)
29	F	H	NO_2	H	M^++H:393 (ESI)
30	F	H	$HOCH_2$–	H	M^++H:378 (ESI)
31	MeO	H	H	Me	M^++H:374 (ESI)
32	F	H	Br	H	M^++H:426 (ESI)
33	F	H	Me	Me	M^++H:376 (ESI)
34	MeO	H	Br	H	M^++H:438 (ESI)
35	MeO	Me	H	H	M^++H:374 (ESI)
36	MeO	H	Et	H	M^++H:388 (ESI)
37	MeO	H	CF_3	H	M^++H:428 (ESI)
38	MeO	H	NC–	H	M^++H:385 (ESI)
39		H	H	H	M^++H:436 (ESI)
40		H	H	H	M^++H:422 (ESI)

– Continued –

[0237]

[Table 2-2]

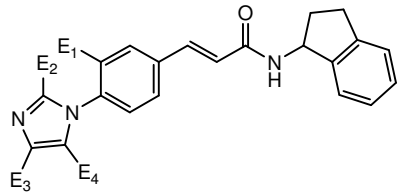


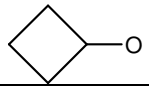
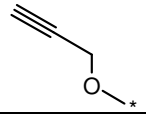
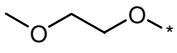
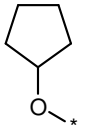
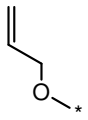
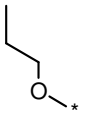
Example	E_1	E_2	E_3	E_4	DATA:MS m/z
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42	Br	H	H	H	M^++H:408 (ESI)
43	Cl	H	Me	H	M^++H:378 (ESI)
44	Br	H	Me	H	M^++H:422 (ESI)
45	MeO	H	$HOCH_2$–	H	M^++H:390 (ESI)
46	MeO	H		H	M^++H:450 (ESI)
47	MeO	H	F	H	M^++H:378 (ESI)
48	MeO	H		H	M^++H:400 (ESI)
49	MeO	H	i-Pr	H	M^++H:402 (ESI)
50	MeO	H		H	M^++H:402 (ESI)
51	H	Me	Me	H	M^++H:358 (ESI)
52	H	H	Me	H	M^++H:344 (ESI)
53	MeO	H	Cl	H	M^++H:394 (ESI)

– Continued –

[0238]

[Table 2-3]



Example	E_1	E_2	E_3	E_4	DATA:MS m/z
54		H	H	H	M^++H:400 (ESI)
55	SMe	H	H	H	M^++H:376 (ESI)
56	SO_2Me	H	H	H	M^++H:408 (ESI)
57		H	Me	H	M^++H:398 (ESI)
58		H	Me	H	M^++H:418 (ESI)
59		H	Me	H	M^++H:428 (ESI)
60		H	Me	H	M^++H:428 (ESI)
61		H	Me	H	M^++H:400 (ESI)
62		H	Me	H	M^++H:402 (ESI)
63	MeO	H		H	M^++H:416 (ESI)
64	MeO	H		H	M^++H:400 (ESI)
65	MeO	H		H	M^++H:486 (ESI)

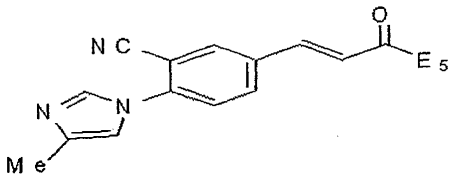
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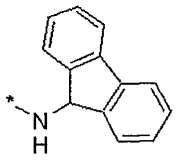
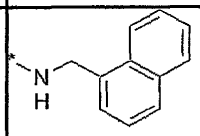
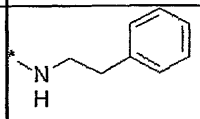
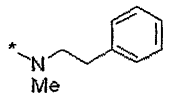
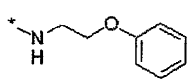
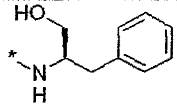
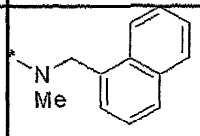
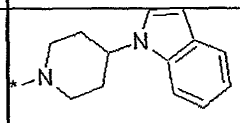
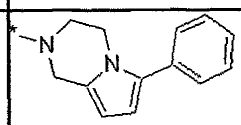
[0239]

The compound shown in Table 3 were synthesized as in Example 10. These structural formulae and physicochemical properties are shown in Table 3, respectively.

[0240]

[Table 3]



Example	E_5	DATA: MS m/z
66		M^++H：417 (ESI)
67		M^++H：393 (ESI)
68		M^++H：357 (ESI)
69		M^++H：371 (ESI)
70		M^++H：373 (ESI)
71		M^++H：387 (ESI)
72		M^++H：407 (ESI)
73		M^++H：436 (ESI)
74		M^++H：434 (ESI)

- Continued -

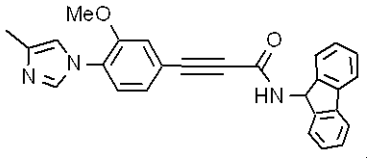
[0241]

Example 75

Synthesis of N-(9H-fluoren-9-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)propiolic acid amide

[0242]

[Formula 77]



Synthesis of N-(4-bromo-2-methoxyphenyl)-2,2,2-trifluoroacetamide

[0243]

Trifluoroacetic anhydride (24 mL) was added dropwise to a pyridine (48 mL) solution of 4-bromo-2-methoxyaniline (23.4 g) under ice-cooling. The reaction solution was stirred for an hour and iced water was added thereto. Crystals deposited were separated by filtering, and air-dried overnight. 32.4 g of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ(ppm): 3.93 (s, 3H), 7.07 (d, J=2.4 Hz, 1H), 7.16 (dd, J=8.8, 2.4 Hz, 1H), 8.21 (d, J=8.8 Hz, 1H), 8.47 (brs, 1H).

[0244]

Synthesis of 1-(4-bromo-2-methoxyphenyl)aminopropan-2-one

Chloroacetone (20 g) was added dropwise to a DMF (160 mL) suspension of N-(4-bromo-2-methoxyphenyl)-

2,2,2-trifluoroacetamide (32.4 g), cesium carbonate (71 g) and potassium iodide (1.8 g), and the reaction solution was agitated at room temperature for 2 hours. Then, The reaction solution was stirred for 1 hour and iced water was added thereto. Crystals deposited were separated by filtering. The obtained crystal was suspended in methanol (360 mL) and 2N sodium hydroxide solution (55 mL), and the suspension was agitated for 30 minutes. An iced water was added thereto. Crystals deposited were separated by filtering, and air-dried overnight. 25.2 g of the title compound was obtained. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.25 (s, 3H), 3.85 (s, 3H), 3.97 (d, J=5.2 Hz, 2H), 5.05 (brs, 1H), 6.29 (d, J=8.4 Hz, 1H), 6.85 (d, J=2.0 Hz, 1H), 6.94 (dd, J=8.4, 2.0 Hz, 1H).

[0245]

Synthesis of N-(4-bromo-2-methoxyphenyl)-N-(2-oxopropyl)acetamide

A mixture of acetic anhydride (40 g) and formic acid (90 g) was agitated under ice-cooling for 30 minutes. A methylene chloride (65 mL) solution of 1-(4-bromo-2-methoxyphenyl)propan-2-one(25.2 g) was added dropwise to the solution, and the reaction solution was agitated for 30 minutes. The reaction solution was extracted with ether after neutralized with a sodium hydroxide solution. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under

reduced pressure. The residue was filtered, washed with ether and air-dried, and 23.4 g of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.17 (s, 3H), 3.84 (s, 3H), 4.43 (s, 2H), 7.09 (d, J=2.0 Hz, 1H), 7.13 (dd, J=8.0, 2.0 Hz, 1H), 7.19 (d, J=8.0 Hz, 1H), 8.23 (s, 1H).

[0246]

Synthesis of 1-(4-bromo-2-methoxyphenyl)-4-methyl-1H-imidazole

A mixture of N-(4-bromo-2-methoxyphenyl)-N-(2-oxopropyl)acetamide (23.4 g), ammonium acetate (31.5 g), and acetic acid (49 g) was agitated under heating at 120°C for 30 minutes. After the reaction solution was neutralized with sodium hydroxide under ice-cooling, the reaction solution was extracted with ethyl acetate. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: hexane-ethyl acetate system), and 19.4 g of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.29 (s, 3H), 3.85 (s, 3H), 6.87 (s, 1H), 7.10-7.18 (m, 3H), 7.65 (s, 1H).

[0247]

Synthesis of 1-(4-iodine-2-methoxyphenyl)-4-methyl-1H-imidazole

A 1,4-dioxane (50 mL) suspension of 1-(4-bromo-2-methoxyphenyl)-4-methyl-1H-imidazole (10.0 g)

and copper iodide (I) (I) (7.13 g), sodium iodide (11.2 g) and N,N'-dimethyl ethylene diamine (6.59 g) was agitated at 110°C for 9 hours. Ethyl acetate and a saturated ammonium chloride solution were added to the reaction solution after cooling reaction solution to room temperature, and the reaction solution was agitated for 30 minutes. After celite filtration, the organic layer of the filtrate was washed with a saturated saline solution, and the reaction solution was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system), and 4.07 g of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.29 (s, 3H), 3.86 (s, 3H), 6.82 (s, 1H), 6.97 (d, J=8.0 Hz, 1H), 7.34 (d, J=2.0 Hz, 1H), 7.36 (dd, J=8.0, 2.0 Hz, 1H), 7.73 (s, 1H).

[0248]

Synthesis of tert-butyl(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propiolic acid ester

A DMF (17 mL) suspension of 1-(4-iodine-2-methoxyphenyl)-4-methyl-1H-imidazole (2.67 g) and tert-butyl propiolate (2.14 g), dichlorobis(triphenylphosphine)palladium(II) (300 mg), potassium carbonate (2.35 g) and iodation copper (I) (162 mg) was agitated under heating at 100°C for 20 minutes. Ethyl acetate and a saturated ammonium chloride solution were added to the reaction solution

after cooling reaction solution to room temperature, and the reaction solution was agitated for 30 minutes. After washed with a saturated saline solution, reaction solution was dried over anhydrous magnesium sulfate and the separated organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane–ethyl acetate system), and 2.45 g of the title compound was obtained. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.56 (s, 9H), 2.29 (s, 3H), 3.87 (s, 3H), 6.93 (s, 1H), 7.21–7.24 (m, 3H), 7.78 (s, 1H).

[0249]

Synthesis of [3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propiolic acid

Trifluoroacetic acid (6.0 mL) was added to a methylene chloride (30 mL) solution of tert-butyl (3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)propiolic acid ester (2.45 g) under ice-cooling, and the reaction solution was agitated at room temperature overnight. The reaction solution was concentrated under reduced pressure and diluted with ethyl acetate. Crystals deposited were separated by filtering, and air-dried overnight. 1.45 g of the title compound was obtained. ^{1}H-NMR (DMSO-d_6) δ(ppm): 2.32 (s, 3H), 3.92 (s, 3H), 7.44 (dd, J=8.0, 1.6 Hz, 1H), 7.61 (d, J=1.6 Hz, 1H), 7.66 (d, J=8.0 Hz, 1H), 7.71 (s, 1H), 9.18 (s, 1H).

[0250]

Synthesis of N-(9H-fluoren-9-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propiolic acid amide

A DMF (2 mL) solution of [3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propiolic acid (74 mg) and 9-aminofluorene (65 mg) and BOP (133 mg) and N, N'-IPEA (77μL) was agitated at room temperature overnight. Water and chloroform were added to the reaction solution, the organic layer was partitioned and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex NH, elution solvent: heptane-ethyl acetate system), and 45 mg of the title compound was obtained.

ESI-MS; m/z420 $[M^+ + H]$.

^{1}H-NMR (DMSO-d_6) δ(ppm): 2.14 (s, 3H), 3.86 (s, 3H), 6.11 (d, J=8.0 Hz, 1H), 7.18 (s, 1H), 7.26 (d, J=6.4 Hz, 1H), 7.34-7.47 (m, 6H), 7.55 (d, J=7.6 Hz, 2H), 7.84 (s, 1H), 7.88 (d, J=7.6 Hz, 2H), 9.47 (d, J=8.0 Hz, 1H).

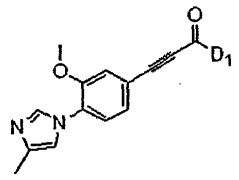
ESI-MS; m/z420 $[M^+ + H]$.

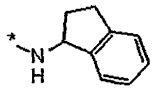
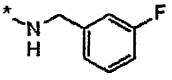
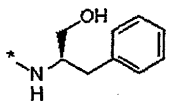
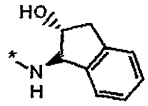
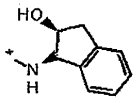
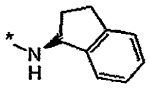
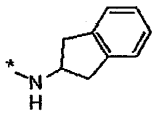
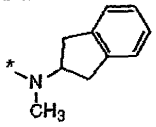
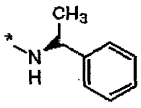
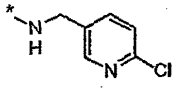
[0251]

The compounds shown in Table 4 were synthesized as in Example 75. The structural formulae and physicochemical properties are shown in Table 4, respectively.

[0252]

[Table 4]



Example	D_1	DATA: MS m/z
76		M^++H : 372 (ESI)
77		M^++H : 364 (ESI)
78		M^++H : 390 (ESI)
79		M^++H : 388 (ESI)
79-1		M^++H : 388 (ESI)
80		M^++H : 372 (ESI)
81		M^++H : 372 (ESI)
82		M^++H : 386 (ESI)
83		M^++H : 360 (ESI)
84		M^++H : 381 (ESI)

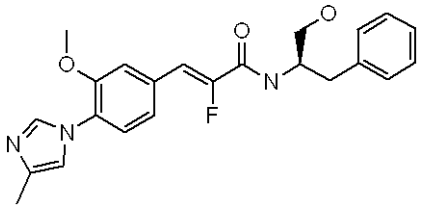
[0253]

Example 85

Synthesis of (E)-2-fluoro-N-[(1R)-hydroxymethyl-2-phenylethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0254]

[Formula 78]



Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid ethyl ester

To a THF (15 mL) solution of sodium hydride (814 mg) triethylphosphonoacetic acid (4.1 mL) was added at 0°C, and the reaction solution was agitated at 0°C for 30 minutes and at room temperature for 1 hour. After cooling the reaction solution at 0°C, the THF (5 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (4.0 g) synthesized in Example 1 was added dropwise to the reaction solution. The reaction solution was further agitated at 0°C for 30 minutes and then at room temperature for 2 hours. Ethyl acetate and water was added to the reaction solution, and the organic layer was separated and washed with a saturated ammonium chloride solution. After drying with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. By re-crystallizing the

obtained solid using a mixed solution of hexane and ethyl acetate, the 4.55 g (86%) title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.71 (t, J=7.8 Hz, 3H), 2.60 (s, 3H), 3.79 (s, 3H), 4.58 (q, J=7.8 Hz, 2H), 6.45 (d, J=16.2 Hz, 1H), 6.95 (m, 1H), 7.17 (d, J=1.6 Hz, 1H), 7.19 (dd, J=8.4, 1.6 Hz, 1H), 7.28 (d, J=8.4 Hz、1H), 7.68 (d, J=16.2 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H).

[0255]

Synthesis of (E)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid ethyl ester

2-fluoro malonic acid diethyl ester (670 μL) was added to a THF (8 mL) suspension of sodium hydride (170 mg) under ice-cooling, and the reaction solution was agitated under ice-cooling for 20 minutes and further agitated at room temperature for 1 hour. After dropping the THF (2 mL) solution of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid ethyl ester (1 g) obtained above to the reaction solution over 10 minutes and the reaction solution was agitated at room temperature for 30 minutes, and heated to reflux for 8 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate and water was added and the organic layer was washed with a saturated ammonium chloride solution. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced

pressure. The obtained residue was purified by silica gel column chromatography (Carrier : Chromatorex™ NH, elution solvent: from hexane to hexane : ethyl acetate = 1:1), and 593 mg (56%) of (E)-2-fluoro-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid ethyl ester was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z305 $[M^+ +H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.42 (t, J=7.8 Hz, 3H), 2.31 (s, 3H), 3.89 (s, 3H), 4.38 (q, J=7.8 Hz, 2H), 6.92 (d, J=36 Hz, 1H), 6.95 (m, 1H), 7.26 (d, J=8.4 Hz, 1H), 7.31 (dd, J=8.4, 1.6 Hz, 1H), 7.37 (brs, 1H), 7.76 (d, J=1.6 Hz, 1H).

[0256]

Synthesis of (E)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid

2N sodium hydroxide solution (2 mL) was added to a solution of (E)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid diethyl ester (593 mg) in THF (1 mL) and ethanol (4 mL). The reaction solution was agitated at room temperature for 15 hours, neutralized with 2N hydrochloric acid (2 mL). The solid deposited from the reaction solution was separated by filtering and 512 mg (95%) of (E)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid was obtained by washing the solid with ethanol. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ(ppm): 2.15 (s, 3H), 3.85 (s, 3H),

7.06 (d, J=36.0 Hz, 1H), 7.18 (m, 1H), 7.38 (dd, J=8.4, 1.6 Hz, 1H), 7.44 (dd, J=8.4, 1H), 7.51 (brs, 1H), 7.84 (d, J=1.6 Hz, 1H).

[0257]

Synthesis of (E)-2-fluoro-N-[(1R)-hydroxymethyl-2-phenylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

71 mg (74%) of the title compound was obtained from (E)-2-fluoro-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (65 mg) and D-phenylalanilol (43 mg) which were obtained by the same method as in Example 121. The physical properties of the compound are as follows.

ESI-MS; m/z410 $[M^+ +H]$. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 3H), 2.98 (d, J=7.2 Hz, 2H), 3.69 (dd, J=6.8, 4.8 Hz, 1H), 3.77 (dd, J=6.8, 4.8 Hz, 1H), 3.87 (s, 3H), 4.30-4.39 (m, 1H), 6.64 (brd, 1H), 6.90 (d, J=36.0 Hz, 1H), 6.94 (brs, 1H), 7.38 (dd, J=8.4, 1.6 Hz, 1H), 7.25-7.38 (m, 8H), 7.74 (d, J=1.6 Hz, 1H).

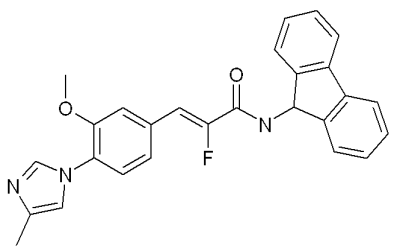
[0258]

Example 86

Synthesis of N-(9H-fluoren-9-yl)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0259]

[Formula 79]



By the same method as in Example 86, 46 mg (36%) of the title compound was obtained from the 2-fluoro-3-(3-methoxy-4-(4-methyl-imidazol-1-yl)phenyl)acrylic acid (80 mg) obtained in the Example 85 and 9-aminofluorene hydrochloride (64 mg). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ(ppm): 2.15 (s, 3H), 3.85 (s, 3H), 6.17 (brd, 1H), 7.10 (d, J=38.0 Hz, 1H), 7.18 (brs, 1H), 7.28-7.55 (m, 9H), 7.83 (d, J=1.6 Hz, 1H), 7.88 (d, J=7.6, 2H), 9.30 (d, J=8.8 Hz, 1H).

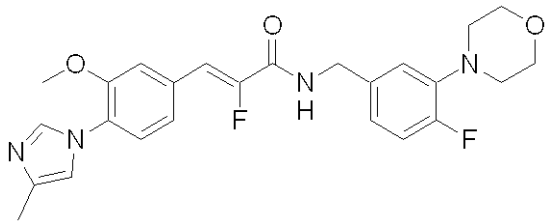
[0260]

Example 87

Synthesis of (E)-2-fluoro-N-(4-fluoro-3-morpholin-4-yl-benzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0261]

[Formula 80]



By the same method as in Example 85, 43.8 mg of the title compound was obtained from (E)-2-fluoro-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (40.0 mg) and 4-fluoro-3-morpholin-4-yl-benzylamine (32.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.74 (d, J=1.6 Hz, 1H), 7.27-7.29 (m, 3H), 7.00-7.05 (m, 2H), 6.89-6.95 (m, 3H), 6.61-6.67 (br, 1H), 4.54 (d, J=6.0 Hz, 2H), 3.88 (s, 3H), 3.86-3.89 (m, 4H), 3.09-3.11 (m, 4H), 2.30 (s, 3H).

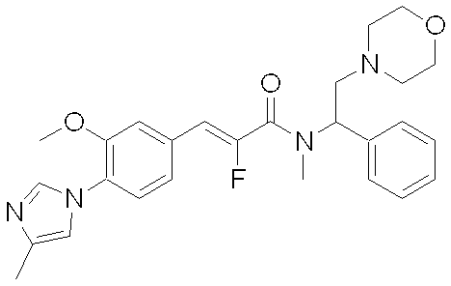
[0262]

Example 88

Synthesis of (E)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-phenyl]-N-methyl-N-(2-morpholin-4-yl-1-phenylethyl)acrylamide

[0263]

[Formula 81]



By the same method as in Example 85, 51.5 mg of the title compound was obtained from (E)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (45.0 mg) and methyl-(2-morpholin-4-yl-phenylethyl)amine (1M DMF solution, 245 μL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H), 7.30-7.42 (m, 4H), 7.21-7.28 (m, 4H), 6.94 (s, 1H), 6.62 (d, J=38 Hz、1H), 3.88 (s, 3H), 3.64-3.74 (m, 4H), 2.94-3.20 (m, 1H), 2.80-2.90 (m, 4H), 2.62-2.74 (br, 2H), 2.43-2.50 (m,

3H), 2.30 (s, 3H)

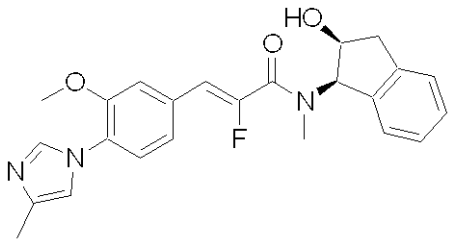
[0264]

Example 89

Synthesis of (E)-2-fluoro-N-[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl-acrylamide

[0265]

[Formula 82]



By the same method as in Example 85, 76.0 mg of the title compound was obtained from (E)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (60.0 mg) and (1R,2S)1-methylamino-indan-2-ol (42.5 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H), 7.24-7.34 (m, 7H), 6.95 (s, 1H), 6.73 (d, J=37 Hz, 1H), 5.66-5.74 (m, 1H), 4.90-4.96 (m, 1H), 3.89 (s, 3H), 3.35 (dd, J=7.2, 17 Hz, 1H), 2.94-3.02 (m, 1H), 2.86-2.90 (m, 3H), 2.30 (s, 3H).

[0266]

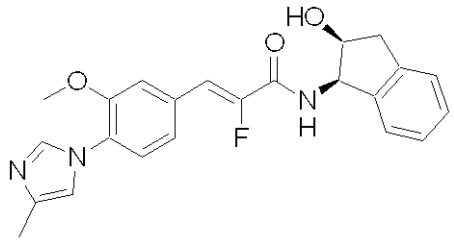
Example 90

Synthesis of (E)-2-fluoro-N-[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)phenyl]acrylamide

[0267]

[Formula 83]



By the same method as in Example 85, (E)-2-fluoro-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (60.0 mg) and 76.0 mg of (1R,2S)1-amino-2-indanol (38.8 mg) title compounds were obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 7.25-7.35 (m, 7H), 7.16 (d, J=8.4 Hz, 1H), 6.98 (d, J=38 Hz, 1H), 6.94 (s, 1H), 5.54 (dd, J=5.2, 8.4 Hz, 1H), 4.77 (dt, J=2.0, 5.2 Hz, 1H), 3.86 (s, 3H), 3.26 (dd, J=5.2, 16 Hz, 1H), 3.05 (dd, J=2.0, 16 Hz, 1H), 2.29 (s, 3H)

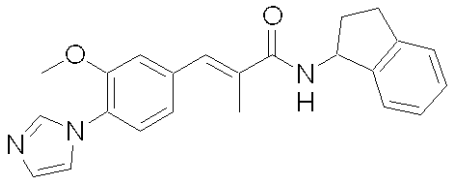
[0268]

Example 91

Synthesis of (E)-3-(4-imidazol-yl-3-methoxyphenyl)-N-indan-yl-2-methyl-acrylamide

[0269]

[Formula 84]



Triethyl-2-phosphonopropionic acid ester (116 μL) and sodium hydride (43.0 mg) were added at 0°C one by one to a DMF (5.0 mL) solution of 4-(1H-imidazol-1-yl)-3-methoxybenzaldehyde (100 mg) obtained in the Example 111. The reaction solution was warmed to room temperature and agitated overnight. Then, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 68.0 mg of crude carboxylic acid was obtained by condensing under reduced pressure. Next, 25.3 mg of the title compound was obtained from the obtained carboxylic acid (30.5 mg) and 1-aminoindan (24.0 μL) by the same method as in Example 324. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.41 (s, 1H), 7.37 (d, J=6.0 Hz, 1H), 7.247.30 (m, 4H), 7.23 (s, 1H), 7.18 (s, 1H), 7.02 (d, J=8.4 Hz, 1H), 7.01 (s, 1H), 6.14 (d, J=7.6 Hz, 1H), 5.64 (q, J=7.6 Hz, 1H), 3.86 (s, 3H), 3.05 (ddd, J=4.0, 8.8, 16 Hz, 1H), 2.94 (td, J=8.0, 16 Hz, 1H), 2.71 (dtd, J=4.0, 8.0, 12 Hz, 1H), 2.16 (s, 3H), 1.86-1.96 (m, 1H)

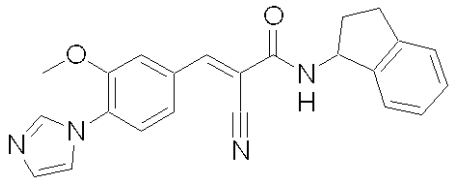
[0270]

Example 92

Synthesis of (E)-2-cyano-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl)-N-indan-1-yl-acrylamide

[0271]

[Formula 85]



Cyano ethyl acetate (76.0 μL) and piperidine were added one by one to an ethanol solution (5.0 mL) of 4-(1H-imidazol-1-yl-3-methoxybenzaldehyde (144 mg) obtained in Example 111 (35.0 μL). The reaction solution was refluxed for 3.5 hours, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain the crude ester product. 2N sodium hydroxide solution (1.0 mL) was added to a THF (2 mL) solution of the obtained ester product, and the reaction solution was agitated for 45 minutes at room temperature. Then, the reaction solution was warmed up to 50°C, it was agitated for further 9 hours. Crude carboxylic acid sodium salt was obtained by condensing the reaction solution as it was under reduced pressure. 1.0 mg of the title compound was obtained from the obtained carboxylic acid sodium salt and 1-aminoindan (41.0 μL) by the same method as in Example 324. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.11 (s, 1H), 7.68 (s, 1H),

7.24–7.38 (m, 9H), 6.41 (d, J=7.6 Hz, 1H), 5.73 (q, J=7.6 Hz, 1H), 3.96 (s, 3H), 3.08 (ddd, J=4.0, 8.8, 16 Hz, 1H), 2.88–3.00 (m, 1H), 2.75 (tdt, J=4.0, 8.0, 13 Hz, 1H), 1.93–2.02 (m, 1H).

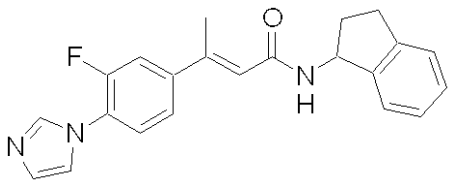
[0272]

Example 93

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)-phenyl]-2-butenone acid indan-1-ylamide

[0273]

[Formula 86]



Synthesis of 1-[3-fluoro-4-(1H-imidazol-1-yl)-phenyl]ethanone

Imidazole (543 mg) and potassium carbonate (1.80 g) were added to a DMF (15 mL) solution of 3,4-difluoroacetophenone (1.0 mL). After agitating reaction solution at 80°C for 4 hours, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane: ethyl acetate = 5:1 -> ethyl acetate), and 1.40 g of the title compound was obtained. The

physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.95 (s, 1H), 7.86-7.92 (m, 2H), 7.52-7.59 (m, 1H), 7.39 (s, 1H), 7.25 (s, 1H), 2.65 (s, 3H).

[0274]

Synthesis of (E)-3-(3-fluoro-4-(1H-imidazol-1-yl)-phenyl]crotonic acid indan-1-ylamide

Dimethylphosphonoacetic acid methyl ester (308 μL) and sodium hydride (44.0 mg) were added to a THF (5.0 mL) solution of 1-[3-fluoro-4-(1H-imidazol-1-yl)phenyl]ethanone (390 mg), and the reaction solution was refluxed for 2 hours. Sodium hydride (40.0 mg) was further added to the reaction solution, the reaction solution was refluxed for 5 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield 525 mg of crude ester product as an isomer mixture (E:Z=2.4:1). 2N sodium hydroxide solution (3.0 mL) was added to a THF (3.0 mL) solution of the obtained ester product (260 mg). The reaction solution was warmed to 50°C, and was agitated for 1 hour and 40 minutes. By condensing reaction solution under reduced pressure, 235 mg of crude carboxylic acid sodium salt was obtained as an isomer mixture. 22.0 mg of the title compound was obtained from the obtained carboxylic acid

sodium salt and 1-aminoindan (234 μL) by the same method as in Example 324. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.80 (s, 1H), 7.31-7.38 (m, 4H), 7.20-7.28 (m, 5H), 6.30 (d, J=7.6 Hz, 1H), 6.12-6.13 (m, 1H), 5.58 (q, J=7.6 Hz, 1H), 3.01 (ddd, J=4.8, 8.8, 16 Hz, 1H), 2.93 (td, J=8.0, 16 Hz, 1H), 2.60-2.69 (m, 1H), 2.60 (s, 3H), 1.85-1.94 (m, 1H)

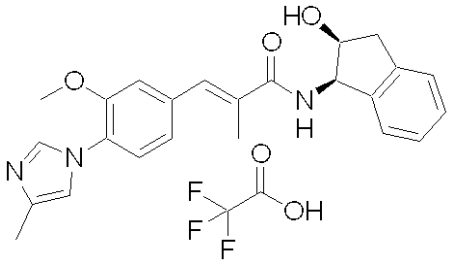
[0275]

Example 94

Synthesis of (E)-N-[(1R,1S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl acrylamide trifluoroacetic acid salt

[0276]

[Formula 87]



Synthesis of (E)-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-acrylic acid

250 mg of the title compound was obtained from 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (200 mg) obtained in Example 1 and diethyl-2-phosphonopropionic acidethyl ester (238 μL) by the same method as in Example 111. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 7.80 (d, J=1.2 Hz, 1H), 7.61 (d, J=1.2 Hz, 1H), 7.41 (d, J=7.4 Hz, 1H), 7.29 (d, J=1.6 Hz, 1H), 7.16 (dd, J=1.6 Hz, 7.4 Hz, 1H), 7.14-7.15 (m, 1H), 3.85 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H).

[0277]

Synthesis of (E)-N-[(1R, 2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-phenyl]-2-methylacrylamide trifluoroacetic-acid salt

To a DMF (3 mL) solution of (E)-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methylacrylic acid (60.0 mg), (1R,2S)-1-amino-2-indanol (39.4 mg), IPEA (0.05 mL), EDC (58 mg) and HOBT (41 mg) were added one by one, and the reaction solution was agitated at room temperature overnight. 55.5 mg of the title compound was obtained by purifying reaction solution by LC-MS as it was. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.66 (s, 1H), 7.48 (s, 1H), 7.24-7.39 (m, 5H), 7.02-7.15 (m, 3H), 6.68 (d, J=7.6 Hz, 1H), 5.53-5.57 (m, 1H), 4.76 (brs, 1H), 3.90 (s, 3H), 3.27 (dd, J=4.8, 16 Hz, 1H), 3.02 (d, J=16 Hz, 1H), 2.48 (s, 3H), 2.18 (s, 3H).

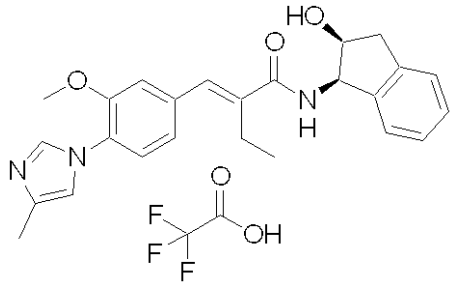
[0278]

Example 95

Synthesis of (E)-N-[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] butyl amide trifluoroacetic acid salt

[0279]

[Formula 88]



Synthesis of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid

269 mg of the title compound was obtained from (348 mg) by the same method as in Example 111 from 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (200 mg) and 2-(diethoxyphosphoryl)butyric acid ethyl ester obtained in Example 1. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 7.81 (d, J=1.2 Hz, 1H), 7.59 (s, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.25 (d, J=1.2 Hz, 1H), 7.16 (s, 1H), 7.11 (d, J=8.0 Hz, 1H), 3.86 (s, 3H), 2.16 (s, 3H), 1.11-1.19 (m, 5H)

[0280]

Synthesis of (E)-N-[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butylamide trifluoroacetic acid salt

26.0 mg of the title compound was obtained by the same method as in Example 111 from (E)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)butyl acid (20.0 mg) and (1R,2S)-1-amino-2-indanol (15.6 mg).

The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.69 (d, J=1.6 Hz, 1H), 7.28-7.36 (m, 6H), 7.04-7.06 (m, 3H), 6.68 (brd, J=7.6 Hz, 1H), 5.56 (dd, J=4.8, 7.6 Hz, 1H), 4.76 (dt, J=2.0, 4.8 Hz, 1H), 3.90 (s, 3H), 3.28 (dd, J=4.8, 16 Hz, 1H), 3.01 (dd, J=2.0, 16 Hz, 1H), 2.56-2.65 (m, 2H), 2.48 (s, 3H), 1.21 (t, J=7.6 Hz, 3H).

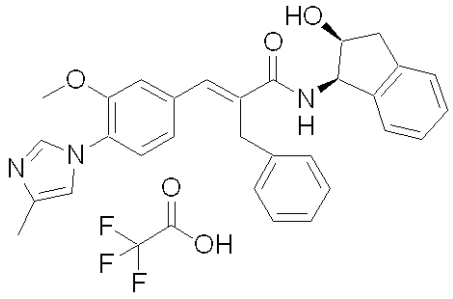
[0281]

Example 96

Synthesis of (E)-2-benzyl-N-[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0282]

[Formula 89]



Synthesis of (E)-2-benzyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid

315 mg of the title compound was obtained by the same method as in Example 111 from 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (200 mg) and 2-(diethoxyphosphoryl)-3-phenylpropionic acid ethyl ester (434 mg) obtained in Example 1. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 7.92 (s, 1H), 7.64 (s, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.28-7.35 (m, 3H), 7.16-7.23 (m, 5H), 3.92 (s, 2H), 3.69 (s, 3H), 2.30 (s, 3H).

[0283]

Synthesis of (E)-2-benzyl-N[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

19.3 mg of the title compound was obtained from (E)-2-benzyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (25.0 mg) and (1R,2S)1-amino-2-indanol (16.1 mg) by the same method as in Example 94. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.64 (s, 1H), 7.76 (s, 1H), 7.22-7.37 (m, 8H), 7.15 (td, J=3.6, 7.6 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 7.02-7.06 (m, 2H), 6.93 (d, J=7.2 Hz, 1H), 6.49 (brd, J=8.0 Hz, 1H), 5.44 (dd, J=5.2, 8.0 Hz, 1H), 4.59 (dt, J=1.6, 5.2 Hz, 1H), 4.00 (d, J=17 Hz, 1H), 3.99 (d, J=17 Hz, 1H), 3.71 (s, 3H), 3.16 (dd, J=5.2, 16 Hz, 1H), 2.90 (dd, J=1.6, 16 Hz, 1H), 2.46 (s, 3H).

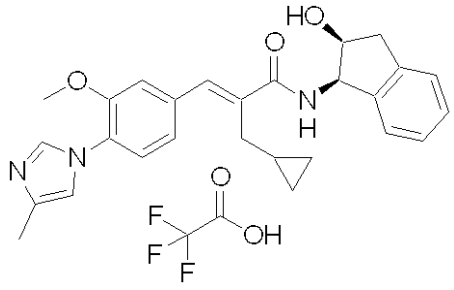
[0284]

Example 97

Synthesis of (E)-2-cyclopropylmethyl-N-[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0285]

[Formula 90]



Synthesis of (E)-2-cyclopropylmethyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid

102 mg of the title compound was by the same method as in Example 111 from 3-methoxy-4-(4-methylimidazol-1-yl)benzaldehyde (200 mg) obtained in Example 1 and 3-cyclopropyl-2-(diethoxyphosphoryl)propionic acid ethyl ester (384 mg). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 7.82 (s, 1H), 7.61 (s, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.31 (s, 1H), 7.17-7.18 (m, 2H), 3.86 (s, 3H), 2.15 (s, 3H), 2.45-2.50 (m, 2H), 0.90-0.98 (m, 1H), 0.39-0.43 (m, 2H), 0.12-0.16 (m, 2H).

[0286]

Synthesis of (E)-2-cyclopropylmethyl-N-[(1R,2S)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

11.5 mg of the title compound was obtained from (E)-2-cyclopropylmethyl-3-(3-methoxy-4-(4-methyl-

1H-imidazol-1-yl)phenyl)acrylic acid (20.0 mg) and (1R,2S)1-amino-2-indanol (11.5 mg) by the same method as in Example 94. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.72 (s, 1H), 7.28-7.40 (m, 6H), 7.07-7.10 (m, 3H), 6.79 (d, J=8.4 Hz, 1H), 5.56 (dd, J=5.2, 8.4 Hz, 1H), 4.77 (dt, J=2.4, 5.2 Hz, 1H), 3.91 (s, 3H), 3.28 (dd, J=5.2, 16 Hz, 1H), 3.02 (dd, J=2.4, 16 Hz, 1H), 2.54 (d, J=6.4 Hz, 2H), 2.48 (s, 3H), 0.88-0.96 (m, 1H), 0.50-0.60 (m, 2H), 0.18-0.26 (m, 2H).

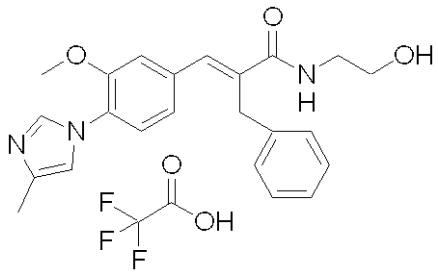
[0287]

Example 98

Synthesis of (E)-2-benzyl-N-(2-hydroxy ethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0288]

[Formula 91]



15.3 mg of the title compound was obtained from (E)-2-benzyl-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (25.0 mg) and ethanolamine (8.8 mg) by the same method as in Example 94. The physical properties of the compound are as follows.

ESI-MS; m/z392 [M^++H].

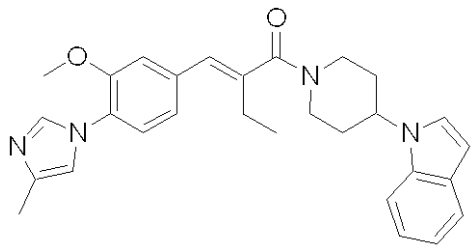
[0289]

Example 99

Synthesis of (E)-1-(4-indol-1-yl-piperidin-1-yl)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butan-1-one

[0290]

[Formula 92]



76.8 mg of the title compound was obtained from (E)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)butyric acid (60.0 mg) and 4-(1-indole)piperidine hydrochloride (74.6 mg) by the same method as in Example 111. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.69 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.18-7.25 (m, 3H), 7.12 (t, J=7.6 Hz, 1H), 6.92-6.96 (m, 3H), 6.53 (d, J=10 Hz, 2H), 4.65-4.95 (brs, 1H), 4.49-4.55 (m, 1H), 4.20-4.50 (br, 1H), 3.85 (s, 3H), 2.80-3.40 (br, 2H), 2.62-2.67 (m, 2H), 2.99 (s, 3H), 2.22-2.25 (m, 2H), 1.80-2.10 (br, 2H), 1.18 (t, J=7.2 Hz, 3H)

[0291]

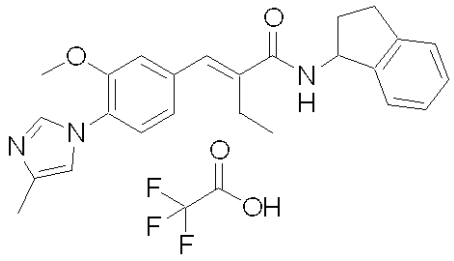
Example 100

Synthesis of (E)-N-indan-1-yl-2-[3-methoxy-4-(4-methyl-

1H-imidazol-1-yl]benzylidene)butyl amide trifluoroacetic acid salt

[0292]

[Formula 93]



6.95 mg of the title compound was obtained from (E)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)butyric acid (13.8 mg) and 1-aminoindane (9.6 mg) by the same method as in Example 111. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.63 (s, 1H), 7.22-7.35 (m, 5H), 7.17 (s, 1H), 7.00-7.02 (m, 3H), 6.08 (brd, J=7.6 Hz, 1H), 5.63 (q, J=7.6 Hz, 1H), 3.48 (s, 3H), 3.05 (ddd, J=4.0, 8.8, 16 Hz, 1H), 2.94 (dt, J=7.6, 16 Hz, 1H), 2.71 (dtd, J=4.0, 7.6, 16 Hz, 1H), 2.51-2.59 (m, 2H), 2.47 (s, 3H), 1.86-1.95 (m, 1H), 1.20 (t, J=7.6 Hz, 3H).

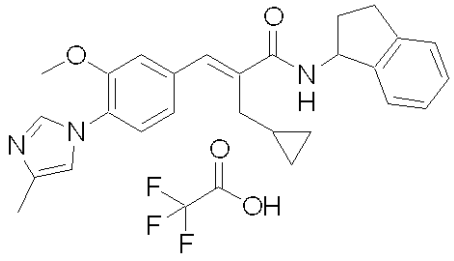
[0293]

Example 101

Synthesis of (E)-2-cyclopropyl methyl-N-indan-1-yl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0294]

[Formula 94]



6.23 mg of the title compound was obtained from (E)-2-cyclopropyl methyl-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (15.0 mg) and 1-aminoindane (9.6 mg) by the same method as in Example 94. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.67 (s, 1H), 7.22-7.36 (m, 5H), 7.18 (s, 1H), 7.04-7.05 (m, 3H), 6.24 (brd, J=7.6 Hz, 1H), 5.62 (q, J=7.6 Hz, 1H), 3.89 (s, 3H), 3.05 (ddd, J=4.0, 8.4, 16 Hz, 1H), 2.93 (dt, J=8.0, 16 Hz, 1H), 2.71 (dtd, J=4.0, 7.6, 16 Hz, 1H), 2.50 (d, J=6.4 Hz, 2H), 2.47 (s, 3H), 1.88-1.97 (m, 1H), 0.82-0.91 (m, 1H), 0.52-0.56 (m, 2H), 0.18-0.22 (m, 2H)

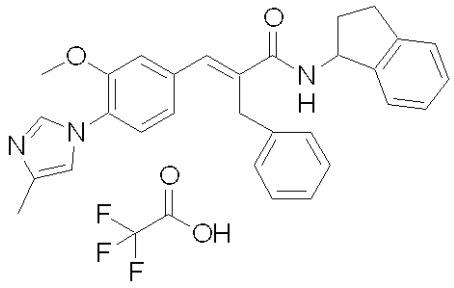
[0295]

Example 102

Synthesis of (E)-2-benzyl-N-indan-1-yl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0296]

[Formula 95]



6.76 mg of the title compound was obtained from (E)-2-benzyl-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (17.0 mg) and 1-aminoindane (9.6 mg) by the same method as in Example 94. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.61 (d, J=2.0 Hz, 1H), 7.71 (s, 1H), 7.20-7.37 (m, 7H), 7.05-7.13 (m, 3H), 6.99-7.01 (m, 2H), 6.87 (d, J=7.2 Hz, 1H), 5.95 (brd, J=7.6 Hz, 1H), 5.50 (q, J=7.6 Hz, 1H), 3.98 (d, J=16 Hz, 1H), 3.88 (d, J=16 Hz, 1H), 3.68 (s, 3H), 2.80-2.94 (m, 2H), 2.59 (dtd, J=4.0, 7.2, 13 Hz, 1H), 2.46 (s, 3H), 1.62-1.71 (m, 1H).

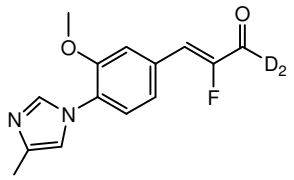
[0297]

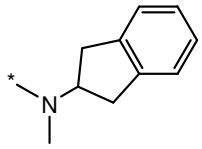
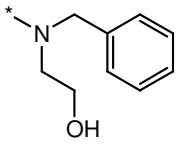
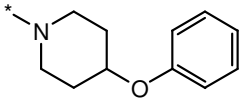
The compounds shown in Table 5 were synthesized as in Example 85.

The structural formulae and physicochemical properties are shown in Table 5, respectively.

[0298]

[Table 5]



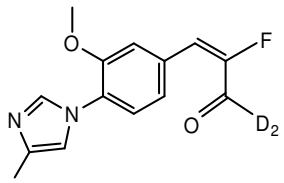
Example	D_2	DATA:MS m/z
103		M^++H:406 (ESI)
104		M^++H:410 (ESI)
105		M^++H:436 (ESI)

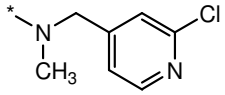
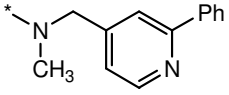
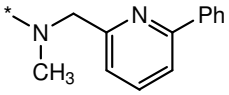
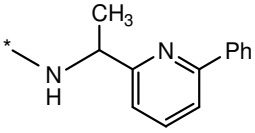
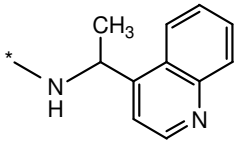
[0299]

The compounds shown in Table 6 were synthesized as in Example 474. The structured formulae and physicochemical properties are shown in Table 6, respectively.

[0300]

[Table 6]



Example	D_2	DATA:MS m/z
106		M^++H:415 (ESI)
107		M^++H:457 (ESI)
108		M^++H:457 (ESI)
109		M^++H:457 (ESI)
110		M^++H:431 (ESI)

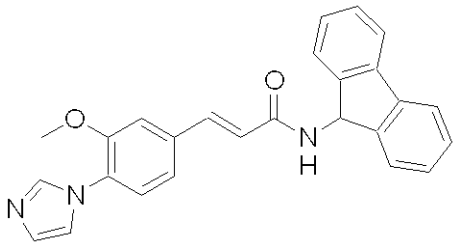
[0301]

Example 111

Synthesis of (E)-N-(9H-fluoren-9-yl)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylamide

[0302]

[Formula 96]



Synthesis of 4-(1H-imidazol-1-yl)-3-methoxybenzaldehyde

Potassium carbonate (6.70 g) and imidazole (2.60 g) were added to a DMF (30 mL) solution of 4-fluoro-3-methoxybenzaldehyde (5.00 g) one by one, and the reaction solution was agitated at 130°C overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 4.76 g of crude aldehyde compounds was obtained by condensing under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 10.01 (s, 1H), 7.92 (s, 1H), 7.57-7.60 (m, 2H), 7.49 (d, J=7.6 Hz, 1H), 7.29 (s, 1H), 7.21 (s, 1H), 3.98 (s, 3H).

[0303]

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl)acrylic acid

Dimethylphosphonoacetic acid methyl ester (3.80 mL) and lithium hydroxide monohydrate (1.20 g) were added one by one to a THF (20 mL) solution of the crude aldehyde compound (4.76 g) obtained above, and the reaction solution was agitated overnight at the room temperature. 2N sodium hydroxide solution was added to the reaction solution after confirming disappearance of the starting materials (20 mL), and the reaction solution was agitated at 50°C for 2 hours. The reaction solution was cooled to 0°C, 2N hydrochloric acid was added to the reaction solution (20 mL), and deposited precipitation was separated by filtering with Kiriyama funnel. The obtained precipitation was washed with water and ethyl acetate, and 4.2 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 7.96 (s, 1H), 7.63 (d, J=16 Hz, 1H), 7.60 (d, J=1.6 Hz, 1H), 7.48 (s, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.39 (dd, J=1.6, 8.0 Hz, 1H), 7.06 (s, 1H), 6.68 (d, J=16 Hz, 1H), 3.90 (s, 3H).

[0304]

(E)-N-(9H-fluoren-9-yl)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylicamide

To a DMF (70 mL) solution of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl)acrylic acid (3.50 g),

9-aminofluorene (2.40 g), IPEA (7.5 mL), EDC (3.00 g) and HOBT (2.10 g) were added one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane : ethyl acetate = 1:1 -> ethyl acetate -> ethyl acetate : ethanol = 10:1), and 2.20 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.80 (s, 1H), 7.76 (d, J=16 Hz, 1H), 7.72 (d, J=7.2 Hz, 2H), 7.63 (d, J=7.2 Hz, 2H), 7.42 (t, J=7.2 Hz, 2H), 7.32 (dt, J=1.2 Hz, 7.2 Hz, 2H), 7.28 (d, J=8.4 Hz, 1H), 7.19-7.22 (m, 2H), 7.16-7.17 (m, 2H), 6.47 (d, J=16 Hz, 1H), 6.39 (d, J=8.8 Hz, 1H), 6.00 (d, J=8.8 Hz, 1H), 3.88 (s, 3H).

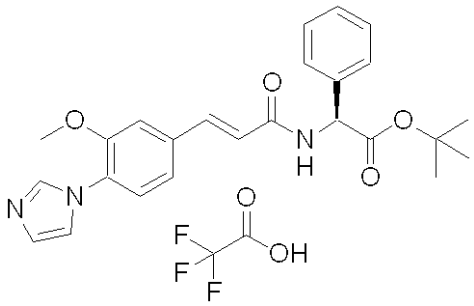
[0305]

Example 112

Synthesis of (E)-{3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acryloylamino}-(S)-phenylacetic acid tert-butyl ester trifluoroacetic acid salt

[0306]

[Formula 97]



By the same method as in Example 94, 14.0 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (20.0 mg) and (S)-2-phenylglycine-tert-butyl ester (25.0 mg). The physical properties of the compound are as follows. ^{1}H-NMR (CD_3OD) δ (ppm): 9.19 (t, J=1.6 Hz, 1H), 7.79 (t, J=1.6 Hz, 1H), 7.63 (t, J=1.6 Hz, 1H), 7.52 (d, J=16 Hz, 1H), 7.50 (d, J=8.4 Hz, 1H), 7.40 (d, J=1.6 Hz, 1H), 7.26-7.36 (m, 6H), 7.32 (d, J=16 Hz, 1H), 5.38 (s, 1H), 3.88 (s, 3H), 1.32 (s, 9H).

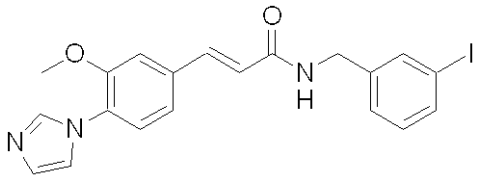
[0307]

Example 113

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-(3-iodo-benzyl)acrylamide

[0308]

[Formula 98]



By the same method as in Example 111, 1.40 g

of the title compound was obtained from (E)-3-(4-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (1.00 g) and 3-iodobenzylamine (550 μL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.76 (s, 1H), 7.65 (s, 1H), 7.64 (d, J=15.2 Hz, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.20 (t, J=1.6 Hz, 1H), 7.11-7.16 (m, 3H), 7.04 (t, J=8.0 Hz, 1H), 6.94 (brs, 1H), 6.54 (d, J=15.2 Hz, 1H), 4.51 (d, J=6.0 Hz, 2H), 3.84 (s, 3H).

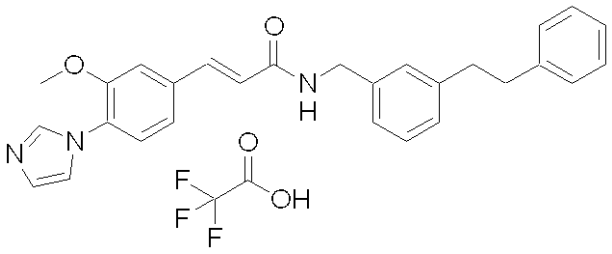
[0309]

Example 114

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-(3-phenethyl-benzyl)acrylamide trifluoroacetic acid salt

[0310]

[Formula 99]



By the same method as in Example 94, 2.30 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (10.0 mg) and 3-phenethyl-benzylamine hydrochloride (14.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.29 (t, J=1.6 Hz, 1H), 7.89 (t,

J=1.6 Hz, 1H), 7.73 (t, J=1.6 Hz, 1H), 7.62 (d, J=16 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.50 (d, J=1.6 Hz, 1H), 7.40 (dd, J=1.2, 8.0 Hz, 1H), 7.08-7.25 (m, 9H), 6.78 (d, J=16 Hz, 1H), 4.48 (s, 2H), 3.98 (s, 3H), 2.90 (s, 4H).

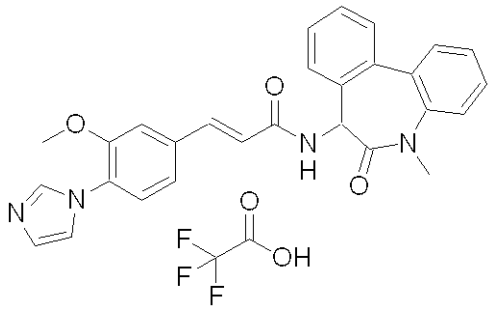
[0311]

Example 115

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)acrylamide trifluoroacetic acid salt

[0312]

[Formula 100]



By the same method as in Example 94, 2.7 mg of the title compound was obtained from (E)-3-(4-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (6.20 mg) and 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one (6.00 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.31 (t, J=1.6 Hz, 1H), 7.90 (t, J=1.6 Hz, 1H), 7.74 (t, J=1.6 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.67 (d, J=3.6, 5.6 Hz, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.61 (d, J=16 Hz, 1H), 7.55-7.58 (m, 3H),

7.40-7.50 (m, 5H), 7.20 (d, J=16 Hz, 1H), 5.46 (s, 1H), 4.00 (s, 3H), 3.37 (s, 3H).

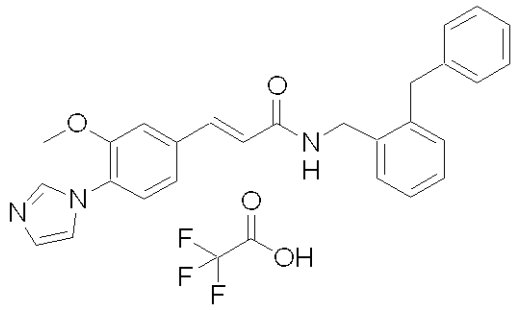
[0313]

Example 116

Synthesis of (E)-N-(2-benzylbenzyl)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylamide trifluoroacetic acid salt

[0314]

[Formula 101]



By the same method as in Example 94, 7.2 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (10.0 mg) and 2-benzylbenzylamine (12.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.29 (t, J=1.6 Hz, 1H), 7.88 (t, J=1.6 Hz, 1H), 7.73 (t, J=1.6 Hz, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.55 (d, J=16 Hz, 1H), 7.45 (d, J=1.6 Hz, 1H), 7.36 (dd, J=1.6, 8.0 Hz, 1H), 7.32-7.34 (m, 1H), 7.19-7.27 (m, 5H), 7.12-7.15 (m, 3H), 6.65 (d, J=16 Hz, 1H), 4.49 (s, 2H), 4.10 (s, 2H), 3.97 (s, 3H).

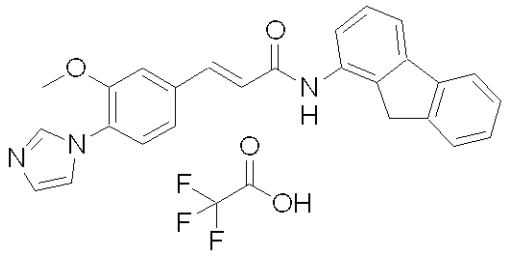
[0315]

Example 117

Synthesis of (E)-N-(9H-fluoren-1-yl)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylamide trifluoroacetic acid salt

[0316]

[Formula 102]



By the same method as in Example 94, 14.0 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (20.0 mg) and 1-aminofluorene (22 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.29 (s, 1H), 7.98 (s, 1H), 7.89 (t, J=1.6 Hz, 1H), 7.72-7.80 (m, 3H), 7.74 (t, J=1.6 Hz, 1H), 7.63 (d, J=8.0 Hz, 2H), 7.53-7.54 (m, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.35 (t, J=7.6 Hz, 1H), 7.26 (dt, J=1.2, 7.6 Hz, 1H), 6.96 (d, J=16 Hz, 1H), 4.01 (s, 3H), 3.92 (s, 2H).

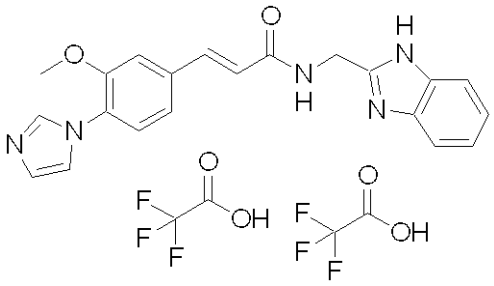
[0317]

Example 118

Synthesis of (E)-N-(1H-benzoimidazol-2-ylmethyl)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylamide nitrilofluoroacetic acid salt

[0318]

[Formula 103]



By the same method as in Example 94, 3.00 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (20.0 mg) and 2-(aminomethyl)benzimidazole dihydrochloride (26.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.28 (d, J=1.6 Hz, 1H), 7.89 (t, J=1.6 Hz, 1H), 7.55-7.61 (m, 2H), 7.74 (t, J=1.6 Hz, 1H), 7.70 (d, J=16 Hz, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.73-7.78 (m, 2H), 7.53 (d, J=1.6, 1H), 7.44 (dd, J=1.6, 8.0 Hz, 1H), 6.90 (d, J=16 Hz, 1H), 4.98 (s, 2H), 3.99 (s, 3H).

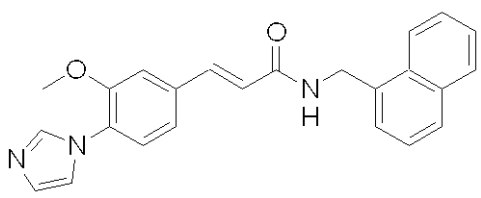
[0319]

Example 119

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-naphthalen-1-ylmethyl-acrylamide

[0320]

[Formula 104]



By the same method as in Example 111, 1.90 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (20.0 mg) and 1-naphthalenemethylamine (19.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.06 (d, J=8.4 Hz, 1H), 7.89 (d, J=7.6 Hz, 1H), 7.86 (d, J=12.4 Hz, 1H), 7.79 (s, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.42-7.58 (m, 4H), 7.11-7.30 (m, 5H), 6.38 (d, J=15.6 Hz, 1H), 5.86 (brs, 1H), 5.05 (d, J=5.2 Hz, 2H), 3.85 (s, 3H)

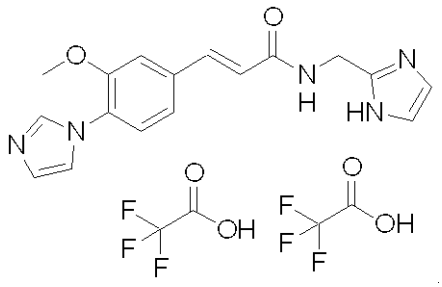
[0321]

Example 120

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-(1H-imidazole-2-ylmethyl)acrylamide nitrilofluoroacetic acid salt

[0322]

[Formula 105]



15.7 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (15.0 mg) and (1H-imidazole-2-yl)-methylamine dihydrochloride (15.3 mg) by the same method as in Example 94. The physical properties of

the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.29 (t, J=1.6 Hz, 1H), 7.88 (t, J=1.6 Hz, 1H), 7.74 (t, J=1.6 Hz, 1H), 7.66 (d, J=16 Hz, 1H), 7.61 (d, J=8.0 Hz, 1H), 7.51 (d, J=1.6 Hz, 1H), 7.48 (s, 2H), 7.42 (dd, J=1.6, 8.0 Hz, 1H), 6.84 (d, J=16 Hz, 1H), 4.78 (s, 2H), 3.99 (s, 3H)

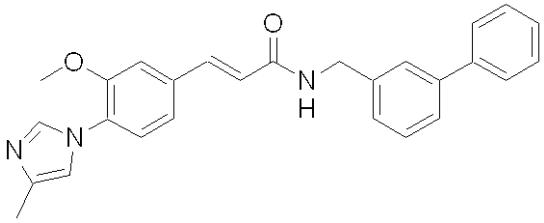
[0323]

Example 121

Synthesis of (E)-N-biphenyl-3-ylmethyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0324]

[Formula 106]



Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid

To a THF (40 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (4.00 g) obtained in Example 1, diethylphosphonoacetic acid ethyl ester (4.00 mL) and lithium hydroxide monohydrate (932 mg) were added one by one, and the reaction solution was agitated overnight at room temperature. 2N sodium hydroxide solution (30 mL) and ethanol (5 mL) were added to the reaction solution after confirming disappearance of the starting materials, and the

reaction solution was agitated at room temperature overnight. The reaction solution was cooled to 0°C, 2N hydrochloric acid (30 mL) was added to the reaction solution, and the precipitation consequently deposited was separated by filtering with Kiriyama funnel. The obtained precipitation was washed with water and ethyl acetate, and 4.61 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 7.81 (s, 1H), 7.60 (d, J=16 Hz, 1H), 7.56 (s, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.16 (s, 1H), 6.66 (d, J=16 Hz, 1H), 3.88 (s, 3H), 2.15 (s, 3H).

[0325]

Synthesis of (E)-N-biphenyl-3-ylmethyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

To a DMF (30 mL) solution of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (2.20 g), 3-phenylbenzylamine hydrochloride (2.30 g), IPEA (4.57 mL), EDC (1.96 g) and HOBT (1.38 g) were added one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography

(elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 3.30 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.71 (d, J=1.2 Hz, 1H), 7.67 (d, J=16 Hz, 1H), 7.52-7.60 (m, 4H), 7.42-7.46 (m, 3H), 7.37 (td, J=1.2, 7.6 Hz, 1H), 7.33 (brd, J=7.6 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.17 (dd, J=1.6 Hz, 6.4 Hz, 1H), 7.13 (d, J=1.6 Hz, 1H), 6.93 (t, J=1.2 Hz, 1H), 6.45 (d, J=16 Hz, 1H), 6.09 (brs, 1H), 4.67 (d, J=5.6 Hz, 2H), 3.87 (s, 3H), 2.29 (s, 3H).

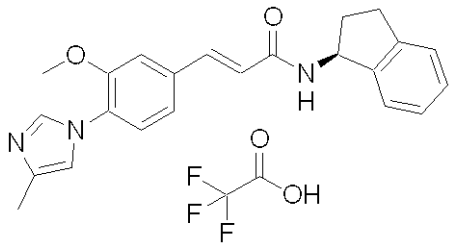
[0326]

Example 122

Synthesis of (E)-N-[(1S)-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0327]

[Formula 107]



To a DMF (0.8 mL) solution of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (15.0 mg), (S)-(+)-1-aminoindan (12.0 mg), IPEA (30 μL), EDC (16.7 mg), and HOBT (11.8 mg) were added one by one, and the reaction solution was agitated at

room temperature for 3 hours. After confirming disappearance of the starting materials, the reaction solution was purified by LC-MS, and 6.6 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 9.15 (d, J=2.0 Hz, 1H), 8.57 (d, J=8.4 Hz, 1H), 7.65 (d, J=16 Hz, 1H), 7.59 (t, J=1.2 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.48 (d, J=1.6 Hz, 1H), 7.34 (dd, J=1.6, 6.8 Hz, 1H), 7.18-7.29 (m, 4H), 6.77 (d, J=16 Hz, 1H), 5.50-5.55 (m, 1H), 3.97 (s, 3H), 3.05 (ddd, J=4.4, 8.8, 16 Hz, 1H), 2.90 (td, J=7.6, 16 Hz, 1H), 2.57 (dtd, J=4.4, 7.6, 16 Hz, 1H), 2.43 (s, 3H), 1.88-1.97 (m, 1H).

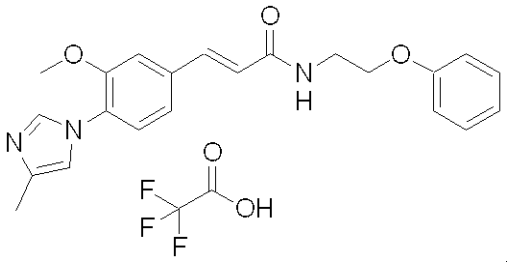
[0328]

Example 123

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-(2-pheoxy ethyl)acrylamide trifluoroacetic acid salt

[0329]

[Formula 108]



By the same method as in Example 94, 5.3 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic

acid (15.0 mg) and 2-pheoxyethylamine (13.0 μL). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.13 (d, J=1.6 Hz, 1H), 8.50 (t, J=5.6 Hz, 1H), 7.54-7.61 (m, 3H), 7.47 (d, J=2.0 Hz, 1H), 7.37 (dd, J=2.0, 8.4 Hz, 1H), 7.20-7.31 (m, 2H), 6.90-6.98 (m, 3H), 6.79 (d, J=15.6 Hz, 1H), 4.12 (t, J=5.6 Hz, 2H), 3.97 (s, 3H), 3.69-3.74 (m, 2H), 2.43 (s, 3H).

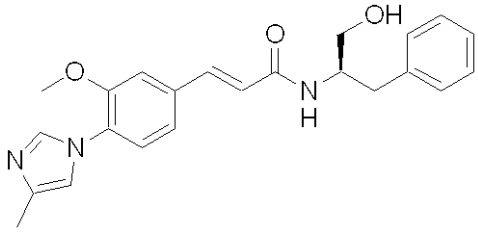
[0330]

Example 124

Synthesis of (E)-N-[(1R)-1-hydroxymethyl-2-phenylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0331]

[Formula 109]



By the same method as in Example 121, 262 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (200 mg) and D-phenylalanilol (176 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.69 (d, J=1.6 Hz, 1H), 7.56 (d, J=15.6 Hz, 1H), 7.20-7.33 (m, 5H), 7.18 (d, J=8.0 Hz, 1H), 7.06-7.10 (m, 2H), 6.91 (t, J=1.2 Hz, 1H), 6.34

(d, J=15.6 Hz, 1H), 6.18 (d, J=7.6 Hz, 1H), 4.31-4.36 (m, 1H), 3.84 (s, 3H), 3.79 (dd, J=3.2, 11 Hz, 1H), 3.68 (dd, J=4.8, 11 Hz, 1H), 2.98 (d, J=7.2 Hz, 2H), 2.29 (s, 3H).

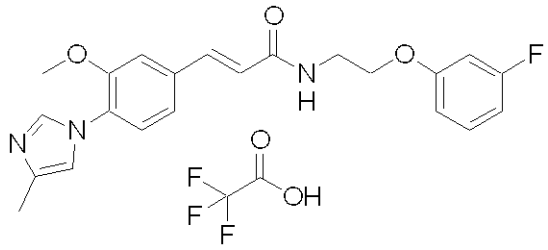
[0332]

Example 125

Synthesis of (E)-N-[2-(3-fluoro-pheoxy)-ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0333]

[Formula 110]



By the same method as in Example 94, 2.10 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and 2-(3-fluoropheoxy) ethyl amine (13.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 8.89 (s, 1H), 7.59 (d, J=16 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.49 (m, 1H), 7.45 (d, J=1.6 Hz, 1H), 7.36 (dd, J=1.6, 8.4 Hz, 1H), 7.26 (dt, J=6.8, 8.0 Hz, 1H), 6.76-6.79 (m, 1H), 6.65-6.75 (m, 3H), 4.12 (t, J=5.2 Hz, 2H), 3.96 (s, 3H), 3.72 (t, J=5.2 Hz, 2H), 2.39 (s, 3H).

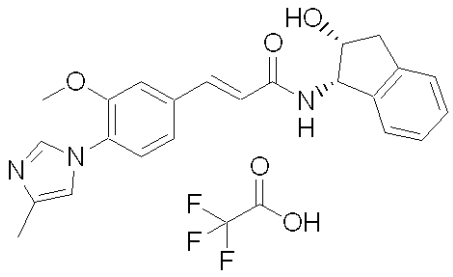
[0334]

Example 126

Synthesis of (E)-N-[(1S,2R)-2-hydroxy-indan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-phenyl]acrylamide trifluoroacetic acid salt

[0335]

[Formula 111]



By the same method as in Example 94, 8.40 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (15.0 mg) and (1S, 2R)-1-amino-2-indanol (13.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.14 (d, J=1.2 Hz, 1H), 8.26 (d, J=8.8 Hz, 1H), 7.67 (d, J=16 Hz, 1H), 7.59 (m, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.52 (d, J=1.6 Hz, 1H), 7.41 (dd, J=1.2, 8.8 Hz, 1H), 7.21-7.29 (m, 3H), 6.98 (d, J=16 Hz, 1H), 5.47 (q, J=5.6 Hz, 1H), 4.63 (dt, J=2.0, 5.6 Hz, 1H), 3.98 (s, 3H), 3.20 (dd, J=5.6, 16 Hz, 1H), 2.87 (dd, J=2.0, 16 Hz, 1H), 2.44 (s, 3H).

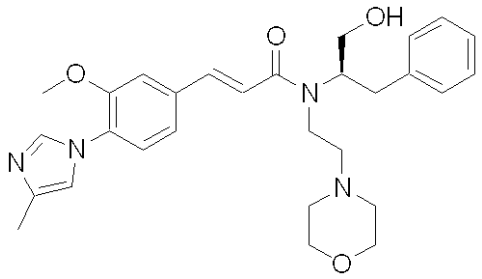
[0336]

Example 127

Synthesis of (E)-N-[(1R)-1-hydroxymethyl-2-phenyl-ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-(2-morpholin-4-yl-ethyl)acrylamide

[0337]

[Formula 112]



Synthesis of (2R)-2-(2-morpholin-4-yl-ethylamino)-3-phenylpropan-1-ol

Sodium iodide (84.5 mg) and sodium hydride (676 mg) and 4-(2-chloroethyl)morpholine hydrochloride (2.1 g) were added to a DMF (20 mL) solution of (R)-4-benzyl-2-oxazolidinone (1.0 g) at 0°C, and the reaction solution was warmed to 60°C and agitated for 3 hours. After agitating the reaction solution at room temperature overnight, water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent:heptane-ethyl acetate = 2:1), and 1.62 g of oxazolidinone compound was obtained. Next, lithium hydroxide (1.61 g) was added to a solution of

the obtained oxazolidinone in ethanol (14 mL) and water (6.0 mL), and the reaction solution was refluxed for 6 hours and 30 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was washed with a saturated salt solution, dried over anhydrous magnesium sulfate, and 549 mg of crude amine compounds was obtained by condensing under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.14–7.32 (m, 5H), 3.67–3.76 (m, 1H), 3.64 (dd, J=4.8, 10 Hz, 1H), 3.51–3.62 (m, 3H), 3.39 (dd, J=5.6, 10 Hz, 1H), 2.86–2.92 (m, 1H), 2.70–2.80 (m, 2H), 2.62–2.68 (m, 2H), 2.42–2.54 (m, 2H), 2.28–2.36 (m, 6H).

[0338]

Synthesis of (E)-N-[(1R)-1-hydroxymethyl-2-phenyl-ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-(2-morpholin-4-yl-ethyl)-acrylamide

18.1 mg of the title compound was obtained by the same method as the in Example 111 from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and (2R)-2-(2-morpholin-4-yl-ethylamino)-3-phenyl-propan-1-ol (23.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.71 (d, J=1.2 Hz, 1H), 7.25–7.29 (m, 1H), 7.14–7.22 (m, 4H), 6.92–7.05 (m, 5H), 6.48 (d, J=15 Hz, 1H), 4.27–4.36 (m, 1H), 3.87 (s, 3H), 3.60–3.86 (m, 7H), 3.52–3.58 (m, 1H), 3.06–3.26 (m,

2H), 2.63-2.76 (m, 4H), 2.42-2.54 (m, 3H), 2.30 (s, 3H).

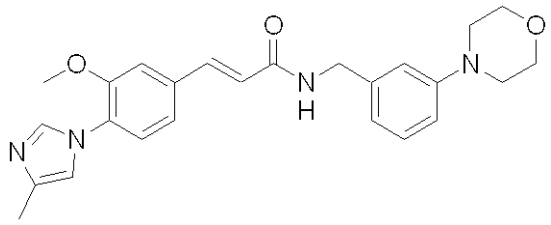
[0339]

Example 128

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-[3-(morpholin-4-yl-benzyl)acrylamide

[0340]

[Formula 113]



By the same method as in Example 121, 12.0 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and (3-morpholin-4-yl)benzylamine (17.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.70 (d, J=1.2 Hz, 1H), 7.65 (d, J=16 Hz, 1H), 7.23-7.27 (m, 2H), 7.16 (dd, J=1.6, 8.4 Hz, 1H), 7.11 (d, J=1.6 Hz, 1H), 6.91 (t, J=1.2 Hz, 1H), 6.836.88 (m, 3H), 6.40 (d, J=16 Hz, 1H), 5.93 (brs, 1H), 4.54 (d, J=5.6 Hz, 2H), 3.87 (s, 3H), 3.85 (t, J=4.8 Hz, 4H), 3.16 (t, J=4.8 Hz, 4H), 2.29 (s, 3H)

[0341]

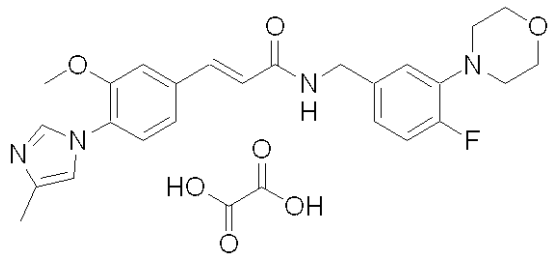
Example 129

Synthesis of (E)-N-(4-fluoro-3-morpholin-4-yl-benzyl)-

3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide oxalic acid salt

[0342]

[Formula 114]



By the same method as in Example 121, free compound of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (200 mg) and 4-fluoro-3-morpholin-4-yl-benzylamine (165 mg). 221 mg of the title compound was obtained by adding 1 equivalent of oxalic acid to a methanol (2 mL) solution of the obtained free compound, and reaction solvent was removed. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 8.59 (t, J=6.0 Hz, 1H), 8.07 (brs, 1H), 7.50 (d, J=15.6 Hz, 1H), 7.427.44 (m, 2H), 7.27 (dd, J=1.6, 8.4 Hz, 1H), 7.26-7.28 (m, 1H), 7.09 (dd, J=8.4, 12.8 Hz, 1H), 6.98 (dd, J=1.6, 8.4 Hz, 1H), 6.88-6.91 (m, 1H), 6.75 (d, J=15.6 Hz, 1H), 4.35 (d, J=5.6 Hz, 2H), 3.87 (s, 3H), 3.74 (t, J=4.8 Hz, 4H), 2.99 (t, J=4.8 Hz, 4H), 2.18 (s, 3H).

[0343]

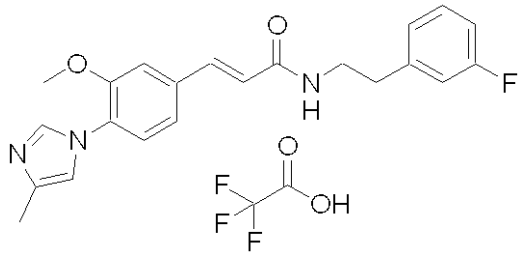
Example 130

Synthesis of (E)-N-[2-(3-fluorophenyl)ethyl]-3-[3-

methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0344]

[Formula 115]



By the same method as in Example 94, 3.1 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and 2-(3-fluorophenyl)ethyl amine (12.0 μL). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.05 (s, 1H), 7.56 (d, J=15.6 Hz, 1H), 7.54 (dd, J=8.4 Hz, 1H), 7.45 (d, J=1.6 Hz, 1H), 7.35 (dd, J=1.6, 8.4 Hz, 1H), 7.29 (dd, J=6.0, 8.0 Hz, 1H), 7.07 (d, J=8.0 Hz, 1H), 7.00 (d, J=10.0 Hz, 1H), 6.94 (dt, J=1.6, 8.0 Hz, 1H), 6.68 (d, J=15.6 Hz, 1H), 3.96 (s, 3H), 3.56 (t, J=7.2 Hz, 2H), 2.89 (t, J=7.2 Hz, 2H), 2.41 (s, 3H).

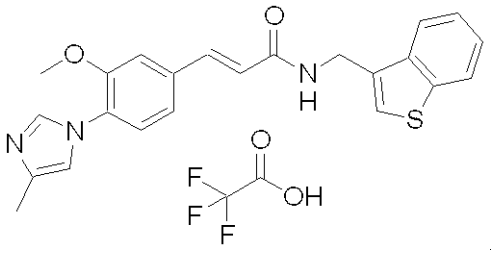
[0345]

Example 131

Synthesis of (E)-N-(benzo[B]thiophen-3-ylmethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide trifluoroacetic acid salt

[0346]

[Formula 116]



By the same method as in Example 94, 1.40 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and 1-benzo[B]thiophen-3-ylmethylamine hydrochloride (17.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.05 (s, 1H), 7.86-7.90 (m, 2H), 7.64 (d, J=16 Hz, 1H), 7.51-7.54 (m, 3H), 7.46 (d, J=1.2 Hz, 1H), 7.35-7.42 (m, 3H), 6.75 (d, J=16 Hz, 1H), 4.78 (s, 2H), 3.96 (s, 3H), 2.41 (s, 3H).

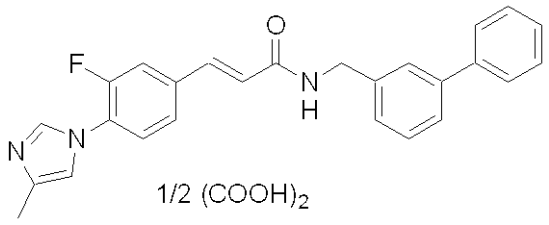
[0347]

Example 132

Synthesis of (E)-N-(biphenyl-3-ylmethyl)-3-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide 1/2 oxalic acid salt

[0348]

[Formula 117]



By the same method as in Example 121, 118 mg of the title compound was obtained from (E)-3-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (60.0 mg) and 3-phenylbenzylamine hydrochloride (80.0m). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 8.75 (t, J=4.8 Hz, 1H), 8.48 (s, 1H), 7.527.68 (m, 8H), 7.41-7.44 (m, 4H), 7.31-7.35 (m, 2H), 6.76 (d, J=16 Hz, 1H), 4.86 (s, 3H), 4.58 (d, J=4.8 Hz, 2H).

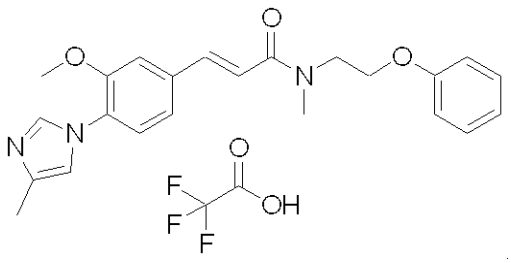
[0349]

Example 133

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl-N-(2-pheoxy ethyl)acrylamide trifluoroacetic acid salt

[0350]

[Formula 118]



By the same method as in Example 94, 41.0 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (70.0 mg) and methyl-(2-pheoxy ethyl)amine (61.0 mg). The physical properties of the compound are as

follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.12 (s, 1H), 7.21-7.63 (m, 8H), 6.87-6.95 (m, 3H), 4.20-4.24 (m, 2H), 4.02 (t, J=4.8 Hz, 1H), 3.98 (s, 1.5H), 3.95 (s, 1.5H), 3.89 (t, J=5.6 Hz, 1H), 3.38 (s, 1.5H), 3.15 (s, 1.5H), 2.42 (s, 3H).

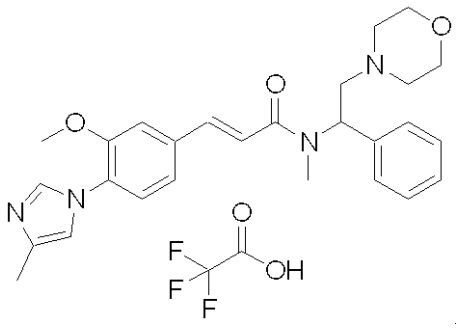
[0351]

Example 134

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl-N-(2-morpholin-4-yl-1-phenylethyl)acrylamide trifluoroacetic acid salt

[0352]

[Formula 119]



By the same method as in Example 94, 139 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (70.0 mg) and a DMF solution (405 μL) of methyl-(2-morpholin-4-yl-phenylethyl)amine of 10mM(s). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.16 (d, J=1.2 Hz, 1H), 7.74 (d, J=16 Hz, 1H), 7.56-7.59 (m, 3H), 7.35-7.47 (m, 6H), 7.2 (d, J=15 Hz, 1H), 6.49 (dd, J=2.8, 12 Hz, 1H), 4.16 (t,

J=12 Hz, 1H), 3.98 (s, 3H), 3.83 (dd, J=2.8, 12 Hz, 1H), 3.81-4.20 (m, 8H), 2.94 (s, 3H), 2.43 (s, 3H)

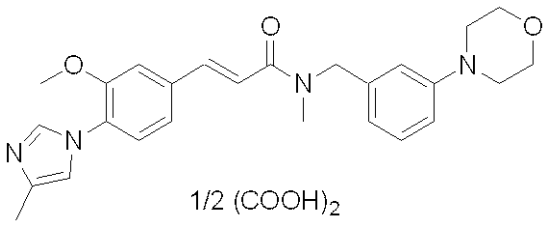
[0353]

Example 135

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl-N-(3-morpholin-4-yl-1-benzyl)acrylamide 1/2 oxalic acid salt

[0354]

[Formula 120]



By the same method as in Example 121, 132 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (68.0 mg) and N-methyl-N-[3-morpholin-4-yl)benzyl]amine (76.0 mg). The physical properties of the compound are as follows.

1H-NMR (DMSO-d6) δ (ppm): 8.01 (brs, 1H), 7.55-7.60 (m, 2H), 7.40-7.44 (m, 2H), 7.32-7.36 (m, 1H), 7.18-7.26 (m, 2H), 6.84-6.86 (m, 2H), 6.65-6.71 (m, 1H), 4.78 (s, 1H), 4.58 (s, 1H), 3.90 (s, 1.5H), 3.87 (s, 1.5H), 3.69-3.74 (m, 4H), 3.12 (s, 1.5H), 3.07-3.10 (m, 4H), 2.93 (s, 1.5H), 2.18 (s, 3H)

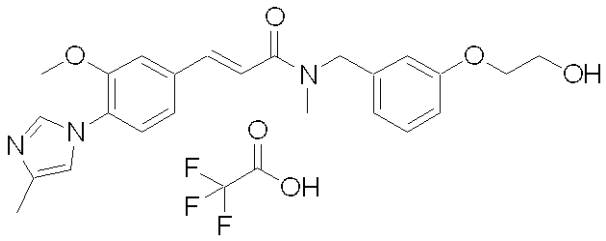
[0355]

Example 136

Synthesis of (E)-N-[3-(2-hydroxy-ethoxy)-benzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl-acrylamide trifluoroacetic acid salt

[0356]

[Formula 121]



By the same method as in Example 94, 36.1 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (20.0 mg) and 2-(3-methylaminomethylpheoxy) ethanol (21.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.72 (s, 0.5H), 8.69 (s, 0.5H), 7.75 (d, J=12 Hz, 0.5H), 7.72 (d, J=12 Hz, 0.5H), 7.28-7.36 (m, 2H), 7.20-7.21 (m, 1H), 6.97-7.12 (m, 2H), 6.79-6.91 (m, 4H), 4.71 (s, 1H), 4.69 (s, 1H), 4.07-4.12 (m, 2H), 3.96-4.00 (m, 2H), 3.95 (s, 1.5H), 3.90 (s, 1.5H), 3.13 (s, 1.5H), 3.12 (s, 1.5H), 2.48 (s, 1.5H), 2.47 (s, 1.5H).

[0357]

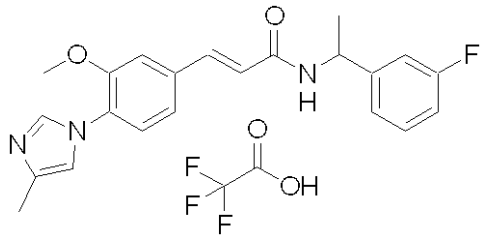
Example 137

Synthesis of (E)-N-[1-(3-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

trifluoroacetic acid salt

[0358]

[Formula 122]



By the same method as in Example 94, 17.3 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (20.0 mg) and 1-(3-fluorophenyl)ethyl amine (16.2 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.68 (d, J=1.6 Hz, 1H), 7.63 (d, J=16 Hz, 1H), 7.30-7.35 (m, 2H), 7.22-7.26 (m, 1H), 7.19 (d, J=1.6 Hz, 1H), 7.15 (dd, J=1.2, 8.4 Hz, 1H), 6.99-7.08 (m, 2H), 6.97 (dt, J=2.4, 8.4 Hz, 1H), 6.55 (d, J=16 Hz, 1H), 6.02-6.08 (brs, 1H), 5.27 (qu, J=7.2 Hz, 1H), 3.99 (s, 3H), 2.47 (s, 3H), 1.57 (d, J=7.2 Hz, 3H).

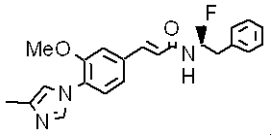
[0359]

Example 139

Synthesis of (E)-N-[(1R)-fluoromethyl-2-phenylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

[0360]

[Formula 360]



Synthesis of (R)-2-(1-fluoromethyl-2-phenylethyl)isoindol-1,3-dione

(R)-2-(1-hydroxymethyl-2-phenylethyl)isoindole-1,3-dione (1.20 g) was added to a methylene chloride (20 mL) solution of DAST (825 mg) at -78°C and the reaction solution was agitated at room temperature. DAST (500 mg) was added to the reaction solution after 2 hours, and the reaction solution was agitated at 50°C for 3 hours. Saturated sodium bicarbonate solution was added for reaction solution to the reaction solution after allowing the reaction solution to be cooled to room temperature, and the organic layer was partitioned. The organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (heptane-ethyl acetate system), and 52 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ(ppm): 3.16 (dd, J=14.0, 6.4 Hz, 1H), 3.28 (dd, J=14.0, 9.6 Hz, 1H), 4.67 (ddd, J=40.8, 8.8, 4.8 Hz, 1H), 4.82-4.94 (m, 1H), 4.98 (dt, J=47.2, 8.8 Hz, 1H), 7.13-7.24 (m, 5H), 7.67-7.70 (m, 2H), 7.77-7.79 (m, 2H).

[0361]

Synthesis of (R)-1-fluoromethyl-2-phenylethylamine on

A mixture of (R)-2-(1-fluoromethyl-2-phenylethyl)isoindol-1,3-dione (52 mg) and hydrazine hydrate (two drops) and ethanol (1 mL) was heated to reflux for 2 hours. The reaction solution was allowed to be cooled to room temperature, and the deposited crystal was separated by filtration and concentrated under reduced pressure. The residue was purified by LC-MS and 6.0 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.61 (dd, J=13.2, 8.4 Hz, 1H), 2.82 (dd, J=13.2, 5.6 Hz, 1H), 3.23-3.39 (m, 1H), 4.20-4.47 (m, 2H), 7.20-7.34 (m, 5H).

ESI-MS; m/z154 [M^++H].

[0362]

Synthesis of (R)-(E)-[(1R)-fluoromethyl-2-phenylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

By the same method as in Example 121, 1.38 mg of the title compound was obtained from 3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (10.0 mg) and (R)-1-fluoromethyl-2-phenylethylamine (6.0 mg).

ESI-MS; m/z394 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.29 (s, 3H), 2.92-3.06 (m, 2H), 3.89 (s, 3H), 4.34-4.56 (m, 3H), 5.85 (d, J=8.2 Hz, 1H), 6.38 (d, J=15.2 Hz, 1H), 6.92 (s, 1H), 7.11-7.17 (m, 2H), 7.23-7.27 (m, 4H), 7.31-7.35 (m, 2H), 7.60 (d, J=15.2 Hz, 1H), 7.71 (s, 1H).

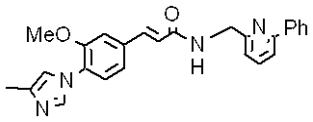
[0363]

Example 140

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-(6-phenylpyridin-2-ylmethyl)acrylic acid amide

[0364]

[Formula 124]



By the same method as in Example 121, the title compound (83 mg) was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (71 mg) and (6-phenylpyridin-2-ylmethyl)amine (61 mg).

ESI-MS; m/z425 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.30 (s, 3H), 3.90 (s, 3H), 4.79 (d, J=4.8 Hz, 2H), 6.57 (d, J=15.6 Hz, 1H), 6.94 (s, 1H), 7.10-7.29 (m, 5H), 7.43-7.56 (m, 3H), 7.64-7.80 (m, 4H), 8.01 (d, J=15.6 Hz, 1H), 8.03 (s, 1H).

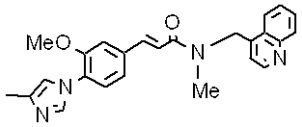
[0365]

Example 141

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl-N-(quinoline-4-ylmethyl)acrylic acid amide

[0366]

[Formula 125]



By the same method as in Example 121 The title compound (18 mg) was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (71 mg) and N-(methylquinoline -4-yl)methylamine (57 mg).

ESI-MS; m/z413 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.26 (s, 0.9H), 2.30 (s, 2.1H), 3.17 (s, 2.1H), 3.24 (s, 0.9H), 3.75 (s, 0.9H), 3.91 (s, 2.1H), 5.20 (s, 0.6H), 5.24 (s, 1.4H), 6.60-7.29 (m, 6H), 7.59-7.83 (m, 4H), 8.08-8.25 (m, 2H), 8.88-8.94 (m, 1H).

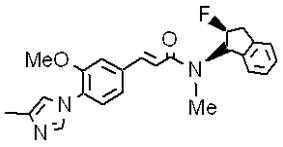
[0367]

Example 142-1 and Example 142-2

Synthesis of (E)-N-[(1R,2S) and (1S,2R)-(2-fluoroindan-1-yl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl acrylic acid amide

[0368]

[Formula 126]



Synthesis of methylamine(1R*,2S*)-(2-fluoroindan-1-yl)

To a THF (1.0 mL) solution of 2-fluoroindan-1-one(100 mg) synthesized according to the method described in Tetrahedron Letters, vol.37, No. 20, p. 3591, 1996, 2M methylamine THF solution (0.67 mL), acetic acid (400 mg) and triacetoxy sodium borohydride (282 mg) were agitated under ice-cooling and the reaction solution was agitated at room temperature

after addition. After 5 hours, 2M methylamine THF solution (0.67 mL) was added to the reaction solution, and the reaction solution was agitated overnight. The organic layer was diluted with a saturated sodium bicarbonate solution and ethyl acetate and partitioned. After drying the organic layer over anhydrous magnesium sulfate the organic layer was washed with a saturation sodium chloride solution and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: from ethyl acetate to ethyl acetate : methanol = 20:1), and the title compound (57 mg) was obtained.

ESI-MS; m/z166 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.67 (s, 3H), 3.09 (ddd, J=37.6, 17.2, 4.4 Hz, 1H), 3.22 (dd, J=23.2, 17.2 Hz, 1H), 4.12 (dd, J=23.2, 4.0 Hz, 1H), 5.48 (dt, J=54.0, 4.0 Hz, 1H), 7.23-7.27 (m, 3H), 7.41-7.45 (m, 1H).

[0369]

Synthesis of (E)-N-[(1R*,2S*)-(2-fluoroindan-1-yl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl acrylamide

By the same method as the in Example 121, the title compound (81 mg) was obtained from (E)-3-(4-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (74 mg) and (1R*,2S*)(2-fluoroindan-1-yl)methylamine (57 mg).

ESI-MS; m/z406 $[M^+ + H]$.^{1}H-NMR ($CDCl_3$) δ(ppm): 2.31 (s, 3H), 3.10 (s, 3H), 3.18-3.28 (m, 2H), 3.92 (s, 3H), 5.46-5.63 (m, 1H), 6.29 (dd, J=27.2, 4.8 Hz, 1H), 6.95

(s, 1H), 7.04 (d, J=15.2 Hz, 1H), 7.18-7.24 (m, 2H), 7.25-7.38 (m, 5H) 7.75 (s, 1H), 7.81 (d, J=15.2 Hz, 1H).

[0370]

Synthesis of (E)-N-[(1R,2S) and (1S,2R)-(2-fluoroindan-1-yl]3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl acrylic acid amide

N-[(1R*,2S*)-(2-fluoroindan-1-yl))-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl acrylic acid amide racemate (80 mg) was separated by CHIRALCEL OD available from Daicel Chemical Industries, Ltd. (2 cm×25 cm : mobile phase; ethanol). The title optically-active substance with a retention time of 17 minutes (Example 142-1: 35.8 mg; 99%e.e) and the title optically-active substance with a retention time of 22 minutes (Example 142-2: 30.9 mg; 99%e.e) were obtained.

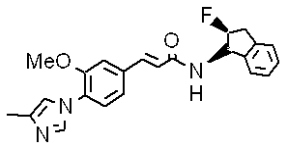
[0371]

Example 143

Synthesis of (E)-N-[(1R*,2S*)-(2-fluoroindan-1-yl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

[0372]

[Formula 127]



By the same method as in Example 121, the

title compound (6.2 mg) was obtained from (E)-3-(4-methyl-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (24 mg) and (1R*,2S*)-(2-fluoroindan-1-yl)amine (17 mg).

ESI-MS; m/z392 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.31 (s, 3H), 3.14-3.29 (m, 2H), 3.91 (s, 3H), 5.43 (dt, J=53.6, 4.0 Hz, 1H), 5.80 (ddd, J=25.6, 9.2, 4.0 Hz, 1H), 6.21 (d, J=9.2 Hz, 1H), 6.54 (d, J=15.6 Hz, 1H), 6.95 (s, 1H), 7.18-7.34 (m, 7H), 7.74 (s, 1H), 7.75 (d, J=15.6 Hz, 1H).

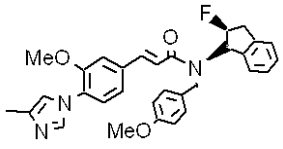
[0373]

Example 144

Synthesis of (E)-N-[(1R*,2S*)-(2-fluoroindan-1-yl)]-N-(4-methoxybenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

[0374]

[Formula 128]



By the same method as in Example 121, the title compound (18.2 mg) was obtained from (E)-3-(4-methyl-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (24 mg) and (1R*,2S*)-(2-fluoroindan-1-yl)-(4-methoxybenzyl)amine (15 mg).

ESI-MS; m/z512 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.28 (s, 3H), 3.24 (d, J=28.4 Hz, 2H), 3.75 (s, 3H), 3.79 (s, 3H), 4.53 (d, J=18.0 Hz, 1H), 4.68 (d, J=18.0 Hz, 1H),

5.59 (d, J=50.0 Hz, 1H), 6.40 (dd, J=25.6, 4.8 Hz, 1H), 6.67 (d, J=15.6 Hz, 1H), 6.82 (s, 1H), 6.87-6.96 (m, 4H), 7.10-7.34 (m, 7H) 7.67 (s, 1H), 7.73 (d, J=15.6 Hz, 1H).

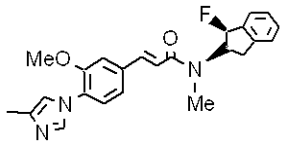
[0375]

Example 145-1 and Example 145-2

Synthesis of (E)-N-[(1R,2S) and (1S,2R) -(1-fluoroindan-2-yl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl acrylic acid amide

[0376]

[Formula 129]



By the same method as in Example 121, the title compound (228 mg) was obtained from (E)-3-(4-methyl-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (190 mg) and (1R*,2S*)-(1-fluoroindan-2-yl)methylamine (146 mg).

ESI-MS; m/z406 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.30 (s, 3H), 3.07-3.14 (m, 1H), 3.27 (s, 3H), 3.36-3.46 (m, 1H), 3.91 (s, 3H), 5.52 (d, J=31.2 Hz, 1H), 5.90 (d, J=57.6 Hz, 1H), 6.94 (s, 1H), 6.98 (d, J=15.6 Hz, 1H), 7.17 (s, 1H), 7.19-7.46 (m, 5H) 7.50-7.55 (m, 1H), 7.73 (s, 1H), 7.74 (d, J=15.6 Hz, 1H).

[0377]

N-[(1R*,2S*)-(1-fluoroindan-2-yl)]-3-[3-

methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methyl acrylic acid amide (270 mg) racemate obtained in the Example 145 was separated by CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm : mobile phase; ethanol). The title optically-active substance with a retention time of 28 minutes (Example 145-1: 105 mg; 99%e.e) and the title optically-active substance with a retention time of 37 minutes (Example 145-2: 124 mg;86%e.e) were obtained.

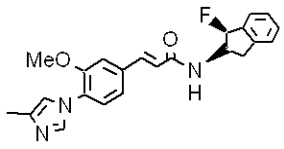
[0378]

Example 146

Synthesis of (E)-N-[(1R*,2S*)-(1-fluoroindan-2-yl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

[0379]

[Formula 130]



The title compound (9.05 mg) was obtained by the same method as in Example 121 from (E)-3-(4-methyl-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (14.3 mg) and (1R*,2S*)-(1-fluoroindan-2-yl)amine (10.1 mg). ESI-MS; m/z392 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 3H), 2.96-2.30 (m, 1H), 3.43 (dd, J=15.2, 8.4 Hz, 1H), 3.91 (s, 3H), 4.90-5.01 (m, 1H), 5.77 (dd, J=58.4, 4.4 Hz, 1H), 6.28 (d, J=8.8 Hz, 1H), 6.51 (d, J=15.6 Hz, 1H),

6.94 (s, 1H), 7.17-7.34 (m, 5H), 7.41-7.44 (m, 1H), 7.52-7.54 (m, 1H), 7.69 (d, J=15.6 Hz, 1H), 7.74 (s, 1H).

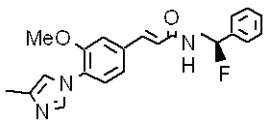
[0380]

Example 147

Synthesis of (E)-N-[(2S)-(2-fluoro-2-phenylethyl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

[0381]

[Formula 131]



To a methylene chloride (1.0 mL) solution of the N-((2R)-(2-hydroxy-2-phenylethyl))-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid amide (36.5 mg) obtained in the Example 195, DAST (23 mg) was added at -78°C, and the reaction solution was agitated for two hours at room temperature. After 2hrs, the reaction solution was diluted with saturated sodium bicarbonate solution and chloroform, and the organic layer was partitioned. The organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by column chromatography (Carrier: Chromatorex™ NH, an elution solvent : heptane-ethyl acetate system), and 5.7 mg of the title compound was obtained.

ESI-MS; m/z380 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.30 (s,

3H), 3.50-3.61 (m, 1H), 3.90 (s, 3H), 4.04-4.19 (m, 1H), 5.63 (ddd, J=48.8, 8.8, 2.8 Hz, 1H), 6.12 (brs, 1H), 6.45 (d, J=15.6 Hz, 1H), 6.94 (s, 1H), 7.14-7.20 (m, 2H), 7.25-7.27 (m, 1H), 7.36-7.46 (m, 5H), 7.65 (d, J=15.6 Hz, 1H), 7.73 (s, 1H).

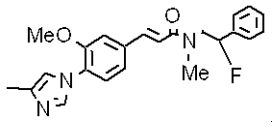
[0382]

Example 148-1 and Example 148-2

Synthesis of (E)-N-[(2R) and (2S) -fluoro-2-phenylethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-methylacrylic acid amide

[0383]

[Formula 132]



By the same method as in Example 147, 100 mg of the racemate of the title compound was obtained from the N-(2-hydroxy-2-phenylethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-methylacrylic acid amide (310 mg) obtained in the Example 202.

ESI-MS; m/z394 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.31 (s, 3H), 3.11 (s, 0.9H), 3.32 (s, 2.1H), 3.38-3.48 (m, 1H), 3.90 (s, 3H), 4.24 (ddd, J=34.8, 14.4, 2.4 Hz, 1H), 5.81 (ddd, J=49.2, 9.2, 2.4 Hz, 1H), 6.68 (d, J=15.2 Hz, 0.3H), 6.90-6.95 (m, 1.7H), 7.05-7.48 (m, 8H), 7.58 (d, J=15.2 Hz, 0.3H), 7.69-7.74 (m, 1.7H).

[0384]

(E)-N-(2-fluoro-2-phenylethyl-3-[3-methoxy-4-

(4-methyl-1H-imidazol-1-yl)phenyl]-N-methylacrylic acid amide (100 mg) racemate obtained above was separated by CHRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (cm: 2 cm×25 mobile phase; ethanol). The title optically active substance with a retention time of 15 minutes (Example 148-1: 49 mg; 99%e.e) and the title optically active substance with a retention time of 22 minutes (Example 148-2: 35 mg; 99%e.e) were obtained.

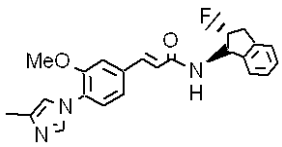
[0385]

Example 149

Synthesis of N-[(1R, 2R)-(2-fluoroindan-1-yl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide

[0386]

[Formula 133]



By the same method as in Example 147, 3.20 mg of the title compound was obtained from the N-[(1R,2S)-(2-hydroxyindan-1-yl)]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid amide (50 mg) obtained in the Example 198.

ESI-MS; m/z392 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.30 (s, 3H), 3.13-3.24 (m, 1H), 3.36-3.49 (m, 1H), 3.88 (s, 3H), 5.28 (d, J=48.0 Hz, 1H), 5.65 (ddd, J=17.2, 7.2, 2.8 Hz, 1H), 5.77 (d, J=7.2 Hz, 1H), 6.41 (d, J=15.2

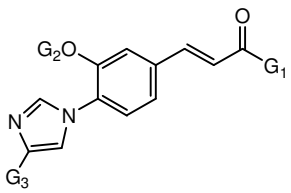
Hz, 1H), 6.93 (s, 1H), 7.12-7.20 (m, 2H), 7.24-7.38 (m, 5H), 7.70 (d, J=15.2 Hz, 1H), 7.74 (s, 1H).

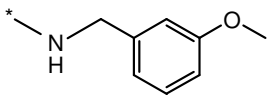
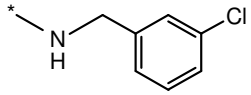
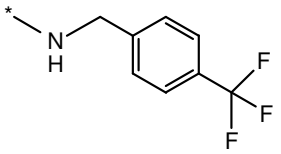
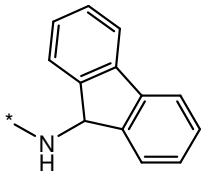
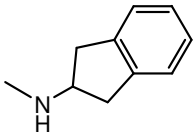
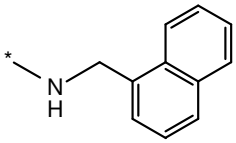
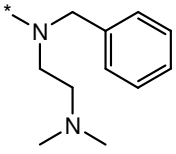
[0387]

The compounds shown in Table 7 were synthesized as in Example 121.

The structural formulae and physicochemical properties are shown in Table 7, respectively.

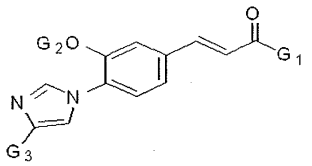
[0388]
[Table 7-1]

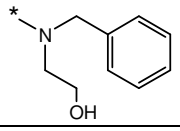
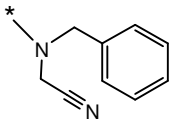
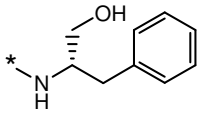
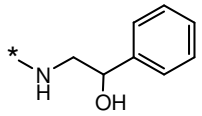
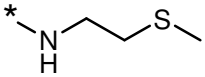
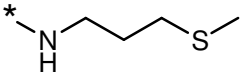
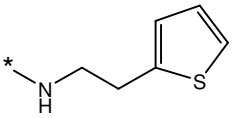
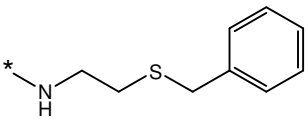
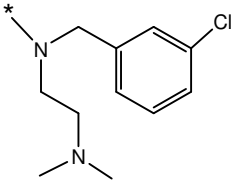


Example	G_1	G_2	E_3	DATA:MS m/z
150		Me	Me	M^++H:378 (ESI)
151		Me	Me	M^++H:382 (ESI)
152		Me	Me	M^++H:416 (ESI)
153		Me	Me	M^++H:422 (ESI)
154		Me	Me	M^++H:374 (ESI)
155		Me	Me	M^++H:398 (ESI)
156		Me	Me	M^++H:419 (ESI)

[0389]

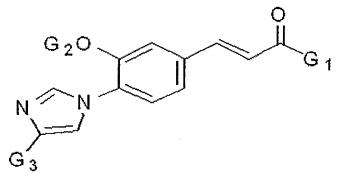
[Table 7-2]

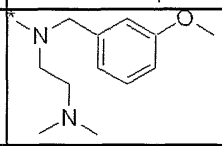
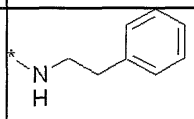
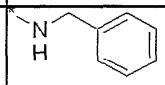
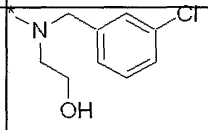
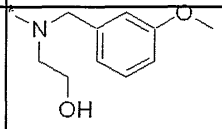
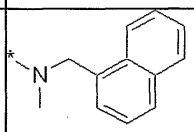
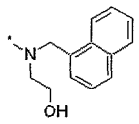
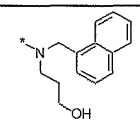


Example	G_1	G_2	E_3	DATA:MS m/z
157		Me	Me	M^++H:392 (ESI)
158		Me	Me	M^++H:387 (ESI)
159		Me	Me	M^++H:392 (ESI)
160		Me	Me	M^++H:378 (ESI)
161		Me	Me	M^++H:332 (ESI)
162		Me	Me	M^++H:346 (ESI)
163		Me	Me	M^++H:368 (ESI)
164		Me	Me	M^++H:408 (ESI)
165		Me	Me	M^++H:453 (ESI)

[0390]

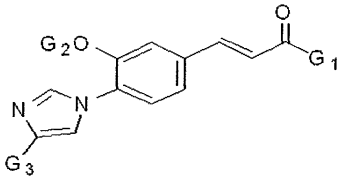
[Table 7-3]

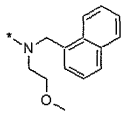
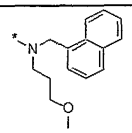
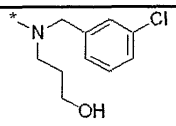
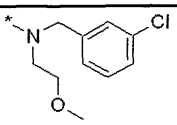
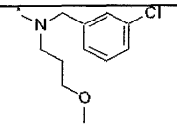
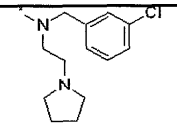
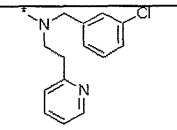


Example	G_1	G_2	E_3	DATA: MS m/z
166		Me	Me	M^++H：449 (ESI)
167		Me	Me	M^++H：362 (ESI)
168		Me	Me	M^++H：348 (ESI)
169		Me	Me	M^++H：426 (ESI)
170		Me	Me	M^++H：422 (ESI)
171		Me	Me	M^++H：412 (ESI)
172		Me	Me	M^++H：442 (ESI)
173		Me	Me	M^++H：456 (ESI)

[0391]

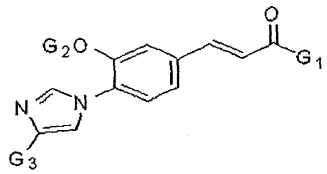
[Table 7-4]

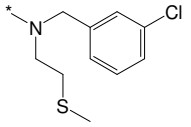
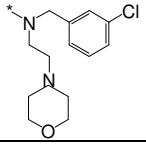
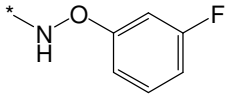
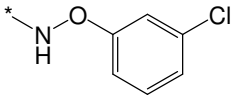
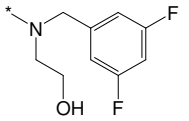
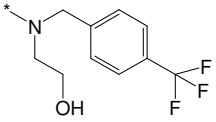
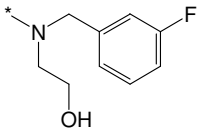
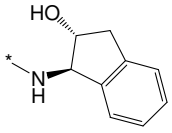
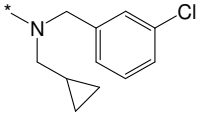
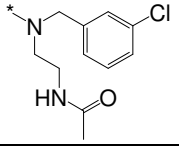


Example	G_1	G_2	E_3	DATA: MS m/z
174		Me	Me	M^++H：456 (ESI)
175		Me	Me	M^++H：470 (ESI)
176		Me	Me	M^++H：440 (ESI)
177		Me	Me	M^++H：440 (ESI)
178		Me	Me	M^++H：454 (ESI)
179		Me	Me	M^++H：479 (ESI)
180		Me	Me	M^++H：487 (ESI)

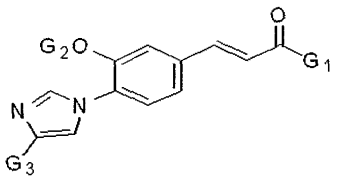
[0392]

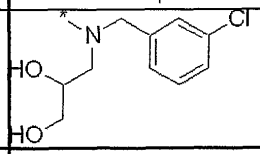
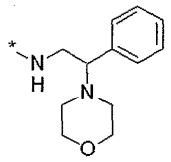
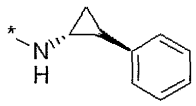
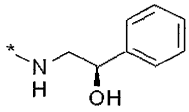
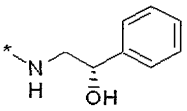
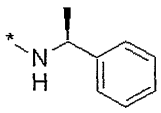
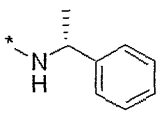
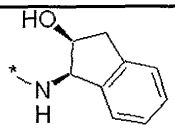
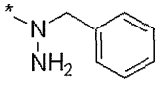
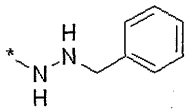
[Table 7-5]



Example	G_1	G_2	E_3	Data:MS m/z
181		Me	Me	M^++H:456 (ESI)
182		Me	Me	M^++H:495 (ESI)
183		Me	Me	M^++H:366 (ESI)
184		Me	Me	M^++H:412 (ESI)
185		Me	Me	M^++H:428 (ESI)
186		Me	Me	M^++H:460 (ESI)
187		Me	Me	M^++H:410 (ESI)
188		Me	Me	M^++H:390 (ESI)
189		Me	Me	M^++H:436 (ESI)
190		Me	Me	M^++H:467 (ESI)

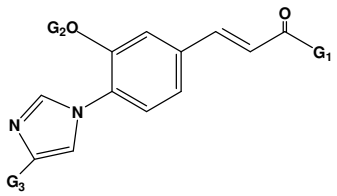
[0393]
[Table 7-6]

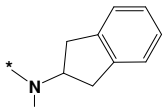
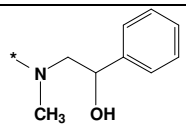
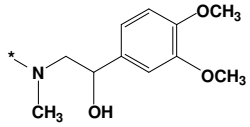
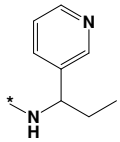
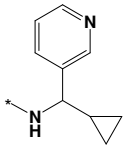
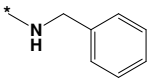
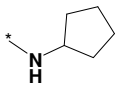
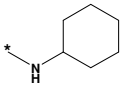
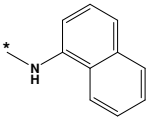
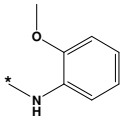


Example	G_1	G_2	E_3	DATA: MS m/z
191		Me	Me	M^++H : 456 (ESI)
192		Me	Me	M^++H : 447 (ESI)
193		Me	Me	M^++H : 374 (ESI)
194		Me	Me	M^++H : 378 (ESI)
195		Me	Me	M^++H : 378 (ESI)
196		Me	Me	M^++H : 362 (ESI)
197		Me	Me	M^++H : 362 (ESI)
198		Me	Me	M^++H : 390 (ESI)
199		Me	Me	M^++H : 363 (ESI)
200		Me	Me	M^++H : 363 (ESI)

[0394]

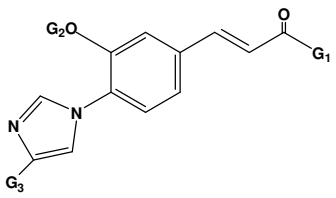
[Table 7-7]

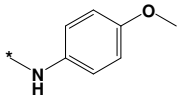
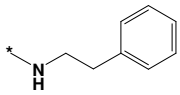
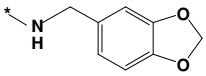
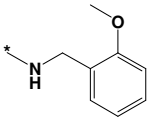
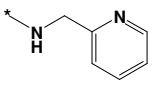
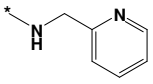
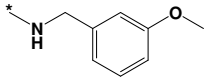
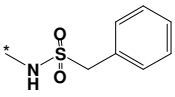
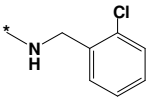
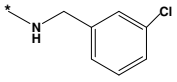


Example	G_1	G_2	G_3	DATA:MS m/z
201		OMe	Me	M^++H:388 (ESI)
202		OMe	Me	M^++H:392 (ESI)
203		OMe	Me	M^++H:452 (ESI)
204		OMe	Me	M^++H:377 (ESI)
205		OMe	Me	M^++H:389 (ESI)
206		F	H	M^++H:322 (ESI)
207		F	H	M^++H:300 (ESI)
208		F	H	M^++H:314 (ESI)
209		F	H	M^++H:358 (ESI)
210		OMe	H	M^++H:350 (ESI)

[0395]

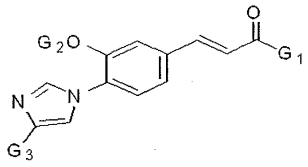
[Table 7-8]

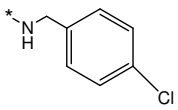
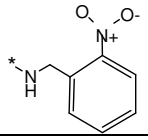
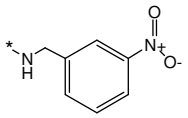
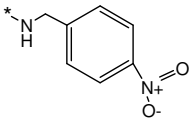
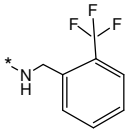
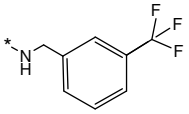
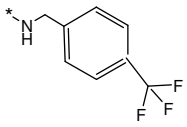
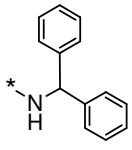
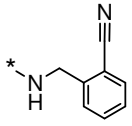
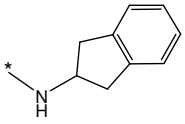


Example	G_1	G_2	E_3	DATA:MS m/z
211		Me	H	M^++H:350 (ESI)
212		Me	H	M^++H:348 (ESI)
213		Me	H	M^++H:378 (ESI)
214		Me	H	M^++H:364 (ESI)
215		Me	H	M^++H:335 (ESI)
216		Me	H	M^++H:335 (ESI)
217		Me	H	M^++H:364 (ESI)
218		Me	H	M^++H:398 (ESI)
219		Me	H	M^++H:368 (ESI)
220		Me	H	M^++H:368 (ESI)

[0396]

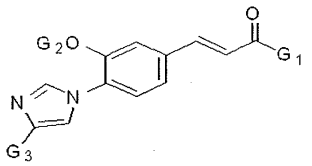
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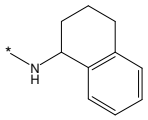
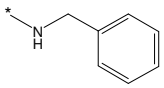
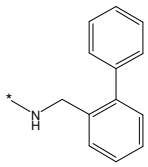
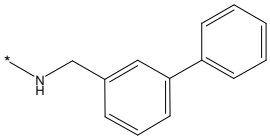
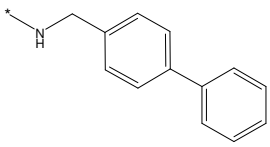
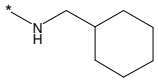
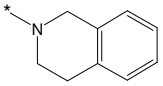
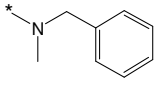
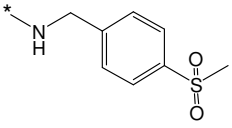
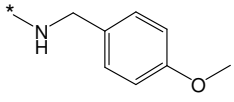


Example	G_1	G_2	G_3	DATA:MS m/z
221		Me	H	M^++H:368 (ESI)
222		Me	H	M^++H:379 (ESI)
223		Me	H	M^++H:379 (ESI)
224		Me	H	M^++H:379 (ESI)
225		Me	H	M^++H:402 (ESI)
226		Me	H	M^++H:402 (ESI)
227		Me	H	M^++H:402 (ESI)
228		Me	H	M^++H:410 (ESI)
229		Me	H	M^++H:359 (ESI)
230		Me	H	M^++H:360 (ESI)

[0397]

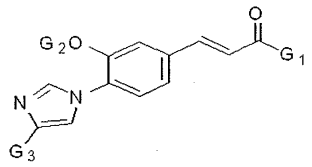
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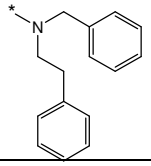
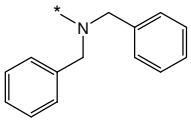
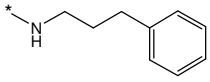
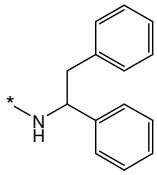
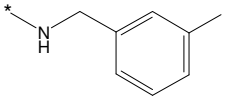
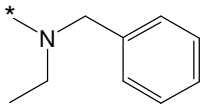
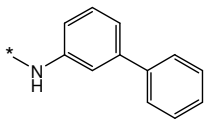
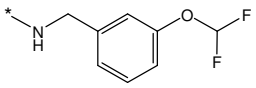
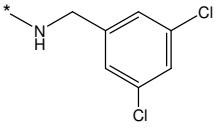
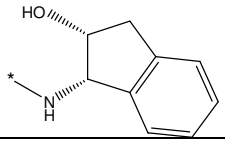


Example	G_1	G_2	G_3	DATA:MS m/z
231		Me	H	M^++H:374 (ESI)
232		Me	H	M^++H:334 (ESI)
233		Me	H	M^++H:410 (ESI)
234		Me	H	M^++H:410 (ESI)
235		Me	H	M^++H:410 (ESI)
236		Me	H	M^++H:340 (ESI)
237		Me	H	M^++H:360 (ESI)
238		Me	H	M^++H:348 (ESI)
239		Me	H	M^++H:412 (ESI)
240		Me	H	M^++H:364 (ESI)

[0398]

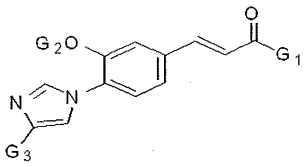
[Table 7-11]

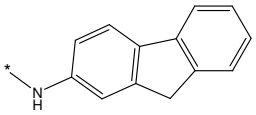
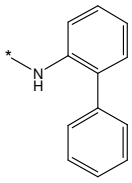
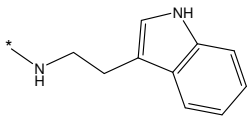
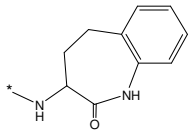
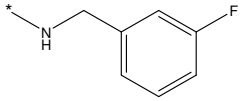
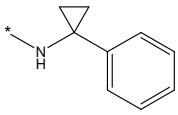
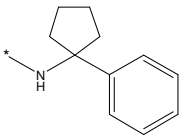
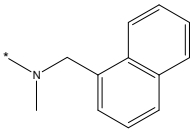
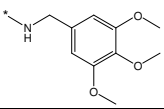
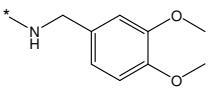


Example	G_1	G_2	G_3	DATA:MS m/z
241		Me	H	M^++H:438 (ESI)
242		Me	H	M^++H:424 (ESI)
243		Me	H	M^++H:362 (ESI)
244		Me	H	M^++H:424 (ESI)
245		Me	H	M^++H:348 (ESI)
246		Me	H	M^++H:362 (ESI)
247		Me	H	M^++H:396 (ESI)
248		Me	H	M^++H:400 (ESI)
249		Me	H	M^++H:402 (ESI)
250		Me	H	M^++H:376 (ESI)

[0399]

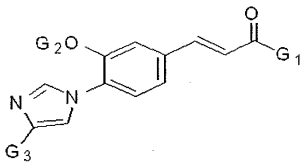
[Table 7-12]

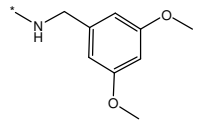
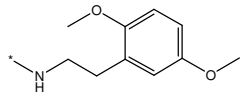
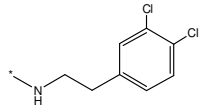
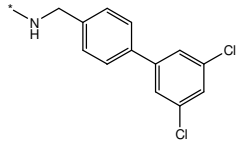
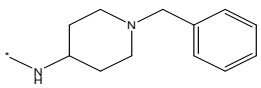
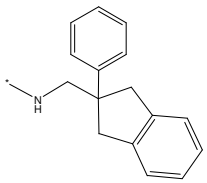
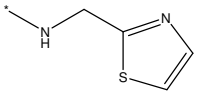
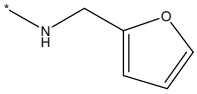
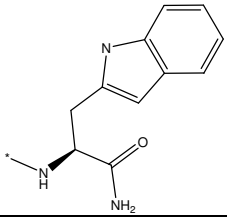
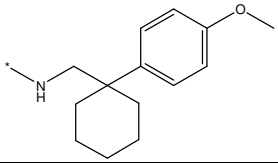


Example	G_1	G_2	G_3	DATA:MS m/z
251		Me	H	M^++H:408(ESI)
252		Me	H	M^++H:396 (ESI)
253		Me	H	M^++H:387 (ESI)
254		Me	H	M^++H:403 (ESI)
255		Me	H	M^++H:352 (ESI)
256		Me	H	M^++H:360 (ESI)
257		Me	H	M^++H:388 (ESI)
258		Me	H	M^++H:398 (ESI)
259		Me	H	M^++H:424 (ESI)
260		Me	H	M^++H:394 (ESI)

[0400]

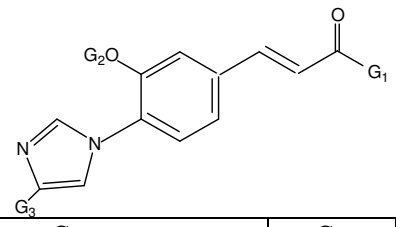
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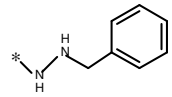
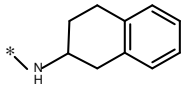
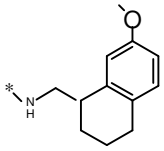
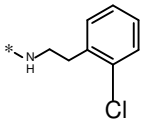
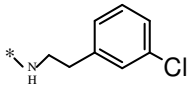
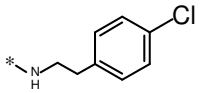
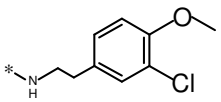
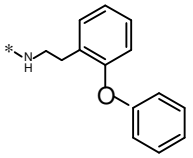
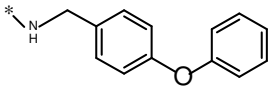
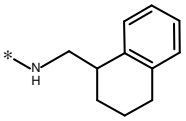


Example	G_1	G_2	G_3	DATA:MS m/z
261		Me	H	M^++H:394 (ESI)
262		Me	H	M^++H:408 (ESI)
263		Me	H	M^++H:416 (ESI)
264		Me	H	M^++H:478 (ESI)
265		Me	H	M^++H:417 (ESI)
266		Me	H	M^++H:450 (ESI)
267		Me	H	M^++H:341 (ESI)
268		Me	H	M^++H:324 (ESI)
269		Me	H	M^++H:430 (ESI)
270		Me	H	M^++H:446 (ESI)

[0401]

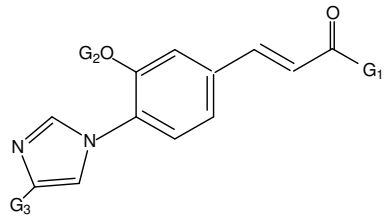
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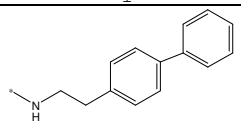
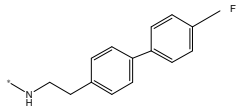
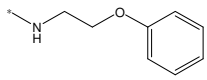
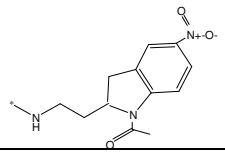
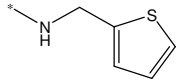
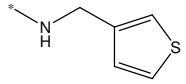
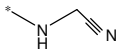
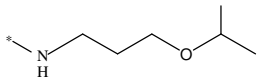
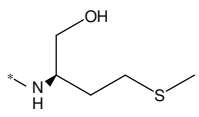
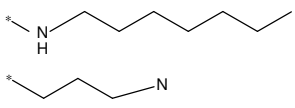


Example	G_1	G_2	E_3	DATA:MS m/z
271		Me	H	M^++H:349 (ESI)
272		Me	H	M^++H:374 (ESI)
273		Me	H	M^++H:418 (ESI)
274		Me	H	M^++H:382 (ESI)
275		Me	H	M^++H:382 (ESI)
276		Me	H	M^++H:382 (ESI)
277		Me	H	M^++H:412 (ESI)
278		Me	H	M^++H:440 (ESI)
279		Me	H	M^++H:426 (ESI)
280		Me	H	M^++H:388 (ESI)

[0402]

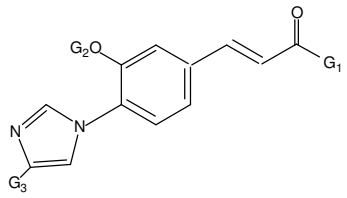
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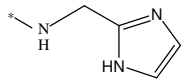
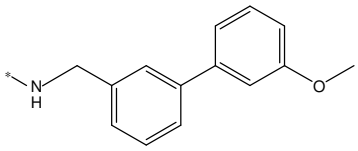
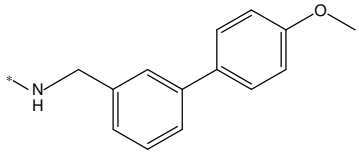
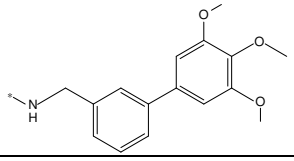
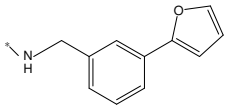
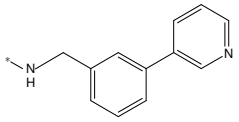
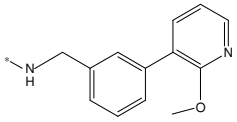
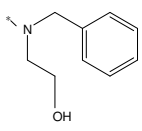
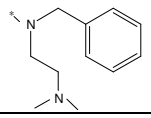
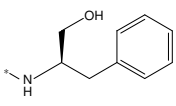


Example	G_1	G_2	E_3	DATA:MS m/z
281		Me	H	M^++H:424 (ESI)
282		Me	H	M^++H:442 (ESI)
283		Me	H	M^++H:364 (ESI)
284		Me	H	M^++H:476 (ESI)
285		Me	H	M^++H:340 (ESI)
286		Me	H	M^++H:340 (ESI)
287		Me	H	M^++H:283 (ESI)
288		Me	H	M^++H:344 (ESI)
289		Me	H	M^++H:362 (ESI)
290		Me	H	M^++H:342 (ESI)

[0403]

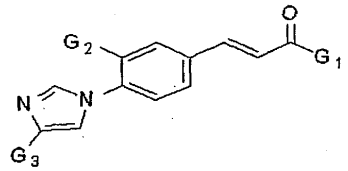
[Table 7-16]

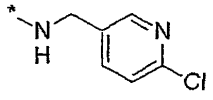
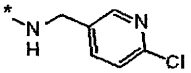
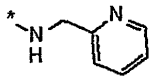
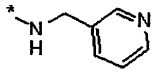
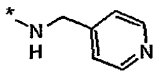
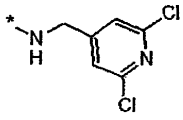
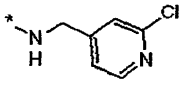
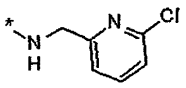
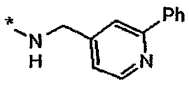
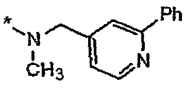


Example	G_1	G_2	E_3	DATA:MS m/z
291		Me	H	M^++H:324 (ESI)
292		Me	H	M^++H:440 (ESI)
293		Me	H	M^++H:440 (ESI)
294		Me	H	M^++H:500 (ESI)
295		Me	H	M^++H:400 (ESI)
296		Me	H	M^++H:411 (ESI)
297		Me	H	M^++H:440 (ESI)
298		Me	H	M^++H:378 (ESI)
299		Me	H	M^++H:405 (ESI)
300			H	M^++H:438 (ESI)

[0404]

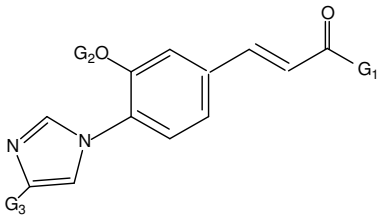
[Table 7-17]

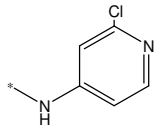
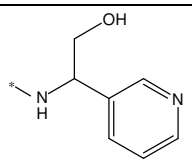
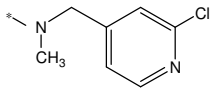
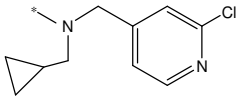
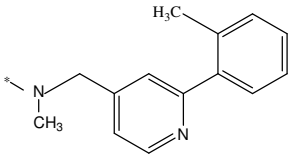
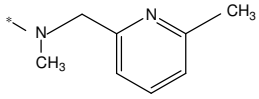
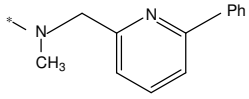
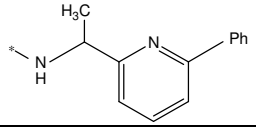
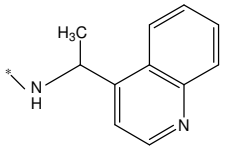


Example	G_1	G_2	G_3	DATA: MS m/z
301			Me	M^+-H : 405 (ESI)
302		Me	Me	M^++H : 383 (ESI)
302		Me	Me	M^++H : 349 (ESI)
304		Me	Me	M^++H : 349 (ESI)
305		Me	Me	M^++H : 349 (ESI)
306		Me	Me	M^++H : 417 (ESI)
307		Me	Me	M^++H : 383 (ESI)
308		Me	Me	M^++H : 383 (ESI)
309		Me	Me	M^++H : 425 (ESI)
310		Me	Me	M^++H : 439 (ESI)

[0405]

[Table 7-18]



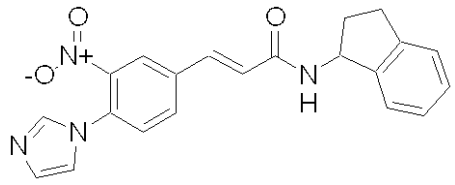
Example	G_1	G_2	E_3	DATA:MS m/z
311		Me	H	M^++H:369 (ESI)
312		Me	H	M^++H:379 (ESI)
313		Me	H	M^++H:397 (ESI)
314		Me	H	M^++H:437 (ESI)
315		Me	H	M^++H:453 (ESI)
316		Me	H	M^++H:377 (ESI)
317		Me	H	M^++H:439 (ESI)
318		Me	H	M^++H:439 (ESI)
319		Me	H	M^++H:413 (ESI)

[0406]
Example 320

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-nitro phenyl]-N-(indan-1-yl)acrylamide

[0407]

[Formula 134]



[0408]

Synthesis of 1-(4-bromo-2-nitro phenyl)-1H-imidazole

Potassium carbonate (1.80 g) and imidazole (667 mg) were added to a DMF (10 mL) solution of 4-bromo-1-fluoro-2-nitro benzene (1.0 mL) one by one, and the reaction solution was agitated at 80°C for 3 hours and 30 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 1.04 g of crude bromo compounds was obtained by condensing under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.15 (d, J=2.0 Hz, 1H), 7.86 (dd, J=2.0, 8.4 Hz, 1H), 7.62 (s, 1H), 7.36 (d, J=8.4 Hz, 1H), 7.22-7.23 (m, 1H), 7.05 (m, 1H).

[0409]

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-nitrophenyl]-N-(indan-1-yl)acrylamide

21.0 mg of the title compound was obtained from 1-(4-bromo-2-nitrophenyl)-1H-imidazole (40.0 mg) and N-(indan-1-yl)acrylamide (42.0 mg) obtained in the Example 9. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.11 (d, J=2.0 Hz, 1H), 7.79 (dd, J=2.0, 8.0 Hz, 1H), 7.73 (d, J=16 Hz, 1H), 7.63 (s, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.34 (d, J=7.2 Hz, 1H), 7.22-7.29 (m, 4H), 7.07 (s, 1H), 6.56 (d, J=16 Hz, 1H), 6.13 (brd, J=8.0 Hz, 1H), 5.64 (q, J=8.0 Hz, 1H), 3.04 (ddd, J=4.4, 8.8, 16 Hz, 1H), 2.93 (td, J=8.0, 16 Hz, 1H), 2.68 (dtd, J=4.4, 8.0, 12 Hz, 1H), 1.87-1.36 (m, 1H).

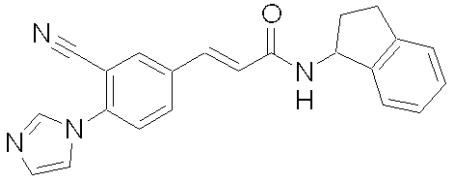
[0410]

Example 321

Synthesis of (E)-3-[3-cyano-4-(1H-imidazol-1-yl)-phenyl]-N-(indan-1-yl)acrylamide

[0411]

[Formula 135]



Synthesis of 5-bromo-2-(1H-imidazol-yl)-benzonitrile

Potassium carbonate (1.80 g) and imidazole

(667 mg) were added to a DMF (10 mL) solution of 5-bromo-2-fluorobenzonitrile (1.78 g) one by one, and the reaction solution was agitated at 80°C for 3 hours and 30 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 1.07 g of crude bromo compounds was obtained by condensing under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.95 (d, J=2.4 Hz, 1H), 7.84-7.88 (m, 2H), 7.34-7.36 (m, 2H), 7.29 (brs, 1H)

[0412]

Synthesis of (E)-3-[3-cyano-4-(1H-imidazol-1-yl)-phenyl)-N-indan-1-yl-acrylamide

By the same method as in Example 9, 5.20 mg of the title compound was obtained from 5-bromo-2-(1H-imidazol-1-yl)benzonitrile (38.0 mg) and N-indan-1-yl-acrylamide (42.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.91 (d, J=1.6 Hz, 1H), 7.85 (s, 1H), 7.81 (dd, J=2.0, 8.4 Hz, 1H), 7.66 (d, J=16 Hz, 1H), 7.45 (d, J=8.4 Hz, 1H), 7.36 (s, 1H), 7.33 (d, J=4.8 Hz, 1H), 7.20-7.28 (m, 4H), 6.54 (d, J=16 Hz, 1H), 6.33 (brs, 1H), 5.63 (q, J=8.4 Hz, 1H), 3.02 (ddd, J=4.8, 8.4, 16 Hz, 1H), 2.88-2.99 (m, 1H), 2.62-2.71 (m, 1H), 1.86-1.96 (m, 1H).

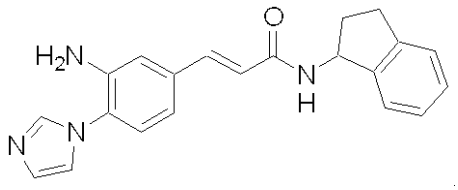
[0413]

Example 322

Synthesis of (E)-3-[3-amino-4-(1H-imidazol-1-yl)-phenyl]-N-indan-1-yl-acrylamide

[0414]

[Formula 136]



Synthesis of 5-bromo-2-(1H-imidazol-1-yl)-phenylamine

To a solution of 1-(4-bromo-2-nitro phenyl)-1H-imidazole (500 mg) in methylene chloride (10 mL) and methanol (10 mL) at 0°C nickel hexahydrate (22.0 mg) and sodium borohydride (177 mg) were added one by one, and the reaction solution was agitated for 20 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH; elution solvent:hexane:ethyl acetate =1:1 -> ethyl acetate), and 431 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.61 (s, 1H), 7.25 (s, 1H), 7.09

(s, 1H), 6.99-6.70 (m, 1H), 6.97 (d, J=8.4 Hz, 1H), 6.94 (m, 1H), 3.78 (brs, 2H).

[0415]

Synthesis of (E)-3-[3-amino-4-(1H-imidazol-1-yl)-phenyl)-N-indan-1-yl-acrylamide

By the same method as in Example 9, 249 mg of the title compound was obtained from 5-bromo-2-(1H-imidazol-1-yl)-phenylamine (200 mg) and N-indan-1-yl-acrylamide (236 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.64 (s, 1H), 7.62 (d, J=16 Hz, 1H), 7.34 (d, J=6.8 Hz, 1H), 7.22-7.29 (m, 4H), 7.13 (s, 1H), 7.11 (d, J=7.6 Hz, 1H), 6.94-6.98 (m, 2H), 6.39 (d, J=16 Hz, 1H), 5.93 (d, J=8.0 Hz, 1H), 5.64 (q, J=8.0 Hz, 1H), 3.77 (brs, 2H), 3.03 (ddd, J=4.4, 8.8, 16 Hz, 1H), 2.93 (td, J=8.0, 16 Hz, 1H), 2.67 (dtd, J=4.4, 8.0, 13 Hz, 1H), 1.85-1.94 (m, 1H).

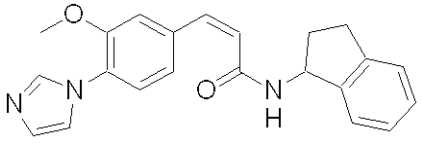
[0416]

Example 323

Synthesis of (Z)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-yl-acrylamide

[0417]

[Formula 137]



To a THF (7.0 mL) solution of 4-(1H-imidazol-

1-yl)-3-methoxy benzaldehyde (300 mg) obtained in Example 328, 18-crown-6 (2.0 g) and potassium bis(trimethylsilyl)amide (0.5M toluene solution, 4.4 mL) and (bis-(2,2,2,-trifluoroethoxy)phosphoryl)ethyl acetate ester (470 μL) were added at -78°C, and the reaction solution was agitated overnight at room temperature. A saturated ammonium chloride solution and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH and elution solvent:hexane:ethyl acetate =1:1 -> ethyl acetate), and 306 mg of ester product was obtained as an isomer mixture (E:Z=1:5.5). 2N sodium hydroxide solution (5.0 mL) was added to a THF (5.0 mL) solution of the obtained ester product, and the reaction solution was agitated at room temperature overnight. The isomer compound impurities were separated by cooling the reaction solution at 0°C, adding 2N hydrochloric acid to the reaction solution, and filtering off the deposited precipitation by Kiriyama funnel. The obtained filtrate was concentrated under reduced pressure and 253 mg of crude carboxylic acid was obtained. TEA (507 μL), 1-aminoindane (133 μL), and PYBOP (812 mg) were added to a DMF (5.0 mL) solution of the obtained

carboxylic acid one by one, and the reaction solution was agitated at room temperature for 1 hour. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane: ethyl acetate = 1:1 -> ethyl acetate), and 9.0 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.81 (s, 1H), 7.41 (s, 1H), 7.21-7.29 (m, 5H), 7.13-7.18 (m, 3H), 6.79 (d, J=12 Hz, 1H), 6.09 (d, J=12 Hz, 1H), 5.83 (brd, J=7.6 Hz, 1H), 5.52 (q, J=7.6 Hz, 1H), 3.87 (s, 3H), 2.82-2.96 (m, 2H), 2.59 (dtd, J=4.8, 7.6, 12 Hz, 1H), 1.70-1.79 (m, 1H).

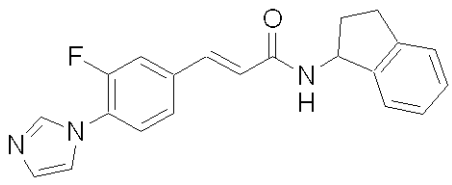
[0418]

Example 324

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)-phenyl]-N-indan-1-yl-acrylamide

[0419]

[Formula 138]



Synthesis of 3-fluoro-4-(1H-imidazol-1-yl)-benzaldehyde

Potassium carbonate (1.71 g) and imidazole (847 mg) were added to a DMF (20 mL) solution of 3,4-difluorobenzaldehyde (2.0 g). The reaction solution was agitated at 100°C overnight, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane : ethyl acetate =1:1 -> ethyl acetate), and 1.11 g of the title compound was obtained. The physical properties of the compound are as follows.

The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 10.0 (s, 1H), 7.96 (s, 1H), 7.82 (d, J=7.2 Hz, 2H), 7.61 (t, J=7.2 Hz, 1H), 7.36 (s, 1H), 7.27 (s, 1H).

[0420]

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl)acrylic acid

By the same method as in Example 111, 1.66 g of the title compound was obtained from 3-fluoro-4-(1H-imidazol-1-yl)-benzaldehyde (1.40 g) and dimethylphosphonoacetic acid methyl ester (1.40 mL). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 8.10 (s, 1H), 7.93 (d, J=13

Hz, 1H), 7.70-7.71 (m, 2H), 7.63 (s, 1H), 7.62 (d, J=16 Hz, 1H), 7.15 (s, 1H), 6.69 (d, J=16 Hz, 1H).

[0421]

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl)-N-(indan-1-yl)acrylamide

To a DMF (4.0 mL) solution of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl]acrylic acid (100 mg), TEA (167 μL), 1-aminoindane (83.0 μL) and PYBOP (448 mg) were added one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane : ethyl acetate =1:1 -> ethyl acetate), and 95.0 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.64 (d, J=16 Hz, 1H), 7.40 (s, 1H), 7.37-7.38 (m, 2H), 7.32 (d, J=7.2 Hz, 1H), 7.20-7.28 (m, 5H), 6.43 (d, J=16 Hz, 1H), 6.02-6.14 (br, 1H), 5.62 (q, J=7.2 Hz, 1H), 3.02 (ddd, J=4.4, 8.8, 16 Hz, 1H), 2.91 (td, J=8.0, 16 Hz, 1H), 2.62-2.70 (m, 1H), 1.85-1.94 (m, 1H)

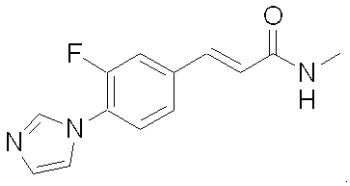
[0422]

Example 325

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl)-N-methylacrylamide

[0423]

[Formula 139]



By the same method as in Example 324, 17.5 mg of the title compound was obtained from (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl]acrylic acid (60.0 mg) and methylamine (650 μL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.86 (s, 1H), 7.61 (d, J=16 Hz, 1H), 7.42 (d, J=8.4 Hz, 1H), 7.36-7.42 (m, 2H), 7.23-7.29 (m, 2H), 6.40 (d, J=16 Hz, 1H), 5.66 (brs, 1H), 2.97 (d, J=4.8 Hz, 3H).

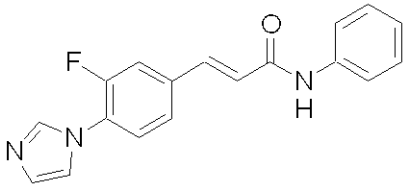
[0424]

Example 326

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl)-N-phenylacrylamide

[0425]

[Formula 140]



By the same method as in Example 324, 32 mg of the title compound was obtained from (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl]acrylic acid (50.0 mg) and aniline (29.0 μL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.94 (brs, 1H), 7.88 (s, 1H), 7.72 (d, J=16 Hz, 1H), 7.67 (d, J=7.6 Hz, 1H), 7.41-7.45 (m, 3H), 7.37 (t, J=8.0 Hz, 1H), 7.30 (d, J=1.2 Hz, 1H), 7.24-7.27 (m, 3H), 7.16 (t, J=8.0 Hz, 1H), 6.64 (d, J=16 Hz, 1H).

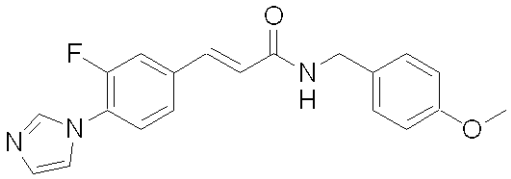
[0426]

Example 327

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl)-N-(4-methoxybenzyl)acrylamide

[0427]

[Formula 141]



By the same method as in Example 324, 55.0 mg of the title compound was obtained from 3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl]acrylic acid (50.0 mg) and 4-methoxybenzylamine (42.0 μL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.86 (s, 1H), 7.63 (d, J=16 Hz, 1H), 7.35-7.42 (m, 3H), 7.23-7.28 (m, 4H), 6.88 (td, J=2.0, 8.8 Hz, 2H), 6.43 (d, J=16 Hz, 1H), 6.05 (brs,

1H), 4.52 (d. J=6.0 Hz, 2H), 3.80 (s, 3H).

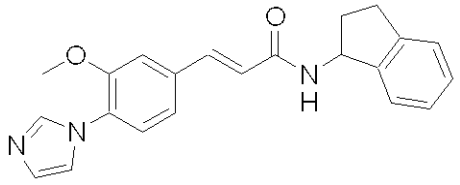
[0428]

Example 328

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-yl-acrylamide

[0429]

[Formula 142]



Synthesis of 4-(1H-imidazol-1-yl)-3-methoxybenzaldehyde

Potassium carbonate (2.0 g) and imidazole (662 mg) were added to a DMF (20 mL) solution of 4-fluoro-3-methoxybenzaldehyde (1.50 g). The reaction solution was agitated at 80°C overnight, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane : ethyl acetate = 3:1 -> ethyl acetate -> ethyl acetate : methanol = 10:1), and 960 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 10.0 (s, 1H), 7.92 (s, 1H),

7.56-7.60 (m, 2H), 7.48 (d, J=7.6 Hz, 1H), 7.30 (s, 1H), 7.21 (s, 1H), 3.98 (s, 3H).

[0430]

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid

11.9 g of the title compound was obtained from 4-(1H-imidazol-1-yl)-3-methoxybenzaldehyde (13.2 g) by the same method as in Example 111. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 7.96 (t, J=1.2 Hz, 1H), 7.63 (d, J=16 Hz, 1H), 7.59 (d, J=1.6 Hz, 1H), 7.48 (t, J=1.2 Hz, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.38 (dd, J=1.6 Hz, 8.0 Hz, 1H), 7.06 (t, J=1.2 Hz, 1H), 6.68 (d, J=16 Hz, 1H), 3.89 (s, 3H).

[0431]

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-yl-acrylamide

By the same method as in Example 111, 142 mg of the title compound was obtained from (E)-3-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid (100 mg) and 1-aminoindane (53.0 μL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.85 (s, 1H), 7.69 (d, J=16 Hz, 1H), 7.35 (d, J=6.8 Hz, 1H), 7.16-7.29 (m, 8H), 6.44 (d, J=16 Hz, 1H), 5.92 (d, J=8.4 Hz, 1H), 5.65 (q, J=8.4 Hz, 1H), 3.88 (s, 3H), 3.04 (ddd, J=4.0, 8.8, 16 Hz, 1H), 2.91-2.96 (m, 1H), 2.64-2.72 (m, 1H), 1.86-1.95 (m, 1H).

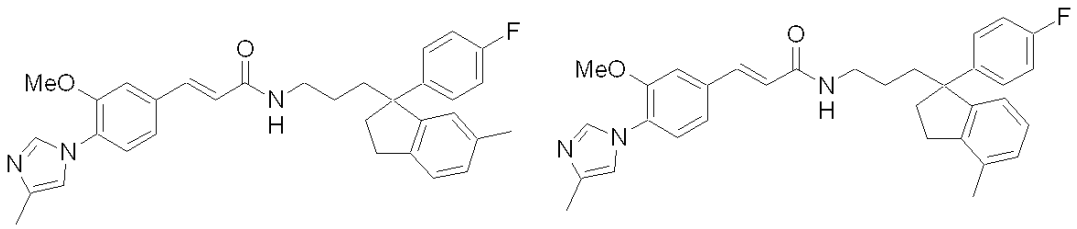
[0432]

Example 329

Synthesis of (E)-N-{3-[1-(4-fluorophenyl)-6-methyl-indan-1-yl]propyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide and (E)-N-{3-[1-(4-fluorophenyl)-4-methyl-indan-1-yl]propyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0433]

[Formula 143]



p-Toluenesulfonate monohydrate (95 mg) was added to a toluene (10 mL) solution of 1-[4-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (45 mg) obtained in Example 350. Heating refluxing of the reaction solution was carried out for 3 hours. Water was added to the reaction solution after the reaction ended, and the reaction solution extracted with ethyl acetate, and the organic layer was washed with a saturated sodium bicarbonate and also a saturated sodium chloride solution. The partitioned organic layer the solvent was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The obtained residue was purified by silica gel column

chromatography (elution solvent: ethanol : ethyl acetate = 1:10), and 10 mg (19%) of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.50 (m, 2H), 2.04 (m, 1H), 2.13 (m, 1H), 2.24 (m, 1H), 2.36 (m, 1H), 2.30 (s, 3H), 2.35 (s, 3H), 2.83 (m, 2H), 3.36 (m, 2H), 3.87 (s, 3H), 5.79 (br.s, 1H), 6.36 (d, J=16.0 Hz, 1H), 6.92 (m, 1H), 6.925 (m, 1H), 6.93 (m, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.11 (br.s, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.20 (m, 2H) 、7.23 (d, J=8.0 Hz, 1H), 7.59 (d, J=16.0 Hz, 1H), 7.71 (s, 1H).

ESI-MS; m/z524 [M^++H].^{1}H-NMR ($CDCl_3$) δ: 1.50 (m, 2H), 2.04 (m, 1H), 2.13 (m, 1H), 2.24 (m, 1H), 2.36 (m, 1H), 2.26 (s, 3H), 2.30 (s, 3H), 2.78 (m, 1H), 2.82 (m, 1H), 3.36 (m, 2H), 3.87 (s, 3H), 5.79 (br.s, 1H), 6.35 (d, J=16.0 Hz, 1H), 6.925 (m, 1H), 6.93 (m, 2H), 6.98 (m, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.11 (br.s, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.20 (m, 2H), 7.23 (d, J=8.0 Hz, 1H), 7.59 (d, J=16.0 Hz, 1H), 7.71 (s, 1H).

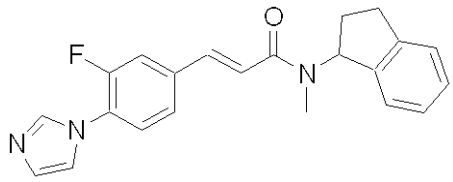
[0434]

Example 330

Synthesis of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl)-N-indan-1-yl-N-methyl-acrylamide

[0435]

[Formula 144]



To a DMF (1.0 mL) solution of (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)phenyl]-N-indan-1-yl-acrylamide (30.0 mg) obtained in Example 324, sodium hydride was added at 0°C (10.0 mg), and the reaction solution was allowed to be warmed to room temperature. Iodomethane (54.0 μL) was added to the reaction solution, the reaction solution was agitated at room temperature for 3 hours, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex NH, elution solvent heptane-ethyl acetate = 1:1), and 8.5 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.86 (s, 0.5H), 7.85 (s, 0.5H), 7.74 (d, J=16 Hz, 0.5H), 7.68 (d, J=16 Hz, 0.5H), 7.38-7.47 (m, 3H), 7.13-7.28 (m, 6H), 7.06 (d, J=16 Hz, 0.5H), 6.95 (d, J=16 Hz, 0.5 Hz), 6.41 (t, J=8.0 Hz, 0.5H), 5.67 (t, J=8.0 Hz, 0.5H), 3.00-3.12 (m, 1H), 2.94 (td, J=8.4 Hz, 16 Hz, 1H), 2.80 (s, 1.5H), 2.88 (s, 1.5H), 2.43-2.55 (m, 1H), 2.10-2.20 (m, 0.5H),

1.89-2.00 (m, 0.5H).

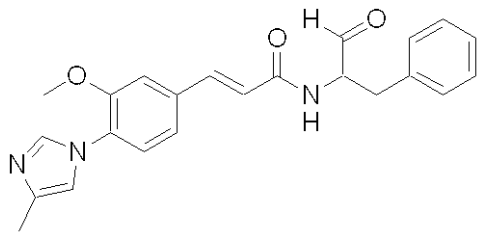
[0436]

Example 331

Synthesis of (E)-N-((1R)-formyl-2-phenylethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0437]

[Formula 145]



Dimethylsulfoxide (136 μL) was added to a methylene chloride (3 mL) solution of oxalyl chloride (100 μL) at -78°C and the reaction solution was agitated for 15 minutes. Next, the methylene chloride (2.0 mL) solution of (E)-N-[(1R)-1-hydroxymethyl-2-phenylethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylamide (150 mg) obtained in Example 124 was added to this reaction solution, and the reaction solution was agitated for 15 minutes. then, TEA (534 μL) was added to this reaction solution to warm the reaction solution up to 0°C, it was agitated for 30 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under

reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 62.0 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 9.72 (s, 1H), 7.73 (s, 1H), 7.64 (d, J=16 Hz, 1H), 7.25-7.34 (m, 4H), 7.16-7.20 (m, 3H), 7.14 (s, 1H), 6.93 (s, 1H), 6.45 (d, J=16 Hz, 1H), 6.33 (brs, 1H), 4.92 (dd, J=5.6, 7.2 Hz, 1H), 3.89 (s, 3H), 3.32 (dd, J=5.6, 14 Hz, 1H), 3.25 (dd, J=7.2, 14 Hz, 1H), 2.30 (s, 3H).

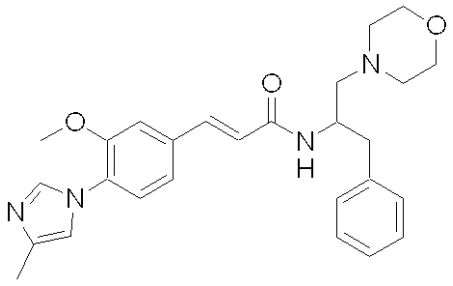
[0438]

Example 332

Synthesis of (E)-3-[3-methoxy-4-(4-(1H-methylimidazol-1-yl)-phenyl]-N-((1R)-morpholin-4-ylmethyl-2-phenylethyl)acrylamide

[0439]

[Formula 146]



To a methylene chloride (1.0 mL) solution of (E)-N-((1R)-formyl-2-phenylethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide (39.0 mg) obtained in Example 331, morpholine (13.0 μL), acetic

acid (1.0 mL) and sodium triacetoxy borohydride (64.0 mg) were added one by one. After agitating the reaction solution at room temperature overnight, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, an elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 13.9 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.70 (s, 1H), 7.59 (d, J=16 Hz, 1H), 7.14-7.32 (m, 7H), 7.12 (s, 1H), 6.92 (s, 1H), 6.38 (d, J=16 Hz, 1H), 5.88 (d, J=7.2 Hz, 1H), 4.39-4.47 (m, 1H), 3.88 (s, 3H), 3.64-3.71 (m, 4H), 3.03 (dd, J=4.8, 14 Hz, 1H), 2.97 (dd, J=6.4, 14 Hz, 1H), 2.48-2.55 (m, 2H), 2.31-2.42 (m, 4H), 2.30 (s, 3H).

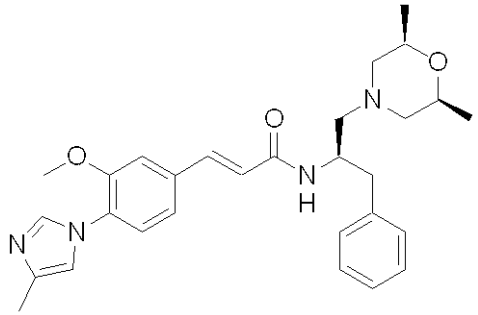
[0440]

Example 333

Synthesis of (E)-N-[(1R)-1-(cis-2,6-dimethylmorpholin-4-ylmethyl)-2-phenylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0441]

[Formula 147]



5.2 mg of the title compound was obtained by the same method as in Example 332 from (E)-N-((1R)-formyl-2-phenylethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide (25.0 mg) and cis-2 and 6-dimethylmorpholine (23.7 μL) obtained in Example 331. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (d, J=1.2 Hz, 1H), 7.61 (d, J=16 Hz, 1H), 7.29-7.33 (m, 2H), 7.17-7.26 (m, 5H), 7.13 (d, J=1.2 Hz, 1H), 6.93 (t, J=1.2 Hz, 1H), 6.38 (d, J=16 Hz, 1H), 5.82 (d, J=6.8 Hz, 1H), 4.38-4.46 (m, 1H), 3.89 (s, 3H), 3.58-3.69 (m, 2H), 3.05 (dd, J=4.8, 14 Hz, 1H), 2.97 (dd, J=6.4, 14 Hz, 1H), 2.67-2.71 (m, 2H), 2.39 (dd, J=9.2, 13 Hz, 1H), 2.28-2.33 (m, 1H), 2.30 (s, 3H), 1.85 (t, J=12 Hz, 1H), 1.67 (t, J=12 Hz, 1H), 1.13-1.16 (m, 6H).

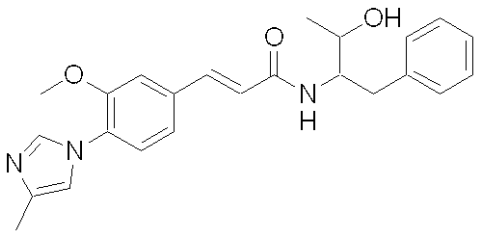
[0442]

Example 334

Synthesis of (E)-N-(1-benzyl-2-hydroxy propyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0443]

[Formula 148]



To a THF (3.0 mL) solution of the (E)-N-((1R)1-formyl-2-phenylethyl)-3-[(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide (100 mg) obtained in Example 331, methyl magnesium chloride (3MTHF solution, 0.17 mL) was added at -78°C. After warming the reaction solution to room temperature, it was agitated for 3 hours and 30 minutes, and methyl magnesium chloride (3MTHF solution, 0.51 mL) was added to the reaction solution. The reaction solution was agitated at room temperature overnight, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 33.0 mg of the title compound was obtained as an isomer mixture. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.70 (m, 1H), 7.59 (d, J=16H, 0.5H), 7.53 (d, J=16 Hz, 0.5H), 7.06-7.35 (m, 8H), 6.92-6.93 (m, 1H), 6.42 (d, J=16 Hz, 0.5H), 6.32 (d,

J=16 Hz, 0.5H), 5.92-6.30 (br, 1H), 4.30-4.39 (m, 0.5H), 4.19-4.28 (m, 0.5H), 4.00-4.10 (m, 0.5H), 3.90-3.99 (m, 0.5H), 3.86 (s, 1.5H), 3.83 (s, 1.5H), 2.92-3.02 (m, 2H), 2.29 (s, 3H), 1.10-1.30 (m, 3H).

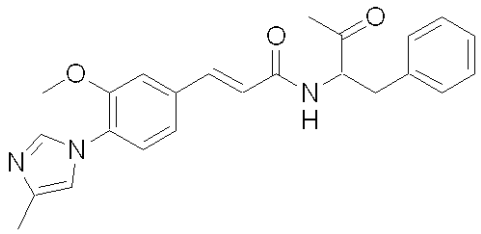
[0444]

Example 335

Synthesis of (E)-N-(1-benzyl-2-oxopropyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0445]

[Formula 149]



To a methylene chloride (2.0 mL) solution of (E)-N-(1-benzyl-2-hydroxy propyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide (29.0 mg), Dess-Martin reagent (60.7 mg) was added. After agitating the reaction solution at room temperature for 4 hours and 30 minutes, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate :

ethanol = 10:1), and 15.4 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.73 (s, 1H), 7.60 (d, J=16 Hz, 1H), 7.27-7.33 (m, 3H), 7.25 (s, 1H), 7.14-7.18 (m, 4H), 6.93 (s, 1H), 6.42 (d, J=16 Hz, 1H), 6.34 (d, J=6.8 Hz, 1H), 5.03 (td, J=5.2, 6.8 Hz, 1H), 3.89 (s, 3H), 3.25 (dd, J=6.8, 14 Hz, 1H), 3.16 (dd, J=5.2, 14 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H).

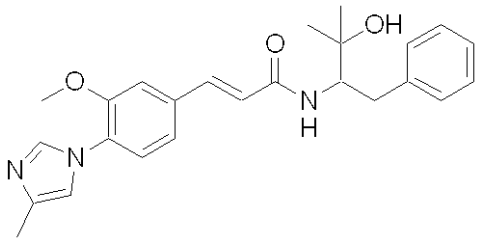
[0446]

Example 336

Synthesis of (E)-N-(1-benzyl-2-hydroxy-2-methylpropyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-phenyl]acrylamide

[0447]

[Formula 150]



To a THF (1.0 mL) solution of (E)-N-(1-benzyl-2-oxopropyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide (12.0 mg), methyl magnesium chloride (3MTHF solution, 198 μL) was added at -78°C, the reaction solution was allowed to be warmed to room temperature and agitated for further 1 hour. Water and ethyl acetate were added to the reaction

solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 6.8 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.70 (s, 1H), 7.48 (d, J=16 Hz, 1H), 7.18-7.30 (m, 6H), 7.10 (d, J=9.6 Hz, 1H), 7.07 (s, 1H), 6.92 (s, 1H), 6.29 (d, J=16 Hz, 1H), 5.84 (d, J=8.8 Hz, 1H), 4.16-4.23 (m, 1H), 3.86 (s, 3H), 3.20 (dd, J=9.6, 14 Hz, 1H), 2.80 (dd, J=11, 14 Hz, 1H), 2.29 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H).

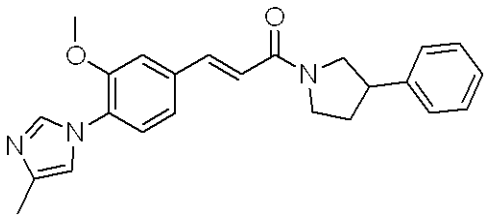
[0448]

Example 337

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(3-phenylpyrrolidine-1-yl)propenone

[0449]

[Formula 151]



By the same method as in Example 121, 65 mg (62%) of the title compound was obtained from (E)-3-[3-

methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (70 mg) and 3-phenylpyrrolidine (40 mg). The physical properties of the compound are as follows. ESI-MS; m/z388 $[M^+ +H]$. ^{1}H-NMR (DMSO-d_6) δ: 1.99-2.22 (m, 1H), 2.28 (s, 1.5H), 2.29 (s, 1.5H), 2.30-2.51 (m, 1H), 3.38-3.81 (m, 3H), 3.85 (s, 1.5H), 3.87 (s, 1.5H), 3.88-4.20 (m, 2H), 6.73 (d, J=15.6 Hz, 0.5H), 6.77 (d, J=15.6 Hz, 0.5H), 6.91 (brs, 0.5H), 6.93 (brs, 0.5H), 7.12-7.39 (m, 8H), 7.68-7.76 (m, 2H).

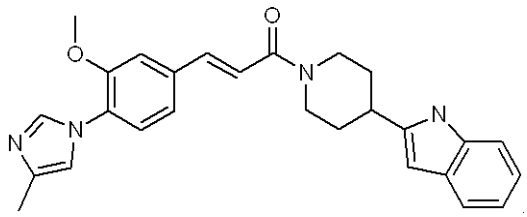
[0450]

Example 338

Synthesis of (E)-1-{4-(1H-indol-2-yl)piperidin-1-yl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0451]

[Formula 152]



By the same method as in Example 121, 47 mg (43%) of the title compound was obtained from (E)-3-[3-methoxy-4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (65 mg) and 2-piperidine-4-yl-1H-indol (50 mg). The physical properties of the compound are as follows. ESI-MS; m/z441 $[M^+ +H]$. ^{1}H-NMR (DMSO-d_6) δ(ppm): 1.70-1.88 (m, 2H), 2.12-2.23 (m, 2H), 2.30 (s, 3H), 2.83-3.11 (m, 2H), 3.27-3.43 (m, 1H), 3.89 (s, 3H), 4.17-4.28 (m,

1H), 4.76-4.87 (m, 1H), 6.27 (s, 1H), 6.93 (brs, 1H), 6.94 (d, J=15.6 Hz, 1H), 7.05-7.28 (m, 5H), 7.33 (d, J=8.0 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.67 (d, J=15.6H, 1H), 7.74 (s, 1H), 8.25 (brs, 1H).

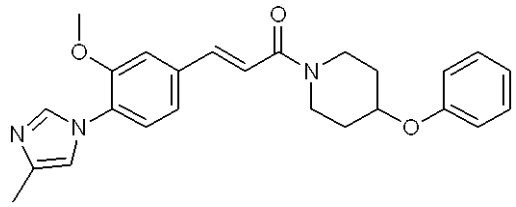
[0452]

Example 339

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(4-pheoxypiperidin-1-yl)propenone

[0453]

[Formula 153]



By the same method as in Example 121, 74 mg (91%) of the title compound was obtained from (E)-3-[3-methoxy-4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (50 mg) and 4-pheoxypiperidine hydrochloride (42 mg). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ(ppm): 1.70-2.10 (m, 4H), 2.30 (s, 3H), 3.62-3.71 (m, 1H), 3.82-3.95 (m, 3H), 3.90 (s, 3H), 4.58-4.65 (m, 1H), 6.88-7.03 (m, 5H), 7.19-7.36 (m, 5H), 7.66 (d, J=15.2 Hz, 1H), 7.73 (s, 1H).

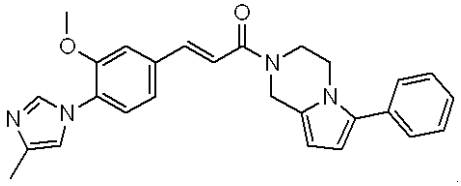
[0454]

Example 340

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(6-phenyl-3, 4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-yl)propenone

[0455]

[Formula 154]



By the same method as in Example 121, 112 mg (94%) of the title compound was obtained from (E)-3-[3-methoxy-4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (70 mg), 6-phenyl 1, 2, and 3, and 4-tetrahydropyrrolo [1,2-a] pyrazine (54 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.31 (s、3H), 3.92 (s, 3H), 3.95-4.22 (m, 4H), 4.96-5.03 (m, 2H), 6.11 (d, J=3.2 Hz, 1H), 6.28 (d, J=3.2 Hz, 1H), 6.86-6.97 (m, 2H), 7.17 (brs, 1H), 7.21-7.45 (m, 7H), 7.73 (d, J=15.6 Hz, 1H), 7.74 (brs, 1H).

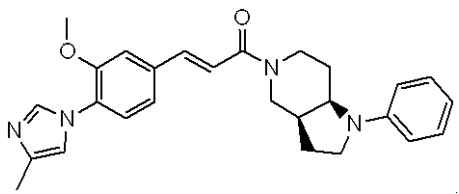
[0456]

Example 341

Synthesis of (E)-3-[3-methoxy-4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-phenyl-octahydropyrrolo[3,2c]pyridine-5-yl)propenone

[0457]

[Formula 155]



By the same method as in Example 121, 46 mg (90%) of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (30 mg) and 1-phenyloctahydropyrrolo[3,2-c] pyridine (24 mg). The physical properties of the compound are as follows.

ESI-MS; m/z443 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.50-1.91 (m, 1H), 1.91-2.25 (m、3H), 2.30 (s, 3H), 2.49-2.64 (m, 1H), 3.01-3.12 (m, 0.5H), 3.24-3.55 (m, 3H), 3.65-3.77 (m, 0.5H), 3.89 (s, 3H), 3.90-4.00 (m, 2H), 4.23-4.42 (m, 1H), 6.54-6.63 (m, 2H), 6.68 (t, J=7.2 Hz, 1H), 6.87 (d, J=15.2 Hz, 1H), 6.92 (brs, 1H), 7.12 (s, 1H), 7.17-7.28 (m, 4H), 7.67 (d, J=15.2 Hz, 1H), 7.72 (s, 1H).

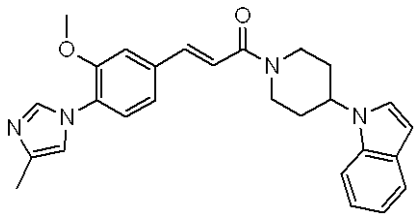
[0458]

Example 342

Synthesis of (E)-1-(4-indol-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenylpropenone

[0459]

[Formula 156]



By the same method as in Example 121, 86 mg (82%) of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (50 mg) and 1-piperidin-4-yl-1H-indol (46 mg).

The physical properties of the compound are as follows. ESI-MS; m/z441 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.93-2.10 (m、2H), 2.19-2.29 (m.2H), 2.30 (s, 3H), 2.83-2.97 (m, 1H), 3.34-3.46 (m, 1H), 3.91 (s, 3H), 4.26-4.43 (m, 1H), 4.48-4.58 (m, 1H), 4.90-5.10 (m, 1H), 6.55 (d, J=3.2 Hz, 1H), 6.94 (s, 1H), 6.96 (d, J=15.6 Hz, 1H), 7.11-7.19 (m, 3H), 7.21-7.29 (m, 3H), 7.40 (d, J=8.0 Hz, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.71 (d, J=15.6 Hz, 1H), 7.73 (s, 1H).

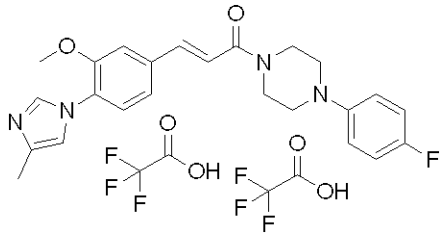
[0460]

Example 343

Synthesis of (E)-1-[4-(4-fluorophenyl)piperazin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone 2 trifluoroacetic acid salt

[0461]

[Formula 157]



5.30 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and 1-(4-fluorophenyl)piperazine (16.0 mg) by the same method as in Example 94. The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.16 (d, J=1.6 Hz, 1H), 7.64 (d,

J=15.6 Hz, 1H), 7.607.61 (m, 2H), 7.58 (d, J=8.4 Hz, 1H), 7.45 (dd, J=1.6 Hz, 8.4 Hz, 1H), 7.38 (d, J=15.6 Hz, 1H), 6.80-7.03 (m, 4H), 4.00 (s, 3H), 3.95 (brs, 2H), 3.88 (brs, 2H), 3.17 (brs, 4H), 2.43 (s, 3H).

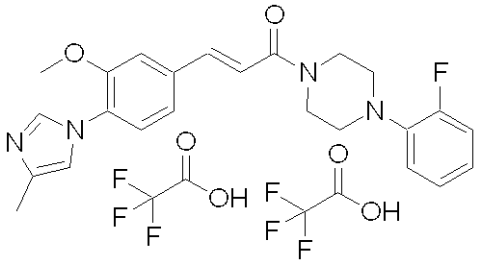
[0462]

Example 344

Synthesis of (E)-1-[4-(2-fluorophenyl)piperazin-1-yl]-3-[3-methoxy-4-(4-(1H-imidazol-1-yl)phenyl]propenone 2 trifluoroacetic acid salt

[0463]

[Formula 158]



By the same method as in Example 94, 7.5 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and 1-(2-fluorophenyl)piperazine monohydrochloride (19.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.16 (d, J=1.6 Hz, 1H), 7.64 (d, J=15.6 Hz, 1H), 7.60-7.61 (m, 2H), 7.58 (d, J=8.4 Hz, 1H), 7.45 (dd, J=1.6 Hz, 8.4 Hz, 1H), 7.38 (d, J=15.6 Hz, 1H), 6.80-7.03 (m, 4H), 4.00 (s, 3H), 3.95 (brs, 2H), 3.88 (brs, 2H), 3.17 (brs, 4H), 2.43 (s, 3H).

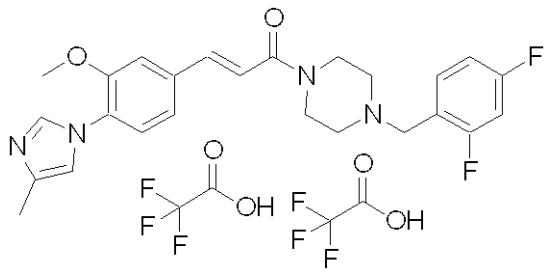
[0464]

Example 345

Synthesis of (E)-1-[4-(2,4-difluorobenzyl)piperazin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone 2 trifluoroacetic acid salt

[0465]

[Formula 159]



By the same method as in Example 94, 4.00 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and 1-(2, 4-difluorobenzyl)piperazine dihydrochloride (25.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.16 (d, J=1.6 Hz, 1H), 7.68 (d, J=16 Hz, 1H), 7.59-7.67 (m, 3H), 7.57 (d, J=8.0 Hz, 1H), 7.45 (dd, J=1.6 Hz, 8.4 Hz, 1H), 7.34 (d, J=16 Hz, 1H), 7.12-7.21 (m, 2H), 4.44 (s, 2H), 3.80-4.20 (brs, 4H), 3.99 (s, 3H), 3.40 (brs, 4H), 2.43 (s, 3H).

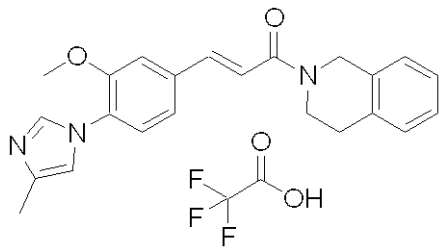
[0466]

Example 346

Synthesis of (E)-1-(3,4-dihydro-1H-isoquinoline-2-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone trifluoroacetic acid salt

[0467]

[Formula 160]



By the same method as in Example 94, 4.90 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (15.0 mg) and 1,2,3,4-tetrahydroisoquinoline (12.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.16 (d, J=1.6 Hz, 1H), 7.65 (d, J=16 Hz, 1H), 7.60-7.63 (m, 2H), 7.57 (d, J=8.0 Hz, 1H), 7.397.48 (m, 2H), 7.20 (brs, 4H), 4.96 (s, 1H), 4.82 (s, 1H), 4.01 (s, 3H), 4.01 (t, J=5.6 Hz, 1H), 3.91 (t, J=5.6 Hz, 1H), 3.00 (t, J=5.6 Hz, 1H), 2.93 (t, J=5.6 Hz, 1H), 2.43 (s, 3H).

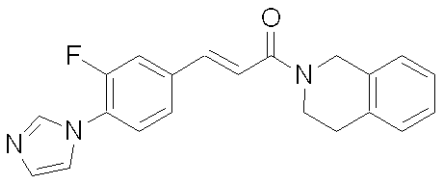
[0468]

Example 347

Synthesis of (E)-1-(3,4-dihydro-1H-isoquinoline-2-yl)-3-[3-fluoro-4-(1H-imidazol-1-yl)-phenyl]propenone

[0469]

[Formula 161]



By the same method as in Example 324, 16.0 mg of the title compound was obtained from (E)-3-[3-fluoro-4-(1H-imidazol-1-yl)-phenyl]acrylic acid (20.0 mg) and 1,2,3,4-tetrahydroisoquinoline (22.0 μL). The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.91 (s, 1H), 7.63 (d, J=16 Hz, 1H), 7.38-7.45 (m, 3H), 7.27 (s, 1H), 7.14-7.24 (m, 4H), 7.13 (s, 1H), 6.96-7.01 (m, 1H), 4.82 (s, 2H), 3.86-3.92 (m, 2H), 2.92-3.00 (m, 2H).

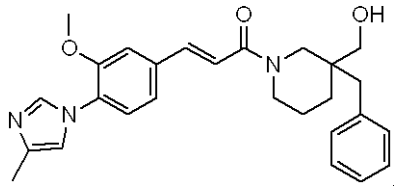
[0470]

Example 348, Example 348-1 and Example 348-2

Synthesis of (E)-1-(3-benzyl-3-hydroxymethylpiperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0471]

[Formula 162]



Synthesis of (±)-(E)-1-(3-benzyl-3-hydroxymethyl-piperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

To a DMF (5 mL) solution of (E)-3-[4-methyl -1H-imidazol-1-yl]-3-methoxyphenyl)acrylic acid (250 mg) obtained in Example 121 and (3-benzyl-piperidin-3-yl)methanol (200 mg), isopropyl ethylamine (0.34 mL), HOBT (158 mg), and EDC (230 mg) were added, and the

reaction solution was agitated at room temperature for 12 hours. Ethyl acetate and a saturated sodium bicarbonate water were added to the reaction solution after the reaction ended, and the organic layer was separated. After drying the obtained organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: from ethyl acetate to ethyl acetate : methanol = 9:1), and 310 mg (71%) of (±)-(E)-1-(3-benzyl-3-hydroxymethylpiperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z446 [M^++H].

[0472]

Synthesis of (+)-(E)-1-(3-benzyl-3-hydroxymethyl-piperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone and (-)-(E)-1-(3-benzyl-3-hydroxymethyl-piperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

(±)-(E)-1-(3-benzyl-3-hydroxymethyl-piperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (310 mg) was separated using CHIRALPAK™AD-H (25 cm x 2 cm; mobile phase hexane: isopropanol 7:3) available from Daicel Chemical Industries, Ltd. 30 mg of (-)-(E)-1-(3-benzyl-3-hydroxymethylpiperidin-1-yl)-3-[3-methoxy-4-(4-methyl—

1H-imidazol-1-yl)phenyl]propenone having a shorter retention time (retention time: 12.9 minutes) was obtained by 99%e.e., and 29 mg of (+)-(E)-1-(3-benzyl-3-hydroxymethylpiperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone having a longer retention time (retention time: 13.5 minutes) was obtained by 94%e.e.

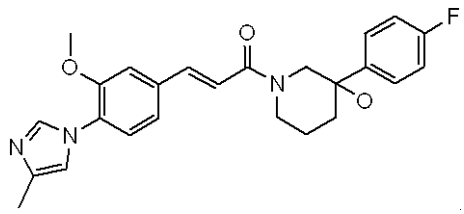
[0473]

Example 349, Example 349-1 and Example 349-2

Synthesis of (±)-(E)-1-[3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl]phenyl]propenone

[0474]

[Formula 163]



Synthesis of (±)-(E)-1-[3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

Isopropylethylamine (0.07 mL), HOBT (45 mg) and EDC (64 mg) were added to a DMF (3 mL) solution of (E)-3-[4-methyl-1H-imidazol-1-yl-3-methoxyphenyl)acrylic acid (71 mg) obtained in Example 121 and 3-(4-fluorophenyl)piperidin-3-ol (54 mg), and the reaction solution was agitated at room temperature for 12 hours. Ethyl acetate and a saturated sodium

bicarbonate water were added to the reaction solution after the reaction ended, and the organic layer was separated. After drying the obtained organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: from ethyl acetate to ethyl acetate : methanol 9:1) and 91 mg (75%) of (±)-(E)-1-[3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z436 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.55-2.20 (m、3H), 2.32 (s、3H), 2.68-2.76 (m、1H), 3.12-3.50 (m、2H), 3.89 (s、3H), 4.08-4.22 (m, 1H), 4.55-90) m, 1H), 6.84-7.04 (m, 2H), 7.05-7.33 (m, 5H), 7.50-5.57 (m, 2H), 7.64-7.78 (m, 2H).

[0475]

<u>Synthesis of (+)-(E)-1-[3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone and (-)-(E)-1-[3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone</u>

(±)-(E)-1-(3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (80 mg) obtained above was separated by CHIRALPAK™AD-H (25 cm x 2 cm; mobile phase hexane: isopropanol 7:3) available from Daicel

Chemical Industries, Ltd. 14 mg of (-)-(E)-1-[3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone having a short retention time (retention time: 16.3 minutes) was obtained by 99%e.e. and 13 mg of (+)-(E)-1-[3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone having a longer retention time (retention time: 20.4 minutes) of-(E)-1-(3-(4-fluorophenyl)-3-hydroxypiperidin-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)propenone was obtained by 89%e.e.

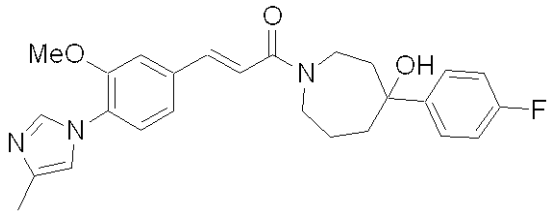
[0476]

Example 350

Synthesis of (E)-1-[4-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0477]

[Formula 164]



Synthesis of 1-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-phenyl]acryloyl}azepan-4-one

The method of Example 121 was followed to synthesize 1-{3-[3-methoxy-4-(4-methylimidazol-1-yl)phenyl]acryloyl)azepan-4-one. The physical

properties of the compound are as follows.

ESI-MS; m/z354 [M^++H]

[0478]

Synthesis of (E)-1-[4-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

Fluorobenzene magnesium bromide (1.0M THF solution, 0.85 mL) was added to a THF (7 mL) solution of the amide (100 mg) obtained above under ice-cooling. The reaction solution was allowed to be warmed to room temperature and agitated for further 2 hours. An ice-cooled water was added after the reaction ended, extracted with ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: ethanol : ethyl acetate = 1:4), and 63 mg (50%) of the title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z450 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.87 (m, 1H), 1.88 (m, 2H), 2.01 (m, 2H), 2.12 (m, 1H), 2.23 (s, 3H), 3.45 (m, 1H), 3.79 (m, 1H), 3.93 (s, 3H), 3.95 (m, 1H), 4.11 (m, 1H), 7.00 (dd, J=9.0, 9.0 Hz, 2H), 7.08 (br.d, J=7.0 Hz, 1H), 7.19 (d, J=15.0 Hz, 1H), 7.32 (m, 1H), 7.36 (m, 1H), 7.44 (m, 1H), 7.47 (m, 2H), 7.61 (d, J=15.0 Hz, 1H), 7.81 (br.d, J=7.0 Hz, 1H).

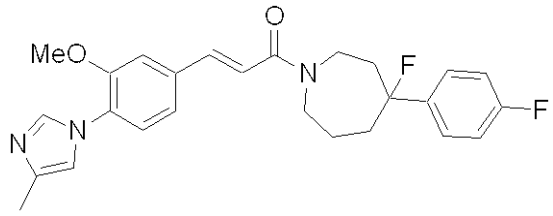
[0479]

Example 351

Synthesis of (E)-1-[4-fluoro-4-(4-fluorophenyl)azepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0480]

[Formula 165]



To a methylene chloride (4 mL) solution of (E)-1-[4-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (50 mg) obtained in Example 350, DAST (0.022 mL) was added at -78°C, and the reaction solution was allowed to be warmed to room temperature and the reaction solution was agitated for 7 hours. Water was added to the reaction solution after the reaction ended, extracted with ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: ethanol : ethyl acetate = 1:10), and 43 mg (86%) of the title compound was obtained. The physical properties of the

compound are as follows.

ESI-MS; m/z452 [M^++H].^{1}H-NMR ($CDCl_3$) δ(ppm): 2.03 (m, 2H), 2.16 (m, 2H), 2.22 (s, 3H), 2.72 (m, 1H), 2.85 (m, 1H), 3.46 (br.dd, J=14.0, 14.0 Hz, 1H), 3.55 (ddd, J=7.0, 7.0, 14.0 Hz, 1H), 3.93 (s, 3H), 3.99 (m, 1H), 4.14 (ddd, J=7.0, 7.0, 14.0 Hz, 1H), 7.06 (dd, J=7.0, 9.0 Hz, 2H), 7.09 (d, J=7.0 Hz, 1H), 7.18 (d, J=15.0 Hz, 1H), 7.32 (m, 1H), 7.37 (m, 1H), 7.39 (m, 2H), 7.46 (br.s, 1H), 7.62 (d, J=15.0 Hz, 1H), 7.83 (d, J=7.0 Hz, 1H).

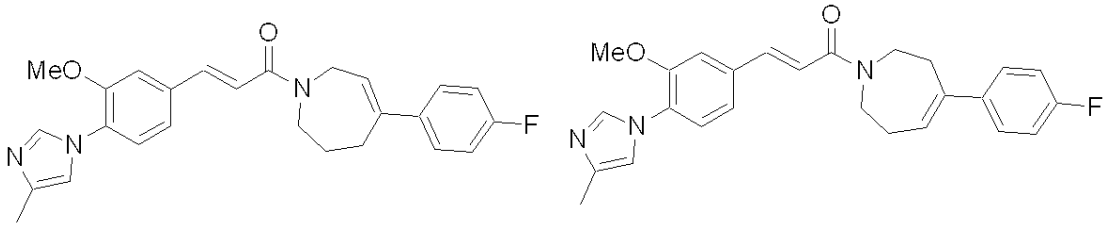
[0481]

Example 352

Synthesis of (E)-1-[5-(4-fluorophenyl)-2,3,4,7-tetrahydroazepin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone and (E)-1-[4-(4-fluorophenyl)-2,3,6,7-tetrahydroazepin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0482]

[Formula 166]



Synthesis of 4-(4-fluorophenyl)-4-hydroxyazepane-1-carboxylic acid tert-butyl ester

To a THF (60 mL) solution of tert-butyl ester of 4-oxoazepane-1-carboxylic acid (5 g), fluoro benzene

magnesium bromide (1.0M THF solution, 82 mL) was added under ice-cooling, and the reaction solution was allowed to be warmed to room temperature and agitated for 1 hour. Water was added to the reaction solution under ice-cooling after the reaction ended, extracted with ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. The organic layer separated was dried over anhydrous magnesium sulfate and then the solvent was evaporated under reduced pressure. The obtained residue is purified by silica gel column chromatography (elution solvent: heptane : ethyl acetate = 2:1), and 3.73 g (52%) of 4-(4-fluorophenyl)-4-hydroxyazepane-1-carboxylic acid tert-butyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.47 (s, 9H), 1.62-2.26 (m, 6H), 3.22-3.44 (m, 2H), 3.37-3.89 (m, 3H) 、6.95-7.07 (m, 2H), 7.36-7.48 (m, 2H).

ESI-MS; m/z332 [M^++Na]

[0483]

Synthesis of 4-(4-fluorophenyl)-2,3,6,7-tetrahydroazepin-1-carboxylic acid tert-butyl ester and 5-(4-fluorophenyl)-2,3,4,7-tetrahydroazepin-1-carboxylic acid 4-(4-fluorophenyl)-4-hydroxy-azepane-1-carboxylic acid tert-butyl ester

To a methylene chloride (20 mL) solution of 4-(4-fluorophenyl)-4-hydroxyazepane-1-carboxylic acid tert-butyl ester (500 mg) obtained above, TEA (1.13 mL)

and methane sulfonylchloride (0.15 mL) were added under ice-cooling, and the reaction solution was agitated at room temperature for 1 hour. Water is added to the reaction solution under ice-cooling liquid after the reaction ended, extracted with ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. The organic layer separated was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane : ethyl acetate 2:1) and 3.73 g (52%) of the olefin compound as an isomer mixture was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.46 (s, 9H), 1.90 (br.s, 1H), 2.44br.s, 1H), 2.60-2.80 (m, 2H), 3.46-3.70 (m, 3H), 3.92-4.14 (m, 1H), 5.95 (t, J=5.6 Hz, 1H), 6.97 (t, J=8.8 Hz, 2H), 7.20-7.32 (m, 2H).

ESI-MS; m/z314 [M^++Na].^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 9H), 1.90 (br.s, 1H), 2.44br.s, 1H), 2.60-2.80 (m, 2H), 3.46-3.70 (m, 3H), 3.92-4.14 (m, 1H), 5.95 (t, J=5.6 Hz, 1H), 6.97 (t, J=8.8 Hz, 2H), 7.20-7.32 (m, 2H).

[0484]

<u>Synthesis of 4-(4-fluorophenyl)-2,3,6,7-tetrahydro-1H-azepine hydrohloride salt and 5-(4-fluorophenyl)-2,3,4,7-tetrahydro-1H-azepine hydrohloride salt</u>

To an ethyl acetate (5 mL) solution of the olefin (250 mg) obtained above, 4N hydrochloric acid

was added at room temperature, and the reaction solution was agitated for 2 hours. It was concentrated under reduced pressure after the reaction ended and used for the next reaction as it was without purification.

[0485]

Synthesis of (E)-1-[5-(4-fluorophenyl)-2,3,4,7-tetrahydroazepin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-phenyl]propenone and (E)-1-[4-(4-fluorophenyl)-2,3,6,7-tetrahydroazepin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-phenyl]propenone

By the same method as in Example 121, 157 mg (55%) of the title compound was obtained from crude amine (150 mg) obtained above and (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid. The physical properties of the compound are as follows.

ESI-MS; m/z454 $[M^+ + Na]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.00-2.12 (m, 2H), 2.30 (s, 3H), 2.54-2.63 (m, 1.5H), 2.66-2.77 (m, 1H), 2.80-2.90 (m, 1.5H), 3.80-3.98 (m, 3H), 3.90 (s, 3H), 4.33 (d, J=5.6 Hz, 1H), 5.95 (t, J=5.6 Hz, 0.5H), 6.09 (t, J=5.6 Hz, 0.5H), 6.82-7.04 (m, 2H), 7.08-7.18 (m, 1H), 7.19-7.34 (m, 4H), 7.62-7.77 (m, 2H).

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.00-2.12 (m, 2H), 2.30 (s, 3H), 2.54-2.63 (m, 1.5H), 2.66-2.77 (m, 1H), 2.80-2.90 (m, 1.5H), 3.80-3.98 (m, 3H), 3.88 (s, 3H), 4.26 (d, J=5.2 Hz, 1H), 5.98-6.06 (m, 1H), 6.82-7.04 (m, 2H), 7.08-7.18 (m, 1H), 7.19-7.34 (m, 4H), 7.62-7.77 (m, 2H).

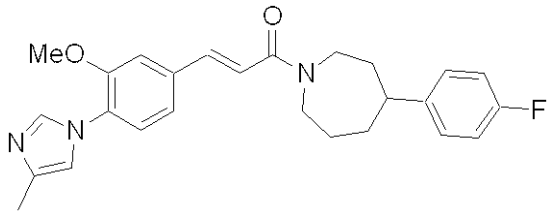
[0486]

Example 353

Synthesis of (E)-1-[4-(4-fluorophenyl)azepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0487]

[Formula 167]



Synthesis of 4-(4-fluorophenyl)azepane-1-carboxylic acid tert-butyl ester

To a methanol (10 mL) solution of 4-(4-fluorophenyl)-4-hydroxyazepane-1-carboxylic acid tert-butyl ester (100 mg) obtained in Example 352, 10% Pd-C (100 mg) was added, and the reaction solution was agitated in hydrogen stream at room temperature for 1 hour. Suction filtration of the reaction solution was carried out using celite after the reaction ended, and the filtrate was concentrated under reduced pressure. The obtained crude product of 4-(4-fluorophenyl)azepane-1-carboxylic acid tert-butyl ester was used for the next reaction, without further purifying.

[0488]

Synthesis of 4-(4-fluorophenyl)azepane

By the same method as in Example 352, 4-(4-fluorophenyl)azepane was obtained from 4-(4-fluorophenyl)azepane-1-carboxylic acid tert-butyl ester (80 mg) obtained above. The obtained crude product was used for the next reaction without further purifying.

[0489]

Synthesis of (E)-1-[4-(4-fluorophenyl)azepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

By the same method as in Example 121, 75 mg (66%) of the title compound was obtained from 4-(4-fluorophenyl)azepane (60 mg) obtained above and (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid. The physical properties of the compound are as follows.

ESI-MS; m/z456 $[M^+ + Na]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.62-2.03 (m, 4H), 2.04-2.20 (m, 2H), 2.29 (s, 1.5H), 2.30 (s, 1.5H), 2.62-2.76 (m, 1H), 3.44-3.72 (m, 2H), 3.73-3.96 (m, 1.5H), 3.88 (s, 1.5H), 3.90 (s, 1.5H), 3.97-4.07 (m, 0.5H), 6.82-7.00 (m, 4H), 7.06-7.16 (m, 3H), 7.17-7.29 (m, 2H), 7.68-7.76 (m, 2H).

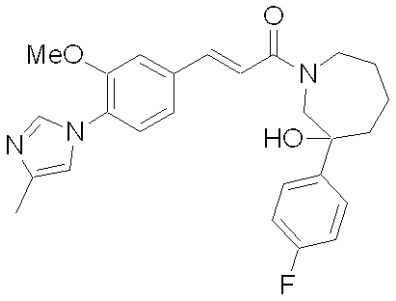
[0490]

Example 354

Synthesis of (E)-1-[3-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0491]

[Formula 168



Synthesis of 3-(4-fluorophenyl)-3-hydroxyazepane-1-carboxylic acid tert-butyl ester

By the same method as in Example 352, 528 mg (72%) of 3-(4-fluorophenyl)-3-hydroxyazepane-1-carboxylic acid tert-butyl ester was obtained from 3-oxoazepine-1-carboxylic acid tert-butyl ester (507 mg). The physical properties of the compound are as follows. ESI-MS; m/z332 $[M^+ + Na]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.50 (s, 9H), 1.60-1.74 (m, 2H), 1.80-2.10 (m, 4H), 2.90-3.40 (m, 2H), 3.80-4.10 (m, 1H), 4.03 (d, J=15.2 Hz, 1H), 4.66 (s, 1H), 6.94-7.08 (m, 2H), 7.40-7.54 (m, 2H).

[0492]

Synthesis of 3-(4-fluorophenyl)azepan-3-ol

By the same method as in Example 352, 3-(4-fluorophenyl)azepan-3-ol was obtained from the 3-(4-fluorophenyl)-3-hydroxyazepane-1-carboxylic acid tert-butyl ester (150 mg) obtained above. The obtained crude product was used for the next reaction, without purifying further.

[0493]

Synthesis of (E)-1-[3-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

By the same method as in Example 121, 160 mg (74%) of the title compound was obtained from the 3-(4-fluorophenyl)azepan-3-ol (119 mg) obtained above and (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid. The physical properties of the compound are as follows.

ESI-MS; m/z472 [M^++Na]. ^{1}H-NMR ($CDCl_3$) δ: 1.64-2.26 (m, 6H), 2.24 (s, 3H), 3.50-3.79 (m, 2H), 3.93 (s, 3H), 3.98-4.32 (m, 2H), 7.00-7.15 (m, 3H), 7.20-7.31 (m, 2H), 7.32-7.44 (m, 2H), 7.46-7.73 (m, 3H), 7.87 (dd, J=1.0, 6.8 Hz, 1H).

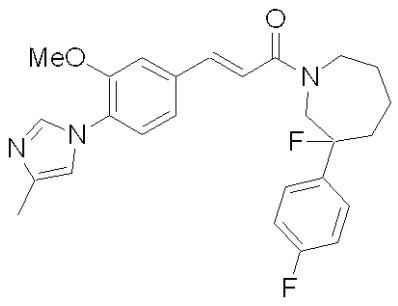
[0494]

Example 355

Synthesis of (E)-1-[3-fluoro-3-(4-fluorophenyl)azepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0495]

[Formula 169]



Synthesis of (E)-1-[3-fluoro-3-(4-fluorophenyl)azepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

To a methylene chloride (5 mL) solution of (E)-1-[3-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (50 mg) obtained in Example 354, DAST (0.022 mL) was added at -78°C, and the reaction solution was allowed to be warmed to room temperature and agitated for 13 hours. Water was added to the reaction solution after the reaction ended, extracted with ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: ethanol : ethyl acetate = 1:5), and 30 mg (60%) of the title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z474 $[M^+ + Na]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.68-2.40 (m, 5H), 2.30 (s, 3H), 3.15-3.30 (m, 1H), 3.52-3.80 (m, 2H), 3.90 (s, 3H), 4.00-4.45 (m, 2H), 6.82-6.98 (m, 2H), 7.00-7.18 (m, 3H), 7.20-7.34 (m, 2H), 7.36-7.54 (m, 2H), 7.66 (d, J=15.6 Hz, 1H), 7.74 (d, J=7.0 Hz, 1H).

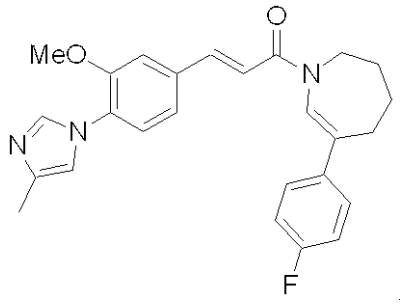
[0496]

Example 356

Synthesis of (E)-1-[6-(4-fluorophenyl)-2,3,4,5-tetrahydroazepin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0497]

[Formula 170]



Synthesis of (E)-1-[6-(4-fluorophenyl)-2,3,4,5-tetrahydroazepin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

By the same method as in Example 352, 5 mg (6%) of the title compound was obtained from (E)-1-[3-(4-fluorophenyl)-4-hydroxyazepan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (52 mg) obtained in Example 354. The physical properties of the compound are as follows.

ESI-MS; m/z432 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (m, 2H), 1.94 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 3.89 (s, 3H), 3.91 (m, 2H), 6.75 (s, 1H), 6.87 (d, J=15.0 Hz, 1H), 6.92 (m, 1H), 7.06 (m, 2H), 7.11 (s, 1H), 7.24 (d, J=6.0 Hz, 1H), 7.27 (d, J=6.0 Hz, 1H), 7.34 (ddd, J=2.0, 5.0, 9.0 Hz, 2H), 7.70 (d, J=15.0 Hz, 1H), 7.76 (m, 1H).

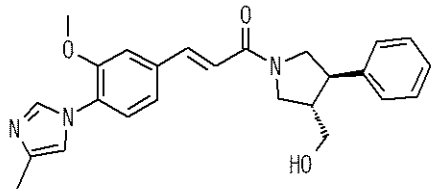
[0498]

Example 357

Synthesis of (E)-1-(3-hydroxymethyl-4-phenylpyrrolidine-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0499]

[Formula 171]



By the same method as in Example 121, 368 mg (76%) of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (290 mg) and trans-(4-phenylpyrrolidine-3-yl)methanol (200 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.28 (d, J=0.8 Hz, 1.5H), 2.30 (d, J-0.8 Hz, 1.5H), 2.55-2.73 (m, 1H), 3.17 (td, J=10.0, 8.0 Hz, 0.5H), 3.35 (td, J=10.0, 8.0 Hz, 0.5H), 3.50-3.82 (m, 4H), 3.87 (s, 1.5H), 3.91 (s, 1.5H), 4.09-4.22 (m, 2H), 6.68 (d, J=15.2 Hz, 0.5H), 6.78 (d, J=15.2 Hz, 0.5H), 6.91 (brt, 0.5H), 6.93 (brt, 0.5H), 7.11-7.40 (m, 8H), 7.70 (d, J=0.8 Hz, 0.5H), 7.71 (d, J=15.2 Hz, 0.5H), 7.72 (d, J=15.2 Hz, 0.5H), 7.73 (d, J=0.8 Hz, 0.5H).

[0500]

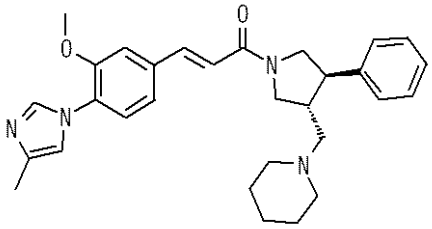
Example 358

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(trans-3-phenyl-4-piperidin-1-

ylmethylpyrrolidin-1-yl)propenone

[0501]

[Formula 172]



To a methylene chloride (3 mL) solution of (E)-1-(3-hydroxymethyl-4-phenyl-pyrrolidine-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)propenone (65 mg) obtained in Example 357, Dess-Martin reagent (128 mg) was added at 0°C, the reaction solution was agitated at the temperature for 1 hour, and then agitated at room temperature for 1 hour. The reaction solution was washed with a saturated sodium bicarbonate water, and after drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained aldehyde compound was used for the following reaction, without carrying out further purifying. Piperidine (5.9 μL) and acetic acid (4.5 μL) were added to the methylene chloride (2 ml) solution of the above-mentioned aldehyde compound (17 mg). Furthermore, sodium triacetoxy borohydride (17 mg) was added to the solution, and the reaction solution was agitated at room temperature for 12 hours. Ethyl acetate was added to the reaction solution after the reaction ended, and the reaction solution was

washed with a saturated sodium bicarbonate water. After drying the separated organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, an elution solvent: from ethyl acetate to ethyl acetate : methanol 9:1), and 19.7 mg (76%) of the title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z507 [M+Na^+]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.35-1.60 (m, 6H), 2.15-2.48 (m, 9H), 2.55-2.72 (m, 1H), 3.01 (q, J=9.6 Hz, 0.5H), 3.15 (q, J=9.6 Hz, 0.5H), 3.38 (dd, J=12.8, 9.2 Hz, 0.5H), 3.52 (t, J=10.0 Hz, 0.5H), 3.61 (dd, J=12.8, 9.2 Hz, 0.5H), 3.67 (t, J=10.0 Hz, 0.5H), 3.87 (s, 1.5H), 3.93 (s, 1.5H), 4.06-4.21 (m, 2H), 6.70 (d, J=15.6 Hz, 0.5H), 6.80 (d, J=15.6 Hz, 0.5H), 6.92 (brt, 0.5H), 6.95 (brt, 0.5H), 7.11 (d, J=1.6 Hz, 0.5H), 7.15-7.40 (m, 7.5H), 7.70 (d, J=15.6 Hz, 0.5H), 7.72 (d, J=1.6 Hz, 0.5H), 7.73 (d, J=15.6 Hz, 0.5H), 7.74 (d, J=1.6 Hz, 0.5H).

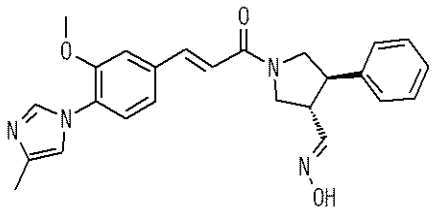
[0502]

Example 359

Synthesis of (E)-1-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl]phenyl}acryloyl)-4-phenylpyrrolidine-3-carbaldehyde oxime

[0503]

[Formula 173]



To an ethanol (2 ml) solution of (E)-1-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acryloyl}-4-phenylpyrrolidine-3-carbaldehyde (34 mg) obtained in Example 358, hydroxylamine hydrochloride and sodium acetate were added, and the reaction solution was agitated at room temperature for 12 hours. After condensing reaction solution under reduced pressure, ethyl acetate and saturated sodium bicarbonate water were added, and the organic layer was partitioned. The obtained organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, an elution solvent: ethyl acetate : methanol = 10:1), and 16.2 mg (46%) of the title compound was obtained as a mixture of oxime moiety Z:E=1:2. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.28 (s, 1.5H), 2.29 (s, 1.5H), 3.19-3.77 (m, 4H), 3.87 (s, 1.5H), 3.90 (s, 1.5H), 4.08-4.37 (m, 2H), 6.67-6.79 (m, 1.3H), 6.92 (brs, 0.5H), 6.94 (brs, 0.5H), 7.11-7.42 (m, 8.7H), 7.71

(brs, 0.5H), 7.72 (brs, 0.5H), 7.75 (brs, 1H), 8.70 (brs, 0.35H), 9.01 (brs, 0.15H), 9.20 (brs, 0.35H), 9.64 (brs, 0.15H).

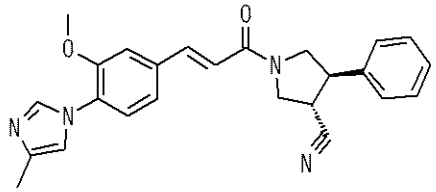
[0504]

Example 360

Synthesis of (E)-1-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acryloyl}-4-phenylpyrrolidine-3-carbonitrile

[0505]

[Formula 174]



To a THF (3 ml) solution of (E)-1-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acryloyl}-4-phenylpyrrolidine-3-carbaldehyde oxime (17.8 mg) obtained in Example 359, CDI (32.4 mg) was added at room temperature, and heat-refluxing was carried out for 3 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate and saturated sodium bicarbonate solution were added to the reaction solution, and the organic layer was partitioned. After drying the obtained organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column

chromatography (elution solvent: ethyl acetate : methanol 10:1), and the 14.6 mg (86%) title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z413 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ(ppm): 2.30 (s, 1.8H), 2.31 (s, 1.2H), 3.18-3.34 (m, 1H), 3.65-3.87 (m, 2.6H), 3.89 (s, 1.8H), 3.92 (s, 1.2H), 4.03 (t, J=9.2 Hz, 0.4H), 4.24-4.35 (m, 2H), 6.67 (d, J=15.6 Hz, 0.6H), 6.68 (d, J=15.6 Hz, 0.4H), 6.93 (brs, 0.6H), 6.95 (brs, 0.4H), 7.13-7.46 (m, 8H), 7.73 (brs, 0.6H), 7.74 (brs, 0.4H), 7.75 (d.J=15.6 Hz, 0.6H), 7.76 (d, J=15.6 Hz, 0.4H).

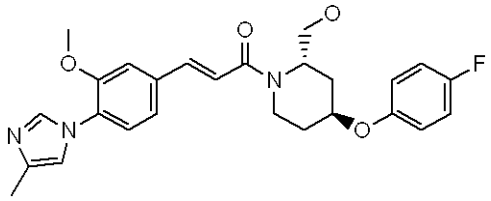
[0506]

Example 361

Synthesis of-(E) trans-1-[4-(4-fluoropheoxy)-2-hydroxymethyl-piperidin-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0507]

[Formula 175]



By the same method as in Example 121, 78 mg (68%) of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (63 mg) and trans-(4-(4-fluoropheoxy)piperidine-2-yl)methanol (55 mg). The physical properties of the

compound are as follows.

ESI-MS; m/z466 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.76-1.86 (m、1H), 2.16-2.35 (m、5H), 2.82-2.99 (m、1H), 3.41-3.58 (m、1H), 3.76-4.13 (m、5H), 4.75-5.06 (m、3H), 6.85 (dd、J=9.2, 4.4 Hz, 2H), 6.93 (brs, 1H), 6.98 (t, J=9.2 Hz, 2H), 7.11 (brs, 1H), 7.14-7.28 (m, 3H), 7.64 (d, J=15.2 Hz, 1H), 7.72 (brs, 1H).

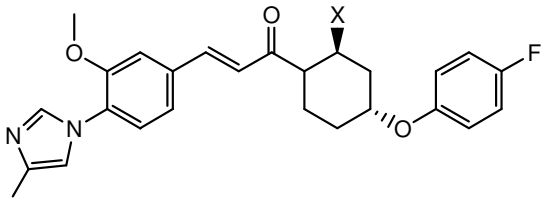
[0508]

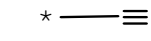
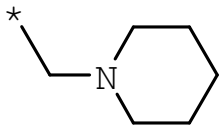
The racemates or racemic compounds shown in Table 8 were synthesized as in Example 358, 359 and 360.

The structural formulae and physicochemical properties are shown in Table 8, respectively.

[0509]

[Table 8]



Example	X	DATA:MS m/z
362		M^++H:461 (ESI)
363		M^++H:493 (ESI)
364		M^++H:533 (ESI)

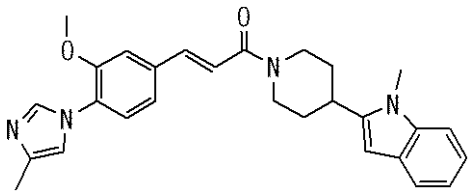
[0510]

Example 365

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-[4-(1-methyl-1H-indol-2-yl)piperidin-1-yl]propenone

[0511]

[Formula 176]



To a THF (1 mL) solution of (E)-1-{4-(1H-indol-2-yl)piperidin-1-yl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (20 mg) obtained in Example 338 and iodomethane (0.04 mL), sodium hydride (2.2 mg) was added at room temperature. The reaction solution was agitated at room temperature for 7 hours. Ethyl acetate and a saturated ammonium chloride solution were added to the reaction solution after the reaction ended, and the organic layer was partitioned. After drying the obtained organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, an elution solvent: ethyl acetate), and 10 mg (49%) of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 1.72-1.85 (m, 2H), 2.09-2.18 (m,

2H), 2.30 (s, 3H), 2.80-2.96 (m, 1H), 2.99-3.07 (m, 1H), 3.28-3.44 (m, 1H), 3.75 (s, 3H), 3.91 (s, 3H), 4.22-4.35 (m, 1H), 4.86-4.95 (m, 1H), 6.23 (s, 1H), 6.94 (s, 1H), 6.95 (d, J=15.6 Hz, 1H), 7.07-7.32 (m, 6H), 7.55 (d, J=7.6 Hz, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.73 (brs, 1H).

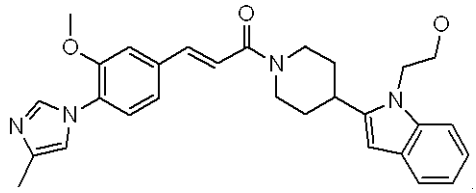
[0512]

Example 366

Synthesis of (E)-1-{4-[1-(2-hydroxy ethyl)-1H-indol-2-yl]piperidin-1-yl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone

[0513]

[Formula 177]



By the same method as in Example 365, (E)-1-{4-(1H-indol-2-yl)piperidine-1-yl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone (6 mg) a obtained in Example 338 and (2-bromoethoxy)tert-butyldimethylsilane (0.04 mL), (E)-1-{4-[1-(2-tert-butyldimethylsiloxyethyl)-1H-indol-2-yl]piperidin-1-yl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]propenone was obtained. TBAF (1M THF solution, 0.02 mL) was added to a THF (1 mL) solution of the obtained silyl protected compound, and the reaction solution was agitated at room temperature

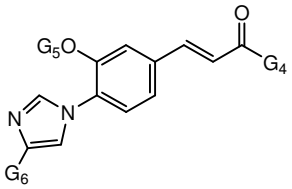
for 3 hours. Ethyl acetate and a saturated ammonium chloride solution were added to the reaction solution after the reaction ended, and the organic layer was separated. After drying the obtained organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: ethyl acetate : methanol = 9:1), and 0.9 mg (14%) of the title compound was obtained. The physical properties of the compound are as follows.

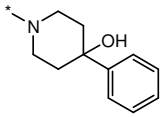
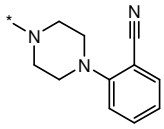
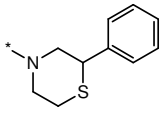
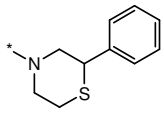
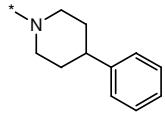
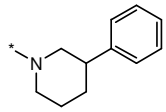
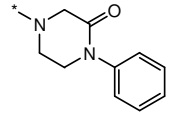
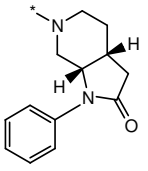
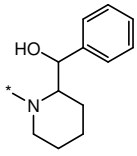
ESI-MS; m/z485 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ(ppm): 1.75-1.83 (m, 2H), 2.09-2.18 (m, 2H), 2.280 (s, 3H), 2.79-2.94 (m, 1H), 3.10-3.20 (m, 1H), 3.23-3.40 (m, 1H), 3.91 (s, 3H), 4.00 (t, J=5.6 Hz, 2H), 4.22-4.33 (m, 1H), 4.34 (t, J=5.2 Hz, 2H), 4.84-4.95 (m, 1H), 6.30 (s, 1H), 6.94 (t, J=1.2 Hz, 1H), 6.95 (d, J=15.6 Hz, 1H), 7.08-7.34 (m, 6H), 7.56 (d, J=7.6 Hz, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H).

[0514]

The compounds shown in Table 9 were synthesized as in Example 121. The structural formulae and physicochemical properties are shown in Table 9, respectively.

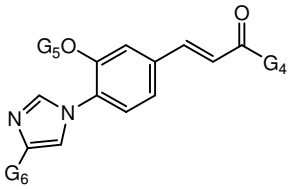
[0515]
[Table 9-1]

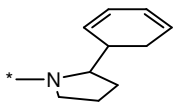
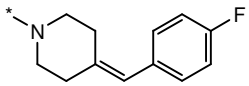
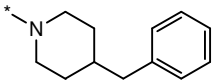
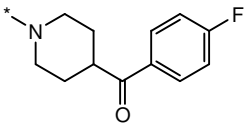
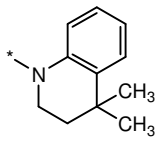
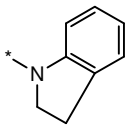
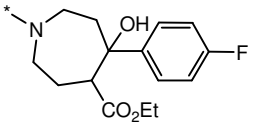
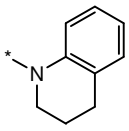


Example	G_4	G_5	G_6	DATA:MS m/z
367		Me	Me	M^++H:418 (ESI)
368		Me	Me	M^++H:428 (ESI)
369		Me	Me	M^++H:420 (ESI)
370		Me	Me	M^++H:404 (ESI)
371		Me	Me	M^++H:402 (ESI)
372		Me	Me	M^++H:402 (ESI)
373		Me	Me	M^++H:417 (ESI)
374		Me	Me	M^++H:457 (ESI)
375		Me	Me	M^++H:432 (ESI)

[0516]

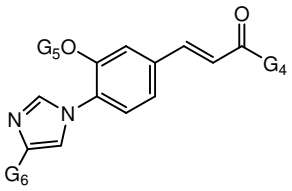
[Table 9-2]

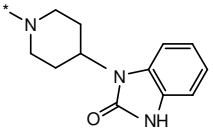
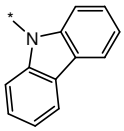
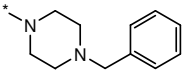
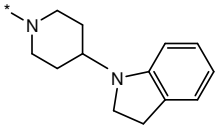
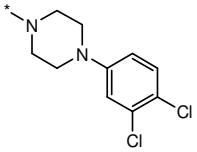
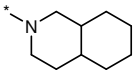
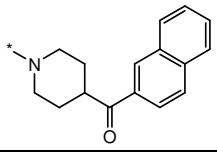
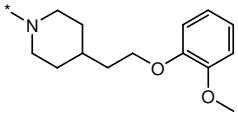
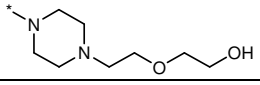
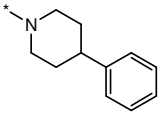
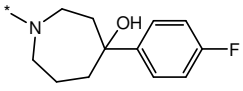


Example	G_4	G_5	G_6	DATA:MS m/z
376		Me	Me	M^++H:388 (ESI)
377		Me	Me	M^++H:432 (ESI)
378		Me	Me	M^++H:416 (ESI)
379		Me	Me	M^++H:448 (ESI)
380		Me	Me	M^++H:402 (ESI)
381		Me	Me	M^++H:360 (ESI)
383		Me	Me	M^+−H:520 (ESI)
384		Me	H	M^++H:360 (ESI)

[0517]

[Table 9-3]



Example	G_4	G_5	G_6	DATA:MS m/z
385		Me	H	M^++H:444 (ESI)
386		Me	H	M^++H:394 (ESI)
387		Me	H	M^++H:403 (ESI)
388		Me	H	M^++H:427 (ESI)
389		Me	H	M^++H:457 (ESI)
390		Me	H	M^++H:366 (ESI)
391		Me	H	M^++H:330 (ESI)
392		Me	H	M^++H:480 (ESI)
393		Me	H	M^++H:462 (ESI)
394		Me	H	M^++H:401 (ESI)
395			Me	M^++Na:448 (ESI)
396			Me	M^++Na:496 (ESI)

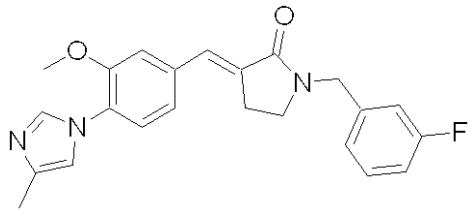
[0518]

Example 397

Synthesis of (E)-1-(3-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]pyrrolidin-2-one

[0519]

[Formula 178]



Synthesis of 4-(tert-butyldimethylsilanyloxy)-2-(diethoxyphosphoryl)butyric acid tert-butyl ester

To a DMF (4.0 mL) solution of dimethylphosphonoacetic acid tert-butyl ester (1.0 mL), sodium hydride (256 mg) was added at 0°C, and the reaction solution was allowed to be warmed to 60°C, and agitated for 2 hours. (2-bromoethoxy)tert-butyldimethylsilane (1.37 mL) was added to the reaction solution, and the reaction solution was agitated at 80°C overnight. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (heptane-ethyl acetate =1:1 -> ethyl acetate), and 510 mg of the title compound was obtained. The physical properties of the compound are

as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 4.09-4.18 (m, 4H), 3.66-3.72 (m, 1H), 3.54 (dt, J=5.2, 9.2 Hz, 1H), 3.15 (ddd, J=3.6, 11, 22 Hz, 1H), 1.97-2.17 (m, 2H), 1.47 (s, 9H), 1.31-1.36 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H).

[0520]

Synthesis of (E)-4-(tert-butyldimethylsilanyloxy)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]butyric acid tert-butyl ester

To a solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (295 mg) obtained in Example 1 in THF (5.0 mL) and ethanol (5.0 mL), 4-(tert-butyldimethylsilanyloxy)-2-(diethoxyphosphoryl)butyric acid tert-butyl ester (509 mg) and lithium hydroxide monohydrate (104 mg) were added one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (heptane-ethyl acetate = 2:1->1:1), and 395 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.73 (s, 1H), 7.69 (s, 1H), 7.22-7.30 (m, 2H), 7.24 (s, 1H), 6.94 (s, 1H), 3.91 (t,

J=6.4 Hz, 2H), 3.87 (s, 3H), 2.77 (t, J=6.4 Hz, 2H), 2.30 (s, 3H), 1.56 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H).

[0521]

Synthesis of (E)-4-hydroxy-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid tert-butyl ester

To a THF (10 mL) solution of (E)-4-(tert-butyldimethylsilanyloxy) -2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)butyric acid tert-butyl ester (122 mg), TBAF (1M THF solution, 318 μL) was added, and the reaction solution was agitated at room temperature for 1 hour. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 49.7 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 7.69 (s, 1H), 7.20-7.25 (m, 3H), 7.07 (d, J=8.0 Hz, 1H), 6.93 (s, 1H), 3.88-3.94 (m, 2H), 3.86 (s, 3H), 2.76-2.84 (s, 2H), 2.30 (s, 3H), 1.56 (s, 9H)

[0522]

Synthesis of (E)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzylidene]butyric acid tert-butyl ester

To an anhydrous THF (3.0 mL) solution of (E)-4-hydroxy-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid tert-butyl ester (100 mg), triphenylphosphine (87.8 mg), phthalimide (49.3 mg) and diisopropyl azodicarboxylate (77.0 μL) were added one by one. After agitating reaction solution at room temperature for 1.5 hours, reaction solution was concentrated under reduced pressure as it was, the residue was purified by silica gel chromatography (elution solvent: ethyl acetate), and 119 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72-7.76 (m, 2H), 7.63-7.68 (m, 4H), 7.13 (d, J=8.0 Hz, 1H), 6.99 (d, J=7.2 Hz, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 3.91 (t, J=6.8 Hz, 2H), 3.77 (s, 3H), 2.95 (t, J=6.8 Hz, 2H), 2.30 (s, 3H), 1.60 (s, 9H).

[0523]

Synthesis of (E)-4-amino-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid tert-butyl ester

To an ethanol (2.0 mL) solution of (E)-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] butyric acid tert-butyl ester (119 mg), hydrazine monohydrate (48.9 mg) was added. The white precipitation was filtered off, after refluxing the reaction solution for 30 minutes and confirming disappearance of the starting materials.

The obtained filtrate was concentrated under reduced pressure and 86 mg of crude amino compounds was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.71 (d, J=1.2 Hz, 1H), 7.63 (s, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.10 (d, J=1.2 Hz, 1H), 7.04 (dd, J=1.2, 8.0 Hz, 1H), 6.92 (t, J=1.2 Hz, 1H), 3.86 (s, 3H), 2.92 (t, J=7.6 Hz, 2H), 2.68 (t, J=7.6 Hz, 2H), 2.30 (s, 3H), 1.56 (s, 9H).

[0524]

Synthesis of (E)-4-(3-fluorobenzylamino)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid tert-butyl ester

To a methylene chloride (2.0 mL) solution of (E)-4-amino-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid tert-butyl ester (71 mg), 3-fluorobenzaldehyde (21.1 μL), acetic acid (0.1 mL) and sodium triacetoxy borohydride (63.3 mg) were added one by one. After agitating reaction solution at room temperature for 5.5 hours, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by NH silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 20:1), and 47.5 mg

of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 7.62 (s, 1H), 7.22-7.28 (m, 2H), 7.10 (s, 1H), 7.00-7.06 (m, 3H), 6.90-6.96 (m, 2H), 3.82 (s, 3H), 3.78 (s, 2H), 2.84 (t, J=6.8 Hz, 2H), 2.74 (t, J=6.8 Hz, 2H), 2.30 (s, 3H), 1.53 (s, 9H).

[0525]

Synthesis of (E)-1-(3-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]pyrrolidin-2-one

To a methylene chloride (0.5 mL) solution of (E) -4-(3-fluorobenzylamino)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid tert-butyl ester (4.50 mg), trifluoroacetic acid (500 μL) was added. After agitating reaction solution at room temperature for 1.5 hours and agitating that materials disappeared, reaction solution was concentrated under reduced pressure as it was. The residue was dissolved in DMF (0.5 mL), IPEA (17.0 μL), EDC (5.58 mg), and HOBT (3.93 mg) were added to the reaction solution one by one, and the reaction solution was agitated at room temperature for 1.5 hours. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue

was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 20:1), and 2.30 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H), 7.42 (t, J=2.8 Hz, 1H), 7.28-7.35 (m, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.13 (s, 1H), 7.07 (d, J=8.0 Hz, 1H), 6.70-7.30 (m, 2H), 6.94 (s, 1H), 4.69 (s, 2H), 3.88 (s, 3H), 3.44 (t, J=6.8 Hz, 2H), 3.09 (dt, J=2.8, 6.8 Hz, 2H), 2.30 (s, 3H).

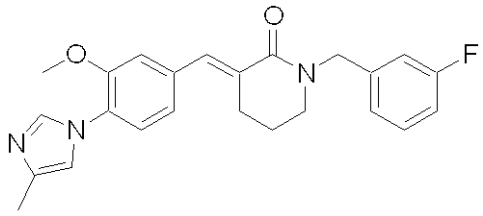
[0526]

Example 398

Synthesis of (E)-1-(3-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0527]

[Formula 179]



Synthesis of 2-(diethoxyphosphoryl)-4-[1,3]dioxolan-2-yl-butyric acid ethyl ester

To a DMF (25 mL) solution of diethylphosphono ethyl acetate ester (10.0 mL), sodium hydride (3.02 g) was added at 0°C, and the reaction solution was heated to 70°C and was agitated for 70 minutes. Next, after adding 2-(2-bromo ethyl)-1,3-dioxolane (14.8 mL) to the reaction solution and the reaction solution was

agitated at 80°C for 15 hours, and sodium hydride (1.40 g) and 2-(2-bromo ethyl)-1,3-dioxolane (7.70 mL) were further added to the reaction solution, and the reaction solution was agitated for 4 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent; heptane–ethyl acetate =1:1 ->1:2 -> ethyl acetate), and 3.58 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 4.87 (t, J=4.4 Hz, 1H), 4.10–4.25 (m, 6H), 3.93–3.99 (m, 2H), 3.81–3.88 (m, 2H), 3.03 (ddd, J=4.4, 11, 23 Hz, 1H), 1.94–2.16 (m, 2H), 1.64–1.84 (m, 2H), 1.30–1.36 (m, 9H)

[0528]

<u>Synthesis of (E)-4-[1,3]dioxolan-2-yl-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid ethyl ester</u>

To a THF (20 mL) solution of (1.75 g) of the 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde obtained in Example 1, 2-(diethoxyphosphoryl)-4-[1,3]dioxolan-2-yl-butyric acid ethyl ester (2.50 g) and lithium hydroxide monohydrate (388 mg) were added one by one, and the reaction solution was agitated at

room temperature overnight. Water and ethyl acetate were added to the reaction solution after confirming disappearance of the starting materials, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent; heptane–ethyl acetate =1:2 -> ethyl acetate), and 1.05 g of the title compound as an isomer mixture (E:Z=4:1) was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H), 7.66 (s, 1H), 7.27 (d, J=8.4 Hz, 1H), 7.13 (s, 1H), 7.09 (d, J=8.4 Hz, 1H), 6.95 (s, 1H), 4.95 (t, J=4.4, 1H), 4.29 (q, J=7.2 Hz, 2H), 3.92–4.00 (m, 2H), 3.90 (s, 3H), 3.82–3.88 (m, 2H), 2.71–2.75 (m, 2H), 2.31 (s, 3H), 1.96–2.10 (m, 2H), 1.37 (t, J=7.2 Hz, 3H).

[0529]

Synthesis of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-oxovaleric acid ethyl ester

To an aqueous solution of (243 mg) of (E)-4-[1,3]dioxolan-2-yl-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]butyric acid ethyl ester, acetic acid (2 mL) and trifluoroacetic acid (2.0 mL) were added one by one, and the reaction solution was agitated at room temperature for 4 hours. After confirming disappearance of the starting materials, a

saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 110 mg of the title compound was obtained by condensing under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 9.81 (s, 1H), 7.72-7.74 (m, 2H), 7.27 (d, J=8.0 Hz, 1H), 6.94-7.01 (m, 3H), 4.30 (q, J=7.2 Hz, 2H), 3.87 (s, 3H), 2.89 (t, J=8.0 Hz, 2H), 2.74 (t, J=8.0 Hz, 2H), 2.30 (s, 3H), 1.37 (t, J=7.2 Hz, 3H).

[0530]

Synthesis of (E)-5-(3-fluorobenzylamino)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl ester

To a methylene chloride (2.0 mL) solution of (E)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-5-oxo-valeric acid ethyl ester (142 mg), 3-fluorobenzylamine (141 μL), acetic acid (1.0 mL) and sodium triacetoxy borohydride (105 mg) were added one by one. After agitating reaction solution at room temperature overnight, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium

sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, an elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 81 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 7.66 (s, 1H), 7.23 (d, J=8.4 Hz, 1H), 6.89-7.07 (m, 7H), 4.29 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 2H), 2.69 (t, J=6.8 Hz, 2H), 2.62 (t, J=8.0 Hz, 2H), 2.30 (s, 3H), 1.74-1.83 (m, 2H), 1.36 (t, J=7.2 Hz, 3H).

[0531]

Synthesis of (E)-1-(3-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

An acetic acid (3 mL) solution of (E)-5-(3-fluorobenzylamino)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ethyl ester (81 mg) was heated to reflux overnight. After cooling the reaction solution to 0°C, it was neutralized with 1N sodium hydroxide solution, and then a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent:heptane-ethyl acetate =1:5 → ethyl acetate),

and 21 mg of the title compound was obtained. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.88 (s, 1H), 7.73 (s, 1H), 7.25-7.34 (m, 3H), 7.09 (d, J=7.2 Hz, 1H), 6.94-7.05 (m, 4H), 4.73 (s, 2H), 3.87 (s, 3H), 3.39 (t, J=6.0 Hz, 2H), 2.84 (dt, J=2.0, 6.4 Hz, 2H), 2.30 (s, 3H), 1.89 (m, 2H).

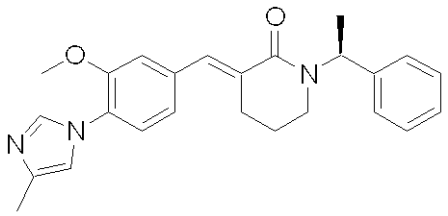
[0532]

Example 399

Synthesis of (E) -3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1S)-1-phenylethyl]piperidin-2-one

[0533]

[Formula 180]



To a methylene chloride (2 mL) solution of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-oxovaleric acid ethyl ester (162 mg), (S)-(-)-alpha-methylbenzylamine (183 μL), acetic acid (1.0 mL) and sodium triacetoxy borohydride (120 mg) were added one by one. After agitating reaction solution at room temperature overnight, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried

over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was dissolved in acetic acid (2 mL), and heat-refluxing of the reaction solution was carried out overnight. After cooling reaction solution to 0°C, neutralized with a saturated sodium bicarbonate water, ethyl acetate was added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent:heptane-ethyl acetate =1:1 -> ethyl acetate : ethanol = 10:1), and 13.7 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.90 (s, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.24-7.29 (m, 6H), 7.04-7.06 (m, 2H), 6.94 (t, J=1.2 Hz, 1H), 6.26 (q, J=7.2 Hz, 1H), 3.85 (s, 3H), 3.25 (ddd, J=3.6, 8.4, 12 Hz, 1H), 2.96 (ddd, J=4.4, 6.8, 11 Hz, 1H), 2.72-2.85 (m, 2H), 2.30 (s, 3H), 1.79-1.83 (m, 1H), 1.68-1.74 (m, 1H), 1.58 (d, J=7.2 Hz, 3H).

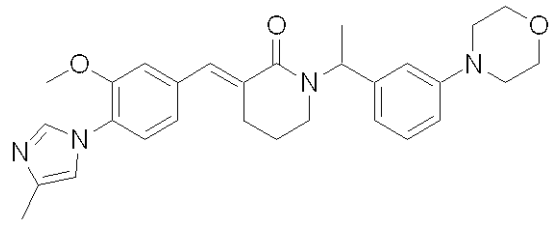
[0534]

Example 400

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[1-(3-morpholin-4-ylphenyl)ethyl]piperidin-2-one

[0535]

[Formula 181]



Synthesis of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]-5-[1-(3-morpholin-4-ylphenyl)ethylamino] valeric acid ethyl ester

To a methylene chloride (10 mL) solution of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]-5-oxovaleric acid ethyl ester (173 mg) obtained in Example 398, 1-(3-morpholin-4-yl-phenyl)ethyl amine (157 mg) and acetic acid (0.1 mL) and sodium triacetoxy borohydride (214 mg) were added one by one. The reaction solution was agitated at room temperature for 1 hour, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex NH, elution solvent:heptane-ethyl acetate = 1:2), and 205 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 7.62 (s, 1H), 7.19-7.23 (m, 2H), 7.02 (d, J=8.4 Hz, 1H), 6.98 (s, 1H), 6.93 (s, 1H), 6.87 (s, 1H), 6.78-6.81 (m, 2H), 4.27 (q, J=7.2 Hz, 2H), 3.82-3.86 (m, 4H), 3.81 (s, 3H), 3.70 (q, J=6.8 Hz, 1H), 3.14 (t, J=4.8 Hz, 4H), 2.43-2.61 (m, 4H), 2.30 (s, 3H), 1.62-1.80 (m, 2H), 1.35 (t, J=7.2 Hz, 3H), 1.31 (d, J=6.8 Hz, 3H).

[0536]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[1-(3-morpholin-4-ylphenyl)ethyl]piperidin-2-one

To a solution of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-[1-(3-morpholin-4-ylphenyl)ethylamino] valeric acid ethyl ester (55.0 mg) in THF (1.0 mL) and ethanol (1.0 mL), 2N sodium hydroxide solution (1.0 m) was added. The reaction solution was agitated at room temperature overnight, 2N hydrochloric acid and ethyl acetate were added, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 50.0 mg of crude carboxylic acid compound was obtained by condensing under reduced pressure. To a DMF (2.0 mL) solution of the obtained carboxylic acid compound, IPEA (51.8 μL), EDC (38.0 mg) and HOBT (26.8 mg) were added one by one, and the reaction solution was agitated at room temperature for 1 hour. After confirming disappearance of the starting materials,

water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex NH, elution solvent: ethyl acetate =1:1 -> heptane-ethyl acetate), and 6.00 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.89 (s, 1H), 7.72 (d, J=1.6 Hz, 1H), 7.22-7.28 (m, 2H), 7.05-7.07 (m, 2H), 6.93 (s, 1H), 6.83-6.90 (m, 3H), 6.21 (q, J=7.2 Hz, 1H), 3.85-3.87 (m, 7H), 3.24 (dd, J=4.0, 8.4, 12 Hz, 1H), 3.16 (t, J=4.8 Hz, 4H), 2.95-3.01 (m, 1H), 2.76-2.82 (m, 2H), 2.30 (s, 3H), 1.76-1.84 (m, 1H), 1.67-1.73 (m, 1H), 1.55 (d, J=7.2 Hz, 3H).

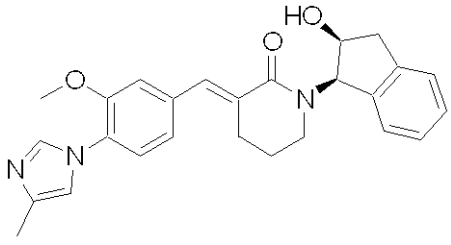
[0537]

Example 401

Synthesis of (E)-1-[(1R,2S)-2-hydroxyindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0538]

[Formula 182]



Synthesis of (E)-5-[(1R,2S)-2-hydroxyindan-1-ylamino]-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl ester

To a methylene chloride (2.0 mL) solution of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-oxovaleric acid ethyl ester (110 mg), (1R,2S)-amino-2-indanol (63.2 mg), acetic acid (0.1 mL) and sodium triacetoxy borohydride (81.7 mg) were added one by one. After agitating reaction solution at room temperature overnight, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: ethyl acetate =1:1 -> heptane-ethyl acetate), and 120 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.71 (d, J=1.6 Hz, 1H), 7.68 (s, 1H), 7.17-7.27 (m, 5H), 7.05 (dd, J=1.6 Hz, 1H), 7.01 (d, J=1.6 Hz, 1H), 6.93 (t, J=1.6 Hz, 1H), 4.39 (dt, J=2.8, 5.2 Hz, 1H), 4.30 (q, J=7.2 Hz, 2H), 4.03 (d, J=5.2 Hz, 1H), 3.85 (s, 3H), 3.04 (dd, J=5.2 Hz, 1H), 2.92-2.99 (m, 2H), 2.75-2.83 (m, 1H), 2.61-2.73 (m, 2H), 2.30 (s, 3H), 1.84 (qu, 7.2 Hz, 2H), 1.37 (t, J=7.2 Hz, 3H).

[0539]

Synthesis of (E)-1-[(1R,2S)-2-hydroxyindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To an ethanol (2.0 mL) solution of (E)-5-[(1R,2S)-2-hydroxyindan-1-ylamino]-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] valeric acid ethyl ester (120 mg), 2N sodium hydroxide solution (1.0 mL) was added. After carrying out heat-refluxing of the reaction solution for 30 minutes and confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent:heptane-ethyl acetate =1:1 -> ethyl acetate -> ethyl acetate : ethanol = 10:1), and 78.9 mg of the title compound was obtained. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.22-7.30 (m, 5H), 7.02 (d, J=7.2 Hz, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 6.01 (d, J=7.2 Hz, 1H), 4.91 (q, J=7.2 Hz, 1H), 3.84 (s, 3H), 3.30 (dd, J=7.2, 16 Hz, 1H), 3.11-3.22 (m, 2H), 2.96 (dd, J=7.2, 16 Hz, 1H), 2.75-2.86 (m, 2H), 2.30 (s, 3H), 1.70-1.90 (m, 2H).

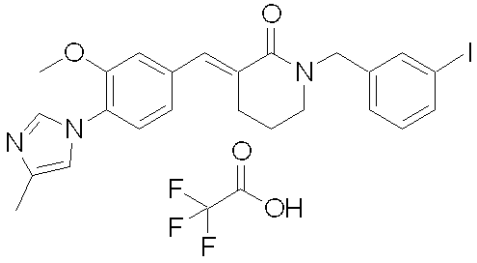
[0540]

Example 402

Synthesis of (E)-1-(3-iodobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one monotrifluoroacetic acid salt

[0541]

[Formula 183]



By the same method as in Example 398, (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-oxovaleric acid ethyl ester (197 mg) and 3-iodobenzylamine (310 μL) were reacted. 7.8 mg of the title compound was obtained by purifying the obtained crude product by LC-MS. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.72 (s, 1H), 7.88 (s, 1H), 7.63-7.66 (m, 2H), 7.34 (d, J=8.0 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.07-7.12 (m, 4H), 4.68 (s, 2H), 3.91 (s, 3H), 3.39 (t, J=5.6 Hz, 2H), 2.80-2.83 (m, 2H), 2.48 (s, 3H), 1.86-1.92 (m, 2H).

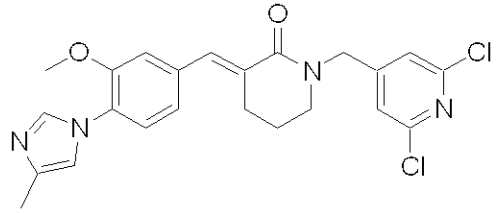
[0542]

Example 403

Synthesis of (E)-1-(2,6-dichloropyridine-4-ylmethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0543]

[Formula 184]



By the same method as in Example 398, 7.4 mg of the title compound was obtained from (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]-5-oxovaleric acid ethyl ester (130 mg) and C-(2,6-dichloro-pyridin-4-yl)methylamine (101 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.87 (s, 1H), 7.73 (s, 1H), 7.27 (d, J=8.4 Hz, 1H), 7.20 (s, 2H), 7.05 (d, J=8.4 Hz, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 4.69 (s, 2H), 3.87 (s, 3H), 3.44 (t, J=5.6 Hz, 2H), 2.89 (t, J=5.6 Hz, 2H), 2.05 (s, 3H), 1.92-1.98 (m, 2H).

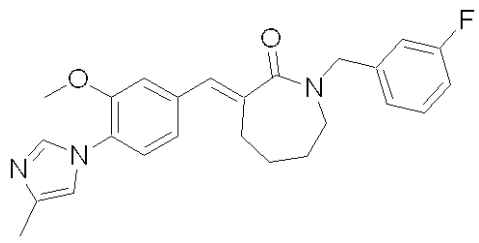
[0544]

Example 404

Synthesis of (E)-1-(3-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]azepan-2-one

[0545]

[Formula 185]



Synthesis of 2-(diethoxyphosphoryl)-5-[1,3]dioxolan-2-yl valeric acid ethyl ester

To a DMF (50 mL) solution of diethylphosphono ethyl acetate ester (2.65 mL), sodium hydride (643 mg) and 2-(3-chloropropyl)-1,3-dioxolane (2.6 g) were added at 0°C one by one, and the reaction solution was allowed to be warmed to 60°C and agitated overnight. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (heptane–ethyl acetate = from 1:2 to 1:5 to ethyl acetate), and 1.62 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 4.84 (t, J=4.8 Hz, 1H), 4.10–4.25 (m, 6H), 3.93–3.97 (m, 2H), 3.80–3.85 (m, 2H), 2.88–2.90 (m, 1H), 1.97–2.10 (m, 1H), 1.82–1.94 (m, 1H), 1.64–1.71 (m, 2H), 1.40–1.57 (m, 2H), 1.21–1.35 (m, 9H).

[0546]

Synthesis of (E)-5-[1,3]dioxolan-2-yl-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl ester

To a solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzaldehyde (580 mg) obtained in

Example 1 in THF (10 mL) and ethanol (10 mL), 2-(diethoxyphosphoryl)-5-[1,3]dioxolan-2-yl valeric acid ethyl ester (826 mg) and lithium hydroxide monohydrate (205 mg) were added one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 20:1), and it was obtained 485 mg, the title compound was obtained as an isomer mixture (E:Z=4:1). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 7.64 (s, 1H), 7.24-7.26 (m, 1H), 7.01-7.04 (m, 2H), 6.93 (s, 1H), 4.89 (t, J=4.0 Hz, 1H), 4.28 (q, J=7.2 Hz, 2H), 3.92-3.95 (m, 2H), 3.87 (s, 3H), 3.81-3.85 (m, 2H), 2.57-2.61 (m, 2H), 2.30 (s, 3H), 1.66-1.78 (m, 4H), 1.36 (t, J=7.2 Hz, 3H).

[0547]

<u>Synthesis of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-6-oxohexanoic acid ethyl ester</u>

To an aqueous solution (2.0 mL) of (E)-5-[1,3] dioxolan-2-yl-2-[3-methoxy-4-(4-methyl-1H-

imidazol-1-yl)benzylidene] valeric acid ethyl ester (480 mg), acetic acid (1.0 mL) and trifluoroacetic acid (1.0 mL) were added one by one, and the reaction solution was agitated at room temperature for 2.5 hours. A saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution after confirming disappearance of the starting materials, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate : ethanol = 10:1), and 400 mg of the title compound was obtained. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 9.78 (s, 1H), 7.50-7.80 (brs, 1H), 7.69 (s, 1H), 7.28-7.31 (m, 1H), 7.08 (d, J=8.0 Hz, 1H), 7.03 (s, 1H), 6.90-6.96 (m, 1H), 4.30 (q, J=7.2 Hz, 2H), 3.89 (s, 3H), 2.47-2.61 (m, 4H), 2.31 (s, 3H), 1.86-1.93 (s, 2H), 1.37 (t, J=7.2 Hz, 3H).

[0548]

Synthesis of (E)-6-(3-fluorobenzylamino)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]hexanoic acid ethyl ester

To a methylene chloride (6 mL) solution of (E)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-6-oxohexanoic acid ethyl ester (231 mg), 3-fluorobenzylamine (88.7 μL), acetic acid (0.5

mL) and sodium triacetoxy borohydride (165 mg) were added one by one. After agitating the reaction solution at room temperature overnight, a saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex NH, elution solvent; heptane–ethyl acetate =1:1 -> ethyl acetate -> ethyl acetate : ethanol = 10:1), and 173 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.71 (s, 1H), 7.62 (s, 1H), 7.20–7.25 (m, 2H), 6.98–7.08 (m, 4H), 6.86–6.93 (m, 2H), 4.27 (q, J=7.2 Hz, 2H), 3.84 (s, 3H), 3.77 (s, 2H), 2.60–2.70 (m, 2H), 2.52–2.60 (m, 2H), 2.30 (s, 3H), 1.76–1.87 (m, 4H), 1.35 (t, J=7.2 Hz, 3H).

[0549]

Synthesis of (E)-1-(3-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]azepan-2-one

To a to ethanol (2.0 mL) solution of (E)-6-(3-fluorobenzylamino)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)hexanoic acid ethyl ester (173 mg), 2N sodium hydroxide solution (2.0 mL) was added. After refluxing the reaction solution for 1 hour and confirming disappearance of the starting

materials, 2N hydrochloric acid and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. IPEA (134 μL), EDC (98.2 mg), and HOBT (69.2 mg) were added to a DMF (5.0 mL) solution of the obtained carboxylic acid compound (112 mg) one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate), and 70.3 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (d, J=1.2 Hz, 1H), 7.28-7.34 (m, 1H), 7.23 (d, J=26 Hz, 1H), 6.95-7.15 (m, 6H), 6.94 (t, J=1.2 Hz, 1H), 4.67 (s, 2H), 3.86 (s, 3H), 3.36 (t, J=5.2 Hz, 2H), 2.62 (t, J=5.2 Hz, 2H), 2.30 (s, 3H), 1.82-1.88 (m, 2H), 1.61-1.68 (m, 2H).

[0550]

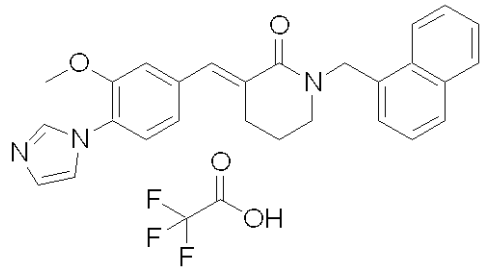
Example 405

Synthesis of 3-[4-(1H-imidazol-1-yl)-3-methoxybenzylidene]-1-naphthalen-1-ylmethyl-piperidin-

2-one trifluoroacetic acid salt

[0551]

[Formula 186]



Synthesis of 1-naphthalen-1-ylmethyl-piperidin-2-one

To a DMF (20 mL) solution of δ-valerolactam (1.0 g), sodium hydride (404 mg), 1-(chloromethyl)naphthalene (1.78 g) and sodium iodide (151 mg) were added one by one at 0°C, and the reaction solution was allowed to be warmed to 60°C, and was agitated for 6 hours. 2N hydrochloric acid and THF were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (heptane: elution solvent; ethyl acetate =1:2 -> ethyl acetate), and 2.42 g of the title compound was obtained. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.08-8.11 (m, 1H), 7.83-7.85 (m, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.45-7.53 (m, 2H), 7.40 (dd, J=6.8, 8.0 Hz, 1H), 7.31 (d, J=6.8 Hz, 1H), 5.08

(s, 2H), 3.09 (t, J=6.0 Hz, 2H), 2.50 (t, J=6.0 Hz, 2H), 1.67-1.79 (m, 4H).

[0552]

Synthesis of 3-[4-(1H-imidazol-1-yl)-3-methoxybenzylidene]-1-naphthalen-1-ylmethylpiperidin-2-one trifluoroacetic acid salt

To a THF (7.0 mL) solution of 1-naphthalen-1-ylmethylpiperidin-2-one (800 mg), lithium bis(trimethylsilyl)amide (1.5M THF capacity, 6.68 mL) was added at 0°C, and the reaction solution was agitated for 20 minutes. A THF (2 mL) solution of 4-(1H-imidazol-1-yl)-3-methoxy benzaldehyde (676 mg) obtained in Example 1 was added dropwise to the reaction solution, and the reaction solution was agitated at room temperature overnight. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane: elution solvent: ethyl acetate = one -> ethyl acetate -> ethyl acetate : ethanol 10:1), and 330 mg of alcoholic compounds was obtained. Next, methane sulfonyl chloride (31 μL) and TEA were added to a methylene chloride (1.0 mL) solution of the obtained alcoholic compound at 0°C (113 μL), and the reaction solution was agitated for 3 hours and 30 minutes. Water and ethyl acetate were

added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. DBU (24.7 mg) was added to the methylene chloride (1.0 mL) solution of the obtained residue, and the reaction solution was agitated at room temperature overnight. The reaction solution was purified in LC-MS as it was, and 3.1 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.24 (s, 1H), 8.10-8.12 (m, 1H), 7.89-7.92 (m, 1H), 7.83-7.85 (m, 2H), 7.72 (s, 1H), 7.51-7.55 (m, 2H), 7.44-7.47 (m, 2H), 7.36 (d, J=6.4 Hz, 1H), 7.25 (s, 1H), 7.08 (d, J=8.0 Hz, 1H), 5.19 (d, J=15 Hz, 1H), 5.07 (d, J=15 Hz, 1H), 3.89 (s, 3H), 3;.41 (dd, J=4.0, 13 Hz, 1H), 3.14-3.24 (m, 2H), 2.95 (dd, J=9.2, 14 Hz, 1H), 2.78-2.84 (m, 1H), 1.78-1.88 (m, 2H), 1.66-1.76 (m, 1H), 1.51-1.60 (m, 1H).

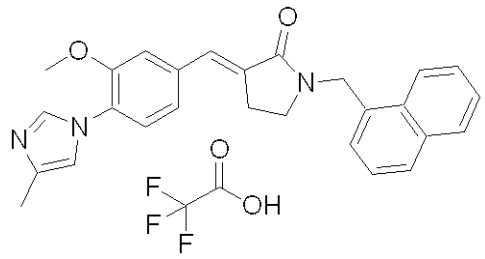
[0553]

Example 406

Synthesis of 3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-naphthalen-1-ylmethylpyrrolidin-2-one trifluoroacetic acid salt

[0554]

[Formula 187]



Synthesis of 1-naphthalen-1-ylmethy-pyrrolidin-2-one

By the same way as Example 405, 2.32 g of the title compound was obtained from 2-pyrrolidone (767 μL) and 1-(chloromethyl)naphthalene (1.78 g). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 9.41 (s, 1H), 8.15-8.17 (m, 1H), 8.00 (s, 1H), 7.94-7.97 (m, 1H), 7.87 (d, J=8.0 Hz, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.47-7.57 (m, 3H), 7.40-7.42 (m, 2H), 7.23 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.89 (s, 3H), 3.32 (t, J=5.6 Hz, 2H), 2.81 (t, J=5.6 Hz, 2H), 1.78 (t, J=5.6 Hz, 2H).

[0555]

Synthesis of 3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-naphthalen-1-ylmethyl-pyrrolidin-2-one mono(trifluoroacetic-acid) salt

By the same method as in Example 405, 1-naphthalen-1-ylmethylpyrrolidin-2-one (300 mg) obtained in Example 1, 3.4 mg of the title compound was obtained from the 3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzaldehyde (431 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.14 (t, J=1.2 Hz, 1H), 8.16-8.18 (m, 1H), 7.88-7.93 (m, 2H), 7.46-7.58 (m, 7H), 7.38-7.41 (m, 1H), 7.32 (d, J=7.6 Hz, 1H), 5.11 (s, 2H), 3.95 (s, 3H), 3.37 (t, J=6.8 Hz, 2H), 3.05-3.10 (m, 2H), 2.42 (s, 3H)

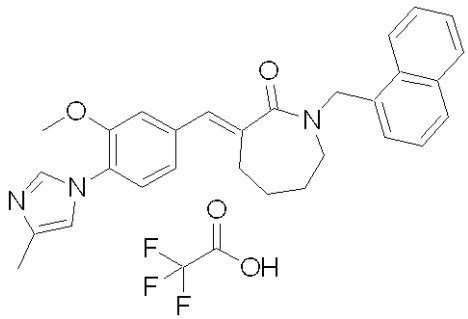
[0556]

Example 407

Synthesis of 3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-naphthalen-1-ylmethylazepan-2-one trifluoroacetic acid salt

[0557]

[Formula 188]



Synthesis of 1-naphthalen-1-ylmethylazepan-2-one

By the same method as in Example 405, 2.53 g of the title compound was obtained from ε-caprolactam (1.14 g) and 1-(chloromethyl)naphthalene (1.78 g). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.12 (d, J=8.4 Hz, 1H), 7.85-7.87 (m, 1H), 7.80 (d, J=8.4 Hz, 1H), 7.48-7.56 (m, 2H), 7.42 (t, J=8.4 Hz, 1H), 7.35 (d, J=6.4 Hz, 1H),

5.06 (s, 2H), 3.26-3.29 (m, 2H), 2.62-2.65 (m, 2H), 1.58-1.70 (m, 4H), 1.21-1.26 (m, 2H).

[0558]

Synthesis of 3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-naphthalen-1-ylmethylazepan-2-one the trifluoroacetic acid salt

By the same method as in Example 405, 1.0 mg of the title compound was obtained from the 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (383 mg) obtained in Example 1 and 1-naphthalen-1-ylmethyl-azepin-2-one(300 mg). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 9.08 (d, J=1.2 Hz, 1H), 8.18 (d, J=9.2 Hz, 1H), 7.92 (dd, J=2.0, 7.6 Hz, 1H), 7.88 (d, J=7.6 Hz, 1H), 7.44-7.57 (m, 6H), 7.31 (d, J=1.2 Hz, 1H), 7.23 (dd, J=1.6, 8.4 Hz, 1H), 7.04 (s, 1H), 5.16 (s, 2H), 3.94 (s, 3H), 3.44 (t, J=5.6 Hz, 2H), 2.59 (t, J=5.6 Hz, 2H), 2.43 (s, 3H), 1.63-1.69 (m, 2H), 1.22-1.25 (m, 2H).

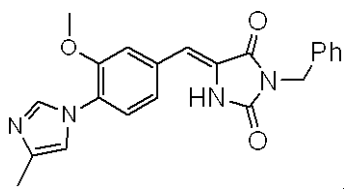
[0559]

Example 408

Synthesis of (Z)-3-benzyl-5-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]imidazolidine-2,4-dione

[0560]

[Formula 189]



Synthesis of (Z)-2-benzyloxycarbonylamino-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid methyl ester

To a methylene chloride (10 mL) suspension of potassium tert-butoxide (290 mg), a methylene chloride (3 mL) solution of benzyloxycarbonylamino(diethoxyphosphono)acetic acid methyl ester (850 mg) was added dropwise at -70°C. After agitating the reaction solution at -70°C for 2 hours, a methylene chloride (7 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (500 mg) obtained in Example 1 was added dropwise. The reaction solution was agitated at -70°C for 1 hour, and then agitated at room temperature for 4 hours. Ethyl acetate and a saturated ammonium chloride solution were added to the reaction solution after the reaction ended, and the organic layer was separated. After drying the obtained organic layer with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate 4:1 -> elution solvent: hexane : ethyl acetate), and 433 mg (45%) of (Z)-2-benzyloxycarbonylamino-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid methyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.37 (s, 3H), 3.68 (s, 3H), 3.86 (s, 3H), 5.11 (s, 2H), 6.50 (brs, 1H), 6.91 (s, 1H),

7.11-7.35 (m, 9H), 7.70 (s, 1H).

[0561]

Synthesis of (Z)-(1-benzylcarbamoyl-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]vinyl)carbamic acid benzyl ester

To a solution of (Z)-2-benzyloxycarbonylamino-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid methyl ester (433 mg) obtained at the above step in THF (1 mL) and methanol (2 mL), 2N sodium hydroxide solution (1.5 mL) was added, and the reaction solution was agitated at room temperature for 12 hours. After the reaction ended, 2N hydrochloric acid (1.5 mL) was added to the reaction solution to neutralize it, and the reaction solution was extracted with ethyl acetate. After the organic layer was washed with a saturated saline solution and dried with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. By adding ether to the obtained residue, 363 mg (87%) of carboxylic acid compound was obtained as a solid. Diethyliso propylamine (0.05 mL), HOBT (30 mg), and EDC (40 mg) were added to a DMF (3 mL) solution of the obtained carboxylic acid (66 mg) and benzylamine (0.018 mL), and the reaction solution was agitated at room temperature for 12 hours. Ethyl acetate and saturated sodium bicarbonate water were added to the reaction solution after the reaction ended, and after separating the organic layer and drying the obtained organic layer

with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: hexane : ethyl acetate = 4:1 → ethyl acetate), and 448 mg (60%) of (Z)-(1-benzylcarbamoyl-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]vinyl)carbamic acid benzyl ester was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.30 (s, 3H), 3.68 (s, 3H), 4.55 (d, J=7.2 Hz, 2H), 5.15 (s, 2H), 6.22-6.38 (m, 1H), 6.55 (brt, J=7.2 Hz, 1H), 6.91 (s, 1H), 7.03-7.39 (m, 14H), 7.68 (s, 1H).

[0562]

<u>Synthesis of (Z)-3-benzyl-5-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]imidazolidine-2, 4-dione</u>

To a THF (3 mL) solution of (Z)-{1-benzylcarbamoyl-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]vinyl}carbamic acid benzyl ester (48 mg) obtained above, TBAF (1M THF solution, 0.01 mL) was added and heat-refluxing of the reaction solution was carried out for 3 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate was added and washed with a saturated ammonium chloride solution. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution

solvent: from hexane: ethyl acetate 1:1 to ethyl acetate), and 28 mg (75%) of (Z)-3-benzyl-5-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]imidazolidine-2,4-dione was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ(ppm): 2.31 (s, 3H), 3.78 (s, 3H), 4.79 (s, 2H), 6.72 (s, 1H), 6.88 (brs, 1H), 7.03-7.45 (m, 9H), 9.95 (s, 1H), 12.7 (brs, 1H).

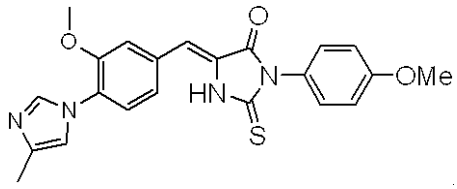
[0563]

Example 409

Synthesis of (Z)-5-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-3-(4-methoxyphenyl)-2-thioxsoimidazolidine-4-one

[0564]

[Formula 190]



Synthesis of (Z)-5-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-3-(4-methoxyphenyl)-2-thioxoimidazolidine-4-one

Piperidine (0.019 mL) was added to an ethanol (2 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (20 mg) obtained in Example 1 and 3-(4-methoxyphenyl)-2-thioxoimidazolidine-4-one (21 mg), and heat-refluxing of the reaction solution was carried out for 12 hours. The reaction solution was allowed to be

cooled to room temperature and the solid deposited was separated by filtering, and 18 mg (47%) of the title compound was obtained by washing with ethanol and ether. The physical properties of the compound are as follows.

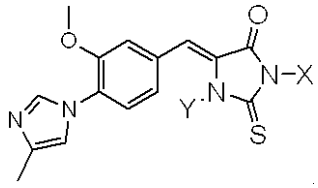
^{1}H-NMR (DMSO-d6) δ(ppm): 2.15 (s, 3H), 3.81 (s, 3H), 3.93 (s, 3H), 6.69 (s, 1H), 7.22 (d, J=9.2 Hz, 2H), 7.20 (s, 1H), 7.38 (d, J=9.2 Hz, 2H), 7.44 (d, J=8.0 Hz, 1H), 7.54 (brs, 1H), 7.56 (brd, J=8.0 Hz, 1H), 7.85 (brs, 1H).

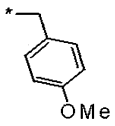
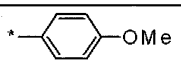
[0565]

The compounds shown in Table 9 were synthesized as in Example 409. The structural formulae and physicochemical properties are shown in Table 9, respectively.

[0566]

[Table 10]



Example	X	Y	DATA: MS m/z
410		H	M$^+$+H: 435 (ESI)
411		H	M$^+$+H: 405 (ESI)
412		Me	M$^+$+H: 435 (ESI)

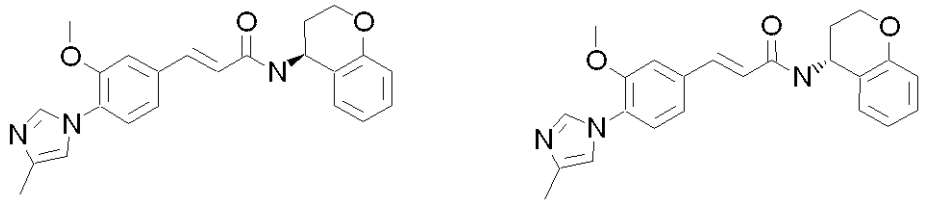
[0567]

Example 413 and Example 414

Synthesis of (E)-N-[(4R) and (4S)-chroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide

[0568]

[Formula 191]



To a DMF (4 mL) solution of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid (70 mg) obtained in Example 121, chroman-4-ylamine (CAS#53981-38-7) (49 mg), EDC (62 mg) and HOBT (44 mg) were added at room temperature under nitrogen atmosphere, and the reaction solution was agitated at room temperature for 17 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed with a saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (elution solvent: methanol-ethyl acetate system), and (E)-N-(chroman-4-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylamide racemate (90 mg) was obtained. This compound (50 mg) was separated

by CHIRALPAK™ AD-H (2 cm×25 cm : mobile phase; hexane-ethanol 20%) available from Daicel Chemical Industries, Ltd., and the title optically-active substance with a retention time of 22 minutes (16 mg;>99%ee) and the title optically-active substance with a retention time of 28 minutes (19 mg;>98%ee) were obtained. The physical properties of the title optically-active substance with a retention time of 22 minutes (Example 413) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.11-2.21 (m, 1H), 2.26-2.36 (m, 1H), 2.29 (s, 3H), 3.88 (s, 3H), 4.15-4.23 (m, 1H), 4.27-4.35 (m, 1H), 5.25-5.32 (m, 1H), 5.88 (d, J=7.2 Hz, 1H), 6.39 (d, J=15.6 Hz, 1H), 6.83-6.95 (m, 3H), 7.11-7.28 (m, 5H), 7.67 (d, J=15.2 Hz, 1H), 7.71 (d, J=1.2 Hz, 1H).

The physical properties of the title optically-active substance with a retention time of 22 minutes (Example 414) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.11-2.21 (m, 1H), 2.26-2.36 (m, 1H), 2.29 (s, 3H), 3.88 (s, 3H), 4.15-4.23 (m, 1H), 4.27-4.35 (m, 1H), 5.25-5.32 (m, 1H), 5.88 (d, J=7.2 Hz, 1H), 6.39 (d, J=15.6 Hz, 1H), 6.83-6.95 (m, 3H), 7.11-7.28 (m, 5H), 7.67 (d, J=15.2 Hz, 1H), 7.71 (d, J=1.2 Hz, 1H).

[0569]

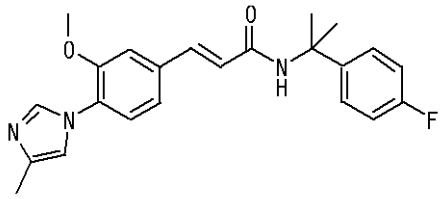
Example 415

Synthesis of (E)-N-[1-(4-fluorophenyl)-1-methyl ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)phenyl]acrylamide

[0570]

[Formula 192]



To a DMF (5 mL) solution of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (60 mg) obtained in Example 121, 1-(4-fluorophenyl)-1-methylethylamine (CAS#17797-10-3) (43 mg), EDC (53 mg) and HOBT (38 mg) were added at room temperature under nitrogen atmosphere, and the reaction solution was agitated at room temperature for 12 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed with a saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (elution solvent: methanol-ethyl acetate system), and the title compound (60 mg) was obtained. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.77 (s, 6H), 2.29 (d, J=0.8 Hz, 3H), 3.87 (s, 3H), 5.90 (brs, 1H), 6.41 (d, J=15.2 Hz, 1H), 6.90-6.94 (m, 1H), 6.97-7.05 (m, 2H), 7.09 (d, J=2.0 Hz, 1H), 7.14 (dd, J=2.0, 8.0 Hz, 1H), 7.20-7.28 (m, 1H), 7.35-7.43 (m, 2H), 7.54 (d, J=15.2 Hz, 1H), 7.71 (d, J=1.2 Hz, 1H).

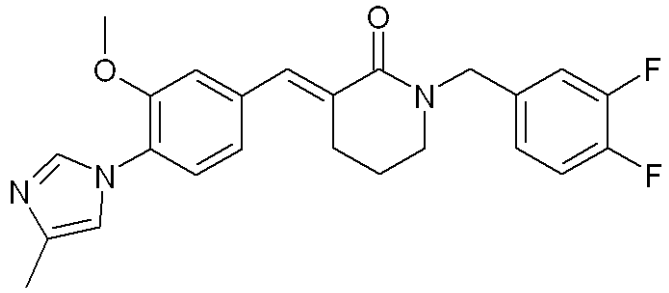
[0571]

Example 416

Synthesis of (E)-1-(3,4-difluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0572]

[Formula 193]



Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To a sodium hydride suspension (40% mineral oil content, 2.77 g) in THF (50 mL) and DMF (200 mL), a solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (10 g) obtained in Example 1 and 1-acetylpiperidin-2-one (7.17 g) in THF (50 mL) and DMF (200 mL) were added dropwise over 20 minutes at 5°C. This reaction solution was agitated at 0°C for 2 hours. The reaction solution was added to iced water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated sodium chloride solution, and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The deposited solids were separated by filtering and 5.0 g of the title compound was obtained

by washing with diethyl ether. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86–1.96 (m, 2H), 2.30 (s, 3H), 2.81–2.87 (m, 2H), 3.42–3.50 (m, 2H), 3.86 (s, 3H), 5.97 (brs, 1H), 6.93 (s, 1H), 7.00–7.08 (m, 2H), 7.22–7.28 (m, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.79 (s, 1H).

[0573]

Synthesis of (E)-1-(3,4-difluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To a DMF (6.0 mL) solution of (E) -3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one (100 mg) obtained above, lithium bis(trimethylsilyl)amide (1M hexane solution, 0.60 mL) was added dropwise at 0°C, and the reaction solution was agitated at 0°C for 30 minutes. 3,4-difluorobenzylbromide (0.06 mL) was added to this solution at 0°C, and the reaction solution was agitated at room temperature for 1 hour. The reaction solution was added to iced water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated sodium chloride solution, and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel column chromatography (elution solvent: heptane–ethyl acetate system), and 110 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83–1.92 (m, 2H), 2.30 (s, 3H),

2.80–2.87 (m, 2H), 3.34–3.41 (m, 2H), 3.86 (s, 3H), 4.66 (s, 2H), 6.91–6.95 (m, 1H), 7.00–7.07 (m, 3H), 7.07–7.18 (m, 2H), 7.22–7.28 (m, 1H), 7.71 (d, J=1.6 Hz, 1H), 7.86 (s, 1H).

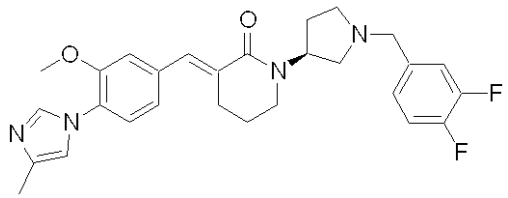
[0574]

Example 417

Synthesis of (E)-1-[1-(3,4-difluorobenzyl)-(3S)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0575]

[Formula 194]



Synthesis of 5-chloro-2-(diethoxyphosphoryl)valeric acid ethyl ester

Sodium hydride (40% mineral oil content, 9.8 g) was washed with hexane (50 mL) 3 times to remove oily substances. A THF (100 mL) solution of phosphonoacetic acid triethyl (50 g) was added dropwise to a THF (400 mL) suspension of this sodium hydride at 0°C for 30 minutes. Then, the reaction solution was allowed to be warmed to room temperature and agitated for further 1 hour. 1-bromo-3-chloropropane (70.2 g) was added dropwise to this reaction solution for 30 minutes. Heating refluxing of the reaction solution was carried out after the dropping end for 15 hours.

This reaction solution was allowed to be cooled to room temperature, ethyl acetate (1 L) and saturated ammonium chloride water (1 L) were added, and the organic layer was partitioned. 61.2 g of the title compound was obtained by drying with anhydrous magnesium sulfate and condensing the obtained organic layer under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.26-1.38 (m, 9H), 1.55-2.36 (m, 4H), 2.89-3.01 (m, 1H), 3.54 (t, J=6.4 Hz, 2H), 4.23-4.58 (m, 6H).

[0576]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl ester

To a solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (5 g) obtained in Example 1 in THF (60 mL) and ethanol (20 mL), 5-chloro-2-(diethoxyphosphoryl)valeric acid ethyl ester (7.6 g) and lithium hydroxide monohydrate (2.9 g) were added one by one, and the reaction solution was agitated at room temperature overnight. Water and ethyl acetate were added to the reaction solution after confirming disappearance of the starting materials, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 3.76 g of the title compound was obtained by purifying the residue by

silica gel chromatography (heptane: elution solvent: ethyl acetate = 1:1), and re-crystallizing the obtained solid from a mixed solvent of ethyl acetate and hexane. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.37 (t, J=7.6 Hz, 3H), 2.02-2.09 (m, 2H), 2.30 (s, 3H), 2.70-2.76 (m, 2H), 3.60 (t, J=6.4 Hz, 2H), 3.88 (s, 3H), 4.29 (q, J=7.6 Hz, 2H), 6.94 (m, 1H), 7.02 (d, J=1.2 Hz, 1H), 7.06 (dd, J=8.4, 1.2 Hz, 1H), 7.26 (d, J=8.4 Hz, 1H), 7.68 (s, 1H), 7.72 (d, J=1.2 Hz, 1H).

[0577]

Synthesis of [(3S)-1-(3,4-difluorobenzyl)pyrrolidine-3-yl]carbamic acid tert-butyl ester

To a methylene chloride (10 mL) solution of (3S)-3-(tert-butoxycarbonylamino) pyrrolidine (916 mg), 3,4-difluorobenzylbromide (0.7 mL) and IPEA (2.2 mL) were added one by one, and the reaction solution was agitated at room temperature for 20 hours. A saturated sodium bicarbonate water was added to the reaction solution after the reaction ended, and the organic layer was partitioned. It was dried over anhydrous magnesium sulfate and the obtained organic layer was concentrated under reduced pressure. 1.55 g of the title compound was obtained by purifying the residue by silica gel chromatography (elution solvent: heptane: ethyl acetate = 1:1). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.44 (s, 9H), 1.55-1.64 (m, 1H),

2.18–2.22 (m, 2H), 2.46–2.81 (m, 3H), 3.52 (d, J=13.6 Hz, 1H), 3.55 (d, J=13.6 Hz, 1H), 4.11–4.23 (m, 1H), 4.82 (brs, 1H), 6.97–7.19 (m, 3H).

[0578]

Synthesis of [(3S)-1-(3,4-difluorobenzyl)pyrrolidine-3-yl]amine dihydrochloride

To an ethyl acetate solution (5 mL) of (3S)-(1-(3,4-difluorobenzyl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (1.55 g), an ethyl acetate (5 mL) solution of 4N hydrochloric acid was added, and the reaction solution was agitated at room temperature. Deposited substances in the reaction solution was separated by filtering after 10 hours, and 904 mg of the title compound was obtained by further washing with ether. The physical properties of the compound are as follows.

ESI-MS; m/z213 [M^++H].

[0579]

Synthesis of (E)-1-[1-(3,4-difluorobenzyl)-(3S)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ethyl ester (200 mg) and ((3S)-1-(3, 4-difluorobenzyl)pyrrolidine-3-yl)amine dihydrochloride (315 mg) in acetonitrile (8 mL) and water (2 mL), potassium carbonate (228 mg) and sodium iodide (831 mg) were added. After carrying out heat-refluxing of the

reaction solution for 12 hours, the reaction solution allowed to be cooled to room temperature and concentrated under reduced pressure. A 2N sodium hydroxide solution (1 mL) in ethanol (5 mL) was added to the obtained residue. After agitating the reaction mixture at room temperature for 12 hours, it was neutralized with a 5N hydrochloric acid solution, and the reaction solution was extracted with ethyl acetate. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 200 mg of the title compound was obtained by purifying the residue by silica gel chromatography (Carrier: Chromatorex™ NH; elution solvent: ethyl acetate). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-1.93 (m, 3H), 2.22-2.33 (m, 2H), 2.29 (s, 3H), 2.50 (dd, J=10.4, 8.4 Hz, 1H), 2.70 (dd, J=10.4, 3.6 Hz, 1H), 2.77-2.95 (m, 3H), 3.45-3.62 (m, 4H), 3.84 (s, 3H), 5.17-5.45 (m, 1H), 6.92 (s, 1H), 6.98-7.27 (m, 6H), 7.70 (d, J=1.2 Hz, 1H), 7.78 (s, 1H).

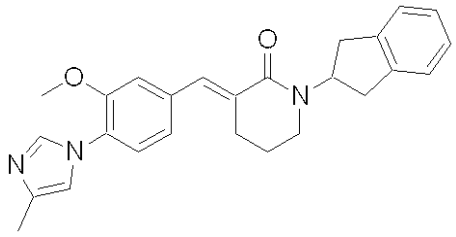
[0580]

Example 418

Synthesis of (E)-1-indan-2-yl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0581]

[Formula 195]



Synthesis of 5-chloro-2-(diethoxyphosphoryl)valeric acid tert-butyl ester

Sodium hydride (40% mineral oil content, 17.4 g) was washed with hexane (100 mL) 3 times to remove oily substances. A THF (100 mL) solution of diethylphosphonoacetic acid tert-butyl ester (100 g) was added dropwise to a THF (500 mL) suspension of this sodium hydride at 0°C for 30 minutes. Then, the reaction solution was allowed to be warmed to room temperature and agitated for further 1 hour. A THF (100 mL) solution of 1-bromo-3-chloropropane (125 g) was added dropwise to this reaction solution for 30 minutes. Heating refluxing of the reaction solution was carried out after the dropping end for 15 hours. This reaction solution was allowed to be cooled to room temperature, ethyl acetate (1 L) and saturated ammonium chloride water (1 L) were added, and the organic layer was partitioned. 113.4 g of the title compound was obtained by drying with anhydrous magnesium sulfate and condensing the obtained organic layer under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.31-1.48 (m, 6H), 1.48 (s, 9H), 1.79-2.14 (m, 4H), 2.73-2.91 (m, 1H), 3.55 (t, J=6.4

Hz, 2H), 4.10-4.19 (m, 4H).

[0582]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid tert-butyl ester

To a solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (50 g) in THF (600 mL) and ethanol (200 mL), 5-chloro-2-(diethoxyphosphoryl)valeric acid tert-butyl ester (83.5 g) and lithium hydroxide monohydrate (29.1 g) were added to the one by one, and the reaction solution was agitated at room temperature overnight. Water and ethyl acetate were added to the reaction solution after confirming disappearance of the starting materials, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 54.9 g of the title compound was obtained by purifying the residue by silica gel chromatography (elution solvent:heptane:ethyl acetate = 1:1), and re-crystallizing the obtained solid from the mixed-solution of ethyl acetate and hexane. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (s, 9H), 1.99-2.08 (m, 2H), 2.30 (s, 3H), 2.63-2.71 (m, 2H), 3.59 (t, J=6.4 Hz, 2H), 3.87 (s, 3H), 6.93 (m, 1H), 7.00 (d, J=1.2 Hz, 1H), 7.09 (dd, J=8.4, 1.2 Hz, 1H), 7.27 (d, J=8.4 Hz, 1H), 7.58 (s, 1H), 7.72 (m, 1H).

[0583]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid trifluoroacetic acid salt

To a methylene chloride (20 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid tert-butyl ester (5 g), trifluoroacetic acid (10 mL) was added and the reaction solution was agitated at room temperature for 2 hours. After confirming disappearance of the starting materials, the reaction solution was concentrated under reduced pressure. The resulted solids were separated by filtering and 5.7 g of the title compound was obtained by washing with ethyl acetate further. The physical properties of the compound are as follows. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.93-2.03 (m, 2H), 2.35 (s, 3H), 2.58-2.66 (m, 2H), 3.70 (t, J=6.4 Hz, 2H), 3.91 (s, 3H), 7.24 (dd, J=8.4, 1.2 Hz, 1H), 7.37 (d, J=1.2 Hz, 1H), 7.64 (d, J=8.4, 1H), 7.66 (m, 1H), 7.76 (s, 1H), 9.36 (m, 1H).

[0584]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid indan-2-ylamide

To a DMF solution (200 mL) of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (13 g) and 2-amino indan hydrochloride (7.8 g), IPEA (24.1 mL), HOBT (9.4 g) and EDC (13.3 g) were added one

by one, and the reaction solution was agitated at room temperature. Ethyl acetate and saturated sodium bicarbonate water were added to the reaction solution after 15 hours, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated sodium chloride solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 6.93 g of the title compound was obtained by purifying the residue by silica gel chromatography (elution solvent: ethyl acetate). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.93–2.04 (m, 2H), 2.28 (s, 3H), 2.67–2.73 (m, 2H), 2.90 (dd, J=16.0, 4.4 Hz, 2H), 3.40 (dd, J=16.0, 7.2 Hz, 2H), 3.56 (t, J=5.6 Hz, 2H), 3.84 (s, 3H), 4.81–4.95 (m, 1H), 6.29 (d, J=7.2 Hz, 1H), 6.90–6.94 (m, 3H), 7.10 (s, 1H), 7.18–7.27 (m, 5H), 7.68 (d, J=1.6 Hz, 1H).

[0585]

Synthesis of (E)-1-indan-2-yl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To a DMF (50 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid indan-2-ylamide (6.9 g), sodium hydride (40% mineral oil content, 740 mg) was added at room temperature, and the reaction solution was agitated at room temperature for 1 hour and 30 minutes. The reaction solution was poured into iced water after the reaction ended, and the deposited

solids were separated by filtering. 4.9 g of the title compound was obtained by recrystallizing the obtained solid from a mixed solvent of ethyl acetate, ethanol, and hexane. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81-1.88 (m, 2H), 2.30 (s, 3H), 2.77-2.84 (m, 2H), 3.00 (dd, J=16.4, 6.0 Hz, 2H), 3.24-3.32 (m, 4H), 3.86 (s, 3H), 5.75-5.83 (m, 1H), 6.93 (d, J=1.2 Hz, 1H), 7.02-7.07 (m, 2H), 7.17-7.28 (m, 5H), 7.71 (d, J=1.2 Hz, 1H), 7.85 (s, 1H).

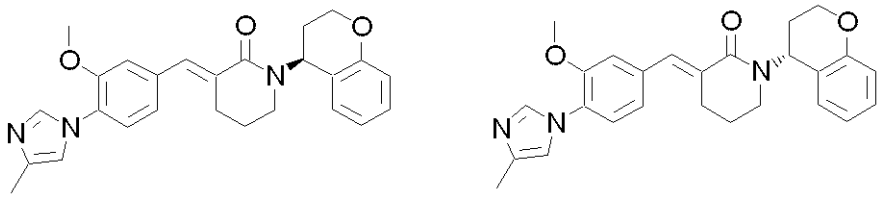
[0586]

Example 419 and Example 420

Synthesis of (E)-1-[(4R) and (4S)-chroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0587]

[Formula 196]



To a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ethyl ester (50 mg) obtained in Example 417 in acetonitrile (2 mL) and water (0.2 mL), chroman-4-ylamine (CAS#53981-38-7) (31 mg) and cesium carbonate (90 mg) were added at room temperature, and the mixture was reacted in a microwave synthesizing equipment

(80W;150°C) for 1 hour. The reaction solution was allowed to be cooled to room temperature, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed with a saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, an elution solvent: heptane-ethyl acetate system), and (E)-5-(chroman-4-ylamino)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl ester (25 mg) was obtained. 2N sodium hydroxide solution (1 mL) was added to an ethanol (3 mL) solution of the (E)-5-(chroman-4-ylamino)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] valeric acid ethyl ester (59 mg) obtained by repeating the above-mentioned operation at room temperature, the reaction solution was agitated at room temperature for 12 hours, and heat-refluxing was carried out for further 1 hour. The reaction solution was allowed to be cooled to room temperature, 2N hydrochloric acid (1 mL) was added to the reaction solution under ice-cooling, and the reaction solution was concentrated under reduced pressure. EDC (50 mg) and HOBT (36 mg) were added to a DMF (3 mL) suspension of the obtained residue, and the reaction solution was agitated at room temperature for 16 hours. Water and ethyl acetate were added to the reaction solution, and

the organic layer was partitioned. The organic layer was washed with a saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, an elution solvent: heptane-ethyl acetate system), and (E)-1-(chroman-4-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one racemate (21 mg) was obtained. This compound (21 mg) was separated in CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm : mobile phase; ethanol), and the title optically-active substance with a retention time of 45 minutes (7 mg;>99%ee) and the title optically-active substance with a retention time of 61 minutes (6 mg;>99%ee) were obtained. The physical properties of the title optically-active substance with a retention time of 45 minutes (Example 419) is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70-1.95 (m, 2H), 2.00-2.28 (m, 2H), 2.30 (s, 3H), 2.74-2.85 (m, 1H), 2.87-2.98 (m, 1H), 3.05-3.14 (m, 1H), 3.15-3.26 (m, 1H), 3.87 (s, 3H), 4.20-4.30 (m, 1H), 4.31-4.40 (m, 1H), 6.23 (dd, J=6.4, 9.6 Hz, 1H), 6.84 (d, J=8.0 Hz, 1H), 6.89 (dd, J=7.2, 7.6 Hz, 1H), 6.94 (s, 1H), 7.02-7.10 (m, 3H), 7.12-7.18 (m, 1H), 7.23-7.29 (m, 1H), 7.72 (s, 1H), 7.91 (s, 1H).

The physical properties of the title optically-active

substance with a retention time of 61 minutes (Example 420) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70-1.95 (m, 2H), 2.00-2.28 (m, 2H), 2.30 (s, 3H), 2.74-2.85 (m, 1H), 2.87-2.98 (m, 1H), 3.05-3.14 (m, 1H), 3.15-3.26 (m, 1H), 3.87 (s, 3H), 4.20-4.30 (m, 1H), 4.31-4.40 (m, 1H), 6.23 (dd, J=6.4, 9.6 Hz, 1H), 6.84 (d, J=8.0 Hz, 1H), 6.89 (dd, J=7.2, 7.6 Hz, 1H), 6.94 (s, 1H), 7.02-7.10 (m, 3H), 7.12-7.18 (m, 1H), 7.23-7.29 (m, 1H), 7.72 (s, 1H), 7.91 (s, 1H).

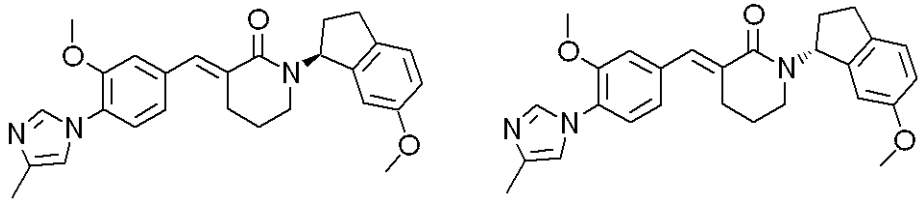
[0588]

Example 421 and Example 422

Synthesis of (E)-1-[(R) and (S)-6-methoxyindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0589]

[Formula 197]



To a DMF (2 mL) suspension of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] valeric acid trifluoroacetic acid salt (50 mg) obtained in Example 418 and 6-methoxyindan-1-ylamine (CAS#103028-81-5) (27 mg), IPEA (0.06 mL), EDC (64 mg) and HOBT (45 mg) were added at room temperature, and the reaction solution was agitated at room temperature

for 12 hours. Saturated sodium bicarbonate solution and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed one by one with a saturated ammonium chloride solution and water, and also saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (elution solvent: methanol-ethyl acetate system) and (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (6-methoxyindan-1-yl)amide (29 mg) was obtained. To a DMF (2 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (6-methoxyindan-1-yl)amide (29 mg) obtained, sodium hydride (40% mineral oil content, 20 mg) was added at room temperature, and the reaction solution was agitated for 10 minutes at room temperature. Saturated sodium bicarbonate solution and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed one by one in a saturated ammonium chloride solution and water, and also saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (elution solvent: methanol-ethyl acetate system), and (E)-1-(6-methoxyindan-1-yl)-3-[3-

methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one racemate (17 mg) was obtained. This compound (17 mg) was separated by CHIRALCEL™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm : mobile phase; ethanol), and the title optically-active substance with a retention time of 36 minutes (6 mg;>99%ee) and the title optically-active substance with a retention time of 43 minutes (6 mg;>95%ee) were obtained. The physical properties of the title optically-active substance with a retention time of 36 minutes (Example 421) is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.73-1.90 (m, 2H), 1.94-2.03 (m, 1H), 2.30 (s, 3H), 2.45-2.56 (m, 1H), 2.74-3.02 (m, 4H), 3.04-3.21 (m, 2H), 3.77 (s, 3H), 3.86 (s, 3H), 6.47 (dd, J=7.6, 8.4 Hz, 1H), 6.70 (d, J=2.4 Hz, 1H), 6.80 (dd, J=2.4, 8.4 Hz, 1H), 6.94 (s, 1H), 7.03-7.10 (m, 2H), 7.15 (d, J=8.4 Hz, 1H), 7.22-7.28 (m, 1H), 7.72 (s, 1H), 7.90 (s, 1H).

The physical properties of the title optically-active substance with a retention time of 43 minutes (Example 422) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.73-1.90 (m, 2H), 1.94-2.03 (m, 1H), 2.30 (s, 3H), 2.45-2.56 (m, 1H), 2.74-3.02 (m, 4H), 3.04-3.21 (m, 2H), 3.77 (s, 3H), 3.86 (s, 3H), 6.47 (dd, J=7.6, 8.4 Hz, 1H), 6.70 (d, J=2.4 Hz, 1H), 6.80 (dd, J=2.4, 8.4 Hz, 1H), 6.94 (s, 1H), 7.03-7.10 (m, 2H), 7.15 (d, J=8.4 Hz, 1H), 7.22-7.28 (m, 1H),

7.72 (s, 1H), 7.90 (s, 1H).

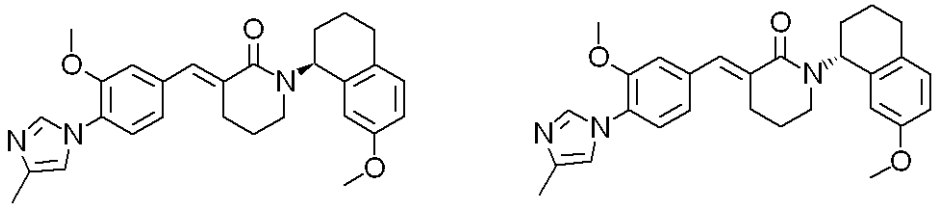
[0590]

Example 423 and Example 424

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(R)and(S)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]piperidin-2-one

[0591]

[Formula 198]



To a solution of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl ester (50 mg) obtained in Example 417 in acetonitrile (3 mL) and water (0.3 mL), 7-methoxy-1,2,3, 4-tetrahydronaphthalen-1-ylamine (CAS#50399-51-4) (25 mg), potassium carbonate (57 mg) and sodium iodide (21 mg) were added at room temperature, and heat-refluxing of the reaction solution was carried out for two days. The reaction solution was allowed to be cooled to room temperature, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed with a saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The

residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, an elution solvent: heptane-ethyl acetate system), and (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylamino)valeric acid ethyl ester (24 mg) was obtained. 2N sodium hydroxide solution (0.3 mL) was added to an ethanol (1 mL) solution of obtained (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylamino)valeric acid ethyl ester (24 mg) at room temperature, and the reaction solution was agitated at room temperature for 16 hours. 2N hydrochloric acid (0.3 mL) was added to the reaction solution under ice-cooling, and the reaction solution was concentrated under reduced pressure. EDC (25 mg) and HOBT (18 mg) were added to a DMF (2 mL) suspension of the obtained residue, and the reaction solution was agitated at room temperature for 24 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed with a saturated sodium chloride solution, and the organic layer was concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, an elution solvent: heptane-ethyl acetate system), and (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)piperidin-2-one

racemate (19 mg) was obtained. This compound (19 mg) was separated in CHIRALCEL™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm : mobile phase; ethanol), and the title optically-active substance with a retention time of 17 minutes (7 mg;>99%ee) and the title optically-active substance with a retention time of 25 minutes (6 mg;>99%ee) were obtained. The physical properties of the title optically-active substance with a retention time of 17 minutes (Example 423) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.82 (m, 4H), 1.96-2.14 (m, 2H), 2.31 (s, 3H), 2.68-2.84 (m, 3H), 2.88-2.98 (m, 1H), 3.05-3.13 (m, 1H), 3.18-3.26 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 6.07-6.15 (m, 1H), 6.66 (d, J=2.8 Hz, 1H), 6.75 (dd, J=2.8, 8.4 Hz, 1H), 6.95 (s, 1H), 7.02-7.11 (m, 3H), 7.24-7.30 (m, 1H), 7.73 (d, J=1.2 Hz, 1H), 7.92 (s, 1H).

The physical properties of the title optically-active substance (Example 424) for retention time 25 minutes are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.82 (m, 4H), 1.96-2.14 (m, 2H), 2.31 (s, 3H), 2.68-2.84 (m, 3H), 2.88-2.98 (m, 1H), 3.05-3.13 (m, 1H), 3.18-3.26 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 6.07-6.15 (m, 1H), 6.66 (d, J=2.8 Hz, 1H), 6.75 (dd, J=2.8, 8.4 Hz, 1H), 6.95 (s, 1H), 7.02-7.11 (m, 3H), 7.24-7.30 (m, 1H), 7.73 (d, J=1.2 Hz, 1H), 7.92 (s, 1H).

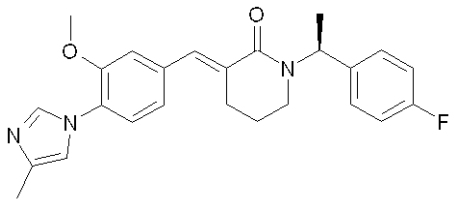
[0592]

Example 425

Synthesis of (E)-1-[(1S)-1-(4-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0593]

[Formula 199]



Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ((1S)-1-(4-fluorophenyl)ethyl)amide

To a DMF (50 mL) solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (8.00 g) and (S)-1-(4-fluorophenyl)ethylamine (2.60 g), IPEA (12.4 mL), EDC (6.82 g) and HOBT (4.81 g) were added one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, the solvent was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. After the organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (elution solvent:

heptane–ethyl acetate = 2:3 ->1:1 -> ethyl acetate), and 3.90 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (d, J=6.8 Hz, 3H), 1.95–2.02 (m, 2H), 2.30 (s, 3H), 2.70–2.74 (m, 2H), 3.58 (t, J=6.0 Hz, 2H), 3.85 (s, 3H), 5.17–5.24 (m, 1H), 6.15 (d, J=6.8 Hz, 1H), 6.92–6.96 (m, 3H), 7.02–7.07 (m, 2H), 7.17 (s, 1H), 7.23–7.25 (m, 1H), 7.32–7.36 (m, 2H), 7.70–7.71 (s, 1H).

[0594]

Synthesis of (E)-1-[(1S)-1-(4-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To a DMF (30 mL) solution of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl]benzylidene valeric acid ((S)-1-(4-fluorophenyl)ethyl)amide (3.90 g), sodium hydride (40% mineral oil content, 410 mg) was added at 0°C, the reaction solution was allowed to be warmed to room temperature and agitated overnight. The reaction solution was cooled to 0°C after confirming disappearance of the starting materials, and water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent; ethyl acetate -> ethyl acetate : ethanol

10:1). The obtained solid was washed with diethyl ether and 2.60 g of the title compound was obtained by further performing recrystallization with ethyl acetate. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.50 (d, J=7.2 Hz, 3H), 1.65-1.74 (m, 1H), 1.78-1.87 (m, 1H), 2.30 (s, 3H), 2.71-2.85 (m, 2H), 2.91-2.97 (m, 1H), 3.24 (ddd, J=3.6, 8.8, 12.0 Hz, 1H), 3.86 (s, 3H), 6.23 (q, J=7.2 Hz, 1H), 6.93 (t, J=1.2 Hz, 1H), 7.00-7.06 (m, 4H), 7.24-7.26 (m, 1H), 7.31-7.34 (m, 2H), 7.72 (d, J=1.2 Hz, 1H), 7.89 (s, 1H).

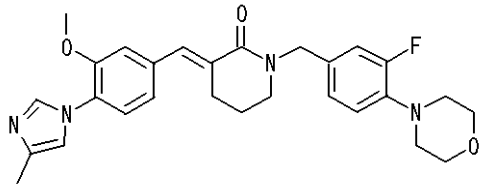
[0595]

Example 426

Synthesis of (E)-1-[3-fluoro-4-(morpholin-4-yl)benzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0596]

[Formula 200]



Synthesis of 3-fluoro-4-(morpholin-4-yl)benzonitrile

To a DMF (20 mL) solution of 3,4-difluorobenzonitrile (3.00 g), morpholine (2.82 g) and potassium carbonate (5.97 g) were added, and the

reaction solution was allowed to be warmed to 100°C and agitated for 5.5 hours. Water and ethyl acetate were added to the reaction solution after confirming disappearance of the starting materials, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and 4.41 g of the title compound was obtained by condensing under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.19-3.22 (m, 4H), 3.86-3.88 (m, 4H), 6.92 (t, J=8.4 Hz, 1H), 7.29 (dd, J=2.0, 13.0 Hz, 1H), 7.37-7.40 (m, 1H).

[0597]

Synthesis of 3-fluoro-4-(morpholin-4-yl)benzylamine

To a THF (30 mL) suspension of lithium aluminum hydride (975 mg), a THF (10 mL) solution of 3-fluoro-4-(morpholin-4-yl)benzonitrile (4.41 g) was added dropwise at -78°C. Then, the reaction solution was allowed to be warmed to room temperature and agitated overnight. The reaction solution was cooled to 0°C after confirming disappearance of the starting materials, water and 5N sodium hydroxide solution, and also ethyl acetate were added to the reaction solution one by one, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. The obtained residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: ethyl acetate =1:1 -> heptane-ethyl acetate), and 3.60 g of the title compound was obtained. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.06-3.08 (m, 4H), 3.81 (s, 2H), 3.87-3.89 (m, 4H), 6.91 (t, J=8.8 Hz, 1H), 7.01-7.05 (m, 2H).

[0598]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid[3-fluoro-4-(morpholin-4-yl)benzyl]amide

To a DMF (4.0 mL) solution of 5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-valeric acid trifluoroacetic acid salt (200 mg) obtained in Example 418 and 3-fluoro-4-(morpholin-4-yl)benzylamine (112 mg), IPEA (231 mg), EDC (171 mg) and HOBT (120 mg) were added one by one, and the reaction solution was agitated at room temperature overnight. After confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 135 mg of the title compound was obtained by purifying the obtained residue by silica gel chromatography (elution solvent: ethyl acetate ->

ethyl acetate : methanol = 90:10). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.99-2.06 (m, 2H), 2.29 (s, 3H), 2.72-2.76 (m, 2H), 3.06-3.09 (m, 4H), 3.58 (t, J=6.0 Hz, 2H), 3.85 (s, 3H), 3.84-3.88 (m, 4H), 4.49 (d, J=5.6 Hz, 2H), 6.28-6.38 (m, 1H), 6.88-6.98 (m, 4H), 7.01-7.06 (m, 2H), 7.17 (s, 1H), 7.22-7.25 (m, 1H), 7.70 (s, 1H).

[0599]

Synthesis of (E)-1-[3-fluoro-4-(morpholin-4-yl)benzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To a DMF (4 mL) solution of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl]benzylidene)valeric acid [3-fluoro-4-(morpholin-4-yl)benzyl] amide (135 mg), sodium hydride was added at 0°C (40% mineral oil content, 35.6 mg) was added, and the reaction solution was allowed to be warmed to room temperature and agitated for 45 minutes. The reaction solution was cooled to 0°C after confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After washed with a saturated saline solution the organic layer, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 113 mg of the title compound was obtained by purifying the obtained residue by silica gel chromatography (elution solvent; ethyl

acetate -> ethyl acetate : ethanol 90:10). The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82-1.90 (m, 2H), 2.30 (s, 3H), 2.83 (t, J=5.6 Hz, 2H), 3.07-3.09 (m, 4H), 3.37 (t, J=5.6 Hz, 2H), 3.86 (s, 3H), 3.86-3.88 (m, 4H), 4.66 (s, 2H), 6.90 (t, J=8.0 Hz, 1H), 6.94 (s, 1H), 7.02-7.05 (m, 4H), 7.25-7.27 (m, 1H), 7.72 (S, 1H), 7.82 (S, 1H).

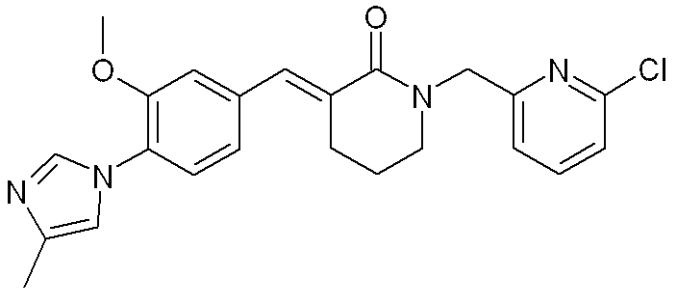
[0600]

Example 427

Synthesis of (E)-1-[(6-chloropyridin-2-yl)methyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0601]

[Formula 201]



To a suspension of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl]benzylidene)valeric acid ethyl ester (200 mg) obtained in Example 417 and 2-(aminomethyl)-6-chloropyridine (CA 188637-75-4) hydrochloride (100 mg) in ethanol (3 mL) and DMF (3 mL), anhydrous potassium carbonate (100 mg) was added and the reaction mixture was agitated at 100°C for 8

hours. After the reaction mixture was allowed to be cooled to room temperature, the reaction mixture was poured into iced water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated sodium chloride solution, and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. Ethanol (10 mL) and sodium hydroxide (1.0 g) aqueous solution (5 mL) were added to the residue, and the reaction solution was agitated at room temperature for 1 hour. The reaction solution was added to iced water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated sodium chloride solution, and it concentrated under reduced pressure after dried over anhydrous magnesium sulfate. 23 mg of the title compound was obtained by the residue was purified by silica gel chromatography (elution solvent: heptane–ethyl acetate system).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.88–1.96 (m, 2H), 2.30 (s, 3H), 2.82–2.89 (m, 2H), 3.54–3.62 (m, 2H), 3.85 (s, 3H), 4.78 (s, 2H), 6.92 (s, 1H), 6.99–7.05 (m, 2H), 7.20–7.28 (m, 2H), 7.31 (d, J=7.6 Hz, 1H), 7.63 (t, J=7.6 Hz, 1H), 7.70 (d, J=1.2 Hz, 1H), 7.83 (s, 1H).

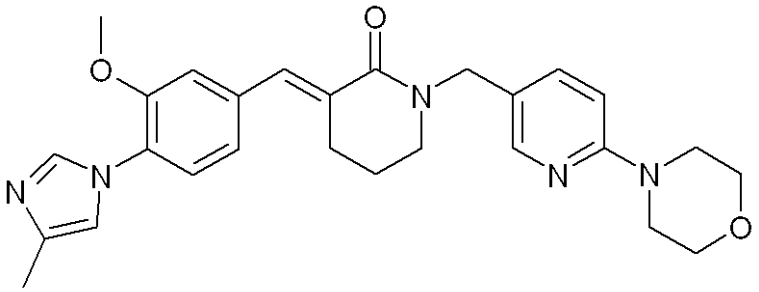
[0602]

Example 428

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(6-(morpholin-4-yl)pyridine-3-yl)methyl]piperidin-2-one

[0603]

[Formula 202]



Synthesis of 2-[6-(morpholin-4-yl)pyridin-3-yl]methylisoindol-1,3-dione

To a THF (200 mL) solution of (6-(morpholin-4-yl)pyridine-3-yl)methanol (CA 388088-73-1) (3.2 g), phthalimide (3.64 g) and triphenylphosphine (6.49 g), diisopropylazodicarboxylate (5.43 mL) was added at 0°C for 5 minutes. The reaction solution was concentrated under reduced pressure after 12-hour stirring at room temperature. 3.8 g of the title compound was obtained by the residue was purified by silica gel chromatography (heptane-ethyl acetate system). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.42-3.50 (m, 4H), 3.74-3.82 (m, 4H), 4.73 (s, 2H), 6.56 (d, J=8.4 Hz, 1H), 7.42-7.72 (m, 1H), 7.64-7.72 (m, 2H), 7.78-7.84 (m, 2H), 8.29 (d, J=2.0 Hz, 1H).

[0604]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl]benzylidene)-1-[(6-(morpholin-4-yl)pyridine-3-yl]methyl)piperidin-2-one

To an ethanol (50 mL) solution of 2-[6-

(morpholin-4-yl)pyridine-3-yl]methylisoindoindol-1,3-dione (3.8 g) obtained above, hydrazine monohydrate (2.95 mL) was added, and heat-refluxing of the reaction solution was carried out for 2 hours. The reaction solution was allowed to be cooled to room temperature, diethyl ether (100 mL) was added to the reaction solution, and the reaction solution was agitated for 30 minutes at room temperature. C-[6-(morpholin-4-yl)pyridine-3-yl]methylamine (3.0 g) was obtained by filtering off insoluble solids in the reaction solution and condensing the obtained filtrate under reduced pressure. To a DMF (30 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (0.20 g) obtained in Example 418 and C-[6-(morpholin-4-yl)pyridine-3-yl]methylamine (0.30 g), HOBT (0.181 g), IPEA (0.388 mL) and EDC (0.257 g) were added at room temperature, and the reaction solution was agitated at room temperature for 12 hours. The reaction solution was added to water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated salt solution, and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (elution solvent: from heptane-ethyl acetate system to methanol-ethyl acetate system) and 0.21 g of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzylidene]valeric acid [6-(morpholin-4-yl)pyridine-3-yl]methyl amide was obtained.

To a DMF (30 mL) solution of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid [6-(morpholin-4-yl)pyridine-3-yl]methyl amide (0.21 g) obtained above, sodium hydrite (40% mineral oil content, 29.7 mg) was added at room temperature, and the reaction solution was agitated for 30 minutes at the temperature. The reaction solution was added to water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated salt solution, and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. 0.125 g of the title compound was obtained by the residue was purified by silica gel chromatography (elution solvent: from heptane-ethyl acetate system to methanol-ethyl acetate system).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.78-1.88 (m, 2H), 2.30 (s, 3H), 2.75-2.83 (m, 2H), 3.32-3.39 (m, 2H), 3.44-3.54 (m, 4H), 3.76-3.88 (m, 4H), 3.85 (s, 3H), 4.59 (s, 2H), 6.62 (d, J=8.8 Hz, 1H), 6.92 (s, 1H), 6.98-7.04 (m, 2H), 7.20-7.28 (m, 1H), 7.57 (dd, J=2.0, 8.8 Hz, 1H), 7.70 (s, 1H), 7.84 (s, 1H), 8.12 (d, J=2.0 Hz, 1H).

[0605]

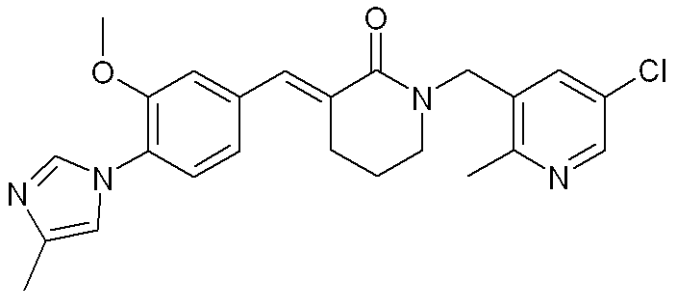
Example 429

Synthesis of (E)-1-[(5-chloro-2-methylpyridin-3-yl)methyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzylidene]piperidin-2-one

[0606]

[Formula 203]



Synthesis of (5-chloro-2-methylpyridin-3-yl)methanol

To a THF (30 mL) solution of 5-chrolo-2-methyl nicotinic acid methyl ester (CAS# 350597-49-8) (1.0 g), boron lithium hydride (0.153 g) was added at 0°C. The reaction solution was agitated at room temperature for 2 hours. The reaction solution was added to iced water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated salt solution, and it concentrated under reduced pressure after dried over anhydrous magnesium sulfate. 0.26 g of the title compound was obtained by the residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system).

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.47 (s, 3H), 4.70 (s, 2H), 7.74 (d, J=2.4 Hz, 1H), 8.33 (d, J=2.4 Hz, 1H).

[0607]

Synthesis of 2-[(5-chloro-2-methylpyridin-3-yl]methyl)isoindole-1,3-dione

To a THF (10 mL) solution of (5-chloro-2-methylpyridin-3-yl)methanol (0.26 g) obtained above, phthalimide (0.364 g) and triphenylphosphine (0.649 g), diisopropylazodicarboxylate (0.585 mL) were added at 0°C for 5 minutes. The reaction solution was agitated for three days at room temperature and concentrated under reduced pressure. 0.20 g of the title compound was obtained by the residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system).

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.68 (s, 3H), 4.83 (s, 2H), 7.55 (s, 1H), 7.70-7.80 (m, 2H), 7.80-7.95 (m, 2H), 8.35 (s, 1H).

[0608]

Synthesis of (E)-1-[(5-chloro-2-methylpyridin-3-yl)methyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

To an ethanol (10 mL) solution of 2-((5-chloro-2-methyl-pyridine-3-yl)methyl)isoindole-1,3-dione (0.20 g), hydrazine monohydrate (0.50 mL) was added, and heat-refluxing of the reaction solution was carried out for 2 hours. The reaction solution was allowed to be cooled to room temperature, diethyl ether (50 mL) was added to the reaction solution, and the reaction solution was agitated for 30 minutes at room temperature. C-(5-chloro-2-methylpyridin-3-yl)methylamine (0.13 g) was obtained by filtering off insoluble matters in the reaction solution and

condensing the obtained filtrate under reduced pressure.

To a DMF (20 mL) solution of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid trifluoroacetic acid salt (0.20 g) obtained according to Example 418 and C-(5-chloro-2-methylpyridin-3-yl)methylamine (0.13 g), HOBT (0.301 g), IPEA (0.397 mL), and EDC (0.428 g) were added, and the reaction solution was agitated under room temperature for 12 hours. The reaction solution was added to water and the reaction solution was extracted with ethyl acetate. The obtained organic layer was washed with a saturated salt solution, and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system) and 0.14 g of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (5-chloro-2-methylpyridin-3-yl)methyl amide was obtained.

To a DMF (10 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (5-chloro-2-methylpyridin-3-yl)methyl amide (0.14 g) obtained above, sodium hydride (40% mineral oil content, 47.4 mg) was added at room temperature, and the reaction solution was agitated at that temperature for 1 hour. The reaction solution was added to water and the reaction solution

was extracted with ethyl acetate. The obtained organic layer was washed with a saturated sodium chloride solution, and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. 0.027 g of the title compound was obtained by the residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.90-2.00 (m, 2H), 2.30 (s, 3H), 2.54 (s, 3H), 2.85-2.92 (m, 2H), 3.34-3.41 (m, 2H), 3.87 (s, 3H), 4.72 (s, 2H), 6.92-6.95 (m, 1H), 7.02-7.08 (m, 2H), 7.24-7.30 (m, 1H), 7.41 (d, J=2.4 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.87 (s, 1H), 8.37 (d, J=2.4 Hz, 1H).

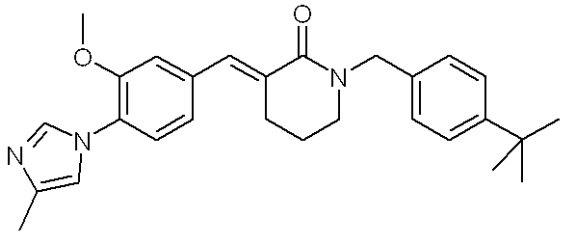
[0609]

Example 430

Synthesis of (E)-1-(4-tert-butylbenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0610]

[Formula 204]



To a DMF (2 mL) solution of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one (70 mg) obtained in Example 416, lithium bis(trimethylsilyl)amide (1M THF solution, 0.47 mL) was

added dropwise under ice-cooling, and the reaction solution was agitated for 30 minutes under ice-cooling. Subsequently, 1-tert-butyl-4-chloromethylbenzene (0.073 mL) was added to the reaction solution, and the reaction solution was agitated for 30 minutes under ice-cooling. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was dried with magnesium sulfate and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system), and 37.8 mg of the title compound was obtained. The physical properties are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.31 (s, 9H), 1.86 (m, 2H), 2.30 (s, 3H), 2.82 (m, 2H), 3.38 (m, 2H), 3.85 (s, 3H), 4.70 (s, 2H), 6.92 (t, J=1.2 Hz, 1H), 7.01 (s, 1H), 7.02 (d, J=8.4 Hz, 1H), 7.22-7.26 (m, 3H), 7.34 (d, J=8.4 Hz, 2H), 7.70 (d, J=1.2 Hz, 1H), 7.86 (s, 1H).

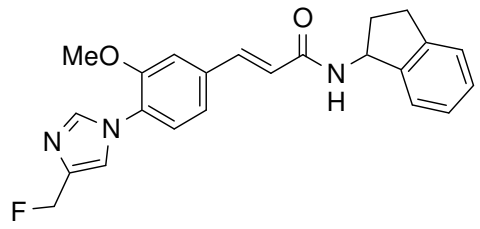
[0611]

Example 431

Synthesis of (E)-3-[4-(4-fluoromethyl-1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-ylacrylamide

[0612]

[Formula 205]



By the same as in Example 147, 11 mg of the title compound was obtained from (E)-3-[4-(4-hydroxymethyl-1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-ylacrylamide (20 mg) obtained in Example 45.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.96 (m, 1H), 2.65-2.73 (m, 1H), 2.90-2.98 (m, 1H), 3.01-3.08 (m, 1H), 3.90 (s, 3H), 5.40 (d, J=49.2 Hz, 2H), 5.66 (q, J=7.6 Hz, 1H), 5.99 (d, J=8 Hz, 1H), 6.46 (d, J=15.6 Hz, 1H), 7.17-7.37 (m, 8H), 7.70 (d, J=15.6 Hz, 1H), 7.79 (s, 1H).

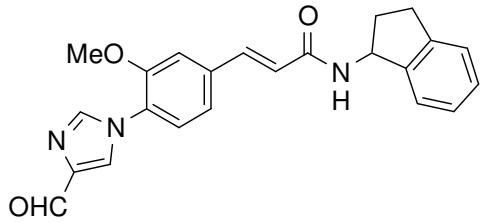
[0613]

Example 432

Synthesis of (E)-3-[4-(4-formyl-1H-imidazol-1-yl)3-methoxyphenyl]-N-indan-1-ylacrylamide

[0614]

[Formula 206]



To a chloroform (5 mL) solution of (E)-3-(4-(4-hydroxymethyl-1H-imidazol-1-yl)-3-methoxyphenyl)-N-indan-1-ylacrylamide (15 mg) obtained in Example 45, activated manganese dioxide (280 mg) was added, and the reaction mixture was agitated at room temperature overnight. The reaction solution was filtered through a filter paper and the filtrate was concentrated under reduced pressure. The residue was purified by silica

gel column chromatography (elution solvent: ethyl acetate), and 30 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.96 (m, 1H), 2.63-2.73 (m, 1H), 2.89-2.97 (m, 1H), 3.00-3.07 (m, 1H), 3.91 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.94 (d, J=8.8 Hz, 1H), 6.47 (d, J=15.6 Hz, 1H), 7.19-7.36 (m, 6H), 7.70 (d, J=15.6 Hz, 1H), 7.84 (d, J=1 Hz, 1H), 7.92 (d, J=1 Hz, 1H), 9.96 (s, 1H).

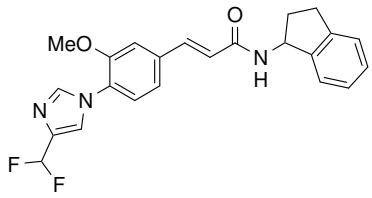
[0615]

Example 433

Synthesis of (E)-3-[4-(4-difluoromethyl-1H-imidazol-1-yl)-3-methoxyphenyl]-N-indan-1-ylacrylamide

[0616]

[Formula 207]



6 mg of the title compound was obtained from the above (E)-3-(4-(4-formyl-1H-imidazol-1-yl)3-methoxyphenyl)-N-indan-1-ylacrylamide (9 mg) and DAST (0.012 mL) in a similar way as in the synthesis in Example 147.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.96 (m, 1H), 2.65-2.73 (m, 1H), 2.89-2.97 (m, 1H), 3.01-3.08 (m, 1H), 3.90 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.85 (d, J=8.8 Hz, 1H), 6.44 (d, J=15.6 Hz, 1H), 6.74 (t, J=56 Hz, 1H), 7.17-7.36 (m, 6H), 7.46 (s, 1H), 7.70 (d, J=15.6 Hz, 1H),

7.80 (s, 1H).

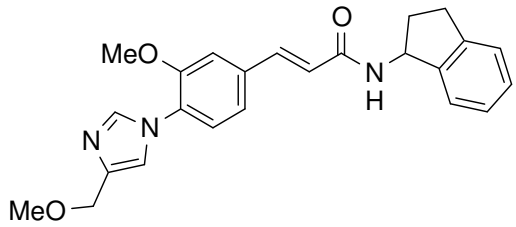
[0617]

Example 434

Synthesis of (E)-N-indan-1-yl-3-[3-methoxy-4-(4-methoxymethyl-1H-imidazol-1-yl]phenyl)acrylamide

[0618]

[Formula 208]



A thionyl chloride (0.4 mL) solution of (E)-3-[4-(4-hydroxymethyl-1H-imidazole-1-yl)-3-methoxyphenyl]-N-indan-1-ylacrylamide (15 mg) obtained in Example 45 was agitated for 40 minutes at 50°C, and then the reaction solution was concentrated under reduced pressure. A solution of sodium methoxide (40% methanol solution, 2 mL) was added to the obtained residue, and the reaction solution was agitated for 90 minutes at room temperature. After the reaction solution was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH,

elution solvent:hexane-ethyl acetate system), and 4 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.95 (m, 1H), 2.64-2.73 (m, 1H), 2.89-2.97 (m, 1H), 3.00-3.07 (m, 1H), 3.47 (s, 3H), 3.88 (s, 3H), 4.48 (s, 2H), 5.65 (q, J=7.6 Hz, 1H), 5.85 (d, J=8.4 Hz, 1H), 6.42 (d, J=15.6 Hz, 1H), 7.15-7.29 (m, 7H), 7.35 (d, J=7.6 Hz, 1H), 7.69 (d, J=15.6 Hz, 1H), 7.78 (s, 1H).

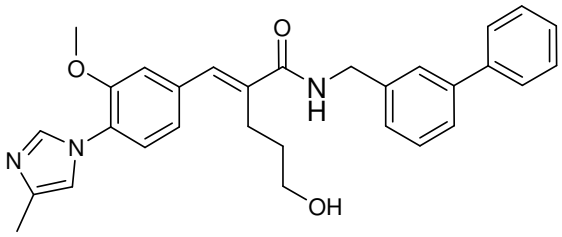
[0619]

Example 435

Synthesis of (E)-5-hydroxy-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (biphenyl-3-ylmethyl)amide

[0620]

[Formula 209]



Synthesis of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] 5-(tetrahydropyran-2-yloxy) valeric acid ethyl ester

To a DMF (30 mL) suspension of sodium hydride (40% mineral oil content, 1.25 g), triethylphosphonoacetic acid (4.89 mL) was added dropwise at room temperature. After agitating the reaction solution at room temperature for 3 hours, a

DMF (10 mL) solution of 2-(3-bromopropoxy)tetrahydro-2H-pyran was added dropwise to the solution. The reaction solution was agitated at 60°C for 6 hours. The reaction solution was allowed to be cooled to room temperature and concentrated under reduced pressure. Ethyl acetate and a saturated ammonium chloride solution were added to the residue, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel chromatography (elution solvent: hexane: ethyl acetate = 2:1 -> ethyl acetate), and 2.9 g of 2-(diethoxyphosphoryl)-5-(tetrahydropyran-2-yloxy) valeric acid ethyl ester was obtained.

To a THF (5 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (283 mg) obtained in Example 1 and 2-(diethoxyphosphoryl)-5-(tetrahydropyran-2-yloxy)valeric acid ethyl ester (480 mg), lithium hydroxide monohydrate (110 mg) was added, and the reaction solution was agitated at room temperature for 19 hours. Ethyl acetate and a saturated ammonium chloride solution were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica

gel chromatography (Carrier: Chromatorex™ NH and elution solvent:hexane:ethyl acetate =1:1 -> ethyl acetate), and 186 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.36 (t, J=7.2 Hz, 3H), 1.47-1.93 (m, 10H), 2.31 (s, 3H), 2.62-2.76 (m, 2H), 3.39-3.53 (m, 2H), 3.76-3.87 (m, 2H), 3.88 (s, 3H), 4.29 (q, J=7.2 Hz, 2H), 4.54 (brs, 1H), 6.94 (brs, 1H), 7.05 (brs, 1H), 7.13 (brd, J=7.6 Hz, 1H), 7.25 (d, J=7.6 Hz, 1H), 7.66 (brs, 1H), 7.72 (brs, 1H).

[0621]

Synthesis of (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-(tetrahydropyran-2-yloxy)valeric acid (biphenyl-3-ylmethyl)amide

To a methanol (3 mL) solution of (E)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)5-(tetrahydropyran-2-yloxy)valeric acid ethyl ester (186 mg), 2N sodium hydroxide aqueous solution (0.5 mL) was added and the reaction solution was agitated at room temperature for 19 hours. 2N hydrochloric acid (0.5 mL) was added to the reaction solution, and the solution was concentrated under reduced pressure. 3-phenylbenzylamine (87 mg), HOBT (86 mg), EDC (108 mg), and IPEA (0.15 mL) were added to a DMF (5 mL) solution of the residue one by one, and the reaction solution was agitated at room temperature for 12 hours. Ethyl acetate and a saturated ammonium chloride solution were

added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate: methanol = 9:1), and 168 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.32-1.71 (m, 6H), 1.84-1.95 (m, 2H), 2.30 (s, 3H), 2.64-2.77 (m, 2H), 3.40-3.47 (m, 2H), 3.70-3.84 (m, 2H), 3.85 (s, 3H), 4.48 (brs, 1H), 4.63 (dd, J=10.4, 5.6 Hz, 1H), 4.70 (dd, J=10.4, 4.5 Hz, 1H), 6.71 (t, J=5.6 Hz, 1H), 6.92 (brs, 1H), 6.98 (brs, 1H), 7.02 (brd, J=8.0 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.33-7.62 (m, 10H), 7.71 (brs, 1H).

[0622]

Synthesis of (E)-5-hydroxy-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (biphenyl-3-ylmethyl)amide

To the methanol (5 mL) solution of (E) -2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-5-(tetrahydropyran-2-yloxy) valeric acid (biphenyl-3-ylmethyl)amide (168 mg), Dow- X^{TM}50W X-8 (300 mg) was added, and the reaction solution was agitated at 45°C for 5 hours. The resin was filtered off, the ammonia water (1 mL) was added to the filtrate, and the solution was concentrated under reduced pressure. The

residue was purified by silica gel chromatography (elution solvent: ethyl acetate -> ethyl acetate: methanol = 9:1), and 120 mg of the title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z482 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81 (quintet, J=6.8 Hz, 2H), 2.30 (s, 3H), 2.73 (t, J=6.8 Hz, 2H), 3.67 (t, J=6.8 Hz, 2H), 3.85 (s, 3H), 4.65 (d, J=5.6 Hz, 2H), 6.63 (t, J=5.6 Hz, 1H), 6.92 (brs, 1H), 6.98-7.02 (m, 2H), 7.25 (d, J=8.8 Hz, 1H), 7.33-7.62 (m, 10H), 7.71 (brs, 1H).

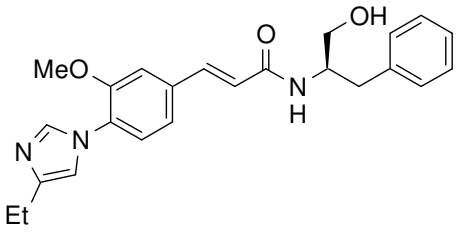
[0623]

Example 436

Synthesis of (E)-3-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxyphenyl]-N-((1S)-1-hydroxymethyl-2-phenylethyl)acrylamide

[0624]

[Formula 210]



Synthesis of (E)-3-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxyphenyl]acrylic acid

By the same method as in Example 121, 3.05 g of the title compound was obtained from 4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzaldehyde (2.72 g) obtained in Example 637 and diethylphosphono ethyl acetate ester

(3.17 g). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 0.46 (t, J=7.6 Hz, 3H), 1.83 (q, J=7.6 Hz, 2H), 3.13 (s, 3H), 5.76 (d, J=16 Hz, 1H), 6.35 (s, 1H), 6.50 (dd, J=2 Hz, 8.4 Hz, 1H), 6.61 (d, J=8.4 Hz, 1H), 6.62 (d, J=1.6 Hz, 1H), 6.61 (d, J=8.4 Hz, 1H), 6.86 (d, J=16 Hz, 1H), 7.18 (s, 1H).

[0625]

Synthesis of (E)-3-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxyphenyl]-N-((1S)-1-hydroxymethyl-2-phenylethyl)acrylamide

[0626]

By the same method as in Example 121, 58 mg of the title compound was obtained from (E)-3-(4-(4-ethyl-1H-imidazol-1-yl)-3-methoxyphenyl)acrylic acid (116 mg) and D-phenylalaninol (78 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.28 (t, J=7.6 Hz, 3H), 2.66 (q, J=7.6 Hz, 2H), 3.68 (dd, J=4.4 Hz, 11.2 Hz, 1H), 3.79 (dd, J=3.6 Hz, 11.2 Hz, 1H), 3.83 (s, 3H), 4.33-4.37 (m, 2H), 6.31 (d, J=7.6 Hz, 1H), 6.38 (d, J=16 Hz, 1H), 6.92 (s, 1H), 7.06 (s, 1H), 7.08 (dd, J=1.6 Hz, 8 Hz, 1H), 7.18-7.33 (m, 6H), 7.57 (d, J=16 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H).

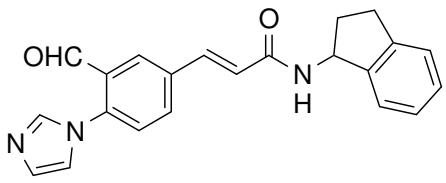
[0627]

Example 437

Synthesis of (E)-3-[3-formyl-4-(1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0628]

[Formula 211]



Synthesis of 5-bromo-2-(1H-imidazol-1-yl)benzaldehyde

By the same method as in Example 11, 2.8 g of the title compound was obtained from 5-bromo-2-fluorobenzaldehyde (5 g) and imidazole(2 g).

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.21 (t, J=1.2 Hz, 1H), 7.28-7.29 (m, 1H), 7.34 (d, J=8.4 Hz, 1H), 7.71 (t, J=1.2 Hz, 1H), 7.86 (dd, J=2.8 Hz, 8.4 Hz, 1H), 8.17 (d, J=2.8 Hz, 1H), 9.75 (s, 1H).

[0629]

Synthesis of (E)-3-[3-formyl-4-(1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

By the same method as in Example 9, 44 mg of the title compound was obtained from 5-bromo-2-(1H-imidazol-1-yl)benzaldehyde (50 mg) and N-indan-1-yl-acrylamide (45 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.96 (m, 1H), 2.64-2.72 (m, 1H), 2.90-3.07 (m, 2H), 5.64 (q, J=7.6 Hz, 1H), 6.19 (d, J=8.4 Hz, 1H), 6.60 (d, J=15.6 Hz, 1H), 7.21-7.35 (m, 5H), 7.44 (d, J=8.4 Hz, 1H), 7.72 (s, 1H), 7.75 (d, J=15.6 Hz, 1H), 7.81 (dd, J=2 Hz, 15.6 Hz, 1H), 8.18 (d, J=2 Hz, 1H), 9.82 (s, 1H).

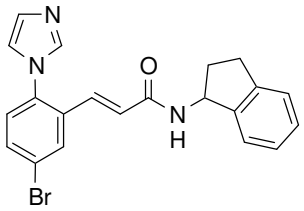
[0630]

Example 438

Synthesis of (E)-3-[5-bromo-2-(1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0631]

[Formula 212]



By the same method as in Example 1, 49 mg of the title compound was obtained from 5-bromo-2-(1H-imidazol-1-yl)benzaldehyde (30 mg) and indan-1-ylcarbamoyl methylphosphonic acid diethyl ester (37 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.80-1.89 (m, 1H), 2.58-2.66 (m, 1H), 2.85-2.93 (m, 1H), 2.96-3.03 (m, 1H), 5.55 (q, J=7.6 Hz, 1H), 5.99 (d, J=8.4 Hz, 1H), 6.20 (d, J=15.6 Hz, 1H), 7.06 (t, J=1.2 Hz, 1H), 7.16-7.28 (m, 5H), 7.38 (d, J=15.6 Hz, 1H), 7.55-7.58 (m, 2H), 7.79 (d, J=2 Hz, 1H).

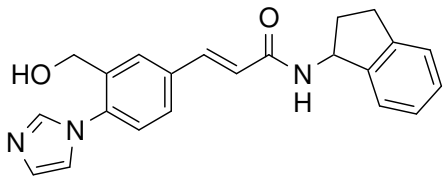
[0632]

Example 439

Synthesis of (E)-3-[3-hydroxymethyl-4-(1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0633]

[Formula 213]



Sodium borohydride (2 mg) is added to an ethanol (1 mL) solution of (E)-3-(3-formyl-4-(1H-imidazol-1-yl)phenyl)-N-indan-1-ylacrylamide (17 mg) obtained in Example 437 and the reaction mixture was agitated for 30 minutes at room temperature. After the reaction solution was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent:methanol-ethyl acetate system), and 1.8 mg of the title compound was obtained. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.95 (m, 1H), 2.63-2.72 (m, 1H), 2.89-2.97 (m, 1H), 3.00-3.07 (m, 1H), 4.55 (s, 2H), 5.65 (q, J=7.6 Hz, 1H), 5.89 (d, J=8.4 Hz, 1H), 6.48 (d, J=15.6 Hz, 1H), 7.18-7.35 (m, 7H), 7.54 (dd, J=2.4 Hz, 8 Hz, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.79 (d, J=2 Hz, 1H).

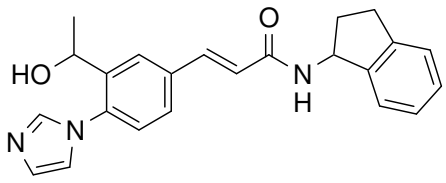
[0634]

Example 440

Synthesis of (E)-3-[3-(1-hydroxy ethyl)-4-(1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0635]

[Formula 214]



To a THF (0.5 mL) solution of (E)-3-(3-formyl-4-(1H-imidazol-1-yl)phenyl)-N-indan-1-ylacrylamide (23 mg) obtained in Example 437, methyl magnesium bromide (3M ether solution, 0.04 mL) was added under nitrogen atmosphere under ice-cooling and the reaction mixture was agitated for 1 hour. A saturated ammonium chloride water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent:methanol-ethyl acetate system), and 10 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.40 (d, J=6.4 Hz, 3H), 1.86-1.95 (m, 1H), 2.66-2.73 (m, 1H), 2.89-2.97 (m, 1H), 3.00-3.07 (m, 1H), 4.79 (q, J=6.4 Hz, 1H), 5.65 (q, J=7.6 Hz, 1H), 5.90 (d, J=8.4 Hz, 1H), 6.50 (d, J=15.6 Hz, 1H), 7.09 (t, J=1.2 Hz, 1H), 7.20-7.35 (m, 5H),

7.49 (dd, J=1.6 Hz, 8 Hz, 1H), 7.61 (s, 1H), 7.73 (d, J=15.6 Hz, 1H), 7.89 (d, J=2 Hz, 1H).

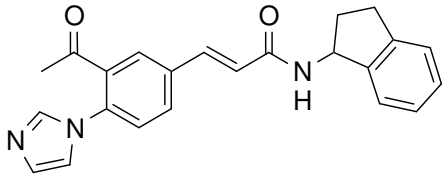
[0636]

Example 441

Synthesis of (E)-3-[3-acetyl-4-(1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0637]

[Formula 215]



To a chloroform (0.5 mL) solution of (E)-3-(3-(1-hydroxyethyl)-4-(1H-imidazol-1-yl)phenyl)-N-indan-1-ylacrylamide (3 mg) obtained in Example 440, activated manganese dioxide (14 mg) was added and the reaction mixture was agitated at room temperature overnight. The reaction solution was filtered through a filter paper and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: ethyl acetate), and 3.8 mg of the title compound was obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.96 (m, 1H), 2.02 (s, 3H), 2.65-2.73 (m, 1H), 2.89-2.97 (m, 1H), 3.00-3.08 (m, 1H), 5.64 (q, J=7.6 Hz, 1H), 5.88 (d, J=8.4 Hz, 1H), 6.49 (d, J=15.6 Hz, 1H), 7.12 (t, J=1.2 Hz, 1H), 7.22-7.39 (m, 6H), 7.64 (t, J=1.2 Hz, 1H), 7.70 (dd, J=1.6

Hz, 8 Hz, 1H), 7.78 (d, J=1.6 Hz, 1H).

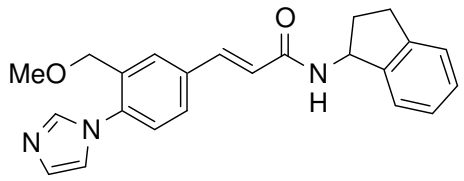
[0638]

Example 442

Synthesis of (E)-3-[4-(1H-imidazol-1-yl)-3-methoxymethylphenyl]-N-indan-1-ylacrylamide

[0639]

[Formula 216]



Sodium borohydride (127 mg) was added to an ethanol (10 mL) solution of the 5-bromo-2-(1H-imidazol-1-yl)benzaldehyde (420 mg) obtained in Example 437, and the reaction mixture was agitated at room temperature for 1 hour. After the reaction solution was concentrated under reduced pressure, water and ethyl acetate was added to the residue and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Sodium methoxide (40% methanol solution, 10 mL) was added to a methanol (2 mL) solution of the obtained crude alcohol compound, and the reaction mixture was agitated at room temperature overnight. After the reaction solution was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned.

The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and a crude methoxymethyl compound (211 mg) was obtained. By the same method as in Example 9, 15 mg of the title compound was obtained from this crude methoxymethyl compound (23 mg) and N-indan-1-yl-acrylamide (16 mg). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.97 (m, 1H), 2.63-2.72 (m, 1H), 2.90-2.96 (m, 1H), 3.00-3.07 (m, 1H), 3.39 (s, 3H), 4.23 (s, 2H), 5.65 (q, J=7.6 Hz, 1H), 5.89 (d, J=8.4 Hz, 1H), 6.47 (d, J=15.6 Hz, 1H), 7.17 (t, J=1.2 Hz, 1H), 7.22-7.35 (m, 7H), 7.54 (dd, J=2 Hz, 8.4 Hz, 1H), 7.70-7.75 (m, 2H).

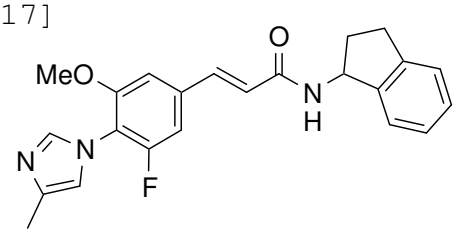
[0640]

Example 443

Synthesis of (E)-3-[3-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0641]

[Formula 217]



By the same method as in Example 9, 32 mg of the title compound was obtained from 1-(4-bromo-2-fluoro-6-methoxyphenyl)-4-methyl-1H-imidazole (30 mg) and N-indan-1-yl-acrylamide (24 mg) synthesized by the same method as in Example 16. The physical properties

of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.85-1.94 (m, 1H), 2.29 (s, 3H), 2.62-2.70 (m, 1H), 2.87-2.95 (m, 1H), 2.98-3.06 (m, 1H), 3.96 (s, 3H), 5.62 (q, J=7.6 Hz, 1H), 6.02 (d, J=8.4 Hz, 1H), 6.39 (d, J=15.6 Hz, 1H), 6.96 (d, J=0.8 Hz, 1H), 7.04-7.08 (m, 2H), 7.20-7.34 (m, 4H), 7.61 (d, J=15.6 Hz, 1H), 7.70 (t, J=1.6 Hz, 1H).

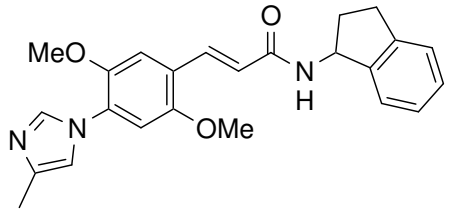
[0642]

Example 444

Synthesis of (E)-3-[2,5-dimethoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0643]

[Formula 218]



35 mg of the title compound was obtained from 1-(4-bromo-2,5-dimethoxyphenyl)-4-methyl-1H-imidazole (58 mg) prepared by a similar method as in Example 18 and N-indan-1-yl-acrylamide (44 mg) by the same method as in Example 9. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.95 (m, 1H), 2.30 (s, 3H), 2.63-2.72 (m, 1H), 2.88-2.96 (m, 1H), 2.99-3.05 (m, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.92 (d, J=8.4 Hz, 1H), 6.59 (d, J=15.6 Hz, 1H), 6.81 (s, 1H), 6.94-6.95 (m, 1H), 7.13 (s, 1H), 7.21-

7.29 (m, 3H), 7.36 (d, J=6.8 Hz, 1H), 7.74 (d, J=1.2 Hz, 1H), 7.86 (d, J=15.6 Hz, 1H).

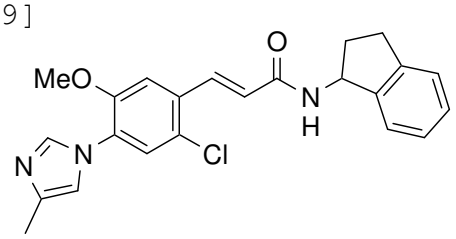
[0644]

Example 445

Synthesis of (E)-3-[2-chloro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0645]

[Formula 219]



19 mg of the title compound was obtained by the same method as in Example 9 from 1-(4-bromo-5-chloro-2-methoxyphenyl)-4-methyl-1H-imidazole (72 mg) prepared by a similar method as in Example 18 and N-indan-1-yl-acrylamide (49 mg).

The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.96 (m, 1H), 2.29 (s, 3H), 2.64-2.73 (m, 1H), 2.89-2.97 (m, 1H), 3.00-3.07 (m, 1H), 3.88 (s, 3H), 5.65 (q, J=7.6 Hz, 1H), 5.96 (d, J=8.4 Hz, 1H), 6.45 (d, J=15.6 Hz, 1H), 6.92 (t, J=1.2 Hz, 1H), 7.17 (s, 1H), 7.22-7.29 (m, 3H), 7.33 (s, 1H), 7.36 (d, J=6.8 Hz, 1H), 7.73 (d, J=1.6 Hz, 1H), 7.98 (d, J=15.6 Hz, 1H).

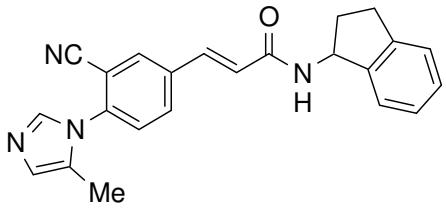
[0646]

Example 446

Synthesis of (E)-3-[3-cyano-4-(5-methyl-1H-imidazol-1-yl)phenyl]-N-indan-1-ylacrylamide

[0647]

[Formula 220]



By the same method as in Example 9, 9 mg of the title compound was obtained from 5-bromo-2-(5-methyl-1H-imidazol-1-yl)benzonitrile (30 mg).

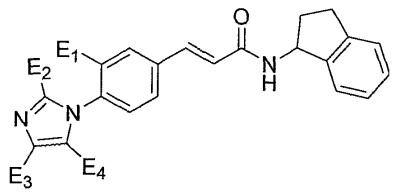
^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.97 (m, 1H), 2.18 (s, 3H), 2.65-2.74 (m, 1H), 2.90-2.98 (m, 1H), 3.01-3.08 (m, 1H), 5.65 (q, J=7.6 Hz, 1H), 5.91 (d, J=8.4 Hz, 1H), 6.50 (d, J=16 Hz, 1H), 6.98 (t, J=1.2 Hz, 1H), 7.22-7.30 (m, 3H), 7.34 (d, J=7.6 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H), 7.58 (d, J=1.2 Hz, 1H) 7.73 (d, J=16 Hz, 1H), 7.83 (dd, J=2.4 Hz, 8.4 Hz, 1H), 7.94 (d, J=2 Hz, 1H).

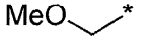
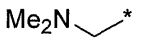
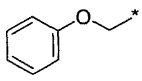
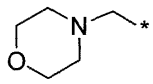
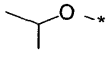
[0648]

Compounds shown in Table 11 were synthesized in which Example 447 to Example 450 followed the method of Example 434, Example 451 to Example 455 followed the method of Example 20 and Example 456 and Example 457 followed the method of Example 1 changing the substitutent groups on the imidazolering ring and the benzene ring. The structural formulae and physical properties are shown in Table 11, respectively.

[0649]

[Table 11]



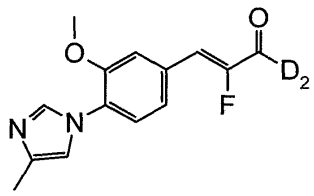
Example	E_1	E_2	E_3	E_4	DATA: MS m/z
447	F	H		H	M^++H：344 (ESI)
448	MeO	H		H	M^++H：362 (ESI)
449	MeO	H		H	M^++H：362 (ESI)
450	MeO	H		H	M^++H：424 (ESI)
451	F	H	H	Cl	M^++H：382 (ESI)
452	MeO	Cl	Cl	Cl	M^++H：462 (ESI)
453	MeO	H	Cl	Cl	M^++H：428 (ESI)
454	MeO	H	Me	Cl	M^++H：408 (ESI)
455	MeO	H	H	Br	M^++H：439 (ESI)
456	EtO	H	H	H	M^++H：374 (ESI)
457		H	H	H	M^++H：388 (ESI)

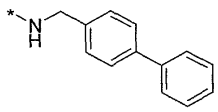
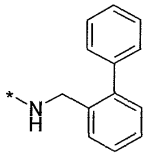
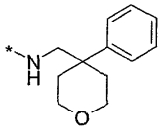
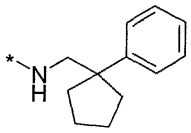
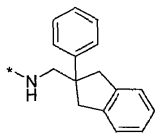
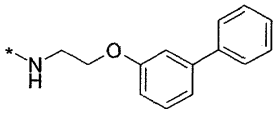
[0650]

The compounds shown in Table 12 were synthesized as in Example 85. The structural formulae and physical properties are shown in Table 12, respectively.

[0651]

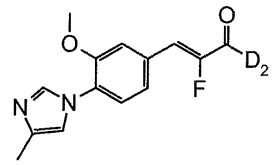
[Table 12-1]

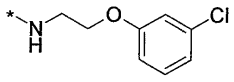
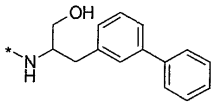
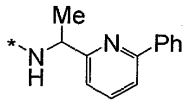
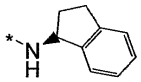
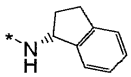
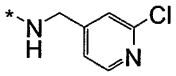
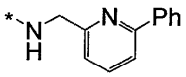
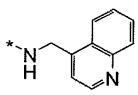
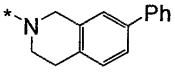
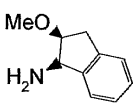


Example	D_2	DATA: MS m/z
458		M^++H : 442 (ESI)
459		M^++H : 442 (ESI)
460		M^++H : 450 (ESI)
461		M^++H : 434 (ESI)
462		M^++H : 482 (ESI)
463		M^++H : 472 (ESI)

[0652]

[Table 12-2]



Example	D_2	DATA: MS m/z
464		M^++H：430 (ESI)
465		M^++H：486 (ESI)
466		M^++H：457 (ESI)
467		M^++H：392 (ESI)
468		M^++H：392 (ESI)
469		M^++H：401 (ESI)
470		M^++H：443 (ESI)
471		M^++H：417 (ESI)
472		M^++H：468 (ESI)
473		M^++H：422 (ESI)

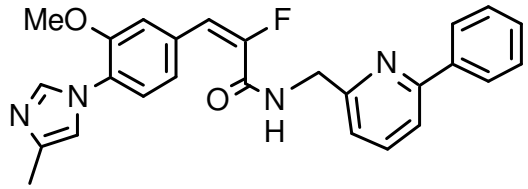
[0653]

Example 474

Synthesis of (Z)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-(6-phenylpyridin-2-ylmethyl)acrylic acid amide

[0654]

[Formula 221]



Synthesis of (Z)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylic acid

By the same method as in Example 111, 4.52 g of the title compound was obtained from 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (4.0 g) synthesized in Example 1, 2-fluoro -2-phosphonoacetic acid triethyl ester (5.82 g) and lithium hydroxide monohydrate (0.664 g). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H), 3.82 (s, 3H), 7.02 (d, J=24 Hz, 1H), 7.20 (s, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.59 (s, 1H), 7.93 (s, 1H).

[0655]

Synthesis of (Z)-2-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-N-(6-phenylpyridin-2-ylmethyl)acrylic acid amide

By the same method as in Example 111, 12.1 mg of the title compound was obtained from (Z)-2-fluoro-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylic acid (10 mg) and (6-phenylpyridin-2-yl)methylamine (10 mg). The physical properties of the compound are as follows.

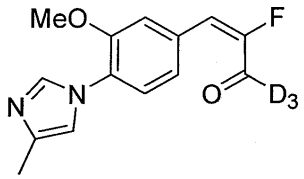
ESI-MS;m/z443[M^++H].

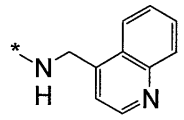
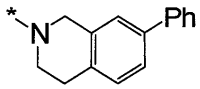
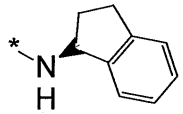
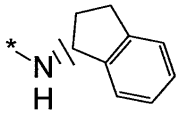
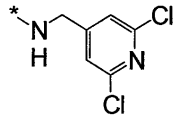
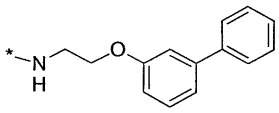
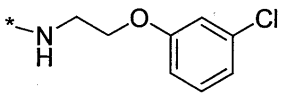
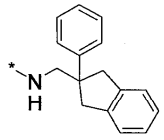
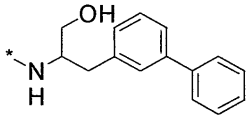
[0656]

The following compounds in Table 13 were synthesized as in Example 474. The structural formulae and physicochemical properties are shown in Table 13, respectively.

[0657]

[Table 13]



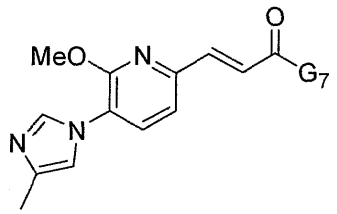
Example	D_3	DATA: MS m/z
475		M^++H：417 (ESI)
476		M^++H：467 (ESI)
477		M^++H：392 (ESI)
478		M^++H：392 (ESI)
479		M^++H：435 (ESI)
480		M^++H：472 (ESI)
481		M^++H：430 (ESI)
482		M^++H：482 (ESI)
483		M^++H：486 (ESI)

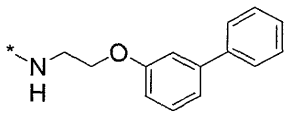
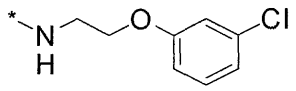
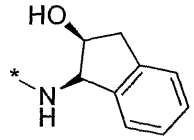
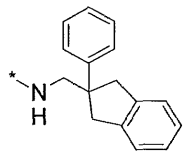
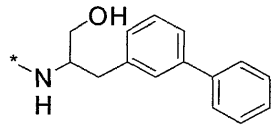
[0658]

The following compounds in Table 14 were synthesized as in Example 23. The structural formulae and physicochemical properties are shown in Table 14, respectively.

[0659]

[Table 14]



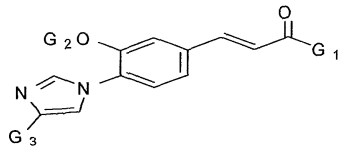
Example	G_7	DATA: MS m/z
484		M^++H : 455 (ESI)
485		M^++H : 413 (ESI)
486		M^++H : 391 (ESI)
487		M^++H : 465 (ESI)
488		M^++H : 469 (ESI)

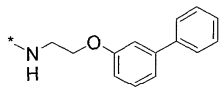
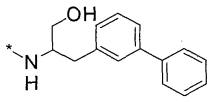
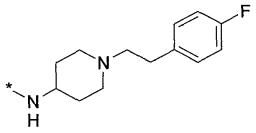
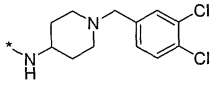
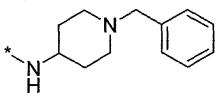
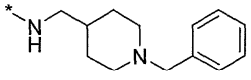
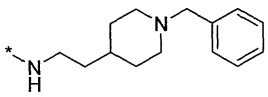
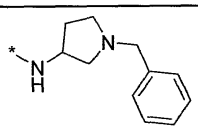
[0660]

The following compounds in Table 15 were synthesized as in Example 121. The structural formulae and physicochemical properties are shown in Table 15, respectively.

[0661]

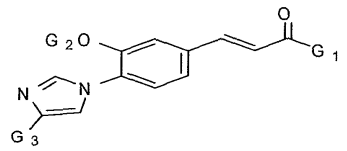
[Table 15-1]

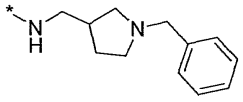
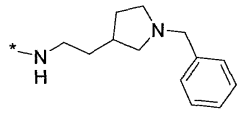
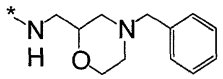
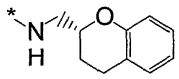
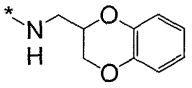
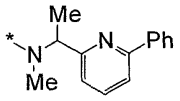
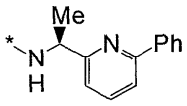
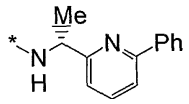
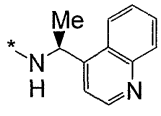


Example	G_1	G_2	G_3	DATA: MS m/z
489		Me	Me	M^++H : 454 (ESI)
490		Me	Me	M^++H : 468 (ESI)
491		Me	Me	M^++H : 463 (ESI)
492		Me	Me	M^++H : 499 (ESI)
493		Me	Me	M^++H : 431 (ESI)
494		Me	Me	M^++H : 445 (ESI)
495		Me	Me	M^++H : 459 (ESI)
496		Me	Me	M^++H : 417 (ESI)

[0662]

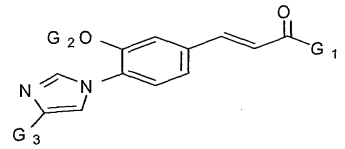
[Table 15-2]

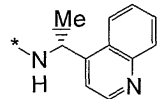
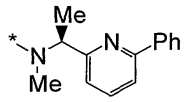
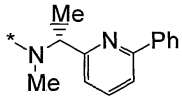
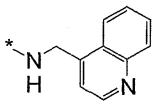
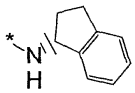
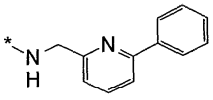
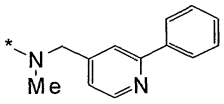
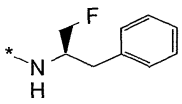


Example	G_1	G_2	G_3	DATA: MS m/z
497		Me	Me	M^++H：431 (ESI)
498		Me	Me	M^++H：445 (ESI)
499		Me	Me	M^++H：447 (ESI)
500		Me	Me	M^++H：404 (ESI)
501		Me	Me	M^++H：406 (ESI)
502		Me	Me	M^++H：453 (ESI)
503		Me	Me	M^++H：439 (ESI)
504		Me	Me	M^++H：439 (ESI)
505		Me	Me	M^++H：413 (ESI)

[0663]

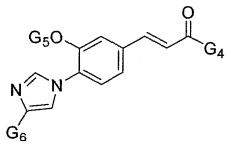
[Table 15-3]

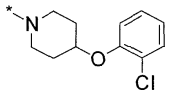
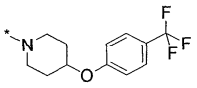
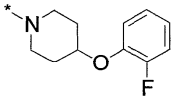
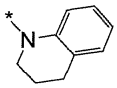
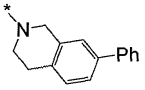
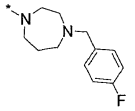
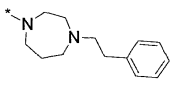


Example	G_1	G_2	G_3	DATA: MS m/z
506		Me	Me	M^++H：413 (ESI)
507		Me	Me	M^++H：453 (ESI)
508		Me	Me	M^++H：453 (ESI)
509		Me	Me	M^++H：399 (ESI)
510		Me	Me	M^++H：374 (ESI)
511		Me	Et	M^++H：439 (ESI)
512		Me	Et	M^++H：453 (ESI)
513		Me	Et	M^++H：408 (ESI)

[0664]

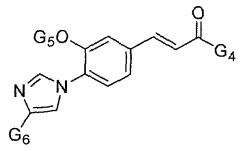
[Table 15-4]

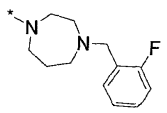
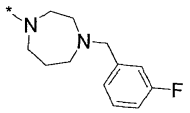
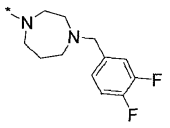
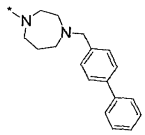
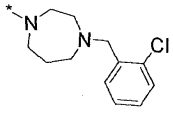
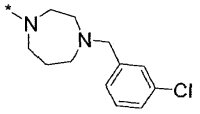
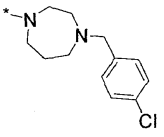
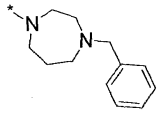


Example	G_4	G_5	G_6	DATA:MS m/z
514		Me	Me	M^++H:452 (ESI)
515		Me	Me	M^++H:486 (ESI)
516		Me	Me	M^++H:436 (ESI)
517		Me	Me	M^++H:374 (ESI)
518		Me	Me	M^++H:450 (ESI)
519		Me	Me	M^++H:374 (ESI)
520		Me	Me	M^++H:449 (ESI)
521		Me	Me	M^++H:445 (ESI)

[0665]

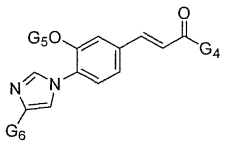
[Table 15-5]

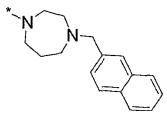
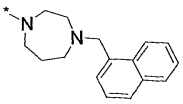
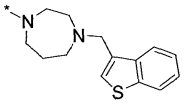
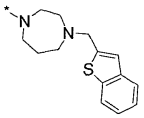
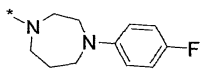
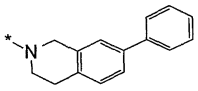
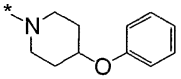
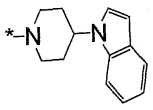


Example	G_4	G_5	G_6	DATA：MS m／z
522		Me	Me	M^++H：449（ESI）
523		Me	Me	M^++H：449（ESI）
524		Me	Me	M^++H：467（ESI）
525		Me	Me	M^++H：507（ESI）
526		Me	Me	M^+：465（ESI）
527		Me	Me	M^+：465（ESI）
528		Me	Me	M^+：465（ESI）
529		Me	Me	M^++H：431（ESI）

[0666]

[Table 15-6]



Example	G_4	G_5	G_6	DATA:MS m/z
530		Me	Me	M^++H:481 (ESI)
531		Me	Me	M^++H:481 (ESI)
532		Me	Me	M^++H:487 (ESI)
533		Me	Me	M^++H:487 (ESI)
534		Me	Me	M^++H:435 (ESI)
535		Me	Et	M^++H:464 (ESI)
536		Me	Et	M^++H:432 (ESI)
537		Me	Et	M^++H:455 (ESI)

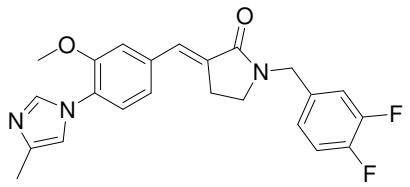
[0667]

Example 538

Synthesis of (E)-1-(3,4-difluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]pyrrolidin-2-one

[0668]

[Formula 222]



Synthesis of (E)-1-acetyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] pyrrolidin-2-one

Triethylamine (45 mL) was added to an ethanol (80 mL) solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (3.0 g) and (1-acetyl-2-oxopyrrolidin-3-yl)triphenylphosphonyl bromide (8.4 g) synthesized by the method described in Journal of Medicinal Chemistry, vol.30, No. 11, p.1995, 1987. The reaction solution was made to react at 60°C for 2 hours. The reaction solution was cooled to room temperature and was added to a mixed-solution of ethyl acetate and iced water. The deposited solids were dried under reduced pressure after separated by filtration, and 3.3 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 2.15 (s, 3H), 2.46-3.54 (m, 3H), 3.08-3.16 (m, 2H), 3.74-3.80 (m, 2H), 3.89 (s, 3H), 7.18 (t, J=1.2 Hz, 1H), 7.28-7.34 (m, 1H), 7.42-

7.50 (m, 3H), 7.84 (d, J=1.2 Hz, 1H).

[0669]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene] pyrrolidin-2-one

A mixed solution of ethanol (100 mL) and methanol (100 mL) of (E)-1-acetyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]pyrrolidin-2-one (7.5 g) and potassium carbonate (1.6 g) was agitated at room temperature for 2 hours. After condensing reaction solution to 1/3, added to iced water and ethyl acetate and deposited solids were separated by filtration to obtain 4.7 g of the title compound. Furthermore, the filtrate was extracted with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate after washed with a saturated saline solution. This solution was concentrated and the deposited solids was obtained by filtration to yield 2.7 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H), 3.15-3.25 (m, 2H), 3.55-3.63 (m, 2H), 3.88 (s, 3H), 5.97 (brs, 1H), 6.94 (d, J=1.2 Hz, 1H), 7.11 (d, J=1.6 Hz, 1H), 7.15 (dd, J=1.6、8.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.35 (t, J=2.8 Hz, 1H), 7.72 (d, J=1.6 Hz, 1H).

[0670]

Synthesis of (E)-1-(3,4-difluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]pyrrolidin-2-one

To a DMF (6.0 mL) solution of (E)-3-(3-

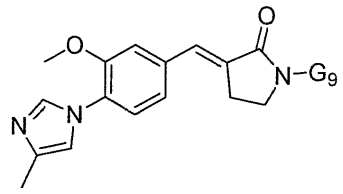
methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)pyrrolidin-2-one (100 mg), lithium bis(trimethylsilyl)amide (1M hexane solution, 0.53 mL) was added at 0°C, and the reaction solution was agitated for 30 minutes at 0°C. 3,4-difluorobenzylbromide (0.060 mL) was added to this solution at 0°C, and that reaction solution was agitated at room temperature for 1 hour. The reaction solution was added to iced water and ethyl acetate, and the organic layer was partitioned. The obtained organic layer was washed with a saturated salt solution, and it concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system), and 80 mg of the title compound was obtained. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H), 3.05-3.13 (m, 2H), 3.38-3.45 (m, 2H), 3.88 (s, 3H), 4.58 (s, 2H), 6.91-6.95 (m, 1H), 6.99-7.05 (m, 1H), 7.08-7.17 (m, 4H), 7.27 (d, J=8.0 Hz, 1H), 7.40 (t, J=2.8 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H).

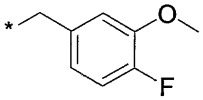
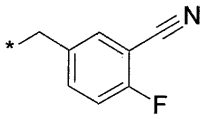
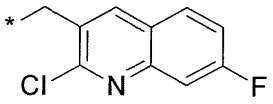
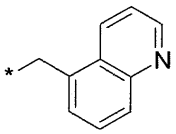
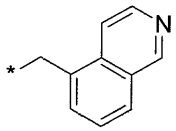
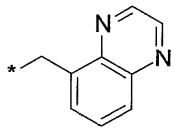
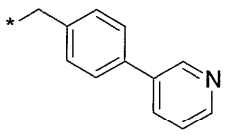
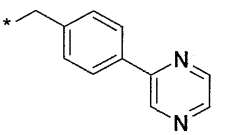
[0671]

The following compounds in Table 16 were synthesized as in Example 538. The structural formulae and physicochemical properties are shown in Table 16, respectively.

[0672]

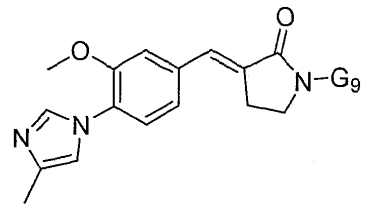
[Table 16-1]

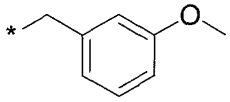
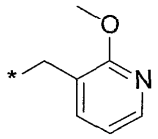
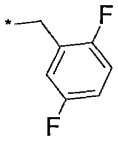
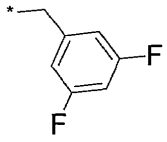
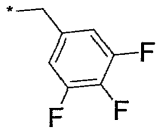
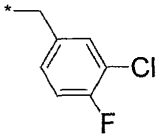
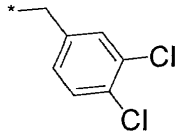


Example	G_9	DATA: MS m/z
539		M^++H：422（ESI）
540		M^++H：417（ESI）
541		M^++H：477（ESI）
542		M^++H：425（ESI）
543		M^++H：425（ESI）
544		M^++H：426（ESI）
545		M^++H：451（ESI）
546		M^++H：452（ESI）

[0673]

[Table 16-2]



Example	G_9	DATA: MS m/z
547		M^++H：404（ESI）
548		M^++H：405（ESI）
549		M++H：410（ESI）
550		M++H：410（ESI）
551		M++H：428（ESI）
552		M++H：426（ESI）
553		M+：442（ESI）

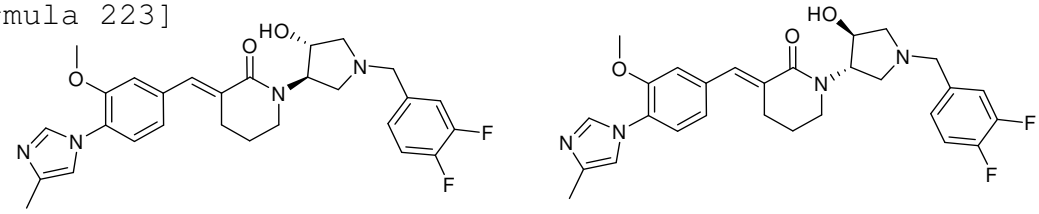
[0674]

Example 554, Example 555 and Example 556

Synthesis of (E)-1-[1-(3,4-difluorobenzyl)-(4R)-hydroxy-(3R)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-[1-(3,4-difluorobenzyl)-(4S)-hydroxy-(3S)-pyrrolidine-3-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0675]

[Formula 223]



Synthesis of (E)-trans-3-hydroxy-4-(3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-yl)pyrrolidine-1-carboxylic acid tert-butyl ester

By the same method as in Example 418, 2.61 g of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (3.66 g) and trans-3-amino-4-hydroxypyrrolidin-1-carbamic acid tert-butyl ester (1.5 g) synthesized according to the method described in The Journal of Organic Chemistry, vol. 62, No. 12, p.4197, 1997. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.47 (s, 9H), 1.83-2.02 (m, 2H), 2.30 (s, 3H), 2.70-2.88 (m, 2H), 3.25-3.63 (m, 4H),

3.79–3.83 (m, 2H), 3.85 (s, 3H), 4.33–4.43 (m, 1H), 4.87–4.95 (m, 1H), 6.92 (brs, 1H), 7.00 (brs, 1H), 7.01 (dd, J=9.6, 1.2 Hz, 1H), 7.24 (d, J=9.6 Hz, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.80 (brs, 1H).

[0676]

Synthesis of (E)-1-[1-(3,4-difluorobenzyl)-trans-4-hydroxy-3-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

Trifluoroacetic acid (1 mL) was added to a methylene chloride (1 mL) solution of tert-butyl ester (100 mg) of (E)-trans-3-hydroxy-4(3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxopiperidin-1-yl)pyrrolidine-1-carboxylic acid and the reaction solution was agitated at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, the residue was dissolved with methylene chloride (3 mL), and 3,4-difluorobenzaldehyde (0.046 mL) and sodium triacetoxyborohydride (132 mg) were added to the solution. After agitating the reaction solution at room temperature for 6 hours, ethyl acetate and a saturated sodium bicarbonate water were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 100 mg of the title compound was obtained by purifying the residue by silica gel

chromatography (Carrier: Chromatorex™ NH and elution solvent:heptane:ethyl acetate =1:1 -> ethyl acetate). The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.79-1.89 (m, 1H), 1.93-2.02 (m, 1H), 2.30 (s, 3H), 2.39-2.45 (m, 1H), 2.63-2.97 (m, 4H), 3.08-3.13 (m, 1H), 3.34-3.42 (m, 1H), 3.49 (d, J=13.2 Hz, 1H), 3.50-3.58 (m, 1H), 3.63 (d, J=13.2 Hz, 1H), 3.72 (brs, 1H), 3.85 (s, 3H), 4.18-4.24 (m, 1H), 4.55-4.61 (m, 1H), 6.92 (brs, 1H), 7.00 (brs, 1H), 7.01 (brd, J=8.0 Hz, 1H), 7.05-7.19 (m, 3H), 7.24 (d, J=8.0 Hz, 1H), 7.71 (d, J=0.8 Hz, 1H), 7.77 (brs, 1H).

[0677]

Synthesis of (E)-1-[1-(3,4-difluorobenzyl)-(4R)-hydroxy-(3R)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-[1-(3,4-difluorobenzyl)-(4S)-hydroxy-(3S)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

The above-mentioned racemate (10 mg) was separated by CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane:iso propanol= 30:70). The title optically active substance with a retention time of 13 minutes (4 mg;>99%ee) and the title optically active substance with a retention time of 16 minutes (4 mg;>99%ee) were obtained. The physical properties of the title optically active substance with a retention time of 13 minutes (Example 555) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.79-1.89 (m, 1H), 1.93-2.02 (m, 1H), 2.30 (s, 3H), 2.39-2.45 (m, 1H), 2.63-2.97 (m, 4H), 3.08-3.13 (m, 1H), 3.34-3.42 (m, 1H), 3.49 (d, J=13.2 Hz, 1H), 3.50-3.58 (m, 1H), 3.63 (d, J=13.2 Hz, 1H), 3.72 (brs, 1H), 3.85 (s, 3H), 4.18-4.24 (m, 1H), 4.55-4.61 (m, 1H), 6.92 (brs, 1H), 7.00 (brs, 1H), 7.01 (brd, J=8.0 Hz, 1H), 7.05-7.19 (m, 3H), 7.24 (d, J=8.0 Hz, 1H), 7.71 (d, J=0.8 Hz, 1H), 7.77 (brs, 1H).

The physical properties of the title optically active substance with a retention time of 16 minutes (Example 556) are as follows.

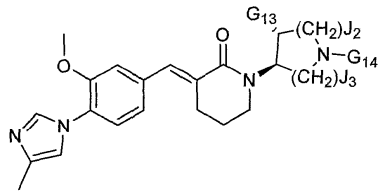
^{1}H-NMR ($CDCl_3$) δ (ppm): 1.79-1.89 (m, 1H), 1.93-2.02 (m, 1H), 2.30 (s, 3H), 2.39-2.45 (m, 1H), 2.63-2.97 (m, 4H), 3.08-3.13 (m, 1H), 3.34-3.42 (m, 1H), 3.49 (d, J=13.2 Hz, 1H), 3.50-3.58 (m, 1H), 3.63 (d, J=13.2 Hz, 1H), 3.72 (brs, 1H), 3.85 (s, 3H), 4.18-4.24 (m, 1H), 4.55-4.61 (m, 1H), 6.92 (brs, 1H), 7.00 (brs, 1H), 7.01 (brd, J=8.0 Hz, 1H), 7.05-7.19 (m, 3H), 7.24 (d, J=8.0 Hz, 1H), 7.71 (d, J=0.8 Hz, 1H), 7.77 (brs, 1H).

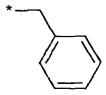
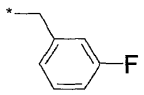
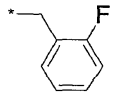
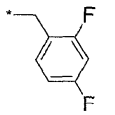
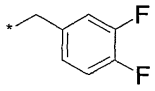
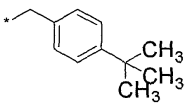
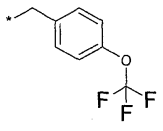
[0678]

The following compounds in Table 17 were synthesized as in Example 554, Example 555 and Example 556. The structural formulae and physicochemical properties are shown in Table 17, respectively.

[0679]

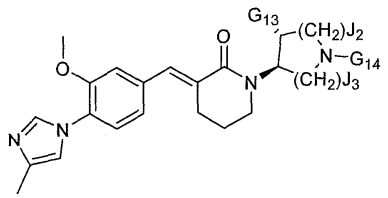
[Table 17-1]

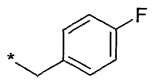
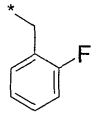
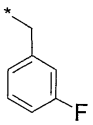
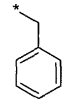
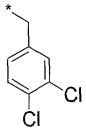
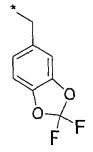
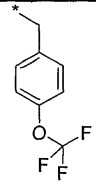


Example	J_2	J_3	G_{13}	G_{14}	DATA: MS m/z
557	1	1	OH		M^++H：473 (ESI)
558	1	1	OH		M^++H：491 (ESI)
559	1	1	OH		M^++H：491 (ESI)
560	1	1	OH		M^++H：491 (ESI)
561	1	1	OH		M^++H：509 (ESI)
562	1	2	H		M^++H：507 (ESI)
563	1	2	H		M^++H：527 (ESI)
564	1	2	H		M^++H：555 (ESI)

[0680]

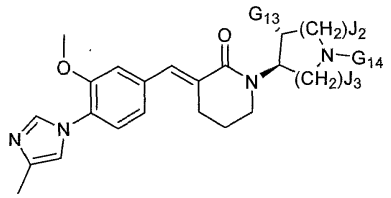
[Table 17-2]

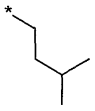
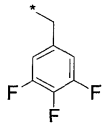


Example	J_2	J_3	G_{13}	G_{14}	DATA: MS m/z
565	2	1	H		M^++H：489 (ESI)
566	2	1	H		M^++H：489 (ESI)
567	2	1	H		M^++H：489 (ESI)
568	2	1	H		M^++H：471 (ESI)
569	2	1	H		M^++H：539 (ESI)
570	2	1	H		M^++H：551 (ESI)
571	2	1	H		M^++H：555 (ESI)

[0681]

[Table 17-3]



Example	J_2	J_3	G_{13}	G_{14}	DATA: MS m/z
572	2	1	H		M^++H：451（ESI）
573	2	1	H		M^++H：451（ESI）
574	2	1	H		M^++H：525（ESI）
575	2	1	H		M^++H：435（ESI）

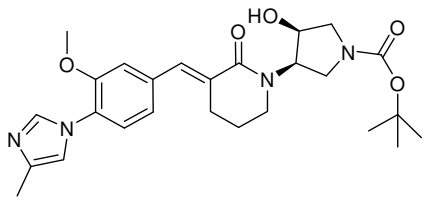
[0682]

Example 576

Synthesis of (E)-cis-3-hydroxy-4-{3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-yl}pyrrolidine-1-carboxylic acid tert-butyl ester

[0683]

[Formula 224]



To a THF (5 mL) solution of (E)-trans-3-

hydroxy-4-(3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxopiperidin-1-yl)pyrrolidine-1-carboxylic acid tert-butyl ester (30 mg) obtained in Example 554, diisopropylazodicarboxylate (0.024 mL), triphenylphosphine (33 mg) and acetic acid (0.007 mL) were added, and the reaction solution was agitated at room temperature for 3 hours. Ethyl acetate and a saturated sodium bicarbonate water were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 10 mg of the title compound was obtained by purifying the residue by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent:ethyl acetate). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.49 (s, 9H), 1.91-1.99 (m, 2H), 2.31 (s, 3H), 2.75-2.90 (m, 2H), 3.20-3.84 (m, 6H), 3.86 (s, 3H), 4.61-4.71 (m, 1H), 4.73-4.80 (m, 1H), 6.93 (brs, 1H), 7.01 (brs, 1H), 7.03 (dd, J=10.0、1.2 Hz, 1H), 7.25 (d, J=10.0 Hz, 1H), 7.72 (d, J=1.6 Hz, 1H), 7.80 (brs, 1H).

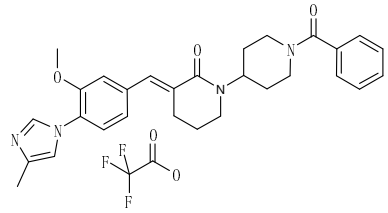
[0684]

Example 577

Synthesis of (E)-1-benzoyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-[1,4'] bipiperidinyl-2-one trifluoroacetic acid salt

[0685]

[Formula 225]



To methylene chloride (1 mL) solution of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxo-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester (20 mg) obtained in Example 716, trifluoroacetic acid (1 mL) was added, and the reaction solution was agitated at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure and IPEA (0.022 mL) and benzoyl chloride (0.01 mL) were added to the methylene chloride (2 mL) solution of the residue. The reaction solution was agitated at room temperature for 12 hours, a saturated sodium bicarbonate water was added to the reaction solution, and the organic layer was partitioned. 9.4 mg of the title compound was obtained by condensing the obtained organic layer and purifying by LC-MS. The physical properties of the compound are as follows.

ESI-MS; m/z485 [M^++H].

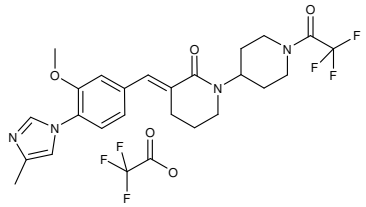
[0686]

Example 578

<u>Synthesis of (E)-1-trifluoroacetyl-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-[1,4'] bipiperidinyl-2-one trifluoroacetic acid salt</u>

[0687]

[Formula 226]



By the same method as in Example 577, 11 mg of the title compound was obtained from (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxo-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester (20 mg) and a trifluoroacetic acid anhydride (0.02 mL). The physical properties of the compound are as follows.

ESI-MS;m/z477 [M^++H].

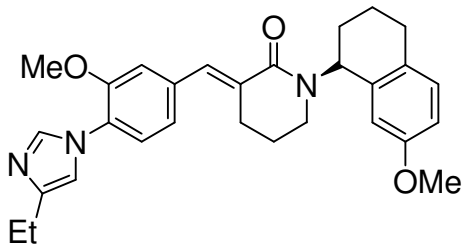
[0688]

Example 579

Synthesis of (E)-3-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene]-1-(7-methoxy-1,2,3 4-tetrahydronaphthalen-1-yl)piperidin-2-one

[0689]

[Formula 227]



Synthesis of 4-(4-ethyl-1H-imidazol-1-yl)-3-methoxy benzaldehyde

7.3 g of the title compound was obtained via series of steps starting from 4-formylamino-3-methoxybenzoic acid methyl ester (24.8 g) in a similar method from 4-formylamino-3-methoxybenzoic acid methyl ester to 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde as in Example 1 except that chloroacetone was changed to 1-bromo-2-butanone.

^{1}H-NMR ($CDCl_3$) δ: 1.30 (t, J=7.6 Hz, 3H), 2.69 (q, J=7.6 Hz, 2H), 3.97 (s, 3H), 7.00 (q, J=1.2 Hz, 1H), 7.46 (d, J=7.6 Hz, 1H), 7.55 (dd, J=1.6 Hz, 7.6 Hz, 1H), 7.58 (d, J=1.6 Hz, 1H), 7.86 (d, J=1.6 Hz, 1H), 10.01 (s, 1H).

[0690]

Synthesis of (E)-5-chloro-2-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene]valeric acid tert-butyl ester

By the same method as in Example 418, 3.2 g of the title compound was obtained from 4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzaldehyde (7.3 g) and 5-chloro-2-(diethoxyphosphoryl)valeric acid tert-butyl ester (12.5 g). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.29 (t, J=7.6 Hz, 3H), 1.60 (s, 9H), 2.00-2.07 (m, 2H), 2.65-2.71 (m, 4H), 3.60 (t, J=6.4 Hz, 2H), 3.88 (s, 3H), 6.94 (s, 1H), 7.01 (s, 1H), 7.03 (d, J=8 Hz, 1H), 7.28 (d, J=8 Hz, 1H), 7.60 (s, 1H), 7.76 (d, J=0.8 Hz, 1H).

[0691]

Synthesis of (E)-5-chloro-2-[4-(4-ethyl-1H-imidazol-1-

yl)-3-methoxybenzylidene]valeric acid trifluoroacetic acid salt

By the same method as in Example 418 and following the synthesis method of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt, 3.5 g of the title compound was obtained from (E)-5-chloro-2-(4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene)valeric acid tert-butyl ester (3.2 g). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d6) δ (ppm): 1.25 (t, J=7.6 Hz, 3H), 1.94-2.01 (m, 2H), 2.60-2.64 (m, 2H), 2.71 (q, J=7.6 Hz, 2H), 3.70 (t, J=6 Hz, 2H), 3.91 (s, 3H), 7.24 (dd, J=8, 1.6 Hz, 1H), 7.37 (d, J=1.6 Hz, 1H), 7.64 (d, J=8 Hz, 1H), 7.69 (s, 1H), 7.75 (d, J=1.2 Hz, 1H), 9.27 (s, 1H).

[0692]

Synthesis of (E)-3-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene]-1-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)piperidin-2-one

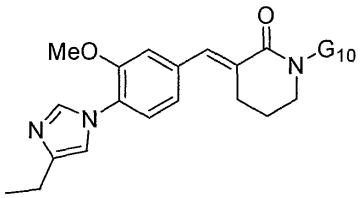
By the same method as in Example 418, 159 mg of the title compound was obtained from (E)-5-chloro-2-(4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene)valeric acid trifluoroacetic acid salt (200 mg) and (S)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylamine (144 mg). The physical properties of the compound are as follows.

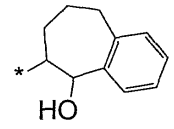
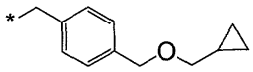
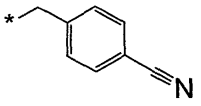
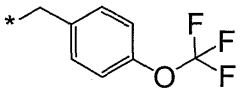
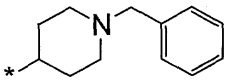
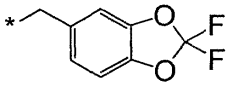
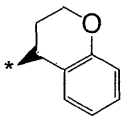
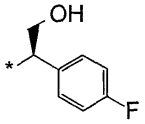
^{1}H-NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.0 Hz, 3H), 1.58-1.89 (m, 4H), 1.98-2.05 (m, 1H), 2.08-2.12 (m, 1H), 2.66-2.82 (m, 5H), 2.90-2.96 (m, 1H), 3.07-3.12 (m, 1H), 3.18-3.25 (m, 1H), 3.75 (s, 3H), 3.88 (s, 3H), 6.08-6.12 (m, 1H), 6.65 (s, 1H), 6.75 (d, J=4.4 Hz, 1H), 6.94 (s, 1H), 7.03-7.10 (m, 3H), 7.26-7.29 (m, 1H), 7.75 (s, 1H), 7.92 (s, 1H).

The following compounds in Table 18 were synthesized as in Example 579. The structural formulae and physicochemical properties are shown in Table 18, respectively.

[0693]

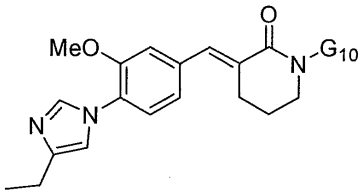
[Table 18-1]

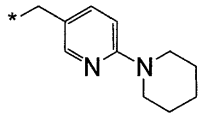
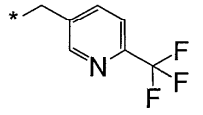
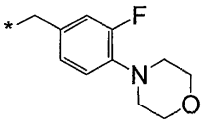
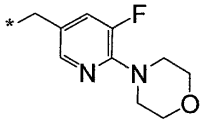
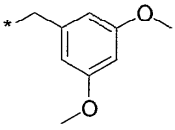
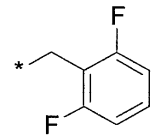
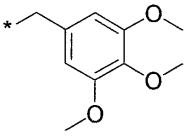
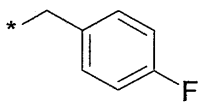


Example	G_{10}	DATA: MS m/z
580		M^++H：472 (ESI)
581		M^++H：486 (ESI)
582		M^++H：427 (ESI)
583		M^++H：486 (ESI)
584		M^++H：485 (ESI)
585		M^++H：482 (ESI)
586		M^++H：444 (ESI)
587		M^++H：450 (ESI)

[0694]

[Table 18-2]



Example	G_{10}	DATA: MS m/z
588		M^++H：486 (ESI)
589		M^++H：471 (ESI)
590		M^++H：505 (ESI)
591		M^++H：506 (ESI)
592		M^++H：462 (ESI)
593		M^++H：438 (ESI)
594		M^++H：492 (ESI)
595		M^++H：420 (ESI)

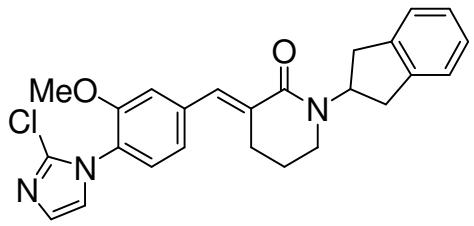
[0695]

Example 596

Synthesis of (E)-3-[4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzylidene]-1-(indan-2-yl)piperidin-2-one

[0696]

[Formula 228]



Synthesis of 1-(4-[1,3]dioxolan-2-yl-2-methoxyphenyl)-1H-imidazole

To a toluene (70 mL) solution of 4-(1H-imidazol-1-yl-3-methoxybenzaldehyde (4.3 g) and ethylene glycol (6.5 g), para-toluenesulfonic acid monohydrate (4.8 g) was added, Dean- Stark equipment was attached and heat-refluxing was carried out for 4 hours. After allowing cool the reaction mixture to room temperature, a saturated sodium bicarbonate water and ethyl acetate were added, and the organic layer was partitioned. The organic layer was washed with a saturated salt solution and concentrated under reduced pressure after dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (elution solvent: hexane-ethyl acetate system), and 3.15 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.88 (s, 3H), 4.06-4.18 (m, 4H), 5.85 (s, 1H), 7.15-7.17 (m, 2H), 7.19-7.20 (m, 2H), 7.29 (d, J=7.6 Hz, 1H), 7.78 (t, J=1 Hz, 1H).

[0697]

Synthesis of 2-chloro-1-(4-[1,3]dioxolan-2-yl-2-methoxyphenyl)-1H-imidazole

To a THF (50 mL) solution of 1-(4-[1,3]dioxolan-2-yl-2-methoxyphenyl)-1H-imidazole (3.85 g), n-butyllithium (1.6M hexane solution, 12 mL) was added dropwise under nitrogen atmosphere at -78°C, and the reaction solution was agitated for 30 minutes. THF (10 mL) solution of hexachloroethane (6.1 g) was added to the reaction solution and the reaction solution was agitated at room temperature for 1 hour after agitating for 30 minutes at -78°C. Water and ethyl acetate were added to the reaction mixture, and the organic layer was partitioned. The organic layer was washed with a saturated saline solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: hexane-ethyl acetate system), and 3.19 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.84 (s, 3H), 4.07-4.19 (m, 4H), 5.85 (s, 1H), 6.98 (d, J=1.6 Hz, 1H), 7.06 (d, J=1.6 Hz, 1H), 7.17 (dd, J=1.6 Hz, 8.0 Hz, 1H), 7.19 (d, J=1.6 Hz, 1H), 7.27 (d, J=8 Hz, 1H).

[0698]

Synthesis of 4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzaldehyde

To a THF (40 mL) solution of 2-chloro-1-(4-[1,3]dioxolan-2-yl -2-methoxyphenyl)-1H-imidazole (3.19 g), 5N hydrochloric acid (15 mL) was added and the reaction solution was agitated for 2 hours. The reaction mixture was made basic with 5N sodium hydroxide aqueous solution, ethyl acetate was added and the organic layer was partitioned. The organic layer obtained was washed with a saturated saline solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to yield 2.69 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.91 (s, 3H), 7.04 (d, J=1.6 Hz, 1H), 7.10 (d, J=1.6 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.57-7.59 (m, 2H), 10.06 (s, 1H).

[0699]

Synthesis of (E)-5-chloro-2-[4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzylidene]valeric acid tert-butyl ester

4.55 g of the title compound was obtained from 4-(2-chloro-1H-imidazol-1-yl)-3-methoxy benzaldehyde (3.19 g) and 5-chloro-2-(diethoxyphosphoryl)valeric acid tert-butyl ester (5.32 g) in a similar way as in the synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid tert-butyl ester in Example

418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (s, 9H), 2.00-2.07 (m, 2H), 2.67-2.71 (m, 2H), 3.60 (t, J=6.4 Hz, 2H), 3.84 (s, 3H), 6.70-7.08 (m, 4H), 7.26-7.29 (m, 1H), 7.27 (s, 1H).

[0700]

Synthesis of (E)-5-chloro-2-[4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzylidene]valeric acid

A trifluoroacetic acid (15 mL) solution of 5-chloro-2-(4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzylidene)valeric acid tert-butyl ester (1.35 g) was agitated under ice-cooling. The reaction solution was concentrated under reduced pressure after 2 hours. When the residue was purified in LC-MS, 0.99 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 1.96-2.00 (m, 2H), 2.60-2.64 (m, 2H), 3.70 (t, J=6.4 Hz, 2H), 3.83 (s, 3H), 7.04 (s, 1H), 7.17 (d, J=8.0 Hz, 1H), 7.28 (s, 1H), 7.40 (s, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.68 (s, 1H).

[0701]

Synthesis of (E)-5-chloro-2-[4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzylidene]valeric acid indan-2-ylamide

By the same method as in Example 418, 11 mg of the title compound was obtained from (E)-5-chloro-2-(4-(2-chloro-1H-imidazol-1-yl)-3-methoxybenzylidene)valeric acid (50 mg) and 2-

aminoindan hydrochloride salt (36 mg). The physical properties of the compound are as follows.

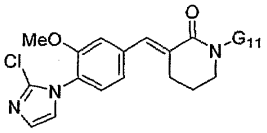
^{1}H-NMR ($CDCl_3$) δ: 1.83-1.87 (m, 2H), 2.79-2.83 (m, 2H), 2.98-3.04 (m, 2H), 3.25-3.32 (m, 4H), 3.82 (s, 3H), 5.76-5.81 (m, 1H), 7.01-7.02 (m, 2H), 7.04-7.07 (m, 2H), 7.16-7.26 (m, 5H), 7.87 (s, 1H).

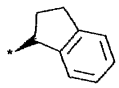
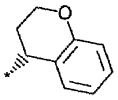
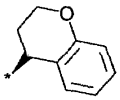
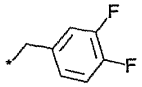
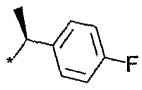
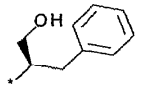
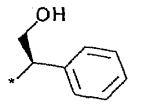
[0702]

The compounds shown in Table 19 were synthesized as in Example 596. The structural formulae and physicochemical properties are shown in Table 19, respectively.

[0703]

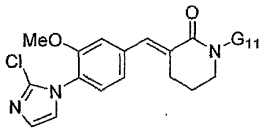
[Table 19-1]

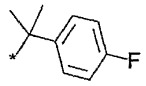
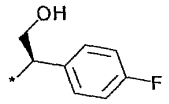
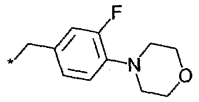
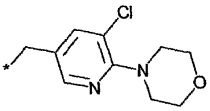
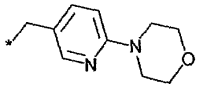
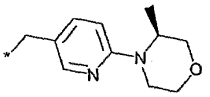
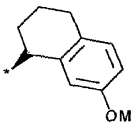


Example	G_{11}	DATA: MS m/z	Note
597		M^++Na : 456 (ESI)	optically active substance
598		M^++H : 450 (ESI)	optically active substance (separation condition A: retention time: 18 minutes; absolute configuration: unknown)
599		M^++H : 450 (ESI)	optically active substance (separation condition A: retention time: 22 minutes; absolute configuration: unknown)
600		M^++H : 444 (ESI)	
601		M^++H : 440 (ESI)	optically active substance
602		M^++H : 452 (ESI)	optically active substance
603		M^++H : 438 (ESI)	optically active substance

[0704]

[Formula 19-2]



Example	G_{11}	DATA: MS m/z	Note
604		M^++H：454 (ESI)	
605		M^++Na：478 (ESI)	optically active substance
606		M^++H：511 (ESI)	
607		M^++H：528 (ESI)	
608		M^++H：494 (ESI)	
609		M^++H：508 (ESI)	optically active substance
610		M^++H：478 (ESI)	optically active substance

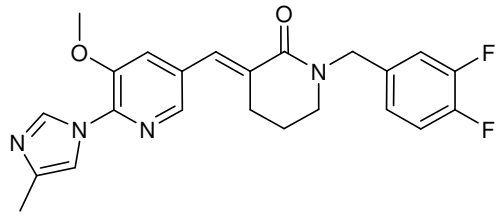
[0705]

Example 611

Synthesis of (E)-1-(3,4-difluorobenzyl)-3-{[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl]methylene}piperidin-2-one

[0706]

[Formula 229]



Synthesis of 5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-carbaldehyde

Ozone was boubled into a methanol (5 mL) solution of (E)-3-(6-chloro-5-methoxypyridin-3-yl)acrylic acid ethyl ester (123 mg) synthesized by the method of Example 22 under agitation at -78°C. After 10 minutes, introduction of ozone was stopped, dimethylsulfide (1 mL) was added to the reaction solution and the reaction mixture was allowed to be warmed to room temperature for 1 hour and 30 minutes under agitation. The reaction solution was concentrated under reduced pressure and 4-methylimidazole(125 mg) was added to a DMF (1 mL) solution of the residue. The reaction solution was agitated at 120°C for 3 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate and saturated sodium bicarbonate water were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated sodium bicarbonate water, it was dried over anhydrous magnesium sulfate

and concentrated under reduced pressure. 50 mg of the title compound was obtained by purifying the residue by silica gel chromatography (elution solvent heptane: ethyl acetate =9:1 to ethyl acetate). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.31 (s, 3H), 4.05 (s, 3H), 7.65 (s, 1H), 7.78 (s, 1H), 8.52 (s, 2H), 10.07 (s, 1H).

[0707]

Synthesis of (E)-5-chloro-2-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-ylmethylene]valeric acid tert-butyl ester

By the same method as in Example 418, 35 mg of the title compound was obtained from 5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridine-3-carbaldehyde (50 mg) and 5-chloro-2-(diethoxyphosphoryl)valeric acid tert-butyl ester (83 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (s, 9H), 1.78-1.90 (m, 2H), 2.30 (s, 3H), 2.66-2.73 (m, 2H), 3.58-3.64 (m, 2H), 3.98 (s, 3H), 7.35 (s, 1H), 7.54 (s, 2H), 8.06 (s, 1H), 8.37 (S, 1H).

[0708]

Synthesis of (E)-1-(3,4-difluorobenzyl)-3-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-ylmethylene]piperidin-2-one

By the same method as in Example 418, 15 mg of the title compound was obtained from (E)-5-chloro-2-[5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-

ylmethylene] valeric acid tert-butyl ester (35 mg) and 3,4-difluorobenzylamine (0.02 mL). The physical properties of the compound are as follows.

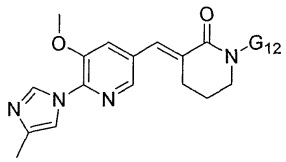
^{1}H-NMR ($CDCl_3$) δ (ppm): 1.76-1.83 (m, 2H), 2.30 (s, 3H), 2.81-2.87 (m, 2H), 3.36-3.41 (m, 2H), 3.97 (s, 3H), 4.66 (s, 2H), 7.02-7.18 (m, 3H), 7.31 (d, J=1.2 Hz, 1H), 7.54 (brs, 1H), 7.82 (brs, 1H), 8.09 (d, J=1.2 Hz, 1H), 8.36 (d, J=1.2 Hz, 1H).

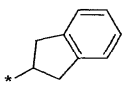
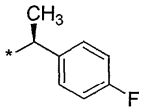
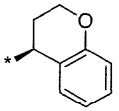
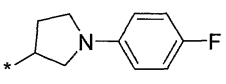
[0709]

The compounds shown in Table 20 were synthesized as in Example 611. The structural formulae and physicochemical properties are shown in Table 20, respectively.

[0710]

[Table 20]



Example	G_{12}	DATA: MS m/z	Note
612		M^++H : 415 (ESI)	
613		M^++H : 421 (ESI)	optically active substance
614		M^++H : 431 (ESI)	optically active substance
615		M^++H : 462 (ESI)	racemate

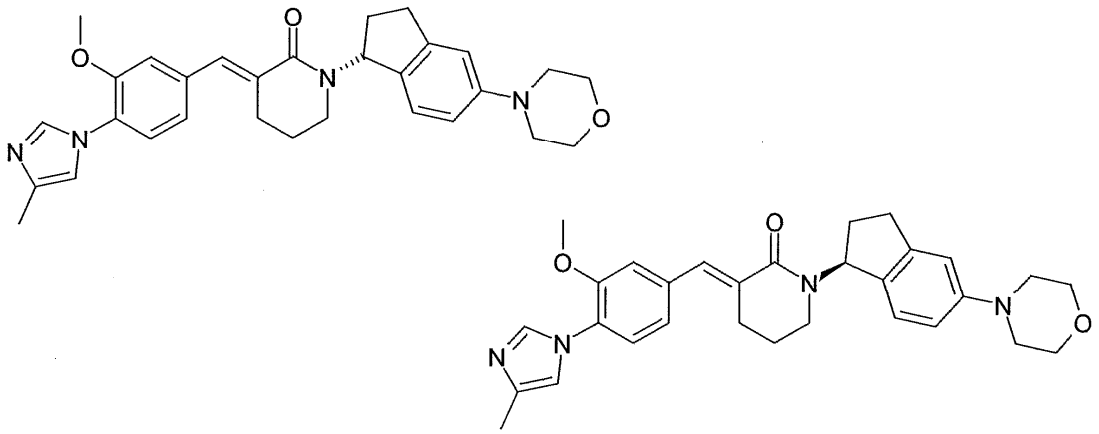
[0711]

Example 616 and Example 617

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-one-[(R)and(S)-(5-morpholin-4-yl-indan-1-yl))piperidin-2-one

[0712]

[Formula 230]



[0713]

Synthesis of 5-morpholin-4-yl-indan-1-one

A 1-methyl-2-pyrrolidone (10 mL) solution of 5-fluoroindanone (1.97 g) and morpholine (1.71 g) was agitated at 100°C for 26 hours and 30 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system), and

2.20 g of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.64-2.67 (m, 2H), 3.03-3.07 (m, 2H), 3.34 (t, J=4.8 Hz, 4H), 3.86 (t, J=4.8 Hz, 4H), 6.82 (s, 1H), 6.88 (dd, J=2.0, 8.8 Hz, 1H), 7.65 (d, J=8.8 Hz, 1H).

[0714]

Synthesis of 5-morpholin-4-yl-indan-1-on-oxime

An ethanol (5.0 mL) solution of 5-morpholin-4-yl-indan-1-one(2.20 g), hydroxyl ammonium chloride (1.05 g) and the triethylamine (4.22 mL) was refluxed for 3 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was washed with a saturated sodium chloride solution, and 2.28 g of the title compound was obtained by condensing under reduce pressure after drying over anhydrous magnesium sulfate. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.92-2.96 (m, 2H), 2.98-3.04 (m, 2H), 3.20-3.26 (m, 4H), 3.85 (t, J=4.8 Hz, 4H), 6.78-6.85 (m, 2H), 7.53 (d, J=8.8 Hz, 1H).

[0715]

Synthesis of 5-morpholin-4-yl-indan-1-ylamine

An ethanol (20 mL) suspension of 5-morpholin-4-yl-indan-1-on-oxime (2.76 g) and 10% palladium carbon (48% water content, 1.0 g) was agitated at room temperature under 0.4 MPa hydrogen atmosphere for 6

hours. After filtering the reaction solution and condensing the filtrate under reduced pressure, 1.64 g of the title compound was obtained by purifying the obtained residue by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent:heptane–ethyl acetate system -> ethyl acetate– methanol system). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.65–1.70 (m, 1H), 2.47–2.53 (m, 1H), 2.78 (td, J=8.4, 16 Hz, 1H), 2.92 (ddd, J=3.6, 8.8, 16 Hz, 1H), 3.13 (t, J=4.8 Hz, 4H), 3.85 (t, J=4.8 Hz, 4H), 4.31 (t, J=7.2 Hz, 1H), 6.79–6.81 (m, 2H), 7.21 (d, J=8.8 Hz, 1H).

[0716]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (5-morpholin-4-yl-indan-1-yl)amide

To a DMF (5.0 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (3.0 g) obtained in Example 418 and 5-morpholin-4-yl-indan-1-ylamine (1.80 g), IPEA (5.18 mg), EDC (3.84 g) and HOBT (2.71 g) were added one by one, and the reaction solution was agitated at room temperature for 1 hour. After confirming disappearance of the starting materials, the solvent was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. After washed with a saturated saline solution the organic

layer, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 2.80 g of the title compound was obtained by purifying the obtained residue by silica gel chromatography (elution solvent: heptane–ethyl acetate system). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.88–1.97 (m, 1H), 2.00–2.08 (m, 2H), 2.30 (s, 3H), 2.63–2.72 (m, 1H), 2.74 (t, J=7.2 Hz, 2H), 2.82–2.94 (m, 1H), 2.87–3.05 (m, 1H), 3.10–3.18 (m, 4H), 3.59 (t, J=6.0 Hz, 2H), 3.82–3.84 (m, 4H), 3.85 (s, 3H), 5.52 (q, J=7.6 Hz, 1H), 6.10 (d, J=7.6 Hz, 1H), 6.80–6.83 (m, 2H), 6.92–6.96 (m, 3H), 7.14 (s, 1H), 7.23–7.25 (m, 2H), 7.70 (s, 1H).

[0717]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(R) and (S)-(5-morpholin-4-yl-indan-1-yl)]-piperidin-2-one

To a DMF (5.0 mL) solution of ((E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (5-morpholin-4-yl-indan-1-yl)amide (2.80 g), sodium hydride (40% mineral oil content, 267 mg) was added at 0°C, and the reaction solution was agitated for 15 minutes. Water and ethyl acetate were added to the reaction solution after confirming disappearance of the starting materials, and the organic layer was partitioned. After the organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and

concentrated under reduced pressure. By purifying the obtained residue by silica gel chromatography (elution solvent: a heptane–ethyl acetate system, ethyl acetate–ethanol system), 2.12 g of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(5-morpholin-4-yl-indan-1-yl)piperidin-2-one racemate was obtained. Next, this compound (140 mg) was separated in CHRIALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm mobile phase; ethanol), and the title optically active substance with a retention time of 14 minutes (64 mg;>99%ee) and the title optically active substance with a retention time of 16 minutes (58 mg;>97%ee) were obtained. The physical properties of the title optically active substance with a retention time of 14 minutes are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72–1.86 (m, 2H), 1.90–2.00 (m, 1H), 2.30 (s, 3H), 2.44–2.56 (m, 1H), 2.78–2.86 (m, 2H), 2.86–3.00 (m, 2H), 3.02–3.14 (m, 2H), 3.14–3.17 (m, 4H), 3.85–3.86 (m, 4H), 3.86 (s, 3H), 6.41 (t, J=6.8 Hz, 1H), 6.78–6.80 (m, 2H), 6.93 (s, 1H), 7.04–7.08 (m, 3H), 7.24–7.25 (m, 1H), 7.71 (s, 1H), 7.88 (s, 1H).

The physical properties of the title optically active substance with a retention time of 16 minutes are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72–1.86 (m, 2H), 1.90–2.00 (m, 1H), 2.30 (s, 3H), 2.44–2.56 (m, 1H), 2.78–2.86 (m,

2H), 2.86-3.00 (m, 2H), 3.02-3.14 (m, 2H), 3.14-3.17 (m, 4H), 3.85-3.86 (m, 4H), 3.86 (s, 3H), 6.41 (t, J=6.8 Hz, 1H), 6.78-6.80 (m, 2H), 6.93 (s, 1H), 7.04-7.08 (m, 3H), 7.24-7.25 (m, 1H), 7.71 (s, 1H), 7.88 (s, 1H).

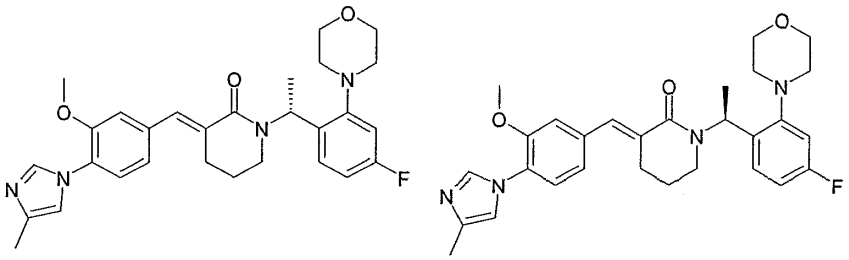
[0718]

Example 618 and Example 619

Synthesis of (E)-1-[(R) and (S)-1-(4-fluoro -2-morpholin-4-ylphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0719]

[Formula 231]



[0720]

Synthesis of 1-(4-fluoro-2-morpholin-4-ylphenyl)-ethanone

A DMF (5.0 mL) solution of 2,4-difluoroacetophenone (1.0 g) and morpholine (558 mg) was agitated at 110°C for 6 hours and 30 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium

sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: heptane–ethyl acetate system), and 642 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.64 (s, 3H), 2.98–3.00 (m, 4H), 3.84–3.87 (m, 4H), 6.71–6.77 (m, 2H), 7.44–7.48 (m, 1H).

[0721]

Synthesis of 1-(4-fluoro-2-morpholin-4-ylphenyl)ethane oxime

An ethanol (5.0 mL) solution of 1-(4-fluoro-2-morpholin-4-ylphenyl)ehanone (630 mg), hydroxylammonium chloride (294 mg) and the triethylamine (1.18 mL) was refluxed for 5 hours. Water was added to the reaction solution and precipitation generated was filtered and air-dried to yield 642 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.24 (s, 0.75H), 2.27 (s, 2.25H), 2.96–2.99 (t, J=4.8 Hz, 4H), 3.81 (t, J=4.8 Hz, 4H), 6.70–6.79 (m, 2H), 7.14 (t, J=6.8 Hz, 0.25H), 7.22 (t, J=6.8 Hz, 0.75H), 7.97 (brs, 0.25H), 8.24 (brs, 0.75H).

[0722]

Synthesis of 1-(4-fluoro-2-morpholin-4-ylphenyl)ethylamine

An ethanol (5.0 mL) suspension of 1-(4-

fluoro-2-morpholin-4-ylphenyl)ethane oxime (548 mg) and 10% palladium carbon (48% water content, 548 mg) was agitated for 32 hours and 30 minutes at room temperature under 0.4 MPa hydrogen atmosphere. After filtering the reaction solution and condensing the filtrate under reduced pressure, 155 mg of the title compound was obtained by purifying the obtained residue by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent:heptane-ethyl acetate system -> ethyl acetate- methanol system). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.38 (d, J=6.4 Hz, 3H), 1.68 (brs, 2H), 2.88 (t, J=4.4 Hz, 4H), 3.85 (t, J=4.4 Hz, 4H), 4.54 (q, J=6.4 Hz, 1H), 6.81-6.85 (m, 2H), 7.35-7.39 (m, 1H).

[0723]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid [1-(4-fluoro-2-morpholin-4-ylphenyl]ethyl)amide

To a DMF (3.0 mL) solution (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (280 mg) obtained in the Example 418 and 1-(4-fluoro-2-morpholin-4-ylphenyl)ethylamine (155 mg), IPEA (484 mg) and EDC (359 mg) and HOBT (253 mg) were added one by one, and the reaction solution was agitated at room temperature for 1 hour and 20 minutes. After confirming disappearance of the starting materials, the

solvent was concentrated under reduced pressure, water and ethyl acetate were added to the residue, and the organic layer was partitioned. After the organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (elution solvent: from heptane : ethyl acetate system to ethyl acetate-methanol system), and 270 mg of the title compound was obtained. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.49 (d, J=6.8 Hz, 3H), 1.95-2.01 (m, 2H), 2.29 (s, 3H), 2.70-2.74 (m, 2H), 2.78-2.82 (m, 2H), 3.13-3.17 (m, 2H), 3.58 (t, J=6.0 Hz, 2H), 3.85 (s, 3H), 3.82-3.93 (m, 4H), 5.53-5.60 (m, 1H), 6.68-6.74 (m, 1H), 6.83-6.95 (m, 4H), 7.15 (s, 1H), 7.23-7.30 (m, 3H), 7.70 (s, 1H).

[0724]

<u>Synthesis of (E)-1-[(R) and (S)-1-(4-fluoro-2-morpholin-4-ylphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one</u>

To a DMF (3.0 mL) solution of (E)-5-chloro-2-(3-methoxy-4- (4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(4-fluoro -2-morpholin-4-ylphenyl)-ethyl)amide (270 mg), sodium hydride (40% mineral oil content, 50 mg) was added at 0°C, the reaction solution was allowed to be warmed to room temperature and agitated for 5 hours and 20 minutes.

The reaction solution was cooled to 0°C after confirming disappearance of the starting materials, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated saline solution, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) 223 mg of (E)-1-(1-(4-fluoro-2-morpholin-4-ylphenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one racemate was obtained. Next, this compound (150 mg) was separated in CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; ethanol), and the title optically active substance with a retention time of 6 minutes (63.6 mg;>99%ee) and the title optically active substance with a retention time of 7 minutes (54.0 mg;>98%ee) were obtained. The physical properties of the title optically active substance with a retention time of 6 minutes is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (d, J=7.2 Hz, 3H), 1.74–1.82 (m, 2H), 2.30 (s, 3H), 2.59–2.72 (m, 1H), 2.79–2.94 (m, 6H), 3.21 (td, J=5.6, 12 Hz, 1H), 3.77–3.88 (m, 4H), 3.86 (s, 3H), 6.27 (q, J=7.2 Hz, 1H), 6.83–6.93 (m, 3H), 7.01–7.03 (m, 2H), 7.22–7.25 (m, 1H), 7.31 (t, J=7.6 Hz, 1H), 7.70 (s, 1H), 7.84 (s, 1H).

The physical properties of the title optically active substance with a retention time of 7 minutes is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (d, J=7.2 Hz, 3H), 1.74-1.82 (m, 2H), 2.30 (s, 3H), 2.59-2.72 (m, 1H), 2.79-2.94 (m, 6H), 3.21 (td, J=5.6, 12 Hz, 1H), 3.77-3.88 (m, 4H), 3.86 (s, 3H), 6.27 (q, J=7.2 Hz, 1H), 6.83-6.93 (m, 3H), 7.01-7.03 (m, 2H), 7.22-7.25 (m, 1H), 7.31 (t, J=7.6 Hz, 1H), 7.70 (s, 1H), 7.84 (s, 1H).

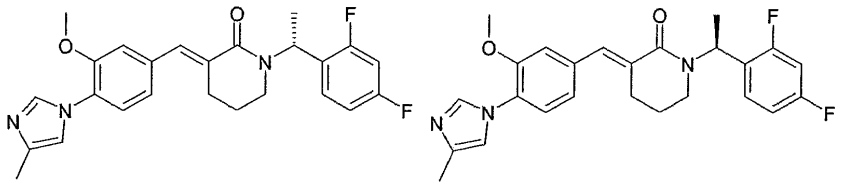
[0725]

Example 620 and Example 621

Synthesis of (E)-1-[(1R) and (1S)-1-(2,4-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0726]

[Formula 232]



To a DMF (5 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (250 mg) obtained in Example 418 and 1-(2,4-difluorophenyl)ethylamine (CAS#603951-43-5,141 mg), IPEA (0.5 mL), EDC (430 mg) and HOBT (303 mg) were added one by one, and the reaction solution was

agitated at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was dried with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system). (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid [1-(2, 4-difluorophenyl)ethyl]amide was obtained. Sodium hydride (40% mineral oil content, 20 mg) was added to a DMF (5 mL) solution of this compound, and that reaction solution was agitated at room temperature for 5 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was dried with anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) 151 mg of (E)-1-(1-(2,4-difluorophenyl)ethyl)-3-(3-methoxy-4-(methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one racemate was obtained. This compound (25 mg) was separated in CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane:ethanol = 7:3), and the title optically active substance with a retention time of 25 minutes (Example 620:11.8 mg;>99%ee) and the title optically active

substance with a retention time of 45 minutes (Example 621:11.2 mg;>99%ee) were obtained. The physical properties of the title optically active compound with a retention time of 25 minutes are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.59 (d, J=7.2 Hz, 3H), 1.77-1.84 (m, 2H), 2.30 (s, 3H), 2.71-2.83 (m, 2H), 2.99-3.05 (m, 1H), 3.27-3.33 (m, 1H), 3.85 (s, 3H), 6.18 (q, J=7.2 Hz, 1H), 6.79-6.85 (m, 1H), 6.86-6.92 (m, 1H), 6.93 (t, J=1.6 Hz, 1H), 7.02 (s, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.33-7.39 (m, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.86 (s, 1H).

The physical properties of the title optically active compound with a retention time of 45 minutes are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.59 (d, J=7.2 Hz, 3H), 1.77-1.84 (m, 2H), 2.30 (s, 3H), 2.71-2.83 (m, 2H), 2.99-3.05 (m, 1H), 3.27-3.33 (m, 1H), 3.85 (s, 3H), 6.18 (q, J=7.2 Hz, 1H), 6.79-6.85 (m, 1H), 6.86-6.92 (m, 1H), 6.93 (t, J=1.6 Hz, 1H), 7.02 (s, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.33-7.39 (m, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.86 (s, 1H).

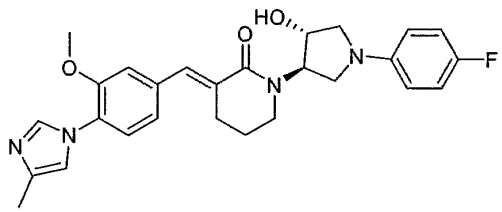
[0727]

Example 622

Synthesis of (E)-1-[1-(4-fluorophenyl)-trans-4-hydroxypyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0728]

[Formula 233]



Synthesis of 3-(4-fluorophenyl)-6-oxa-3-azabicyclo[3.1.0]hexane

To a methanol (5 mL) solution of 1-(4-fluorophenyl)-2,5-dihydro-1H-pyrrole (300 mg) synthesized according to the method described in The Journal of Organic Chemistry vol. 25, p.2230, 1960, acetonitrile (0.8 mL), potassium hydrogen carbonate (221 mg) and 20% hydrogen peroxide (0.8 mL) were added one by one, and the reaction solution was agitated at room temperature for 10 hours. Ethyl acetate and saturated sodium thiosulfate solution were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated sodium bicarbonate water, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 75 mg of the title compound was obtained by purifying the residue by silica gel chromatography (heptane: elution solvent; ethyl acetate = 3:1). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.25 (d, J=8.1 Hz, 2H), 3.69 (d, J=8.1 Hz, 2H), 3.87 (brs, 2H), 6.37-6.43 (m, 2H), 6.88-6.96 (m, 2H).

[0729]

Synthesis of trans-4-amino-1-(4-fluorophenyl)pyrrolidine-3-ol

To a 1,4-dioxane (3 mL) solution of 3-(4-fluorophenyl)-6-oxa-3-azabicyclo[3.1.0]hexane (75 mg), an aqueous (1 mL) solution of sodium azide (82 mg) was added, and the reaction solution was agitated at 100°C for 7 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate and a saturated sodium chloride solution were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 10% Palladium carbon (48% water content, 10 mg) was added to an ethanol (5 mL) solution of the residue, and the reaction solution was agitated at room temperature under a hydrogen current for 3 hours. 61 mg of the title compound was obtained by carrying out celite filtration of the reaction solution, and condensing the filtrate under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD_3) δ (ppm): 3.05-3.17 (m, 2H), 3.38-3.44 (m, 1H), 3.57-3.67 (m, 2H), 4.10-4.14 (m, 1H), 6.44-6.49 (m, 2H), 6.87-6.94 (m, 2H).

Synthesis of (E)-1-[1-(4-fluorophenyl)-trans-4-hydroxypyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

By the same method as in Example 418, 70 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (175 mg) and trans-4-amino-1-(4-fluorophenyl)pyrrolidine-3-ol (61 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83-2.00 (m, 2H), 2.30 (s, 3H), 2.72-2.96 (m, 2H), 3.22 (dd, J=10.0, 5.6 Hz, 1H), 3.41-3.48 (m, 3H), 3.62 (dd, J=10.0, 8.0 Hz, 1H), 3.70 (dd, J=10.0, 6.8 Hz, 1H), 3.86 (s, 3H), 4.50-4.56 (m, 1H), 5.03-5.10 (m, 1H), 6.50-6.55 (m, 2H), 6.92-7.05 (m, 5H), 7.25 (d, J=8.6 Hz, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.82 (brs, 1H).

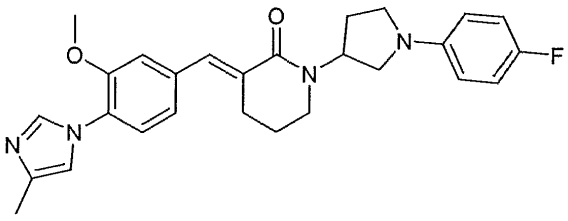
[0730]

Example 623, Example 624 and Example 625

Synthesis of (E)-1-[1-(4-fluorophenyl)-(3S) and (3R)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0731]

[Formula 234]



Synthesis of 1-(4-fluorophenyl)-3-pyrrolidinol of 1-(4-fluorophenyl)pyrrolidin-3-ylamine

Sodium azide (722 mg) was added to a DMSO (10 mL) solution of methane sulphonate (CAS#618068-72-7, 289 mg). The reaction solution was agitated at 50°C for 15 hours. The reaction solution was allowed to be cooled to room temperature, ether and saturated sodium bicarbonate water were added to the reaction solution, and the organic layer was partitioned. After the obtained organic layer was washed with a saturated sodium bicarbonate water, it was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 10% Palladium carbon (48% water, 10 mg) was added to the ethanol (5 mL) solution of the obtained residue, and the reaction solution was agitated at room temperature under a hydrogen stream for 20 hours. 187 mg of the title compound was obtained by carrying out celite filtration of the reaction solution, and condensing filtrate under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-1.85 (m, 1H), 2.18-2.28 (m, 1H), 2.96-3.01 (m, 1H), 3.25-3.32 (m, 1H), 3.38-3.50 (m, 2H), 3.68-3.75 (m, 1H), 6.43-6.49 (m, 2H), 6.90-6.97 (m, 2H).

[0732]

Synthesis of (E)-1-(1-(4-fluorophenyl)-pyrrolidin-3-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one (Example 623)

By the same method as in Example 418, 82 mg of the title compound was obtained from (E)-5-chloro-2-

(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (278 mg) and 1-(4-fluorophenyl)pyrrolidin-3-ylamine (142 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83-1.97 (m, 2H), 2.11-2.21 (m, 1H), 2.30 (s, 3H), 2.31-2.39 (m, 1H), 2.75-2.90 (m, 2H), 3.23-3.30 (m, 2H), 3.39-3.55 (m, 4H), 3.86 (s, 3H), 5.53-5.61 (m, 1H), 6.48-6.54 (m, 2H), 6.91-7.05 (m, 5H), 7.24 (dd, J=8.0, 2.0 Hz, 1H), 7.71 (s, 1H), 7.83 (brs, 1H).

[0733]

Synthesis of (E)-1-[1-(4-fluorophenyl)-(3S) and (3R)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

The above-mentioned racemate (14 mg) was separated in CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane:ethanol = 70:30). The title optically active substance with a retention time of 36 minutes (4.6 mg;>99%ee) and the title optically active substance with a retention time of 39 minutes (4.3 mg;>88%ee) were obtained. The physical properties of the title optically active substance with a retention time of 36 minutes (Example 624) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83-1.97 (m, 2H), 2.11-2.21 (m, 1H), 2.30 (s, 3H), 2.31-2.39 (m, 1H), 2.75-2.90 (m, 2H), 3.23-3.30 (m, 2H), 3.39-3.55 (m, 4H), 3.86 (s,

3H), 5.53-5.61 (m, 1H), 6.48-6.54 (m, 2H), 6.91-7.05 (m, 5H), 7.24 (dd, J=8.0, 2.0 Hz, 1H), 7.71 (s, 1H), 7.83 (brs, 1H).

The physical properties of the title optically active substance with a retention time of 39 minutes (Example 625) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83-1.97 (m, 2H), 2.11-2.21 (m, 1H), 2.30 (s, 3H), 2.31-2.39 (m, 1H), 2.75-2.90 (m, 2H), 3.23-3.30 (m, 2H), 3.39-3.55 (m, 4H), 3.86 (s, 3H), 5.53-5.61 (m, 1H), 6.48-6.54 (m, 2H), 6.91-7.05 (m, 5H), 7.24 (dd, J=8.0, 2.0 Hz, 1H), 7.71 (s, 1H), 7.83 (brs, 1H).

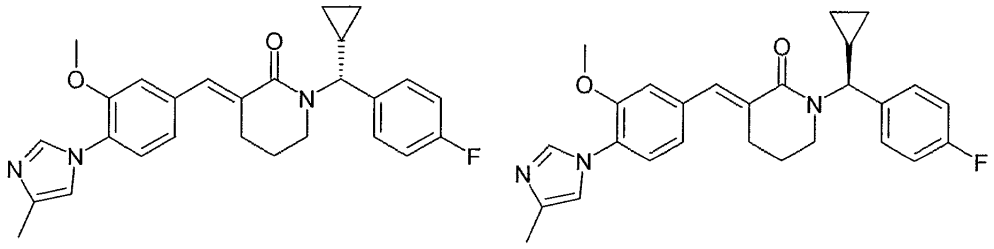
[0734]

Example 626 and Example 627

Synthesis of (E)-1-[(R) and (S)-cyclopropyl-(4-fluorophenyl)methyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0735]

[Formula 235]



By the same method as in Example 418, 133 mg of (E)-1-cyclopropyl-(4-fluorophenyl)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one racenate was obtained

from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (250 mg) and cyclopropyl-(4-fluorophenyl)methylamine (CAS#705-14-6, 187 mg). Next, this compound (8.0 mg) was separated by CHIRALCEL™ OJ available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane:ethanol = 80:20), the title optically active substance with a retention time of 9 minutes (0.9 mg;>87%ee) and the title optically active substance with a retention time of 12 minutes (0.8 mg;>88%ee) were obtained.

The physical properties of the title optically active substance with a retention time of 9 minutes are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.50-0.68 (m, 3H), 0.86-0.92 (m, 1H), 1.29-1.38 (m, 1H), 1.68-1.78 (m, 1H), 1.86-1.94 (m, 1H), 2.30 (s, 3H), 2.75-2.82 (m, 1H), 2.91 (td, J=4.8, 16 Hz, 1H), 3.10-3.16 (m, 1H), 3.51 (ddd, J=3.6, 10, 12 Hz, 1H), 3.86 (s, 3H), 5.22 (d, J=10 Hz, 1H), 6.94 (s, 1H), 7.00-7.07 (m, 4H), 7.25-7.27 (m, 1H), 7.44 (dd, J=5.6, 6.8 Hz, 2H), 7.73 (s, 1H), 7.89 (s, 1H).

The physical properties of the title optically active substance with a retention time of 12 minutes are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.50-0.68 (m, 3H), 0.86-0.92 (m, 1H), 1.29-1.38 (m, 1H), 1.68-1.78 (m, 1H), 1.86-1.94 (m, 1H), 2.30 (s, 3H), 2.75-2.82 (m, 1H), 2.91 (td,

J=4.8, 16 Hz, 1H), 3.10-3.16 (m, 1H), 3.51 (ddd, J=3.6, 10, 12 Hz, 1H), 3.86 (s, 3H), 5.22 (d, J=10 Hz, 1H), 6.94 (s, 1H), 7.00-7.07 (m, 4H), 7.25-7.27 (m, 1H), 7.44 (dd, J=5.6, 6.8 Hz, 2H), 7.73 (s, 1H), 7.89 (s, 1H).

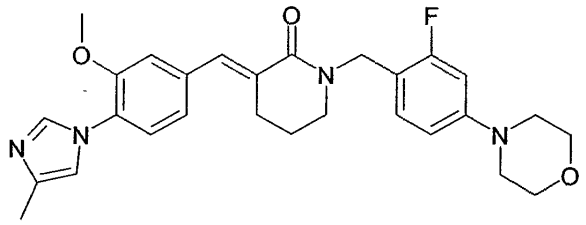
[0736]

Example 628

Synthesis of (E)-1-[2-fluoro-4-morpholin-4-ylbenzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0737]

[Formula 236]



Synthesis of 2-fluoro-4-morpholin-4-ylbenzylamine

By the same method as in Example 426, 740 mg of the title compound was obtained using 2-fluoro-4-morpholin-4-ylbenzonitrile (CAS#554448-62-3, 1.0 g). The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (brs, 2H), 3.13 (t, J=4.8 Hz, 4H), 3.80 (s, 2H), 3.84 (t, J=4.8 Hz, 4H), 6.56 (dd, J=2.4, 13 Hz, 1H), 6.63 (dd, J=2.4, 8.4 Hz, 1H), 7.17 (t, J=8.8 Hz, 1H).

Synthesis of (E)-1-[2-fluoro-4-morpholin-4-ylbenzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzylidene]piperidin-2-one

By the same method as in Example 418, 126 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (200 mg) and 2-fluoro -4-morpholin-4-ylbenzylamine (141 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82-1.88 (m, 2H), 2.30 (s, 3H), 2.78-2.81 (m, 2H), 3.15 (t, J=3.6 Hz, 4H), 3.41 (t, J=5.6 Hz, 2H), 3.83-3.86 (m, 4H), 3.84 (s, 3H), 4.69 (s, 2H), 6.56 (dd, J=2.4, 13 Hz, 1H), 6.64 (dd, J=2.4, 8.8 Hz, 1H), 6.92 (s, 1H), 7.00-7.02 (m, 2H), 7.23 (d, J=8.4, 1H), 7.32 (t, J=8.8 Hz, 1H), 7.70 (s, 1H), 7.83 (s, 1H).

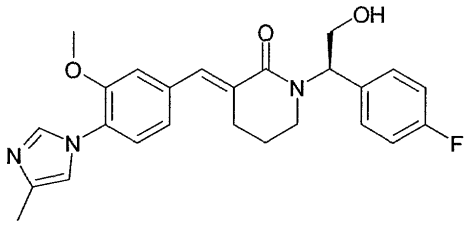
[0738]

Example 629

Synthesis of (E)-1-[(1R)-(4-fluorophenyl)-2-hydroxy ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0739]

[Formula 237]



Synthesis of (2R)-amino-2-(4-fluorophenyl)ethanol

A THF (5.0 mL) solution of D-(-)-4-fluorophenylglycine (500 mg) was cooled to 0°C. Sodium borohydride (246 mg) and iodine (751 mg) were added to the reaction solution. After refluxing the reaction solution overnight, methanol was added to the reaction solution and the reaction solution was concentrated under reduced pressure. Next, 5N sodium hydroxide solution and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. 389 mg of the title compound was obtained by drying with anhydrous magnesium sulfate and condensing under reduced pressure, after the obtained organic layer was washed with a saturated sodium chloride solution. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.24 (brs, 3H), 3.52 (dd, J=8.0, 11 Hz, 1H), 3.70 (dd, J=4.0, 11 Hz, 1H), 4.04 (dd, J=4.0, 8.0 Hz, 1H), 7.00-7.04 (m, 2H), 7.27-7.31 (m, 2H).

Synthesis of (E)-1-[(1R)-(4-fluorophenyl)-2-hydroxyethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

By the same method as in Example 418, 25 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (250 mg) and (2R)-amino-2-(4-fluorophenyl)ethanol (104 mg). The physical properties of the compound are as

follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.90 (m, 2H), 2.30 (s, 3H), 2.79-2.84 (m, 2H), 3.09 (ddd, J=4.4, 7.6, 12 Hz, 1H), 3.33 (ddd, J=4.4, 8.0, 12 Hz, 1H), 3.85 (s, 3H), 4.17-4.25 (m, 2H), 5.86 (dd, J=6.0, 8.0 Hz, 1H), 6.92-6.93 (m, 1H), 7.02-7.08 (m, 4H), 7.20-7.32 (m, 3H), 7.71 (d, J=1.2 Hz, 1H), 7.87 (s, 1H).

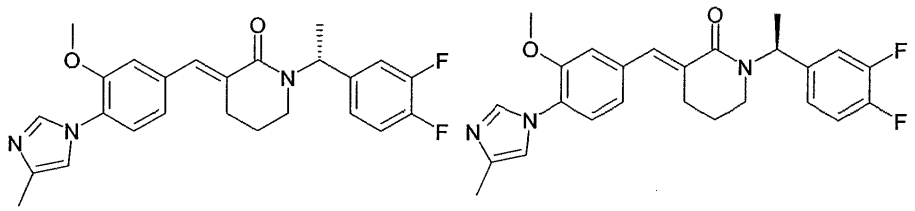
[0740]

Example 630 and Example 631

Synthesis of (E)-1-[(1R) and (1S)-(3,4-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0741]

[Formula 238]



Synthesis of (E)-1-((1R) and (1S)-(3,4-difluorophenyl)-ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one

By the same method as in Example 418, 150 mg of (E)-1-(1-(3,4-difluorophenyl)-ethyl-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (250 mg) and 1-(3,4-

difluorophenyl)ethylamine (CAS#276875-21-9, 140 mg). Next, this compound (150 mg) was separated by CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase : ethanol), and the title optically active substance with a retention time of 6 minutes (68.0 mg;>99%ee) and the title optically active substance with a retention time of 7 minutes (66.2 mg;>91%ee) were obtained. The physical properties of the title optically active substance with a retention time of 6 minutes is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.54 (d, J=7.2 Hz, 3H), 1.62-1.76 (m, 1H), 1.80-1.90 (m, 1H), 2.30 (s, 3H), 2.72-2.80 (m, 1H), 2.83-2.90 (m, 1H), 2.92-2.98 (m, 1H), 3.26 (ddd, J=3.6, 8.8, 12 Hz, 1H), 3.86 (s, 3H), 6.19 (q, J=7.2 Hz, 1H), 6.92 (s, 1H), 7.03-7.18 (m, 5H), 7.24-7.25 (m, 1H), 7.71 (s, 1H), 7.88 (s, 1H).

The physical properties of the title optically active substance with a retention time of 7 minutes is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.54 (d, J=7.2 Hz, 3H), 1.62-1.76 (m, 1H), 1.80-1.90 (m, 1H), 2.30 (s, 3H), 2.72-2.80 (m, 1H), 2.83-2.90 (m, 1H), 2.92-2.98 (m, 1H), 3.26 (ddd, J=3.6, 8.8, 12 Hz, 1H), 3.86 (s, 3H), 6.19 (q, J=7.2 Hz, 1H), 6.92 (s, 1H), 7.03-7.18 (m, 5H), 7.24-7.25 (m, 1H), 7.71 (s, 1H), 7.88 (s, 1H).

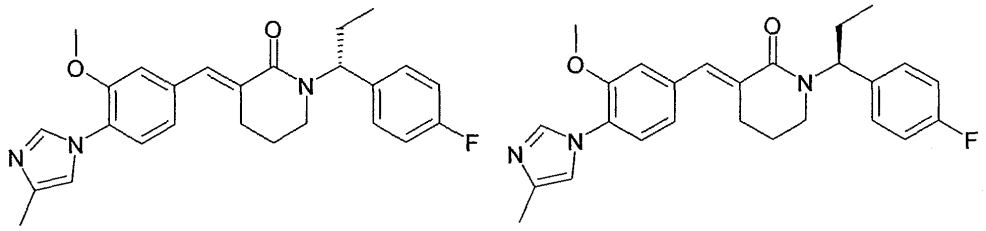
[0742]

Example 632 and Example 633

Synthesis of (E)-1-[(1R) and (1S)-(4-fluorophenyl)propyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0743]

[Formula 239]



Synthesis of (E)-1-[(1R) and (1S)-(4-fluorophenyl)propyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

By the same method as in Example 418, 21.9 mg of (E)-1-(1-(4-fluorophenyl)propyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (150 mg) and 1-(4-fluorophenyl)propylamine (CAS#74877-10-4, 76.8 mg). Next, this compound (20.0 mg) was separated by CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm:mobile phase : ethanol), and the title optically active substance with a retention time of 6 minutes (6.10 mg;>99%ee) and the title optically active substance with a retention time of 7 minutes (5.10 mg;>92%ee) were obtained. The physical properties of the title optically active

substance with a retention time of 6 minutes is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.02 (t, J=7.2 Hz, 3H), 1.57-1.70 (m, 1H), 1.76-1.88 (m, 1H), 1.89-1.97 (m, 1H), 1.99-2.07 (m, 1H), 2.30 (s, 3H), 2.71-2.84 (m, 2H), 2.92-2.97 (m, 1H), 3.21 (ddd, J=3.6, 8.4, 12 Hz, 1H), 3.85 (s, 3H), 6.01 (dd, J=6.0, 10 Hz, 1H), 6.92 (s, 1H), 6.99-7.04 (m, 4H), 7.23-7.25 (m, 1H), 7.31-7.35 (m, 2H), 7.71 (s, 1H), 7.87 (s, 1H).

The physical properties of the title optically active substance with a retention time of 7 minutes is as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.02 (t, J=7.2 Hz, 3H), 1.57-1.70 (m, 1H), 1.76-1.88 (m, 1H), 1.89-1.97 (m, 1H), 1.99-2.07 (m, 1H), 2.30 (s, 3H), 2.71-2.84 (m, 2H), 2.92-2.97 (m, 1H), 3.21 (ddd, J=3.6, 8.4, 12 Hz, 1H), 3.85 (s, 3H), 6.01 (dd, J=6.0, 10 Hz, 1H), 6.92 (s, 1H), 6.99-7.04 (m, 4H), 7.23-7.25 (m, 1H), 7.31-7.35 (m, 2H), 7.71 (s, 1H), 7.87 (s, 1H).

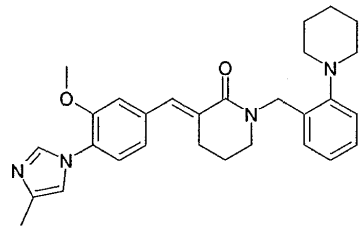
[0744]

Example 634

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-(2-piperidin-1-ylbenzyl)piperidin-2-one

[0745]

[Formula 240]



By the same method as in Example 641, 8.40 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid tert-butyl ester (50 mg) and 2-piperidin-1-ylbenzylamine (1M DMF solution, 256 μL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52-1.74 (m, 6H), 1.82-1.88 (m, 2H), 2.30 (d, J=1.2 Hz, 3H), 2.82-2.86 (m, 6H), 3.28-3.31 (m, 2H), 3.86 (S, 3H), 4.86 (s, 2H), 6.93 (m, 1H), 7.02-7.06 (m, 3H), 7.09 (dd, J=1.2, 8.4 Hz, 1H), 7.20-7.26 (m, 3H), 7.79 (d, J=1.2 Hz, 1H), 7.88 (S, 1H).

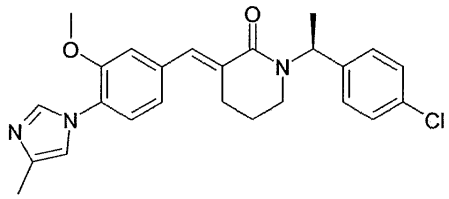
[0746]

Example 635

Synthesis of (E)-1-[(1S)-(4-chlorophenyl)ethyl]-3-[3-methoxy-4-(4-methylimidazole-2-yl)benzylidene]piperidin-2-one

[0747]

[Formula 241]



By the same method as in Example 641, 10.5 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid tert-butyl ester (50 mg) and (S)-1-(4-chlorophenyl)ethylamine (32.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (d, J=6.8 Hz, 3H), 1.64-1.73 (m, 1H), 1.76-1.88 (m, 1H), 2.30 (s, 3H), 2.71-2.85 (m, 2H), 2.91-2.96 (m, 1H), 3.24 (dtd, J=4.0, 8.8, 12 Hz, 1H), 3.85 (s, 3H), 6.21 (q, J=6.8 Hz, 1H), 6.92-6.93 (m, 1H), 7.03-7.05 (m, 2H), 7.22-7.32 (m, 5H), 7.70 (d, J=1.6 Hz, 1H), 7.88 (s, 1H).

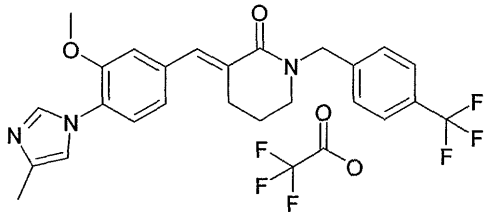
[0748]

Example 636

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-(4-trifluoromethylbenzyl)piperidin-2-one trifluoroacetic acid salt

[0749]

[Formula 242]



By the same method as in Example 416, 12.5 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid tert-butyl ester (50 mg) and 4-(trifluoromethyl)benzylamine (36.0 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.93 (m, 2H), 2.48 (S, 3H), 2.82 (t, J=5.6 Hz, 2H), 3.41 (t, J=6.0 Hz, 2H), 3.90 (s, 3H), 4.78 (s, 2H), 7.06 (d, J=6.4 Hz, 2H), 7.09 (d, J=8.0 Hz, 1H), 7.33 (d, J=8.0 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.60 (d, J=8.0 Hz, 2H), 7.87 (s, 2H), 8.71 (d, J=1.2 Hz, 1H).

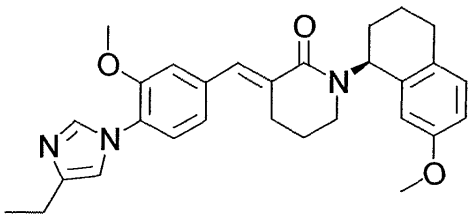
[0750]

Example 637

Synthesis of (E)-3-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene]-1-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)piperidin-2-one

[0751]

[Formula 243]



Synthesis of (E)-5-chloro-2-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene]valeric acid trifluoroacetic acid salt

By the same method as in Example 418, 3.5 g of the title compound was obtained from (E)-5-chloro-2-(4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene)valeric acid tert-butyl ester (3.2 g) obtained above. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 1.25 (t, J=7.6 Hz, 3H), 1.94-2.01 (m, 2H), 2.60-2.64 (m, 2H), 2.71 (q, J=7.6 Hz, 2H), 3.70 (t, J=6 Hz, 2H), 3.91 (s, 3H), 7.24 (dd, J=1.6 Hz, 8 Hz, 1H), 7.37 (d, J=1.6 Hz, 1H), 7.64 (d, J=8 Hz, 1H), 7.69 (s, 1H), 7.75 (d, J=1.2 Hz, 1H), 9.27 (s, 1H).

[0752]

Synthesis of (E)-3-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene]-1-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)piperidin-2-one

By the same method as in Example 641, 159 mg of the title compound was obtained from (E)-5-chloro-2-(4-(4-ethyl-1H-imidazol-1-yl)-3-methoxybenzylidene)valeric acid trifluoroacetic acid salt (200 mg) and (S)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1ylamine (144 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.0 Hz, 3H), 1.58-1.89 (m, 4H), 1.98-2.05 (m, 1H), 2.08-2.12 (m, 1H),

2.66-2.82 (m, 5H), 2.90-2.96 (m, 1H), 3.07-3.12 (m, 1H), 3.18-3.25 (m, 1H), 3.75 (s, 3H), 3.88 (s, 3H), 6.08-6.12 (m, 1H), 6.65 (s, 1H), 6.75 (d, J=4.4 Hz, 1H), 6.94 (s, 1H), 7.03-7.10 (m, 3H), 7.26-7.29 (m, 1H), 7.75 (s, 1H), 7.92 (s, 1H).

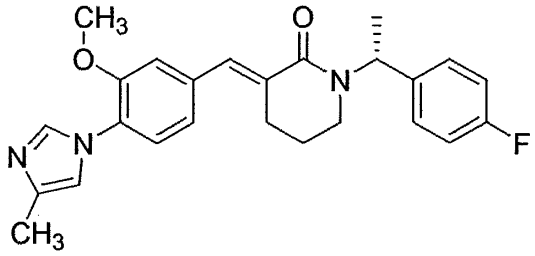
[0753]

Example 638

Synthesis of (E)-1-[(1R)-(4-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0754]

[Formula 244]



By the same method as Example 418, 1.0 g of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (1.6 g) and (R)-1-(4-fluorophenyl)ethylamine (495 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.50 (d, J=7.2 Hz, 3H), 1.65-1.74 (m, 1H), 1.78-1.87 (m, 1H), 2.30 (s, 3H), 2.71-2.85 (m, 2H), 2.91-2.97 (m, 1H), 3.24 (ddd, J=3.6, 8.8, 12.0 Hz, 1H), 3.86 (s, 3H), 6.23 (q, J=7.2 Hz, 1H), 6.93 (t, J=1.2 Hz, 1H), 7.00-7.06 (m, 4H), 7.24-7.26

(m, 1H), 7.31-7.34 (m, 2H), 7.72 (d, J=1.2 Hz, 1H), 7.89 (s, 1H).

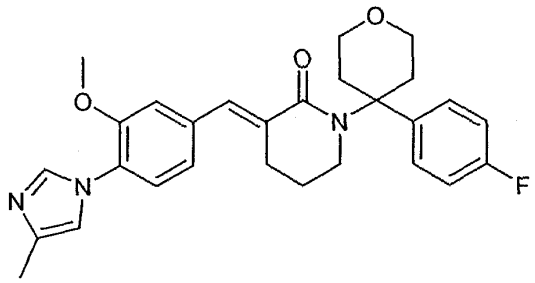
[0755]

Example 639

Synthesis of (E)-1-[4-(4-fluorophenyl)tetrahydropyran-4-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0756]

[Formula 245]



By the same method as in Example 418, 1.15 g of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (2.1 g) and 4-(4-fluorophenyl)tetrahydropyran-4-ylamine (833 mg) synthesized according to the method described in Journal of Medicinal Chemistry, vol.10, No. 1 p.128 1967. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-1.84 (m, 2H), 2.30 (s, 3H), 2.32-2.38 (m, 2H), 2.74-2.88 (m, 4H), 3.34-3.39 (m, 2H), 3.71-3.78 (m, 2H), 3.80-3.88 (m, 5H), 6.92 (brs, 1H), 6.99-7.07 (m, 4H), 7.23 (d, J=8.0 Hz, 1H), 7.44-7.50 (m, 2H), 7.68 (brs, 1H), 7.72 (s, 1H).

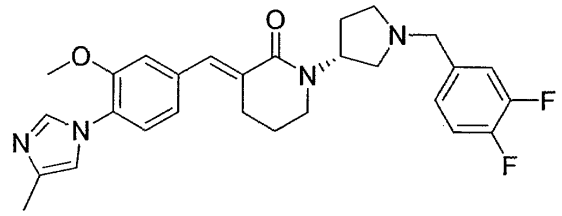
[0757]

Example 640

Synthesis of (E)-1-[1-(3,4-difluorobenzyl)-(3R)-pyrrolidin-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0758]

[Formula 246]



By the same method as in Example 417, 12 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ethyl ester (50 mg) and (3R)-1-(3, 4-difluorobenzyl)pyrrolidin-3-ylamine dihydrochloride (40 mg)

The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-1.93 (m, 3H), 2.22-2.33 (m, 2H), 2.29 (s, 3H), 2.50 (dd, J=10.4, 8.4 Hz, 1H), 2.70 (dd, J=10.4, 3.6 Hz, 1H), 2.77-2.95 (m, 3H), 3.45-3.62 (m, 4H), 3.84 (s, 3H), 5.17-5.45 (m, 1H), 6.92 (s, 1H), 6.98-7.27 (m, 6H), 7.70 (d, J=1.2 Hz, 1H), 7.78 (s, 1H).

[0759]

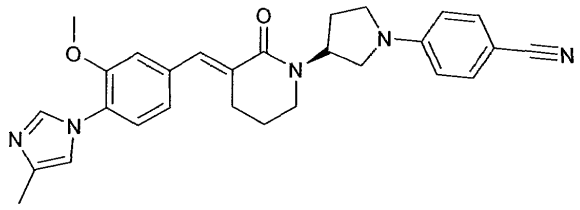
Example 641

Synthesis of (E)-4-{(3S)-(3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-

yl)pyrrolidine-1-yl}benzonitrile

[0760]

[Formula 247]



Synthesis of [(1S)-(4-silanophenyl)pyrrolidin-3-yl]carbamic acid tert-butyl ester

DMF (10 mL) suspension of (3S)-3-(tertbutoxycarbonylamino)pyrrolidine (837 mg) and 4-fluorobenzonitrile (544 mg) and potassium carbonate (1.24 g) was agitated at 120°C for 22 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate and saturated sodium bicarbonate water were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was dried over anhydrous magnesium sulfate and was concentrated under reduced pressure. 320 mg of the title compound was obtained by re-crystallizing the residue from the mixed-solution of ethyl acetate and hexane. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.45 (s, 9H), 1.94-2.05 (m, 1H), 2.25-2.37 (m, 1H), 3.16-3.67 (m, 4H), 4.36 (brs, 1H), 4.67 (brs, 1H), 6.49 (d, J=6.8 Hz, 2H), 7.45 (d, J=6.8 Hz, 2H).

[0761]

Synthesis of 4-[(3S)-aminopyrrolidin-1-yl]benzonitrile 2 trifluoroacetic-acid salt

Trifluoroacetic acid (1 mL) was added to a methylene chloride (3 mL) solution of ((1S)-(4-silanophenyl)pyrrolidin-3-yl)carbamic acid tert-butyl ester (100 mg), and the reaction solution was agitated at room temperature for 15 hours. 144 mg of the title compound was obtained by condensing reaction solution under reduced pressure. The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 2.18-2.28 (m, 1H), 2.45-2.56 (m, 1H), 3.43-3.75 (m, 4H), 3.99-4.07 (m, 1H), 6.67 (d, J=6.8 Hz, 2H), 7.53 (d, J=6.8 Hz, 2H).

[0762]

Synthesis of (E)-4-{(3S)-{(3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-yl}pyrrolidin-1-yl}benzonitrile

To a mixed solution of 4-((3S)-aminopyrrolidin-1-yl)benzonitrile 2 trifluoroacetic-acid salt (144 mg) and (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid tert-butyl ester (136 mg) in acetonitrile (5 mL) and water (0.5 mL), potassium carbonate (239 mg) and sodium iodide (52 mg) were added, and heat-refluxing of the reaction mixture was carried out for 34 hours. After the reaction solution was allowed to be cooled to room temperature, ethyl acetate and water were added to the

reaction solution, and the organic layer was partitioned. The obtained organic layer was dried over anhydrous magnesium sulfate and was concentrated under reduced pressure. Trifluoroacetic acid (1 mL) was added to a methylene chloride (3 mL) solution of the residue, and the reaction solution was agitated at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure and HOBT (188 mg), EDC (266 mg), and IPEA (0.36 mL) were added to a DMF (3 mL) solution of the obtained residue. The reaction mixture was agitated at room temperature for 6 hours. Ethyl acetate and saturated sodium bicarbonate water were added to the reaction solution, and the organic layer was partitioned. The obtained organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 47 mg of the title compound was obtained by purifying the residue by silica gel chromatography (Carrier: Chromatorex™ NH and elution solvent:heptane:ethyl acetate =1:1 -> ethyl acetate). The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-2.00 (m, 2H), 2.19-2.38 (m, 5H), 2.75-2.92 (m, 2H), 3.29-3.4 (m, 4H), 3.53-3.67 (m, 2H), 3.86 (s, 3H), 5.48-5.57 (m, 1H), 6.53 (d, J=6.8 Hz, 2H), 6.93 (brs, 1H), 7.01 (brs, 1H), 7.04 (brd, J=7.0 Hz, 1H), 7.25 (d, J=7.0 Hz, 1H), 7.47 (d, J=6.8 Hz, 2H), 7.70 (s, 1H), 7.83 (brs, 1H).

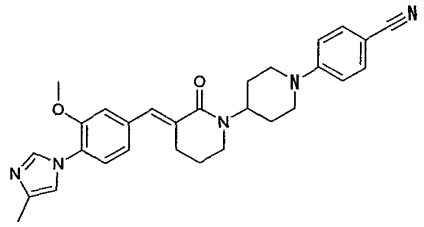
[0763]

Example 642

Synthesis of (E)-4-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-yl}piperidin-1-yl)benzonitrile

[0764]

[Formula 248]



By the same method as in Example 641, 72 mg of the title compound was obtained from 4-(4-aminopiperidin-1-yl)benzonitrile (142 mg) and (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid tert-butyl ester (129 mg). The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 1.60-1.81 (m, 6H), 2.14 (s, 3H), 2.73-2.78 (m, 2H), 2.92-3.02 (m, 2H), 3.24-3.30 (m, 2H), 3.84 (s, 3H), 4.01-4.10 (m, 2H), 4.60-4.71 (m, 1H), 7.04 (d, J=9.2 Hz, 2H), 7.08 (dd, J=9.2, 1.6 Hz, 1H), 7.14 (s, 1H), 7.23 (d, J=1.6 Hz, 1H), 7.38 (d, J=9.2 Hz, 1H), 7.55 (d, J=9.2 Hz, 2H), 7.62 (brs, 1H), 7.77 (dd, J=1.2 Hz, 1H).

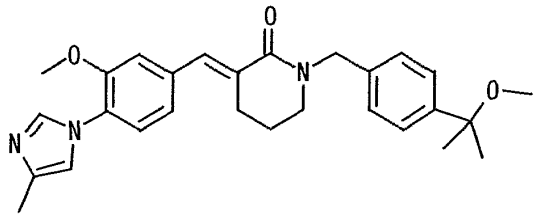
[0765]

Example 643

Synthesis of (E)-1-[4-(1-methoxy-1-methylethyl)benzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0766]

[Formula 249]



By the same method as in Example 418, 100 mg of the title compound was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (250 mg) and 4-(1-methoxy-1-methylethyl)benzylamine (174 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (s, 6H), 1.84-1.91 (m, 2H), 2.30 (s, 3H), 2.82-2.85 (m, 2H), 3.07 (s, 3H), 3.38-3.41 (m, 2H), 3.86 (s, 3H), 4.73 (s, 2H), 6.94 (t, J=1.2 Hz, 1H), 7.03 (s, 1H), 7.03-7.05 (m, 1H), 7.25-7.30 (m, 3H), 7.38 (d, J=8.0 Hz, 2H), 7.72 (d, J=1.2 Hz, 1H), 7.89 (s, 1H).

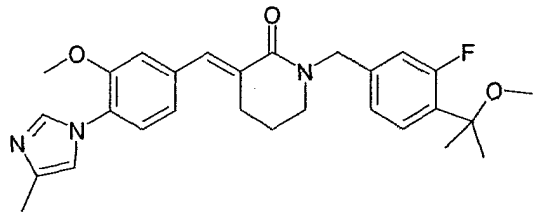
[0767]

Example 644

Synthesis of (E)-1-[3-fluoro-4-(1-methoxy-1-methylethyl)benzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0768]

[Formula 250]



By the same method as in Example 418, 57 mg of the title compound was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid (250 mg) and 3-fluoro 4-(1-methoxy-1-methyl-ethyl)benzylamine (132 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.59 (s, 6H), 1.86-1.92 (m, 2H), 2.30 (s, 3H), 2.81-2.86 (m, 2H), 3.18 (s, 3H), 3.38-3.42 (m, 2H), 3.86 (s, 3H), 4.70 (s, 2H), 6.92 (s, 1H), 6.97 (d, J=12 Hz, 1H), 7.02 (s, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.04 (t, J=8.0 Hz, 1H), 7.24 (m, 1H), 7.37 (t, J=8.0 Hz, 1H), 7.71 (1H, s, 1H), 7.86 (1H, s, 1H).

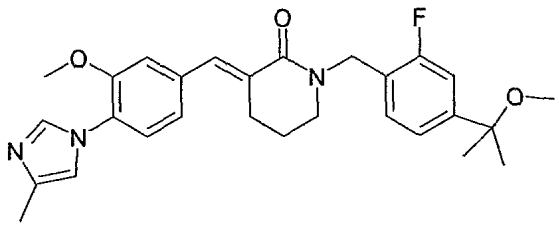
[0769]

Example 645

Synthesis of (E)-1-[2-fluoro-4-(1-methoxy-1-methylethyl)benzyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0770]

[Formula 251]



By the same method as Example 418, 110 mg of the title compound was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (250 mg) and 3-fluoro 4-(1-methoxy-1-methyl-ethyl)benzylamine (154 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.50 (s, 6H), 1.86-1.92 (m, 2H), 2.30 (s, 3H), 2.81-2.85 (m, 2H), 3.08 (s, 3H), 3.45-3.48 (m, 2H), 3.85 (s, 3H), 4.76 (s, 2H), 6.92 (t, J=1.2 Hz, 1H), 7.00 (s, 1H), 7.00-7.03 (m, 1H), 7.09-7.15 (m, 2H), 7.22-7.24 (m, 1H), 7.36 (t, J=8.0 Hz, 1H), 7.70 (d, J=1.2 Hz, 1H), 7.85 (s, 1H).

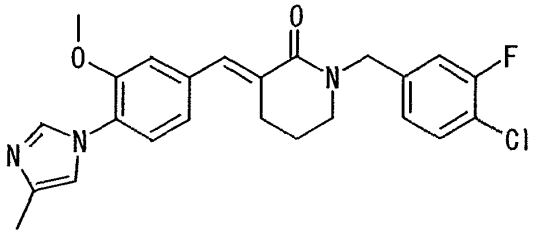
[0771]

Example 646

Synthesis of (E)-1-(4-chloro-3-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0772]

[Formula 252]



By the same method as in Example 416, 100 mg of the title compound was obtained from (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one (80 mg) and 4-chloro-3-fluorobenzylbromide (0.070 mL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.84-1.92 (m, 2H), 2.30 (s, 3H), 2.80-2.88 (m, 2H), 3.34-3.42 (m, 2H), 3.86 (s, 3H), 4.68 (s, 2H), 6.93 (s, 1H), 7.00-7.08 (m, 3H), 7.11 (d, J=8.8 Hz, 1H), 7.22-7.30 (m, 1H), 7.35 (t, J=8.4 Hz, 1H), 7.71 (s, 1H), 7.86 (s, 1H).

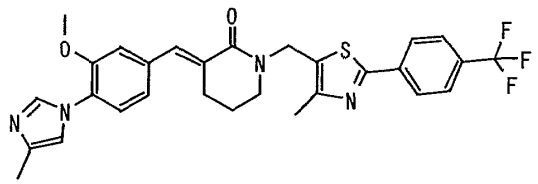
[0773]

Example 647

Synthesis of (E)-1-[4-methyl-2-(4-trifluoromethylphenyl)-1,3-thioazol-5-ylmethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0774]

[Formula 253]



By the same method as in Example 416, 24 mg of the title compound was obtained from (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one (80 mg) and 5-(chloromethyl)-4-methyl-2-(4-trifluoromethylphenyl)-

1,3-thiazole (94.2 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.85-1.95 (m, 2H), 2.30 (s, 3H), 2.55 (s, 3H), 2.80-2.85 (m, 2H), 3.45-3.54 (m, 2H), 3.85 (s, 3H), 4.83 (s, 2H), 6.91-6.93 (m, 1H), 6.98-7.05 (m, 2H), 7.22-7.27 (m, 1H), 7.65 (d, J=8.4 Hz, 2H), 7.70 (d, J=1.2 Hz, 1H), 7.86 (s, 1H), 8.00 (d, J=8.4 Hz, 2H).

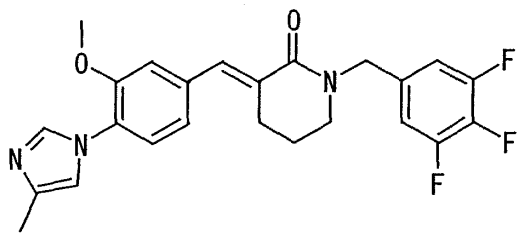
[0775]

Example 648

Synthesis of (E)-1-(3,4,5-trifluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0776]

[Formula 254]



By the same method as in Example 416, 55 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one (50 mg) and 3, 4,5-trifluorobenzylchloride (0.027 mL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.86-1.94 (m, 2H), 2.30 (s, 3H), 2.80-2.88 (m, 2H), 3.35-3.42 (m, 2H), 3.86 (s, 3H), 4.64 (s, 2H), 6.90-6.98 (m, 3H), 7.00-7.05 (m, 2H),

7.22–7.28 (m, 1H), 7.69–7.73 (m, 1H), 7.85 (s, 1H).

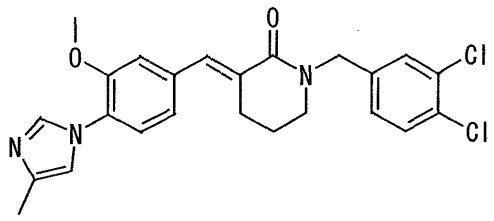
[0777]

Example 649

Synthesis of (E)-1-(3,4-dichlorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0778]

[Formula 255]



By the same method as in Example 416, 30 mg of the title compound was obtained from (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one (30 mg) and 3,4-dichlorobenzylchloride (0.020 mL). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.84–1.92 (m, 2H), 2.30 (s, 3H), 2.80–2.88 (m, 2H), 3.34–3.41 (m, 2H), 3.86 (s, 3H), 4.67 (s, 2H), 6.90–6.95 (m, 1H), 7.00–7.06 (m, 2H), 7.17 (dd, J=2.0, 8.4 Hz, 1H), 7.23–7.27 (m, 1H), 7.40 (d, J=2.0 Hz, 1H), 7.40 (d, J=8.4 Hz, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.86 (s, 1H).

[0779]

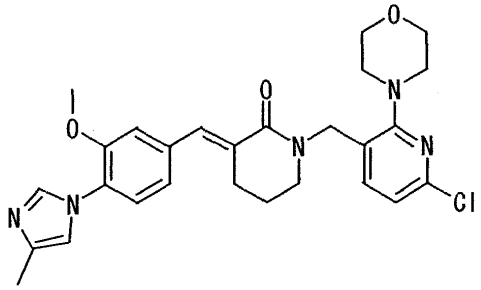
Example 650

Synthesis of (E)-1-[6-chloro-2-(morpholin-4-yl)pyridin-3-ylmethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzylidene]piperidin-2-one

[0780]

[Formula 256]



By the same method as in Example 418, 27 mg of the title compound was obtained from (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid trifluoroacetic acid salt (200 mg) and (6-chloro-2-(morpholin-4-yl)-pyridin-3-yl)methylamine (250 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82-1.92 (m, 2H), 2.31 (s, 3H), 2.82-2.90 (m, 2H), 3.12-3.20 (m, 4H), 3.22-3.30 (m, 2H), 3.80-3.90 (m, 4H), 3.87 (s, 3H), 4.71 (s, 2H), 6.90-7.00 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 7.04 (s, 1H), 7.05 (d, J=8.4 Hz, 1H), 7.20-7.30 (m, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.74 (brs, 1H), 7.88 (s, 1H).

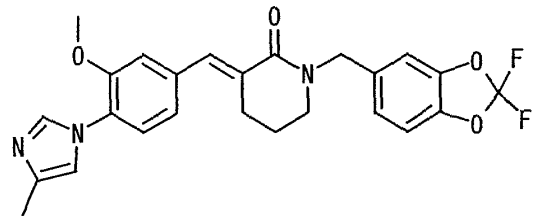
[0781]

Example 651

Synthesis of (E)-(2,2-difluorobenzo[1,3] dioxol-5-ylmethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0782]

[Formula 257]



By the same method as in Example 427, 44 mg of the title compound was obtained from (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl (100 mg) and methylamine (2,2-difluorobenzo [1,3]dioxol-5-ylmethyl)(77.5 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83-1.92 (m, 2H), 2.30 (s, 3H), 2.80-2.86 (m, 2H), 3.35-3.41 (m, 2H), 3.86 (s, 3H), 4.68 (s, 2H), 6.91-6.94 (m, 1H), 6.98-7.05 (m, 4H), 7.07-7.10 (m, 1H), 7.22-7.27 (m, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.86 (s, 1H).

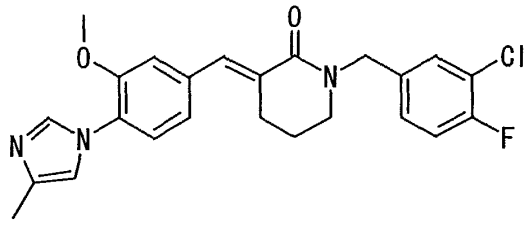
[0783]

Example 652

Synthesis of (E)-1-(3-chloro-4-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0784]

[Formula 258]



By the same method as in Example 427, 27 mg of the title compound was obtained from (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ethyl (100 mg) and 3-chloro-4-fluorobenzylamine (100 mg). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.84-1.92 (m, 2H), 2.30 (s, 3H), 2.80-2.87 (m, 2H), 3.34-3.41 (m, 2H), 3.88 (s, 3H), 4.66 (s, 2H), 6.91-6.94 (m, 1H), 7.00-7.05 (m, 2H), 7.10 (t, J=8.8 Hz, 1H), 7.17-7.23 (m, 1H), 7.23-7.28 (m, 1H), 7.36 (dd, J=2.0, 6.8 Hz, 1H), 7.71 (d, J=1.6 Hz, 1H), 7.86 (s, 1H).

[0785]

The compounds shown in Table 21 were synthesized as in Example 418.

The structural formulae and physical properties are shown in Table 21, respectively.

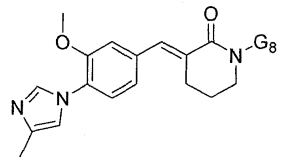
The separation conditions in the notes to Table 21 are as follows:

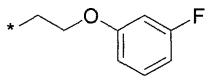
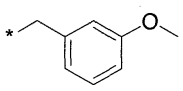
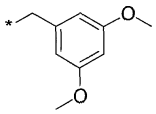
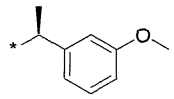
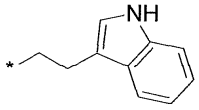
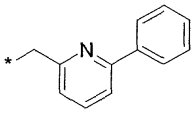
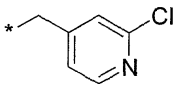
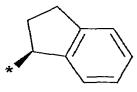
Separation Condition A: CHIRALPAK™ AD-H (2 cm×25 cm: mobile phase : hexane-ethanol system)

Separation Condition B: CHIRALPAK™ OJ-H (2 cm×25 cm: mobile phase : hexane-ethanol system)

[0786]

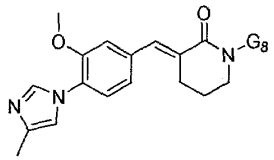
[Table 21-1]

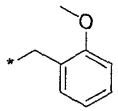
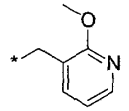
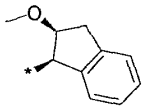
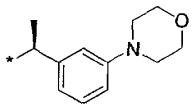
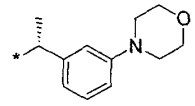
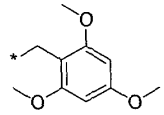
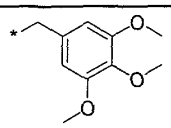
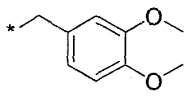
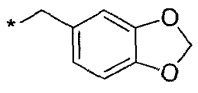
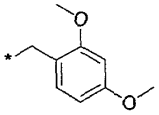


Example	G_8	DATA: MS m/z	Note
653		M^++H : 436 (ESI)	
654		M^++H : 418 (ESI)	
655		M^++H : 448 (ESI)	
656		M^++H : 432 (ESI)	optically active substance
657		M^++H : 441 (ESI)	
658		M^++H : 465 (ESI)	
659		M^++H : 423 (ESI)	
660		M^++H : 414 (ESI)	optically active substance

[0787]

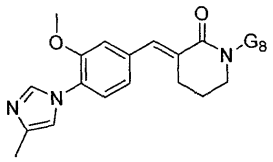
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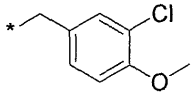
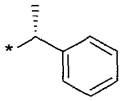
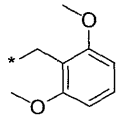
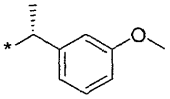
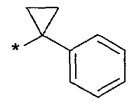
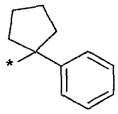
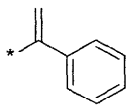
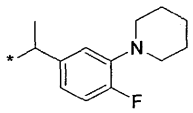
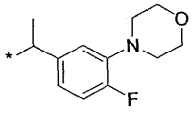
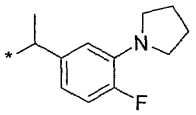


Example	G_8	DATA: MS m/z	Note
661		M^++H : 418 (ESI)	
662		M^++H : 419 (ESI)	
663		M^++H : 444 (ESI)	optically active substance
664		M^++H : 487 (ESI)	optically active substance (separation condition A; retention time: 9 minutes; absolute configuration: unknown)
665		M^++H : 487 (ESI)	optically active substance (separation condition A; retention time: 11 minutes; absolute configuration: unknown)
666		M^++H : 478 (ESI)	
667		M^++H : 478 (ESI)	
668		M^++H : 448 (ESI)	
669		M^++H : 432 (ESI)	
670		M^++H : 448 (ESI)	

[0788]

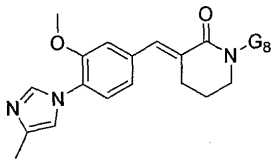
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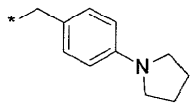
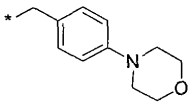
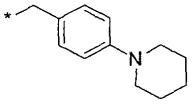
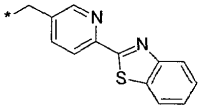
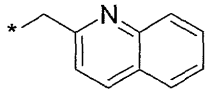
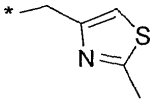
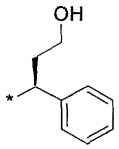
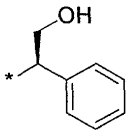
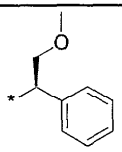
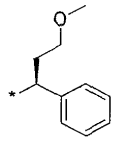


Example	G_8	DATA: MS m/z	Note
671		M^++H : 452 (ESI)	
672		M^++H : 402 (ESI)	optically active substance
673		M^++H : 448 (ESI)	
674		M^++H : 432 (ESI)	optically active substance
675		M^++H : 414 (ESI)	
676		M^++H : 442 (ESI)	
677		M^++H : 400 (ESI)	
678		M^++H : 503 (ESI)	racemate
679		M^++H : 505 (ESI)	racemate
680		M^++H : 489 (ESI)	racemate

[0789]

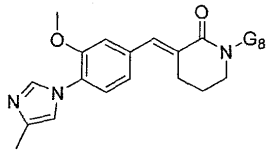
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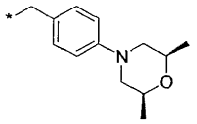
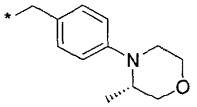
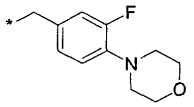
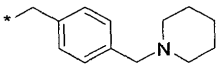
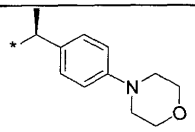
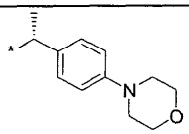
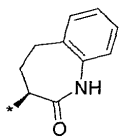
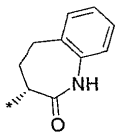
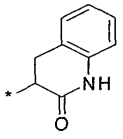
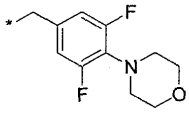


Example	G_8	DATA: MS m/z	Note
681		M^++H : 457 (ESI)	
682		M^++H : 473 (ESI)	
683		M^++H : 471 (ESI)	
684		M^++H : 522 (ESI)	
685		M^++H : 439 (ESI)	
686		M^++H : 409 (ESI)	
687		M^++H : 432 (ESI)	optically active substance
688		M^++H : 418 (ESI)	optically active substance
689		M^++H : 432 (ESI)	optically active substance
690		M^++H : 446 (ESI)	optically active substance

[0790]

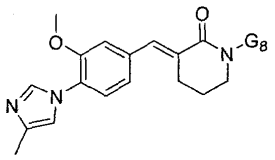
[Table 21-5]

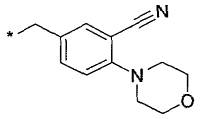
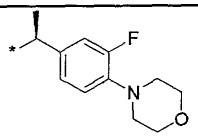
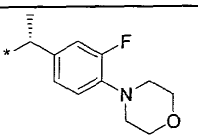
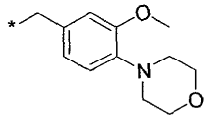
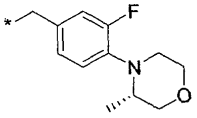
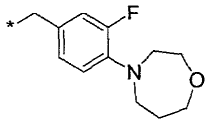
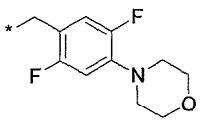
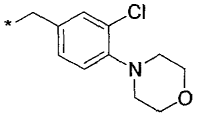
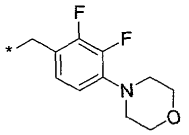
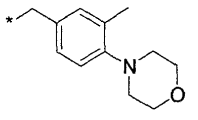


Example	G_8	DATA: MS m/z	Note
691		M^++H : 501 (ESI)	
692		M^++H : 487 (ESI)	optically active substance
693		M^++H : 491 (ESI)	
694		M^++H : 485 (ESI)	
695		M^++H : 487 (ESI)	optically active substance (separation condition A: retention time: 16 minutes; absolute configuration: unknown)
696		M^++H : 487 (ESI)	optically active substance (separation condition A: retention time: 20 minutes; absolute configuration: unknown)
697		M^++H : 457 (ESI)	optically active substance (separation condition B: retention time: 12 minutes; absolute configuration: unknown)
698		M^++H : 457 (ESI)	optically active substance (separation condition B: retention time: 15 minutes; absolute configuration: unknown)
699		M^++H : 443 (ESI)	racemate
700		M^++H : 509 (ESI)	

[0791]

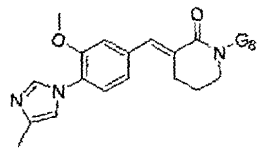
[Table 21-6]

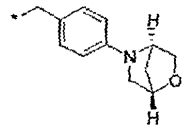
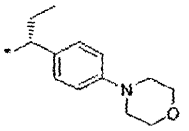
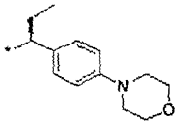
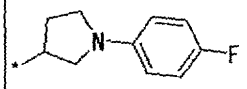
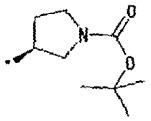
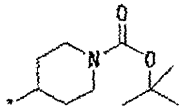
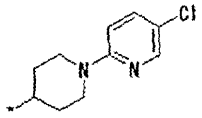
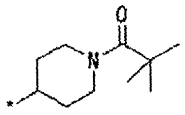
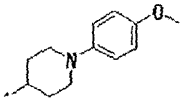
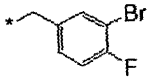


Example	G_8	DATA: MS m/z	Note
701		M^++H : 498 (ESI)	
702		M^++H : 505 (ESI)	optically active substance (separation condition A: retention time: 13 minutes; absolute configuration: unknown)
703		M^++H : 505 (ESI)	optically active substance (separation condition A: retention time: 16 minutes; absolute configuration: unknown)
704		M^++H : 503 (ESI)	
705		M^++H : 505 (ESI)	optically active substance
706		M^++H : 505 (ESI)	
707		M^++H : 509 (ESI)	
708		M^++H : 507 (ESI)	
709		M^++H : 509 (ESI)	
710		M^++H : 487 (ESI)	

[0792]

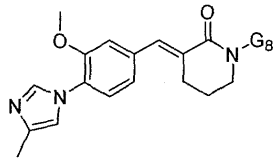
[Table 21-7]

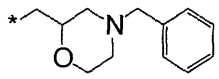
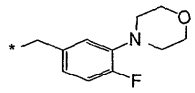
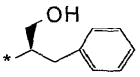
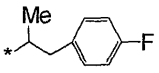
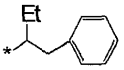
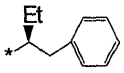
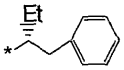
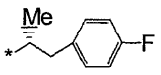
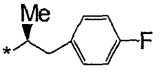


Example	G_8	DATA: MS m/z	Note
711		M^++H : 485 (ESI)	optically active substance
712		M^++H : 501 (ESI)	optically active substance (separation conditionA: retention time: 13 minutes; absolute configuration: unknown)
713		M^++H : 501 (ESI)	optically active substance (separation conditionA: retention time: 15 minutes; absolute configuration: unknown)
714		M^++H : 461 (ESI)	racemate
715		M^++H : 467 (ESI)	optically active substance
716		M^++H : 481 (ESI)	
717		M^++H : 492 (ESI)	
718		M^++H : 465 (ESI)	
719		M^++H : 487 (ESI)	
720		M^++H : 485 (ESI)	

[0793]

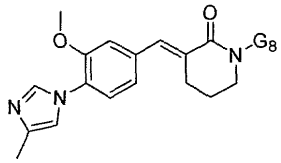
[Table 21-8]

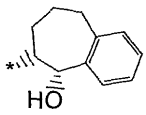
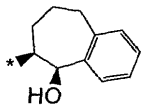
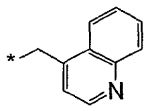
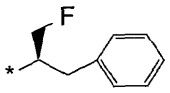
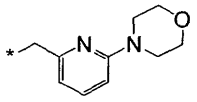
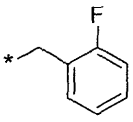
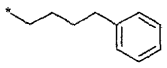
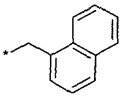
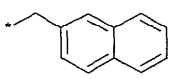
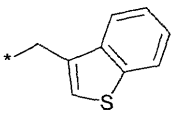


Example	G_8	DATA: MS m/z	Note
721		M^++H : 4 8 7 (E S I)	
722		M^++H : 4 9 1 (E S I)	
723		M^++H : 3 7 4 (E S I)	
724		M^++H : 4 3 2 (E S I)	optically active substance
725		M^++H : 4 3 4 (E S I)	racemate
726		M^++H : 4 3 0 (E S I)	racemate
727		M^++H : 4 3 0 (E S I)	optically active substance (separation condition A: retention time: 11 minutes; absolute configuration: unknown)
728		M^++H : 4 3 0 (E S I)	optically active substance (separation condition A: retention time: 14 minutes; absolute configuration: unknown)
729		M^++H : 4 3 4 (E S I)	optically active substance (separation condition B: retention time: 24 minutes; absolute configuration: unknown)
730		M^++H : 4 3 4 (E S I)	optically active substance (separation condition B: retention time: 30 minutes; absolute configuration: unknown)

[0794]

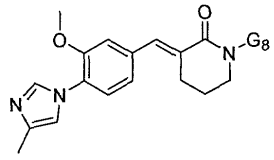
[Table 21-9]

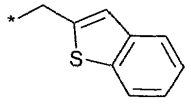
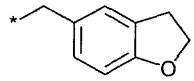
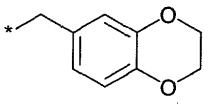
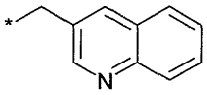
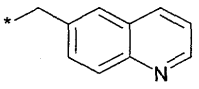
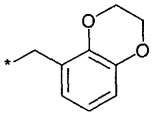
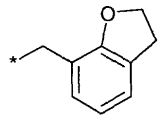
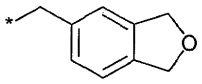
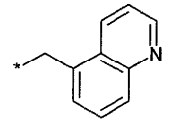
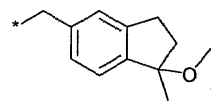


Example	G_8	DATA: MS m/z	Note
731		M^++H : 458 (ESI)	optically active substance (separation condition A: retention time: 10 minutes; absolute configuration: unknown)
732		M^++H : 458 (ESI)	optically active substance (separation condition A: retention time: 16 minutes; absolute configuration: unknown)
733		M^++H : 439 (ESI)	
734		M^++H : 434 (ESI)	optically active substance
735		M^++H : 474 (ESI)	
736		M^++H : 406 (ESI)	
737		M^++H : 430 (ESI)	
738		M^++H : 438 (ESI)	
739		M^++H : 438 (ESI)	
740		M^++H : 444 (ESI)	

[0795]

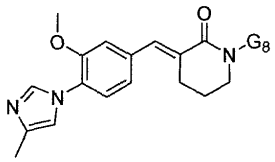
[Table 21-10]

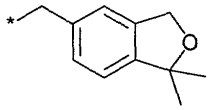
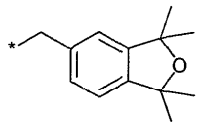
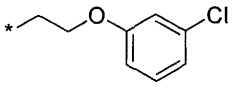
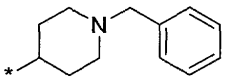
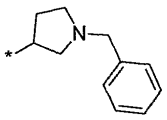
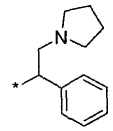
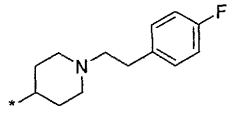
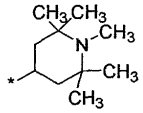
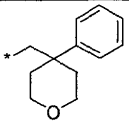


Example	G_8	DATA: MS m/z	Note
741		M^++H : 444 (ESI)	
742		M^++H : 430 (ESI)	
743		M^++H : 446 (ESI)	
744		M^++H : 439 (ESI)	
745		M^++H : 439 (ESI)	
746		M^++H : 446 (ESI)	
747		M^++H : 430 (ESI)	
748		M^++H : 430 (ESI)	
749		M^++H : 439 (ESI)	
750		M^++H : 472 (ESI)	racemate

[0796]

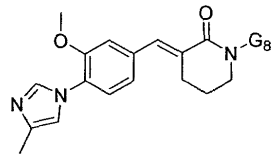
[Table 21-11]

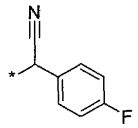
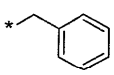
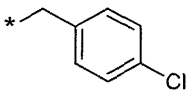
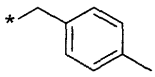
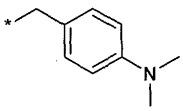
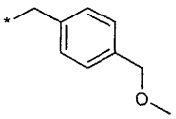
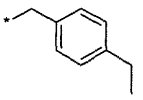
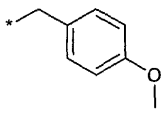
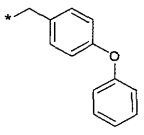
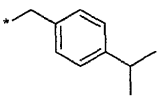


Example	G_8	DATA: MS m/z	Note
751		M^++H：458 (ESI)	
752		M^++H：486 (ESI)	
753		M^++H：452 (ESI)	
754		M^++H：471 (ESI)	
755		M^++H：457 (ESI)	racemate
756		M^++H：471 (ESI)	racemate
757		M^++H：503 (ESI)	
758		M^++H：380 (ESI)	
759		M^++H：451 (ESI)	
760		M^++H：472 (ESI)	

[0797]

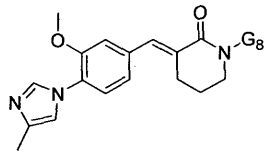
[Table 21-12]

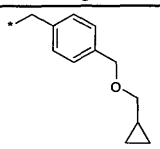
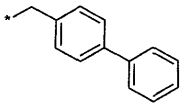
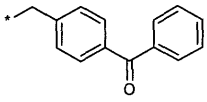
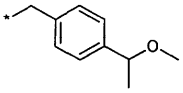
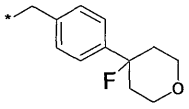
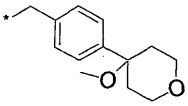
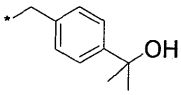
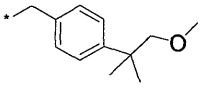
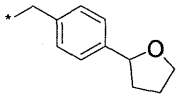
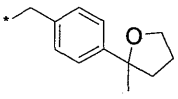


Example	G_8	DATA: MS m/z	Note
761		M^++H : 431 (ESI)	racemate
762		M^++H : 388 (ESI)	
763		M^++H : 422 (ESI)	
764		M^++H : 402 (ESI)	
765		M^++H : 431 (ESI)	
766		M^++H : 432 (ESI)	
767		M^++H : 416 (ESI)	
768		M^++H : 418 (ESI)	
769		M^++H : 480 (ESI)	
770		M^++H : 430 (ESI)	

[0798]

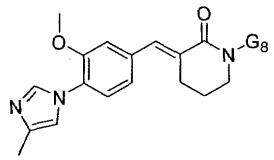
[Table 21-13]

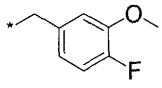
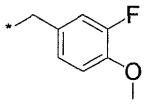
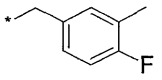
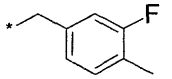
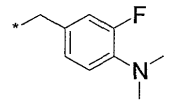
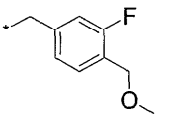
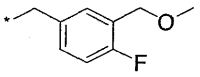
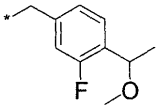
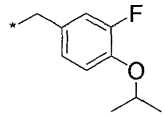
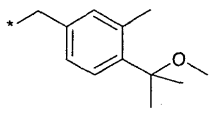


Example	G_8	DATA: MS m/z	Note
771		M^++H : 472 (ESI)	
772		M^++H : 464 (ESI)	
773		M^++H : 492 (ESI)	
774		M^++H : 446 (ESI)	racemate
775		M^++H : 490 (ESI)	
776		M^++H : 502 (ESI)	
777		M^++H : 446 (ESI)	
778		M^++H : 474 (ESI)	
779		M^++H : 458 (ESI)	
780		M^++H : 472 (ESI)	racemate

[0799]

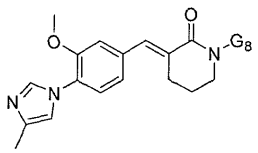
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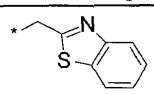
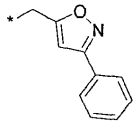
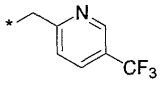
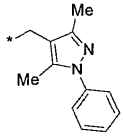
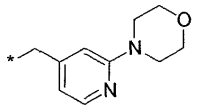
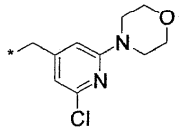
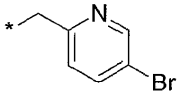
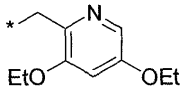
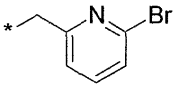
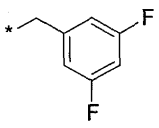


Example	G_8	DATA: MS m/z	Note
781		M^++H：436 (ESI)	
782		M^++H：436 (ESI)	
783		M^++H：420 (ESI)	
784		M^++H：420 (ESI)	
785		M^++H：449 (ESI)	
786		M^++H：450 (ESI)	
787		M^++H：450 (ESI)	
788		M^++H：464 (ESI)	racemate
789		M^++H：464 (ESI)	
790		M^++H：474 (ESI)	

[0800]

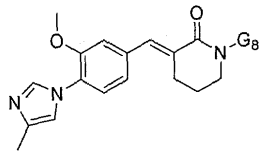
[Table 21-15]

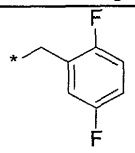
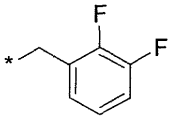
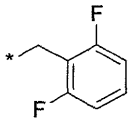
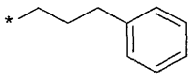
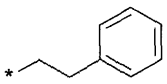
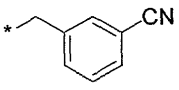
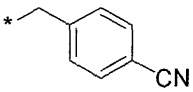
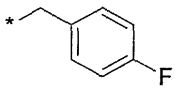
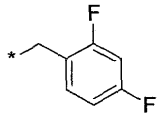
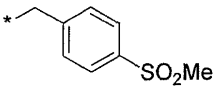


Example	G_8	DATA: MS m/z	Note
791		M^++H : 4 4 5 (E S I)	
792		M^++H : 4 5 5 (E S I)	
793		M^++H : 4 5 7 (E S I)	
794		M^++H : 4 8 2 (E S I)	
795		M^++H : 4 7 4 (E S I)	
796		M^++H : 5 0 8 (E S I)	
797		M^++H : 4 6 7 (E S I)	
798		M^++H : 4 7 7 (E S I)	
799		M^++H : 4 6 7 (E S I)	
800		M^++H : 4 2 4 (E S I)	

[0801]

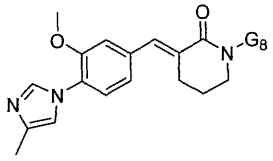
[Table 21-16]

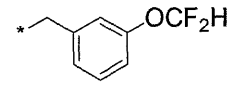
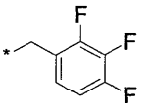
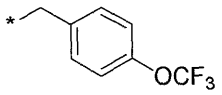
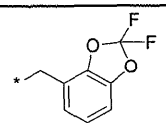
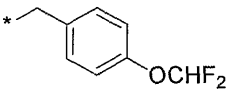
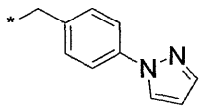
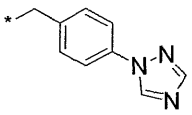
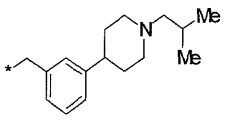
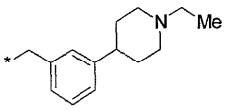
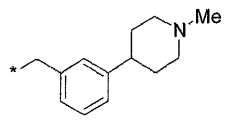


Example	G_8	DATA: MS m/z	Note
801		M^++H : 424 (ESI)	
802		M^++H : 424 (ESI)	
803		M^++H : 424 (ESI)	
804		M^++H : 416 (ESI)	
805		M^++H : 402 (ESI)	
806		M^++H : 413 (ESI)	
807		M^++H : 413 (ESI)	
808		M^++H : 406 (ESI)	
809		M^++H : 424 (ESI)	
810		M^++H : 466 (ESI)	

[0802]

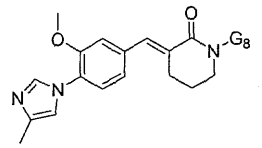
[Table 21-17]

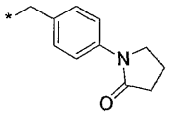
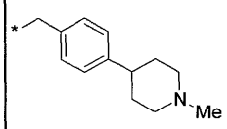
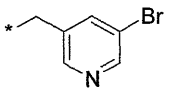
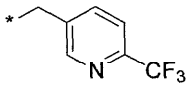
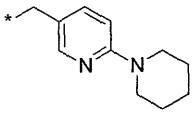
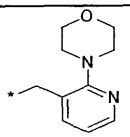
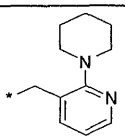
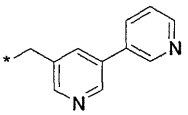
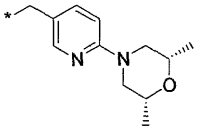
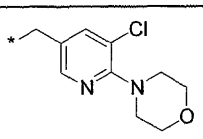


Example	G_8	DATA: MS m/z	Note
811		M^++H : 454 (ESI)	
812		M^++H : 442 (ESI)	
813		M^++H : 472 (ESI)	
814		M^++H : 468 (ESI)	
815		M^++H : 454 (ESI)	
816		M^++H : 454 (ESI)	
817		M^++H : 455 (ESI)	
818		M^++H : 527 (ESI)	
819		M^++H : 499 (ESI)	
820		M^++H : 485 (ESI)	

[0803]

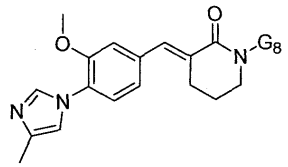
[Table 21-18]

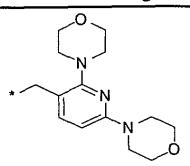
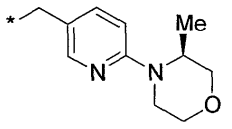
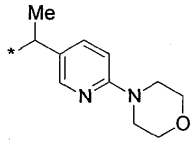
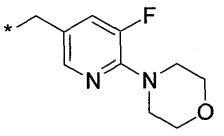
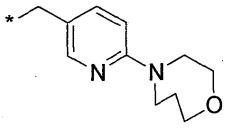
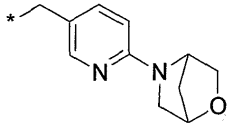
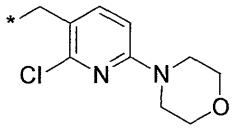
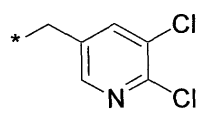


Example	G_8	DATA: MS m/z	Note
821		M^++H : 471 (ESI)	
822		M^++H : 485 (ESI)	
823		M^++H : 467 (ESI)	
824		M^++H : 457 (ESI)	
825		M^++H : 472 (ESI)	
826		M^++H : 474 (ESI)	
827		M^++H : 472 (ESI)	
828		M^++H : 466 (ESI)	
829		M^++H : 502 (ESI)	
830		M^++H : 508 (ESI)	

[0804]

[Table 21-19]



Example	G_8	DATA: MS m/z	Note
831		M^++H : 559 (ESI)	
832		M^++H : 488 (ESI)	optically active substance
833		M^++H : 488 (ESI)	
834		M^++H : 492 (ESI)	
835		M^++H : 488 (ESI)	
836		M^++H : 486 (ESI)	optically active substance
837		M^++H : 508 (ESI)	
838		M^++H : 457 (ESI)	

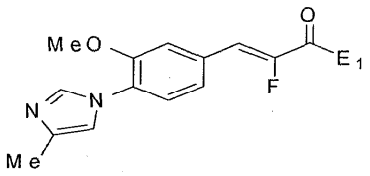
[0805]

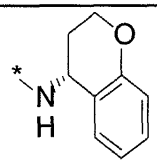
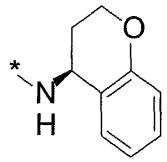
The compounds shown in Table 22 were synthesized as in Example 85. The structural formulae and physical properties are shown in Table 21, respectively. The separation conditions in the notes to the table are as follows:

Separation Condition E: CHIRALCELK™ OD available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase : hexane-ethanol)

[0806]

[Table 22]



Example	E_1	DATA: MS m/z	Note
839		M^++H : 408 (ESI)	optically active substance (separation condition E: retention time: 8.7 minutes; absolute configuration: unknown)
840		M^++H : 408 (ESI)	optically active substance (separation condition E: retention time: 13.6 minutes; absolute configuration: unknown)

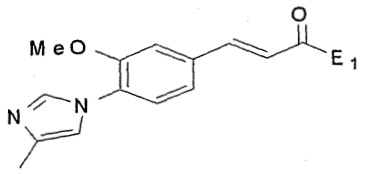
[0807]

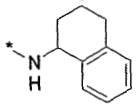
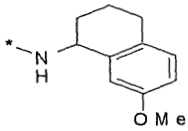
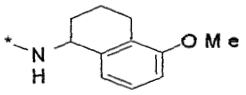
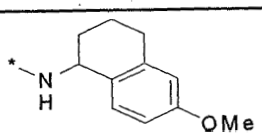
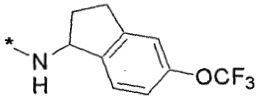
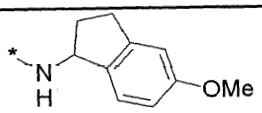
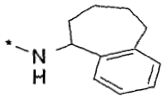
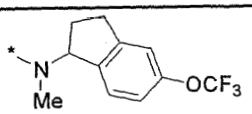
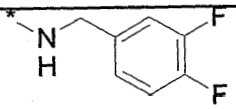
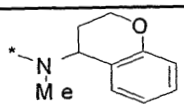
The compounds shown in Table 23 were synthesized as in the Example 121. The structural formulae and physical properties are shown in

Table 23, respectively.

[0808]

[Table 23]



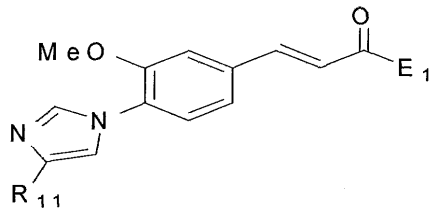
Example	E_1	DATA: MS m/z
841		M^++H : 388 (ESI)
842		M^++H : 418 (ESI)
843		M^++H : 418 (ESI)
844		M^++H : 418 (ESI)
845		M^++H : 458 (ESI)
846		M^++H : 404 (ESI)
847		M^++H : 402 (ESI)
848		M^++H : 472 (ESI)
849		M^++H : 384 (ESI)
850		M^++H : 404 (ESI)

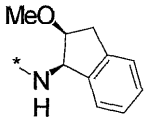
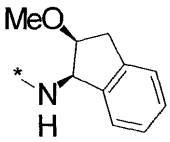
[0809]

The compound shown in Table 24 was synthesized as in Example 1. The structural formulae and physical properties are shown in Table 24, respectively.

[0810]

[Table 24]



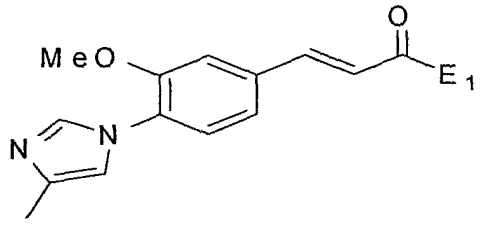
Example	R11	E_1	DATA: MS m/z	Note
851	Me		M^++H : 404 (ESI)	optically active substance
852	Et		M^++H : 418 (ESI)	optically active substance

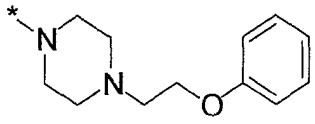
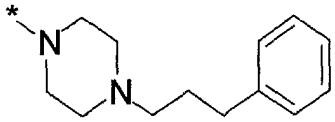
[0811]

The compounds shown in Table 25 were synthesized as in Example 121. The structural formulae and physical properties are shown in Table 25, respectively.

[0812]

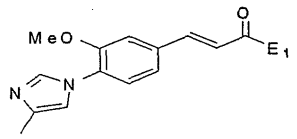
[Table 25-1]

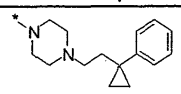
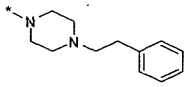
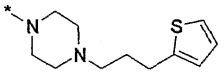
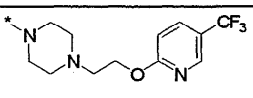
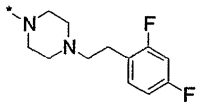
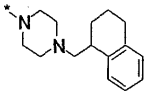
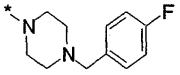
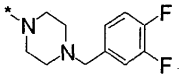
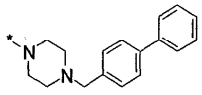
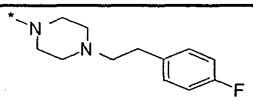
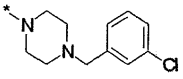
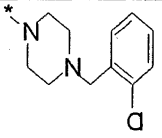
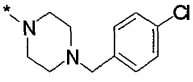


Example	E_1	DATA: MS m/z
853		M^++H : 447 (ESI)
854		M^++H : 445 (ESI)

[0813]

[Table 25-2]



Example	E_1	DATA: MS m/z
855		M^++H：471 (ESI)
856		M^++H：431 (ESI)
857		M^++H：451 (ESI)
858		M^++H：516 (ESI)
859		M^++H：467 (ESI)
860		M^++H：471 (ESI)
861		M^++H：435 (ESI)
862		M^++H：453 (ESI)
863		M^++H：493 (ESI)
864		M^++H：449 (ESI)
865		M^++H：451 (ESI)
866		M^++H：451 (ESI)
867		M^++H：451 (ESI)

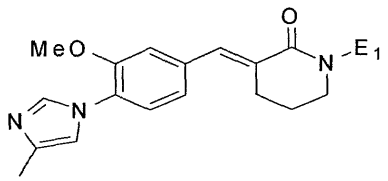
[0814]

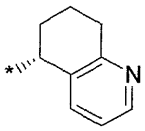
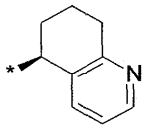
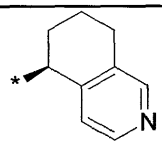
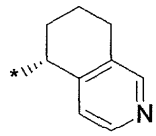
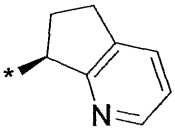
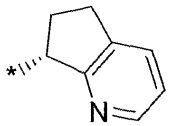
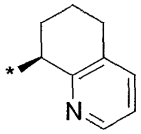
The compounds shown in Table 26 were synthesized as in Example 418. The structural formulae and physical properties are shown in Table 26, respectively. The separation conditions in the notes to the table are as follows:

Separation Condition A: CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase : hexane-ethanol system)

[0815]

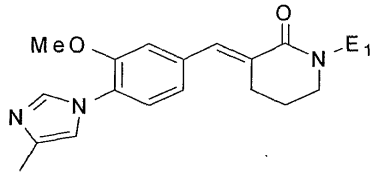
[Table 26-1]

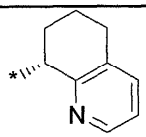
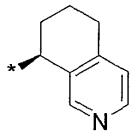
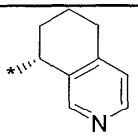
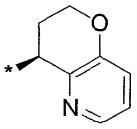
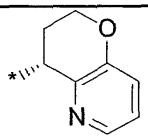
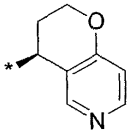
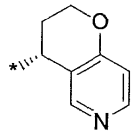
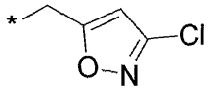


Example	E_1	DATA: MS m/z	Note
868		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 71.1 minutes; absolute configuration: unknown)
869		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 77.9 minutes; absolute configuration: unknown)
870		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 8.7 minutes; absolute configuration: unknown)
871		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 10.6 minutes; absolute configuration: unknown)
872		M^++H : 415 (ESI)	optically active substance (separation condition A: retention time: 9.5 minutes; absolute configuration: unknown)
873		M^++H : 415 (ESI)	optically active substance (separation condition A: retention time: 11.0 minutes; absolute configuration: unknown)
874		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 8.7 minutes; absolute configuration: unknown)

[0816]

[Table 26-2]



Example	E_1	DATA: MS m/z	Note
875		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 9.7 minutes; absolute configuration: unknown)
876		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 12.8 minutes; absolute configuration: unknown)
877		M^++H : 429 (ESI)	optically active substance (separation condition A: retention time: 15.9 minutes; absolute configuration: unknown)
878		M^++H : 431 (ESI)	optically active substance (separation condition A: retention time: 10.4 minutes; absolute configuration: unknown)
879		M^++H : 431 (ESI)	optically active substance (separation condition A: retention time: 13.5 minutes; absolute configuration: unknown)
880		M^++H : 431 (ESI)	optically active substance (separation condition A: retention time: 5.1 minutes; absolute configuration: unknown)
881		M^++H : 431 (ESI)	optically active substance (separation condition A: retention time: 6.3 minutes; absolute configuration: unknown)
882		M^++H : 413 (ESI)	

[0817]

The compounds shown in Table 27 were synthesized as in Example 418. The structural formulae and physical properties are shown in Table 27, respectively. The separation conditions in the notes to the table are as follows:

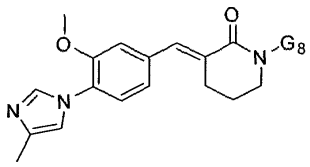
Separation Condition A: CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase : hexane-ethanol system)

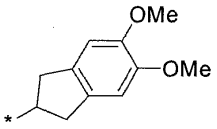
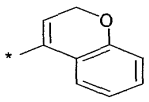
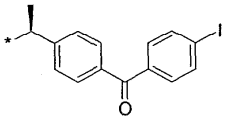
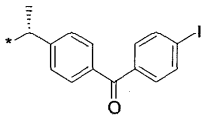
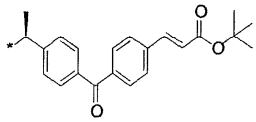
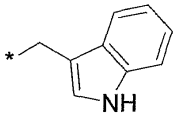
Separation Condition B: CHIRALCEL™ OJ-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase : hexane-ethanol system)

Separation Condition C: CHIRALCEL™ OD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase : hexane-ethanol system)

[0818]

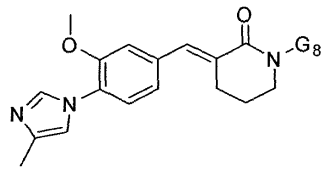
[Table 27-1]

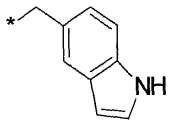
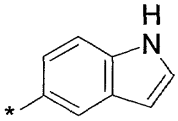
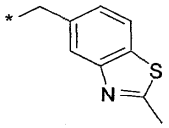
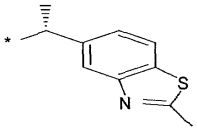
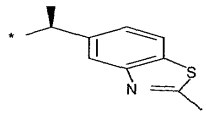
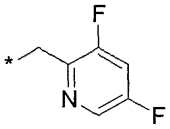
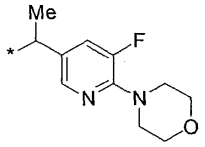
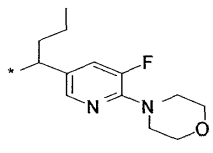


Example	G_8	DATA: MS m/z	Note
883		M^++H : 474 (ESI)	
884		M^++H : 428 (ESI)	
885		M^++H : 634 (ESI)	optically active substance (separation condition B: retention time: 7 minutes; absolute configuration: unknown)
886		M^++H : 634 (ESI)	optically active substance (separation condition B: retention time: 19 minutes; absolute configuration: unknown)
887		M^++H : 632 (ESI)	optically active substance
888		M^++H : 427 (ESI)	

[0819]

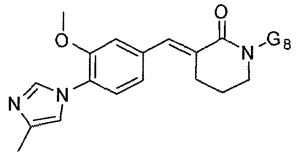
[Table 27-2]

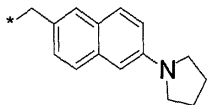
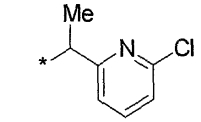
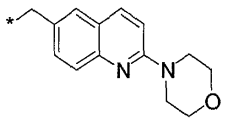
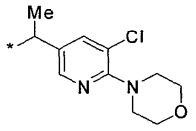
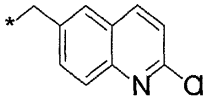
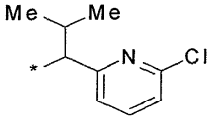
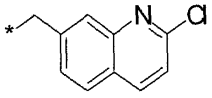
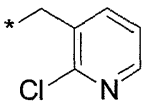
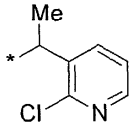


Example	G_8	DATA: MS m/z	Note
889		M^++H : 427 (ESI)	
890		M^++H : 413 (ESI)	
891		M^++H : 459 (ESI)	
892		M^++H : 473 (ESI)	optically active substance (separation condition A: retention time: 12 minutes; absolute configuration: unknown)
893		M^++H : 473 (ESI)	optically active substance (separation condition A: retention time: 17 minutes; absolute configuration: unknown)
894		M^++H : 425 (ESI)	
895		M^++H : 506 (ESI)	racemate
896		M^++H : 534 (ESI)	racemate

[0820]

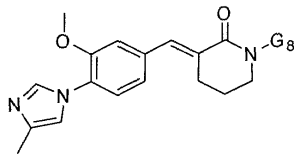
[Table 27-3]

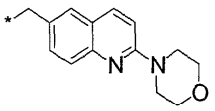
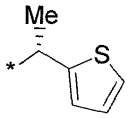
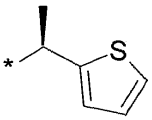
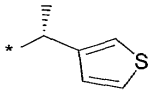
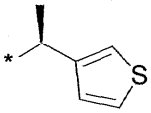
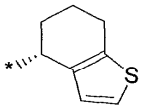
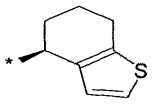
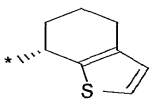
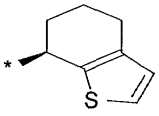


Example	G_8	DATA: MS m/z	Note
897		M^++H：507 (ESI)	
898		M^++H：437 (ESI)	racemate
899		M^++H：524 (ESI)	
900		M^+：522 (ESI)	racemate
901		M^++H：473 (ESI)	
902		M^++H：465 (ESI)	racemate
903		M^++H：473 (ESI)	
904		M^++H：423 (ESI)	
905		M^++H：437 (ESI)	racemate

[0821]

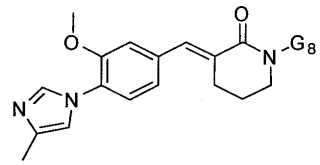
[Table 27-4]

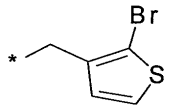
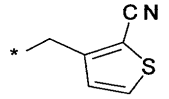
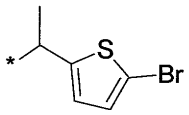
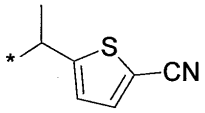
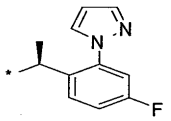
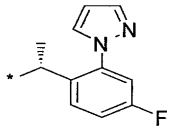
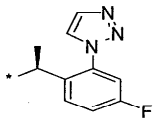
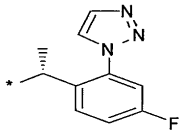
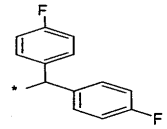


Example	G_8	DATA: MS m/z	Note
906		M^++H : 524 (ESI)	
907		M^++H : 408 (ESI)	optically active substance (separation condition A: retention time: 22 minutes; absolute configuration: unknown)
908		M^++H : 408 (ESI)	optically active substance (separation condition A: retention time: 30 minutes; absolute configuration: unknown)
909		M^++H : 408 (ESI)	optically active substance (separation condition A: retention time: 26 minutes; absolute configuration: unknown)
910		M^++H : 408 (ESI)	optically active substance (separation condition A: retention time: 33 minutes; absolute configuration: unknown)
911		M^++H : 434 (ESI)	optically active substance (separation condition A: retention time: 42 minutes; absolute configuration: unknown)
912		M^++H : 434 (ESI)	optically active substance (separation condition A: retention time: 54 minutes; absolute configuration: unknown)
913		M^++H : 434 (ESI)	optically active substance (separation condition A: retention time: 32 minutes; absolute configuration: unknown)
914		M^++H : 434 (ESI)	optically active substance (separation condition A: retention time: 39 minutes; absolute configuration: unknown)

[0822]

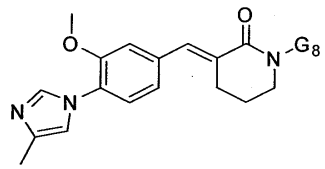
[Table 27-5]

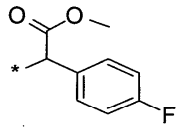
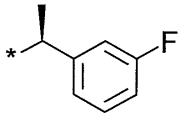
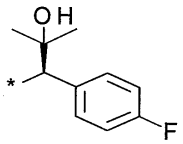


Example	G_8	DATA: MS m/z	Note
915		M^++H : 473 (ESI)	
916		M^++H : 419 (ESI)	
917		M^++H : 487 (ESI)	racemate
918		M^++H : 433 (ESI)	racemate
919		M^++H : 500 (ESI)	optically active substance (separation condition C: retention time: 10 minutes; absolute configuration: unknown)
920		M^++H : 464 (ESI)	optically active substance (separation condition C: retention time: 12 minutes; absolute configuration: unknown)
921		M^++H : 420 (ESI)	optically active substance (separation condition A: retention time: 9 minutes; absolute configuration: unknown)
922		M^++H : 464 (ESI)	optically active substance (separation condition A: retention time: 14 minutes; absolute configuration: unknown)
923		M^++H : 500 (ESI)	

[0823]

[Table 27-6]



Example	G_8	DATA: MS m/z	Note
924		M^++H : 464 (ESI)	racemate
925		M^++H : 420 (ESI)	optically active substance
926		M^++H : 464 (ESI)	optically active substance

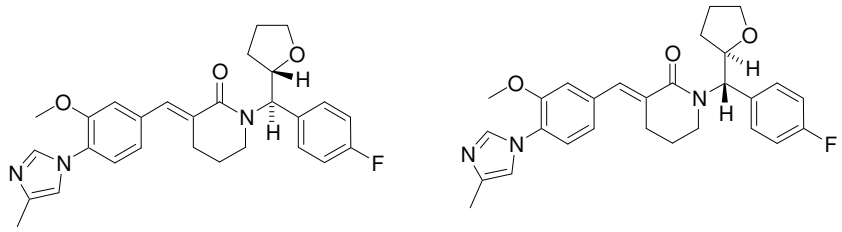
[0824]

Example 927 and Example 928

Synthesis of (E)-1-{(R)-(4-fluorophenyl)-[(S)-tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-{(S)-(4-fluorophenyl)-[(R)-tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0825]

[Formula 259]



Synthesis of erythro-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methyl azide

Diethyl azodicarboxylate (120 mg), threo-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methanol (90 mg) synthesized in accordance with a method described in Chem. Comm., 1999, p. 1745, and diphenylphosphoryl azide (0.099 mL) were sequentially added to a solution of triphenylphosphine (180 mg) in THF (5 mL) at 0°C, and the reaction solution was stirred for 1 hour. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane -> heptane:ethyl acetate = 4:1) to obtain 28 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.79-1.94 (m, 4H), 3.76-3.82 (m, 1H), 3.85-3.93 (m, 1H), 4.08-4.14 (m, 1H), 4.63 (d, J=4.8 Hz, 1H), 7.01-7.08 (m, 2H), 7.26-7.33 (m, 2H).

[0826]

Synthesis of erythro-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methylamine

10% palladium-carbon (water content: 50%, 5 mg) was added to a solution of erythro-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methylazide (28 mg) in ethanol, and the reaction solution was stirred in a hydrogen stream at room temperature for 10 hours. The reaction solution was filtered on a celite, and the filtrate was concentrated under reduced pressure to obtain 25 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55-1.99 (m, 4H), 3.66-3.83 (m, 2H), 4.25-4.40 (m, 2H), 6.97-7.06 (m, 2H), 7.44-7.55 (m, 2H), 8.78-9.02 (brs, 2H).

[0827]

Synthesis of (E)-1-{(R)-(4-fluorophenyl)-[(S)-tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-{(S)-(4-fluorophenyl)-[(R)-tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

41 mg of a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (63 mg) and erythro-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methylamine (25 mg) in the same manner as in Example 418.

The racemate (41 mg) was fractionated using

CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 3:7) to obtain the title optically active substance with a retention time of 43 minutes (13.5 mg; >99% ee) and the title optically active substance with a retention time of 64 minutes (10.5 mg; >99% ee).

The physical properties of the optically active substance with a retention time of 43 minutes (Example 927) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.61-1.72 (m, 1H), 1.77-2.12 (m, 5H), 2.30 (s, 3H), 2.74-2.80 (m, 2H), 3.06-3.14 (m, 1H), 3.27-3.35 (m, 1H), 3.82-3.96 (m, 5H), 4.52-4.59 (m, 1H), 5.92 (d,J=8.8 Hz, 1H), 6.93 (brs, 1H), 6.99-7.05 (m, 4H), 7.24 (d, J=8.0 Hz, 1H), 7.46-7.50 (m, 2H), 7.72 (d, J=1.2 Hz, 1H), 7.87 (brs, 1H).

The physical properties of the optically active substance with a retention time of 64 minutes (Example 928) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.61-1.72 (m, 1H), 1.77-2.12 (m, 5H), 2.30 (s, 3H), 2.74-2.80 (m, 2H), 3.06-3.14 (m, 1H), 3.27-3.35 (m, 1H), 3.82-3.96 (m, 5H), 4.52-4.59 (m, 1H), 5.92 (d, J=8.8 Hz, 1H), 6.93 (brs, 1H), 6.99-7.05 (m, 4H), 7.24 (d, J=8.0 Hz, 1H), 7.46-7.50 (m, 2H), 7.72 (d, J=1.2 Hz, 1H), 7.87 (brs, 1H).

[0828]

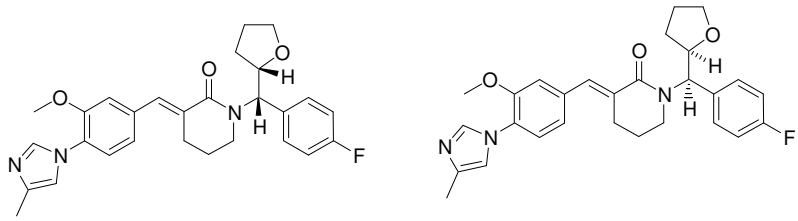
Example 929 and Example 930

Synthesis of (E)-1-{(R)-(4-fluorophenyl)-[(R)-

tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-{(S)-(4-fluorophenyl)-[(S)-tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0829]

[Formula 260]



Synthesis of erythro-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methanol

Diethyl azodicarboxylate (491 mg), threo-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methanol (368 mg), and benzoic acid (251 mg) were sequentially added to a solution of triphenylphosphine (736 mg) in THF (20 mL) at 0°C. The reaction solution was stirred at 0°C for 1 hour, and was further stirred at room temperature for 12 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane -> heptane:ethyl acetate = 3:1) to obtain 187 mg of (4-fluorophenyl)-(tetrahydrofuran-2-yl)methyl benzoate. A 1 N aqueous solution of sodium

hydroxide (3 mL) was added to a solution of the resulting (4-fluorophenyl)-(tetrahydrofuran-2-yl)methyl benzoate (187 mg) in methanol (5 mL), and the reaction solution was stirred at room temperature for 4 hours. Brine and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to obtain 120 mg of the title compound.

The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.54-1.90 (m, 4H), 3.77-3.85 (m, 1H), 3.89-3.96 (m, 1H), 4.02-4.08 (m, 1H), 4.90 (d, J=4.0 Hz, 1H), 6.99-7.05 (m, 2H), 7.31-7.36 (m, 2H).

[0830]

Synthesis of threo-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methylamine

81 mg of threo-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methylamine was obtained from erythro-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methanol (120 mg) in the same manner as in Example 927.

The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.49-1.69 (m, 2H), 1.80-1.90 (m, 2H), 3.79-3.92 (m, 4H), 6.97-7.03 (m, 2H), 7.30-7.36 (m, 2H).

[0831]

Synthesis of (E)-1-{(R)-(4-fluorophenyl)-[(R)-

tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-{(S)-(4-fluorophenyl)-[(S)-tetrahydrofuran-2-yl]methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

A racemate obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (205 mg) and threo-(4-fluorophenyl)-(tetrahydrofuran-2-yl)methylamine (81 mg) in the same manner as in Example 418 was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 1:1) to obtain the title optically active substance with a retention time of 18 minutes (653 mg; >99% ee) and the title optically active substance with a retention time of 27 minutes (59 mg; >99% ee).

The physical properties of the optically active substance with a retention time of 18 minutes (Example 929) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56-1.73 (m, 2H), 1.82-2.12 (m, 4H), 2.31 (s, 3H), 2.74-2.82 (m, 2H), 3.10-3.18 (m, 1H), 3.50-3.58 (m, 1H), 3.81-3.98 (m, 5H), 4.58 (q, J=7.6 Hz, 1H), 5.97 (d, J=7.6 Hz, 1H), 6.92 (s, 1H), 6.99-7.06 (m, 4H), 7.23 (d, J=8.8 Hz, 1H), 7.40-7.46 (m, 2H), 7.73 (s, 1H), 7.86 (brs, 1H).

The physical properties of the optically active substance with a retention time of 27 minutes

(Example 930) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56-1.73 (m, 2H), 1.82-2.12 (m, 4H), 2.31 (s, 3H), 2.74-2.82 (m, 2H), 3.10-3.18 (m, 1H), 3.50-3.58 (m, 1H), 3.81-3.98 (m, 5H), 4.58 (q, J=7.6 Hz, 1H), 5.97 (d, J=7.6 Hz, 1H), 6.92 (s, 1H), 6.99-7.06 (m, 4H), 7.23 (d, J=8.8 Hz, 1H), 7.40-7.46 (m, 2H), 7.73 (s, 1H), 7.86 (brs, 1H).

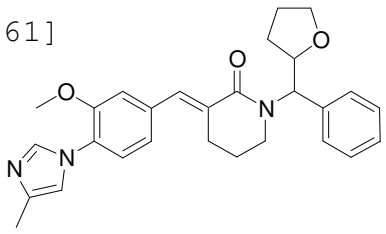
[0832]

Example 931

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[phenyl(tetrahydrofuran-2-yl)methyl]piperidin-2-one

[0833]

[Formula 261]



125 mg of the title compound was obtained in the same manner as in Example 418 from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (232 mg) and phenyl(tetrahydrofuran-2-yl)methylamine (92 mg) obtained in the same manner as in Example 927. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.58-2.14 (m, 6H), 2.30 (s, 3H), 2.73-2.80 (m, 2H), 3.07-3.21 (m, 1H), 3.27-3.35 (m, 0.3H), 3.50-3.58 (m, 0.7H), 3.82-3.97 (m, 5H), 4.58-

4.67 (m, 1H), 5.97 (d, J=8.8 Hz, 0.3H), 6.00 (d, J=8.0 Hz, 0.7H), 6.92 (s, 1H), 7.01-7.05 (m, 2H), 7.22-7.53 (m, 6H), 7.71 (s, 1H), 7.87 (brs, 1H).

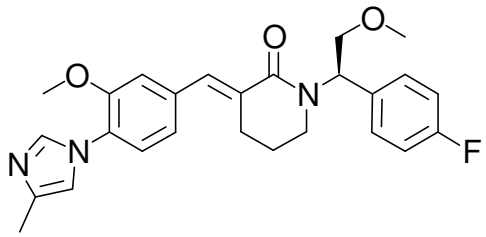
[0834]

Example 932

Synthesis of (E)-1-[(1R)-1-(4-fluorophenyl)-2-methoxyethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0835]

[Formula 262]



Sodium hydride (containing mineral oil at 40%, 24 mg) was added to a solution of (E)-1-(1-(4-fluorophenyl)-2-hydroxyethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one synthesized by the method described in Example 629 (216 mg) in THF (5 mL), and the reaction solution was stirred at room temperature for 50 minutes. Then, methyl iodide (85 mg) was added to the reaction solution, and the reaction solution was stirred at room temperature for 14 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The

residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane:ethyl acetate = 1:1 -> ethyl acetate) to obtain 185 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.64-1.76 (m, 1H), 1.81-1.92 (m, 1H), 2,31 (s, 3H), 2.73-2.85 (m, 2H), 3.07-3.15 (m, 1H), 3.34-3.42 (m, 1H), 3.45 (s, 3H), 3.85 (s, 3H), 3.86-4.01 (m, 2H), 6.17 (brt, J=6.4 Hz, 1H), 6.94 (brs, 1H), 7.00-7.09 (m, 4H), 7.25 (d, J=8.0 Hz, 1H), 7.31-7.39 (m, 2H), 7.73 (brs, 1H), 7.88 (brs, 1H).

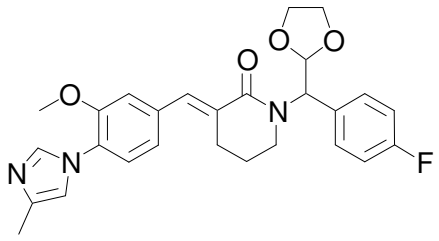
[0836]

Example 933

Synthesis of (E)-1-{(1,3]dioxolan-2-yl-(4-fluorophenyl)methyl}-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0837]

[Formula 263]



A solution of dimethyl sulfoxide (0.19 mL) in methylene chloride (1 mL) was added dropwise to a solution of oxalyl chloride (167 mg) in methylene chloride (2 mL) at -78°C. The reaction solution was stirred at -78°C for 5 minutes, and then a solution of (E)-1-(1-(4-fluorophenyl)-2-hydroxyethyl)-3-(3-methoxy-

4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one synthesized by the method described in Example 629 (260 mg) in methylene chloride (3 mL) was added dropwise to the reaction solution. The reaction solution was stirred at -78°C for 1 hour, and then triethylamine (0.42 mL) was added to the reaction solution. The reaction solution was stirred at -78°C for 15 minutes, and further stirred at room temperature for 45 minutes. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to obtain 250 mg of crude (E)-(4-fluorophenyl)-(3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxopiperidin-1-yl)acetaldehyde. p-Toluenesulfonic acid (107 mg) and ethylene glycol (0.29 mL) were added to a solution of the resulting crude (E)-(4-fluorophenyl)-(3-(3-methoxy-4-(4-methyl-1H)benzylidene)-2-oxopiperidin-1-yl)acetaldehyde (225 mg) in toluene (5 mL), and the reaction solution was heated to reflux for 1 hour and 20 minutes. After allowing the reaction solution to be cooled to room temperature, saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane:ethyl acetate = 1:1 -> ethyl acetate) to obtain 7 mg of the title compound. The physical properties of the compound are as follows.

ESI-MS; m/z478 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.63-1.75 (m, 1H), 1.82-1.93 (m, 1H), 2,33 (s, 3H), 2.77-2.84 (m, 2H), 3.16-3.24 (m, 1H), 3.47-3.55 (m, 1H), 3.86 (s, 3H), 3.92-4.10 (m, 4H), 5.52 (d, J=5.6 Hz, 1H), 6.07 (d, J=5.6 Hz, 1H), 6.94 (brs, 1H), 7.01-7.07 (m, 4H), 7.24 (d, J=8.0 Hz, 1H), 7.44-7.49 (m, 2H), 7.79 (brs, 1H), 7.89 (brs, 1H).

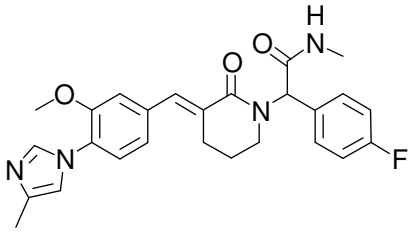
[0838]

Example 934

Synthesis of (E)-2-(4-fluorophenyl)-2-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-yl}-N-methylacetamide

[0839]

[Formula 264]



A 1 N aqueous solution of sodium hydroxide (0.8 mL) was added to a solution of a solution of methyl (E)-(4-fluorophenyl)-(3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxopiperidin-1-yl)acetate synthesized by the method described in Example 924 (74 mg) in methanol (3 mL), and the

reaction solution was stirred at room temperature for 13 hours. 2 N hydrochloric acid (0.4 mL) was added to the reaction solution, and the reaction solution was concentrated under reduced pressure to obtain 72 mg of crude (E)-(4-fluorophenyl)-(3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxopiperidin-1-yl)acetic acid. HOBT (16 mg) and EDC (23 mg) were added to a solution of the resulting crude (E)-(4-fluorophenyl)-(3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxopiperidin-1-yl)acetic acid (36 mg) and methylamine (2M THF solution, 0.4 mL) in DMF (3 mL), and the reaction solution was stirred at room temperature for 5 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: ethyl acetate -> ethyl acetate:methanol = 9:1) to obtain 32 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.96 (m, 2H), 2,31 (s, 3H), 2.68-2.78 (m,1H), 2.82-2.93 (m, 4H), 3.03-3.11 (m, 1H), 3.57-3.66 (m, 1H), 3.85 (s, 3H), 5.99 (brd, J=4.8 Hz, 1H), 6.35 (s, 1H), 6.93 (s, 1H), 6.99-7.09 (m, 4H), 7.25 (d, J=8.0 Hz, 1H), 7.37-7.45 (m, 2H), 7.74 (s, 1H), 7.83 (brs, 1H).

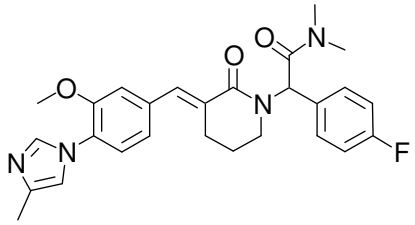
[0840]

Example 935

Synthesis of (E)-2-(4-fluorophenyl)-2-{3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-yl}-N,N-dimethylacetamide

[0841]

[Formula 265]



17 mg of the title compound was obtained from crude (E)-(4-fluorophenyl)-(3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-2-oxopiperidin-1-yl)acetic acid (36 mg) and dimethylamine (2M THF solution, 0.4 mL) in the same manner as in Example 934. The physical properties of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.66-1.76 (m, 1H), 1.89-1.99 (m, 1H), 2,31 (s, 3H), 2.67-2.75 (m, 1H), 2.81-2.91 (m, 2H), 2.95 (s, 3H), 3.04 (s, 3H), 3.63-3.70 (m, 1H), 3.85 (s, 3H), 6.79(s, 1H), 6.92(brs, 1H), 7.00-7.12 (m, 4H), 7.26 (d, J=8.0 Hz,1H), 7.28-7.32 (m, 2H), 7.72 (s, 1H), 7.82 (brs, 1H).

[0842]

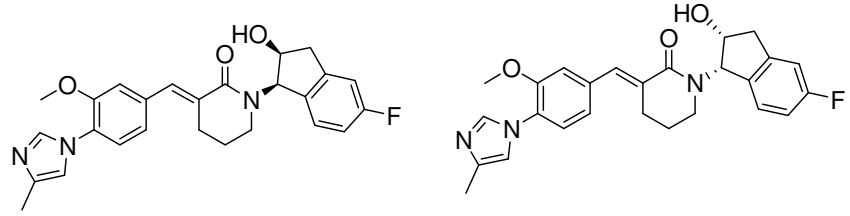
Example 936 and Example 937

Synthesis of (E)-1-[5-fluoro-(2R)-hydroxyindan-(1S)-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-[5-fluoro-

(2S)-hydroxyindan-(1R)-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0843]

[Formula 266]



Synthesis of 2-bromo-5-fluoroindan-1-one

Bromine (1.98 mL) was added to a solution of 5-fluoroindanone (5.53 g) in acetic acid (100 mL), and the reaction solution was stirred at 60°C for 10 minutes. After allowing the reaction solution to be cooled to room temperature, the solvent was evaporated under reduced pressure. Ethyl acetate and a saturated aqueous solution of sodium bicarbonate were added to the residue and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: heptane–ethyl acetate system) to obtain 8.43 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.41 (dd, J=18.6, 2.8 Hz, 1H), 3.83 (dd, J=18.6, 7.6 Hz, 1H), 4.66 (dd, J=7.6, 2.8 Hz, 1H), 7.10–7.16 (m, 2H), 7.85 (dd, J=8.4, 5.2 Hz, 1H).

[0844]

Synthesis of cis-2-bromo-5-fluoroindan-1-ol

Sodium borohydride (2.09 g) was added to a solution of 2-bromo-5-fluoroindan-1-one (8.43 g) in a mixture of tetrahydrofuran (120 mL) with methanol (30 mL) while cooling with ice, and the reaction solution was stirred for 20 minutes. Water and ethyl acetate were added to the reaction solution while cooling with ice and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The resulting solid was washed with heptane to obtain 7.54 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.42 (d, J=9.2 Hz,1H), 3.32-3.44 (m, 2H), 4.88-4.95 (m, 2H), 6.93-7.00 (m, 2H), 7.38 (dd, J=8.0, 5.2Hz, 1H).

[0845]

Synthesis of 2-bromo-5-fluoroindan-1-yl trans-4-nitrobenzoate

Diisopropyl azodicarboxylate (13.3 mL) was added dropwise to a solution of cis-2-bromo-5-fluoroindan-1-ol (7.74 g), 4-nitrobenzoic acid (10.9 g) and triphenylphosphine (17.1 g) in THF (250 mL), and the reaction solution was stirred at room temperature for 3 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by

silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 7.19 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.34 (dd, J=17.2, 3.6 Hz, 1H), 3.82 (dd, J=17.2, 6.8 Hz, 1H), 4.67-4.70 (m, 1H), 6.51 (d, J=3.2 Hz, 1H), 6.70-7.03 (m, 2H), 7.46 (dd, J=8.0, 4.8 Hz, 1H), 8.17 (d, J=9.2 Hz, 2H), 8.26 (d, J=9.2 Hz, 2H).

[0846]

Synthesis of 4-fluoro-6,6a-dihydro-1aH-oxacycloprop[a]indene

Sodium methoxide (25 wt% methanol solution, 3.52 mL) was added to a solution of (2-bromo-5-fluoro-indan-1-yl)trans-4-nitrobenzoate (4.18 g) in dichloromethane (120 mL), and the reaction solution was stirred for 5 minutes while cooling with ice. Water and dichloromethane were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 2.07 g of a crude purified product containing the title compound at Ca 30%. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.99 (dd, J=18.0 Hz, 2.4 Hz, 1H), 3.20 (d, J=18.0 Hz, 1H), 4.14 (dd, J=2.4, 2.4 Hz,

1H), 4.23 (d, J=2.4Hz, 1H), 6.83-6.93 (m, 2H), 7.42 (dd, J=8.0, 5.2Hz, 1H).

[0847]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]valeric acid (5-fluoro-2-hydroxyindan-1-yl)amide

Concentrated sulfuric acid (0.7 mL) was added to a solution of 4-fluoro-6,6a-dihydro-1aH-oxa-cycloprop[a]indene (purity: about 30 wt%, 2.07 g) in acetonitrile (30 mL), and the reaction solution was stirred at room temperature for 1 hour. Then, concentrated sulfuric acid (1 mL) and water (10 mL) were added to the reaction solution, and the reaction solution was heated to reflux for 4 hours. The reaction solution was returned to room temperature, made basic by the addition of 5 N sodium hydroxide, and then extracted with chloroform. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (1.86 g), IPEA (2 mL), EDC (2.38 g) and HOBT (1.68 g) were added to a solution of the resulting residue in DMF (20 mL), and the reaction solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated

under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 916 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.05 (m, 2H), 2.28 (d, J=1.2 Hz, 3H), 2.76 (m, 2H), 3.01 (dd, J=16.8 Hz, 2.0 Hz, 1H), 3.24 (dd, J=16.8 Hz, 5.2 Hz, 1H), 3.60 (t, J=6.0 Hz, 2H), 3.84 (s, 3H), 4.78 (td, J=5.2 Hz, J=2.0 Hz,1H), 5.48 (m, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.92–6.98 (m, 4H), 7.17 (d, J=8.0 Hz, 1H), 7.20 (s, 1H), 7.27 (dd, J=8.0 Hz, 4.8 Hz, 1H), 7.70 (d, J=1.2 Hz, 1H).

[0848]

Synthesis of (E)-1-[5-fluoro-(2R)-hydroxyindan-(1S)-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-[5-fluoro-(2S)-hydroxyindan-(1R)-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

Sodium hydride (containing mineral oil at 40%, 136 mg) was added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (5-fluoro-2-hydroxyindan-1-yl)amide (915 mg) in DMF (10 mL), and the reaction solution was stirred at room temperature for 20 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried

over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 535 mg of the title compound as a racemate. The compound (16 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 1:1) to obtain the title optically active substance with a retention time of 40 minutes (5.0 mg; >99% ee) and the title optically active substance with a retention time of 48 minutes (4.1 mg; >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.77–1.88 (m, 2H), 2.31 (d, J=1.2 Hz, 3H), 2.75–2.88 (m, 2H), 2.91–2.97 (m, 1H), 3.10–3.13 (m, 2H), 3.27 (dd, J=16.8, 7.6 Hz, 1H), 3.86 (s, 3H), 4.90 (dd, J=7.6, 7.3 Hz, 1H), 5.91 (d, J=7.2 Hz, 1H), 6.92–6.98 (m, 3H), 7.03 (s, 1H), 7.03–7.06 (m, 1H), 7.19 (dd, J=8.0, 5.2 Hz, 1H), 7.24–7.26 (m, 1H), 7.75 (d, J=1.2 Hz, 1H), 7.84 (s, 1H).

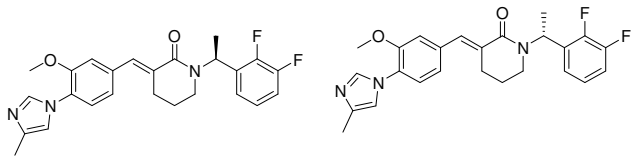
[0849]

Example 938 and Example 939

Synthesis of (E)-1-[(1S) and (1R)-(2,3-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0850]

[Formula 267]



Synthesis of 1-(2,3-difluorophenyl)ethylamine

Triethylamine (2.66 mL) and hydroxylamine hydrochloride (712 mg) were added to a solution of 2,3-difluoroacetophenone (1 g) in ethanol (35 mL), and the reaction solution was heated to reflux for 3 hours. The reaction solution was returned to room temperature, and the solvent was evaporated under reduced pressure. Zinc (2.29 g) was added to a solution of the resulting residue in trifluoroacetic acid (30 mL), and the reaction solution was stirred at room temperature for 2 hours. The reaction solution was made basic with a 5 N aqueous solution of sodium hydroxide, and then extracted with chloroform. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 1.4 g of a crude purified product containing the title compound (purity: 72 wt%). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.40 (d, J=6.8 Hz, 3H), 4.43 (q, J=6.8 Hz, 1H), 7.01-7.07 (m, 2H), 7.15-7.19 (m, 1H).

[0851]

Synthesis of (E)-1-[(1R) and (1S)-(2,3-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

1-(2,3-difluorophenyl)ethylamine (purity: 72 wt%, 195 mg), IPEA (1 mL), EDC (257 mg) and HOBT (181 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (200 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2,3-difluorophenyl)ethyl)amide. Sodium hydride (containing mineral oil at 40%, 30 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2,3-difluorophenyl)ethyl)amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 5 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier:

Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 95 mg of the title compound as a racemate. The compound (18 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 5:5) to obtain the title optically active substance with a retention time of 28 minutes (7.5 mg; >99% ee) and the title optically active substance with a retention time of 37 minutes (7.5 mg; >90% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.61 (d, J=7.2 Hz, 3H), 1.79–1.86 (m, 2H), 2.33 (s, 3H), 2.75–2.80 (m, 2H), 3.03–3.10 (m, 1H), 3.30–3.36 (m, 1H), 3.85 (s, 3H), 6.19 (q, J=7.2 Hz, 1H), 6.93 (t, J=1.2 Hz, 1H), 7.01 (s, 1H), 7.01–7.04 (m, 1H), 7.07–7.15 (m, 3H), 7.24–7.25 (m, 1H), 7.82 (s, 1H), 7.85 (s, 1H).

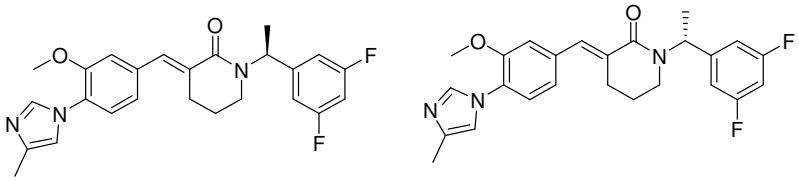
[0852]

Example 940 and Example 941

Synthesis of (E)-1-[(1S) and (1R)-(3,5-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0853]

[Formula 268]



Synthesis of 1-(3,5-difluorophenyl)ethylamine

A crude purified product containing the title compound (purity: 83 wt%, 738 mg) was obtained from 3,5-difluoroacetophenone (611 mg) in the same manner as in Example 938. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.48 (d, J=6.8 Hz, 3H), 4.19 (q, J=6.8 Hz, 1H), 6.72 (tt, J=8.4, 2.4 Hz, 1H), 6.90 (dd, J=8.4 Hz, 2.4 Hz, 2H).

[0854]

Synthesis of (E)-1-[(1S) and (1R)-(3,5-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

1-(2,3-difluorophenyl)ethylamine (purity: 83 wt%, 253 mg), IPEA (1 mL), EDC (320 mg) and HOBT (226 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (250 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzylidene)valeric acid (1-(3,5-difluorophenyl)ethyl)amide. Sodium hydride (containing mineral oil at 40%, 40 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(3,5-difluorophenyl)ethyl)amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 5 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system), and the resulting oil was solidified with diethyl ether to obtain 80 mg of the title compound as a racemate. The compound (20 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 23 minutes (8.7 mg; >99% ee) and the title optically active substance with a retention time of 25 minutes (7.0 mg; >90% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (d, J=7.2 Hz, 3H) 1.70-1.79 (m, 1H), 1.82-1.89 (m, 1H), 2.32 (d, J=1.2 Hz, 3H), 2.71-2.79 (m, 1H), 2.84-2.90 (m, 1H), 2.95-3.00 (m,

1H), 3.25-3.31 (m, 1H), 3.86 (s, 3H), 6.18 (q, J=7.2 Hz, 1H), 6.72 (tt, J=8.8, 2.0 Hz, 1H), 6.83-6.89 (m, 2H), 6.93 (t, J=1.2 Hz, 1H), 7.03 (s, 1H), 7.03-7.06 (m, 1H), 7.23-7.27 (m, 1H), 7.77 (d, J=1.2 Hz, 1H), 7.88 (s, 1H).

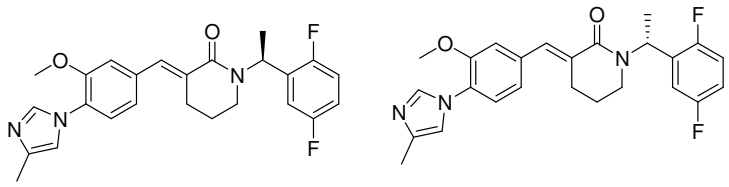
[0855]

Example 942 and Example 943

Synthesis of (E)-1-[(1S) and (1R)-(2,5-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0856]

[Formula 269]



Synthesis of 1-(2,5-difluorophenyl)ethylamine

884 mg of the title compound was obtained from 2,5-difluoroacetophenone (1 g) in the same manner as in Example 938. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.42 (d, J=6.4 Hz, 3H), 4.40 (q, J=6.4 Hz, 1H), 6.85-6.91 (m, 1H), 6.94-6.99 (m, 1H), 7.12-7.16 (m, 1H).

[0857]

Synthesis of (E)-1-[(1S) and (1R)-(2,5-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-

imidazol-1-yl)benzylidene]piperidin-2-one

IPEA (1 mL), EDC (320 mg) and HOBT (226 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (250 mg) and 1-(2,5-difluorophenyl)ethylamine (175 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2,5-difluorophenyl)ethyl)amide. Sodium hydride (containing mineral oil at 40%, 30 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2,5-difluorophenyl)ethyl)amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 5 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was

purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 140 mg of the title compound as a racemate. The compound (15 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 3:7) to obtain the title optically active substance with a retention time of 25 minutes (6.2 mg; >99% ee) and the title optically active substance with a retention time of 39 minutes (5.8 mg; >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.57 (d, J=7.2 Hz, 3H), 1.79–1.86 (m, 2H), 2.30 (d, J=1.2 Hz, 3H), 2.75–2.81 (m, 2H), 3.02–3.09 (m, 1H), 3.28–3.35 (m,1H), 3.85 (s, 3H), 6.15 (q, J=7.2Hz, 1H), 6.92–7.09 (m, 6H), 7.22–7.25 (m, 1H), 7.73 (d, J=1.2 Hz, 1H), 7.85 (s, 1H).

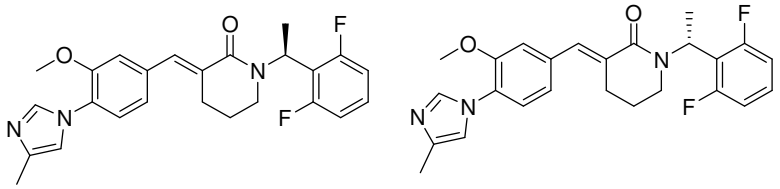
[0858]

Example 944 and Example 945

Synthesis of (E)-1-[(1S) and (1R)-(2,6-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0859]

[formula 270]



Synthesis of 1-(2,6-difluorophenyl)ethylamine

Triethylamine (2.37 mL) and hydroxylamine hydrochloride (634 mg) were added to a solution of 2,6-difluoroacetophenone (890 mg) in ethanol (30 mL), and the reaction solution was heated to reflux for 4 hours. The reaction solution was returned to room temperature, and the solvent was evaporated under reduced pressure. Zinc (1.86 g) was added to a solution of the resulting residue in trifluoroacetic acid (10 mL), and the reaction solution was stirred at room temperature overnight. The reaction solution was filtered on a celite, made basic with a 5 N aqueous solution of sodium hydroxide, and then extracted with chloroform. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 210 mg of a crude purified product containing the title compound (purity: 50 wt%). The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.57 (d, J=6.8 Hz, 3H), 4.57 (q, J=6.8z, 1H), 6.72-6.77 (m, 1H), 7.07-7.31 (m, 2H).

[0860]

Synthesis of (E)-1-[(1S) and (1R)-(2,6-difluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

IPEA (1 mL), EDC (257 mg) and HOBT (181 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (200 mg) and 1-(2,6-

difluorophenyl)ethylamine (purity: 50 wt%, 210 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2,6-difluorophenyl)ethyl)amide. Sodium hydride (containing mineral oil at 40%, 30 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2,6-difluorophenyl)ethyl)amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 5 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 105 mg of the title compound as a racemate. The compound (15 mg) was fractionated using CHIRALPAK™ AD-H

manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 1:1) to obtain the title optically active substance with a retention time of 29 minutes (6.9 mg; >99% ee) and the title optically active substance with a retention time of 34 minutes (6.2 mg; >93% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.65 (dt, J=7.2, 1.6 Hz, 3H), 1.83-1.90 (m, 2H), 2.33 (s, 3H), 2.72-2.82 (m, 2H), 3.33-3.39 (m, 1H), 3.51-3.57 (m, 1H), 3.84 (s, 3H), 6.24 (q, J=7.2Hz, 1H), 6.87-6.94 (m, 3H), 7.01 (s, 1H), 7.01-7.04 (m, 1H), 7.19-7.27 (m, 2H), 7.81 (s, 1H), 7.83 (s, 1H).

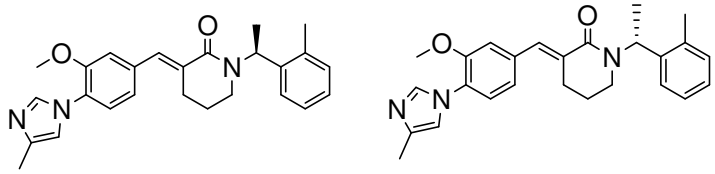
[0861]

Example 946 and Example 947

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1S) and (1R)-o-tolylethyl]piperidin-2-one

[0862]

[Formula 271]



Synthesis of 1-o-tolyl-ethanol

Sodium borohydride (564 mg) was added to a solution of 2-methylacetophenone (1 g) in a mixture of THF (8 mL) with methanol (32 mL), and the reaction

solution was stirred at room temperature for 20 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (heptane-ethyl acetate system) to obtain 911 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.47 (d, J=6.4 Hz, 3H), 1.68 (brs, 1H), 2.35 (s, 3H), 5.14 (q, J=6.4 Hz, 1H) 7.14 (t, J=6.8 Hz, 1H), 7.18(t, J=6.8 Hz, 1H), 7.23 (d, J=6.8 Hz, 1H), 7.52 (d, J=6.8 Hz, 1H).

[0863]

Synthesis of 1-(1-azidoethyl)-2-methylbenzene

Triethylamine (2.78 mL) and methanesulfonyl chloride (777 μL) were added to a solution of 1-o-tolylethanol (911 mg) in dichloromethane (30 mL), and the reaction solution was stirred at room temperature for 5 hours. Water and dichloromethane were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Sodium azide (0.87 g) was added to a solution of the residue in DMF (20 mL), and the reaction solution was stirred at room temperature overnight. Water and ethyl acetate were added to the reaction solution and the organic layer was

partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (heptane–ethyl acetate system) to obtain 744 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (d, J=6.8 Hz, 3H), 2.37 (s, 3H), 4.83 (q, J=6.8 Hz, 1H), 7.15–7.25 (m, 3H), 7.35–7.38 (m, 1H).

[0864]

Synthesis of 1-o-tolylethylamine

10% palladium–carbon (water content: 50%, 50 mg) was added to a solution of 1-(1-azidoethyl)-2-methylbenzene (744 mg) in methanol (5 mL), and the reaction solution was stirred in a hydrogen atmosphere at room temperature for 1 hour. The reaction solution was filtered on a celite, and the filtrate was concentrated under reduced pressure to obtain 482 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.35 (d, J=6.8 Hz, 3H), 2.36 (s, 3H), 4.36 (q, J=6.8 Hz, 1H), 7.11–7.13 (m, 2H), 7.19–7.23 (m, 1H), 7.45 (d, J=7.6 Hz, 1H).

[0865]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-((1S) and (1R)-o-tolylethyl)piperidin-2-one

IPEA (0.5 mL), EDC (128 mg) and HOBT (90.4

mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (100 mg) and 1-o-tolylethylamine (60 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-o-tolylethyl)amide. Sodium hydride (containing mineral oil at 40%, 50 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-o-tolylethyl)amide in DMF (4 mL), and the reaction solution was stirred at room temperature for 10 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-

methanol system) to obtain 60 mg of the title compound as a racemate. The compound (10 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 7:3) to obtain the title optically active substance with a retention time of 39 minutes (4.4 mg; >99% ee) and the title optically active substance with a retention time of 48 minutes (4.4 mg; >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.57 (d, J=6.8 Hz, 3H), 1.66-1.75 (m, 2H), 2.78 (s, 3H), 2.32 (s, 3H), 2.61-2.71 (m, 2H), 2.79-2.86 (m, 1H), 3.08-3.15 (m, 1H), 3.85 (s, 3H), 6.15 (q, J=6.8 Hz, 1H), 6.93 (s, 1H), 7.03 (s, 1H), 7.03-7.04 (m, 1H), 7.17-7.24 (m, 4H), 7.35-7.38 (m, 1H), 7.76 (s, 1H), 7.87 (s, 1H).

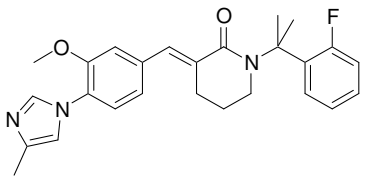
[0866]

Example 948

Synthesis of 1-[1-(2-fluorophenyl)-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0867]

[Formula 272]



Synthesis of methyl (2-fluorophenyl)acetate

Trimethylsilyl chloride (4.12 mL) was added to a solution of 2-fluorophenylacetic acid (2 g) in methanol (40 mL) in a nitrogen atmosphere, and the reaction solution was stirred at room temperature for 2 days. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system) to obtain 1.978 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.68 (s, 2H), 3.72 (s, 3H), 7.04-7.13 (m, 2H), 7.24-7.29 (m, 2H).

[0868]

Synthesis of methyl 2-(2-fluorophenyl)-2-methylpropionate

A solution of methyl (2-fluorophenyl)acetate (1.98 g) in THF (30 mL) was added dropwise to a suspension of sodium hydride (containing mineral oil at 40%, 1.7 g) in THF (70 mL) in a nitrogen atmosphere. Then, methyl iodide (1.76 mL) was added to the reaction solution, and the reaction solution was stirred at room temperature overnight. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: heptane-

ethyl acetate system) to obtain 1.36 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.57 (s, 6H), 3.67 (s, 3H), 7.00 (ddd, J=11.6, 8.0, 1.2 Hz, 1H), 7.12 (td, J=7.6, 1.2Hz, 1H), 7.21-7.26 (m, 1H), 7.31 (td, J=7.6, 1.6 Hz, 1H).

[0869]

Synthesis of 2-(2-fluorophenyl)-2-methylpropionic acid

A 5 N aqueous solution of sodium hydroxide (10 mL) was added to a solution of methyl 2-(2-fluorophenyl)-2-methylpropionate (1.357 g) in methanol (10 mL), and the reaction solution was stirred at 80°C for 3 hours. The reaction solution was returned to room temperature, made acidic with 5 N hydrochloric acid, and then extracted with ethyl acetate. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 1.15 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.61 (s, 6H), 7.03 (dd, J=11.2, 8.4 Hz, 1H), 7.13 (t, J=7.6 Hz, 1H), 7.22-7.28 (m, 1H), 7.33 (td, J=7.6, 1.6 Hz, 1H).

[0870]

Synthesis of 1-(2-fluorophenyl)-1-methylethylamine

t-Butyl alcohol (30 mL), diphenylphosphoryl azide (1.63 mL) and triethylamine (1.05 mL) were added to a solution of 2-(2-fluorophenyl)-2-methylpropionic acid (1.15 g) in toluene (60 mL), and the reaction

solution was heated to reflux overnight. The reaction solution was returned to room temperature, and water and ethyl acetate were added thereto and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. 10 mL of 5 N hydrochloric acid was added to a solution of the residue in THF (5 mL), and the reaction solution was heated to reflux for 3 hours. The reaction solution was returned to room temperature, made basic with 5 N sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 735 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (s, 6H). 6.99-7.07 (m, 1H), 7.10 (dd, J=7.6, 1.2 Hz, 1H), 7.18-7.24 (m, 1H), 7.41-7.45 (m, 1H).

[0871]

Synthesis of 1-[1-(2-fluorophenyl)-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

IPEA (0.5 mL), EDC (192 mg) and HOBT (135 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and 1-(2-fluorophenyl)-1-methylethylamine (102 mg) in DMF (5 mL), and the

reaction solution was stirred at room temperature for 3 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2-fluorophenyl)-1-methylethyl)amide. Sodium hydride (containing mineral oil at 40%, 40 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2-fluorophenyl)-1-methylethyl)amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 20 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 70 mg of the title compound. The physical properties of the compound are as follows.

ESI-MS; m/z434 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.79 (s,

6H), 1.90–1.97 (m, 2H), 2.29 (d, J=1.2 Hz, 3H), 2.73–2.77 (m, 2H), 3.64–3.67 (m, 2H), 3.80 (s, 3H), 6.89–6.99 (m, 4H), 7.10–7.21 (m, 3H), 7.40–7.45 (m, 1H), 7.58 (s, 1H), 7.69 (d, J=1.2 Hz, 1H).

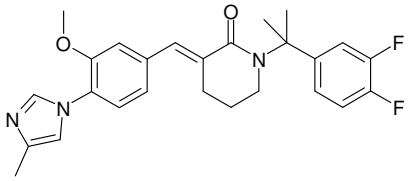
[0872]

Example 949

Synthesis of 1-[1-(3,4-difluorophenyl)-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0873]

[Formula 273]



Synthesis of 1-(3,4-difluorophenyl)-1-methylethylamine

928 mg of the title compound was obtained from 3,4-difluorophenylacetic acid (2 g) in the same manner as in Example 948. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.47 (s, 6H), 7.04-7.11 (m, 1H), 7.17-7.21 (m, 1H), 7.30-7.35 (m, 1H).

[0874]

Synthesis of 1-[1-(3,4-difluorophenyl)-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

IPEA (0.5 mL), EDC (192 mg) and HOBT (135 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and 1-(3,4-difluorophenyl)-1-methylethylamine (114 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 3 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate

system -> ethyl acetate–methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(3,4-difluorophenyl)-1-methylethyl)amide. Sodium hydride (containing mineral oil at 40%, 40 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(3,4-fluorophenyl)-1-methylethyl)-amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 20 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 85 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.71 (s, 6H), 1.95–2.01 (m, 2H), 2.30 (d, J=1.2 Hz, 3H), 2.78–2.82 (m, 2H), 3.62–3.65 (m, 2H), 3.82 (s, 3H), 6.92 (t, J=1.2 Hz, 1H), 6.97–7.13 (m, 5H), 7.22–7.24 (m, 1H), 7.61 (s, 1H), 7.71 (d, J=1.2 Hz, 1H).

[0875]

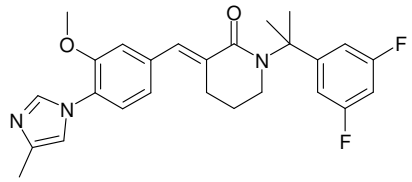
Example 950

Synthesis of 1-[1-(3,5-difluorophenyl)-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-

yl)benzylidene]piperidin-2-one

[0876]

[Formula 274]



Synthesis of 1-(3,5-difluorophenyl)-1-methylethylamine

780 mg of the title compound was obtained from 3,5-difluorophenylacetic acid (1.56 g) in the same manner as in Example 948. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.47 (s, 6H), 6.65 (tt, J=8.8, 2.4 Hz, 1H), 7.00-7.05 (m, 2H).

[0877]

Synthesis of 1-[1-(3,5-difluorophenyl)-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

IPEA (0.5 mL), EDC (192 mg) and HOBT (135 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and 1-(3,4-difluorophenyl)-1-methylethylamine (114 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 3 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was

purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(3,5-difluorophenyl)-1-methylethyl)amide. Sodium hydride (containing mineral oil at 40%, 40 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(3,5-fluorophenyl)-1-methylethyl)amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 20 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 84 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.69 (s, 6H), 1.96–2.04 (m, 2H), 2.31 (d, J=1.2 Hz, 3H), 2.78–2.82 (m, 2H), 3.63–3.65 (m, 2H), 3.82 (s, 3H), 6.61 (tt, J=8.8, 2.4 Hz, 1H), 6.78–6.83 (m, 2H), 6.92 (t, J=1.2 Hz, 1H), 6.96 (d, J=1.2 Hz, 1H), 6.99 (dd, J=8.0,1.2 Hz, 1H), 7.22 (d, J=8.0 Hz, 1H), 7.60 (s, 1H), 7.74 (d, J=1.2 Hz, 1H).

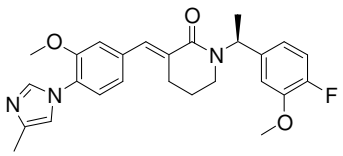
[0878]

Example 951

Synthesis of (E)-1-[(1S)-(4-fluoro-3-methoxyphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0879]

[Formula 275]



Synthesis of 1-(4-fluoro-3-methoxyphenyl)ethanol

Methyl magnesium chloride (3 M tetrahydrofuran solution, 7.8 mL) was added to a solution of 4-fluoro-3-methoxybenzaldehyde (3 g) in THF (200 mL) while cooling with ice, and the reaction solution was stirred for 2 hours while cooling with ice. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system) to obtain 2.65 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.48 (d, J=6.4 Hz, 3H), 1.82 (brs, 1H), 3.90 (s, 3H), 4.86 (q, J=6.4 Hz, 1H), 6.83-

6.87 (m, 1H), 6.99–7.04 (m, 2H).

[0880]

Synthesis of 4-fluoro-3-methoxyacetophenone

A solution of dimethyl sulfoxide (1.33 mL) in dichloromethane (5 mL) was added dropwise to a solution of oxalyl chloride (1.63 mL) in dichloromethane (80 mL) in a nitrogen atmosphere at −78°C. After stirring the reaction solution at −78°C for 3 minutes, a solution of 1-(4-fluoro-3-methoxyphenyl)ethanol (2.6 g) in dichloromethane (15 mL) was added dropwises to the reaction solution. Further, the reaction solution was stirred at −78°C for 20 minutes, and triethylamine (10.8 mL) was added dropwise to the reaction solution. Then, the reaction solution was stirred at −78°C for 10 minutes, and further stirred at room temperature for 30 minutes. Water and dichloromethane were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane–ethyl acetate system) to obtain 2.54 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.59 (s, 3H), 3.94 (s, 3H), 7.13 (dd, J=10.8, 8.4 Hz, 1H), 7.49–7.53 (m, 1H), 7.60 (dd, J=8.4, 2.0 Hz, 1H).

[0881]

Synthesis of (1R)-(4-fluoro-3-methoxyphenyl)ethanol

A solution of 4-fluoro-3-methoxyacetophenone (1 g) in THF (10 mL) was added dropwise to a solution of (+)-DIPCl™ (2.29 g) in THF (30 mL) in a nitrogen atmosphere at -20°C, and the reaction solution was stirred at -20°C for 5 hours. The reaction solution was heated to room temperature, and the solvent was evaporated under reduced pressure. The residue was diluted with an ether, diethanolamine (1.25 mL) was added to the diluent, and the reaction solution was stirred at room temperature overnight. The reaction solution was filtered on a celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system) to obtain 918 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.48 (d, J=6.4 Hz, 3H), 1.82 (brs, 1H), 3.90 (s, 3H), 4.86 (q, J=6.4 Hz, 1H), 6.83-6.87 (m, 1H), 6.99-7.04 (m, 2H).

[0882]

Synthesis of 4-[(1S)-azidoethyl]-1-fluoro-2-methoxybenzene

1,8-diazabicyclo[5.4.0]undec-7-ene (1 mL) was added dropwise to a solution of (1R)-(4-fluoro-3-methoxyphenyl)ethanol (910 mg) and diphenylphosphoryl azide (1.44 mL) in toluene (12.5 mL) in a nitrogen atmosphere while cooling with ice. The reaction

solution was stirred at that temperature for 2 hours, and further stirred at room temperature overnight. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system) to obtain 789 mg of the title compound.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52 (d, J=6.8 Hz, 3H), 3.92 (s, 3H), 4.59 (q, J=6.8 Hz, 1H), 6.82-6.86 (m, 1H), 6.93 (dd, J=8.0, 2.4 Hz, 1H), 7.60 (dd, J=11.2, 8.0Hz, 1H).

[0883]

Synthesis of (1S)-(4-fluoro-3-methoxyphenyl)ethylamine

10% palladium-carbon (water content: 50%, 80 mg) was added to a solution of 4-((1S)-azido-ethyl)-1-fluoro-2-methoxybenzene (789 mg) in methanol (8 mL), and the reaction solution was stirred in a hydrogen atmosphere at room temperature for 1 hour. The reaction solution was filtered on a celite, and the filtrate was concentrated under reduced pressure to obtain 352 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.37 (d, J=6.4 Hz, 3H), 3.91 (s, 3H), 4.11 (q, J=6.4 Hz, 1H), 6.83-6.87 (m, 1H), 6.99-7.04 (m, 2H).

[0884]

Synthesis of 1-[(1S)-(4-fluoro-3-methoxyphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

IPEA (0.5 mL), EDC (192 mg) and HOBT (135 mg) were added to a solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and (1S)-(4-fluoro-3-methoxy phenyl)ethylamine (114 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ((1S)-(4-fluoro-3-methoxyphenyl)ethyl)amide. Sodium hydride (containing mineral oil at 40%, 40 mg) was added to a solution of the resulting 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ((1S)-(4-fluoro-3-methoxyphenyl)ethyl)amide in DMF (5 mL), and the reaction solution was stirred at room temperature for 20 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried

over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 60 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.54 (d, J=6.8 Hz, 3H), 1.60–1.73 (m, 1H), 1.80–1.86 (m, 1H), 2.32 (s, 3H), 2.75–2.84 (m, 2H), 2.92–2.98 (m, 1H), 3.21–3.27 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 6.20 (q, J=6.8 Hz, 1H), 6.85–6.89 (m, 1H), 6.19–6.95 (m, 2H), 7.01–7.06 (m, 3H), 7.24–7.27 (m, 1H), 7.78 (s, 1H), 7.88 (s, 1H).

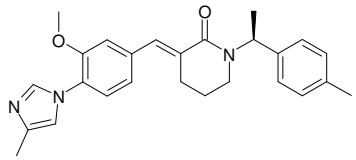
[0885]

Example 952

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-((1S)-p-tolylethyl)piperidin-2-one

[0886]

[Formula 276]



80 mg of the title compound was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (100 mg) and (1S)-(p-tolyl)ethylamine (60 mg) in the same manner as in Example 418. The physical properties of the

compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (d, J=6.8 Hz, 3H), 1.66-1.73 (m, 1H), 1.75-1.83 (m, 1H), 2.30 (d, J=0.8 Hz, 3H), 2.34 (s, 3H), 2.71-2.83 (m, 2H), 2.92-2.97 (m, 1H), 3.19-3.25 (m, 1H), 3.85 (s, 3H), 6.21 (q, J=6.8 Hz, 1H), 6.93 (t, J=1.2 Hz, 1H), 7.03 (s, 1H), 7.04 (dd, J=6.4, 1.2 Hz, 1H) 7.14 (d, J=8.0 Hz, 2H), 7.21-7.7.24 (m, 3H), 7.73 (d, J=0.8 Hz, 1H), 7.88 (s, 1H).

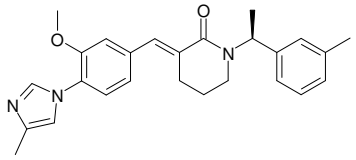
[0887]

Examples 953 and 954

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1S) and (1R)-m-tolylethyl]piperidin-2-one

[0888]

[Formula 277]



67 mg of the title compound as a racemate was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and 1-(m-tolyl)ethylamine (90.3 mg) in the same manner as in Example 418. The compound (16 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 7:3) to obtain the title optically active substance with a retention time of 108

minutes (2.8 mg; >99% ee) and the title optically active substance with a retention time of 112 minutes (1.8 mg; >83% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (d, J=6.8 Hz, 3H), 1.57-1.74 (m, 1H), 1.76-1.84 (m, 1H), 2.31 (s, 3H), 2.36 (s, 3H), 2.75-2.82 (m, 2H), 2.93-2.99(m,1H),3.21-3.27(m,1H),3.86(s,3H),6.22 (q, J=6.8 Hz, 1H), 6.94 (s, 1H), 7.05 (s, 1H), 7.05-7.10 (m, 2H), 7.14-7.16 (m, 2H), 7.22-7.27 (m, 2H), 7.76 (s, 1H), 7.90 (s, 1H).

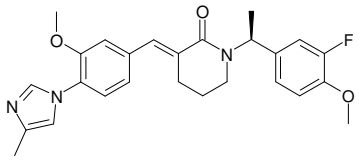
[0889]

Example 955

Synthesis of (E)-1-[(1S)-(3-fluoro-4-methoxyphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0890]

[Formula 278]



67 mg of the title compound was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 m) and (1S)-(3-fluoro-4-methoxyphenyl)ethylamine (114 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.53 (d, J=7.2 Hz, 3H), 1.57-

1.84 (m, 2H), 2.31 (d, J=1.2 Hz, 3H), 2.71-2.85 (m, 2H), 2.92-2.98 (m, 1H), 3.19-3.26 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 6.17 (q, J=7.2 Hz, 1H), 6.91-6.94 (m, 2H), 7.03-7.08 (m, 3H), 7.23-7.27 (m, 2H), 7.74 (d, J=1.2 Hz, 1H), 7.88 (s, 1H).

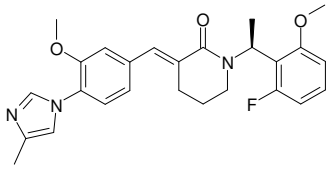
[0891]

Example 956

Synthesis of (E)-1-[(1S)-(2-fluoro-6-methoxyphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0892]

[Formula 279]



70 mg of the title compound was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and (1S)-(2-fluoro-6-methoxyphenyl)ethylamine (114 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (dd, J=7.2, 2.4 Hz, 3H), 1.81-1.88 (m, 2H), 2.31 (d, J=0.8 Hz, 3H), 2.69-2.83 (m, 2H), 3.32-3.38 (m, 1H), 3.47-3.54 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 6.23 (q, J=7.2 Hz, 1H), 6.68 (t, J=8.0 Hz, 2H), 6.93 (t, J=1.2 Hz, 1H), 7.01-7.03 (m, 2H), 7.17-7.24 (m, 2H), 7.73 (d, J=0.8 Hz, 1H), 7.82(s, 1H).

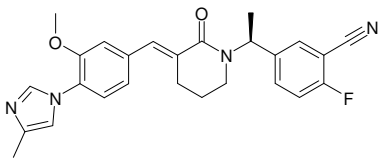
[0893]

Example 957

(E)-2-fluoro-5-[(1S)-{3-[methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-2-oxopiperidin-1-yl}ethyl)benzonitrile

[0894]

[Formula 280]



38 mg of the title compound was obtained from (E)-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (250 mg) and 5-((1S)-aminoethyl)-2-fluorobenzonitrile (220 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.59 (d, J=6.8 Hz, 3H), 1.60-1.88 (m, 2H), 2.34 (s, 3H), 2.71-2.78 (m, 1H), 2.85-2.95 (m, 2H), 3.28-3.34 (m, 1H), 3.87 (s, 3H), 6.20 (q, J=6.8 Hz, 1H), 6.94 (s, 1H), 7.04-7.06 (m, 2H), 7.19 (t, J=8.0 Hz, 1H), 7.25-7.27 (m, 1H), 7.58-7.62 (m, 2H), 7.82 (s, 1H), 7.88 (s, 1H).

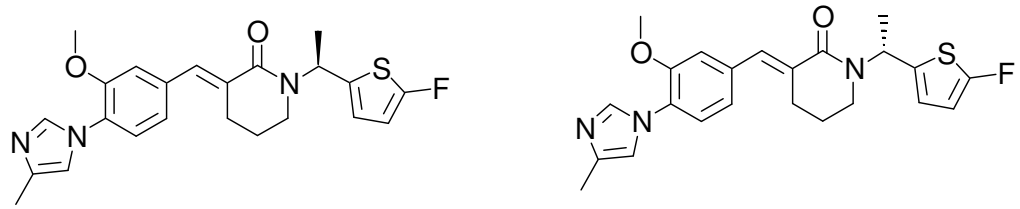
[0895]

Example 958 and Example 959

Synthesis of (E)-1-[(1S) and (1R)-(5-fluorothiophen-2-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-piperidin-2-one

[0896]

[Formula 281]



Synthesis of 2-(1-azidoethyl)-5-fluorothiophene

Methyl magnesium bromide (0.84 M, tetrahydrofuran solution, 20 mL) was added to a solution of 5-fluorothiophene-2-carboxyaldehyde (977 mg) in THF (10 mL) while cooling with ice, and the reaction solution was stirred for 30 minutes. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. 1,8-diazabicyclo[5.4.0]undec-7-ene (1.1 mL) was added to a solution of the resulting crude oil (952 mg) and diphenylphosphoryl azide (2.06 g) in toluene (5 mL) while cooling with ice. The reaction solution was stirred for 2 hours, and further stirred at room temperature overnight. Water and ethyl acetate were added to the reaction mixture and the organic layer was partitioned. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system) to obtain 518 mg

of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (d, J=6.8 Hz,3H), 4.63-4.69 (m, 1H), 6.34-6.35 (m, 1H), 6.62-6.64 (m, 1H).

[0897]

Synthesis of 1-(5-fluorothiophen-2-yl)ethylamine

Triphenylphosphine (873 mg) was added to a solution of 2-(1-azidoethyl)-5-fluorothiophene (518 mg) in THF (10 mL), and the reaction solution was stirred at room temperature for 1 hour. Water (2 mL) was added to the reaction mixture, and the mixture was heated to reflux for 3 hours. After allowing the reaction mixture to be cooled, a 5 N aqueous solution of hydrochloric acid and ethyl acetate were added thereto to separate the aqueous layer. A 5 N aqueous solution of sodium hydroxide was added to the aqueous layer to make the layer basic, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain 324 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.44 (d, J=6.8 Hz, 3H), 4.20-4.25 (m, 1H), 6.27 (dd, J=1.6, 4 Hz, 1H), 6.48 (t, J=3.6 Hz, 1H).

[0898]

Synthesis of (E)-1-[(1S)-(5-fluorothiophen-2-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-)benzylidene]-1-piperidin-

2-one and (E)-1-[(1R)-(5-fluorothiophen-2-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-piperidin-2-one

72 mg of a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (112 mg) and 1-(5-fluorothiophen-2-yl)ethylamine (67 mg) in the same manner as in Example 418.

The racemate (58 mg) was fractionated using CHIRALCEL™ OD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 8:2; flow rate: 5 mL/min) to obtain the title optically active substance with a retention time of 43 minutes (19 mg; >99% ee) and the title optically active substance with a retention time of 49 minutes (16 mg; >99% ee).

The physical properties of the optically active substance with a retention time of 43 minutes (Example 958) are as follows.

^{1}H-NMR ($CDCl_3$) δ :1.55 (d, J=7.2 Hz, 3H), 1.73-1.91 (m, 2H), 2.30 (s, 3H), 2.69-2.77 (m, 1H), 2.83-2.90 (m, 1H), 3.16-3.22 (m, 1H), 3.26-3.32 (m, 1H), 3.86 (s, 3H), 6.16-6.23 (m, 1H), 6.30 (dd, J=1.6, 4.0 Hz, 1H), 6.57-6.59 (m, 1H), 6.93 (t, J=1.2 Hz, 1H), 7.03-7.05 (m, 2H), 7.25 (dd, J=1.6, 6.8 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.86 (s, 1H).

The physical properties of the optically active substance with a retention time of 49 minutes

(Example 959) are as follows.

^{1}H-NMR ($CDCl_3$) δ :1.55 (d, J=7.2 Hz, 3H), 1.73-1.91 (m, 2H), 2.30 (s, 3H), 2.69-2.77 (m, 1H), 2.83-2.90 (m, 1H), 3.16-3.22 (m, 1H), 3.26-3.32 (m, 1H), 3.86 (s, 3H), 6.16-6.23 (m, 1H), 6.30 (dd, J=1.6, 4.0 Hz, 1H), 6.57-6.59 (m, 1H), 6.93 (t, J=1.2 Hz, 1H), 7.03-7.05 (m, 2H), 7.25 (dd, J=1.6, 6.8 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.86 (s, 1H).

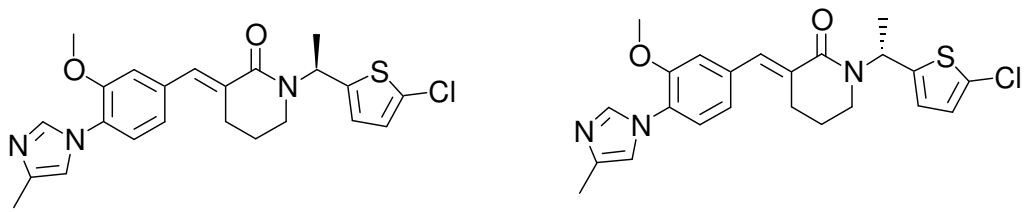
[0899]

Example 960 and Example 961

Synthesis of (E)-1-[(1S) and (1R)-(5-chlorothiophen-2-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-piperidin-2-one

[0900]

[Formula 282]



65 mg of a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (112 mg) and 1-(5-chlorothiophen-2-yl)ethylamine (48 mg) in the same manner as in Example 418.

The racemate (11 mg) was fractionated using CHIRALCEL™ OD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 8:2; flow rate: 5 mL/min) to obtain

the title optically active substance with a retention time of 54 minutes (4.0 mg; >99% ee) and the title optically active substance with a retention time of 60 minutes (4.6 mg; >99% ee).

The physical properties of the optically active substance with a retention time of 54 minutes (Example 960) are as follows.

^{1}H-NMR ($CDCl_3$) δ :1.57 (d, J=7.6 Hz, 3H), 1.72-1.80 (m, 1H), 1.84-1.92 (m, 1H), 2.30 (s, 3H), 2.69-2.77 (m, 1H), 2.84-2.91 (m, 1H), 3.16-3.22 (m, 1H), 3.27-3.33 (m, 1H), 3.86 (s, 3H), 6.25 (q, J=7.2 Hz, 1H), 6.75-6.78 (m, 2H), 6.94 (s, 1H), 7.04-7.06 (m, 2H), 7.26 (d, J=8.8 Hz, 1H), 7.72 (d, J=1.6 Hz, 1H), 7.88 (s, 1H).

The physical properties of the optically active substance with a retention time of 60 minutes (Example 961) are as follows.

^{1}H-NMR ($CDCl_3$) δ: 1.57 (d, J=7.6 Hz, 3H), 1.72-1.80 (m, 1H), 1.84-1.92 (m, 1H), 2.30 (s, 3H), 2.69-2.77 (m, 1H), 2.84-2.91 (m, 1H), 3.16-3.22 (m, 1H), 3.27-3.33 (m, 1H), 3.86 (s, 3H), 6.25 (q, J=7.2 Hz, 1H), 6.75-6.78 (m, 2H), 6.94 (s, 1H), 7.04-7.06 (m, 2H), 7.26 (d, J=8.8 Hz, 1H), 7.72 (d, J=1.6 Hz, 1H), 7.88 (s, 1H).

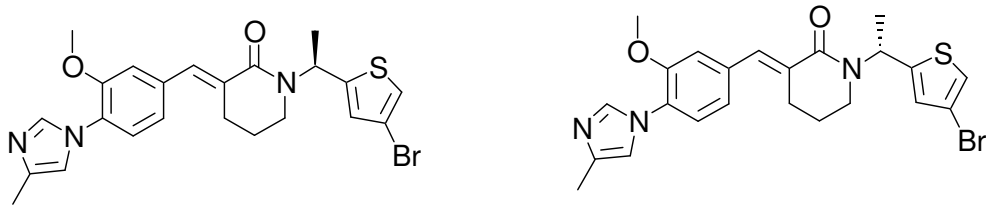
[0901]

Example 962 and Example 963

Synthesis of (E)-1-[(1S) and (1R)-(4-bromothiophen-2-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-piperidin-2-one

[0902]

[Formula 283]



85 mg of a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (112 mg) and 1-(4-bromothiophen-2-yl)ethylamine (62 mg) in the same manner as in Example 418.

The racemate (10 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol; flow rate: 5 mL/min) to obtain the title optically active substance with a retention time of 44 minutes (3.3 mg; >99% ee) and the title optically active substance with a retention time of 53 minutes (2.6 mg; >99% ee).

The physical properties of the optically active substance with a retention time of 44 minutes (Example 962) are as follows.

^{1}H-NMR ($CDCl_3$) δ :1.60 (d, J=7.2 Hz, 3H), 1.72-1.92 (m, 2H), 2.30 (s, 3H), 2.70-2.78 (m, 1H), 2.85-2.92 (m, 1H), 3.14-3.20 (m, 1H), 3.28-3.35 (m, 1H), 3.86 (s, 3H), 6.33 (q, J=7.2 Hz, 1H), 6.90 (d, J=1.2 Hz, 1H), 6.95 (s, 1H), 7.04-7.06 (m, 2H), 7.16 (d, J=1.2 Hz,

1H), 7.26 (d, J=8 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.89 (s, 1H).

The physical properties of the optically active substance with a retention time of 53 minutes (Example 963) are as follows.

^{1}H-NMR ($CDCl_3$) δ: 1.60 (d, J=7.2 Hz, 3H), 1.72–1.92 (m, 2H), 2.30 (s, 3H), 2.70–2.78 (m, 1H), 2.85–2.92 (m, 1H), 3.14–3.20 (m, 1H), 3.28–3.35 (m, 1H), 3.86 (s, 3H), 6.33 (q, J=7.2 Hz, 1H), 6.90 (d, J=1.2 Hz, 1H), 6.95 (s, 1H), 7.04–7.06 (m, 2H), 7.16 (d, J=1.2 Hz, 1H), 7.26 (d, J=8 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.89 (s, 1H).

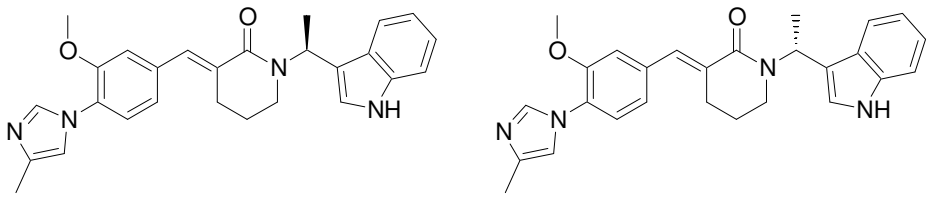
[0903]

Example 964 and Example 965

Synthesis of (E)-1-[(1R) and (1S)-(1H-indol-3-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0904]

[Formula 284]



Synthesis of 1-(1H-indol-3-yl)ethanone oxime

Triethylamine (3.93 mL) was added to a solution of 3-acetylindole (500 mg) and hydroxylamine hydrochloride (981 mg) in ethanol (20 mL), and the reaction solution was heated to reflux at 90°C for 14

hours. The reaction solution was allowed to be cooled to room temperature, the solvent was concentrated under reduced pressure, and ethyl acetate and water were added to the resulting residue and the organic layer was partitioned. The resulting organic layer was washed with brine, and then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: ethyl acetate) to obtain 0.53 g of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 2.17 (s, 3H), 7.05 (dd, J=7.2, 14.4 Hz, 1H), 7.13 (dd, J=7.2, 14.4 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.67 (s, 1H), 8.13 (d, J=8.0 Hz, 1H), 10.49 (s, 1H), 11.29 (s, 1H).

[0905]

Synthesis of 1-(1H-indol-3-yl)ethylamine

10% palladium-carbon (water content: 50%, 12.2 mg) was added to a solution of 1-(1H-indol-3-yl)ethanone oxime (0.20 g) obtained as above and acetic acid (0.7 mL) in ethanol (7 mL) at room temperature. The reaction mixture was stirred in a hydrogen stream at room temperature for 10 hours, and then filtered on a celite. The filtrate was concentrated under reduced pressure. The residue was extracted with chloroform. The organic layer was washed sequentially with a 1 N aqueous solution of sodium hydroxide and brine, dried over anhydrous magnesium sulfate, and concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: chloroform–methanol system) to obtain 0.137 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (d, J=6.4 Hz, 3H), 1.68 (s, 2H), 4.48 (q, J=6.4 Hz, 1H), 7.11–7.23 (m, 3H), 7.37 (d, J=8.0 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 8.02 (s, 1H).

[0906]

Synthesis of (E)-1-[(1R) and (1S)-1-(1H-indol-3-yl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

EDC (384 mg), HOBT (271 mg) and IPEA (0.582 mL) were sequentially added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 1-(1H-indol-3-yl)ethylamine (130 mg) in DMF (5 mL), and the reaction solution was stirred at room temperature for 12 hours. After confirming that the raw materials disappeared, ethyl acetate and water were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was sequentially washed with a saturated aqueous solution of ammonium chloride and brine, and then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: chloroform:methanol system) to obtain (E)-5-

chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(1H-indol-3-yl)ethyl)amide (332 mg). Sodium hydride (containing mineral oil at 40%, 19.3 mg) was added to a solution of the resulting (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(1H-indol-3-yl)ethyl)amide (92 mg) in THF (3 mL) at 0°C, and the reaction solution was stirred at room temperature for 90 minutes. The reaction solution was cooled to 0°C, water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: chloroform:methanol system) to obtain (E)-1-[1-(1H-indol-3-yl)ethyl]-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one as a racemate (37.3 mg). The compound (37 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 10 minutes (15 mg; >99% ee) and the title optically active substance with a retention time of 14 minutes (14.2 mg; >99% ee).

The physical properties of the optically

active substance with a retention time of 10 minutes (Example 964) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.58–1.64 (m, 1H), 1.63 (d, J=6.8 Hz, 3H), 1.69–1.74 (m, 1H), 2.31 (s, 3H), 2.71–2.78 (m, 2H), 2.92–2.99 (m, 1H), 3.18–3.25 (m, 1H), 3.86 (s, 3H), 6.51 (q, J=6.8 Hz, 1H), 6.94 (s, 1H), 7.06–7.26 (m, 6H), 7.38 (d, J=8.0 Hz, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.74 (s, 1H), 7.96 (s, 1H), 8.39 (s, 1H).

The physical properties of the optically active substance with a retention time of 14 minutes (Example 965) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.58–1.64 (m, 1H), 1.63 (d, J=6.8 Hz, 3H), 1.69–1.74 (m, 1H), 2.31 (s, 3H), 2.71–2.78 (m, 2H), 2.92–2.99 (m, 1H), 3.18–3.25 (m, 1H), 3.86 (s, 3H), 6.51 (q, J=6.8 Hz, 1H), 6.94 (s, 1H), 7.06–7.26 (m, 6H), 7.38 (d, J=8.0 Hz, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.74 (s, 1H), 7.96 (s, 1H), 8.37 (s, 1H).

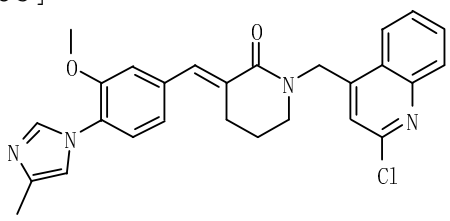
[0907]

Example 966

Synthesis of (E)-1-(2-chloroquinolin-4-ylmethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0908]

[Formula 285]



28 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (263 mg) and (2-chloroquinolin-4-yl)methylamine (200 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.90-2.00 (m, 2H), 2.30 (s, 3H), 2.85-2.94 (m, 2H), 3.38-3.45 (m, 2H), 3.87 (s, 3H), 5.20 (s, 2H), 6.92-6.95 (m, 1H), 7.03-7.08 (m, 2H), 7.21-7.29 (m, 2H), 7.58-7.65 (m, 1H), 7.70-7.79 (m, 2H), 7.91 (s, 1H), 8.04-8.09 (m, 2H).

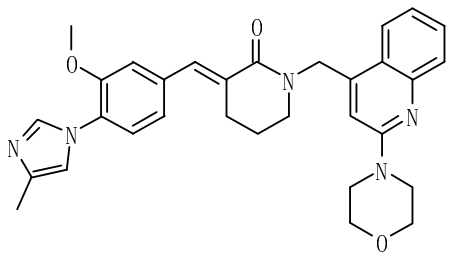
[0909]

Example 967

Synthesis of (E)-1-(2-morpholin-4-yl-quinolin-4-ylmethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0910]

[Formula 286]



100 mg of the title compound was obtained from ethyl (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valerate (230 mg) and (2-morpholin-4-yl-quinolin-4-yl)methylamine (230 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82-1.90 (m, 2H), 2.34 (s, 3H), 2.81-2.88 (m, 2H), 3.30-3.38 (m, 2H), 3.67-3.75 (m, 4H), 3.80-3.90 (m, 4H), 3.88 (s, 3H), 5.14 (s, 2H), 6.88 (s, 1H), 6.96 (s, 1H), 7.02-7.10 (m, 2H), 7.24-7.34 (m, 2H), 7.56-7.62 (m, 1H), 7.74-7.84 (m, 1H), 7.83 (s, 1H), 7.86-7.92 (m, 1H), 7.93 (s, 1H).

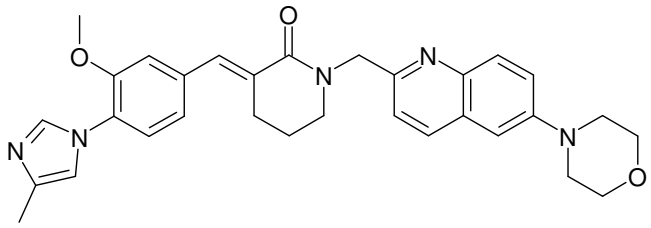
[0911]

Example 968

Synthesis of (E)-1-(6-morpholin-4-yl-quinolin-2-ylmethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0912]

[Formula 287]



14 mg of the title compound was obtained from ethyl (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valerate (300 mg) and (6-morpholin-4-yl-quinolin-2-yl)methylamine (200 mg) in

the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83–1.93 (m, 2H), 2.36 (s, 3H), 2.80–2.90 (m, 2H), 3.25–3.33 (m, 4H), 3.50–3.57 (m, 2H), 3.87 (s, 3H), 3.85–3.97 (m, 4H), 5.00 (s, 2H), 6.96 (s, 1H), 7.02–7.10 (m, 3H), 7.24–7.30 (m, 1H), 7.43–7.52 (m, 2H), 7.84–7.92 (m, 2H), 7.92–8.04 (m, 2H).

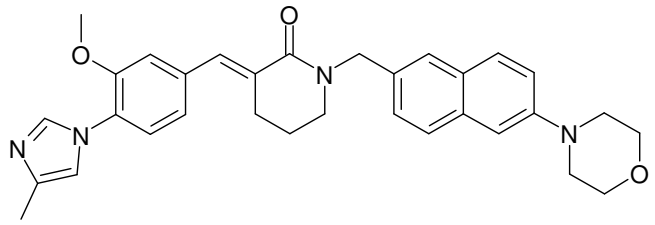
[0913]

Example 969

Synthesis of (E)-1-(6-morpholin-4-yl-naphthalen-2-ylmethyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0914]

[Formula 288]



173 mg of the title compound was obtained from ethyl (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valerate (350 mg) and (6-morpholin-4-yl-naphthalen-2-yl)methylamine (259 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.78–1.88 (m, 2H), 2.32 (s, 3H), 2.78–2.85 (m, 2H), 3.22–3.30 (m, 4H), 3.35–3.42 (m, 2H), 3.86 (s, 3H), 3.87–3.95 (m, 4H), 4.85 (s, 2H),

6.93 (s, 1H), 7.02–7.07 (m, 2H), 7.10 (d, J=2.0 Hz, 1H), 7.22–7.28 (m, 2H), 7.39 (dd, J=2.0, 8.4 Hz, 1H), 7.62 (s, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.76 (s, 1H), 7.90 (s, 1H).

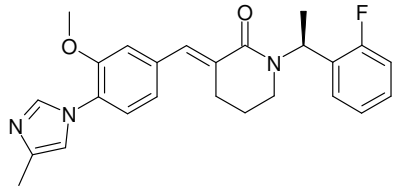
[0915]

Example 970

Synthesis of (E)-1-[(1S)-(2-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0916]

[Formula 289]



Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid ((1S)-(2-fluorophenyl)ethyl)amide

IPEA (300 μL), EDC (165 mg) and HOBT (116 mg) were sequentially added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (193 mg) and (S)-1-(2-fluorophenyl)ethylamine (60.0 mg) in DMF (3.0 mL) at room temperature, and the reaction solution was stirred at room temperature for 1 hour. After confirming that the raw materials disappeared, water and ethyl acetate were added to the residue and the organic layer was partitioned. The organic layer was

washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 258 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (d, J=7.2 Hz, 3H), 1.95–2.02 (m, 2H), 2.32 (s, 3H), 2.69–2.73 (m, 2H), 3.57 (t, J=6.4 Hz, 2H), 3.86 (s, 3H), 5.35 (quint, J=7.2Hz, 1H), 6.43 (d, J=7.2 Hz, 1H), 6.93–6.97 (m, 3H), 7.05–7.16 (m, 2H), 7.16 (s, 1H), 7.23–7.28 (m, 2H), 7.34 (t, J=7.2 Hz, 1H), 7.78 (s, 1H).

[0917]

Synthesis of (E)-1-[(1S)-(2-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

Sodium hydride (containing mineral oil at 40%, 34.5 mg) was added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ((1S)-(2-fluorophenyl)ethyl)amide (258 mg) in DMF (3.0 mL) at 0°C, and the reaction solution was stirred at room temperature for 20 minutes. After confirming that the raw materials disappeared, water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate

and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane–ethyl acetate system -> ethyl acetate–methanol system) to obtain 180 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (d, J=7.2 Hz, 3H), 1.77–1.82 (m, 2H), 2.26 (s, 3H), 2.68–2.86 (m, 2H), 2.96–3.02 (m, 1H), 3.29 (td, J=5.6, 12 Hz, 1H), 3.84 (s, 3H), 6.23 (q, J=7.2 Hz, 1H), 6.92 (t, J=1.2 Hz, 1H), 7.01–7.07 (m, 3H), 7.14 (dt, J=1.2, 7.6 Hz, 1H), 7.23 (d, J=8.4 Hz, 1H), 7.24–7.31 (m, 1H), 7.38 (dt, J=1.2, 7.6 Hz, 1H), 7.72 (d, J=1.2 Hz, 1H), 7.86 (brs, 1H).

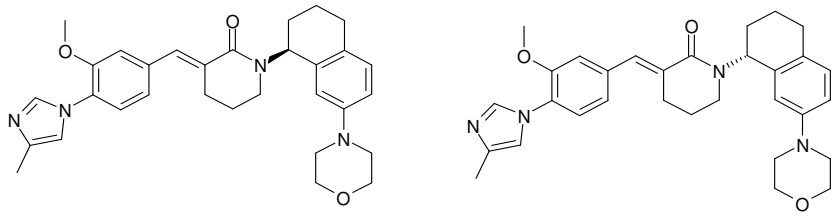
[0918]

Example 971 and Example 972

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R) and (1S)-7-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl]piperidin-2-one

[0919]

[Formula 290]



Synthesis of 7-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one

A solution of 7-bromo-3,4-dihydro-2H-naphthalen-1-one (600 mg), morpholine (1.16 g), tripotassium phosphate (850 mg), tris(dibenzylideneacetone)dipalladium (0) (24.4 mg) and 2-(di-tert-butylphosphino)biphenyl (15.9 mg) in toluene (5.0 mL) was stirred in a nitrogen atmosphere at 100°C overnight. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 360 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.11 (quint, J=6.0 Hz, 2H), 2.63 (t, J=6.0 Hz, 2H), 2.89 (t, J=6.0 Hz, 2H), 3.16-3.18 (m, 4H), 3.85-3.87 (m, 4H), 7.07 (dd, J=2.8, 8.4 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 7.53 (d, J=2.8 Hz, 1H).

[0920]

Synthesis of 7-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one oxime

A solution of 7-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one (360 mg), hydroxylammonium chloride (163 mg) and sodium acetate (384 mg) in ethanol (5.0 mL) was heated to reflux for 1 hour and 50 minutes. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The

resulting organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 384 mg of the title compound as a crude product. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.80-1.89 (m, 2H), 2.69 (t, J=6.8 Hz, 2H), 2.78 (t, J=6.8 Hz, 2H), 3.14-3.16 (m, 4H), 3.85-3.87 (m, 4H), 6.90 (dd, J=2.0,8.4 Hz,1H), 7.06 (d, J=8.4 Hz, 1H), 7.43 (s, 1H).

[0921]

Synthesis of 7-morpholin-4-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamine

A solution of crude 7-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one oxime (384 mg) and 10% palladium-carbon (water content: 48%, 350 mg) in ethanol (10 mL) was stirred in a hydrogen atmosphere (0.4 Mpa) at room temperature for 8 hours. The reaction solution was filtered on a celite, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 110 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.62-1.79 (m, 2H), 1.86-1.95 (m, 1H), 1.98-2.04 (m, 1H), 2.62-2.77 (m, 2H), 3.12-3.14 (m, 4H), 3.84-3.86 (m, 4H), 3.93 (t, J=5.6 Hz, 1H),

6.75 (dd, J=2.8, 8.4 Hz, 1H), 6.98-7.00 (m, 2H).

[0922]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]valeric acid (7-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl)amide

IPEA (330 μL), EDC (181 mg) and HOBT (128 mg) were sequentially added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (276 mg) and 7-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-ylamine (110 mg) in DMF (3.0 mL) at room temperature, and the reaction solution was stirred at room temperature for 30 minutes. After confirming that the raw materials disappeared, water and ethyl acetate were added to the residue and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 213 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.80-1.96 (m, 3H), 2.00-2.11 (m, 3H), 2.30 (s, 3H), 2.68-2.80 (m, 4H), 3.10-3.12 (m, 4H), 3.57 (t, J=6.4 Hz, 2H), 3.83-3.86 (m, 4H), 3.86 (s, 3H), 5.24-5.29 (m, 1H), 6.19 (d, J=8.8 Hz, 1H), 6.81-6.84 (m, 2H), 6.92-6.95 (m, 3H), 7.04 (d, J=8.4

Hz, 1H), 7.11 (s, 1H), 7.24 (d, J=8.8 Hz, 1H), 7.72 (s, 1H).

[0923]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R) and (1S)-7-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl]piperidin-2-one

Sodium hydride (containing mineral oil at 40%, 37.8 mg) was added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene)valeric acid (7-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl)amide (213 mg) in DMF (5.0 mL) at 0°C, and the reaction solution was stirred for 30 minutes. After confirming that the raw materials disappeared, water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 195 mg of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(7-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl)piperidin-2-one as a racemate.

Next, the compound (8.00 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a

retention time of 7.6 minutes (Example 971, 3.60 mg; >99% ee) and the title optically active substance with a retention time of 12 minutes (Example 972, 1.40 mg; >99% ee). Properties data of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.68–1.90 (m, 3H), 1.90–2.24 (m, 2H), 2.07–2.14 (m, 1H), 2.31 (s, 3H), 2.68–2.74 (m, 2H), 2.74–2.85 (m, 1H), 2.85–2.98 (m, 1H), 3.04–3.08 (m, 4H), 3.05–3.12 (m, 1H), 3.17–3.25 (m, 1H), 3.81–3.84 (m, 4H), 3.87 (s, 3H), 6.07–6.11 (m, 1H), 6.63 (d, J=2.4 Hz, 1H), 6.77 (dd, J=2.4, 8.4 Hz, 1H), 6.94 (s, 1H), 7.03 (d, J=8.4 Hz, 1H), 7.08–7.10 (m, 2H), 7.26 (d, J=8.4 Hz, 1H), 7.74 (brs, 1H), 7.91 (brs, 1H).

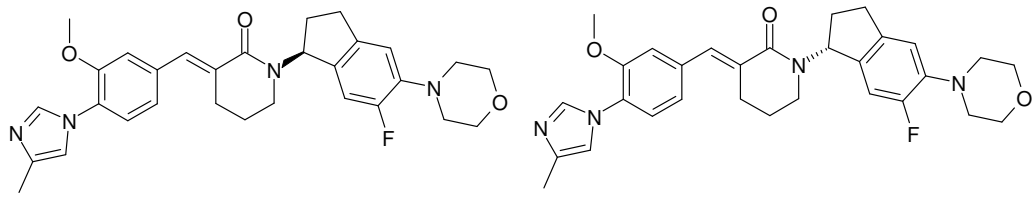
[0924]

Example 973 and Example 974

Synthesis of (E)-1-[(1R) and (1S)-6-fluoro-5-morpholin-4-ylindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0925]

[Formula 291]



Synthesis of 5,6-difluoro-1-indanone

Oxalyl chloride (1.12 mL) and DMF (78.2 mg) were added to a solution of 3,4-difluorohydrocinnamic acid (2.00 g) in dichloromethane (3.0 mL) at 0°C, and the reaction solution was stirred at room temperature overnight. After confirming that the raw materials disappeared, the reaction solution was concentrated under reduced pressure. Next, a solution of the resulting residue in dichloromethane (10 mL) was added to a solution of aluminum chloride (2.13 g) in dichloromethane (20 mL) at -30°C. The reaction solution was stirred at room temperature for 1.5 hours. After confirming that the raw materials disappeared, the reaction solution was poured into ice water. The solution was extracted with ethyl acetate. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 535 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.72-2.75 (m, 2H), 3.11-3.14 (m, 2H), 7.27 (t, J=8.0 Hz, 1H), 7.53 (t, J=8.0 Hz, 1H).

[0926]

Synthesis of 6-fluoro-5-morpholin-4-ylindan-1-one

A solution of 5,6-difluoro-1-indanone (535 mg) and morpholine (554 mg) in 1-methyl-2-pyrrolidinone (6.0 mL) was stirred at 100°C for 7 hours. After

confirming that the raw materials disappeared, water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 635 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.67-2.69 (m, 2H), 3.03-3.06 (m, 2H), 3.20-3.22 (m, 4H), 3.87-3.89 (m, 4H), 6.89 (d, J=7.2 Hz, 1H), 7.35 (d, J=12 Hz, 1H).

[0927]

Synthesis of 6-fluoro-5-morpholin-4-ylindan-1-ylamine

A solution of 6-fluoro-5-morpholin-4-ylindan-1-one (200 mg), hydroxylammonium chloride (102 mg) and sodium acetate (241 mg) in ethanol (5.0 mL) was heated to reflux for 1 hour. After confirming that the raw materials disappeared, water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure to obtain 218 mg of 6-fluoro-5-morpholin-4-ylindan-1-one oxime. Next, 10% palladium-carbon (water content: 48%, 200 mg) was added to a solution of the resulting 6-fluoro-5-morpholin-4-ylindan-1-one oxime (218 mg) in

ethanol (5.0 mL), and the reaction solution was stirred in a hydrogen atmosphere (0.4 MPa) at room temperature for 9 hours. The reaction solution was filtered on a celite, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 56.0 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60-1.72 (m, 1H), 2.50 (dtd, J=3.6, 7.2, 16 Hz, 1H), 2.74 (td, J=7.2, 16 Hz, 1H), 2.89 (ddd, J=3.6, 8.8,16 Hz, 1H), 3.03-3.05 (m, 4H), 3.85-3.88 (m, 4H), 4.30 (t, J=7.2 Hz, 1H), 6.79 (d, J=7.6 Hz, 1H), 6.98 (d, J=12 Hz, 1H).

[0928]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (6-fluoro-5-morpholin-4-ylindan-1-yl)amide

IPEA (165 μL), EDC (90.9 mg) and HOBT (64.0 mg) were sequentially added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (138 mg) and 6-fluoro-5-morpholin-4-ylindan-1-ylamine (56.0 mg) in DMF (3.0 mL), and the reaction solution was stirred at room temperature for 1 hour. After confirming that the raw materials disappeared, the solvent was concentrated under reduced pressure, and water and

ethyl acetate were added to the residue and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane–ethyl acetate system, ethyl acetate–methanol system) to obtain 123 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.88–1.98 (m, 1H), 2.00–2.08 (m, 2H), 2.30 (s, 3H), 2.62–2.78 (m, 3H), 2.82–3.20 (m, 2H), 3.05–3.08 (m, 4H), 3.61 (t, J=6.0 Hz, 2H), 3.87 (s, 3H), 3.87–3.89 (m, 4H), 5.55 (q, J=7.6 Hz, 1H), 6.16–6.22 (m, 1H), 6.84 (d, J=7.2 Hz, 1H), 6.94–6.99 (m, 3H), 7.03 (d, J=12 Hz, 1H), 7.19 (s, 1H), 7.25–7.27 (m, 1H), 7.74 (s, 1H).

[0929]

Synthesis of (E)-1-[(1R) and (1S)-6-fluoro-5-morpholin-4-ylindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

Sodium hydride (containing mineral oil at 40%, 19.0 mg) was added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (6-fluoro-5-morpholin-4-ylindan-1-yl)amide (123 mg) in DMF (3.0 mL) at 0°C, and the reaction solution was stirred for 15 minutes. After confirming that the raw materials disappeared, water and ethyl acetate were added to the reaction

solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system, ethyl acetate-methanol system) to obtain 85 mg of (E)-1-(6-fluoro-5-morpholin-4-ylindan-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one as a racemate. Next, the compound (12.0 mg) was fractionated using CHIRALCEL™ OD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 70:30) to obtain the title optically active substance with a retention time of 13 minutes (Example 973, 4.60 mg; >99% ee) and the title optically active substance with a retention time of 15 minutes (Example 974, 4.70 mg; >99% ee). The physical properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.76-2.04 (m, 3H), 2.31 (s, 3H), 2.46-2.58 (m, 1H), 2.74-3.00 (m, 5H), 3.04-3.10 (m, 4H), 3.08-3.18 (m, 1H), 3.87 (s, 3H), 3.87-3.89 (m, 4H), 6.43 (t, J=7.6 Hz, 1H), 6.82-6.88 (m, 2H), 6.95 (s, 1H), 7.06 (d, J=0.8 Hz, 1H), 7.26-7.27 (m, 2H), 7.74 (s, 1H), 7.89 (s, 1H).

[0930]

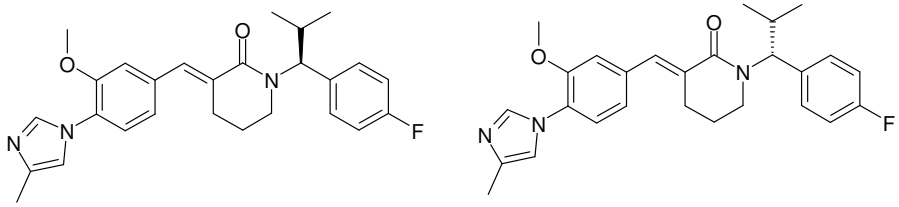
Example 975 and Example 976

Synthesis of (E)-1-[(1S) and (1R)-1-(4-fluorophenyl)-2-

methylpropyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0931]

[Formula 292]



Synthesis of 1-(4-fluorophenyl)-2-methylpropan-1-one oxime

1.06 g of the title compound was obtained from 1-(4-fluorophenyl)-2-methylpropan-1-one (1.00 g) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.11 (d, J=6.8 Hz, 3H), 1.19 (d, J=7.2 Hz, 3H), 2.78-2.85 (m, 1/2H), 3.55-3.62 (m, 1/2H), 7.02 (t, J=8.8 Hz, 1H), 7.09 (t, J=8.8 Hz, 1H), 7.28 (dd, J=5.6, 8.8 Hz, 1H), 7.34 (dd, J=5.6, 8.8 Hz, 1H).

[0932]

Synthesis of 1-(4-fluorophenyl)-2-methylpropylamine

364 mg of the title compound was obtained from 1-(4-fluorophenyl)-2-methylpropan-1-one oxime (500 mg) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.75 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H), 1.75-1.85 (m, 1H), 3.60 (d, J=7.6 Hz, 1H), 6.99 (t, J=8.8 Hz, 2H), 7.24 (dd, J=5.6, 8.8 Hz,

2H).

[0933]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (1-(4-fluorophenyl)-2-methylpropyl)amide

219 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 1-(4-fluorophenyl)-2-methylpropylamine (168 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.94 (d, J=6.4 Hz, 3H), 1.04 (d, J=6.0 Hz, 3H), 1.91-2.01 (m, 2H), 2.01-2.19 (m, 1H), 2.30 (s, 3H), 2.70-2.75 (m, 2H), 3.58 (s, 2H), 3.85 (s, 3H), 4.81 (t, J=8.4 Hz, 1H), 6.24 (d, J=8.4 Hz, 1H), 6.92-6.96 (m, 3H), 7.03 (t, J=8.4 Hz, 2H), 7.18 (s, 1H), 7.23-7.28 (m, 3H), 7.71 (s, 1H).

[0934]

Synthesis of (E)-1-[(1R) and (1S)-1-(4-fluorophenyl)-2-methylpropyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

177 mg of (E)-1-(1-(4-fluorophenyl)-2-methylpropyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(4-fluorophenyl)-2-methylpropyl)amide (219 mg) in the same manner as in Example 418. Next, the compound (10.0 mg)

was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 5.0 minutes (Example 975, 2.4 mg; >99% ee) and the title optically active substance with a retention time of 5.9 minutes (Example 976, 2.2 mg; >98% ee). The physical properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.93 (d, J=6.4 Hz, 3H), 1.05 (d, J=6.0 Hz, 3H), 1.60-1.72 (m, 1H), 1.76-1.86 (m, 1H), 2.29 (s, 3H), 2.36-2.46 (m, 1H), 2.62-2.72 (m, 1H), 2.72-2.82 (m, 1H), 3.00-3.08 (m, 1H), 3.24-3.32 (m, 1H), 3.84 (s, 3H), 5.68 (d, J=12 Hz, 1H), 6.91 (s, 1H), 7.00-7.04 (m, 4H), 7.21-7.28 (m, 1H), 7.37 (t, J=6.4 Hz, 2H), 7.69 (s, 1H), 7.84 (s, 1H).

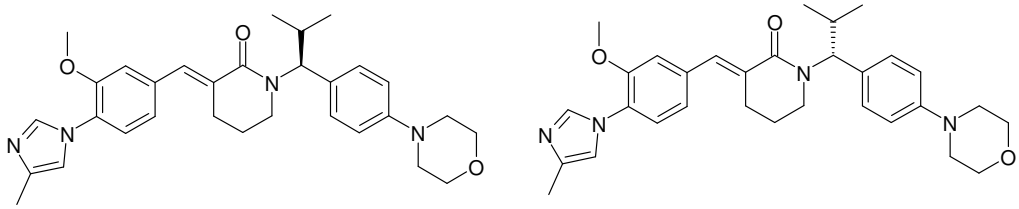
[0935]

Example 977 and Example 978

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1S) and (1R)-2-methyl-1-(4-morpholin-4-ylphenyl)propyl]piperidin-2-one

[0936]

[Formula 293]



Synthesis of 2-methyl-1-(4-morpholin-4-ylphenyl)propan-

1-one

491 mg of the title compound was obtained from 1-(4-fluorophenyl)-2-methylpropan-1-one (500 mg) in the same manner as in Example 973. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.20 (d, J=6.8 Hz, 6H), 3.31 (t, J=4.8 Hz, 4H), 3.46-3.56 (m, 1H), 3.86 (t, J=4.8 Hz, 4H), 6.88 (d, J=9.2 Hz, 2H), 7.92 (d, J=9.2 Hz, 2H).

[0937]

Synthesis of 2-methyl-1-(4-morpholin-4-ylphenyl)propan-1-one oxime

424 mg of the title compound was obtained from 1-(4-fluorophenyl)-2-methylpropan-1-one (491 mg) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.12 (d, J=6.8 Hz, 3H), 1.22 (d, J=6.8 Hz, 3H), 2.80-2.87 (m, 1/2H), 3.17-3.22 (m, 4H), 3.53-3.60 (m, 1/2H), 3.86 (t, J=4.8 Hz, 4H), 6.86 (d, J=8.4 Hz, 1H), 6.93 (d, J=8.4 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H).

[0938]

Synthesis of 2-methyl-1-(4-morpholin-4-ylphenyl)propylamine

300 mg of the title compound was obtained from 2-methyl-1-(4-morpholin-4-ylphenyl)propan-1-one oxime (424 mg) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.75 (d, J=6.4 Hz, 3H), 0.97 (d,

J=6.8 Hz, 3H), 1.64 (brs, 2H), 1.77-1.86 (m, 1H), 3.14 (t, J=4.8 Hz, 4H), 3.53 (d, J=7.2 Hz, 1H), 3.85 (t, J=4.8 Hz, 4H), 6.86 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.8 Hz, 2H).

[0939]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (2-methyl-1-(4-morpholin-4-ylphenyl)propyl)amide

290 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 2-methyl-1-(4-morpholin-4-ylphenyl)propylamine (235 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (d, J=6.4 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H), 1.94-2.01 (m, 2H), 2.06-2.14 (m, 1H), 2.30 (s, 3H), 2.69-2.73 (m, 2H), 3.15 (t, J=4.8 Hz, 4H), 3.57 (dt, J=2.4, 6.0 Hz, 2H), 3.85 (t, J=4.8 Hz, 4H), 3.85 (s, 3H), 4.78 (t, J=8.4 Hz ,1H), 6.26 (d, J=8.4 Hz, 1H), 6.88 (d, J=8.4 Hz, 2H), 6.92-6.95 (m, 3H), 7.14 (s, 1H), 7.19 (d, J=8.8 Hz, 2H), 7.23 (d, J=8.4 Hz, 1H), 7.70 (s, 1H).

[0940]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R) and (1S)-2-methyl-1-(4-morpholin-4-ylphenyl)propyl]piperidin-2-one

210 mg of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(2-methyl-1-(4-morpholin-

4-ylphenyl)propyl)piperidin-2-one as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (2-methyl-1-(4-morpholin-4-ylphenyl)propyl)amide (290 mg) in the same manner as in Example 418. Next, the compound (100 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 11 minutes (Example 977, 50.0 mg; >99% ee) and the title optically active substance with a retention time of 26 minutes (Example 978, 46.0 mg; >99% ee). The physical properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.93 (d, J=6.4 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H), 1.56-1.72 (m, 1H), 1.74-1.84 (m, 1H), 2.29 (s, 3H), 2.36-2.45 (m, 1H), 2.60-2.70 (m, 1H), 2.72-2.80 (m, 1H), 3.06 (ddd, J=3.6, 7.6, 12 Hz, 1H), 3.15-3.18 (m, 4H), 3.25 (ddd, J=2.0, 7.2, 12 Hz, 1H), 3.83 (s, 3H), 3.84-3.87 (m, 4H), 5.65 (d, J=12 Hz, 1H), 6.86 (d, J=8.8 Hz ,2H), 6.91 (s, 1H), 6.99-7.00 (m, 2H), 7.21 (d, J=8.4 Hz, 1H), 7.29 (d, J=8.8 Hz, 2H), 7.69 (s, 1H), 7.84 (s, 1H).

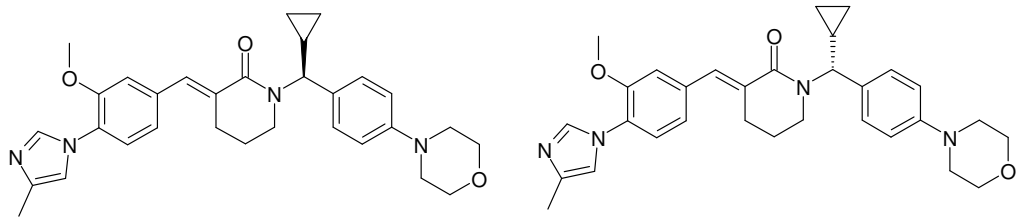
[0941]

Examples 979 and 980

<u>Synthesis of (E)-1-[(S) and (R)-cyclopropyl-(4-morpholin-4-ylphenyl)methyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one</u>

[0942]

[Formula 294]



Synthesis of cyclopropyl-(4-morpholin-4-ylphenyl)methanone

680 mg of the title compound was obtained from cyclopropyl 4-fluorophenyl ketone (750 mg) in the same manner as in Example 973. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95-0.99 (m, 2H), 1.17-1.21 (m, 2H), 2.59-2.65 (m, 1H), 3.30 (t, J=4.8 Hz, 4H), 3.85 (t, J=4.8 Hz, 4H), 6.88 (d, J=9.2 Hz, 2H), 7.96 (d, J=9.2 Hz, 2H).

[0943]

Synthesis of cyclopropyl-(4-morpholin-4-ylphenyl)methanone oxime

267 mg of the title compound was obtained from cyclopropyl-(4-morpholin-4-ylphenyl)methanone (680 mg) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.64-0.68 (m, 2H), 0.92-0.97 (m, 2H), 2.18-2.25 (m, 1H), 3.18 (t, J=4.8 Hz, 4H), 3.86 (t, J=4.8 Hz, 4H), 6.85 (d, J=8.8 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H).

[0944]

Synthesis of cyclopropyl-(4-morpholin-4-ylphenyl)methylamine

131 mg of the title compound was obtained from cyclopropyl-(4-morpholin-4-ylphenyl)methanone oxime (267 mg) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.22-0.33 (m, 2H), 0.43-0.50 (m, 1H), 0.56-0.62 (m, 1H), 1.04-1.13 (m, 1H), 3.14-3.17 (m, 5H), 3.85-3.88 (m, 4H), 6.90 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H).

[0945]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid (cyclopropyl-(4-morpholin-4-ylphenyl)methyl)amide

The title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and cyclopropyl-(4-morpholin-4-ylphenyl)methylamine (131 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.37-0.43 (m, 1H), 0.49-0.54 (m, 1H), 0.60-0.66 (m, 2H), 1.20-1.28 (m, 1H), 1.97-2.02 (m, 2H), 2.04 (s, 3H), 2.66-2.76 (m, 2H), 3.14-3.17 (m, 4H), 3.54-3.66 (m, 2H), 3.82-3.88 (m, 4H), 3.84 (s, 3H), 4.50 (t, J=8.4 Hz, 1H), 6.39 (brd, J=8.4 Hz, 1H), 6.89-6.96 (m, 5H), 7.16 (s, 1H), 7.22 (d, J=8.8 Hz, 1H), 7.32 (d, J=8.4 Hz, 2H), 7.79 (d, J=1.2 Hz, 1H).

[0946]

Synthesis of (E)-1-[(R) and (S)-cyclopropyl-(4-morpholin-4-ylphenyl)methyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

270 mg of (E)-1-(cyclopropyl-(4-morpholin-4-ylphenyl)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (cyclopropyl-(4-morpholin-4-ylphenyl)methyl)amide in the same manner as in Example 418. Next, the compound (20 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 13 minutes (Example 979, 7.9 mg; >99% ee) and the title optically active substance with a retention time of 17 minutes (Example 980, 4.6 mg; >99% ee). The physical properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.48-0.64 (m, 3H), 0.82-0.90 (m, 1H), 1.28-1.39 (m, 1H), 1.66-1.76 (m, 1H), 1.84-1.92 (m, 1H), 2.30 (s, 3H), 2.72-2.82 (m, 1H), 2.82-2.94 (m, 1H), 3.10-3.20 (m, 1H), 3.15-3.17 (m, 4H), 3.44-3.50 (m, 1H), 3.85-3.87 (m, 4H), 3.86 (s, 3H), 5.20 (d, J=10 Hz, 1H), 6.88 (d, J=8.4 Hz, 2H), 6.93 (s, 1H), 7.04 (s, 1H), 7.04 (d, J=7.2 Hz, 1H), 7.24 (d, J=7.2 Hz, 1H), 7.36 (d, J=8.4 Hz, 2H), 7.71 (s, 1H), 7.87 (s, 1H).

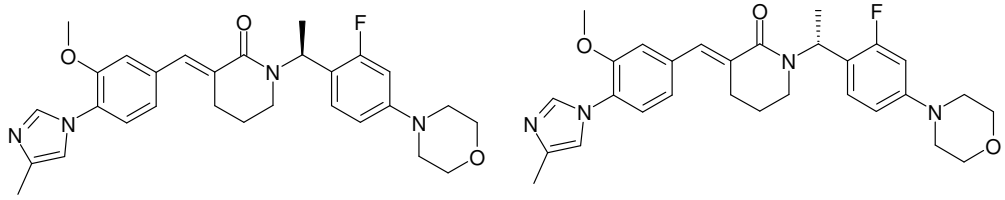
[0947]

Example 981 and Example 982

Synthesis of (E)-[(1S) and (1R)-(2-fluoro-4-morpholin-4-ylphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0948]

[Formula 295]



1-(2-fluoro-4-morpholin-4-yl-phenyl)ethanone

350 mg of the title compound was obtained from 2, 4-difluoroacetophenone (1.0 g) in the same manner as in Example 793. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.56 (d, J=5.6 Hz, 3H), 3.30 (t, J=4.8 Hz, 4H), 3.84 (t, J=4.8 Hz, 4H), 6.46 (dd, J=2.8, 15 Hz, 1H), 6.64 (dd, J=2.8, 9.2 Hz, 1H), 7.83 (t, J=8.8 Hz, 1H).

[0949]

Synthesis of 1-(2-fluoro-4-morpholin-4-yl-phenyl)ethanone oxime

364 mg of the title compound was obtained from 1-(2-fluoro-4-morpholin-4-yl-phenyl)ethanone (350 mg) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.27 (d, J=2.4 Hz, 3H), 3.18-

3.20 (m, 4H), 3.83–3.86 (m, 4H), 6.56 (dd, J=2.4, 12 Hz, 1H), 6.65 (dd, J=2.4, 8.8 Hz, 1H), 7.37 (t, J=8.8 Hz, 1H).

[0950]

Synthesis of 1-(2-fluoro-4-morpholin-4-yl-phenyl)ethylamine

140 mg of the title compound was obtained from 1-(2-fluoro-4-morpholin-4-ylphenyl)ethanone oxime (364 mg) in the same manner as in Example 971. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.38 (d, J=6.4 Hz, 3H), 3.11-3.14 (m, 4H), 3.83–3.85 (m, 4H), 4.24 (q, J=6.4 Hz, 1H), 6.54 (dd, J=2.4, 14 Hz, 1H), 6.64 (dd, J=2.4, 8.4 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H).

[0951]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid [1-(2-fluoro-4-morpholin-4-ylphenyl)ethyl]amide

406 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 1-(2-fluoro-4-morpholin-4-yl-phenyl)ethylamine (140 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (d, J=6.8 Hz, 3H), 1.94-2.04 (m, 2H), 2.31 (s, 3H), 2.70 (t, J=7.2 Hz, 2H), 3.13–3.15 (m, 4H), 3.56 (t, J=6.0 Hz, 2H), 3.83–3.85 (m, 4H), 3.85 (s, 3H), 5.22–5.30 (m, 1H), 6.36 (brd,

J=6.8 Hz, 1H), 6.58 (d, J=15 Hz, 1H), 6.64 (d, J=8.8 Hz, 1H), 6.93-6.99 (m, 3H), 7.14 (s, 1H), 7.16-7.23 (m, 2H), 7.76 (s, 1H).

[0952]

Synthesis of (E)-1-[(1R) and (1S)-(2-fluoro-4-morpholin-4-ylphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

267 mg of (E)-1-(1-(2-fluoro-4-morpholin-4-ylphenyl)ethyl)-3-(3-methoxy-4-(4-methylimidazol-1-yl)benzylidene)piperidin-2-one as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2-fluoro-4-morpholin-4-ylphenyl)ethyl)amide (406 mg) in the same manner as in Example 418. Next, the compound (160 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 12 minutes (Example 981, 61 mg; >99% ee) and the title optically active substance with a retention time of 14 minutes (Example 982, 31 mg; >92% ee). The physical properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.55 (d, J=7.2 Hz, 3H), 1.72-1.80 (m,2H), 2.31 (s, 3H), 2.66-2.84 (m, 2H), 2.97-3.03 (m, 1H), 3.15-3.18 (m, 4H), 3.24-3.29 (m, 1H), 3.80-3.88 (m, 4H), 3.85 (s,3H), 6.18 (q, J=7.2 Hz, 1H), 6.58 (dd, J=2.0, 9.6 Hz, 1H), 6.65 (dd, J=2.0, 8.4 Hz, 1H), 6.93 (s, 1H), 7.02-7.04 (m, 2H), 7.23-7.28 (m, 2H),

7.74 (s, 1H), 7.87 (s, 1H).

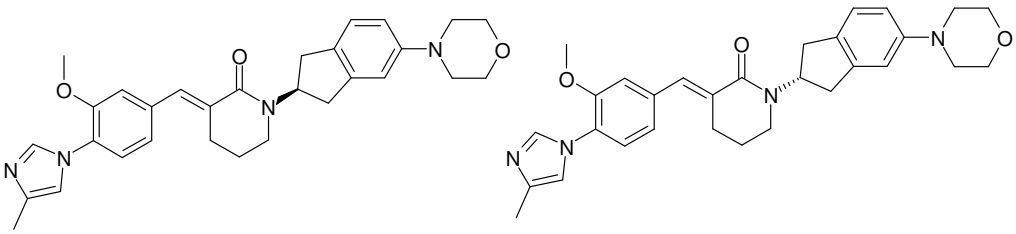
[0953]

Example 983 and Example 984

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(2R) and (2S)-5-morpholin-4-ylindan-2-yl]piperidin-2-one

[0954]

[Formula 296]



Synthesis of 5-morpholin-4-ylindan-1,2-dinone 2-oxime

1.30 g of the title compound was obtained from 5-morpholin-4-ylindan-1-one (1.50 g) synthesized in accordance with the method described in The Journal of Medicinal Chemistry, 1991, vol.34, no.5, p.1662. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.64-2.66 (m, 4H), 2.91 (s, 2H), 3.00-3.03 (m, 4H), 6.18 (d, J=2.0 Hz, 1H), 6.21 (dd, J=2.0, 8.8 Hz, 1H), 6.87 (d, J=8.8 Hz, 1H).

[0955]

Synthesis of 5-morpholin-4-ylindan-2-ylamine

258 mg of the title compound was obtained from 5-morpholin-4-ylindan-1,2-dinone 2-oxime (300 mg) synthesized in accordance with the method described in The Journal of Medicinal Chemistry, 1982, vol.25,

no.12, p.1442. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.78-2.88 (m, 2H), 3.09-3.12 (m, 4H), 3.16-3.25 (m, 2H), 3.78-3.98 (m, 1H), 3.84-3.87 (m, 4H), 4.90-5.44 (brs, 2H), 6.75 (dd, J=2.4, 8.4Hz, 1H), 6.80 (s, 1H), 7.11 (d, J=8.4 Hz, 1H).

[0956]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]valeric acid (5-morpholin-4-ylindan-2-yl)amide

258 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (288 mg) and 5-morpholin-4-ylindan-2-ylamine (100 mg) in the same manner as in Example 418. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.95-2.02 (m, 2H), 2.30 (s, 3H), 2.67-2.95 (m, 4H), 3.12-3.14 (m, 4H), 3.33 (dd, J=6.8, 13 Hz, 1H), 3.37 (dd, J=6.8, 13 Hz, 1H), 3.57 (t, J=6.4 Hz, 2H), 3.85 (s, 3H), 3.86-3.88 (m, 4H), 4.80-4.88 (m, 1H), 6.25 (brd, J=6.0 Hz, 1H), 6.74-6.80 (m, 1H), 6.84 (s, 1H), 6.92-6.94 (m, 3H), 7.10 (s, 1H), 7.15 (d, J=8.0, 1H), 7.23 (d, J=8.4 Hz, 1H), 7.77 (s, 1H).

[0957]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(2R) and (2S)-5-morpholin-4-ylindan-2-yl]piperidin-2-one

149 mg of (E)-3-(3-methoxy-4-(4-

methylimidazol-1-yl)benzylidene)-1-(5-morpholin-4-ylindan-2-yl)piperidin-2-one as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (5-morpholin-4-ylindan-2-yl)amide in the same manner as in Example 418. Next, the compound (149 mg) was fractionated using CHIRALCEL™ OJ manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 14 minutes (Example 983, 30.0 mg; >99% ee) and the title optically active substance with a retention time of 26 minutes (Example 984, 31.0 mg; >99% ee). The physical properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81-1.87 (m, 2H), 2.30 (s, 3H), 2.78-2.81 (m, 2H), 2.90-2.98 (m, 2H), 3.10-3.14 (m, 4H), 3.17-3.27 (m, 4H), 3.84-3.88 (m, 4H), 3.85 (s, 3H), 5.73-5.81 (m, 1H), 6.76 (dd, J=2.4, 8.4 Hz, 1H), 6.81 (s, 1H), 6.92 (s, 1H), 7.02 (s, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.12 (d, J=8.4 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.71 (s, 1H), 7.83 (s, 1H).

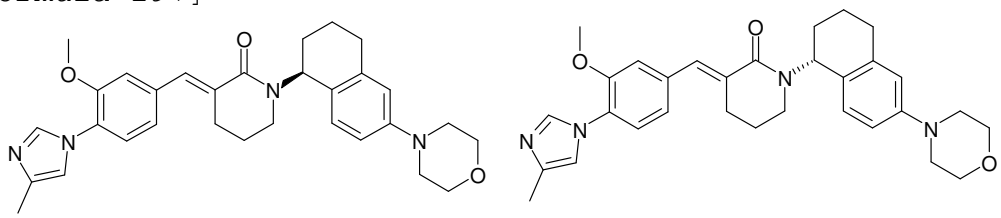
[0958]

Example 985 and Example 986

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R) and (1S)-(6-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl)]piperidin-2-one

[0959]

[Formula 297]



Synthesis of 5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate

Trifluoromethanesulfonic anhydride (2.51 mL) was added to a solution of 6-hydroxy-3,4-dihydro-2H-naphthalen-1-one (2.00 g) and triethylamine (4.11 mL) in dichloromethane (20 mL) at -20°C, and the reaction solution was stirred at that temperature for 20 minutes. After confirming that the raw materials disappeared, the reaction solution was concentrated under reduced pressure, and water and chloroform were added to the residue and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 3.30 g of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.15-2.21 (m, 2H), 2.69 (t, J=6.0 Hz, 2H), 3.02 (t, J=6.4 Hz, 2H), 7.17-7.21 (m, 2H), 8.12 (d, J=8.4 Hz, 1H).

[0960]

Synthesis of 6-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one

A solution of 5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate (3.40 g), morpholine (5.18 g), tripotassium phosphate (3.79 g), tris(dibenzylideneacetone) dipalladium (0) (109 mg) and 2-(di-tert-butylphosphino)biphenyl (71 mg) in 1,2-dimethoxyethane (24 mL) was stirred in a nitrogen atmosphere at 80°C for one and a half hours. The reaction solution was returned to room temperature, and water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 2.56 g of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.07-2.13 (m, 2H), 2.59 (t, J=6.4 Hz, 2H), 2.89 (t, J=6.4 Hz, 2H), 3.31 (t, J=4.8 Hz, 4H), 3.85 (t, J=4.8 Hz, 4H), 6.61 (d, J=2.4 Hz, 1H), 6.79 (dd, J=2.4, 9.2 Hz, 1H), 7.96 (d, J=8.8 Hz, 1H).

[0961]

Synthesis of 6-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one oxime

630 mg of the title compound was obtained

from 6-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one (700 mg) in the same manner as in Example 971. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82-1.89 (m, 2H), 2.71 (t, J=6.4 Hz, 2H), 2.78 (t, J=6.4 Hz, 2H), 3.20 (t, J=4.8 Hz, 4H), 3.85 (t, J=4.8 Hz, 4H), 6.62 (d, J=2.4, 8.8 Hz, 1H), 6.77 (dd, J=2.4, 8.8 Hz, 1H), 7.78 (d, J=8.8 Hz, 1H).

[0962]

Synthesis of 6-morpholin-4-yl-1,2,3,4-tetrahydro-naphthalen-1-ylamine

429 mg of the title compound was obtained from 6-morpholin-4-yl-3,4-dihydro-2H-naphthalen-1-one oxime (547 mg) in the same manner as in Example 971. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52-1.68 (m, 1H), 1.70-1.78 (m, 1H), 1.86-2.04 (m, 2H), 2.65-2.81 (m, 2H), 3.12 (t, J=4.8 Hz, 4H), 3.84 (t, J=4.8 Hz, 4H), 3.92 (t, J=5.6 Hz, 1H), 6.60 (d, J=2.4 Hz, 1H), 6.77 (dd, J=2.4, 8.4 Hz, 1H), 7.29 (d, J=8.4 Hz, 1H).

[0963]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]valeric acid (6-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl)amide

300 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (377 mg) and 6-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-

ylamine (150 mg) in the same manner as in Example 418. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82-1.95 (m, 3H), 2.00-2.11 (m, 3H), 2.30 (s, 3H), 2.72-2.81 (m, 4H), 3.13-3.16 (m, 4H), 3.58 (t, J=6.4 Hz, 2H), 3.84-3.86 (m, 4H), 3.85 (s, 3H), 5.20-5.25 (m, 1H), 6.11 (d, J=8.4 Hz, 1H), 6.63 (d, J=2.4, 1H), 6.79 (dd, J=2.4, 8.4 Hz, 1H), 6.92-6.95 (m, 2H). 6.93 (s, 1H), 7.09 (s, 1H), 7.20-7.24 (m, 2H), 7.71 (s, 1H).

[0964]

<u>Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R) and (1S)-(6-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl]piperidin-2-one</u>

259 mg of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(6-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl)piperidin-2-one as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (6-morpholin-4-yl-1,2,3,4-tetrahydronaphthalen-1-yl)amide (300 mg) in the same manner as in Example 418. Next, the compound (70.0 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 30:70) to obtain the title optically active substance with a retention time of 10 minutes (Example 985, 27.0 mg; >98% ee) and the title optically active substance with a retention time of 14 minutes (Example 986, 28.0 mg; >97% ee). The physical

properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.71-1.88 (m, 4H), 1.95-2.02 (m, 1H), 2.06-2.12 (m, 1H), 2.30 (s, 3H), 2.72-2.82 (m, 4H), 3.03-3.12 (m, 1H), 3.12-3.16 (m, 4H), 3.14-3.22 (m, 1H), 3.83-3.86 (m, 4H), 3.86 (s, 3H), 6.60 (dd, J=6.4, 10Hz, 1H), 6.62 (d, J=2.4 Hz, 1H), 6.73 (dd, J=2.4, 8.4 Hz, 1H), 6.93 (s, 1H), 7.01 (d, J=8.8 Hz, 1H), 7.06 (s, 1H), 7.07 (d, J=8.8 Hz, 1H), 7.25 (d, J=8.4 Hz, 1H), 7.72 (s, 1H), 7.90 (s, 1H).

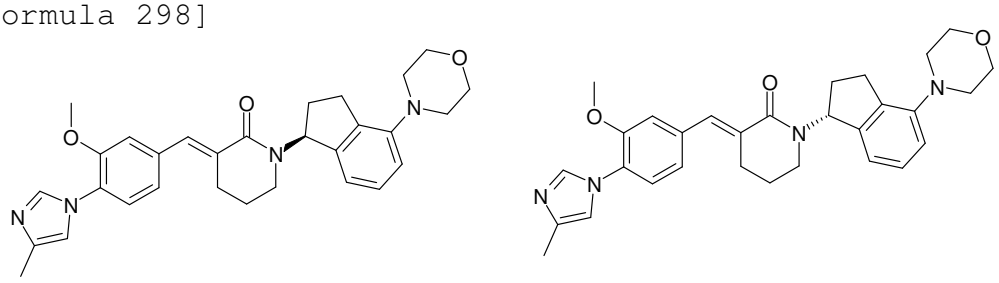
[0965]

Example 987 and Example 988

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R) and [(1S)-4-morpholin-4-ylindan-1-yl]piperidin-2-one

[0966]

[Formula 298]



Synthesis of 1-oxo-indan-4-yl trifluoromethanesulfonate

1.30 g of the title compound was obtained from 4-hydroxyindanone (2.00 g) in the same manner as in Example 985. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.77-2.80 (m, 2H), 3.24-3.27 (m,

2H), 7.47–7.52 (m, 2H), 7.79 (dd, J=2.0, 6.0 Hz, 1H).

[0967]

Synthesis of 4-morpholin-4-ylindan-1-one

627 mg of the title compound was obtained from 1-oxo-indan-4-yl trifluoromethansulfonate (3.28 g) in the same manner as in Example 985. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.69–2.72 (m, 2H), 3.06–3.10 (m, 6H), 3.87–3.89 (m, 4H), 7.14 (d, J=8.0 Hz, 1H), 7.35 (t, J=8.0 Hz, 1H), 7.44 (d, J=8.0 Hz, 1H).

[0968]

Synthesis of 4-morpholin-4-ylindan-1-one oxime

178 mg of the title compound was obtained from 4-morpholin-4-ylindan-1-one (250 mg) in the same manner as in Example 971. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.80–3.01 (m, 4H), 3.01–3.04 (m, 4H), 3.85–3.87 (m, 4H), 6.77 (dd, J=0.8, 8.0 Hz, 1/3H), 6.93 (dd, J=0.8, 8.0 Hz, 2/3H), 7.14 (t, J=8.0, 1/3H), 7.22–7.26 (m, 1H), 7.35 (dd, J=0.8, 8.0 Hz, 2/3H).

[0969]

Synthesis of 4-morpholin-4-ylindan-1-ylamine

140 mg of the title compound was obtained from 4-morpholin-4-ylindan-1-one oxime (178 mg) in the same manner as in Example 971. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.71–1.79 (m, 1H), 2.45–2.53 (m, 1H), 2.71 (td, J=8.0, 16 Hz, 1H), 2.92–3.01 (m, 3H),

3.03–3.09 (m, 2H), 3.80–3.88 (m, 4H), 4.39 (t, J=7.6 Hz, 1H), 6.78 (d, J=7.6 Hz, 1H), 7.04 (d, J=7.6 Hz, 1H), 7.21 (t, J=7.6 Hz, 1H).

[0970]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]valeric acid (4-morpholin-4-ylindan-1-yl)amide

203 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (432 mg) and 4-morpholin-4-ylindan-1-ylamine (140 mg) in the same manner as in Example 418. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82–1.94 (m, 2H), 2.02–2.09 (m, 1H), 2.29 (s, 3H), 2.65–2.73 (m, 1H), 2.72–2.79 (m, 2H), 2.79–2.88 (m, 1H), 2.93–2.99 (m, 2H), 2.97–3.05 (m, 1H), 3.07–3.12 (m, 2H), 3.60 (t, J=6.0 Hz, 2H), 3.84–3.87 (m, 4H), 3.86 (s, 3H), 5.59 (q, J=8.0 Hz, 1H), 6.21 (d, J=8.0 Hz, 1H), 6.84 (d, J=8.0 Hz, 1H), 6.92 (t, J=0.8 Hz, 1H), 6.95–6.97 (m, 2H), 7.00 (d, J=8.0 Hz, 1H), 7.18 (s, 1H), 7.21–7.26 (m, 2H), 7.70 (s, 1H).

[0971]

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R) and (1S)-4-morpholin-4-ylindan-1-yl]piperidin-2-one

118 mg of (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(4-morpholin-4-ylindan-1-

yl)piperidin-2-one as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (4-morpholin-4-ylindan-1-yl)amide (203 mg) in the same manner as in Example 418. Next, the compound (5.00 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 70:30) to obtain the title optically active substance with a retention time of 45 minutes (Example 987, 0.80 mg; >99% ee) and the title optically active substance with a retention time of 47 minutes (Example 988, 0.90 mg; >87% ee). The physical properties of the optically active substances are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.74-1.90 (m, 2H), 1.92-2.04 (m, 1H), 2.30 (s, 3H), 2.44-2.53 (m, 1H), 2.74-3.04 (m, 6H), 3.06-3.18 (m, 4H), 3.81-3.90 (m, 4H), 3.86 (s, 3H), 6.50 (t, J=8.0 Hz, 1H), 6.81 (d, J=7.6 Hz, 1H), 6.83 (d, J=7.6 Hz, 1H), 6.93 (s, 1H), 7.05 (s, 1H), 7.06 (d, J=7.6 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.25 (d, J=7.6 Hz, 1H), 7.72 (s, 1H), 7.90 (s, 1H).

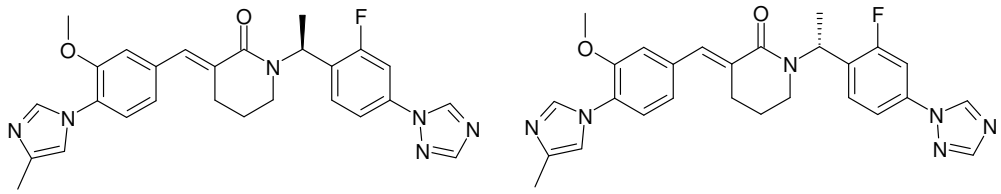
[0972]

Example 989 and Example 990

Synthesis of (E)-1-[(1R) and (1S)-(2-fluoro-4-[1,2,4]triazol-1-ylphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0973]

[Formula 299]



Synthesis of 1-(2-fluoro-4-[1,2,4]triazol-1-ylphenyl)ethanone

A solution of 2,4-difluoroacetophenone (2.43 mL), 1,2,4-triazole (1.59 g) and potassium carbonate (5.32 g) in toluene (10 mL) was stirred at 100°C overnight. The reaction solution was returned to room temperature, and then water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain 187 mg of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.68 (d, J=4.8 Hz, 3H), 7.56 (dd, J=2.5, 8.0 Hz, 1H), 7.60 (dd, J=2.5, 12 Hz, 1H), 8.05 (t, J=8.4 Hz, 1H), 8.13 (s, 1H), 8.65 (s, 1H).

[0974]

Synthesis of 1-(2-fluoro-4-[1,2,4]triazol-1-ylphenyl)ethylamine

80 mg of the title compound was obtained from 1-(2-fluoro-4-[1,2,4]triazol-1-yl-phenyl)ethanone (187 mg) via a crude oxime in the same manner as in Example

971. Properties data of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.44 (d, J=6.8 Hz, 3H), 4.45 (q, J=6.8 Hz, 1H), 7.41-7.47 (m, 2H), 7.58-7.63 (m, 1H), 8.10 (s, 1H), 8.55 (s, 1H).

[0975]

Synthesis of (E)-5-chloro-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]valeric acid [1-(2-fluoro-4-[1,2,4]-triazol-1-ylphenyl)ethyl]amide

171 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (226 mg) and 1-(2-fluoro-4-[1,2,4]triazol-1-ylphenyl)ethylamine (80 mg) in the same manner as in Example 418. Properties data of the compound are as follows. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.64 (d, J=7.2 Hz, 3H), 1.95-2.03 (m, 2H), 2.30 (s, 3H), 2.70-2.74 (m, 2H), 3.57-3.60 (m, 2H), 3.86 (s, 3H), 5.36 (quint, 7.2 Hz, 1H), 6.44-6.50 (brs, 1H), 6.93-6.97 (m, 3H), 7.21 (s, 1H), 7.25 (d, J=7.6 Hz, 1H), 7.45 (dd, J=2.0, 8.4 Hz, 1H) 7.48-7.51 (m, 2H), 7.72 (s, 1H), 8.09 (s, 1H), 8.54 (s, 1H).

[0976]

Synthesis of (E)-1-[(1R) and (1S)-(2-fluoro-4-[1,2,4]triazol-1-ylphenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

121 mg of (E)-1-(1-(2-fluoro-4-[1,2,4]triazol-1-ylphenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one as

a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1-(2-fluoro-4-[1,2,4]-triazol-1-ylphenyl)ethyl)amide (171 mg) in the same manner as in Example 418. Next, the compound (10.0 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 13 minutes (Example 989, 2.6 mg; >99% ee) and the title optically active substance with a retention time of 15 minutes (Example 990, 3.9 mg; >94% ee). Properties data of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.65 (d, J=7.2 Hz, 3H), 1.80-1.88 (m, 2H), 2.30 (s, 3H), 2.75-2.84 (m, 2H), 3.09-3.15 (m, 1H), 3.35-3.41 (m, 1H), 3.85 (s, 3H), 6.17 (q, J=7.2 Hz, 1H), 6.93 (s, 1H), 7.02-7.04 (m, 2H), 7.25 (d, J=8.4 Hz, 1H), 7.47-7.57 (m, 3H), 7.72 (s, 1H), 7.86 (s, 1H), 8.11 (s, 1H), 8.57 (s, 1H).

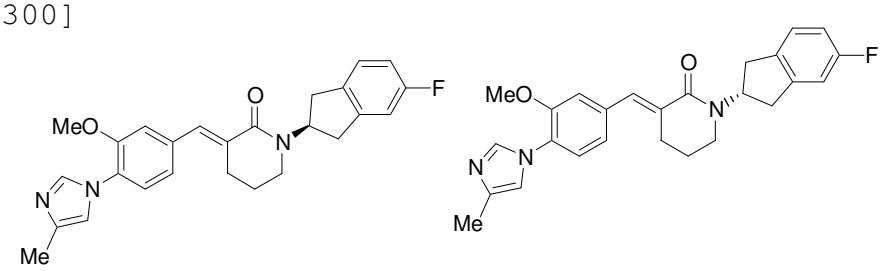
[0977]

Example 991 and Example 992

Synthesis of (E)-1-[(2S) and (2R)-5-fluoroindan-2-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0978]

[Formula 300]



IPEA (0.58 mL), EDC (0.38 g) and HOBT (0.27 g) were added to a suspension of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 5-fluoroindan-2-ylamine (CAS #2340-06-9, 151 mg) in DMF (10 mL) at room temperature, and the reaction solution was stirred at room temperature for 14 hours. A saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed sequentially with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: ethyl acetate-methanol system) to obtain (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (5-fluoroindan-2-yl)amide (318 mg). Sodium hydride (containing mineral oil at 40%, 60 mg) was added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (5-fluoroindan-2-yl)amide (318 mg) in DMF (6 mL) at room temperature, and the reaction solution was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution and the organic layer was

partitioned. The organic layer was washed sequentially with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system) to obtain (E)-1-(5-fluoroindan-2-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one as a racemate (170 mg). The compound (10 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 9.1 minutes (Example 991, 4 mg; >95% ee) and the title optically active substance with a retention time of 9.8 minutes (Example 992, 4 mg; >94% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82–1.90 (m, 2H), 2.29 (s, 3H), 2.77–2.84 (m, 2H), 2.91–3.04 (m, 2H), 3.18–3.30 (m, 4H), 3.85 (s, 3H), 5.72–5.81 (m, 1H), 6.83–6.94 (m, 3H), 7.00–7.05 (m, 2H), 7.15 (dd, J=5.2 Hz, 8.0 Hz, 1H), 7.22–7.26 (m, 1H), 7.70 (d, J=1.6 Hz, 1H), 7.82–7.85 (m, 1H).

[0979]

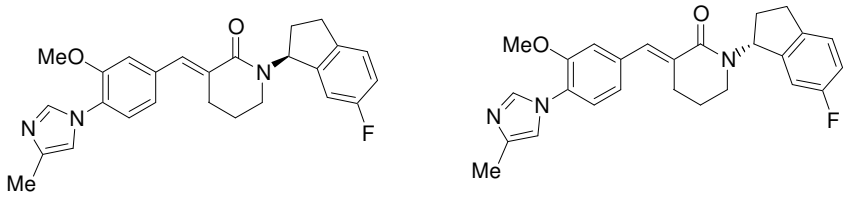
Example 993 and Example 994

Synthesis of (E)-1-[(1R and 1S)-6-fluoroindan-1-yl]-3-

[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzyliden])piperidin-2-one

[0980]

[Formula 301]



IPEA (0.58 mL), EDC (0.38 g) and HOBT (0.27 g) were added to a suspension of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 6-fluoroindan-1-ylamine (CAS #168902-77-0, 151 mg) in DMF (10 mL) at room temperature, and the reaction solution was stirred at room temperature for 12 hours. A saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed sequentially with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system) to obtain (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (6-fluoroindan-1-yl)amide

(270 mg). Sodium hydride (containing mineral oil at 40%, 60 mg) was added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (6-fluoroindan-1-yl)amide (270 mg) in DMF (5 mL) at room temperature, and the reaction solution was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed sequentially with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system) to obtain (E)-1-(6-fluoroindan-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one as a racemate (200 mg). The compound (200 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 7.4 minutes (Example 994, 72 mg; >99% ee) and the title optically active substance with a retention time of 8.4 minutes (Example 993, 68 mg; >96% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-1.92 (m, 2H), 1.97-2.10 (m, 1H), 2.30 (s, 3H), 2.48-2.57 (m, 1H), 2.74-3.22 (m, 6H), 3.87 (s, 3H), 6.44-6.50 (m, 1H), 6.83-6.88 (m, 1H), 6.90-6.96 (m, 2H), 7.03-7.08 (m, 2H), 7.16-7.21 (m, 1H), 7.23-7.28 (m, 1H), 7.71 (d, J=0.8 Hz, 1H), 7.87-7.91 (m, 1H).

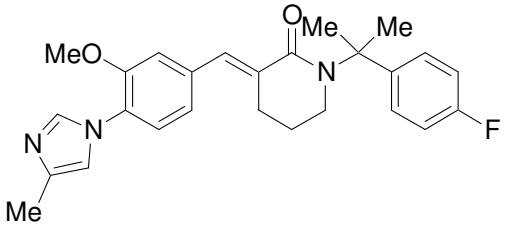
[0981]

Example 995

Synthesis of (E)-1-[1-(4-fluorophenyl)-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0982]

[Formula 302]



43 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (100 mg) and 1-(4-fluorophenyl)-1-methylethylamine (CAS #17797-10-3, 51 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75 (s, 6H), 1.90-2.00 (m, 2H), 2.32 (s, 3H), 2.76-2.85 (m, 2H), 3.57-3.64 (m, 2H), 3.83 (s, 3H), 6.91-7.05 (m, 5H), 7.20-7.33 (m, 3H), 7.63 (brs, 1H), 7.79 (brs, 1H).

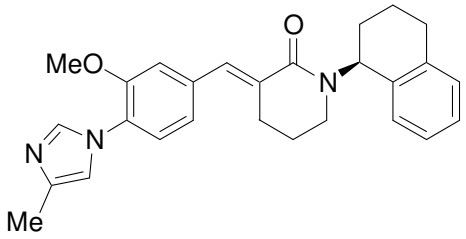
[0983]

Example 996

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]piperidin-2-one

[0984]

[Formula 303]



72 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and (1S)-1,2,3,4-tetrahydronaphthalen-1-ylamine (74 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70-1.96 (m, 4H), 1.98-2.16 (m, 2H), 2.30 (s, 3H), 2.73-2.98 (m, 4H), 3.03-3.10 (m, 1H), 3.17-3.26 (m, 1H), 3.87 (s, 3H), 6.10-6.17 (m, 1H), 6.93 (s, 1H), 7.04-7.18 (m, 6H), 7.22-7.28 (m, 1H), 7.71 (d, J=1.2 Hz, 1H), 7.91 (brs, 1H).

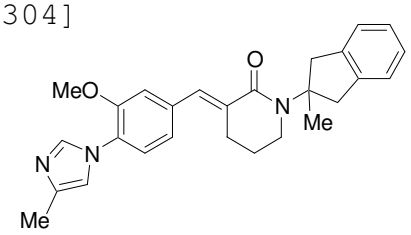
[0985]

Example 997

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-(2-methylindan-2-yl)piperidin-2-one

[0986]

[Formula 304]



80 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (150 mg) and 2-methylindan-2-ylamine (CAS #312753-94-9, 98 mg) in the same manner as in Example 418. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.42 (s, 3H), 1.88-1.96 (m, 2H), 2.30 (s, 3H), 2.76-2.83 (m, 2H), 3.39 (s, 4H), 3.53-3.59 (m, 2H), 3.85 (s, 3H), 6.91-6.93 (m, 1H), 7.00-7.05 (m,2H), 7.13-7.25 (m, 5H), 7.70 (d, J=1.6 Hz, 1H), 7.76-7.78 (m, 1H).

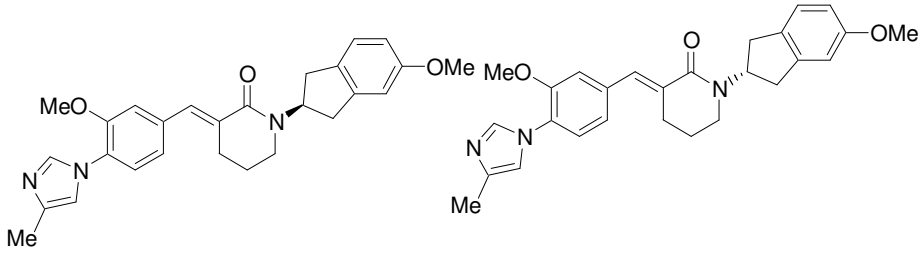
[0987]

Example 998 and Example 999

Synthesis of (E)-1-[(2R and 2S)-5-methoxyindan-2-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0988]

[Formula 305]



135 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 5-methoxyindan-2-ylamine (CAS #73305-09-6, 164 mg) in the same manner as in Example 418. The compound (8 mg) was fractionated using CHIRALCEL™ OJ manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 8.8 minutes (Example 999, 1.3 mg, >99% ee) and the title optically active substance with a retention time of 11.7 minutes (Example 998, 1.9 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81-1.89 (m, 2H), 2.37 (s, 3H), 2.75-2.82 (m, 2H), 2.88-3.00 (m, 2H), 3.18-3.30 (m, 4H), 3.79 (s, 3H), 3.87 (s, 3H), 5.73-5.82 (m, 1H), 6.72-6.80 (m, 2H), 6.97 (s, 1H), 7.02-7.14 (m, 3H), 7.24-7.28 (m, 1H), 7.83 (s, 1H), 8.08 (s, 1H).

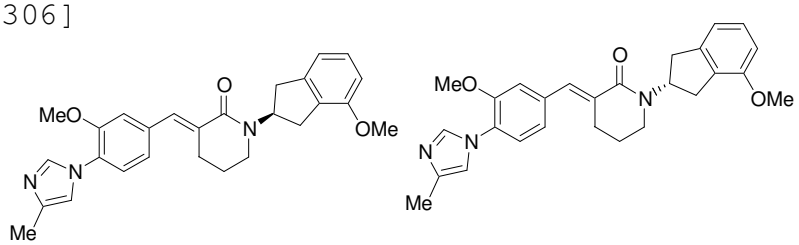
[0989]

Example 1000 and Example 1001

Synthesis of (E)-1-[(2R and 2S)-4-methoxyindan-2-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0990]

[Formula 306]



205 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 4-methoxyindan-2-ylamine (CAS #76413-92-8, 164 mg) in the same manner as in Example 418. The compound (3 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 10.3 minutes (Example 1000, 1.1 mg, >99% ee) and the title optically active substance with a retention time of 10.9 minutes (Example 1001, 1.2 mg, >93% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.80-1.88 (m, 2H), 2.30 (s, 3H), 2.77-2.82 (m, 2H), 2.87-3.00 (m, 2H), 3.20-3.35 (m, 4H), 3.83 (s, 3H), 3.87 (s, 3H), 5.77-5.86 (m, 1H), 6.69 (d, J=8.0 Hz, 1H), 6.84 (d, J=7.6 Hz, 1H) 6.91-6.93 (m, 1H), 7.00-7.05 (m, 2H), 7.16 (dd, J=7.6 Hz, 8.0 Hz, 1H), 7.22-7.26 (m, 1H), 7.70 (d, J=1.2 Hz, 1H), 7.82-7.85 (m, 1H).

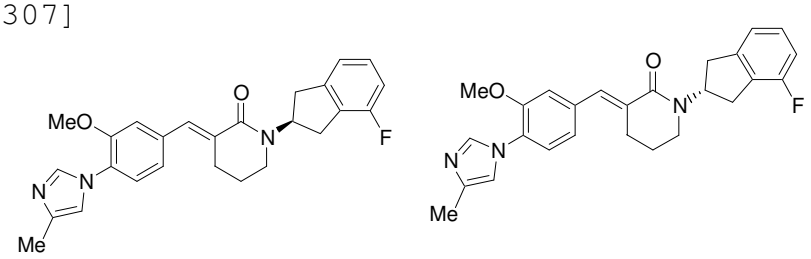
[0991]

Example 1002 and Example 1003

Synthesis of (E)-1-[(2R and 2S)-4-fluoroindan-2-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0992]

[Formula 307]



97 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (500 mg) and 4-fluoroindan-2-ylamine (CAS #162752-09-2, 230 mg) in the same manner as in Example 418. The compound (8 mg) was fractionated using CHIRALCEL™ OJ manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol-hexane system) to obtain the title optically active substance with a retention time of 18.2 minutes (Example 1003, 1.2 mg, >99% ee) and the title optically active substance with a retention time of 22.8 minutes (Example 1002, 1.0 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82-1.90 (m, 2H), 2.30 (s, 3H), 2.78-2.83 (m, 2H), 2.97-3.06 (m, 2H), 3.25-3.36 (m, 4H), 3.85 (s, 3H), 5.76-5.84 (m, 1H), 6.84-6.94 (m, 2H), 6.98-7.05 (m, 3H), 7.12-7.18 (m, 1H), 7.22-7.26 (m, 1H), 7.71 (d, J=1.6 Hz, 1H), 7.84 (brs, 1H).

[0993]

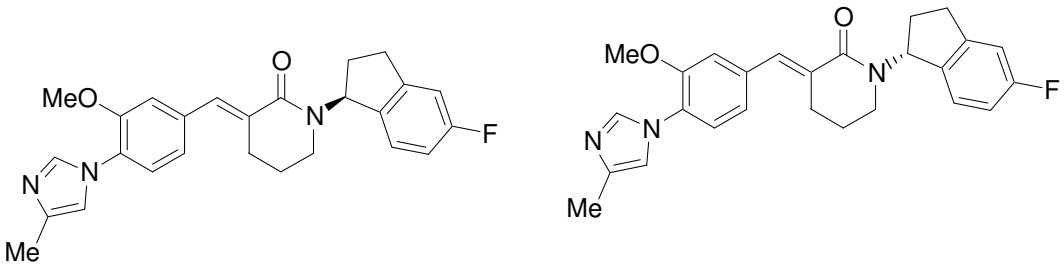
Example 1004 and Example 1005

Synthesis of (E)-1-[(1R and 1S)-5-fluoroindan-1-yl]-3-

[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0994]

[Formula 308]



26 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (80 mg) and 5-fluoroindan-1-ylamine (CAS #148960-33-2, 54 mg) in the same manner as in Example 418. The compound (20 mg) was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 8.0 minutes (Example 1005, 6.9 mg, >99% ee) and the title optically active substance with a retention time of 8.8 minutes (Example 1004, 5.3 mg, >95% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-2.08 (m, 3H), 2.30 (s, 3H), 2.49-2.58 (m, 1H), 2.75-3.20 (m, 6H), 3.86 (s, 3H), 6.42-6.48 (m, 1H), 6.86-6.97 (m, 3H), 7.04-7.14 (m, 3H), 7.24-7.28 (m,1H), 7.71 (s, 1H), 7.89 (brs, 1H).

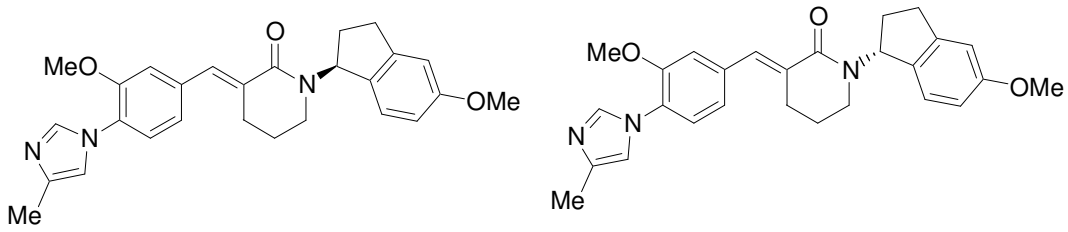
[0995]

Example 1006 and Example 1007

Synthesis of (E)-1-[(1R and 1S)-5-methoxyindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0996]

[Formula 309]



27 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (80 mg) and 5-methoxyindan-1-ylamine (CAS #52372-95-9, 58 mg) in the same manner as in Example 418. The compound (27 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane-ethanol system) to obtain the title optically active substance with a retention time of 16.0 minutes (Example 1007, 3.5 mg, >99% ee) and the title optically active substance with a retention time of 17.2 minutes (Example 1006, 2.1 mg, >95% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-2.05 (m, 3H), 2.37 (s, 3H), 2.47-2.58 (m, 1H), 2.76-3.18 (m, 6H), 3.80 (s, 3H), 3.88 (s, 3H), 6.39-6.45 (m, 1H), 6.74-6.81 (m, 2H), 6.97 (s, 1H), 7.04-7.10 (m, 3H), 7.24-7.29 (m, 1H),

7.88 (s, 1H), 8.07 (brs, 1H).

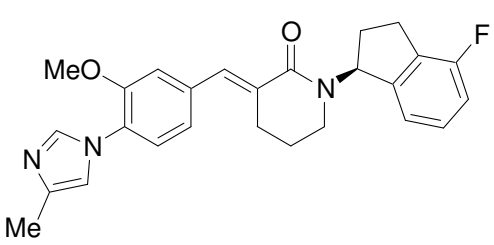
[0997]

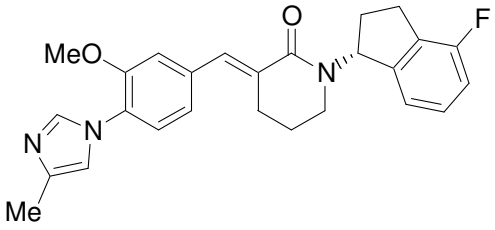
Example 1008 and Example 1009

Synthesis of (E)-1-[(1R and 1S)-4-fluoroindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[0998]

[Formula 310]





178 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 4-fluoroindan-1-ylamine (CAS #148960-34-3, 151 mg) in the same manner as in Example 418. The compound (178 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 7.2 minutes (Example 1009, 71 mg, >99% ee) and the title optically active substance with a retention time of 9.5 minutes (Example 1008, 72 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.90 (m, 2H), 1.98-2.08 (m, 1H), 2.30 (s, 3H), 2.50-2.60 (m, 1H), 2.75-2.98 (m,

3H), 3.02-3.21 (m, 3H), 3.86 (s, 3H), 6.49-6.55 (m, 1H), 6.90-7.00 (m, 3H), 7.02-7.08 (m, 2H), 7.16-7.28 (m, 2H), 7.71 (s, 1H), 7.89 (brs, 1H).

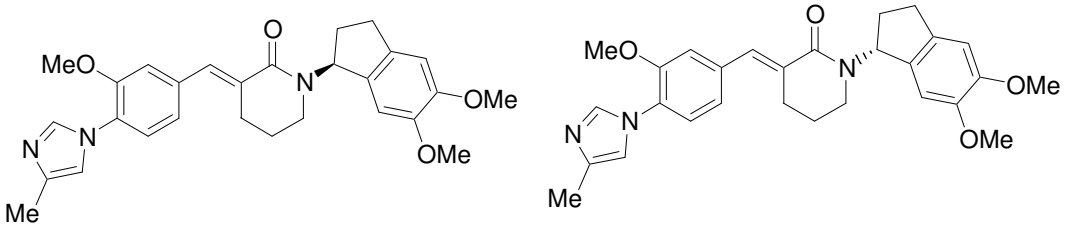
[0999]

Example 1010 and Example 1011

Synthesis of (E)-1-[(1R and 1S)-5,6-dimethoxyindan-1-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1000]

[Formula 311]



[1001]

178 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 5,6-dimethoxyindan-1-ylamine (CAS #91247-06-2, 151 mg) in the same manner as in Example 418. The compound (178 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 9.3 minutes (Example 1011, 71 mg, >99% ee) and the title optically active substance with a retention time of 10.9 minutes (Example 1010, 72 mg,

>93% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70-1.89 (m, 2H), 1.93-2.03 (m, 1H), 2.30 (s, 3H), 2.49-2.59 (m, 1H), 2.75-3.07 (m, 5H), 3.11-3.20 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.47 (dd, J=6.4 Hz, 8.4 Hz, 1H), 6.69 (s, 1H), 6.78 (s, 1H), 6.94 (brs, 1H), 7.04-7.10 (m, 2H), 7.24-7.30 (m, 1H), 7.72 (brs, 1H), 7.91 (brs, 1H).

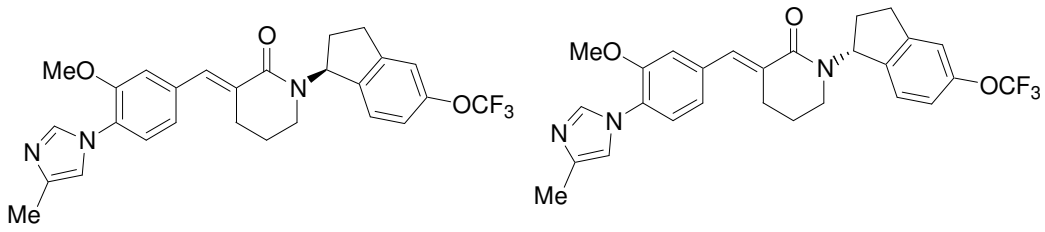
[1002]

Example 1012 and Example 1013

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R and 1S)-5-trifluoromethoxyindan-1-yl]piperidin-2-one

[1003]

[Formula 312]



6.8 mg of the title compound as a racemate was obtained from 5-trifluoromethoxyindanone (CAS #173252-76-1, 1 g) in the same manner as in Example 973. The compound (6.8 mg) was fractionated using CHIRALCEL™ OJ manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane-ethanol system) to obtain the title optically active substance with a retention time of 10.2 minutes (Example 1012, 1.9 mg, >99% ee) and the title optically

active substance with a retention time of 17.3 minutes (Example 1013, 1.9 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72–2.10 (m, 3H), 2.30 (s, 3H), 2.50–2.60 (m, 1H), 2.75–3.22 (m, 6H), 3.86 (s, 3H), 6.48 (dd, J=8.0 Hz, 8.4 Hz, 1H), 6.92–6.94 (m, 1H), 7.02–7.08 (m, 3H), 7.10 (brs, 1H), 7.17 (d, J=8.4 Hz, 1H), 7.24–7.28 (m, 1H), 7.71 (d, J=0.8 Hz, 1H), 7.89 (brs, 1H).

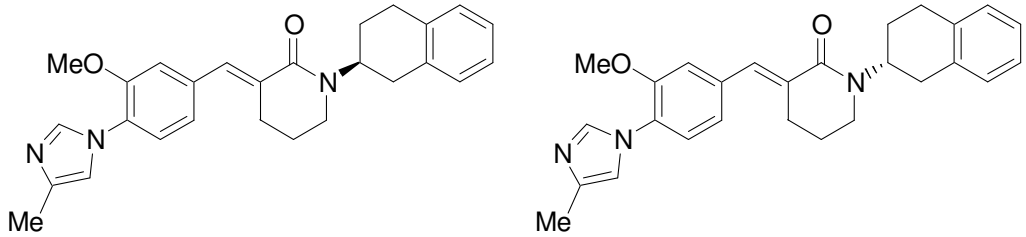
[1004]

Example 1014 and Example 1015

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(2R and 2S)-1,2,3,4-tetrahydronaphthalen-2-yl]piperidin-2-one

[1005]

[Formula 313]



IPEA (0.58 mL), EDC (0.38 g) and HOBT (0.27 g) were added to a suspension of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 1,2,3,4-tetrahydronaphthalen-2-ylamine (148 mg) in DMF (10 mL) at room temperature, and the reaction solution was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium bicarbonate and

ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed sequentially with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system) to obtain (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1,2,3,4-tetrahydronaphthalen-2-yl)amide (255 mg). Sodium hydride (containing mineral oil at 40%, 50 mg) was added to a solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid (1,2,3,4-tetrahydronaphthalen-2-yl)amide (255 mg) in DMF (6 mL) at room temperature, and the reaction solution was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed sequentially with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica

gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane–ethyl acetate system) to obtain (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(1,2,3,4-tetrahydronaphthalen-2-yl)piperidin-2-one as a racemate (210 mg). The compound (12 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 9.5 minutes (Example 1014, 6.0 mg; >99% ee) and the title optically active substance with a retention time of 13.0 minutes (Example 1015, 5.9 mg; >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.80–2.05 (m, 4H), 2.31 (s, 3H), 2.76–3.10 (m, 6H), 3.41 (t, J=5.6 Hz, 2H), 3.86 (s, 3H), 5.03–5.13 (m, 1H), 6.94 (s, 1H), 7.02–7.15 (m, 6H), 7.22–7.28 (m, 1H), 7.74 (s, 1H), 7.85 (brs, 1H).

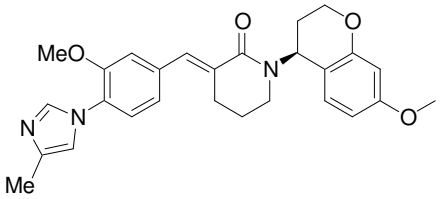
[1006]

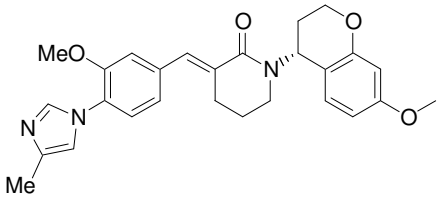
Example 1016 and Example 1017

Synthesis of (E)-1-[(4R and 4S)-7-methoxychroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1007]

[Formula 314]





285 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 7-methoxychroman-4-ylamine (CAS #802037-18-9, 180 mg) in the same manner as in Example 418. The compound (10 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 12.9 minutes (Example 1016, 2.3 mg, >99% ee) and the title optically active substance with a retention time of 20.5 minutes (Example 1017, 2.8 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.71-1.91 (m, 2H), 2.08-2.22 (m, 2H), 2.30 (s, 3H), 2.74-2.84 (m, 1H), 2.87-2.96 (m, 1H), 3.07-3.23 (m, 2H), 3.77 (s, 3H), 3.87 (s, 3H), 4.18-4.27 (m, 1H), 4.30-4.37 (m, 1H), 6.12-6.18 (m, 1H), 6.40 (d, J=2.4 Hz, 1H), 6.50 (dd, J=2.4 Hz, 8.8 Hz, 1H), 6.92-6.97 (m, 2H), 7.05-7.10 (m, 2H), 7.23-7.29 (m, 1H), 7.73 (d, J=1.6 Hz, 1H), 7.91 (brs, 1H).

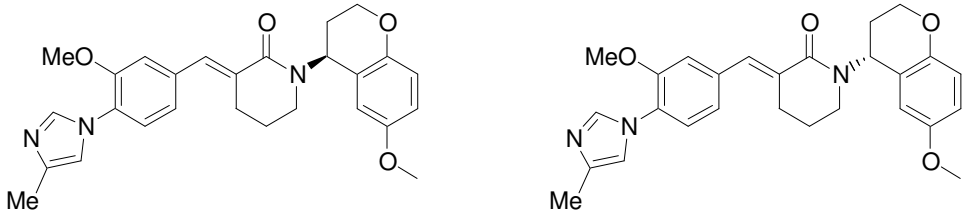
[1008]

Example 1018 and Example 1019

Synthesis of (E)-1-[(4R and 4S)-6-methoxychroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1009]

[Formula 315]



215 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 6-methoxychroman-4-ylamine (CAS #81816-60-6, 180 mg) in the same manner as in Example 418. The compound (12 mg) was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 10.7 minutes (Example 1018, 5.8 mg, >99% ee) and the title optically active substance with a retention time of 15.3 minutes (Example 1019, 5.5 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70-1.93 (m, 2H), 2.10-2.24 (m, 2H), 2.31 (s, 3H), 2.75-2.85 (m, 1H), 2.89-2.98 (m, 1H), 3.08-3.27 (m, 2H), 3.73 (s, 3H), 3.88 (s, 3H), 4.15-4.22 (m, 1H), 4.28-4.35 (m, 1H), 6.18-6.25 (m, 1H), 6.59 (d, J=3.2 Hz, 1H), 6.73-6.82 (m, 2H), 6.95 (s, 1H), 7.05-7.11 (m, 2H), 7.25-7.29 (m, 1H), 7.73 (d, J=1.2 Hz, 1H), 7.91 (brs, 1H).

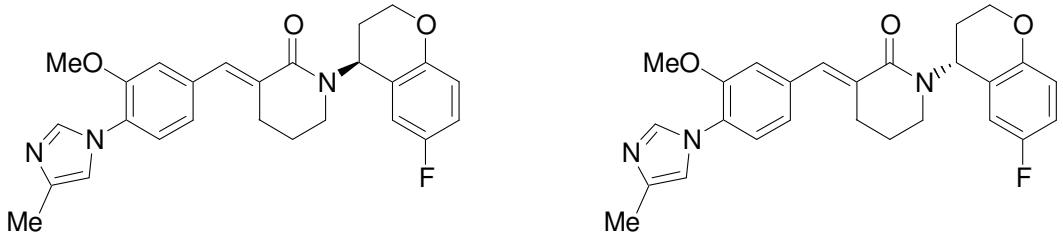
[1010]

Example 1020 and Example 1021

Synthesis of (E)-1-[(4R and 4S)-6-fluorochroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1011]

[Formula 316]



207 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 6-fluorochroman-4-ylamine (CAS #238764-22-2, 220 mg) in the same manner as in Example 418. The compound (11 mg) was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 9.4 minutes (Example 1020, 4.0 mg, >99% ee) and the title optically active substance with a retention time of 12.8 minutes (Example 1021, 3.9 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-1.94 (m, 2H), 2.07-2.26 (m, 2H), 2.31 (s, 3H), 2.74-2.84 (m, 1H), 2.91-3.01 (m, 1H), 3.07-3.15 (m, 1H), 3.19-3.28 (m, 1H), 3.88 (s,

3H), 4.17-4.26 (m, 1H), 4.32-4.40 (m, 1H), 6.19-6.25 (m, 1H), 6.75-6.82 (m, 2H), 6.84-6.90 (m, 1H), 6.95 (s, 1H), 7.05-7.11 (m, 2H), 7.25-7.30 (m, 1H), 7.74 (d, J=1.2 Hz, 1H), 7.92 (brs, 1H).

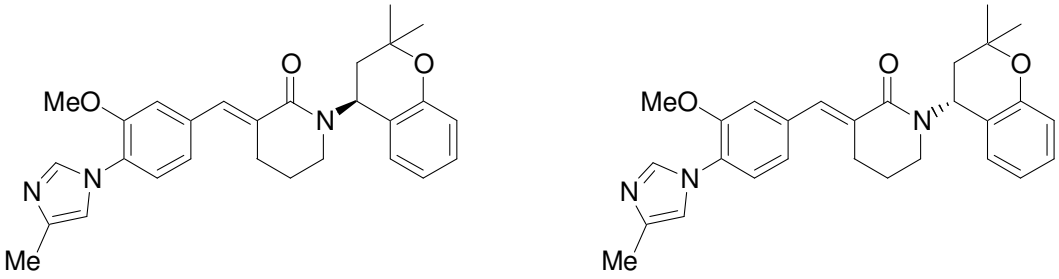
[1012]

Example 1022 and Example 1023

Synthesis of (E)-1-[(4R and 4S)-2,2-dimethylchroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1013]

[Formula 317]



217 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 2,2-dimethylchroman-4-ylamine (CAS #220634-41-3, 145 mg) in the same manner as in Example 418. The compound (20 mg) was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 8.2 minutes (Example 1022, 8.1 mg, >99% ee) and the title optically active substance with a retention time of 9.6 minutes (Example

1023, 8.0 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.37 (s, 3H), 1.48 (s, 3H), 1.73-2.04 (m, 4H), 2.31 (s, 3H), 2.74-2.83 (m, 1H), 2.89-2.98 (m, 1H), 3.04-3.22 (m, 2H), 3.88 (s, 3H), 6.23-6.33 (m, 1H), 6.83 (dd, J=1.2 Hz, 8.4 Hz, 1H), 6.86-6.91 (m, 1H), 6.95 (s, 1H), 7.05-7.12 (m, 3H), 7.14-7.19 (m, 1H), 7.24-7.30 (m, 1H), 7.73 (s, 1H), 7.92 (brs, 1H).

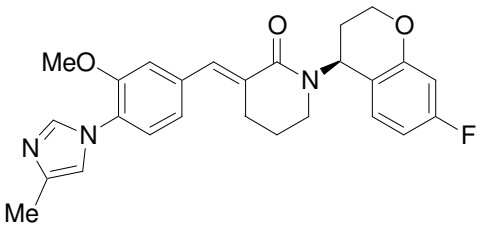
[1014]

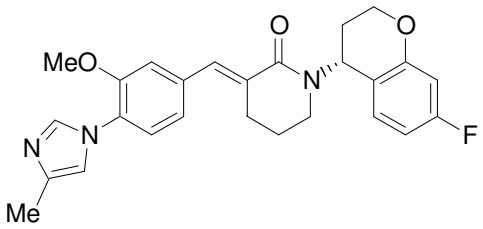
Example 1024 and Example 1025

Synthesis of (E)-1-[(4R) and (4S)-7-fluorochroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1015]

[Formula 318]





217 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (300 mg) and 7-fluorochroman-4-ylamine (CAS #774163-31-4, 168 mg) in the same manner as in Example 418. The compound (20 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical

Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 9.6 minutes (Example 1024, 8.1 mg, >99% ee) and the title optically active substance with a retention time of 14.0 minutes (Example 1025, 8.0 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72–1.93 (m, 2H), 2.10–2.25 (m, 2H), 2.30 (s, 3H), 2.74–2.83 (m, 1H), 2.89–2.97 (m, 1H), 3.04–3.11 (m, 1H), 3.17–3.25 (m, 1H), 3.87 (s, 3H), 4.21–4.28 (m, 1H), 4.33–4.40 (m, 1H), 6.15–6.21 (m, 1H), 6.57 (dd, J=2.4 Hz, 9.6 Hz, 1H), 6.62 (ddd, J=2.4 Hz, 8.4 Hz, 8.4 Hz, 1H), 6.93–7.04 (m, 2H), 7.05–7.10 (m, 2H), 7.25–7.30 (m, 1H), 7.74 (brs, 1H), 7.91 (brs, 1H).

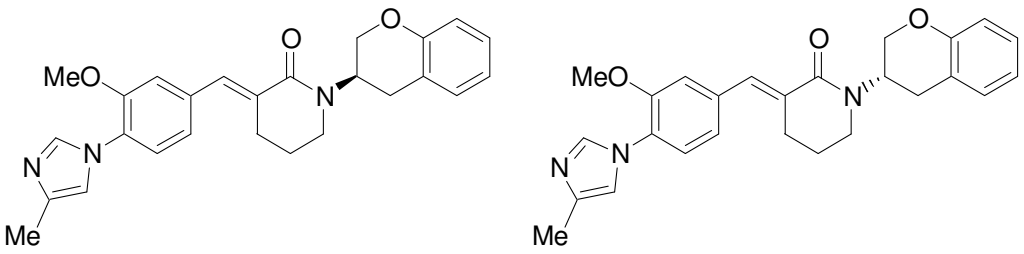
[1016]

Example 1026 and Example 1027

Synthesis of (E)-1-[(3R and 3S)-chroman-3-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1017]

[Formula 319]



171 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (250 mg) and chroman-3-ylamine (CAS #60575-19-1, 75 mg) in the same manner as in Example 418. The compound (10 mg) was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 11.6 minutes (Example 1026, 4.3 mg, >99% ee) and the title optically active substance with a retention time of 13.9 minutes (Example 1027, 4.3 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.75-1.94 (m, 2H), 2.31 (s, 3H), 2.78-2.84 (m, 2H), 3.04 (dd, J=6.8 Hz, 17.2 Hz, 1H), 3.15 (dd, J=6.4 Hz, 17.2 Hz, 1H), 3.40 (t, J=6.0 Hz, 2H), 3.86 (s, 3H), 4.21-4.32 (m, 2H), 5.09-5.16 (m, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.89-6.95 (m, 2H), 7.01-7.16 (m, 1H), 7.24-7.28 (m, 1H), 7.74 (s, 1H), 7.84 (brs, 1H).

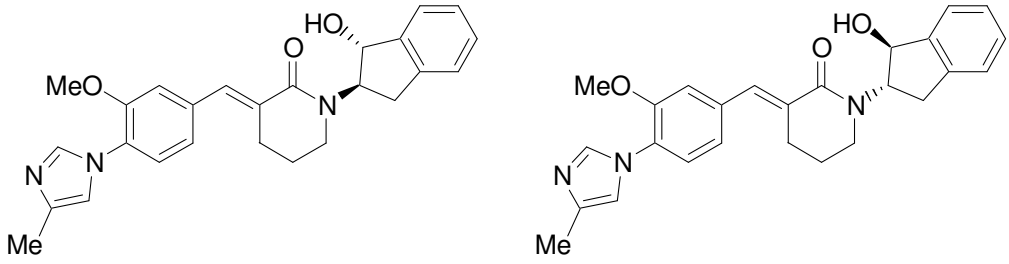
[1018]

Example 1028 and Example 1029

Synthesis of (E)-1-[(1R,2R and 1S,2S)-1-hydroxyindan-2-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1019]

[Formula 320]



125 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (800 mg) and trans-2-aminoindan-1-ol (CAS #13575-72-9, 446 mg) in the same manner as in Example 418. The compound (13 mg) was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol-hexane system) to obtain the title optically active substance with a retention time of 11.1 minutes (Example 1028, 5.7 mg, >99% ee) and the title optically active substance with a retention time of 13.7 minutes (Example 1029, 5.4 mg, >99% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.90-2.03 (m, 2H), 2.32 (s, 3H), 2.76-2.95 (m, 2H), 3.06-3.22 (m, 2H), 3.46-3.57 (m, 2H), 3.87 (s, 3H), 5.14-5.22 (m, 1H), 5.34 (d, J=7.6 Hz, 1H), 6.95 (s, 1H), 7.02-7.07 (m, 2H), 7.22-7.33 (m, 4H), 7.43-7.48 (m, 1H), 7.76 (s, 1H), 7.86 (s, 1H).

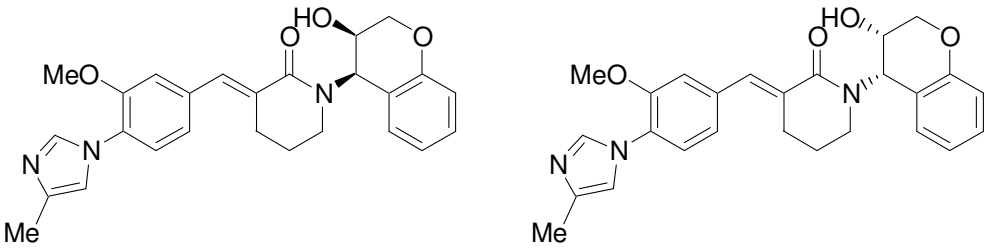
[1020]

Example 1030 and Example 1031

Synthesis of (E)-1-[(3R,4S and 3S,4R)-3-hydroxychroman-4-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1021]

[Formula 321]



198 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (600 mg) and cis-4-aminochroman-3-ol (CAS #58810-67-6, 332 mg) in the same manner as in Example 418. The compound (12 mg) was fractionated using CHIRALCEL™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol-hexane system) to obtain the title optically active substance with a retention time of 9.6 minutes (Example 1030, 5.4 mg, >99% ee) and the title optically active substance with a retention time of 12.6 minutes (Example 1031, 5.3 mg, >97% ee). The physical properties of the compounds are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70-1.95 (m, 2H), 2.31 (s, 3H), 2.78-2.92 (m, 2H), 3.15-3.23 (m, 1H), 3.30-3.39 (m, 1H), 3.85-3.97 (m, 1H), 3.87 (s, 3H), 4.02 (dd, J=8.0 Hz, 11.2 Hz, 1H), 4.26-4.32 (m, 1H), 4.43-4.48 (m, 1H),

6.00 (d, J=4.4 Hz, 1H), 6.91-7.01 (m, 3H), 7.05-7.13 (m, 3H), 7.22-7.29 (m, 2H), 7.75 (d, J=1.2 Hz, 1H), 7.89 (brs, 1H).

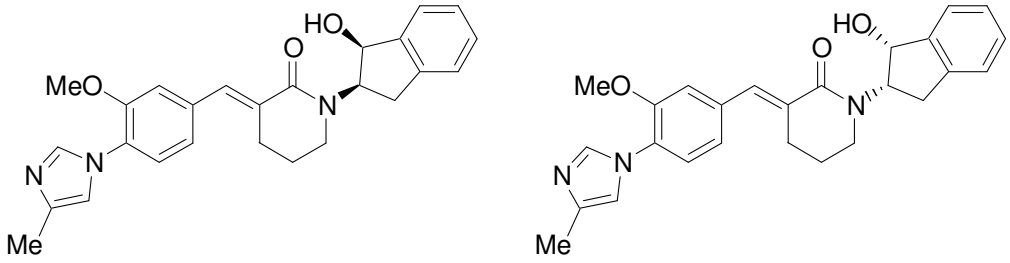
[1022]

Example 1032 and Example 1033

Synthesis of (E)-1-[(1S,2R and 1R,2S)-1-hydroxyindan-2-yl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1023]

[Formula 322]



198 mg of the title compound as a racemate was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (400 mg) and cis-2-aminoindan-1-ol (CAS #23337-80-6, 188 mg) in the same manner as in Example 418. The compound (12 mg) was fractionated using CHIRALCEL™ OJ manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 5.4 minutes (Example 1032, 3.5 mg, >99% ee) and the title optically active substance with a retention time of 7.9 minutes (Example 1033, 2.8 mg, >97% ee). The physical properties of the compound are

as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83-1.91 (m, 2H), 2.34 (s, 3H), 2.72-2.89 (m, 2H), 3.18 (dd, J=8.4 Hz, 16.4 Hz, 1H), 3.30-3.45 (m, 3H), 3.87 (s, 3H), 5.17-5.24 (m, 1H), 5.39 (d, J=5.2 Hz, 1H), 6.95 (s, 1H), 7.02-7.07 (m, 2H), 7.24-7.34 (m, 4H), 7.44-7.48 (m, 1H), 7.80-7.85 (m, 2H).

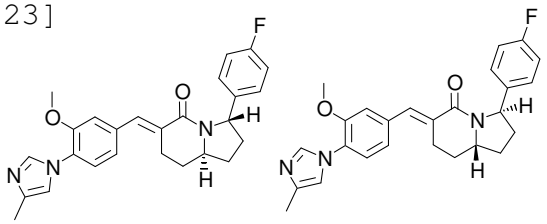
[1024]

Example 1034 and Example 1035

Synthesis of (E)-(3S)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9R)-hexahydroindolizin-5-one and (E)-(3R)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9S)-hexahydroindolizin-5-one

[1025]

[Formula 323]



Synthesis of 6-chloro-(3S*)-(4-fluorophenyl)-(9S*)-hexahydroindolizin-5-one

Sec-butyl lithium (1 M cyclohexane solution, 0.65 mL) was added to a solution of (3S*)-(4-fluorophenyl)-(9R*)-hexahydroindolizin-5-one (130 mg) synthesized in accordance with the method described in The Journal of Organic Chemistry, 2001, vol.66, p.886 in THF (5 mL) at -40°C, and the reaction solution was

stirred at -40°C for 1 hour. The reaction solution was added dropwise to a solution of p-toluenesulfonic acid chloride (117 mg) in THF (2 mL) at -40°C. The reaction solution was stirred at -40°C for 30 minutes, and further stirred at room temperature for 1 hour. Then, a saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane:ethyl acetate = 1:1 -> ethyl acetate) to obtain 84 mg of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.44-1.63 (m, 2H), 1.75-1.85 (m, 1H), 2.12-2.30 (m, 3H), 2.40-2.56 (m, 2H), 3.87-3.96 (m, 1H), 4.36 (dd, J=9.6, 6.8 Hz, 1H), 5.12 (t, J=8.0 Hz, 1H), 6.96-7.02 (m, 2H), 7.15-7.20 (m, 2H).

[1026]

Synthesis of diethyl [(3S*)-(4-fluorophenyl)-5-oxo-(9S*)-octahydroindolizin-6-yl]phosphonate

A mixture of 6-chloro-(3S*)-(4-fluorophenyl)-(9S*)-hexahydroindolizin-5-one (84 mg) with triethyl phosphite (1 mL) was stirred at 170°C for 10 hours. After allowing the reaction solution to be cooled to room temperature, the reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution

solvent: ethyl acetate -> ethyl acetate:methanol = 9:1) to obtain 86 mg of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.22-1.38 (m, 6H), 1.49-1.79 (m, 2H), 2.07-2.29 (m, 4H), 2.36-2.54 (m, 1H), 3.70-3.88 (m, 1H), 4.02-4.25 (m, 5H), 5.13 (t, J=8.0 Hz, 1H), 6.93-6.99 (m, 2H), 7.15-7.27 (m, 2H).

[1027]

Synthesis of (E)-(3S*)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9R*)-hexahydroindolizin-5-one

Lithium hydroxide monohydrate (29 mg) was added to a solution of diethyl ((3S*)-(4-fluorophenyl)-5-oxo-(9S*)-octahydroindolizin-6-yl)phosphonate (86 mg) and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (51 mg) obtained in Example 1 in THF (2 mL) and ethanol (0.4 mL), and the reaction solution was stirred at room temperature for 19 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane:ethyl acetate = 1:1 -> ethyl acetate) to obtain 74 mg of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.43-1.55 (m, 1H), 1.56-1.67 (m,

1H), 1.78-1.89 (m, 1H), 2.21-2.33 (m, 5H), 2.44-2.53 (m, 1H), 2.69 (tt, J=16.0, 3.6 Hz, 1H), 3.10 (dt, J=16.0, 2.8 Hz, 1H), 3.84 (S, 3H), 3.92-4.02 (m, 1H), 5.20 (t, J=8.4 Hz, 1H), 6.93 (brs, 1H), 6.98-7.06 (m, 4H), 7.23-7.28 (m, 3H), 7.72 (brs, 1H), 7.73 (d, J=2.4 Hz, 1H).

[1028]

Synthesis of (E)-(3S)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9R)-hexahydroindolizin-5-one and (E)-(3R)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9S)-hexahydroindolizin-5-one

(E)-(3S*)-(4-fluorophenyl)-6-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-(9R*)-hexahydroindolizin-5-one as a racemate (50 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 3:7) to obtain the title optically active substance with a retention time of 16 minutes (22.7 mg; >99% ee) and the title optically active substance with a retention time of 33 minutes (17.2 mg; >99% ee).

The physical properties of the optically active substance with a retention time of 16 minutes (Example 1034) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.43-1.55 (m, 1H), 1.56-1.67 (m, 1H), 1.78-1.89 (m, 1H), 2.21-2.33 (m, 5H), 2.44-2.53 (m, 1H), 2.69 (tt, J=16.0, 3.6 Hz, 1H), 3.10 (dt,

J=16.0, 2.8 Hz, 1H), 3.84 (S, 3H), 3.92-4.02 (m, 1H), 5.20 (t, J=8.4 Hz, 1H), 6.93 (brs, 1H), 6.98-7.06 (m, 4H), 7.23-7.28 (m, 3H), 7.72 (brs, 1H), 7.73 (d, J=2.4 Hz, 1H).

The physical properties of the optically active substance with a retention time of 33 minutes (Example 1035) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.43-1.55 (m, 1H), 1.56-1.67 (m, 1H), 1.78-1.89 (m, 1H), 2.21-2.33 (m, 5H), 2.44-2.53 (m, 1H), 2.69 (tt, J=16.0, 3.6 Hz, 1H), 3.10 (dt, J=16.0, 2.8 Hz, 1H), 3.84 (S, 3H), 3.92-4.02 (m, 1H), 5.20 (t, J=8.4 Hz, 1H), 6.93 (brs, 1H), 6.98-7.06 (m, 4H), 7.23-7.28 (m, 3H), 7.72 (brs, 1H), 7.73 (d, J=2.4 Hz, 1H).

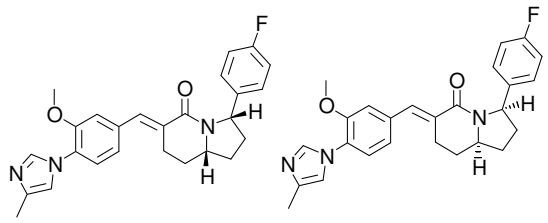
[1029]

Example 1036 and Example 1037

Synthesis of (E)-(3S)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9S)-hexahydroindolizin-5-one and (E)-(3R)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9R)-hexahydroindolizin-5-one

[1030]

[Formula 324]



Synthesis of (E)-(3S*)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9S*)-hexahydroindolizin-5-one

43 mg of the title compound as a racemate was obtained from (3S*)-(4-fluorophenyl)-(9S*)-hexahydroindolizin-5-one (115 mg) in the same manner as in Example 1034. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.88 (m, 3H), 2.05-2.11 (m, 1H), 2.27-2.37 (m, 5H), 2.70-2.81 (m, 1H), 3.15 (dt, J=16.8, 2.4 Hz, 1H), 3.76-3.84 (m, 1H), 3.85 (s, 3H), 5.21 (d, J=8.8 Hz, 1H), 6.94 (brs, 1H), 7.00 (t, J=8.8 Hz, 2H), 7.05 (d, J=1.2 Hz, 1H), 7.09 (dd, J=8.4, 1.2 Hz, 1H), 7.16 (dd, J=8.8, 5.2 Hz, 2H), 7.25 (d, J=8.4 Hz, 1H), 7.74 (s, 1H), 7.76 (d, J=2.0 Hz, 1H).

[1031]

Synthesis of (E)-(3S)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9S)-hexahydroindolizin-5-one and (E)-(3R)-(4-fluorophenyl)-6-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(9R)-hexahydroindolizin-5-one

(E)-(3S*)-(4-fluorophenyl)-6-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-(9S*)-hexahydroindolizin-5-one as a racemate (30 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 1:1) to obtain the title optically active substance with a retention time of 19

minutes (12.5 mg; >99% ee) and the title optically active substance with a retention time of 26 minutes (11.3 mg; >99% ee).

The physical properties of the optically active substance with a retention time of 19 minutes (Example 1036) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.88 (m, 3H), 2.05-2.11 (m, 1H), 2.27-2.37 (m, 5H), 2.70-2.81 (m, 1H), 3.15 (dt, J=16.8, 2.4 Hz, 1H), 3.76-3.84 (m, 1H), 3.85 (s, 3H), 5.21 (d, J=8.8 Hz, 1H), 6.94 (brs, 1H), 7.00 (t, J=8.8 Hz, 2H), 7.05 (d, J=1.2 Hz, 1H), 7.09 (dd, J=8.4, 1.2 Hz, 1H), 7.16 (dd, J=8.8, 5.2 Hz, 2H), 7.25 (d, J=8.4 Hz, 1H), 7.74 (s, 1H), 7.76 (d, J=2.0 Hz, 1H).

The physical properties of the optically active substance with a retention time of 26 minutes (Example 1037) are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.72-1.88 (m, 3H), 2.05-2.11 (m, 1H), 2.27-2.37 (m, 5H), 2.70-2.81 (m, 1H), 3.15 (dt, J=16.8, 2.4Hz, 1H), 3.76-3.84 (m, 1H), 3.85 (s, 3H), 5.21 (d, J=8.8 Hz, 1H), 6.94 (brs, 1H), 7.00 (t, J=8.8 Hz, 2H), 7.05 (d, J=1.2 Hz, 1H), 7.09 (dd, J=8.4, 1.2 Hz, 1H), 7.16 (dd, J=8.8, 5.2 Hz, 2H), 7.25 (d, J=8.4 Hz, 1H), 7.74 (s, 1H), 7.76 (d, J=2.0 Hz, 1H).

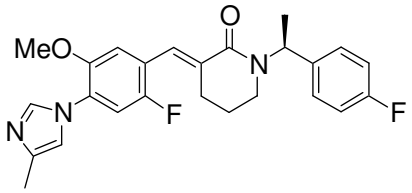
[1032]

Example 1038

Synthesis of (E)-3-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-((1S)-(4-fluorophenyl)ethyl)piperidin-2-one

[1033]

[Formula 325]



Synthesis of 2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzonitrile

Zinc cyanide (4.05 g), tris(dibenzylideneacetone)dipalladium (527 mg) and 1,1'-bis(diphenylphosphino)ferrocene (638 mg) were added to a solution of 1-(4-bromo-5-fluoro-2-methoxyphenyl)-4-methyl-1H-imidazole (16.7 g) obtained in Example 18 in DMF (100 mL) at room temperature, and the reaction solution was stirred with heat in a nitrogen atmosphere at 120°C for 7 hours. Further, zinc cyanide (4.05 g), tris(dibenzylideneacetone)dipalladium (527 mg) and 1,1'-bis(diphenylphosphino)ferrocene (638 mg) were added to the reaction solution, and the reaction solution was stirred with heat for 7 hours. After allowing the reaction solution to be cooled, concentrated aqueous ammonia and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to obtain 9.5 g of the title compound.

Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.35 (s, 3H), 3.93 (s, 3H), 6.98 (s, 1H), 7.20 (d, J=8.8 Hz, 1H), 7.23 (d, J=5.6 Hz, 1H), 7.80 (s, 1H).

[1034]

Synthesis of 2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde

Sodium bis(2-methoxyethoxy)aluminum hydride (65% solution in toluene, 11.4 mL) was added dropwise to a suspension of 2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzonitrile (8.85 g) in THF (180 mL) in a nitrogen atmosphere at -15°C, and the reaction solution was stirred for 1 hour. Water was added to the reaction mixture, and the mixture was stirred at room temperature for 10 minutes. Then, a 5 N aqueous solution of sodium hydroxide and ethyl acetate were added to the mixture and the organic layer was partitioned. The resulting organic layer was made acidic with 5 N aqueous hydrochloric acid, and the mixture was stirred. Then, the mixture was neutralized with 5 N aqueous sodium hydroxide and the organic layer was partitioned. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: ethyl acetate) to obtain 3.32 g of the title compound.

Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H), 3.94 (s, 3H), 7.00

(t, J=1.2 Hz, 1H), 7.14 (d, J=10 Hz, 1H), 7.49 (d, J=5.6 Hz, 1H), 7.88 (d, J=1.2 Hz, 1H), 10.35 (s, 1H).

[1035]

Synthesis of (E)-5-chloro-2-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]valeric acid trifluoroacetate

Sodium hydride (containing mineral oil at 40%, 0.68 g) was added to a solution of tert-butyl 5-chloro-2-(diethoxyphosphoryl)valerate (5.59 g) in THF (50 mL) in a nitrogen atmosphere at room temperature, and the reaction solution was stirred at room temperature for 30 minutes. A solution of 2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (3.19 g) in THF (10 mL) was added to the reaction mixture, and the reaction solution was stirred at room temperature for 4 hours. Water and ethyl acetate were added to the reaction mixture and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (elution solvent: heptane-ethyl acetate system) to obtain tert-butyl (E)-5-chloro-2-(2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valerate (5.93 g). A solution of tert-butyl (E)-5-chloro-2-(2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valerate in trifluoroacetic acid (30 mL) was stirred while cooling with ice. After 2 hours, the

reaction solution was concentrated under reduced pressure. Tert-butyl methyl ether was added to the resulting residue, and the resulting deposited solid was filtered to obtain 3 g of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 2.03-2.10 (m, 2H), 2.52 (s, 3H), 2.65-2.69 (m, 2H), 3.60 (t, J=6.4 Hz, 2H), 3.94 (s, 3H), 7.08 (d, J=6.4 Hz, 1H), 7.10 (t, J=1.6 Hz, 1H), 7.21 (d, J=8.8 Hz, 1H), 7.78 (s, 1H), 7.88 (d, J=2 Hz, 1H).

[1036]

Synthesis of (E)-3-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1S)-(4-fluorophenyl)ethyl]piperidin-2-one

0.57 g of the title compound was obtained from (E)-5-chloro-2-(2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (1.0 g) and (S)-1-(4-fluorophenyl)ethylamine (447 mg) in the same manner as in Example 418. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ: 1.56 (d, J=7.2 Hz, 3H), 1.65-1.74 (m, 1H), 1.78-1.87 (m, 1H), 2.30 (s, 3H), 2.62-2.66 (m, 2H), 2.91-2.96 (m, 1H), 3.22-3.28 (m, 1H), 3.83 (s, 3H), 6.23 (q, J=7.2 Hz, 1H), 6.92-6.93 (m, 2H), 7.01-7.06 (m, 3H), 7.30-7.35 (m, 2H), 7.75 (s, 1H), 7.84 (s, 1H).

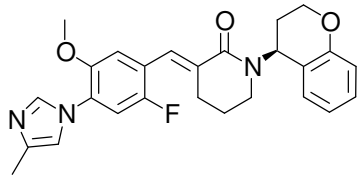
[1037]

Example 1039

Synthesis of (E)-1-[(4S)-chroman-4-yl]-3-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1038]

[Formula 326]



14 mg of the title compound was obtained from (E)-5-chloro-2-(2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene)valeric acid trifluoroacetate (20 mg) and (4S)chroman-4-ylamine (10 mg) in the same manner as in Example 418. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70-1.90 (m, 2H), 2.12-2.25 (m, 2H), 2.30 (s, 3H), 2.64-2.80 (m, 2H), 3.07-3.13 (m, 1H), 3.05-3.14 (m, 1H), 3.85 (s, 3H), 4.22-4.28 (m, 1H), 4.35-4.39 (m, 1H), 6.23 (dd, J=6.4, 9.6 Hz, 1H), 6.84-6.96 (m, 4H), 7.05 (s, 1H), 7.08 (s, 1H), 7.15-7.19 (m, 1H), 7.76 (d, J=1.2 Hz, 1H), 7.87 (s, 1H).

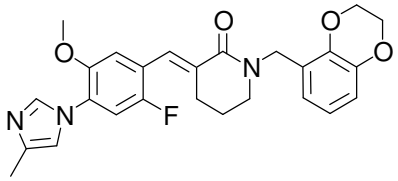
[1039]

Example 1040

Synthesis of (E)-1-[2,3-dihydrobenzo[1,4]dioxin-5-ylmethyl]-3-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1040]

[Formula 327]



10 mg of the title compound was obtained from (E)-5-chloro-2-(2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetate (20 mg) and 2,3-dihydro-1,4-benzodioxin-5-ylmethylamine hydrochloride (14 mg) in the same manner as in Example 418. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.85-1.91 (m, 2H), 2.30 (s, 3H), 2.68 (t, J=6.4 Hz, 2H), 3.43 (t, J=6.0 Hz, 1H), 3.83 (s, 3H), 4.26-4.32 (m, 4H), 4.73 (s, 2H), 6.78-6.86 (m, 3H), 6.92 (d, J=6.4 Hz, 1H), 6.93 (s, 1H), 7.05 (d, J=9.6 Hz, 1H), 7.75 (d, J=1.2 Hz, 1H), 7.89 (s, 1H).

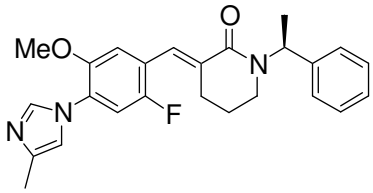
[1041]

Example 1041

Synthesis of (E)-3-[2-fluoro-5-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-((1S)-phenylethyl)piperidin-2-one

[1042]

[Formula 328]



8 mg of the title compound was obtained from (E)-5-chloro-2-(2-fluoro-5-methoxy-4-(4-methyl-1H-

imidazol-1-yl)-benzylidene)valeric acid trifluoroacetate (20 mg) and (S)-1-phenylethylamine (10 mg) in the same manner as in Example 418. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ: 1.58 (d, J=7.2 Hz, 3H), 1.65-1.74 (m, 1H), 1.65-1.84 m, 3H), 2.32 (s, 3H), 2.62-2.65 (m, 2H), 2.92-2.98 (m, 1H), 3.22-3.28 (m, 1H), 3.84 (s, 3H), 6.25 (q, J=7.2 Hz, 1H), 6.93-6.95 (m, 2H), 6.25 (q, J=8.8 Hz, 1H), 7.26-7.36 (m, 5H), 7.84 (s, 1H).

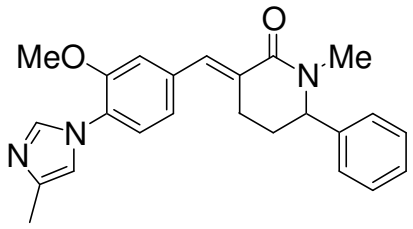
[1043]

Example 1042

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-methyl-6-phenylpiperidin-2-one

[1044]

[Formula 329]



Lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 1.59 mL) was added dropwise to a solution of 1-methyl-6-phenylpiperidin-2-one (200 mg) synthesized in accordance with a technique described in a document (see N.P. Baens et al., "Tetrahedron", 1993, vol.49, pp.3193-3202, for example) in THF (5 mL) at -78°C, and the reaction solution was stirred at room temperature for 30 minutes. This solution was added dropwise to a solution of 3-methoxy-4-(4-methyl-1H-

imidazol-1-yl)benzaldehyde (248 mg) and a boron trifluoride-dimethyl ether complex (134 μL) in THF at -78°C, and the reaction solution was stirred overnight while heating to room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane-ethyl acetate system) to collect the part in which an aldol derivative eluted. The elution part was concentrated under reduced pressure. Methanesulfonyl chloride (33.9 mg), triethylamine (206 μL) and methylene chloride (25 mL) were added to the residue, and the reaction solution was stirred at room temperature for 3 days. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by LC-MS to obtain 4.54 mg of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ: 1.94-2.01 (m, 1H), 2.24-2.33 (m, 1H), 2.29 (s, 3H), 2.53-2.62 (m, 1H), 2.73-2.79 (m, 1H), 3.02 (s, 3H), 3.84 (s, 3H), 4.67 (t, J=4.4 Hz, 1H), 6.92 (s, 1H), 6.93-7.02 (m, 2H), 7.21-7.23 (m, 2H),

7.29–7.36 (m, 2H), 7.38–7.44 (m, 2H), 7.71 (s, 1H), 7.90 (s, 1H).

ESI–MS; m/z388 [M^++H].

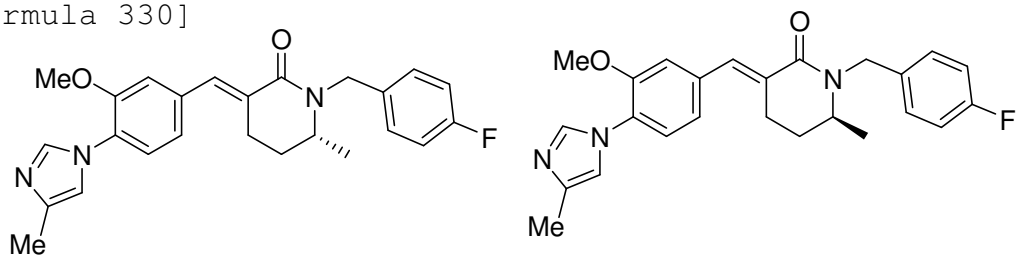
[1045]

Example 1043 and Example 1044

Synthesis of (E)–1–(4–fluorobenzyl)–3–[3–methoxy–4–(4–methyl–1H–imidazol–1–yl)benzylidene]–(6R and S)–methylpiperidin–2–one

[1046]

[Formula 330]



28.7 mg of the title compound as a racemate was obtained from 1–(4–fluorobenzyl)–6–methylpiperidin–2–one (198 mg) and 3–methoxy–4–(4–methyl–1H–imidazol–1–yl)benzaldehyde (194 mg) in the same manner as in Example 1042. The racemate (28.7 mg) was fractionated using CHIRALPAK™ AD–H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 60:40) to obtain the title optically active substance with a retention time of 29 minutes (Example 1043, 5.97 mg; >99% ee) and the title optically active substance with a retention time of 31 minutes (Example 1044, 6.76 mg; >95% ee). The physical properties of the optically active compounds are as follows.

ESI-MS; m/z420 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (d, J=6.8 Hz, 3H), 1.74-1.80 (m, 1H), 1.86-1.95 (m, 1H), 2.31 (s, 3H), 2.87-2.96 (m, 2H), 3.58-3.62 (m, 1H), 3.88 (s, 3H), 4.11 (d, J=14.8 Hz, 1H), 5.33 (d, J=14.8 Hz, 1H), 6.95 (s, 1H), 6.99-7.11 (m, 4H), 7.24-7.31 (m, 3H), 7.74 (s, 1H), 7.88 (s, 1H).

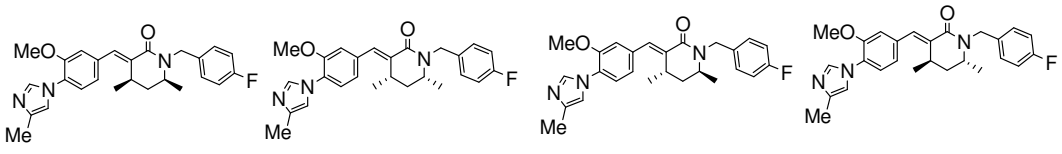
[1047]

Example 1045, Example 1046, Example 1047 and Example 1048

Synthesis of (E)-1-(4-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(4R,6S)-dimethylpiperidin-2-one, (E)-1-(4-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(4S,6R)-dimethylpiperidin-2-one, (E)-1-(4-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(4S,6S)-dimethylpiperidin-2-one and (E)-1-(4-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(4R,6R)-dimethylpiperidin-2-one

[1048]

[Formula 331]



Synthesis of diethyl[1-(4-fluorobenzyl)-4,6-dimethyl-2-oxopiperidin-3-yl]phosphonate

A solution of tert-butyl 2-

diethoxyphosphoryl-3-methyl-5-oxohexanoate (500 mg) synthesized in accordance with a technique described in a document (see A.N. Pudovik et al., "Chemical Abstracts", 1956, vol.50, p.2429, for example) and trifluoroacetic acid (5.0 mL) in chloroform (5.0 mL) was stirred at room temperature for 4 hours, and then concentrated under reduced pressure. 4-fluorobenzylamine (170 μL), acetic acid (512 μL), and sodium triacetoxyborohydride (947 mg) were added to a solution of the residue in THF (10 mL). The reaction solution was stirred at room temperature overnight, and further stirred with heat at 50°C for 10 hours. Ethyl acetate and water were added to the reaction solution, and the solution was adjusted to about pH 8 with a 5 N aqueous solution of sodium hydroxide and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: hexane-ethyl acetate system) to obtain 292.8 mg of the title compound as a low-polar diastereomer and 88.4 mg of the title compound as a high-polar diastereomer.

Properties data of the low-polar diastereomer are as follows.

ESI-MS; m/z372 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (d, J=6.8 Hz, 3H), 1.20 (d, J=6.4 Hz, 3H), 1.33 (d, J=7.6 Hz, 3H), 1.37 (d, J=7.2 Hz, 3H) 1.95-2.01 (m, 1H), 2.32-

2.48 (m, 1H), 2.80 (dd, J=26.8, 8.0 Hz, 1H), 3.54-3.62 (m, 1H), 4.14-4.26 (m, 4H), 4.38 (d, J=19.2 Hz, 1H), 4.44 (d, J=19.2 Hz, 1H), 5.39 (d, J=15.6 Hz, 1H), 6.97-7.04 (m, 2H), 7.23-7.31 (m, 2H).

Properties data of the high-polar diastereomer are as follows.

ESI-MS; m/z372 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, J=6.8 Hz, 3H), 1.22 (d, J=6.4 Hz, 3H), 1.34 (d, J=6.8 Hz, 3H), 1.38 (d, J=6.8 Hz, 3H), 1.48-1.56 (m, 1H), 1.86-1.93 (m, 1H), 2.55-2.68 (m, 1H), 2.78 (dd, J=27.6, 6.0 Hz, 1H), 3.42-3.51 (m, 1H), 4.16-4.26 (m, 5H), 5.04 (d, J=14.8 Hz, 1H), 5.04 (d, J=14.8 Hz, 1H), 6.96-7.01 (m, 2H), 7.23-7.27 (m, 2H).

[1049]

<u>Synthesis of (E)-1-(4-fluorobenzyl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-4,6-dimethylpiperidin-2-one</u>

Lithium hydroxide (175 mg) was added to a solution of low-polar diethyl[1-(4-fluorophenyl)-4,6-dimethyl-2-oxopiperidin-3-yl]phosphorate (292.8 mg) obtained as above and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (150 mg) in a mixture of THF (3.0 mL) with ethanol (1.0 mL), and the reaction solution was stirred at room temperature. After 1 hour, the reaction solution was diluted with water and ethyl acetate and the organic layer was partitioned. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: hexane–ethyl acetate system) to obtain 309.5 mg of the title compound as a single diastereomer. The diastereomer was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×50 cm; mobile phase: ethanol) to obtain an optically active substance with a retention time of 52 minutes (Example 1045, 36.8 mg; >99% ee) and an optically active substance with a retention time of 56 minutes (Example 1046, 15.3 mg; >85% ee). The physical properties of the optically active compounds are as follows.

ESI-MS; m/z434 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (d, J=7.6 Hz, 3H), 1.41 (d, J=6.8 Hz, 3H), 1.64–1.70 (m, 1H), 2.11–2.18 (m, 1H), 2.32 (s, 3H), 3.34–3.41 (m, 1H), 3.57–3.66 (m, 1H), 3.86 (s, 3H), 4.33 (d, J=15.6 Hz, 1H), 5.26 (d, J=15.6 Hz, 1H), 6.95 (s, 1H), 6.99–7.08 (m, 5H), 7.24–7.28 (m, 2H), 7.75 (s, 1H), 7.76 (s, 1H).

Lithium hydroxide (52.5 mg) was added to a solution of high-polar diethyl[1-(4-fluorophenyl)-4,6-dimethyl-2-oxopiperidin-3-yl]phosphorate (88.4 mg) obtained as above and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (45 mg) in a mixture of THF (1.0 mL) with ethanol (0.3 mL), and the reaction solution was stirred at room temperature. After 1 hour, the reaction solution was diluted with water and ethyl acetate and the organic layer was partitioned.

The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: hexane–ethyl acetate system) to obtain 102.8 mg of the title compound as a single diastereomer. The diastereomer was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×50 cm; mobile phase: ethanol) to obtain an optically active substance with a retention time of 47 minutes (Example 1047, 41.5 mg; >97% ee) and an optically active substance with a retention time of 55 minutes (Example 1048, 45.4 mg; >86% ee). The physical properties of the optically active compounds are as follows.

ESI-MS; m/z434 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (d, J=6.8 Hz, 3H), 1.22 (d, J=6.4 Hz, 3H), 1.76–1.81 (m, 2H), 2.35 (s, 3H), 3.22–3.32 (m, 1H), 3.58–3.64 (m, 1H), 3.87 (s, 3H), 4.32 (d, J=15.2 Hz, 1H), 5.31 (d, J=15.2 Hz, 1H), 6.96 (s, 1H), 7.00–7.06 (m, 5H), 7.25–7.31 (m, 2H), 7.68 (s, 1H), 7.86 (s, 1H).

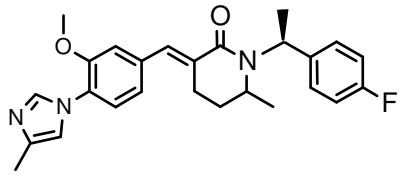
[1050]

Example 1049 and Example 1050

Synthesis of (E)-1-[(1S)-(4-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-(6R and S)-methylpiperidin-2-one

[1051]

[Formula 332]



Synthesis of tert-butyl (E)-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-5-oxohexanoate

5 N aqueous hydrochloric acid (1.0 mL) was added to a solution of tert-butyl 2-diethoxyphosphoryl-4-(2-methyl-[1,3]dioxolan-2-yl)butyrate (500 mg) synthesized in the same manner as in Example 425 in THF (5.0 mL), and the reaction solution was stirred at room temperature for 6 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (278 mg) and lithium hydroxide (93 mg) were added to a solution of the residue in a mixture of THF (6.0 mL) with ethanol (2.0 mL), and the reaction solution was stirred at room temperature overnight. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (elution solvent: hexane–ethyl acetate system) to obtain 250 mg of the title compound.

ESI–MS; m/z385 [M^++H]. ^{1}H–NMR ($CDCl_3$) δ: 1.56 (s, 9H), 2.17 (s, 3H), 2.31 (s, 3H), 2.68–2.72 (m, 2H), 2.76–2.81 (m, 2H), 3.87 (s, 3H), 6.94 (s, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.02 (s, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.58 (s, 1H), 7.74 (s, 1H).

[1052]

Synthesis of (E)–1–[(1S)–(4–fluorophenyl)ethyl]–3–[3–methoxy–4–(4–methyl–1H–imidazol–1–yl)benzylidene]–(6S and R)–methylpiperidin–2–one

(1S)–(4–fluorophenyl)ethylamine (90.5 mg), acetic acid (223 μL) and sodium triacetoxyborohydride (413 mg) were added to a solution of tert–butyl (E)–2–(3–methoxy–4–(4–methyl–1H–imidazol–1–yl)benzylidene)–5–oxohexanoate (250 mg) in THF (5.0 mL), and the reaction solution was stirred at room temperature overnight. Water and ethyl acetate were added to the reaction solution, and the reaction solution was adjusted to about pH 8 with a 5 N aqueous solution of sodium hydroxide and the organic layer was partitioned. The organic layer was concentrated under reduced pressure, and then the residue was purified by silica gel column chromatography (elution solvent: chloroform–methanol system) to obtain 224 mg of an amino derivative. Trifluoroacetic acid (2.0 mL) was added to a solution of the amino derivative in chloroform (1.0 mL), and the reaction solution was stirred at room temperature for 6

hours. IPEA (167 μL), EDC (137 mg) and HOBT (132 mg) were sequentially added to a solution of the residue obtained by concentrating the reaction solution under reduced pressure in DMF (20 mL), and the reaction solution was stirred at room temperature for 5.5 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was washed with brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: hexane–ethyl acetate system) to obtain 68.5 mg of the title compound as a racemate. The racemate (68.5 mg) was fractionated using CHIRALPAK™ IA manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane:ethanol = 50:50) to obtain the title optically active substance with a retention time of 28 minutes (Example 1049, 19.9 mg; >99% de) and the title optically active substance with a retention time of 31 minutes (Example 1050, 23.44 mg; >91% de).

Title optically active substance with a retention time of 28 minutes (Example 1049)

^{1}H–NMR ($CDCl_3$) δ: 0.74 (d, J=6.8 Hz, 3H), 1.61 (d, J=7.2 Hz, 3H), 1.78–1.91 (m, 2H), 2.34 (s, 3H), 2.85–2.88 (m, 2H), 3.68–3.71 (m, 1H), 3.87 (s, 3H), 5.99 (q, J=7.2 Hz, 1H), 6.96 (s, 1H), 6.99–7.07 (m, 2H), 7.10 (s, 1H), 7.14 (d, J=8.4 Hz, 1H), 7.27 (d, J=8.4 Hz, 1H), 7.38–

7.42 (m, 2H), 7.81 (s, 1H), 7.84 (s, 1H).

ESI-MS; m/z434 [M^++H].

Title optically active substance with a retention time of 31 minutes (Example 1050)

ESI-MS; m/z434 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (d, J=6.8 Hz, 3H), 1.52-1.69 (m, 2H), 1.64 (d, J=7.6 Hz, 3H), 2.34 (s, 3H), 2.79-3.00 (m, 2H), 3.40-3.45 (m, 1H), 3.88 (s, 3H), 6.13 (q, J=7.6 Hz, 1H), 6.96 (s, 1H), 7.00-7.07 (m, 2H), 7.12 (s, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.33-7.37 (m, 2H), 7.81 (s, 1H), 7.83 (s, 1H).

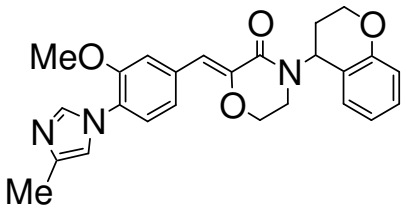
[1053]

Example 1051 and Example 1052

Synthesis of (Z)-[(R) and (S)-chroman-4-yl]-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]morpholin-3-one

[1054]

[Formula 333]



8.49 mg of the title compound as a racemate was obtained from 4-chroman-4-yl-morpholin-3-one (200 mg) synthesized in accordance with a technique described in a document (see T. Morie et al., "J. Heterocycles", 1994, vol.38, p.1033, for example) and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde

(185 mg) in the same manner as in Example 1042. The racemate (8.49 mg) was fractionated using CHIRALPAK™ AD-H manufactured by Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: ethanol) to obtain the title optically active substance with a retention time of 23 minutes (Example 1051, 1.47 mg; >99% ee) and the title optically active substance with a retention time of 31 minutes (Example 1052, 1.72 mg; >99% ee). The physical properties of the optically active compounds are as follows.

ESI-MS; m/z432 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 2.17-2.22 (m, 2H), 2.32 (s, 3H), 3.21-3.26 (m, 1H), 3.43-3.49 (m, 1H), 3.87 (s, 3H), 4.16-4.28 (m, 3H), 4.32-4.35 (m, 1H), 6.13 (t, J=8.4 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 6.91-6.95 (m, 3H), 7.07 (d, J=7.6 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.22 (d, J=8.0 Hz, 1H), 7.39-7.44 (m, 2H), 7.77 (s, 1H).

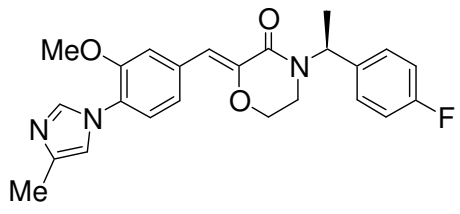
[1055]

Example 1053

Synthesis of (Z)-4-[(1S)-(4-fluorophenyl)ethyl]-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]morpholin-3-one

[1056]

[Formula 334]



1.4 mg of the title compound was obtained from 4-((1S)-(4-fluorophenyl)ethyl)morpholin-3-one (200 mg) synthesized in accordance with a technique described in a document (see T. Morie et al., "J. Heterocycles", 1994, vol.38, p.1033, for example) and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (194 mg) in the same manner as in Example 1042. Properties data of the compound are as follows. ESI-MS; m/z422 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (d, J=7.6 Hz, 3H), 2.30 (s, 3H), 3.05-3.11 (m, 1H), 3.44-3.50 (m, 1H), 3.86 (s, 3H), 4.04-4.09 (m, 1H), 4.20-4.25 (m, 1H), 6.14 (q, J=7.6 Hz, 1H), 6.91 (s, 1H), 6.93 (s, 1H), 7.04-7.08 (m, 2H), 7.21 (d, J=8.0 Hz, 1H), 7.32-7.41 (m, 4H), 7.73 (s, 1H).

[1057]

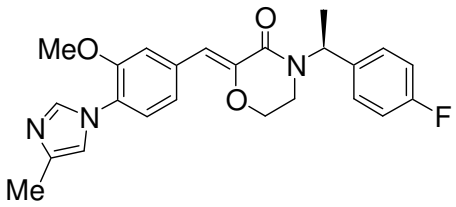
(Z)-4-[(1S)-(4-fluorophenyl)ethyl]-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]morpholin-3-one can also be separately synthesized by the following method.

[1058]

Synthesis of (Z)-4-[(1S)-(4-fluorophenyl)ethyl]-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]morpholin-3-one

[1059]

[Formula 335]



Synthesis of tert-butyl (Z)-2-(2-chloroethoxy)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]acrylate

Lithium hydroxide (52.1 mg) was added to a solution of tert-butyl 2-chloroethoxy-(diethoxyphosphoryl)acetate (240 mg) synthesized by a technique described in a document (see C.J. Moody et al., "Tetrahedron", 1992, vol.48, p.3991, for example) and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (173 mg) in a mixture of THF (5.0 mL) with ethanol (1.0 mL), and the reaction solution was stirred at room temperature for 2.5 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane-ethyl acetate system) to obtain 51 mg of the title compound.

ESI-MS; m/z393 $[M^+H]$. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (s, 9H), 2.30 (s, 3H), 3.79 (t, J=5.2 Hz, 2H), 3.90 (s, 3H), 4.25 (t, J=5.2 Hz, 2H) 6.89 (s, 1H), 6.96 (s, 1H), 7.24 (d, J=8.4 Hz, 1H), 7.32 (dd, J=8.4, 2.0 Hz, 1H), 7.64 (d, J=2.0 Hz, 1H), 7.76 (s, 1H).

[1060]

Synthesis of (Z)-4-[(1S)-(4-fluorophenyl)ethyl]-2-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]morpholin-3-one

44.3 mg of the title compound was obtained from tert-butyl (Z)-2-(2-chloroethoxy)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylate (51 mg) obtained as above and (S)-1-(4-fluorophenyl)ethylamine (26.3 μL) in the same manner as in Example 418. Properties data of the compound are as follows. ESI-MS; m/z422 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (d, J=7.6 Hz, 3H), 2.30 (s, 3H), 3.05-3.11 (m, 1H), 3.44-3.50 (m, 1H), 3.86 (s, 3H), 4.04-4.09 (m, 1H), 4.20-4.25 (m, 1H), 6.14 (q, J=7.6 Hz, 1H), 6.91 (s, 1H), 6.93 (s, 1H), 7.04-7.08 (m, 2H), 7.21 (d, J=8.0 Hz, 1H), 7.32-7.41 (m, 4H), 7.73 (s, 1H).

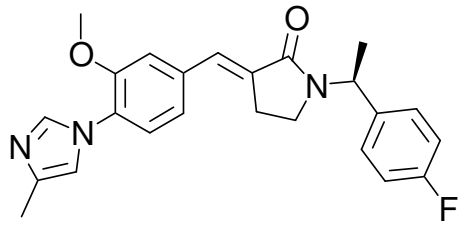
[1061]

Example 1054

Synthesis of (E)-1-[(1S)-(4-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]pyrrolidin-2-one

[1062]

[Formula 336]



Synthesis of diethyl {1-[(1S)-(4-fluorophenyl)ethyl]-2-oxo-pyrrolidin-3-yl}phosphonate

A mixture of 3-bromo-1-((1S)-(4-fluorophenyl)ethyl)pyrrolidin-2-one (117 mg) synthesized in accordance with the method described in

Journal of Medicinal Chemistry, 1987, vol.30, p.1995 with triethyl phosphite (0.71 mL) was stirred at 150°C for 2 hours. The reaction solution was allowed to be cooled to room temperature, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (elution solvent: ethyl acetate:methanol = 9:1) to obtain 60 mg of the title compound. Properties data of the compound are as follows.

ESI-MS; m/z344 [M^++H].

[1063]

Synthesis of (E)-1-[(1S)-(4-fluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]pyrrolidin-2-one

Lithium hydroxide monohydrate (12.5 mg) was added to a solution of 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (21 mg) obtained in Example 1 and diethyl (1-((1S)-(4-fluorophenyl)ethyl)-2-oxopyrrolidin-3-yl)phosphonate (34 mg) in a mixture of THF (2 mL) and ethanol (0.4 mL), and the reaction solution was stirred at room temperature for 14 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane:ethyl acetate = 1:1 -> ethyl

acetate) to obtain 26 mg of the title compound. Properties data of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (d, J=7.2 Hz, 3H), 2,30 (s, 3H), 2.92-3.15 (m, 3H), 3.44-3.51 (m, 1H), 3.87 (s, 3H), 5.68 (q, J=7.2 Hz, 1H), 6.93 (brs, 1H), 7.00-7.05 (m, 2H), 7.09 (d, J=1.6 Hz, 1H), 7.12 (dd, J=8.0, 1.6 Hz, 1H), 2.78 (d, J=8.0Hz, 1H), 7.30-7.34 (m, 2H), 7.37 (t, J=2.8 Hz, 1H), 7.73 (d, J=1.2 Hz, 1H).

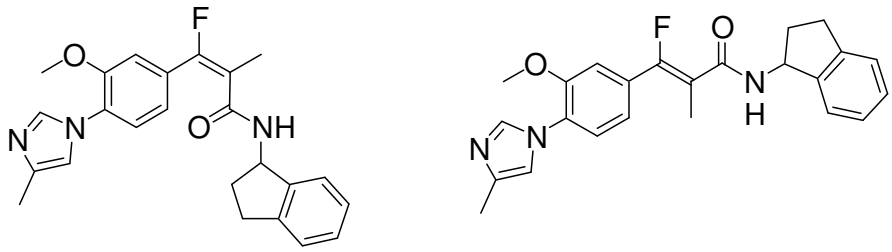
[1064]

Example 1055 and Example 1056

Synthesis of (E) and (Z)-3-fluoro-N-(indan-1-yl)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methylacrylamide

[1065]

[Formula 337]



Synthesis of methyl 3-fluoro-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methylacrylate

Diethyl (fluoro-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)methyl)phosphonate (1.1 g) was obtained from 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (1 g) in accordance with the method described in Tetrahedron Letters, 1996, vol.37, no. 5, p.629. Lithium diisopropylamide (1.5 M solution in

THF, 0.25 mL) was added to a solution of the resulting diethyl (fluoro-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)methyl)phosphonate (110 mg) in THF at -78°C, and the reaction solution was stirred at -78°C for 2 hours. Methyl pyruvate (32 mg) was added to the reaction solution at -78°C. The reaction solution was stirred at -78°C for 15 minutes, and then further stirred at room temperature for 45 minutes. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution solvent: heptane:ethyl acetate = 1:1 -> ethyl acetate) to obtain 39 mg of methyl 3-fluoro-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-2-methylacrylate as a mixture of isomers (E) and (Z). Properties data of the compounds are as follows.

ESI-MS; m/z305 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.02 (d, J=3.2 Hz, 1.5H), 2.07 (d, J=4.0 Hz, 1.5H), 2.31 (s, 3H), 3.66 (s, 1.5H), 3.86 (s, 1.5H), 3.87 (s, 1.5H), 3.89 (s, 1.5H), 6.96 (s, 1H), 7.09 (brd, J=8.8 Hz, 0.5H), 7.13 (brs, 1H), 7.16 (brd, J=8.8 Hz, 0.5H), 1.18 (brs, 1H), 7.26 (d, J=8.8 Hz, 0.5H), 7.31 (d, J=8.8 Hz, 0.5H), 7.77 (brs, 1H).

[1066]

Synthesis of (E) and (Z)-3-fluoro-N-indan-1-yl-3-[3-

methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methylacrylamide

A 1 N aqueous solution of sodium hydroxide (1.3 mL) was added to a solution of methyl 3-fluoro-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-2-methylacrylate (39 mg) in methanol (3 mL), and the reaction solution was stirred at room temperature for 18 hours. 5 N hydrochloric acid (0.26 mL) was added to the reaction solution, and the solution was concentrated under reduced pressure. IPEA (0.09 mL) was added to a solution of the resulting residue in DMF (5 mL). Further, 1-aminoindan (0.032 mL), HOBT (34.5 mg) and EDC (49 mg) were sequentially added thereto. The reaction solution was stirred at room temperature for 3 hours, and saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The resulting organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane:ethyl acetate = 1:1 -> ethyl acetate) to obtain 16.8 mg of an isomer (E) of the title compound and 21.9 mg of an isomer (Z) of the title compound. Properties data of the compounds are as follows.

(E)-3-fluoro-N-(indan-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-2-methylacrylamide (Example 1055)

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.52-1.63 (m, 1H), 2.11 (d, J=3.2 Hz, 3H), 2.33 (s, 3H), 2.45-2.54 (m, 1H), 2.80 (t, J=6.8 Hz, 2H), 3.86 (s, 3H), 5.40 (q, J=3.2 Hz, 1H), 5.55 (d, J=8.4 Hz, 1H), 6.87 (d, J=7.2 Hz, 1H), 6.93 (brs, 1H), 7.06-7.29 (m, 7H).

(Z)-3-fluoro-N-(indan-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-2-methylacrylamide (Example 1056)

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87-1.97 (m, 1H), 2.08 (d, J=2.8 Hz, 3H), 2.30 (s, 3H), 2.65-2.74 (m, 1H), 2.88-2.97 (m, 1H), 2.99-3.08 (m, 1H), 3.87 (s, 3H), 5.64 (q, J=2.8 Hz, 1H), 6.59 (t, J=8.4 Hz, 1H), 6.94 (brs, 1H), 7.11-7.40 (m, 7H), 7.74 (brs, 1H).

[1067]

The compounds shown in Table 28 were synthesized as in Example 418. The structural formulae and physical properties are shown in Table 28, respectively. The separation conditions in the notes to the table are as follows:

Separation Condition A: CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane-ethanol system)

Separation Condition B: CHIRALCEL™ OJ-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane-ethanol)

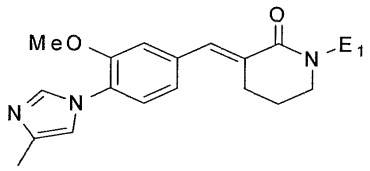
Separation Condition C: CHIRALCEL™ OD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane-ethanol)

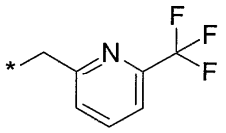
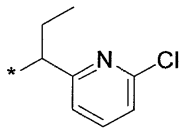
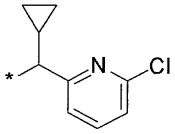
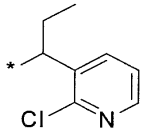
Separation Condition D: CHIRALCEL™ IA available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane-ethanol)

Separation Condition E: CHIRALCEL™ OD available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane-ethanol)

[1068]

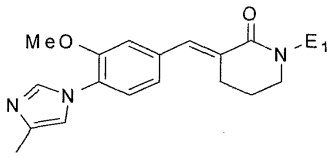
[Table 28-1]

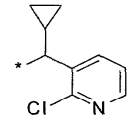
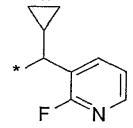
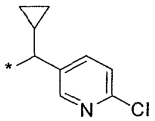
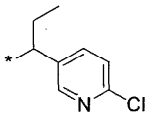
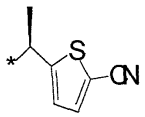
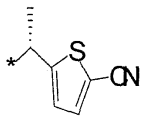
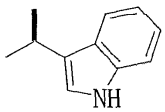
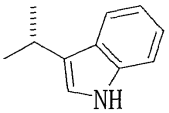
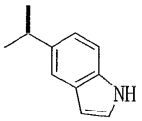
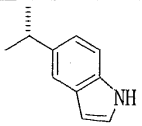


Example	E_1	DATA: MS m/z	Note
1057		M^++H：457（ESI）	
1058		M^++H：451（ESI）	
1059		M^++H：463（ESI）	
1060		M^++H：451（ESI）	

[1069]

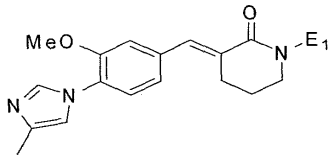
[Table 28-2]

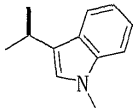
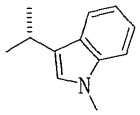
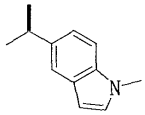
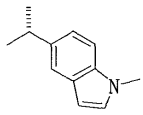
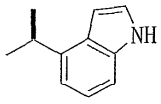
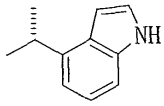
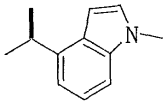
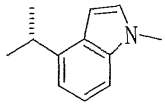
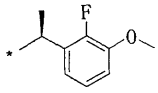
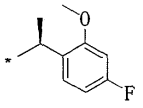
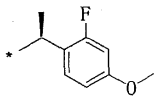


Example	E_1	DATA: MS m/z	Note
1061		M^++H : 463 (ESI)	
1062		M^++H : 447 (ESI)	
1063		M^++H : 463 (ESI)	
1064		M^++H : 451 (ESI)	
1065		M^++H : 433 (ESI)	optically active substance (separation condition E: retention time: 48 minutes; absolute configuration: unknown)
1066		M++H : 433 (ESI)	optically active substance (separation condition E: retention time: 55 minutes; absolute configuration: unknown)
1067		M^++H : 441 (ESI)	optically active substance (separation condition A: retention time: 5.1 minutes; absolute configuration: unknown)
1068		M^++H : 441 (ESI)	optically active substance (separation condition A: retention time: 7.3 minutes; absolute configuration: unknown)
1069		M^++H : 441 (ESI)	optically active substance (separation condition C: retention time: 16.1 minutes; absolute configuration: unknown)
1070		M^++H : 441 (ESI)	optically active substance (separation condition C: retention time: 19.2 minutes; absolute configuration: unknown)

[1070]

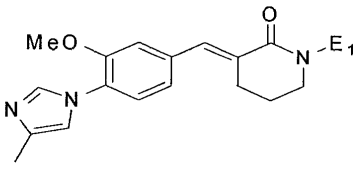
[Table 28-3]

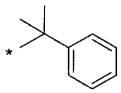
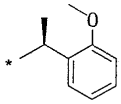
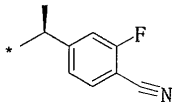
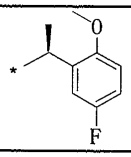
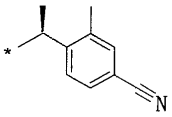
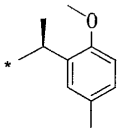
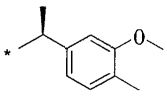
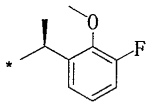
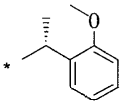
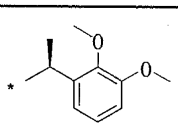


Example	E_1	DATA: MS m/z	Note
1071		M^++Na : 477 (ESI)	optically active substance (separation condition C: retention time: 13.6 minutes; absolute configuration: unknown)
1072		M^++Na : 477 (ESI)	optically active substance (separation condition C: retention time: 15.9 minutes; absolute configuration: unknown)
1073		M^++H : 455 (ESI)	optically active substance (separation condition D: retention time: 8.9 minutes; absolute configuration: unknown)
1074		M^++H : 455 (ESI)	optically active substance (separation condition D: retention time: 11.5 minutes; absolute configuration: unknown)
1075		M^++Na : 463 (ESI)	optically active substance (separation condition C: retention time: 13.3 minutes; absolute configuration: unknown)
1076		M^++Na : 463 (ESI)	optically active substance (separation condition C: retention time: 16.5 minutes; absolute configuration: unknown)
1077		M^++Na : 477 (ESI)	optically active substance (separation condition D: retention time: 8.4 minutes; absolute configuration: unknown)
1078		M^++Na : 477 (ESI)	optically active substance (separation condition D: retention time: 10.5 minutes; absolute configuration: unknown)
1079		M^++H : 450 (ESI)	optically active substance
1080		M^++H : 450 (ESI)	optically active substance
1081		M^++H : 450 (ESI)	optically active substance

[1071]

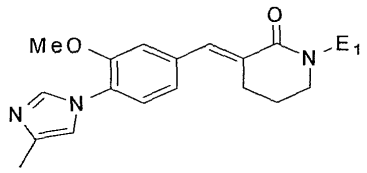
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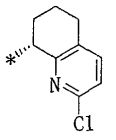
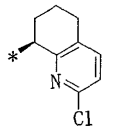
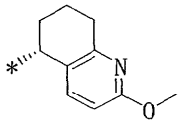
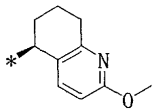
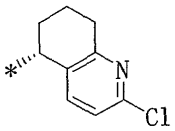
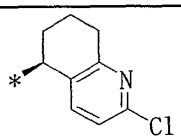
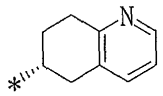
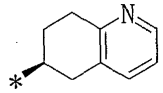
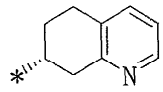
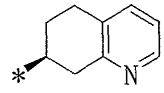


Example	E_1	DATA: MS m/z	Note
1082		M^++H：416 (ESI)	
1083		M^++H：432 (ESI)	optically active substance
1084		M^++H：445 (ESI)	optically active substance
1085		M^++H：450 (ESI)	optically active substance
1086		M^++H：441 (ESI)	optically active substance
1087		M^++H：446 (ESI)	optically active substance
1088		M^++H：446 (ESI)	optically active substance
1089		M^++H：450 (ESI)	optically active substance
1090		M^++H：432 (ESI)	optically active substance
1091		M^++H：462 (ESI)	optically active substance

[1072]

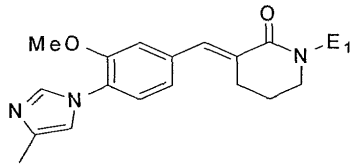
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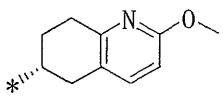
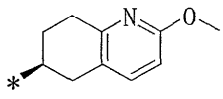
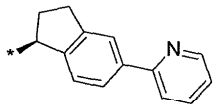
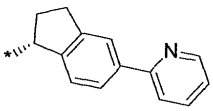
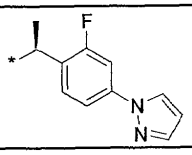
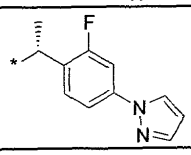
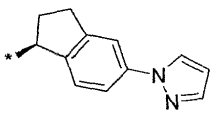
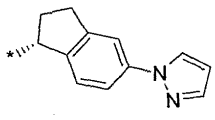
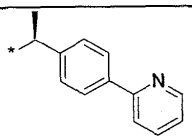
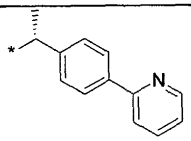


Example	E_1	DATA: MS m/z	Note
1092		M^++H : 463 (ESI)	optically active substance (separation condition C: retention time: 15.9 minutes; absolute configuration: unknown)
1093		M^++H : 463 (ESI)	optically active substance (separation condition C: retention time: 19.7 minutes; absolute configuration: unknown)
1094		M^++H : 459 (ESI)	optically active substance (separation condition A: retention time: 7.5 minutes; absolute configuration: unknown)
1095		M^++H : 459 (ESI)	optically active substance (separation condition A: retention time: 8.5 minutes; absolute configuration: unknown)
1096		M^++H : 463 (ESI)	optically active substance (separation condition C: retention time: 15.8 minutes; absolute configuration: unknown)
1097		M^++H : 463 (ESI)	optically active substance (separation condition C: retention time: 18.5 minutes; absolute configuration: unknown)
1098		M^++H : 429 (ESI)	optically active substance (separation condition B: retention time: 5.4 minutes; absolute configuration: unknown)
1099		M^++H : 429 (ESI)	optically active substance (separation condition B: retention time: 6.6 minutes; absolute configuration: unknown)
1100		M^++H : 429 (ESI)	optically active substance (separation condition C: retention time: 7.6 minutes; absolute configuration: unknown)
1101		M^++H : 429 (ESI)	optically active substance (separation condition C: retention time: 8.9 minutes; absolute configuration: unknown)

[1073]

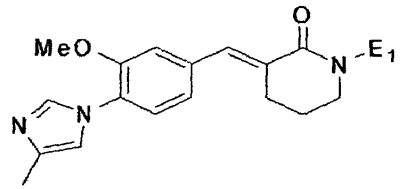
[Table 28-6]

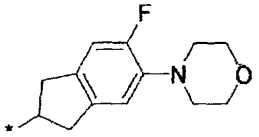


Example	E_1	DATA: MS m/z	Note
1102		M^++H : 459 (ESI)	optically active substance (separation condition B: retention time: 5.8 minutes; absolute configuration: unknown)
1103		M^++H : 459 (ESI)	optically active substance (separation condition B: retention time: 7.8 minutes; absolute configuration: unknown)
1104		M^++H : 491 (ESI)	optically active substance (separation condition A: retention time: 18.7 minutes; absolute configuration: unknown)
1105		M^++H : 491 (ESI)	optically active substance (separation condition A: retention time: 20.5 minutes; absolute configuration: unknown)
1106		M^++H : 486 (ESI)	optically active substance (separation condition C: retention time: 11.8 minutes; absolute configuration: unknown)
1107		M^++H : 486 (ESI)	optically active substance (separation condition C: retention time: 13.6 minutes; absolute configuration: unknown)
1108		M^++H : 480 (ESI)	optically active substance (separation condition C: retention time: 4.3 minutes; absolute configuration: unknown)
1109		M^++H : 480 (ESI)	optically active substance (separation condition C: retention time: 7.4 minutes; absolute configuration: unknown)
1110		M^++H : 479 (ESI)	optically active substance (separation condition A: retention time: 13.2 minutes; absolute configuration: unknown)
1111		M^++H : 479 (ESI)	optically active substance (separation condition A: retention time: 16.6 minutes; absolute configuration: unknown)

[1074]

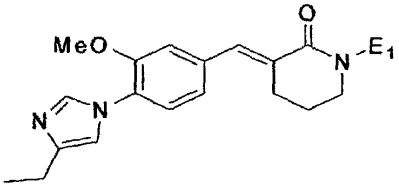
[Table 28-7]

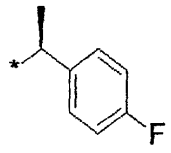


Example	E_1	DATA: MS m/z	Note
1112		M^++H 517 (ESI)	racemate

[1075]

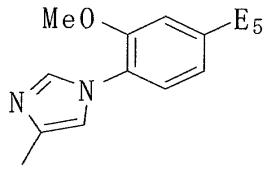
[Table 28-8]

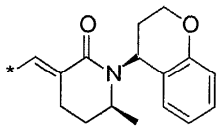
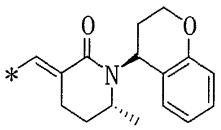
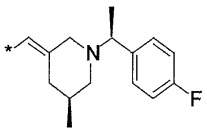
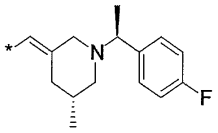
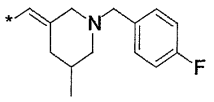


Example	E_1	DATA. MS m/z	Note
1113		M^++H · 434 (ESI)	optically active substance (absolute configuration: unknown)

[1076]

[Table 28-9]



Example	E5	DATA: MS m/z	Note
1114		M^++H : 444 (ESI)	optically active substance (separation condition A: retention time: 20.7 minutes; absolute configuration: unknown)
1115		M^++H : 444 (ESI)	optically active substance (separation condition A: retention time: 23.5 minutes; absolute configuration: unknown)
1116		M^++H : 434 (ESI)	optically active substance (separation condition D: retention time: 60 minutes; absolute configuration: unknown)
1117		M^++H : 434 (ESI)	optically active substance (separation condition D: retention time: 67 minutes; absolute configuration: unknown)
1118		M^++H : 420 (ESI)	racemate

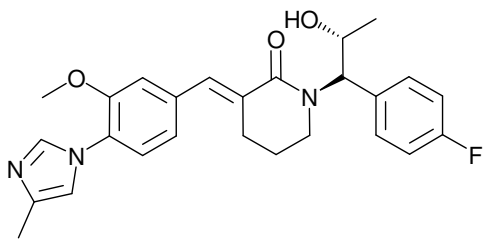
[1077]

Example 1119

Synthesis of (E)-1-[1-(4-fluorophenyl)-(1R,2R)-2-hydroxy propyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1078]

[Formula 338]



By the same method as in Example 418, 8 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (17 mg) and (1R,2R)-1-amino-1-(4-fluorophenyl)propan-2-ol 1 trifluoroacetic-acid salt (8.4 mg) synthesized according to the method described in Tetrahedoron: Asymmetry, 2000, vol. 11, p. 3079.

The physical properties of the compound are as follows.

ESI-MS; m/z450 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.29 (d, J=6.4 Hz, 3H), 1.72-1.93 (m, 2H), 2.31 (s, 3H), 2.69-2.88 (m, 2H), 3.15-3.23 (m, 1H), 3.44-3.53 (m, 1H), 3.86 (s, 3H), 4.51 (dq, J=8.4, 6.4 Hz,1H), 5.44 (d, J=8.4 Hz, 1H), 6.94 (s, 1H), 7.02-7.09 (m, 4H), 7.25 (d, J=8.0 Hz, 1H), 7.34-7.40 (m, 2H), 7.77 (d, J=0.8 Hz, 1H), 7.86 (brs, 1H).

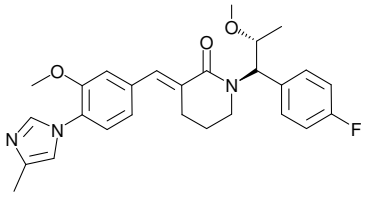
[1079]

Example 1120

Synthesis of (E)-1-[1-(4-fluorophenyl)-(1R,2R)-2-methoxypropyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1080]

[Formula 339]



To a THF (1 mL) solution of (E)-1-(1-(4-fluorophenyl)-(1R,2R)-2-hydroxy propyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one(4 mg) obtained in Example 1119, sodium hydride (40% mineral oil content, 0.5 mg) was added, and the reaction solution was agitated at room temperature for 30 minutes. Methyl iodide (2 mg) was added to the reaction solution, and the reaction solution was agitated at room temperature for 2 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer obtained was dried over magnesium sulfate and concentrated under reduced pressure. By purifying the residue with silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: ethyl acetate -> ethyl acetate: methanol 9:1), 3 mg of the title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z464 [M^++H].

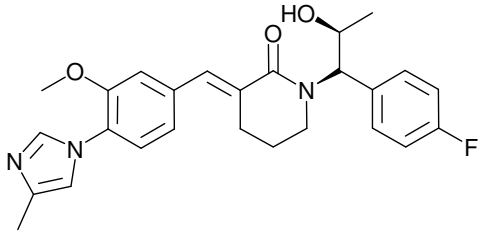
[1081]

Example 1121

<u>Synthesis of (E)-1-[1-(4-fluorophenyl)-(1R,2S)-2-hydroxy propyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one</u>

[1082]

[Formula 340]



By the same method as in Example 418, 15 mg of the title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (126 mg) and (1R,2S)-1-amino-1-(4-fluorophenyl)propan-2-ol 1 trifluoroacetic-acid salt (63 mg) synthesized according to the method described in Tetrahedoron: Asymmetry, 2000, vol. 11, p. 3079.

The physical properties of the compound are as follows.

ESI-MS; m/z450 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.36 (d, J=6.0 Hz, 3H), 1.68-1.84 (m, 2H), 2.30 (s, 3H), 2.67-2.85 (m, 2H), 3.15-3.20 (m, 1H), 3.25-3.35 (m, 1H), 3.84 (s, 3H), 4.55 (dq, J=7.6, 6.0 Hz,1H), 5.44 (d, J=7.6 Hz, 1H), 6.92 (s, 1H), 7.02-7.09 (m, 4H), 7.24 (d, J=8.0 Hz, 1H), 7.45-7.50 (m, 2H), 7.72 (d, J=0.8 Hz, 1H), 7.86 (brs, 1H).

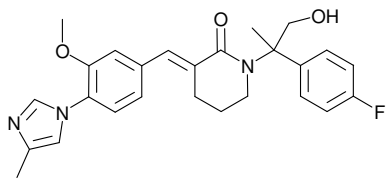
[1083]

Examples 1122 and 1123

<u>Synthesis of (E)-1-[(1R and 1S)-1-(4-fluorophenyl)-2-hydroxy-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one</u>

[1084]

[Formula 341]



[1085]

Synthesis of 2-(4-fluorophenyl)-3-methoxymethoxy-2-methylpropionic acid

To a methyl chloride (10 mL)-and-THF (5 mL) solution of 2-(4-fluorophenyl)-3-hydroxy-2-methylpropionic acid methyl ester (825 mg) synthesized according to the method described in Tetrahedron Letters, 1999, vol. 40, p. 5467, IPEA (2 mL) and chloromethyl methyl ether (0.74 mL) were added at 0°C. The reaction solution was agitated at 0°C for 1 hour, and then at room temperature for 10 hours. 1N hydrochloric acid and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer obtained was washed with saturated sodium bicarbonate water, dried over magnesium sulfate, and then concentrated under reduced pressure. To a methanol (5 mL) solution of the obtained residue, 5N sodium hydroxide aqueous solution (4 mL) was added, and the reaction solution was agitated at room temperature for 10 hours. 5N hydrochloric acid (4 mL) and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer obtained was dried over magnesium sulfate and concentrated under reduced pressure to obtain 850 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (s, 3H), 3.25 (s, 3H), 3.69 (d, J=9.2 Hz, 1H), 4.00 (d, J=9.2 Hz, 1H), 4,55 (d,

J=6.4 Hz,1H), 4.60 (d, J=6.4 Hz, 1H), 6.97 (t, J=8.4 Hz, 2H), 7.31 (dd, J=8.4, 4.8 Hz, 2H).

[1086]

Synthesis of [1-(4-fluorophenyl)-2-hydroxy-1-methylethyl]carbamic acid tertiary butyl ester

252 mg of the title compound was obtained from 2-(4-fluorophenyl)-3-methoxymethoxy-2-methylpropionic acid (850 mg) obtained above according to the method described in Tetrahedron Letters, 1998, vol. 39, p. 3749. The physical properties of the compound are as follows.

ESI-MS; m/z270 [M^++H].

[1087]

Synthesis of 2-amino-2-(4-fluorophenyl)propan-1-ol hydrochloric acid salt

To an ethyl acetate (1 mL) solution of (1-(4-fluorophenyl)-2-hydroxy-1-methylethyl)carbamic acid tertiary butyl ester (252 mg), 4 N hydrochloric acid ethyl acetate solution (3 mL) was added, and the reaction solution was agitated at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure to obtain 192 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.69 (s, 3H), 3.72 (d, J=11.6 Hz, 1H), 3.81 (d, J=11.6 Hz, 1H), 7.16-7.29 (m, 2H), 7.48-7.56 (m, 2H).

[1088]

Synthesis of (E)-1-[(1R and 1S)-1-(4-fluorophenyl)-2-hydroxy-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

By the same method as in Example 418, 36 mg of the racemic title compound was obtained from 2-amino-2-(4-fluorophenyl)propan-1-ol hydrochloric acid salt (192 mg) and (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (526 mg). The racemate obtained (36 mg) was separated by CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm × 25 cm: mobile phase; IPA) to obtain the title optically-active substance with a retention time of 11 minutes (Example 1122, 15 mg; > 99% ee) the title optically-active substance with a retention time of 12 minutes (Example 1123, 15 mg; > 99% ee).

The physical properties of the title optically-active substance with a retention time of 11 minutes (Example 1122) are as follows.

ESI-MS; m/z450 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.65-1.78 (m, 4H), 1.82-1.96 (m, 1H), 2.31 (s, 3H), 2.76-2.82 (m, 2H),2.94-3.02 (m, 1H), 3.13-3.21 (m, 1H), 3.51 (brd, J=11.2 Hz, 1H), 3.86 (s, 3H), 4.29 (d, J=11.2 Hz, 1H), 5.37 (brs, 1H),6.93 (d, J=1.2 Hz, 1H), 7.03-7.09 (m, 4H), 7.26 (d, J=7.6 Hz, 1H), 7.32 (dd, J=8.0, 5.2 Hz, 2H), 7.73 (s, 1H), 7.82 (brs, 1H).

The physical properties of the title optically-active substance with a retention time of 12

minutes (Example 1123) are as follows.

ESI-MS; m/z450 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.65-1.78 (m, 4H), 1.82-1.96 (m, 1H), 2.31 (s, 3H), 2.76-2.82 (m, 2H), 2.94-3.02 (m, 1H), 3.13-3.21 (m, 1H), 3.51 (brd, J=11.2 Hz, 1H), 3.86 (s, 3H), 4.29 (d, J=11.2 Hz, 1H), 5.37 (brs, 1H), 6.93 (d, J=1.2 Hz, 1H), 7.03-7.09 (m, 4H), 7.26 (d, J=7.6 Hz, 1H), 7.32 (dd, J=8.0, 5.2 Hz, 2H), 7.73 (s, 1H), 7.82 (brs, 1H).

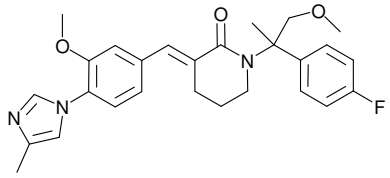
[1089]

Examples 1124 and 1125

Synthesis of (E)-1-[(1R and 1S)-1-(4-fluorophenyl)-2-methoxy-1-methylethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1090]

[Formula 342]



By the same method as in Examples 1122 and 1123, 10 mg of the racemic title compound was obtained from 1-(4-fluorophenyl)-2-methoxy-1-methylethylamine (11 mg) and (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (33 mg). The racemate obtained (5 mg) was separated by CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane:IPA 8:1) to obtain the title optically-active

substance with a retention time of 41 minutes (Example 1124, 2.3 mg; > 99% ee) and the title optically-active substance with a retention time of 50 minutes (Example 1125, 1.6 mg; > 99% ee).

The physical properties of the title optically-active substance with a retention time of 41 minutes (Example 1124) are as follows.

ESI-MS; m/z464 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.78 (s, 3H), 1.90-1.98 (m, 2H), 2.31 (s, 3H), 2.76-2.83 (m, 2H), 3.36(s, 3H), 3.63-3.67 (m, 2H), 3.76 (brd, J=10.0 Hz, 1H), 3.83 (s, 3H), 4.07 (d, J=10.0 Hz, 1H), 6.93 (brs, 1H), 6.97-7.07 (m, 4H), 7.22-7.28 (m, 3H), 7.62 (brs, 1H), 7.75 (s, 1H).

The physical properties of the title optically-active substance with a retention time of 50 minutes (Example 1125) are as follows.

ESI-MS; m/z464 $[M^+ + H]$. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.78 (s, 3H), 1.90-1.98 (m, 2H), 2.31 (s, 3H), 2.76-2.83 (m, 2H), 3.36 (s, 3H), 3.63-3.67 (m, 2H), 3.76 (brd, J=10.0 Hz, 1H), 3.83 (s, 3H), 4.07 (d, J=10.0 Hz, 1H), 6.93 (brs, 1H), 6.97-7.07 (m, 4H), 7.22-7.28 (m, 3H), 7.62 (brs, 1H), 7.75 (s, 1H).

[1091]

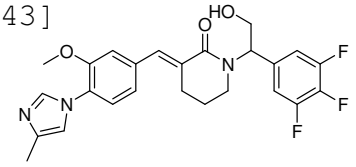
Examples 1126 and 1127

Synthesis of (E)-1-[(1S)-2-hydroxy-1-(3,4,5-trifluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-[(1R)-2-hydroxy-1-(3,4,5-trifluorophenyl)ethyl]-3-[3-

methoxy-4-(4-methyl-1H-imidazol-1-yl)-benzylidene]piperidin-2-one

[1092]

[Formula 343]



Synthesis of amino-(3,4,5-trifluorophenyl)acetonitrile

To a THF solution (20 mL) of 3,4,5-trifluorobenzaldehyde (1.3 g), trimethylsilylcyanide (1.35 mL) and zinc iodide (259 mg) were added, and the reaction solution was agitated at room temperature for 40 minutes. 2N ammonia solution in ethanol (15 mL) was added to the reaction solution, and the reaction solution was agitated at 50°C for 4 hours. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. Ethyl acetate and saturated sodium bicarbonate water were added to the residue, and the organic layer was partitioned. The organic layer obtained was dried over magnesium sulfate, the solvent was removed under reduced pressure, and 780 mg of the title compound was obtained by purifying the residue with silica gel chromatography (Carrier: Chromatorex, elution solvent: heptane-ethyl acetate system). The physical properties of the compound are as follows.

^{1}H-NMR (CD_3OD) δ (ppm): 5.02 (s, 1H), 7.32-7.37 (m,

2H).

[1093]

Synthesis of amino-(3,4,5-trifluorophenyl)acetic acid hydrochloric acid salt

To amino-(3,4,5-trifluorophenyl)acetonitrile (780 mg), 5N hydrochloric acid (10 mL) was added and the reaction solution was heated under reflux overnight. The reaction mixture was allowed to cool to room temperature, washed with ether, and then the aqueous layer was separated. The aqueous layer obtained was concentrated under reduced pressure to obtain 933 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR (DMSO-d_6) δ (ppm): 7.18-7.46 (m, 2H), 7.54-7.58 (m, 1H), 9.10 (brs, 1H).

[1094]

Synthesis of 2-amino-2-(3,4,5-trifluorophenyl)ethanol

To a THF suspension (10 mL) of LAH (641 mg), THF suspension (15 mL) of amino-(3,4,5-trifluorophenyl)acetic acid hydrochloric acid salt (933 mg) was added dropwise under cooling with ice. The reaction mixture was warmed to room temperature, and then agitated at room temperature for 7 hours. The reaction solution was once again cooled with ice, and methanol (4 mL) and water (2 mL) were consecutively added to the reaction solution. The insoluble matter formed in the reaction solution was filtered off by celite, and the insoluble matter was further washed

with ether. The filtrate collected was dried over magnesium sulfate and the solvent was removed under reduced pressure to obtain 587 mg of the title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.50 (dd, J=10.8, 8.0 Hz, 1H), 3.71 (dd, J=10.8, 4.0 Hz, 1H), 4.03 (dd, J=8.0, 4.0 Hz, 1H), 6.97-7.02 (m, 2H).

[1095]

Synthesis of (E)-1-[(1S)-2-hydroxy-1-(3,4,5-trifluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one and (E)-1-[(1R)-2-hydroxy-1-(3,4,5-trifluorophenyl)ethyl]-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

By the same method as in Example 418, 140 mg of the racemic title compound was obtained from (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (400 mg) and 2-amino-2-(3,4,5-trifluorophenyl)ethanol (180 mg). The racemate obtained (15 mg) was separated by CHIRALPAK™ AD-H available from Daicel Chemical Industries, Ltd. (2 cm × 25 cm:

[1096]

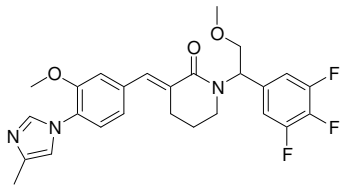
Examples 1128 and 1129

Synthesis of (E)-3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1S)-2-methoxy-1-(3,4,5-trifluorophenyl)ethyl]piperidin-2-one and (E)-3-[3-

methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-[(1R)-2-methoxy-1-(3,4,5-trifluorophenyl)ethyl]piperidin-2-one

[1097]

[Formula 344]



To a THF (2 mL) solution of racemic (E)-1-(2-hydroxy-1-(3,4,5-trifluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl-benzylidene)piperidin-2-one (85 mg) obtained in Examples 1126 and 1127, sodium hydride (40% mineral oil content, 9.5 mg) was added under cooling with ice, and the reaction solution was agitated for 30 minutes. Then, methyl iodide (12.3 μL) was added to the reaction solution, and the reaction mixture was further agitated at room temperature for 3 hours. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer obtained was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex NH, elution solvent: heptane-ethyl acetate system -> ethyl acetate-methanol system) to obtain 50 mg of the racemic title compound. The racemate obtained (50 mg) was separated by CHIRALPAK™ AD-H available from Daicel Chemical

Industries, Ltd. (2 cm×25 cm: mobile phase; ethanol), and the title optically-active substance with a retention time of 43 minutes (Example 1128, 10.5 mg; > 99% ee) and the title optically-active substance with a retention time of 50 minutes (Example 1129, 6.9 mg; 95% ee) of the title compound were obtained. The physical properties of these title compounds are as follows. ESI-MS; m/z486 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.71-1.92 (m, 2H), 2.30 (s, 3H), 2.74-2.90 (m, 2H), 3.10-3.17 (m, 1H), 3.36-3.43 (m, 1H), 3.43 (s, 3H), 3.82-3.92 (m, 2H), 3.85 (s, 3H), 6.03 (t, J=6.0 Hz, 1H), 6.93 (s, 1H), 6.98-7.05 (m, 4H), 7.25 (d, J=8.0 Hz, 1H), 7.74 (s, 1H), 7.86 (s, 1H).

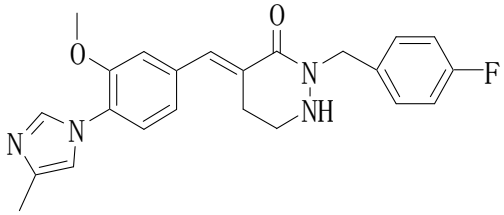
[1098]

Example 1130

Synthesis of (E)-2-(4-fluorobenzyl)-4-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]tetrahydropyrazine-3-one

[1099]

[Formula 345]



Synthesis of 4-bromo-2-(4-fluorobenzyl)-3-oxotetrahydropyrazine-1-carboxylic acid tertiary butyl ester

N'-(4-fluorobenzyl)hydrazine carboxylic acid

tertiary butyl ester (1.5 g) synthesized according to the method described in the literature (see, for example, H. L. Sham et al., J. Chem. Soc., Chem. Commun., 1993, vol. 13, p. 1052-1053) and 2,4-dibromo dibromobutyrylchloride (908 uL) in a mixture of dichloromethane (30 mL)-and-2N sodium hydroxide aqueous solution (5.0 mL) mixture of were vigorously agitated at room temperature. After 4.5 hours, the organic layer was separated. The organic layer obtained was washed with aqueous saline solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was diluted with acetonitrile (21 mL), potassium carbonate (1.55 g) was added, and the reaction mixture was agitated at room temperature for 3.5 hours. Water and ethyl acetate were added to reaction solution and the organic layer was partitioned. The organic layer was washed with saturated saline solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. By purifying the residue with silica gel chromatography (elution solvent: heptane-ethyl acetate system), 614 mg of the title compound was obtained. The physical properties of the compound are as follows. ESI-MS; m/z331 [M^+-tert-butyl].

[1100]

Synthesis of (E)-2-(4-fluorobenzyl)-4-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-3-oxotetrahydropyrazine-1-carboxylic acid tertiary butyl

ester

A mixture of 4-bromo-2-(4-fluorobenzyl)-3-oxotetrahydropyrazine-1-carboxylic acid tertiary butyl ester (500 mg) and triethyl phosphite (3 mL) was agitated under heating overnight at 120°C. The reaction solution was concentrated under reduced pressure, the residue was diluted with THF (20 mL) and ethanol (2 mL), lithium hydroxide (271 mg) and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (279 mg) were added, and the reaction mixture was agitated at room temperature for 4 hours. Water and ethyl acetate were added to the reaction solution and the organic layer was partitioned. The organic layer was washed with saturated saline solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane-ethyl acetate system) to obtain 614 mg of the title compound. The physical properties of the compound are as follows.
ESI-MS; m/z507 $[M^+H]$.

[1101]

Synthesis of (E)-2-(4-fluorobenzyl)-4-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]tetrahydropyrazine-3-one

A mixture of (E)-2-(4-fluorobenzyl)-4-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-3-oxotetrahydropyrazine-1-carboxylic acid tertiary butyl ester (582 mg) and trifluoroacetic acid (5 mL) was

agitated at room temperature for 1 hour, and then concentrated under reduced pressure. Saturated sodium bicarbonate water and ethyl acetate were added to the residue and the organic layer was partitioned. The organic layer obtained was washed with saturated saline solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: hexane–ethyl acetate system), and 385 mg of the title compound was obtained. The physical properties of the compound are as follows.

ESI–MS; m/z407 [M^++H]. ^{1}H–NMR ($CDCl_3$) δ : 3.31 (s, 3H), 2.91–2.95 (m, 2H), 3.15–3.21 (m, 2H), 3.87 (s, 3H), 4.08 (t, J=7.6 Hz, 1H), 4.78 (s, 2H), 6.94 (s, 1H), 7.00–7.05 (m, 2H), 7.07 (s, 1H), 7.08 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.36–7.40 (m, 2H), 7.76 (s, 1H), 7.86 (s, 1H).

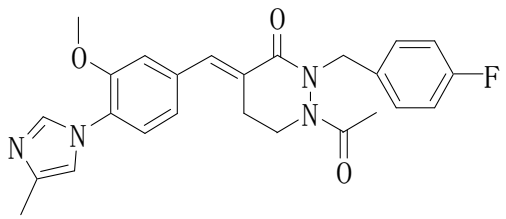
[1102]

Example 1131

Synthesis of (E)–1–acetyl–2–(4–fluorobenzyl)–4–[3–methoxy–4–(4–methyl–1H–imidazol–1–yl)benzylidene]tetrahydropyrazine–3–one

[1103]

[Formula 346]



(E)-2-(4-fluorobenzyl)-4-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)tetrahydropyrazine-3-one (31 mg) and a mixture of acetic anhydride (1 mL) and pyridine (1 mL) were agitated for 1 hour at room temperature. The reaction solution was concentrated under reduced pressure, saturated sodium bicarbonate water and ethyl acetate were added to the residue, and the organic layer was partitioned. The organic layer obtained was washed with saturated saline solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: chloroform-2-propanol system) to obtain 26.0 mg of the title compound. The physical properties of the compound are as follows.

ESI-MS; m/z449 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ : 2.13 (s, 3H), 2.33 (s, 3H), 2.44-2.52 (m, 1H), 2.61-2.66 (m, 1H), 3.15-3.26 (m, 1H), 3.87 (s, 3H), 4.19 (d, J=14.4 Hz, 1H), 4.49-4.55 (m, 1H), 5.51 (d, J=14.4 Hz, 1H), 6.95 (s, 1H), 6.99-7.11 (m, 4H),7.27 (d, J=8.4 Hz, 1H), 7.38-7.42 (m, 2H), 7.67 (s, 1H), 7.84 (s, 1H).

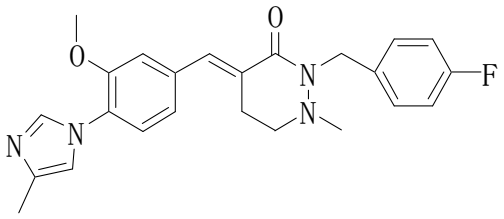
[1104]

Example 1132

Synthesis of (E)-2-(4-fluorobenzyl)-4-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]-1-methyltetrahydropyrazine-3-one

[1105]

[Formula 347]



(E)-2-(4-fluorobenzyl)-4-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)tetrahydropyrazine-3-one (50 mg) and a mixture of formic acid (2 mL) and formalin (2 mL) were heated under reflux for 2 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer obtained was washed with saturated saline solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: chloroform-2-propanol system) to obtain 36.7 mg of the title compound. The physical properties of the compound are as follows.

ESI-MS; m/z421 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ : 2.31 (s, 3H), 2.68 (s, 3H), 3.04-3.07 (m, 2H), 3.13-3.17 (m, 2H), 3.87 (s, 3H), 4.70 (s, 2H), 6.95 (s, 1H), 6.98-7.03 (m, 2H), 7.11 (d, J=1.6 Hz, 1H), 7.15 (dd, J=8.0, 1.6 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.37-7.41 (m, 2H), 7.75 (s, 1H), 7.80 (s, 1H).

[1106]

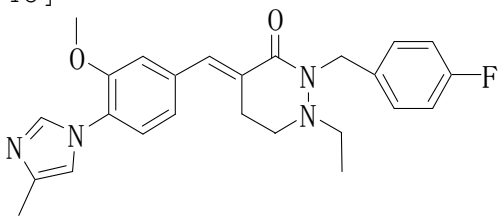
Example 1133

Synthesis of (E)-1-ethyl-2-(4-fluorobenzyl)-4-(3-methoxy-4-[4-methyl-1H-imidazol-1-

yl)benzylidene]tetrahydropyrazine-3-one

[1107]

[Formula 348]



(E)-2-(4-fluorobenzyl)-4-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)tetrahydropyrazine-3-one (50 mg) and a mixture of acetaldehyde (20.7 μL) and acetic acid (42.2 μL) and triacetoxy sodium borohydride (78.2 mg) were agitated overnight at room temperature. Ethyl acetate and water were added to the reaction solution, the solution was adjusted to around pH 8 with 5N sodium hydroxide aqueous solution, and the organic layer was separated. The organic layer was washed with saturated saline solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (elution solvent: chloroform-2-propanol system), and 38.8 mg of the title compound was obtained. The physical properties of the compound are as follows.

ESI-MS; m/z435 [M^++H]. ^{1}H-NMR ($CDCl_3$) δ : 1.13 (t, J=7.2 Hz, 3H), 2.34 (s, 3H), 2.93 (q, J=7.2 Hz, 2H), 2.90-2.98 (m, 2H), 3.11-3.15 (m, 2H), 3.88 (s, 3H), 4.70 (s, 2H), 6.96 (s, 1H), 6.98-7.03 (m, 2H), 7.11 (s, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.39-

7.43 (m, 2H), 7.74 (s, 1H), 7.85 (s, 1H).

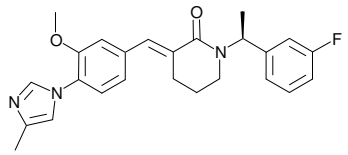
[1108]

Example 925

Synthesis of (E)-1-[(1R)-1-(3-fluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene]piperidin-2-one

[1109]

[Formula 349]



To a DMF (3 mL) solution of (E)-5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid trifluoroacetic acid salt (100 mg) obtained according to the method described in Example 418 and (S)-1-(3-fluorophenyl)ethylamine hydrochloric acid salt(31 mg), IPEA (0.2 mL) and HOBT (36 mg) and EDC (51 mg) were added, and the reaction solution was agitated at room temperature for 3 hours. Saturated sodium bicarbonate water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer obtained was dried over magnesium sulfate and concentrated under reduced pressure. By purifying the residue with silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane:ethyl acetate 1:1 -> ethyl acetate), 79 mg of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ((1S)-1-(3-

fluorophenyl)ethyl)amide was obtained. Sodium hydride (40% mineral oil content, 8 mg) was added to the DMF (3 mL) solution of 5-chloro-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)valeric acid ((1S)-1-(3-fluorophenyl)ethyl)amide obtained, and the reaction solution was agitated at room temperature for 5 minutes. Water and ethyl acetate were added to the reaction solution, and the organic layer was partitioned. The organic layer obtained was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (Carrier: Chromatorex™ NH, elution solvent: heptane:ethyl acetate system 1:1 -> ethyl acetate) to obtain 48 mg of the racemic title compound. The physical properties of the compound are as follows.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.56 (d, J=7.2 Hz, 3H), 1.60-1.80 (m, 2H), 2.32 (s, 3H), 2.72-2.90 (m, 2H), 2.94-3.00 (m, 1H), 3.22-3.30 (m, 1H), 3.86 (s, 3H), 6.23 (d, J=7.2, 1H), 6.92-7.00 (m, 2H), 7.02-7.07 (m, 3H), 7.12 (dd, J=7.2, 0.8 Hz, 1H), 7.25 (d, J=7.2 Hz, 1H), 7.28-7.34 (m, 2H), 7.76 (d, J=1.2 Hz, 1H), 7.89 (s, 1H).

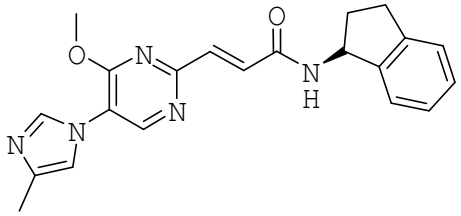
[1110]

Example 1134

Synthesis of (E)-N-[(1S)-indan-1-yl-3-[4-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrimidin-2-yl]acrylamide

[1111]

[Formula 350]



Synthesis of 4-methoxy-5-nitro-2-pyrimidine

To a solution of 2-chloro-3-methoxy-5-nitropyrimidine (CASNo. 282102-07-02, 670 mg), vinyl tri-n-butyltin (2.07 mL) and 2,6-di-t-butyl-4-methylphenol (30 mg) in DMF (15 mL) was added bis(triphenylphosphine)palladium(II) dichloride (124 mg), and the reaction mixture was stirred at 35°C for 2 hrs. To the reaction mixture was added water and ethyl acetate, and the organic layer was separated. The obtained organic layer was sequentially washed with water and saturated saline solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluting solvent: heptane/ethyl acetate) to give the title compound (261 mg). The physical data of the title compound was described as below.

ESI-MS; m/z182 $[M^+H]$. ^{1}H-NMR($CDCl_3$) δ (ppm): 4.21 (s, 3H), 5.94 (dd, J=9.6, 2.8 Hz, 1H), 6.75-6.88 (m, 2H), 9.15 (s, 1H).

[1112]

Synthesis of (E)-3-(4-methoxy-5-nitropyrimidin-2-yl)acrylic acid ethyl ester

A solution of 4-methoxy-5-nitro-2-

vinylpyrimidine (260 mg) in methylene chloride (15 mL) was stirred with an ozone stream of bubbling at −50°C for 1 hr. After the reaction mixture was warmed to −20°C, the ozone stream was stopped and dimethyl sulfide (1.06 mL) was added to the reaction mixture. The reaction mixture was gradually warmed up to room temperature with stirring for 30 min. The reaction mixture was concentrated under reduced pressure to obtain the corresponding crude aldehyde. To a solution of the crude aldehyde and triethyl phosphonoacetate (0.432 mL) in THF (5 mL) was added lithium hydroxide monohydrate (90.6 mg) at 0°C. After stirring for 1.5 hr at room temperature, water and ethyl acetate was added to the reaction mixture and an organic layer was separated. The obtained organic layer was sequentially washed with water and saturated saline solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent: heptane/ethyl acetate) to give the title compound (100 mg). The physical data of the title compound was described as below.

^{1}H-NMR($CDCl_3$) δ (ppm): 1.37 (t, J=6.8 Hz, 3H), 4.23 (s, 3H), 4.32 (q, J=6.8 Hz, 2H), 7.25 (d, J=15.6 Hz, 1H), 7.60 (d, J=15.6 Hz, 1H), 9.18 (s, 1H).

[1113]

Synthesis of (E)-3-[4-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrimidin-2-yl]acrylic acid ethyl ester

According to the method described in Example 23, the title compound (27.8 mg) was obtained from (E)-3-(4-methoxy-5-nitropyrimidin-2-yl)acrylic acid ethyl ester (100 mg). The physical data of the title compound was described as below.

^{1}H-NMR($CDCl_3$) δ(ppm): 1.37 (t, J=7.2 Hz, 3H), 2.31 (s, 3H), 4.14 (s, 3H), 4.31 (q, J=7.2 Hz, 2H), 6.99 (d, J=1.6 Hz, 1H), 7.15 (d, J=15.6 Hz, 1H), 7.61 (d, J=15.6 Hz, 1H), 7.82 (d, J=1.6 Hz, 1H), 8.50 (s, 1H).

[1114]

Synthesis of (E)-[(1S)-N-indan-1-yl]-3-[4-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrimidin-2-yl]acrylamide

To a solution of (E)-3-[4-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyrimidin-2-yl]acrylic acid ethyl ester (27.8 mg) in THF (1 mL) and ethanol (0.5 mL) was added 1N sodium hydroxide aqueous solution (1.0 mL) at 0°C. After the reaction mixture was stirred at room temperature for 2hrs, saturated aqueous ammonium chloride was added to the reaction mixture, and the reaction mixture was concentrated under reduced pressure. The residue was diluted with MeOH, and the diluted solution was filtrated on florisil. The filtrate was concentrated under reduced pressure to give the corresponding crude carboxylic acid. According to the method described in Example 23, the title compound (7.1 mg) was obtained from the crude carboxylic acid and (S)-1-aminoindan (61.8 μL). The physical data of the title compound was described as

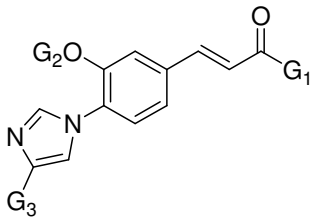
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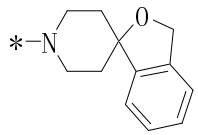
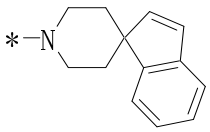
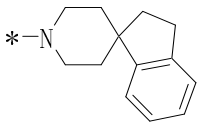
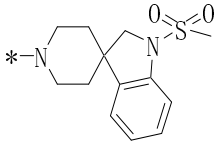
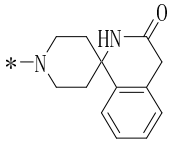
ESI-MS; m/z376 [M^++H]. ^{1}H-NMR($CDCl_3$) δ(ppm): 1.87-1.96 (m, 1H), 2.30 (s, 3H), 2.64-2.73 (m, 1H), 2.88-3.06 (m, 2H), 4.11 (s, 3H), 5.65 (dd, J=15.2, 7.6 Hz, 1H), 6.08 (d, J=7.6 Hz, 1H), 6.98 (s, 1H), 7.18 (d, J=15.2 Hz, 1H), 7.20 -7.36 (m, 4H), 7.60 (d, J=15.2 Hz, 1H), 7.81 (s, 1H), 8.47 (s, 1H).

[1115]

The compounds shown in Table 29 were synthesized as in Example 121. The structural formulae and physical properties are shown in Table 29, respectively.

[Table 29]

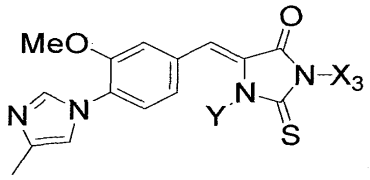


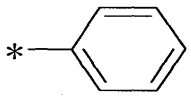
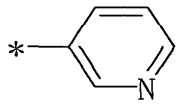
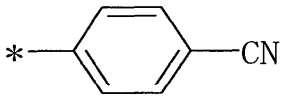
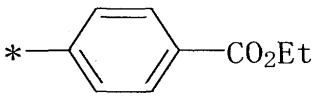
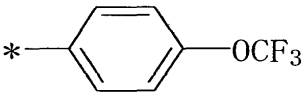
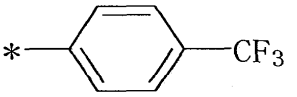
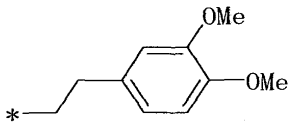
Example	G1	G2	G3	DATA: MS m/z
1135		Me	Me	M^++H:430 (ESI)
1136		Me	Me	M^++H:426 (ESI)
1137		Me	Me	M^++H:428 (ESI)
1138		Me	Me	M^++H:507 (ESI)
1139		Me	Me	M^++H:457 (ESI)

[1116]

The compounds shown in Table 30 were synthesized as in Example 409. The structural formulae and physical properties are shown in Tables 30 and 31, respectively.

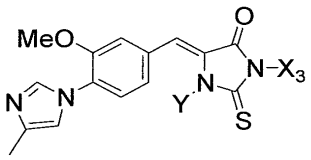
[Table 30-1]

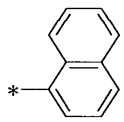
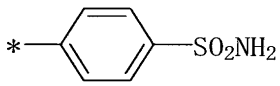
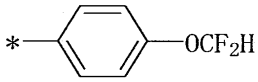
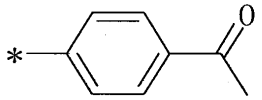
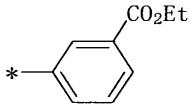
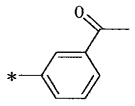
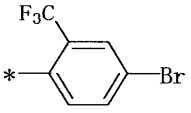
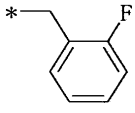
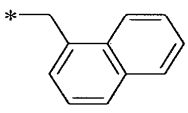
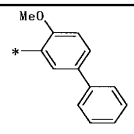


Example	X3	Y	DATA: MS m/z
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1141		H	M^++H : 392 (ESI)
1142		H	M^++H : 416 (ESI)
1143		H	M^++H : 463 (ESI)
1144		H	M^++H : 475 (ESI)
1145		H	M^++H : 459 (ESI)
1146		H	M^++H : 479 (ESI)

[1117]

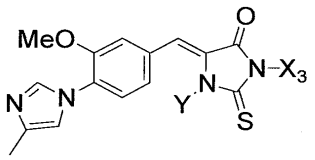
[Table 30-2]

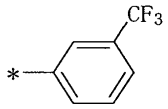
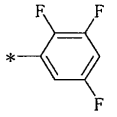
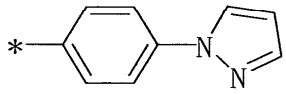
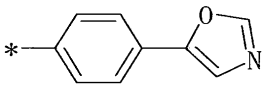
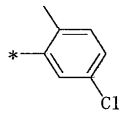
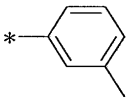
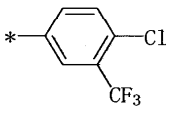
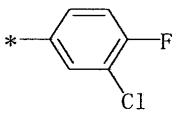
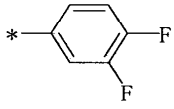
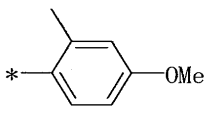


Example	X3	Y	DATA: MS m/z
1147		H	M^++H：441（ESI）
1148		H	M^++H：470（ESI）
1149		H	M^++H：457（ESI）
1150		H	M^++H：433（ESI）
1151		H	M^++H：463（ESI）
1152		H	M^++H：433（ESI）
1153		H	M^++H：537（ESI）
1154		H	M^++H：423（ESI）
1155		H	M^++H：455（ESI）
1156		H	M^++H：497（ESI）

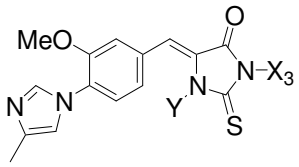
[1118]

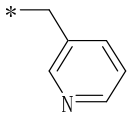
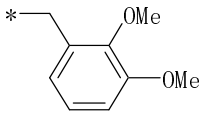
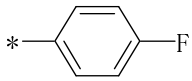
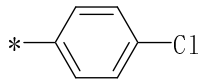
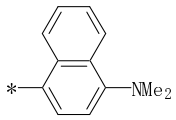
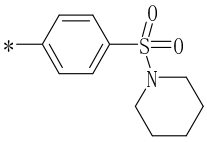
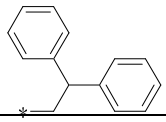
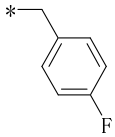
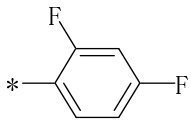
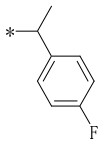
[Table 30-3]



Example	X3	Y	DATA: MS m/z
1157		H	M^++H：459（ESI）
1158		H	M^++H：445（ESI）
1159		H	M^++H：457（ESI）
1160		H	M^++H：458（ESI）
1161		H	M^++H：439（ESI）
1162		H	M^++H：405（ESI）
1163		H	M^++H：493（ESI）
1164		H	M^++H：443（ESI）
1165		H	M^++H：427（ESI）
1166		H	M^++H：435（ESI）

[1119]
[Table 30-4]



Example	X3	Y	DATA: MS m/z
1167		H	M^++H:406 (ESI)
1168		H	M^++H:465 (ESI)
1169		H	M^++H:409 (ESI)
1170		H	M^++H:425 (ESI)
1171		H	M^++H:484 (ESI)
1172		H	M^++H:538 (ESI)
1173		H	M^++H:495 (ESI)
1174		H	M^++H:423 (ESI)
1175		H	M^++H:427 (ESI)
1176		H	M^++H:437 (ESI)

[1120]

The compounds shown in Table 31 were synthesized as in Example 418. The structural formulae and physical properties are shown in Table 31, respectively.

Separation Condition A: CHIRALPAK™AD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane-ethanol system)

Separation Condition B: CHIRALCEL™ OJ-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase: hexane-ethanol)

Separation Condition C: CHIRALCEL™ OD-H available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane-ethanol)

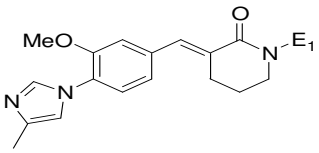
Separation Condition D: CHIRALCEL™ IA available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane-ethanol)

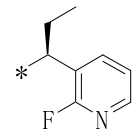
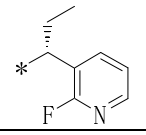
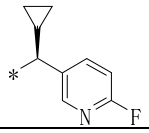
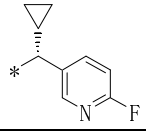
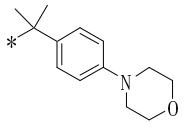
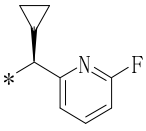
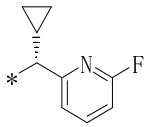
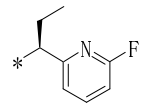
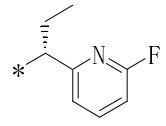
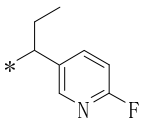
Separation Condition E: CHIRALCEL™ OD available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane-ethanol)

Separation Condition F: CHIRALCEL™ OJ available from Daicel Chemical Industries, Ltd. (2 cm×25 cm: mobile phase; hexane-ethanol)

[1121]

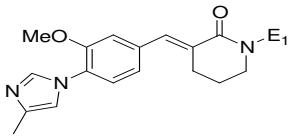
[Table 31-1]

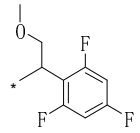
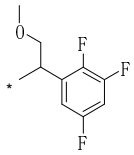
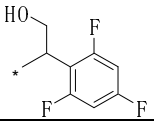
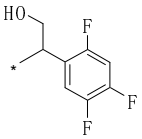
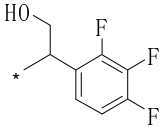
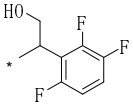
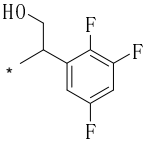
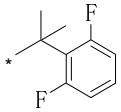
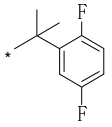
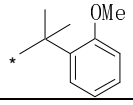


Example	E_1	DATA: MS m/z	Notes
1177		M^++H:435 (ESI)	optically active substance (separation condition C: retention time: 11.2 minutes; absolute configuration: unknown)
1178		M^++H:435 (ESI)	optically active substance (separation condition C: retention time: 12.4 minutes; absolute configuration: unknown)
1179		M^++H:447 (ESI)	optically active substance (separation condition A: retention time: 6.5 minutes; absolute configuration: unknown)
1180		M^++H:447 (ESI)	optically active substance (separation condition A: retention time: 7.4 minutes; absolute configuration: unknown)
1181		M^++H:501 (ESI)	
1182		M^++H:447 (ESI)	optically active substance (separation condition A: retention time: 5.5 minutes; absolute configuration: unknown)
1183		M^++H:447 (ESI)	optically active substance (separation condition A: retention time: 6.6 minutes; absolute configuration: unknown)
1184		M^++H:435 (ESI)	optically active substance (separation condition A: retention time: 7.2 minutes; absolute configuration: unknown)
1185		M^++H:435 (ESI)	optically active substance (separation condition A: retention time: 8.0 minutes; absolute configuration: unknown)
1186		M^++H:435 (ESI)	Racemate

[1122]

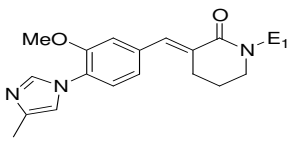
[Table 31-2]

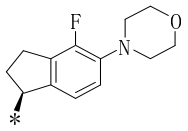
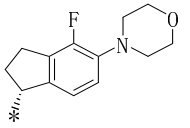
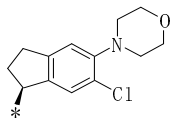
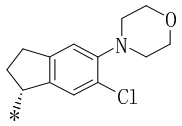
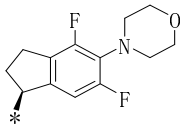
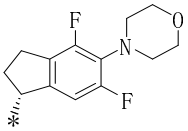
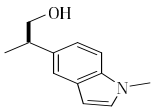
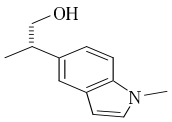
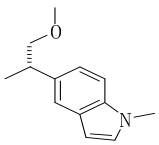
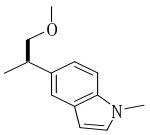


Example	E_1	DATA: MS m/z	Notes
1187		M^++H:486 (ESI)	racemate
1188		M^++H:486 (ESI)	racemate
1189		M^++H:472 (ESI)	racemate
1190		M^++H:472 (ESI)	racemate
1191		M^++H:472 (ESI)	racemate
1192		M^++H:472 (ESI)	racemate
1193		M^++H:472 (ESI)	racemate
1194		M^++H:452 (ESI)	
1195		M^++H:452 (ESI)	
1196		M^++H:446 (ESI)	

[1123]

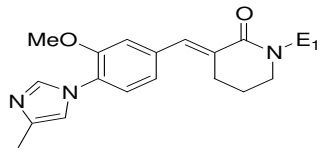
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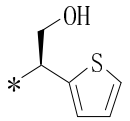
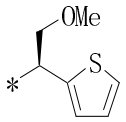
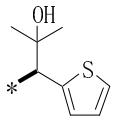
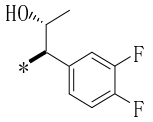
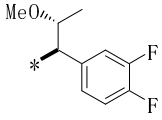
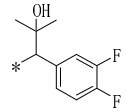
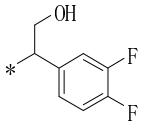
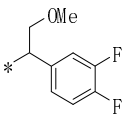
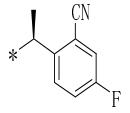
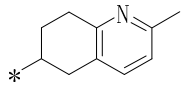


Example	E_1	DATA: MS m/z	Notes
1197		M^++H:517 (ESI)	optically active substance (separation condition C: retention time: 7.7 minutes; absolute configuration: unknown)
1198		M^++H:517 (ESI)	optically active substance (separation condition C: retention time: 9.6 minutes; absolute configuration: unknown)
1199		M^++H:533 (ESI)	optically active substance (separation condition C: retention time: 6.9 minutes; absolute configuration: unknown)
1200		M^++H:533 (ESI)	optically active substance (separation condition C: retention time: 8.6 minutes; absolute configuration: unknown)
1201		M^++H:535 (ESI)	optically active substance (separation condition A: retention time: 8.4 minutes; absolute configuration: unknown)
1202		M^++H:535 (ESI)	optically active substance (separation condition A: retention time: 10.2 minutes; absolute configuration: unknown)
1203		M^++Na:493 (ESI)	optically active substance (separation condition D: retention time: 8.2 minutes; absolute configuration: unknown)
1204		M^++Na:493 (ESI)	optically active substance (separation condition D: retention time: 10.4 minutes; absolute configuration: unknown)
1205		M^++Na:507 (ESI)	optically active substance (separation condition C: retention time: 17.8 minutes; absolute configuration: unknown)
1206		M^++Na:507 (ESI)	optically active substance (separation condition C: retention time: 21.7 minutes; absolute configuration: unknown)

[1124]

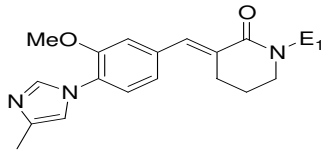
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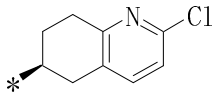
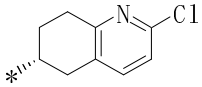
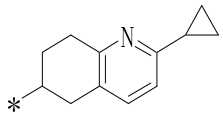
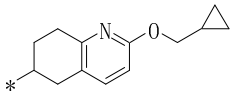
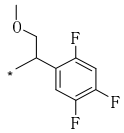
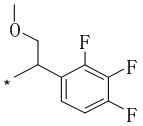
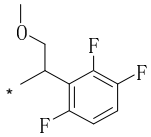
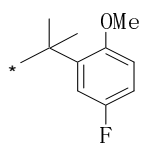


Example	E_1	DATA: MS m/z	Notes
1207		M^++H:424(ESI)	optically active substance
1208		M^++H:438(ESI)	optically active substance
1209		M^++H:452(ESI)	optically active substance
1210		M^++H:468(ESI)	optically active substance
1211		M^++H:482(ESI)	optically active substance
1212		M^++H:482(ESI)	racemate
1213		M^++H:454(ESI)	racemate
1214		M^++H:468(ESI)	racemate
1215		M^++H:445(ESI)	racemate
1216		M^++H:443(ESI)	racemate

[1125]

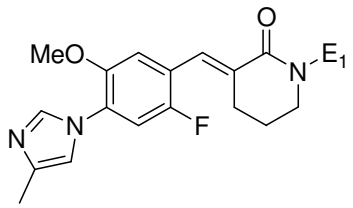
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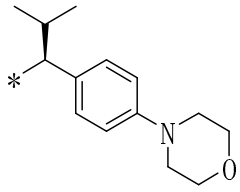
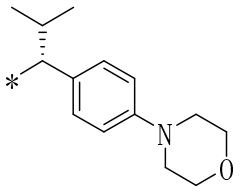


Example	E_1	DATA: MS m/z	Notes
1217		M^++H:463(ESI)	optically active substance (separation condition A: retention time: 11.7 minutes; absolute configuration: unknonw)
1218		M^++H:463(ESI)	optically active substance (separation condition A: retention time: 15.4 minutes; absolute configuration: unknonw)
1219		M^++H:469(ESI)	racemate
1220		M^++H:499(ESI)	racemate
1235		M^++H:486(ESI)	racemate
1236		M^++H:486(ESI)	racemate
1237		M^++H:486(ESI)	racemate
1238		M^++H:464(ESI)	

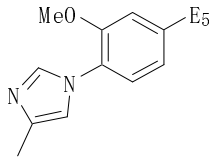
[1126]

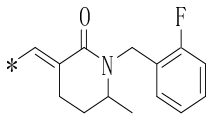
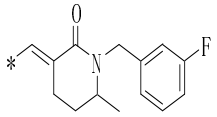
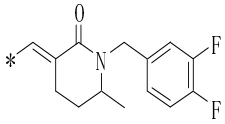
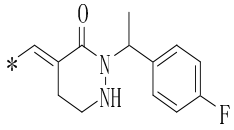
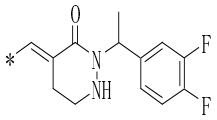
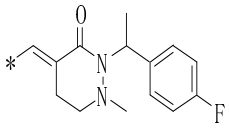
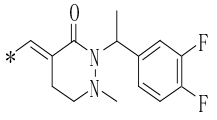
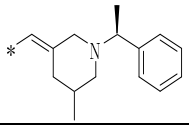
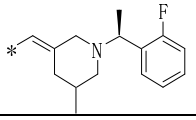
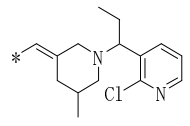
[Table 31-6]



Example	E_1	DATA: MS m/z	Notes
1221		M^++H:533(ESI)	optically active substance (separation condition A: retention time: 11 minutes; absolute configuration: unknonw)
1222		M^++H:533(ESI)	optically active substance (separation condition A: retention time: 25 minutes; absolute configuration: unknonw)

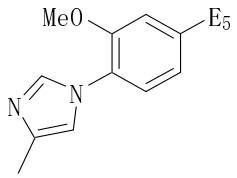
[1127]
[Table 31-7]

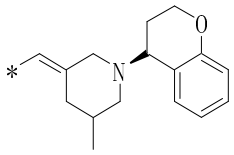
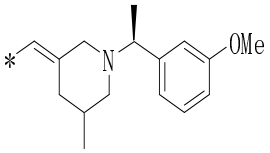


Example	E5	DATA: MS m/z	Notes
1223		M^++H:420(ESI)	racemate
1224		M^++H:420(ESI)	racemate
1225		M^++H:438(ESI)	racemate
1226		M^++H:421(ESI)	racemate
1227		M^++H:439(ESI)	racemate
1228		M^++H:435(ESI)	racemate
1229		M^++H:453(ESI)	racemate
1230		M^++H:416(ESI)	racemate
1231		M^++H:434(ESI)	racemate
1232		M^++H:466(ESI)	diasteromers-containing racemate

[1128]

[Table 31-8]



Example	E5	DATA: MS m/z	Notes
1233		M^++H:444(ESI)	racemate
1234		M^++H:446(ESI)	racemate

Industrial Applicability

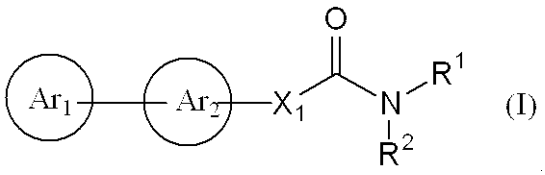
[1129]

The compound of the general formula (I) of the present invention has an effect to reduce the production of Aβ40 and Aβ42, hence is useful as a preventive or therapeutic agent for neurodegenerative diseases caused by Aβ, such as in particular Alzheimer's disease and Down syndrome.

CLAIMS

[1]. A compound or a pharmacologically acceptable salt thereof represented by Formula (I):

[Formula 1]



(I)

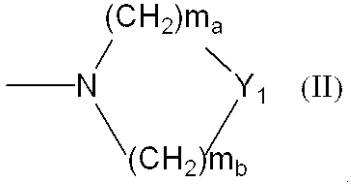
(wherein Ar_1 represents an imidazolyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A1 shown below; Ar_2 represents a pyridinyl group, a pyrimidinyl group, or a phenyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A2 shown below; X_1 represents (1) $-C\equiv C-$ or (2) $-CR^3=CR^4-$ (wherein R^3 and R^4 represents a substituent selected from Substituent Group A3 shown below); and

(1) R^1 and R^2 represent groups selected from Substituent Group A4 shown below or

R^1 and R^2, together with a nitrogen atom to which they bind, form one of the following groups:

(2-1) a 5- to 11-membered non-aromatic heterocyclic group represented by Formula (II):

[Formula 2]



(II)

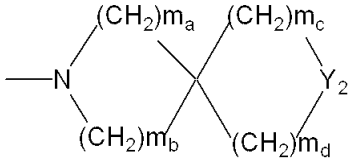
(wherein Y_1 represents (1) $-NH-$, (2) $-O-$, (3) $-S-$, (4) $-SO-$, (5) $-SO_2-$, (6) $-CH_2-$, (7) $-CO-$, (8) $-CONH-$, (9)

–NHCO–, (10) $-CR^5=CR^6-$ (wherein R^5 and R^6 represent substituents selected from Substituent Group A4 shown below), (11) a single bond or (12) $>C=CR^{13}R^{14}$ (wherein R^{13} and R^{14} represent groups selected from Substituent Group A4 shown below); and

m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(2–2) a 6– to 20–membered non–aromatic heterocyclic group represented by Formula (III):

[Formula 3]



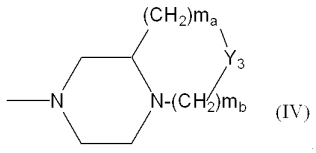
(III)

(wherein Y_2 represents (1) –NH–, (2) –O–, (3) –S–, (4) –SO–, (5) $-SO_2-$, (6) $-CH_2-$, (7) –CO–, (8) –CONH–, (9) –NHCO–, (10) $-CR^{5a}=CR^{6a}-$ (wherein R^{5a} and R^{6a} represent groups selected from Substituent Group A4 shown below or R^{5a} and R^{6a}, together with a carbon atom to which they bind, form a 6– to 14–membered aromatic hydrocarbon ring group or a 6– to 14–membered non–aromatic hydrocarbon ring group) or (11) a single bond; and

m_a, m_b, m_c and m_d represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(2–3) a 9– to 16–membered non–aromatic heterocyclic group represented by Formula (IV):

[Formula 4]



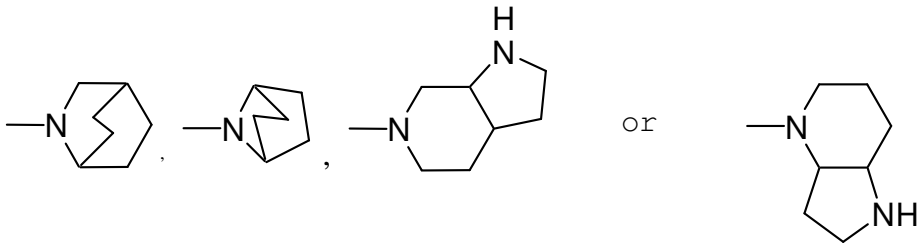
(IV)

(wherein Y_3 represents (1) –NH–, (2) –O–, (3) –S–, (4) –SO–, (5) $-SO_2-$, (6) $-CH_2-$, (7) –CO–, (8) –CONH–, (9) –NHCO– or (10) a single bond; and

m_a and m_b are the same as defined above) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(2-4) a group represented by the following formula:

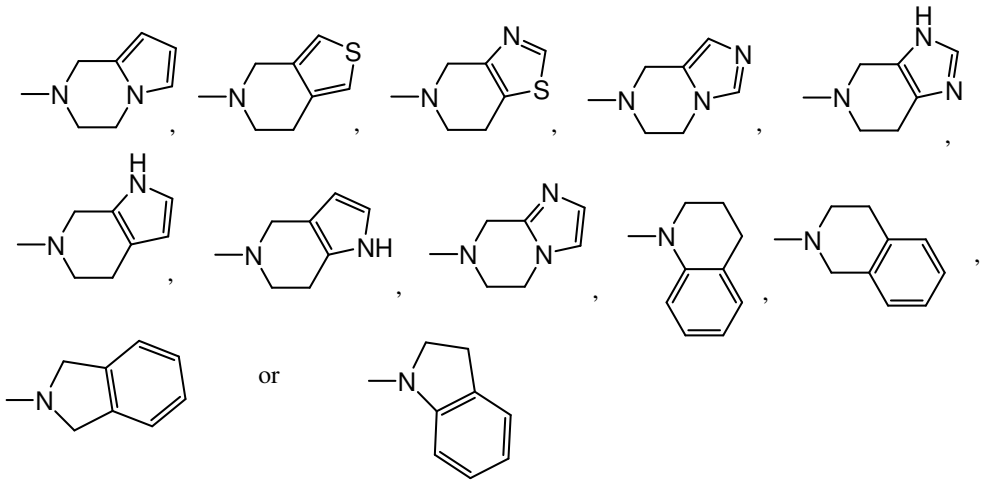
[Formula 5]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below;

(2-5) a group represented by the following formula:

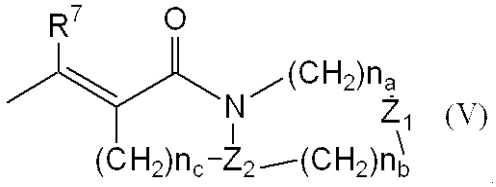
[Formula 6]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below; or R^1 and R^2, together with $-X_1-CO-N-$, form one of the following ring structures:

(3-1) a cyclic group represented by Formula (V):

[Formula 7]

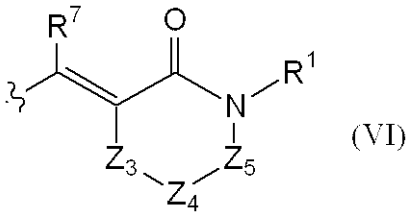


(V)

(wherein Z_1 represents (1) $-NH-$, (2) $-O-$, (3) $-S-$, (4) $-SO-$, (5) $-SO_2-$, (6) $-CH_2-$, (7) $-CO-$, (8) $-CONH-$, (9) $-NHCO-$ or (10) a single bond; Z_2 represents (1) a methine group or (2) a nitrogen atom; R^7 represents a substituent selected from Substituent Group A3 shown below; and n_a, n_b and n_c represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4;

(3-2) a cyclic group represented by Formula (VI):

[Formula 8]



(VI)

(wherein Z_3 represents (1) a single bond, (2) $-CO-$, (3) $-(CH_2)n_d-$ (wherein n_d represents an integer of 1 to 3) or (4) $-CR^8R^9-$ (wherein R^8 and R^9 represent a substituent selected from Substituent Group A4 shown below;

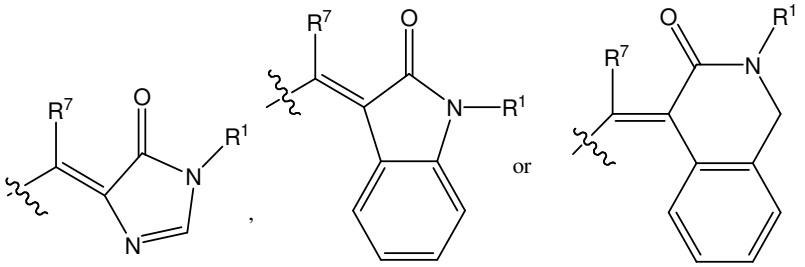
Z_4 represents (1) a single bond, (2) –O–, (3) –NRCO–, (4) –CONR–, (5) –CSNR–, (6)–NRCS–(wherein R represents a substituent selected from Substituent Group A4 shown below) or (7) –S–;

Z_5 represents (1) a single bond, (2) an imino group which may be substituted with a substituent selected from Substituent Group A4 shown below, (3) $-(CH_2)n_e-$ (wherein n_e represents an integer of 1 to 3), (4) $-CR^8R^9-$ (wherein R^8 and R^9 are the same as defined above) or (5) –O–; and

R^1 and R^7 are the same as defined above);or

(3-3) a cyclic group represented by the following formula:

[Formula 9]



(wherein R^1 and R^7 are the same as defined above) which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below.

Substituent Group A1: (1) a hydrogen atom, (2) a halogen atom, (3) a cyano group, (4) a nitro group, (5) a C3–8 cycloalkyl group, (6) a C2–6 alkenyl group, (7) a C2–6 alkynyl group, (8) a C1–6 alkoxy group, (9) a C3–8 cycloalkoxy group, (10) a formyl group, (11) a C1–6 alkylcarbonyl group, and (12) a C1–6 alkyl group

(wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C1–6 alkoxy group, a C3–8 cycloalkyl group and a C1–6 alkylcarbonyl group).

Substituent Group A2: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a cyano group, a C1–6 alkoxy group, a C2–6 alkeny group, a C2–6 alkyny group and a C3–8 cycloalkyl group), (6) a C3–8 cycloalkoxy group, (7) a C2–6 alkenyloxy group and (8) a C2–6 alkynyloxy group.

Substituent Group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2–6 alkenyl group, a C2–6 alkynyl group, a C3–8 cycloalkyl group, a C1–6 alkoxy group, a C1–6 alkylthio group, a C1–6 alkylsulfinyl

group, a C1-6 alkylsulfonyl group, a C1-6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4) and (6) a C1-6 alkoxyl group.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18)

a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the

same as defined above).

[2]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein Ar_1 is an imidazolyl group which may be substituted with 1 to 2 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group, (4) a C2-6 alkeny group, (5) a C2-6 alkyny group, (6) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 halogen atoms).

[3]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein Ar_2 is a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (6) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 substituents selected from a C2-6 alkenyl group, a C2-6 alkynyl group and a C3-8 cycloalkyl group), (7) a C2-6 alkenyloxy group and (8) a C2-6 alkynyloxy group.

[4]. The compound or pharmacologically acceptable salt thereof according to claim 2 wherein Ar_1 is an imidazolyl group which may be substituted with 1 to 2 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group and (4) a C1-6 alkyl group.

[5]. The compound or pharmacologically acceptable

salt thereof according to claim 3 wherein Ar_2 is a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a cyano group and (4) a C1–6 alkoxy group.

[6]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein X_1 is –C≡C–.

[7]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein X_1 is –CR^3=CR^4– (wherein R^3 and R^4 represent substituents selected from Substituent Group A3 shown below).

Substituent Group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2–6 alkenyl group, a C2–6 alkynyl group, a C3–8 cycloalkyl group, a C1–6 alkoxy group, a C1–6 alkylthio group, a C1–6 alkylsulfinyl group, a C1–6 alkylsulfonyl group, a C1–6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having

1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) and (6) a C1-6 alkoxy group.
Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxy group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3

substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[8]. The compound or pharmacologically acceptable salt thereof according to claim 7 wherein X_1 is -

$CR^{31}=CR^{41}-$ (wherein R^{31} is a group selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a C1-6 alkyl group and (4) a C1-6 alkoxy group; and R^{41} represents a group selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 and (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C1-6 alkyl group, a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5 and $-O-A^1$ (wherein A^1 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3

substituents selected from Substituent Group A5 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A5))).

Substituent Group A5: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 halogen atoms), (8) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms) and (9) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms).

[9]. The compound or pharmacologically acceptable salt thereof according to claim 8 wherein X_1 is -CR^{32}=CR^{42}- (wherein R^{32} represents a hydrogen atom or a halogen atom, and R^{42} represents a substituent selected from the group consisting of a hydrogen atom, a halogen atom, a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with a C3-8 cycloalkyl group or a phenyl group) and a phenyl group).

[10]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2 are groups selected from substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group,

(5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8

cycloalkylsulfonyl group, (30) –X–A (wherein X represents an imino group, –O– or –S– and A represents a 6– to 14–membered aromatic hydrocarbon ring group or 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) –CO–A (wherein A is the same as defined above) and (32) =CH–A (wherein A is the same as defined above).

[11]. The compound or pharmacologically acceptable salt thereof according to claim 10 wherein R^1 is a group selected from Substituent Group A8 shown below and R^2 is a group selected from Substituent Group A6 shown below.

Substituent Group A6: (1) a hydrogen atom, (2) a C3–8 cycloalkyl group, (3) a C3–8 cycloalkoxy group, (4) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkylthio group, a hydroxyimino group, a C1–6 alkoxyimino group, a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6– to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5– to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent

Group A7 shown below, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below and -O-A^2 (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below)) and (5) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkylthio group, a hydroxyimino group, a C1-6 alkoxyimino group, a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below and -O-A^2 (wherein A^2 is the same as defined above)).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3–8 cycloalkyl group, (6) a C3–8 cycloalkoxy group, (7) a C1–6 alkylcarbonyl group, (8) a C1–6 alkylthio group, (9) a C1–6 alkylsulfinyl group, (10) a C1–6 alkylsulfonyl group, (11) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and –O–A^3 (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group)), (12) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) –CO–A^3 (wherein A^3 is

the same as defined above).

Substituent Group A8: (1) a hydrogen atom, (2) C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and -X-A^2 (wherein X represents an imino group, -O- or -S- and A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 or a 5- to 14-

membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7)), (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (5) $-X-A^2$ (wherein X and A^2 are the same as defined above).

[12]. The compound or pharmacologically acceptable salt thereof according to claim 11 wherein R^1 is a C1-6 alkyl group (wherein said C1-6 alkyl group is a hydrogen atom, a C3-8 cycloalkoxy group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and $-O-A^4$ (wherein A^4 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 or

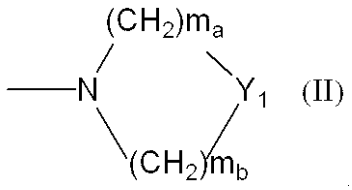
a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9)), and R^2 is (1) a hydrogen atom or (2) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a C1-6 alkylthio group, an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9).

Substituent Group A9: (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group, (4) a C3-8 cycloalkoxy group, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1-6 alkyl group), (6) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (7) an amino group

(wherein said amino group may be substituted with a C1-6 alkyl group optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

[13]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a 5- to 11-membered heterocyclic group represented by Formula (II):

[Formula 10]



(II)

(wherein Y_1 represents (1) $-NH-$, (2) $-O-$, (3) $-S-$, (4) $-SO-$, (5) $-SO_2-$, (6) $-CH_2-$, (7) $-CO-$, (8) $-CONH-$, (9) $-NHCO-$, (10) $-CR^5=CR^6-$ (wherein R^5 and R^6 represent groups selected from Substituent Group A4 shown below), (11) a single bond or (12) $>C=CR^{13}R^{14}$ (wherein R^{13} and R^{14} represent substituents selected from Substituent Group

A4 shown below); and; m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1

to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[14]. The compound or pharmacologically acceptable salt thereof according to claim 13 wherein a 5- to 11-membered heterocyclic group is a piperidinyl group, a pyrrolidinyl group, an azepinyl group, an azocanyl group, a piperazinyl group, a 1,4-diazepanyl group, a morpholinyl group or a thiomorpholinyl group.

[15]. The compound or pharmacologically acceptable salt thereof according to claim 14 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a piperidinyl group, a pyrrolidinyl group, an azepinyl group, an azocanyl group, a piperazinyl group, a 1,4-diazepanyl group, a morpholinyl group or a thiomorpholinyl group which may be substituted with 1 to 3 substituents selected from the group consisting of

(1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a formyl group, (5) a hydroxyimino group, (6) a C1-6 alkoxyimino group, (7) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 hydroxyl groups or 1 to 3 substituents selected from the group consisting of a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below), (8) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from substituents of A7 shown below, (9) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below, (10) $-O-A^2$ (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below), (11) $-CO-A^2$ (wherein A^2 is the same as defined above) and (12) $=CH-A^2$ (wherein A^2 is the same as defined above).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group,

(5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkylcarbonyl group, (8) a C1-6 alkylthio group, (9) a C1-6 alkylsulfinyl group, (10) a C1-6 alkylsulfonyl group, (11) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1-6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group)), (12) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

[16]. The compound or pharmacologically acceptable

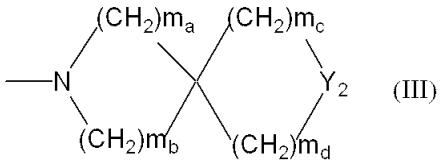
salt thereof according to claim 15 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a piperidinyl group, a pyrrolidinyl group, an azepinyl group, an azocanyl group, a piperazinyl group, a 1,4-diazepanyl group, a morpholinyl group or a thiomorpholinyl group which may be substituted with 1 to 4 substituents selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 hydroxyl groups or 1 to 3 substituents selected from the group consisting of a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A10 shown below), (5) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from substituents of A10 shown below, (6) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A10 shown below, (7) $-O-A^6$ (wherein A^6 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A10 shown below) and (8) $=CH-A^6$ (wherein A^6 is the same as defined above).

Substituent Group A10: (1) a hydrogen atom, (2) a halogen atom, (3) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 halogen

atoms), (4) a C1-6 alkoxy group and (5) a 6- to 14-membered aromatic hydrocarbon ring group.

[17]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a 6- to 20-membered non-aromatic heterocyclic group represented by Formula (III):

[Formula 11]



(III)

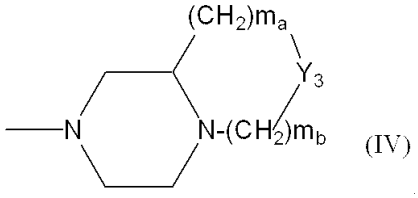
(wherein Y_2 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9) -NHCO-, (10) $-CR^5= CR^6-$ (wherein R^5 and R^6 represent groups selected from Substituent Group A4 shown below or R^5 and R^6, together with a carbon atom to which they bind, form a 6- to 14-membered aromatic hydrocarbon ring group or a 6- to 14-membered non-aromatic hydrocarbon ring group) or (11) a single bond; and m_a, m_b, m_c and m_d represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4 shown below.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group,

(13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may

be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) –CO–A (wherein A is the same as defined above) and (32) =CH–A (wherein A is the same as defined above).

[18]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a 9- to 16-membered non-aromatic heterocyclic group represented by Formula (IV):



(IV)

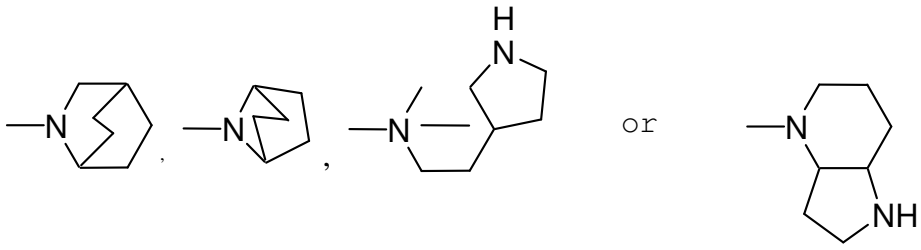
(wherein Y_3 represents (1) –NH–, (2) –O–, (3) –S–, (4) –SO–, (5) $-SO_2-$, (6) $-CH_2-$, (7) –CO–, (8) –CONH–, (9) –NHCO– or (10) a single bond; and m_a and m_b represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3

substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[19]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a group represented by the following formula:

[Formula 13]



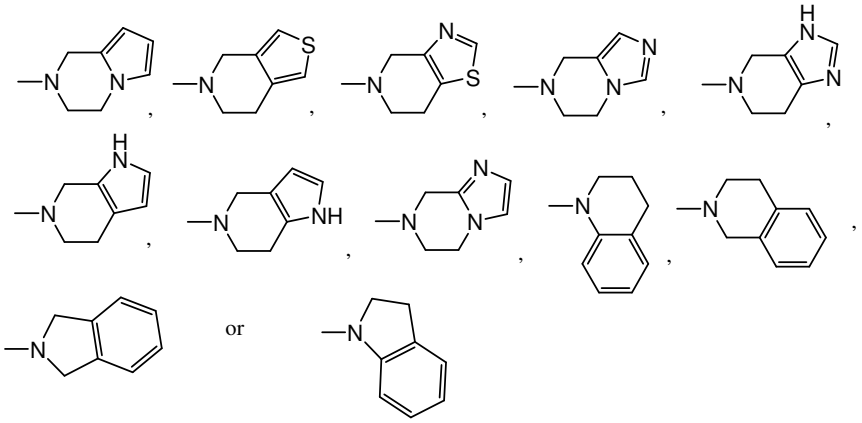
which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a

6- to 14-membered aromatic hyrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[20]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a group represented by the following formula:

[Formula 14]



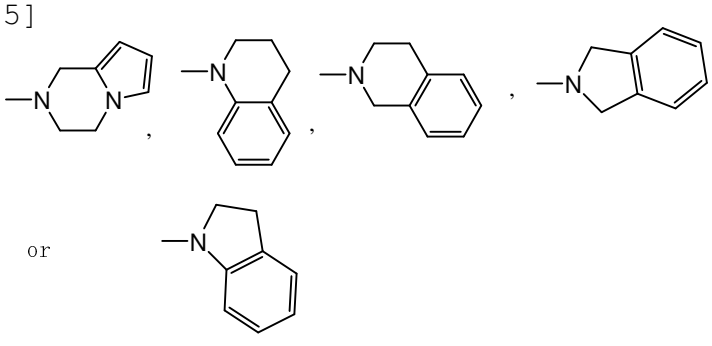
which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hyrocarbon ring group which may be substituted with 1 to 5 substituents selected

from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[21]. The compound or pharmacologically acceptable salt thereof according to claim 20 wherein R^1 and R^2, together with a nitrogen atom to which they bind, form a group represented by the following formula:

[Formula 15]



which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

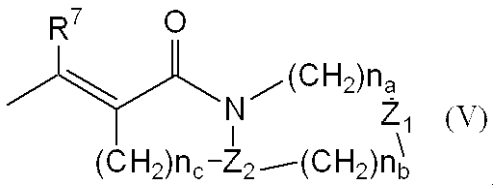
Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic

group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[22]. The compound or pharmacologically acceptable salt thereof according to claim 21 wherein the group formed by R^1 and R^2, together with a nitrogen atom to which they bind, may be substituted with 1 to 4 fluorine atoms.

[23]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with $-X_1-CO-N-$, form a cyclic group represented by Formula (V):

[Formula 16]



(V)

(wherein Z_1 represents (1) -NH-, (2) -O-, (3) -S-, (4) -SO-, (5) $-SO_2-$, (6) $-CH_2-$, (7) -CO-, (8) -CONH-, (9)

–NHCO– or (10) a single bond; Z_2 represents (1) a methine group or (2) a nitrogen atom; R^7 represents a substituent selected from Substituent Group A3 shown below; and n_a, n_b and n_c represent an integer of 0 to 4) which may be substituted with 1 to 4 substituents selected from Substituent Group A4.

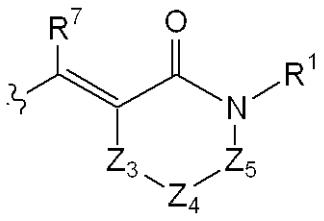
Substituent Group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2–6 alkenyl group, a C2–6 alkynyl group, a C3–8 cycloalkyl group, a C1–6 alkoxy group, a C1–6 alkylthio group, a C1–6 alkylsulfinyl group, a C1–6 alkylsulfonyl group, a C1–6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from

Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) and (6) a C1-6 alkoxy group. Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a

6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[24]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with $-X_1-CO-N-$, form a cyclic group represented by Formula (VI):

[Formula 17]



(VI)

(wherein Z_3 represents (1) a single bond, (2) –CO–, (3) $-(CH_2)n_d-$ (wherein n_d represents an integer of 1 to 3) or (4) $-CR^8R^9-$ (wherein R^8 and R^9 represent a substituent selected from Substituent Group A4 shown below;
Z_4 represents (1) a single bond, (2) –O–, (3) –NRCO–, (4) –CONR–, (5) –CSNR–, (6)–NRCS–(wherein R represents a substituent selected from Substituent Group A4 shown below) or (7) –S–;
Z_5 represents (1) a single bond, (2) an imino group which may be substituted with a substituent selected from Substituent Group A4 shown below, (3) $-(CH_2)n_e-$ (wherein n_e represents an integer of 1 to 3), (4) $-CR^8R^9-$ (wherein R^8 and R^9 are the same as defined above) or (5) –O–; and R^1 represents a substituent selected from Substituent Group A4 and R^7 represents a substituent selected from Substituent Group A3) which may be substituted with 1 to 4 substituents selected from Substituent Group A4.
Substituent Group A3: (1) a hydrogen atom, (2) a halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group

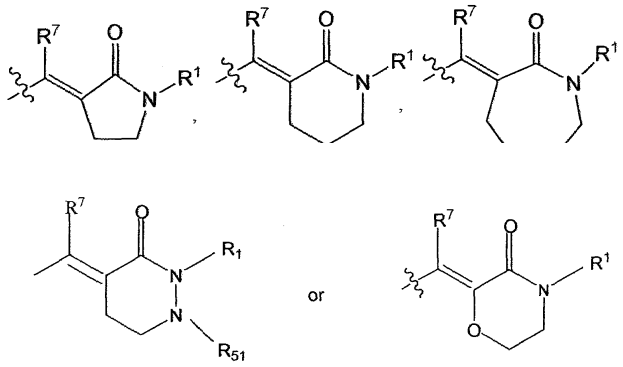
which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2-6 alkenyl group, a C2-6 alkynyl group, a C3-8 cycloalkyl group, a C1-6 alkoxy group, a C1-6 alkylthio group, a C1-6 alkylsulfinyl group, a C1-6 alkylsulfonyl group, a C1-6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) and (6) a C1-6 alkoxy group.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6

alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[25]. The compound or pharmacologically acceptable salt thereof according to claim 24 wherein Formula (VI) is a cyclic group:

[Formula 18]



(wherein R^1 and R_{51} represents a substituent selected

(wherein R^1 and R_{51} represents a substituent selected

from Substituent Group A4 and R^7 represents a substituent selected from Substituent Group A3) which may be substituted with 1 to 4 substituents selected from Substituent Group A7.

Substituent Group A3: (1) a hydrogen atom, (2) a

halogen atom, (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a formyl group, a halogen atom, a hydroxyl group, a hydroxyl group having a protecting group, a cyano group, a C2-6 alkenyl group, a C2-6 alkynyl group, a C3-8 cycloalkyl group, a C1-6 alkoxy group, a C1-6 alkylthio group, a C1-6 alkylsulfinyl group, a C1-6 alkylsulfonyl group, a C1-6 alkylcarbonyl group, an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 and -X-A (wherein X represents an imino group, -O- or -S- and A represents

a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4)) and (6) a C1-6 alkoxy group. Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxy group, (4) a cyano group, (5) a nitro group, (6) a C3-8 cycloalkyl group, (7) a C2-6 alkenyl group, (8) a C2-6 alkynyl group, (9) a C3-8 cycloalkoxy group, (10) a C3-8 cycloalkylthio group, (11) a formyl group, (12) a C1-6 alkylcarbonyl group, (13) a C1-6 alkylthio group, (14) a C1-6 alkylsulfinyl group, (15) a C1-6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1-6 alkoxyimino group, (18) a C1-6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1-6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1

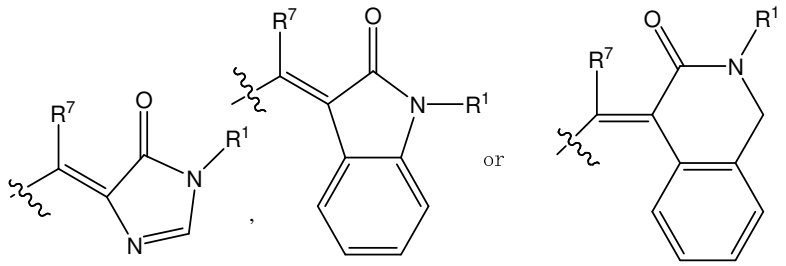
to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkylcarbonyl group, (8) a C1-6 alkylthio group, (9) a C1-6 alkylsulfinyl group, (10) a C1-6 alkylsulfonyl group, (11) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1-6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group)), (12) a C1-6 alkoxy group (wherein said C1-6

alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

[26]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 and R^2, together with $-X_1-CO-N-$, form a cyclic group represented by the following formula:

[Formula 19]



(wherein R^1 and R^7 are the same as defined above) which may be substituted with 1 to 4 substituents

selected from Substituent Group A4.

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents

selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[27]. The compound or pharmacologically acceptable salt thereof according to any one of claims 24 and 26 wherein R^1 is a substituent selected from Substituent Group A8.

Substituent Group A8: (1) a hydrogen atom, (2) C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8 cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, an amino group (wherein

said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and $-X-A^2$ (wherein X represents an imino group, -O- or -S- and A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7)), (3) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (4) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (5) $-X-A^2$ (wherein X and A^2 are the same as defined above).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkylcarbonyl group, (8) a C1-6 alkylthio group, (9) a C1-6 alkylsulfinyl group, (10) a

C1-6 alkylsulfonyl group, (11) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1-6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group), (12) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

[28]. The compound or pharmacologically acceptable salt thereof according to claim 27 wherein R^1 is a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 substituents selected from the

group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 6- to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, a 5- to 14–membered non–aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and –X–A^4 (wherein X represents an imino group, –O– or –S– and A^4 represents a 6- to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 or a 5- to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9)).

Substituent Group A9: (1) a hydrogen atom, (2) a

halogen atom, (3) a C3-8 cycloalkyl group, (4) a C3-8 cycloalkoxy group, (5) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1-6 alkyl group), (6) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (7) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

[29]. The compound or pharmacologically acceptable salt thereof according to any one of claims 10, 24 and 26 wherein R^1 is $-X_{21}-X_{22}-Ar_3$ (wherein X_{21} represents 1) a C1-6 alkylene group (wherein said C1-6 alkylene group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C3-8

cycloalkyl group, a C3-8 cycloalkoxy group, a formyl group, a C1-6 alkyl group (wherein 1 or 2 of said C1-6 alkyl group may substitute the same carbon atom in the C1-6 alkylene group and said two C1-6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1-6 alkoxy group, an amino group (wherein said amino group may be substituted with C1-6 alkyl(s)), a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7) or 2) a single bond, and X_{22} represents a single bond, an imino group which may be substituted with a substituent selected from Substituent Group A7, -O- or -S- and Ar_3 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3-8 cycloalkyl group, (6) a C3-8 cycloalkoxy group, (7) a C1-6 alkylcarbonyl group, (8) a C1-6 alkylthio group, (9) a C1-6 alkylsulfinyl group, (10) a C1-6 alkylsulfonyl group, (11) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with

1 to 5 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and –O–A^3 (wherein A^3 represents a 6- to 14–membered aromatic hydrocarbon ring group or a 5- to 14–membered aromatic heterocyclic group), (12) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1–6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having 1 to 5 halogen atoms), (14) a 6- to 14–membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14–membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14–membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) –CO–A^3 (wherein A^3 is the same as defined above).

[30]. The compound or pharmacologically acceptable salt thereof according to claim 29 wherein R^1 is $-X_{21a}-X_{22a}-Ar_{3a}$ (wherein X_{21a} represents a C1–6 alkylene group (wherein said C1–6 alkylene group may be substituted with 1 to 3 substituents selected from the group consisting of a hydrogen atom, a halogen atom, a

hydroxyl group, a cyano group, a C3–8 cycloalkyl group, a C3–8 cycloalkoxy group, a formyl group, a C1–6 alkyl group (wherein 1 or 2 of said C1–6 alkyl group may substitute the same carbon atom in the C1–6 alkylene group and said two C1–6 alkyl groups may, together with the carbon atom to which they bind, form a cyclic group (wherein a methylene group in the cyclic group which constitutes the ring may be substituted with one oxygen atom)), a C1–6 alkoxy group, an amino group (wherein said amino group may be substituted with C1–6 alkyl group(s) optionally having 1 to 5 halogen atoms), a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9), and X_{22a} represents a single bond or an oxygen atom and Ar_{3a} represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9).

Substituent Group A9: (1) a hydrogen atom, (2) a halogen atom, (3) a C3–8 cycloalkyl group, (4) a C3–8 cycloalkoxy group, (5) a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1–6 alkyl group), (6) a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together

with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (7) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) -CO-A^3 (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

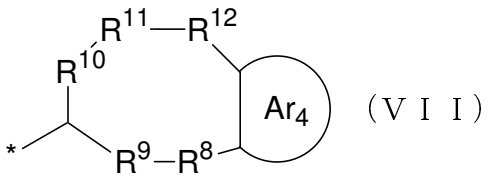
[31]. The compound or pharmacologically acceptable salt thereof according to claim 30 wherein Ar_{3a} is a 6- to 14-membered aromatic hydrocarbon ring group selected from the group consisting of a phenyl group, a naphthyl group and a fluorenyl group or a 5- to 14-membered aromatic heterocyclic group selected from the group consisting of a thienyl group, a pyridinyl group, a quinolinyl group, an isoquinolinyl group, an indolyl group, a benzothiazolyl group, a benzoxazolyl group and a furyl group, which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

Substituent Group A9: (1) a hydrogen atom, (2) a halogen atom, (3) a C3-8 cycloalkyl group, (4) a C3-8 cycloalkoxy group, (5) a C1-6 alkyl group (wherein said

C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom and a C1-6 alkyl group), (6) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (7) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms), (8) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9, (9) $-CO-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group), (10) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A9 and (11) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A9.

[32]. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein R^1 is a 6- to 14-membered non-aromatic hydrocarbon ring group or a 5- to 14-membered non-aromatic heterocyclic group represented by Formula (VII):

[Formula 20]



(VII)

(wherein R^8 to R^{12} represent 1) a single bond, 2) –CO–, 3) a methylene group which may be substituted with 1 or 2 substituents selected from Substituent Group A4, 4) –O–, 5) an imino group which may have a substituent selected from Substituent Group A4 or 6) –S–, and Ar_4 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4 shown below).

Substituent Group A4: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a nitro group, (6) a C3–8 cycloalkyl group, (7) a C2–6 alkenyl group, (8) a C2–6 alkynyl group, (9) a C3–8 cycloalkoxy group, (10) a C3–8 cycloalkylthio group, (11) a formyl group, (12) a C1–6 alkylcarbonyl group, (13) a C1–6 alkylthio group, (14) a C1–6 alkylsulfinyl group, (15) a C1–6 alkylsulfonyl group, (16) a hydroxyimino group, (17) a C1–6 alkoxyimino group, (18) a C1–6 alkyl group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (19) a C1–6 alkoxy group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (20) an amino group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (21) a carbamoyl group which may be substituted with 1 to 2 substituents selected from Substituent Group A4, (22) a

6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 5 substituents selected from Substituent Group A4, (23) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (24) a 6- to 14-membered non-aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (25) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4, (26) a C2-6 alkenyloxy group, (27) a C2-6 alkynyloxy group, (28) a C3-8 cycloalkylsulfinyl group, (29) a C3-8 cycloalkylsulfonyl group, (30) -X-A (wherein X represents an imino group, -O- or -S- and A represents a 6- to 14-membered aromatic hydrocarbon ring group or 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A4), (31) -CO-A (wherein A is the same as defined above) and (32) =CH-A (wherein A is the same as defined above).

[33]. The compound or pharmacologically acceptable salt thereof according to claim 32 wherein Ar_4 represents a phenyl group or a 5- to 14-membered aromatic heterocyclic group selected from the group consisting of a pyridinyl group, a pyrimidinyl group, a pyrazinyl group, a thienyl group, an oxazolyl group, a pyrrolyl group, a thiazolyl group and a furyl group,

which may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom, a C1–6 alkyl group (wherein said C1–6 alkyl group may be substituted with 1 to 3 substituents selected from the group consisting of a halogen atom and a C1–6 alkyl group), a C1–6 alkoxy group (wherein said C1–6 alkoxy group may be substituted with 1 to 3 halogen atoms), an amino group (wherein said amino group may be substituted with C1–6 alkyl groups optionally having 1 to 5 halogen atoms), a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and –CO–A^2 (wherein A^2 represents a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below or a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 shown below).

Substituent Group A7: (1) a hydrogen atom, (2) a halogen atom, (3) a hydroxyl group, (4) a cyano group, (5) a C3–8 cycloalkyl group, (6) a C3–8 cycloalkoxy group, (7) a C1–6 alkylcarbonyl group, (8) a C1–6

alkylthio group, (9) a C1-6 alkylsulfinyl group, (10) a C1-6 alkylsulfonyl group, (11) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 5 substituents selected from the group consisting of a halogen atom, a C1-6 alkyl group, a 6- to 14-membered aromatic hydrocarbon ring group, a 5- to 14-membered aromatic heterocyclic group and $-O-A^3$ (wherein A^3 represents a 6- to 14-membered aromatic hydrocarbon ring group or a 5- to 14-membered aromatic heterocyclic group), (12) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 5 halogen atoms or may, together with a carbon atom to which said adjacent C1-6 alkoxy groups bind, form a cyclic group), (13) an amino group (wherein said amino group may be substituted with C1-6 alkyl groups optionally having 1 to 5 halogen atoms), (14) a 6- to 14-membered aromatic hydrocarbon ring group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (15) a 5- to 14-membered aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7, (16) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with 1 to 3 substituents selected from Substituent Group A7 and (17) $-CO-A^3$ (wherein A^3 is the same as defined above).

[34]. The compound or pharmacologically acceptable salt thereof according to claim 33 wherein R^1 is an indanyl group, an azaindanyl group, a

tetrahydronaphthyl group, an azatetrahydronaphthyl group, a chromanyl group, an azachromanyl group, a tetrahydrobenzofuranyl group or a tetrahydrobenzothienyl group, which may be substituted with 1 to 3 substituents selected from the group consisting of (1) a halogen atom, (2) a hydroxyl group, (3) a cyano group, (4) a C3-8 cycloalkyl group, (5) a C3-8 cycloalkoxy group, (6) a C1-6 alkyl group (wherein said C1-6 alkyl group may be substituted with 1 to 3 halogen atoms or C1-6 alkyl groups), (7) a C1-6 alkoxy group (wherein said C1-6 alkoxy group may be substituted with 1 to 3 halogen atoms), (8) an amino group (wherein said amino group may be substituted with C1-6 alkyl group(s) optionally having 1 to 5 halogen atoms) and (9) a 5- to 14-membered non-aromatic heterocyclic group.

[35]. The compound or pharmacologically acceptable salt thereof according to claim 1 selected from the following group:

1) (E)-N-biphenyl-3-ylmethyl-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylamide,

2) (E)-N-((1S)-indan-1-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylamide,

3) (E)-N-(chroman-4-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)acrylamide,

4) (E)-1-(3,4-difluorobenzyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

5) (E)-1-indan-2-yl-3-(3-methoxy-4-(4-methyl-1H-

imidazol-1-yl)benzylidene)piperidin-2-one,

6) (E)-1-(chroman-4-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

7) (E)-1-((1S)-1-(4-fluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

8) (E)-1-((6-chloropyridin-2-yl)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

9) (E)-1-(4-tert-butylbenzyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

10) (E)-1-(3,4-difluorobenzyl)-3-((5-methoxy-6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl) methylene) piperidin-2-one,

11) (E)-1-((1H-indol-3-yl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

12) (E)-1-(5-fluoroindan-2-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

13) (E)-1-(7-fluorochroman-4-yl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one,

14) (E)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)-1-(1,2,3,4-tetrahydronaphthalen-2-yl) piperidin-2-one and

15) (E)-1-((2,4-difluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one.

[36]. A preventive or therapeutic agent for a disease resulting from amyloid betas comprising a compound represented by general formula (I) or pharmacologically acceptable salt thereof as an active ingredient.

[37]. The preventive or therapeutic agent according to claim 36 wherein the disease resulting from amyloid betas is Alzheimer's disease, senile dementia, Down syndrome or amyloidosis.