

DESCRIPTION

Title of Invention: COMPOUND AND COMPOSITION AS PDGF RECEPTOR
KINASE INHIBITOR

5 Technical Field
[0001]

The present invention relates to a prophylactic and/or
therapeutic agent for pulmonary hypertension comprising a novel
heterocyclic derivative as an active ingredient.

10

Background Art
[0002]

With regard to pulmonary arterial hypertension (PAH), a
large scale symposium on pulmonary hypertension is held every 5
15 years in the Western countries, and at the Dana Point Conference
in 2008, pulmonary hypertension was defined as a mean value of
the pulmonary arterial pressure (PAP) measured using a right
heart catheter test at rest (mean PAP) being 25 mmHg or more, and
this definition was continued at the Nice Conference in 2013. In
20 the Dana Point classification, pulmonary hypertension is
classified into five groups, that is, Group 1: PAH, Group 2:
pulmonary hypertension caused by a left heart disease, Group 3:
pulmonary hypertension caused by a pulmonary disease and/or
hypoxemia, Group 4: chronic thromboembolic pulmonary hypertension
25 (CTEPH) and Group 5: pulmonary hypertension caused by a
multifactorial mechanism for which details are unknown. This
basic structure has been maintained in the Revised Clinical
Classification of Pulmonary Hypertension (Nice classification
[2013]) (Non-patent Literature 1).

30 Furthermore, an updated definition of pulmonary
hypertension was proposed at the 6th World Symposium on Pulmonary
Hypertension (Nice Conference 2018). In that proposal, $24 \text{ mmHg} \geq$
mean pulmonary arterial pressure (mPAP) $> 20 \text{ mmHg}$ is also defined
to be included in the above pulmonary hypertension.

35 [0003]

Platelet-Derived Growth Factors (PDGFs) can stimulate the migration of arterial smooth muscle cells from the inside of the artery to the intimal layer where muscle cells can proliferate. The cell proliferation induced by all isoforms of PDGFs is mediated by ligands that bind to the PDGF receptor.

The PDGF receptor belongs to the class III tyrosine kinase family and consists of two receptor subtypes, called type A (or type alpha) and type B (or type beta). Other members of the PDGF receptor family include the colony stimulating factor 1 receptor (CSF1R), KIT, and FLT3.

KIT is another receptor tyrosine kinase belonging to the PDGF receptor family and is usually expressed on hematopoietic progenitor cells, mast cells, and embryonic cells. The expression of KIT has been known to be involved in several cancers including mast cell leukemia, germ cell tumors, small cell lung carcinoma, gastrointestinal stromal tumor (GIST), acute myeloid leukemia (AML), neuroblastoma, melanoma, ovarian carcinoma, and breast carcinoma (Non-patent Literature 1).
[0004]

Imatinib has an inhibitory action against the PDGF receptor kinase and exhibited effectiveness in a P3 study for pulmonary arterial hypertension. However, it was not well tolerated due to side effects such as bone marrow suppression and therefore did not reach approval.

[0005]

Patent Literature 1 describes that a compound of a general formula [1] or a pharmaceutically acceptable salt thereof is an inhibitor of the PDGF receptor kinase or the PDGF receptor kinase and KIT.

[0006]

However, up to now, the relationship between the myelosuppressive action and the inhibitory action against KIT, which is a receptor tyrosine kinase involved in bone marrow hematopoiesis, has not been known.

Citation List

Patent Literature

[0007]

PTL 8: WO 2013/033620

5 Non-patent Literature

[0008]

NPL 1: Smolich et al., Blood, 97, 1413-1421.

Summary of Invention

10 Technical Problem

[0009]

The problem that the present invention seeks to solve is to provide a prophylactic and/or therapeutic agent for pulmonary arterial hypertension that has an excellent balance
15 between effectiveness and safety.

Solution to Problem

[0010]

The present inventors have found a relationship between the myelosuppressive action and the inhibitory action against
20 KIT, which is a receptor tyrosine kinase involved in bone marrow hematopoiesis. That is, the present inventors have found that a compound represented by the following general formula [1] having a high inhibitory activity against the PDGF receptor kinase in the inhibitory activity against the KIT kinase, or a
25 pharmaceutically acceptable salt thereof, or a solvate thereof (in the present specification, it may be referred to as a compound of the present invention) exhibits a suppression action against the proliferation of pulmonary arterial smooth muscle cells and also reduces the suppression action against the
30 formation of erythroid colonies, thereby completing the present invention.

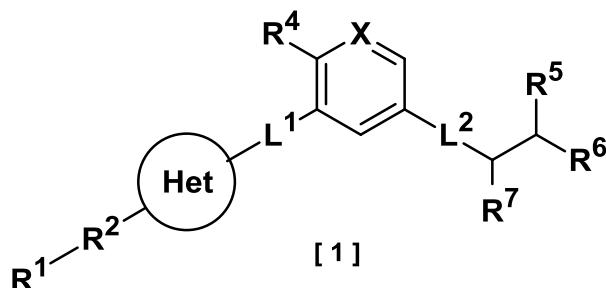
[0011]

That is, disclosed herein are the following (Item 1) to (Item 8).

35 (Item 1)

A compound represented by the following formula [1]:

[Formula 1]



wherein

5 R^1 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, a C_1 - C_6 haloalkyl, a C_2 - C_6 alkenyl, a C_2 - C_6 haloalkenyl, a C_2 - C_6 alkynyl, a C_2 - C_6 haloalkynyl, a C_1 - C_6 alkoxy, hydroxy, carboxy, an alkylcarbonyloxy, amino, a monoalkylamino, a dialkylamino, an aminoalkyl, an alkylcarbonylamino, nitro, an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted C_3 - C_6 cycloalkenyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl;

15 R^2 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$, wherein

R^a in R^2 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl and

20 R^b in R^2 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl, or

R^a and R^b in R^2 are taken together with the carbon atom to which they are bonded to form $C=O$,

each R^c in R^2 is independently a hydrogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl, and

25 m is an integer of 0 to 3;

Het is a 5- to 10-membered heteroaryl;

L^1 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$, wherein

30 R^a in L^1 is a hydrogen atom, a halogen atom, a C_1 - C_6

alkyl, or a C₁-C₆ haloalkyl and

R^b in L¹ is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl, or a C₁-C₆ haloalkyl, or

R^a and R^b in L¹ are taken together with the carbon
5 atom to which they are bonded to form C=O,

each R^c in L¹ is independently a hydrogen atom, a C₁-C₆ alkyl, or a C₁-C₆ haloalkyl, and

m in L¹ is an integer of 0 to 3;

X is N or C-R³, wherein

10 R³ is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl, or a C₁-C₆ haloalkyl;

R⁴ is a hydrogen atom, a halogen atom, or methyl;

L² is a bonding hand, -(CR^aR^b)_m-NR^c-, -NR^c-(CR^aR^b)_m-, -(CR^aR^b)_m-O-, -O-(CR^aR^b)_m-, -(CR^aR^b)_m-, -NR^c-, -O-, -NR^c-CO-NR^c-, -
15 CR^a=CR^b-, or -C≡C-, wherein

R^a in L² is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl, or a C₁-C₆ haloalkyl and

R^b in L² is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl, or a C₁-C₆ haloalkyl, or

20 R^a and R^b in L² are taken together with the carbon atom to which they are bonded to form C=O,

each R^c in L² is independently a hydrogen atom, a C₁-C₆ alkyl, or a C₁-C₆ haloalkyl, and

m in L² is an integer of 0 to 3;

25 R⁵ is a hydrogen atom, a halogen atom, hydroxy, amino, a C₁-C₆ alkyl, a C₁-C₆ haloalkyl, a C₁-C₆ alkoxy, or a C₁-C₆ haloalkoxy; and

R⁶ is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl, a C₁-C₆ haloalkyl, or an optionally substituted phenyl and

30 R⁷ is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl, a C₁-C₆ haloalkyl, a hydroxyalkyl, an optionally substituted phenyl, or an optionally substituted C₃-C₆ cycloalkyl, or

R⁶ and R⁷ are taken together with the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, an optionally
35 substituted aryl, or an optionally substituted heteroaryl

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

(Item 2)

The compound according to Item 1, wherein:

5 R^1 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, a C_2 - C_6 alkenyl, a C_1 - C_6 alkoxy, amino, a monoalkylamino, a dialkylamino, an aminoalkyl, an alkylcarbonylamino, an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an
10 optionally substituted heteroaryl;

R^2 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-(CR^aR^b)_m-O-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$;

L^1 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$,
15 wherein

R^a in L^1 is a hydrogen atom, a halogen atom, or a C_1 - C_6 alkyl and

R^b in L^1 is a hydrogen atom, a halogen atom, or a C_1 - C_6 alkyl, or

20 R^a in L^1 and R^b in L^1 are taken together with the carbon atom to which they are bonded to form $C=O$,

each R^c in L^1 is independently a hydrogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl, and

m in L^1 is an integer of 0 to 2;

25 X is N or $C-R^3$, wherein

R^3 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl;

R^4 is a hydrogen atom, a halogen atom, or methyl;

L^2 is $-(CR^aR^b)_m-NR^c-$ or $-NR^c-CO-NR^c-$, wherein

30 R^a and R^b in L^2 are taken together with the carbon atom to which they are bonded to form $C=O$,

each R^c in L^2 is independently a hydrogen atom, and

m in L^2 is 1;

R^5 is hydroxy; and

35 R^6 is a hydrogen atom, a C_1 - C_6 alkyl, or an optionally

substituted phenyl and

R^7 is a hydrogen atom, a C_1 - C_6 alkyl, a hydroxyalkyl, or an optionally substituted phenyl, or

R^6 and R^7 are taken together with the carbon atoms to
5 which they are bonded to form a C_3 - C_6 cycloalkyl or an optionally substituted aryl

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

(Item 3)

10 The compound according to Item 1, wherein:

R^1 is a hydrogen atom, a C_1 - C_6 alkoxy, amino, a monoalkylamino, an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl;

15 R^2 is a bonding hand, $-(CR^aR^b)_m-O-$, $-(CR^aR^b)_m-$, or $-NR^c-$;

L^1 is $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, or $-CR^a=CR^b-$,

wherein

R^a in L^1 is a hydrogen atom or a halogen atom and

R^b in L^1 is a hydrogen atom, or

20 R^a and R^b in L^1 are taken together with the carbon atom to which they are bonded to form $C=O$,

each R^c in L^1 is independently a hydrogen atom, and

m in L^1 is 0 or 1;

X is N or $C-R^3$, wherein

25 R^3 is a hydrogen atom;

R^4 is a halogen atom or methyl;

L^2 is $-(CR^aR^b)_m-NR^c-$, wherein

R^a and R^b in L^2 are taken together with the carbon atom to which they are bonded to form $C=O$,

30 each R^c in L^2 is independently a hydrogen atom, and m in L^2 is 1;

R^5 is hydroxy; and

R^6 and R^7 are taken together with the carbon atoms to which they are bonded to form a C_3 - C_6 cycloalkyl

35 or a pharmaceutically acceptable salt thereof, or a solvate

thereof.

(Item 4)

The compound according to Item 1, selected from the group consisting of the following (1) to (207):

- 5 (1) 2-(cyclopropylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- (2) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide,
- 10 (3) 2-(cyclopropylmethyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- (4) 5-(cyclopropylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-
- 15 carboxamide,
- (5) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-phenyl-1,3-oxazole-5-carboxamide,
- (6) N-(5-{[(1S)-2-hydroxy-1-phenylethyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide,
- 20 (7) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(propan-2-yl)oxy]pyridine-3-carboxamide,
- (8) 2-[(cyclopropylmethyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- 25 (9) 5-(4-chlorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (10) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-propyl-1,3-thiazole-5-carboxamide,
- 30 (11) 5-(3-chlorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (12) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-(2-methylphenyl)pyridine-3-carboxamide,
- 35 (13) 5-(2-chlorophenyl)-N-(5-{[(1S,2S)-2-

hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(14) N-(5-{[(2S)-1-hydroxypentan-2-yl] carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide,

5 (15) 5-[(E)-2-cyclopropylethenyl]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(16) 5-[(cyclopropylmethyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

10 (17) 5-[cyclopropyl (methyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(18) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-

15 methylphenyl)-5-(4-methoxyphenyl)pyridine-3-carboxamide,

(19) 5-(4-fluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(20) 5-(3-fluorophenyl)-N-(5-{[(1S,2S)-2-

20 hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(21) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-[4-(trifluoromethyl)phenyl]pyridine-3-carboxamide,

25 (22) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-[3-(trifluoromethyl)phenyl]pyridine-3-carboxamide,

(23) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-(2-methylprop-1-en-1-yl)pyridine-3-carboxamide,

30 (24) 5-(cyclopropylmethoxy)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(25) 2-[(3,3-difluorocyclobutyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-1,3-thiazole-5-

35 carboxamide,

- (26) 2-[(2-cyclopropylethyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- (27) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-[(propan-2-yl)amino]-1,3-thiazole-5-carboxamide,
- 5 (28) 5-[(4,4-difluorocyclohexyl)oxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (29) 5-(2-fluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- 10 (30) 5-(2,3-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (31) 5-(2,4-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- 15 (32) 5-(3,5-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- 20 (33) 5-(2-fluoro-4-methoxyphenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (34) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[3-(trifluoromethoxy)phenyl]pyridine-3-carboxamide,
- 25 (35) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[2-(trifluoromethoxy)phenyl]pyridine-3-carboxamide,
- (36) 5-[2-fluoro-4-(trifluoromethyl)phenyl]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- 30 (37) 5-(2,6-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
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- (38) 2-(tert-butylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- (39) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-[(1-methylcyclopropyl)amino]-1,3-thiazole-5-carboxamide,
- (40) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-[(1-methylcyclobutyl)amino]-1,3-thiazole-5-carboxamide,
- 10 (41) 2-[(2,2-dimethylpropyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- (42) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-(3,4,5-trifluorophenyl)pyridine-3-carboxamide,
- 15 (43) 5-(4-cyclopropylphenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (44) N-(2-chloro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)-5-(cyclopropylmethoxy)pyridine-3-carboxamide,
- 20 (45) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)imidazo[2,1-b][1,3]thiazole-5-carboxamide,
- (46) 5-(cyclopropylmethoxy)-N-(3-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- 25 (47) 5-[(3,3-difluorocyclobutyl)oxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (48) 2-(cyclopropylmethyl)-N-(3-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- 30 (49) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-methoxypyridine-3-carboxamide,
- (50) 5-ethoxy-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
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- (51) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(pyridin-2-yl)oxy]pyridine-3-carboxamide,
- (52) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(pyrimidin-2-yl)oxy]pyridine-3-carboxamide,
- 5 (53) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(1-methylcyclopropyl)methoxy]pyridine-3-carboxamide,
- (54) 5-[(3,3-difluorocyclobutyl)methoxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-
- 10 carboxamide,
- (55) N-(2-chloro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)-2-(cyclopropylmethyl)-1,3-thiazole-5-carboxamide,
- (56) 5-(cyclopropylmethoxy)-N-(2-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)pyridine-3-carboxamide,
- 15 (57) 3-[(5-bromopyridin-3-yl)ethynyl]-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- (58) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(5-phenylpyridin-3-yl)ethynyl]benzamide,
- 20 (59) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(5-methylpyridin-3-yl)ethynyl]benzamide,
- (60) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(5-phenylpyridin-3-yl)ethynyl]benzamide,
- (61) 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 25 (62) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]ethynyl}benzamide,
- (63) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrazin-2-yl)pyridin-3-yl]ethynyl}benzamide,
- 30 (64) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]ethynyl}benzamide,
- (65) 3-[(6-aminopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (66) 3-[[2,3'-bipyridin]-5'-yl]ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
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- (67) 3-[(5-cyclopropylpyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (68) 3-[(6-cyclopropylpyrazin-2-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 5 (69) 3-{[6-(2-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (70) 3-{[6-(3-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (71) 3-{[6-(4-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 10 (72) 3-({6-[(cyclopropylmethyl)amino]pyrazin-2-yl}ethynyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (73) 5-[(5-cyclopropylpyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
- 15 (74) 3-[(6-bromopyrazin-2-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (75) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-phenylpyrazin-2-yl)ethynyl]benzamide,
- (76) 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,
- 20 (77) N¹-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-N³-(5-phenylpyridin-3-yl)benzene-1,3-dicarboxamide,
- (78) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzamide,
- 25 (79) N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[2-(isoquinolin-4-yl)pyrimidin-4-yl]amino}-4-methylbenzamide,
- (80) N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-3-{[2-(isoquinolin-4-yl)pyrimidin-4-yl]amino}-4-methylbenzamide,
- (81) 3-[(2,3'-bipyridin]-6-yl)amino]-5-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 30 (82) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[2-(methylamino)quinazolin-5-yl]amino}benzamide,
- (83) 3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,
- 35 (84) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(1S)-1-(5-

- phenylpyridin-3-yl)ethyl]amino}benzamide,
- (85) 3-{ [(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (86) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({(1S)-1-[5-(phenylethynyl)pyridin-3-yl]ethyl}amino)benzamide,
- 5 (87) 3-{ [(1S)-1-([3,4'-bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (88) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({(1S)-1-[5-(pyrimidin-2-yl)pyridin-3-yl]ethyl}amino)benzamide,
- 10 (89) 3-{ [(1S)-1-([2,3'-bipyridin]-5'-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (90) 3-{ [(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- (91) 3-{ [(5-bromopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-
- 15 hydroxycyclohexyl]-4-methylbenzamide,
- (92) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{ [(5-phenylpyridin-3-yl)methyl]amino}benzamide,
- (93) 3-{ [([3,3'-bipyridin]-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 20 (94) 3-({ [5-(cyclopropylethynyl)pyridin-3-yl]methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (95) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({ [5-(pyrimidin-2-yl)pyridin-3-yl]methyl}amino)benzamide,
- (96) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{ [(quinolin-3-
- 25 yl)methyl]amino}benzamide,
- (97) N-[(1S,2S)-2-hydroxycyclohexyl]-3-[({5-[(1-hydroxycyclopropyl)ethynyl]pyridin-3-yl)methyl}amino]-4-methylbenzamide,
- (98) 3-[({5-[4-(2-aminopropan-2-yl)phenyl]pyridin-3-
- 30 yl)methyl}amino]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (99) 3-({ [5-(4-aminophenyl)pyridin-3-yl]methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (100) 3-({ [5-(3,5-difluorophenyl)pyridin-3-yl]methyl}amino)-N-
- 35 [(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

- (101) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(6-phenylpyrazin-2-yl)methyl]amino}benzamide,
- (102) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(thiophen-2-yl)pyridin-3-yl]methyl}amino)benzamide,
- 5 (103) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(thiophen-3-yl)pyridin-3-yl]methyl}amino)benzamide,
- (104) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]methyl}amino)benzamide,
- (105) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(pyrazolo[5,1-
10 b][1,3]thiazol-7-yl)methyl]amino}benzamide,
- (106) 3-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-5-({[5-(pyrimidin-2-yl)pyridin-3-yl]methyl}amino)benzamide,
- (107) 3-({[5-(5-fluoropyrimidin-2-yl)pyridin-3-yl]methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 15 (108) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(thieno[3,2-b]pyridin-6-yl)methyl]amino}benzamide,
- (109) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(1H-pyrazolo[3,4-b]pyridin-5-yl)methyl]amino}benzamide,
- (110) N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[(imidazo[1,2-
20 b]pyridazin-3-yl)methyl]amino}-4-methylbenzamide,
- (111) N-[(1S,2S)-2-hydroxycyclohexyl]-3-({[5-(imidazo[1,2-a]pyrazin-6-yl)pyridin-3-yl]methyl}amino)-4-methylbenzamide,
- (112) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[1-(pyridin-2-yl)-1H-pyrazol-4-yl]methyl}amino)benzamide,
- 25 (113) 3-{[(2-aminopyrimidin-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (114) 3-({[2-(cyclopropylamino)pyrimidin-5-yl]methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (115) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(pyrazin-2-
30 yl)pyridin-3-yl]methyl}amino)benzamide,
- (116) 3-{[(6-acetamidopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (117) 3-({[6-[(cyclopropylmethyl)amino]pyridin-3-yl]methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-
35 methylbenzamide,

- (118) 3-{[(2,2'-bipyridin]-5-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (119) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(pyrazolo[1,5-a]pyrimidin-3-yl)methyl}amino}benzamide,
- 5 (120) 3-[(6-[(cyclopropanecarbonyl)amino]pyridin-3-yl)methyl}amino]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (121) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(2-phenylpyrimidin-5-yl)methyl}amino}benzamide,
- 10 (122) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl}amino}benzamide,
- (123) N-[(1S,2S)-2-hydroxycyclohexyl]-6-methyl-5-{[(pyrazolo[1,5-a]pyridin-3-yl)methyl}amino}pyridine-3-carboxamide,
- (124) methyl {5-[(5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl)-2-methylanilino)methyl}pyridin-2-yl}carbamate,
- 15 (125) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(oxan-4-yl)amino]pyridin-3-yl)methyl}amino}benzamide,
- (126) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(pyridin-2-yl)amino]pyrimidin-5-yl)methyl}amino}benzamide,
- 20 (127) N-{5-[(5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl)-2-methylanilino)methyl}pyridin-2-yl}morpholine-4-carboxamide,
- (128) N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(2-(4-methoxyphenyl)pyrimidin-5-yl)methyl}amino}-4-methylbenzamide,
- (129) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(pyridin-3-yl)carbamoyl]amino}pyridin-3-yl)methyl}amino}benzamide,
- 25 (130) 3-[(6-(cyclobutylamino)pyridin-3-yl)methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
- (131) 3-{[(5-aminopyrazin-2-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 30 (132) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(oxan-4-yl)amino]pyrimidin-5-yl)methyl}amino}benzamide,
- (133) 3-[(6-[(cyclopropyl(methyl)carbamoyl]amino}pyridin-3-yl)methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 35 (134) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(propan-2-

- yl) amino]pyridin-3-yl)methyl) amino] benzamide,
(135) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(2-{{(3R)-oxolan-3-yl} amino}pyrimidin-5-yl)methyl} amino} benzamide,
(136) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(2-{{(3S)-oxolan-3-yl} amino}pyrimidin-5-yl)methyl} amino} benzamide
5 (137) N-{5-[(5-{{(1S,2S)-2-hydroxycyclohexyl} carbamoyl)-2-methylanilino)methyl}pyridin-2-yl} oxane-4-carboxamide,
(138) N-[(1S,2S)-2-hydroxycyclohexyl]-3-{{(6-{{(1r,3r)-3-methoxycyclobutane-1-carbonyl} amino}pyridin-3-yl)methyl} amino}-4-
10 methylbenzamide,
(139) N-{5-[(5-{{(1S,2S)-2-hydroxycyclohexyl} carbamoyl)-2-methylanilino)methyl}pyridin-2-yl} oxolane-3-carboxamide,
(140) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl} amino} benzamide,
15 (141) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[6-(oxetan-3-yl) amino]pyridin-3-yl)methyl} amino} benzamide,
(142) 3-{{(2-aminopyrimidin-5-yl)methyl} amino}-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl] benzamide,
(143) 3-{{(2-aminopyrimidin-5-yl)methyl} amino}-5-fluoro-N-
20 [(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(144) 3-{{(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)methyl} amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(145) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl} amino} benzamide,
25 (146) 3-{{[[3,3'-bipyridin]-5-yl) amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(147) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl] amino}methyl} benzamide,
30 (148) 3-{{[[2,3'-bipyridin]-5'-yl) amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(149) N-[(1R,2R)-2-hydroxycyclohexyl]-4-methyl-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl] amino}methyl} benzamide,
(150) N-[(1S,2S)-2-hydroxycyclohexyl]-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl] amino}methyl} benzamide,
35

- (151) 4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl)benzamide,
- (152) 3-([5-bromopyridin-3-yl]amino)methyl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,
- 5 (153) N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-([5-phenylpyridin-3-yl]amino)methyl)benzamide,
- (154) 3-([5-cyclopropylpyridin-3-yl]amino)methyl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,
- (155) 3-([2,3'-bipyridin]-5'-yl)amino)methyl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,
- 10 (156) N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-([6-phenylpyrazin-2-yl]amino)methyl)benzamide,
- (157) 5-([5-(cyclopropylethynyl)pyridin-3-yl]amino)methyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
- 15 (158) N-[3-([6-(3,4-dimethoxyphenyl)pyrazin-2-yl]amino)methyl]phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea,
- (159) N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[3-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]urea,
- (160) N-[2-fluoro-5-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea,
- 20 (161) N-[4-fluoro-3-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea,
- (162) N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]urea,
- 25 (163) N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[2-methyl-5-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]urea,
- (164) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{1-[6-phenylpyrazin-2-yl]amino}ethyl)benzamide,
- (165) 3-([3,3'-bipyridin]-5-yl)methoxy]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 30 (166) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl]methoxy)benzamide,
- (167) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-([5-(pyrimidin-2-yl)pyridin-3-yl]methoxy)benzamide,
- 35 (168) 3-([3,3'-bipyridin]-5-yl)oxy)methyl)-N-[(1S,2S)-2-

hydroxycyclohexyl]-4-methylbenzamide,

(169) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl]oxy)methyl)benzamide,

(170) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-([5-(pyrimidin-2-yl)pyridin-3-yl]oxy)methyl)benzamide,

(171) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{1-[5-(pyrimidin-2-yl)pyridin-3-yl]ethoxy}benzamide,

(172) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[1-(5-phenylpyridin-3-yl)ethoxy]benzamide,

(173) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(E)-2-(5-phenylpyridin-3-yl)ethenyl]benzamide,

(174) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[2-(5-phenylpyridin-3-yl)ethyl]benzamide,

(175) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[methyl(5-phenylpyridin-3-yl)amino]methyl}benzamide,

(176) 3-{[ethyl(5-phenylpyridin-3-yl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(177) 3-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(178) 4-fluoro-3-{(Z)-2-fluoro-2-[5-(pyrimidin-2-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(179) 3-[(Z)-2-fluoro-2-(imidazo[1,2-b]pyridazin-3-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(180) 5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-N-

[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,

(181) 3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(182) 3-[(Z)-2-fluoro-2-{5-[(morpholin-4-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(183) 3-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(184) 4-fluoro-3-{(Z)-2-fluoro-2-[5-(morpholin-4-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(185) 4-fluoro-3-[(Z)-2-fluoro-2-{5-[(oxan-4-yl)amino]pyridin-3-

- yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
(186) 4-fluoro-3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
5 (187) 5-{(Z)-2-[5-(cyclopropylmethoxy)pyridin-3-yl]-2-fluoroethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
(188) 5-{(Z)-2-fluoro-2-[5-(morpholin-4-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
10 (189) 5-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
(190) 5-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
(191) 3-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
15 (192) 3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
(193) 3-[(Z)-2-fluoro-2-{5-[(1-methylpiperidin-4-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
20 (194) 3-[(Z)-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(195) 5-[(Z)-2-fluoro-2-{5-[(oxetan-3-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
25 (196) 4-fluoro-3-[(Z)-2-fluoro-2-{5-[(oxetan-3-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
(197) 3-[(Z)-2-(6-{[2-(dimethylamino)ethyl]amino}pyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
30 (198) 3-[(Z)-2-(5-{[2-(dimethylamino)ethyl]amino}pyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(199) 5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
35 (200) 3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-

yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-4-methylbenzamide,

(201) 3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-(2-hydroxy-3,3-dimethylbutyl)-4-methylbenzamide,

(202) 3-[(Z)-2-{2-[(cyclopropylmethyl)amino]pyrimidin-5-yl}-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(203) 3-{(Z)-2-[2-(cyclopropylamino)pyrimidin-5-yl]-2-fluoroethenyl}-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(204) 3-[(Z)-2-(2-amino-4-methylpyrimidin-5-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(205) 4-fluoro-3-{(Z)-2-fluoro-2-[2-(methylamino)pyrimidin-5-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(206) 3-[(Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide, and

(207) 4-fluoro-3-[(Z)-2-fluoro-2-(5-fluoropyridin-3-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

(Item 5)

The compound according to Item 1, selected from the group consisting of the following (1) to (15):

(1) 2-(cyclopropylmethyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,

(2) 5-[cyclopropyl(methyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(3) 5-(3-fluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(4) 5-(cyclopropylmethoxy)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(5) 5-ethoxy-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-

methylphenyl)pyridine-3-carboxamide,

(6) 3-[(2-aminopyrimidin-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(7) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(pyrazolo[1,5-a]pyrimidin-3-yl)methyl]amino}benzamide,

(8) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(oxan-4-yl)amino]pyrimidin-5-yl)methyl]amino}benzamide,

(9) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl]amino}benzamide,

(10) 3-[(2,3'-bipyridin]-5'-yl)amino}methyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(11) 5-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,

(12) 3-[(Z)-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(13) 4-fluoro-3-[(Z)-2-fluoro-2-[2-(methylamino)pyrimidin-5-yl]ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(14) 3-[(Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide, and

(15) 4-fluoro-3-[(Z)-2-fluoro-2-(5-fluoropyridin-3-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

(Item 6)

A pharmaceutical composition comprising the compound according to any one of Items 1 to 5 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

(Item 7)

A PDGF receptor kinase inhibitor comprising the compound according to any one of Items 1 to 5 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

(Item 8)

A therapeutic agent for pulmonary hypertension,

scleroderma, asthma, bronchiolitis obliterans, pulmonary fibrosis, acute myelogenous leukemia (AML), hypereosinophilic syndrome, T-lymphoblastic leukemia, chronic myelomonocytic leukemia (CMML), chronic myelogenous leukemia (CML), chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, glioma, ovarian cancer, vascular restenosis, atherosclerosis/arteriosclerosis obliterans, moyamoya disease (idiopathic occlusion of the circle of Willis), leiomyoma, lymphangioma, or age-related macular degeneration (AMD), in which a PDGF receptor kinase is involved, the therapeutic agent comprising the compound according to any one of Items 1 to 5 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

Advantageous Effects of Invention

[0012]

Since the compound of the present invention inhibits the PDGF receptor kinase, it is useful as a therapeutic agent for diseases in which the PDGF receptor kinase is involved (for example, respiratory diseases, cancers, smooth muscle proliferative diseases, vasoproliferative diseases, autoimmune/inflammatory diseases, metabolic diseases, vasoocclusive diseases, and the like).

Description of Embodiments

[0013]

Hereinafter, the meaning of each term used in the present specification will be described. Each term is used in the same sense, whether used alone or used in combination with other terms, unless otherwise noted.

[0014]

The term "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

[0015]

Examples of "alkyl" may include, for example, a straight or branched alkyl having 1 to 6 carbon atoms, preferably

1 to 4 carbon atoms, and more preferably 1 to 3 carbon atoms. Specific examples thereof may include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, 1-ethylpropyl, 1,2-dimethylpropyl, tert-pentyl, 2-methylbutyl, isopentyl, neopentyl, n-hexyl, sec-hexyl, 1-ethylbutyl, isohexyl, neohexyl, 1,1-dimethylbutyl, 2-ethylbutyl, 1,2,2-trimethylpropyl, 2,2-dimethylbutyl, and the like.

[0016]

As the alkyl moiety in "monoalkylamino", "alkylcarbonyloxy", "monoalkylamino", "dialkylamino", "alkylcarbonylamino", "alkylsulfonyl", "aminoalkyl", and "alkylcarbonyl", mention may be made of the same "alkyl" as described above.

[0017]

The term "alkenyl" refers to a straight or branched hydrocarbon group having one or more double bonds at an arbitrary position and having 2 to 10 carbon atoms, preferably 2 to 8 carbon atoms, more preferably 2 to 6 carbon atoms, and further preferably 2 to 4 carbon atoms. Specific examples thereof may include vinyl, allyl, 2-methylpropenyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, and the like.

[0018]

The term "amino" refers to -NH_2 .

[0019]

The term "aminoalkyl" refers to a group in which a hydrogen atom bonded to a carbon atom in the "alkyl" described above is substituted with an amino group. Specific examples thereof may include, for example, aminomethyl, 1-aminoethyl, 2-aminoethyl, 1-aminopropyl, 2-aminopropyl, 2-aminopropan-2-yl, 3-aminopropyl, and the like.

[0020]

The term "monoalkylamino" refers to a group in which one hydrogen atom bonded to the nitrogen atom in an amino group is substituted with the "alkyl" described above. Specific

examples may include methylamino, ethylamino, isopropylamino, and the like.

[0021]

5 The term "hydroxyalkyl" refers to a group in which a hydrogen atom bonded to a carbon atom in the "alkyl" described above is substituted with a hydroxy group. Specific examples thereof may include, for example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, and the like.

[0022]

10 The term "alkylcarbonyl" refers to a group in which the "alkyl" described above is bonded to a carbonyl group. Examples thereof may include, for example, methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, tert-butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, pentylcarbonyl, 15 isopentylcarbonyl, hexylcarbonyl, and the like.

[0023]

The term "haloalkyl" refers to a group in which a hydrogen atom in the "alkyl" described above is substituted with the "halogen atom" described above. Specific examples thereof may 20 include, for example, fluoromethyl, chloromethyl, fluoroethyl, difluoromethyl, dichloromethyl, difluoroethyl, trifluoromethyl, trichloromethyl, trifluoroethyl, and the like.

[0024]

The term "alkoxy" refers to a group in which the 25 "alkyl" described above is bonded to an oxygen atom. Examples thereof may include, for example, a straight or branched alkoxy having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Specific examples thereof may include, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, 30 tert-butoxy, n-pentyloxy, n-hexyloxy, and the like.

[0025]

As the alkoxy moiety in "haloalkoxy", mention may be made of the same "alkoxy" as described above.

[0026]

35 Examples of "aryl" may include, for example, a

monocyclic to tricyclic, aromatic hydrocarbon group having 6 to 14 carbon atoms. Specific examples thereof may include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl, 9-anthryl, 1-phenanthryl, 2-phenanthryl, 3-phenanthryl, 4-phenanthryl, 10-phenanthryl, and the like. Among the above, phenyl is preferable.
[0027]

Examples of "cycloalkyl" may include a monocyclic to tricyclic, cyclic non-aromatic hydrocarbon group. Specific examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.
[0028]

The "non-aromatic carbocyclic group" described above may be a bridged hydrocarbon group. Examples of such a bridged hydrocarbon group may include, for example, the following:

- bicyclo[2.2.1]heptanyl (for example, bicyclo[2.2.1]heptan-1-yl, bicyclo[2.2.1]heptan-2-yl, and bicyclo[2.2.1]heptan-7-yl);
- bicyclo[1.1.1]pentanyl (for example, bicyclo[1.1.1]pentan-1-yl and bicyclo[1.1.1]pentan-2-yl);
- bicyclo[4.1.0]heptanyl (for example, bicyclo[4.1.0]heptan-1-yl, bicyclo[4.1.0]heptan-2-yl, bicyclo[4.1.0]heptan-3-yl, and bicyclo[4.1.0]heptan-7-yl);
- bicyclo[2.2.2]octanyl (for example, bicyclo[2.2.2]octan-1-yl and bicyclo[2.2.2]octan-2-yl);
- bicyclo[3.1.1]heptanyl (for example, bicyclo[3.1.1]heptan-1-yl, bicyclo[3.1.1]heptan-2-yl, bicyclo[3.1.1]heptan-3-yl, and bicyclo[3.1.1]heptan-6-yl); and
- cuban-1-yl.

[0029]

The "non-aromatic carbocyclic group" described above may be a spirocyclic group. Examples of such a spirocyclic group may include, for example, the following:

- spiro[3.3]heptanyl (for example, spiro[3.3]heptan-1-yl and spiro[3.3]heptan-2-yl);
- spiro[4.4]nonanyl (for example, spiro[4.4]nonan-1-yl and spiro[4.4]nonan-2-yl);

- spiro[5.5]undecanyl (for example, spiro[5.5]undecan-1-yl, spiro[5.5]undecan-2-yl, and spiro[5.5]undecan-3-yl); and
 - spiro[2.5]octanyl (for example, spiro[2.5]octan-1-yl, spiro[2.5]octan-4-yl, spiro[2.5]octan-5-yl, and spiro[2.5]octan-6-yl).
- [0030]

Examples of "heteroaryl" may include, for example, a monocyclic to tricyclic aromatic ring having 6 to 14 carbon atoms and having 1 to 3 heteroatoms selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom as the

10 constituent atoms. Specific examples thereof may include, for example, the following:

- furyl (for example, 2-furyl and 3-furyl);
- thienyl (for example, 2-thienyl and 3-thienyl);
- 15 · pyrrolyl (for example, 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl);
- imidazolyl (for example, 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl);
- pyrazolyl (for example, 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl);
- 20 · triazolyl (for example, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, and 1,2,4-triazol-4-yl);
- tetrazolyl (for example, 1-tetrazolyl, 2-tetrazolyl, and 5-tetrazolyl);
- oxazolyl (for example, 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl);
- 25 · isoxazolyl (for example, 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl);
- oxadiazolyl (for example, 1,3,4-oxadiazol-2-yl);
- thiazolyl (for example, 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl);
- 30 · thiadiazolyl (for example, 1,3,4-thiadiazolyl, 1,2,4-thiadiazolyl, and 1,2,3-thiadiazolyl);
- isothiazolyl (for example, 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl);
- pyridyl (for example, 2-pyridyl, 3-pyridyl, and 4-pyridyl);
- 35 · pyridazinyl (for example, 3-pyridazinyl, and 4-pyridazinyl);

- pyrimidinyl (for example, 2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl);
 - pyrazinyl (for example, 2-pyrazinyl);
 - benzothiadiazolyl (for example, 1,2,3-benzothiadiazol-4-yl,
5 1,2,3-benzothiadiazol-5-yl, 2,1,3-benzothiadiazol-4-yl, and
2,1,3-benzothiadiazol-5-yl);
 - benzothiazolyl (for example, benzothiazol-2-yl, benzothiazol-4-yl,
benzothiazol-5-yl, benzothiazol-6-yl, and benzothiazol-7-yl);
 - indolyl (for example, indol-3-yl, indol-4-yl, indol-5-yl, indol-
10 6-yl, and indol-7-yl);
 - benzothiophenyl (for example, 1-benzothiophen-2-yl, 1-benzothiophen-3-yl,
1-benzothiophen-4-yl, 1-benzothiophen-5-yl,
1-benzothiophen-6-yl, and 1-benzothiophen-7-yl);
 - 1,1-dioxo-1-benzothiophenyl (for example, 1,1-dioxo-1-
15 benzothiophen-2-yl, 1,1-dioxo-1-benzothiophen-3-yl, 1,1-dioxo-1-benzothiophen-4-yl,
1,1-dioxo-1-benzothiophen-5-yl, 1,1-dioxo-1-benzothiophen-6-yl, and 1,1-dioxo-1-benzothiophen-7-yl);
 - quinolyl (quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl,
quinolin-6-yl, quinolin-7-yl, and quinolin-8-yl); and
 - 20 · 1,3-benzoxazol-2-yl.
- [0031]

Examples of "heterocycloalkyl" may include a cyclic non-aromatic heterocyclic group having one ring or two or more rings and having one or more heteroatoms selected from a nitrogen
25 atom, an oxygen atom, and a sulfur atom in the ring, which may be the same as or different from each other. Specific examples thereof may include, for example, the following:

- oxetanyl (for example, 2-oxetanyl and 3-oxetanyl);
- azetidiny (for example, 2-azetidiny and 3-azetidiny);
- 30 · tetrahydropyranyl (for example, 2-tetrahydropyranyl, 3-tetrahydropyranyl, and 4-tetrahydropyranyl);
- 1,4-dioxanyl (for example, 1,4-dioxan-2-yl);
- 1,3-dioxanyl (for example, 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, and 1,3-dioxan-5-yl);
- 35 · pyrrolidinyl (for example, 1-pyrrolidinyl, 2-pyrrolidinyl, and

3-pyrrolidinyl);

· piperidinyl (for example, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, and 4-piperidinyl);

· piperazinyl (for example, 1-piperazinyl, 2-piperazinyl, and 3-piperazinyl);

· azepanyl (for example, 1-azepanyl, 2-azepanyl, 3-azepanyl, and 4-azepanyl);

· azocanyl (for example, 1-azocanyl, 2-azocanyl, 3-azocanyl, 4-azocanyl, and 5-azocanyl);

· homopiperidinyl (for example, 2-homopiperidinyl, 3-homopiperidinyl, and 4-homopiperidinyl);

· morpholinyl (for example, 2-morpholinyl, 3-morpholinyl, and 4-morpholinyl);

· thiomorpholinyl (for example, 2-thiomorpholinyl, 3-thiomorpholinyl, and 4-thiomorpholinyl); and

· tetrahydrofuryl (2-tetrahydrofuryl and 3-tetrahydrofuryl).

[0032]

The "heterocycloalkyl" described above may be a bridged cyclic group. Examples of such a bridged cyclic group may

include, for example, the following:

· 3-azabicyclo[3.2.1]octanyl (for example, 3-azabicyclo[3.2.1]octan-1-yl, 3-azabicyclo[3.2.1]octan-2-yl, 3-azabicyclo[3.2.1]octan-3-yl, 3-azabicyclo[3.2.1]octan-6-yl, and 3-azabicyclo[3.2.1]octan-8-yl);

· quinuclidinyl (for example, quinuclidin-2-yl, quinuclidin-3-yl, and quinuclidin-4-yl); and

· 6-oxa-3-azabicyclo[3.1.1]heptanyl (for example, 6-oxa-3-azabicyclo[3.1.1]heptan-1-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-2-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl, and 6-oxa-3-

azabicyclo[3.1.1]heptan-7-yl).

[0033]

The "heterocycloalkyl" described above may be a spirocyclic group. Examples of such a spirocyclic group may include, for example, the following:

· 6-azaspiro[2.5]octan-1-yl (for example, 6-azaspiro[2.5]octan-1-

yl, 6-azaspiro[2.5]octan-4-yl, and 6-azaspiro[2.5]octan-5-yl);
· 3,9-diazaspiro[5.5]undecan-1-yl (for example, 3,9-
diazaspiro[5.5]undecan-1-yl, 3,9-diazaspiro[5.5]undecan-2-yl, and
3,9-diazaspiro[5.5]undecan-3-yl);
5 · 2,7-diazaspiro[3.5]nonan-1-yl (for example, 2,7-
diazaspiro[3.5]nonan-1-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-
diazaspiro[3.5]nonan-5-yl, 2,7-diazaspiro[3.5]nonan-6-yl, and
2,7-diazaspiro[3.5]nonan-7-yl);
· 7-azaspiro[3.5]nonanyl, (7-azaspiro[3.5]nonan-1-yl, 7-
10 azaspiro[3.5]nonan-2-yl, 7-azaspiro[3.5]nonan-5-yl, and 7-
azaspiro[3.5]nonan-6-yl); and
· 2,5-diazabicyclo[2.2.1]heptanyl (2,5-diazabicyclo[2.2.1]heptan-
1-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 2,5-
diazabicyclo[2.2.1]heptan-3-yl, and 2,5-
15 diazabicyclo[2.2.1]heptan-7-yl).
[0034]

Hereinafter, each symbol in the formula [1] will be
described.

[0035]
20 R¹ in the formula [1] is a hydrogen atom, a halogen
atom, a C₁-C₆ alkyl, a C₁-C₆ haloalkyl, a C₂-C₆ alkenyl, a C₂-C₆
haloalkenyl, a C₂-C₆ alkynyl, a C₂-C₆ haloalkynyl, a C₁-C₆ alkoxy,
hydroxy, carboxy, an alkylcarbonyloxy, amino, a monoalkylamino, a
dialkylamino, an alkylcarbonylamino, nitro, an optionally
25 substituted C₃-C₆ cycloalkyl, an optionally substituted C₃-C₆
cycloalkenyl, an optionally substituted heterocycloalkyl, an
optionally substituted aryl, or an optionally substituted
heteroaryl.

It is preferably a hydrogen atom, a halogen atom, a C₁-
30 C₆ alkyl, a C₂-C₆ alkenyl, amino, a monoalkylamino, a
dialkylamino, an alkylcarbonylamino, an optionally substituted C₃-
C₆ cycloalkyl, an optionally substituted heterocycloalkyl, an
optionally substituted aryl, or an optionally substituted
heteroaryl.

35 It is more preferably an optionally substituted

heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl.

It is further preferably oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, piperidinyl, piperazinyl, phenyl,
5 pyridyl, pyrimidinyl, pyrazinyl, isoquinolinyl, thienyl, pyrazolyl, imidazo[1,2-a]pyrazinyl, 1,2,3-triazolyl, or imidazo[1,2-b]pyridazinyl.

[0036]

R^2 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$.

It is preferably a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-(CR^aR^b)_m-O-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$.

15 It is more preferably a bonding hand, $-(CR^aR^b)_m-NR^c-$, or $-NR^c-$.

[0037]

R^a in R^2 is a hydrogen atom, a halogen atom, a C_1-C_6 alkyl, or a C_1-C_6 haloalkyl.

20 It is preferably a hydrogen atom, or is taken together with the carbon atom to which R^a and R^b are bonded to form $C=O$.

[0038]

R^b in R^2 is a hydrogen atom, a halogen atom, a C_1-C_6 alkyl, or a C_1-C_6 haloalkyl.

25 It is preferably a hydrogen atom, or is taken together with the carbon atom to which R^a and R^b are bonded to form $C=O$.

[0039]

Each R^c in R^2 is independently a hydrogen atom, a C_1-C_6 alkyl, or a C_1-C_6 haloalkyl.

30 It is preferably a hydrogen atom.

[0040]

Het is a 5- to 10-membered heteroaryl.

It is preferably thiazolyl, pyridyl, oxazolyl, pyrazinyl, pyrimidinyl, pyrazolyl, imidazothiazolyl, quinazolynyl, quinolinyl, 7,8-dihydropyrido[4,3-d]pyrimidin-

35

6(5H)-yl, thieno[3,2-b]pyridinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, pyrazolo[1,5-a]pyrimidinyl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazinyl, pyrazolo[5,1-b]thiazolyl, pyrazolo[3,4-b]pyridyl, or pyrazolo[1,5-a]pyridyl.

5 It is more preferably thiazolyl, pyridyl, or pyrimidinyl.

[0041]

L^1 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$.

10 It is preferably a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$.

15 It is further preferably $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$.

[0042]

R^a in L^1 is a hydrogen atom, a halogen atom, a C_1-C_6 alkyl, or a C_1-C_6 haloalkyl, or is taken together with the carbon atom to which R^a and R^b are bonded to form $C=O$.

20 It is preferably a hydrogen atom, a halogen atom, or a C_1-C_6 alkyl, or is taken together with the carbon atom to which R^a and R^b are bonded to form $C=O$.

[0043]

25 R^b in L^1 is a hydrogen atom, a halogen atom, a C_1-C_6 alkyl, or a C_1-C_6 haloalkyl, or is taken together with the carbon atom to which R^a and R^b are bonded to form $C=O$.

It is preferably a hydrogen atom, or is taken together with the carbon atom to which R^a and R^b are bonded to form $C=O$.

[0044]

30 Each R^c in L^1 is independently a hydrogen atom, a C_1-C_6 alkyl, or a C_1-C_6 haloalkyl.

It is preferably a hydrogen atom or a C_1-C_6 alkyl.

It is more preferably a hydrogen atom.

[0045]

35 L^2 is $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-$

$(\text{CR}^a\text{R}^b)_m-$, $-(\text{CR}^a\text{R}^b)_m-$, $-\text{NR}^c-$, $-\text{O}-$, $-\text{NR}^c-\text{CO}-\text{NR}^c-$, $-\text{CR}^a=\text{CR}^b-$, or $-\text{C}\equiv\text{C}-$.

It is preferably a bonding hand, $-(\text{CR}^a\text{R}^b)_m-\text{NR}^c-$, or $-\text{NR}^c-\text{CO}-\text{NR}^c-$.

It is more preferably a bonding hand or $-(\text{CR}^a\text{R}^b)_m-\text{NR}^c-$.

5 [0046]

R^a in L^2 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl, or is taken together with R^b and the carbon atom to which they are bonded to form $\text{C}=\text{O}$.

[0047]

10 R^a in L^2 is preferably taken together with R^b and the carbon atom to which they are bonded to form $\text{C}=\text{O}$.

[0048]

R^b in L^2 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl, or is taken together with R^a and the
15 carbon atom to which they are bonded to form $\text{C}=\text{O}$.

[0049]

R^b in L^2 is preferably taken together with R^a and the carbon atom to which they are bonded to form $\text{C}=\text{O}$.

[0050]

20 R^c in L^2 is a hydrogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl.

Preferably, each R^c in L^2 is independently a hydrogen atom.

[0051]

25 R^4 is a hydrogen atom, a halogen atom, or methyl.

It is preferably a halogen atom or methyl.

[0052]

R^5 is a hydrogen atom, a halogen atom, hydroxy, amino, a C_1 - C_6 alkyl, a C_1 - C_6 haloalkyl, a C_1 - C_6 alkoxy, or a C_1 - C_6
30 haloalkoxy.

It is preferably hydroxy.

[0053]

R^6 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, a C_1 - C_6 haloalkyl, or an optionally substituted phenyl.

35 R^7 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, a

C₁-C₆ haloalkyl, a hydroxyalkyl, an optionally substituted phenyl, or a C₃-C₆ cycloalkyl.

Alternatively, R⁶ and R⁷ are taken together with the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl,
5 an optionally substituted aryl, or an optionally substituted heteroaryl.

[0054]

R⁶ is preferably a hydrogen atom, a C₁-C₆ alkyl, or an optionally substituted phenyl.

10 R⁷ is preferably a C₁-C₆ alkyl, a hydroxyalkyl, or an optionally substituted phenyl.

Alternatively, R⁶ and R⁷ are preferably taken together with the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl or an optionally substituted aryl.

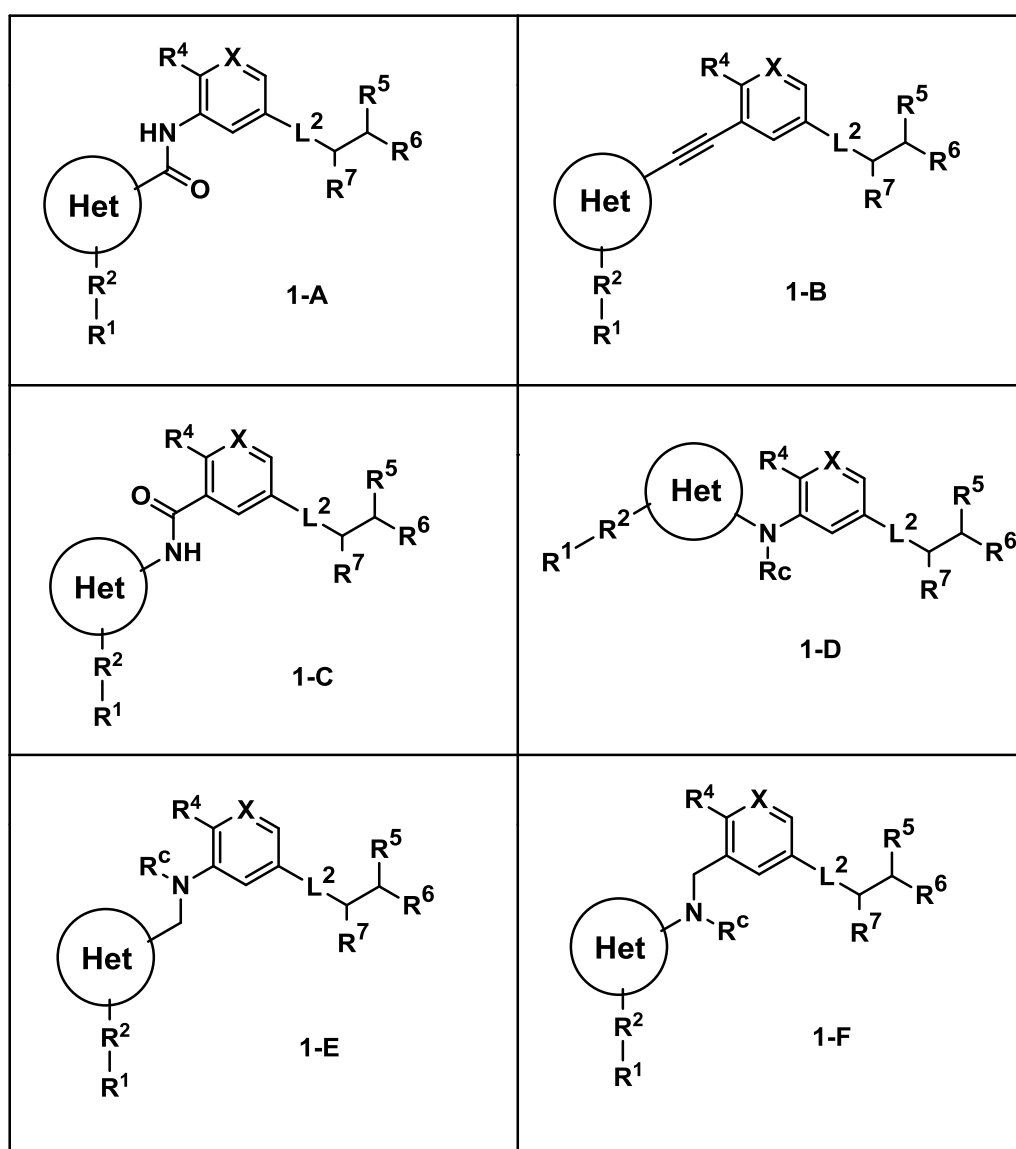
15 R⁶ and R⁷ are further preferably taken together with the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

[0055]

More specifically, the compound of the present
20 invention encompasses the compounds shown in the following Table 1 depending on the type of L¹.

[0056]

[Table 1]



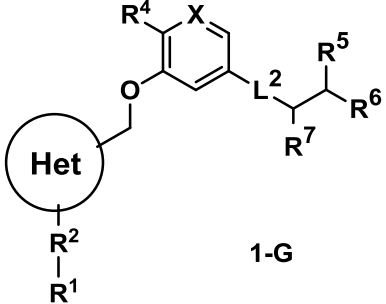
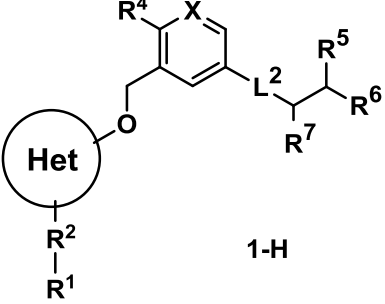
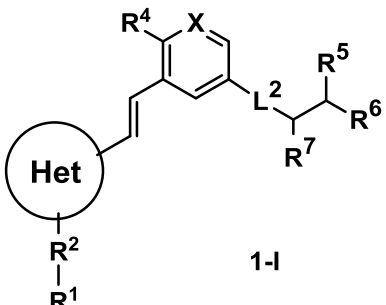
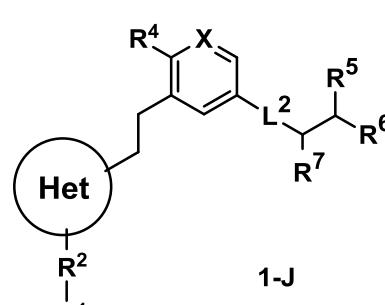
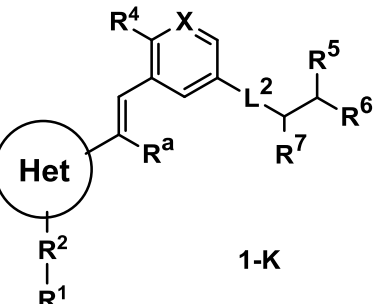
(In the table, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^c , L^1 , L^2 , and Het are as defined above.)

- 1-A: Compound [1], wherein L^1 is $-(CR^aR^b)_m-NR^c-$, m is 1, and R^a and R^b are taken together with the carbon atom to which they are bonded to form $C=O$.
- 1-B: Compound [1], wherein L^1 is $-C\equiv C-$.
- 1-C: Compound [1], wherein L^1 is $-NR^c-(CR^aR^b)_m-$, m is 1, and R^a and R^b are taken together with the carbon atom to which they are bonded to form $C=O$.
- 1-D: Compound [1], wherein L^1 is $-NR^c-$.
- 1-E: Compound [1], wherein L^1 is $-(CR^aR^b)_m-NR^c-$, m is 1, and R^a and R^b are each a hydrogen atom.

· 1-F: Compound [1], wherein L^1 is $-NR^c-(CR^aR^b)_m-$, m is 1, and R^a and R^b are each a hydrogen atom.

[0057]

[Table 2]

 1-G	 1-H
 1-I	 1-J
 1-K	

5

(In the table, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^c , L^1 , L^2 , and Het are as defined above.)

· 1-G: Compound [1], wherein L^1 is $-(CR^aR^b)_m-O-$, m is 1, and R^a and R^b are each a hydrogen atom.

10 · 1-H: Compound [1], wherein L^1 is $-O-(CR^aR^b)_m-$, m is 1, and R^a and R^b are each a hydrogen atom.

· 1-I: Compound [1], wherein L^1 is $-CR^a=CR^b-$ and R^a and R^b are each H.

· 1-J: Compound [1], wherein L^1 is $-(CR^aR^b)_m-$, m is 2, and R^a and R^b are each H.

5 · 1-K: Compound [1], wherein L^1 is $-CR^a=CR^b-$, R^a is a halogen atom, and R^b is H.

[0058]

R^1 in the compound 1-A is preferably H, a halogen atom, a C_1 - C_6 alkyl, a C_2 - C_6 alkenyl, a C_1 - C_6 alkoxy, amino, an
10 alkylcarbonylamino, an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl, and is more preferably a C_1 - C_6 alkyl, a C_1 - C_6 alkoxy, an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted
15 heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl.

R^2 in the compound 1-A is preferably a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-(CR^aR^b)_m-O-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, or $-CR^a=CR^b-$, and is more preferably a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-(CR^aR^b)_m-O-$, $-(CR^aR^b)_m-$, $-NR^c-$, or $-O-$.
20

m of R^2 in the compound 1-A is preferably 0, 1, or 2, and is more preferably 0 or 1.

Het in the compound 1-A is preferably thiazolyl, pyridyl, oxazolyl, or imidazothiazolyl, and is more preferably
25 thiazolyl or pyridyl.

R^4 in the compound 1-A is preferably a halogen atom or methyl, and is more preferably methyl.

L^2 in the compound 1-A is preferably $-(CR^aR^b)_m-NR^c-$.

m of L^2 in the compound 1-A is preferably 1.

30 R^5 in the compound 1-A is preferably hydroxy.

R^6 in the compound 1-A is preferably H or a C_1 - C_6 alkyl, or is taken together with R^7 and the carbon atoms to which they are bonded to form a C_3 - C_6 cycloalkyl, and is more preferably taken together with R^7 and the carbon atoms to which they are
35 bonded to form a C_3 - C_6 cycloalkyl.

R⁷ in the compound 1-A is preferably a C₁-C₆ alkyl or an optionally substituted phenyl, or is taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.
5 [0059]

R¹ in the compound 1-B is preferably H, a halogen atom, a C₁-C₆ alkyl, amino, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted aryl, or an optionally substituted
10 heteroaryl, and is more preferably a halogen atom, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl.

R² in the compound 1-B is preferably a bonding hand or -(CR^aR^b)_m-NR^c-, and is more preferably a bonding hand.

15 m of R² in the compound 1-B is preferably 0 or 1.

Het in the compound 1-B is preferably pyridyl or pyrazinyl.

R⁴ in the compound 1-B is preferably a halogen atom or methyl, and is more preferably methyl.

20 L² in the compound 1-B is preferably -(CR^aR^b)_m-NR^c-.
m of L² in the compound 1-B is preferably 1.

R⁵ in the compound 1-B is preferably hydroxy.

R⁶ in the compound 1-B is preferably an optionally substituted phenyl, or is taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is
25 more preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

R⁷ in the compound 1-B is preferably a hydroxyalkyl, or is taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken
30 together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.
[0060]

R¹ in the compound 1-C is preferably H, a halogen atom, a C₁-C₆ alkyl, a C₂-C₆ alkenyl, a C₁-C₆ alkoxy, amino, an
35

alkylcarbonylamino, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl, and is more preferably an optionally substituted aryl.

5 R² in the compound 1-C is preferably a bonding hand, - (CR^aR^b)_m-NR^c-, - (CR^aR^b)_m-O-, - (CR^aR^b)_m-, -NR^c-, -O-, or -CR^a=CR^b-, and is more preferably a bonding hand.

 Het in the compound 1-C is preferably thiazolyl, pyridyl, oxazolyl, or imidazothiazolyl, and is more preferably
10 pyridyl.

 R⁴ in the compound 1-C is preferably a halogen atom or methyl, and is more preferably methyl.

 R⁵ in the compound 1-C is preferably hydroxy.

 R⁶ in the compound 1-C is preferably H or a C₁-C₆ alkyl,
15 or is taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

 R⁷ in the compound 1-C is preferably a C₁-C₆ alkyl or an
20 optionally substituted phenyl, or is taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.
[0061]

25 R¹ in the compound 1-D is preferably H, a halogen atom, a C₁-C₆ alkyl, a C₂-C₆ alkenyl, a C₁-C₆ alkoxy, a monoalkylamino, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl, and is more preferably a
30 monoalkylamino or an optionally substituted heteroaryl.

 R² in the compound 1-D is preferably a bonding hand, - (CR^aR^b)_m-NR^c-, - (CR^aR^b)_m-O-, - (CR^aR^b)_m-, -NR^c-, -O-, or -CR^a=CR^b-, and is more preferably a bonding hand.

 Het in the compound 1-D is preferably pyrimidinyl,
35 pyridyl, or quinazolyl, and is more preferably pyrimidinyl.

R⁴ in the compound 1-D is preferably a halogen atom or methyl, and is more preferably methyl.

R⁵ in the compound 1-D is preferably hydroxy.

R⁶ in the compound 1-D is preferably an optionally substituted aryl, or is taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

R⁷ in the compound 1-D is preferably a hydroxyalkyl or an optionally substituted phenyl, or is taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.
[0062]

R¹ in the compound 1-E is preferably H, a halogen atom, a C₁-C₆ alkyl, a C₁-C₆ haloalkyl, a C₂-C₆ alkenyl, a C₂-C₆ haloalkenyl, a C₂-C₆ alkynyl, a C₂-C₆ haloalkynyl, a C₁-C₆ alkoxy, hydroxy, carboxy, an alkylcarbonyloxy, amino, an aminoalkyl, a monoalkylamino, a dialkylamino, an alkylcarbonylamino, nitro, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted C₃-C₆ cycloalkenyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl, and is more preferably H, amino, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl.

R² in the compound 1-E is preferably a bonding hand, - (CR^aR^b)_m-NR^c-, -NR^c-, -NR^c-CO-NR^c-, or -C≡C-, and is more preferably a bonding hand, - (CR^aR^b)_m-NR^c-, or -NR^c-.

m of R² in the compound 1-E is preferably 0 or 1.

Het in the compound 1-E is preferably thiazolyl, pyridyl, oxazolyl, pyrazinyl, pyrimidinyl, pyrazolyl, imidazothiazolyl, quinazolynyl, quinolinyl, 7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl, thieno[3,2-b]pyridinyl, 1H-pyrrolo[2,3-b]pyridinyl, imidazo[1,2-b]pyridazinyl,

imidazo[1,2-a]pyrazinyl, pyrazolo[1,5-a]pyrimidinyl, 3,4-dihydro-
2H-pyrido[3,2-b][1,4]oxazinyl, pyrazolo[5,1-b]thiazolyl,
pyrazolo[3,4-b]pyridyl, or pyrazolo[1,5-a]pyridyl, and is more
preferably pyridyl, pyrazinyl, pyrimidinyl, or pyrazolo[1,5-
5 a]pyrimidinyl.

R^4 in the compound 1-E is preferably H, a halogen atom,
or methyl, and is more preferably a halogen atom or methyl.

L^2 in the compound 1-E is preferably $-(CR^aR^b)_m-NRc-$.

m of L^2 in the compound 1-E is preferably 1.

10 R^5 in the compound 1-E is preferably hydroxy.

R^6 in the compound 1-E is more preferably taken
together with R^7 and the carbon atoms to which they are bonded to
form a C_3-C_6 cycloalkyl.

R^7 in the compound 1-E is more preferably taken
15 together with R^6 and the carbon atoms to which they are bonded to
form a C_3-C_6 cycloalkyl.

[0063]

R^1 in the compound 1-F is preferably a halogen atom, an
optionally substituted C_3-C_6 cycloalkyl, an optionally substituted
20 aryl, or an optionally substituted heteroaryl, and is more
preferably an optionally substituted C_3-C_6 cycloalkyl, an
optionally substituted aryl, or an optionally substituted
heteroaryl.

R^2 in the compound 1-F is preferably a bonding hand or
25 $-C\equiv C-$, and is preferably a bonding hand.

Het in the compound 1-F is preferably pyridyl or
pyrazinyl, and is more preferably pyridyl.

R^4 in the compound 1-F is preferably H, a halogen atom,
or methyl, and is more preferably H or methyl.

30 L^2 in the compound 1-F is preferably $-(CR^aR^b)_m-NRc-$ or $-$
 $NRc-CO-NRc-$.

m of L^2 in the compound 1-F is preferably 1.

R^5 in the compound 1-F is preferably hydroxy.

R^6 in the compound 1-F is preferably an optionally
35 substituted phenyl, or is taken together with R^7 and the carbon

atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

5 R⁷ in the compound 1-F is preferably a hydroxyalkyl, or is taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl, and is more preferably taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

[0064]

10 R¹ in the compound 1-G is preferably an optionally substituted aryl or an optionally substituted heteroaryl, and is more preferably an optionally substituted heteroaryl.

R² in the compound 1-G is preferably a bonding hand.

Het in the compound 1-G is preferably pyridyl.

15 R⁴ in the compound 1-G is preferably H, a halogen atom, or methyl, and is more preferably a halogen atom or methyl.

R⁵ in the compound 1-G is preferably hydroxy.

R⁶ in the compound 1-G is preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a
20 C₃-C₆ cycloalkyl.

R⁷ in the compound 1-G is preferably taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

[0065]

25 R¹ in the compound 1-H is preferably an optionally substituted heteroaryl.

R² in the compound 1-H is preferably a bonding hand.

Het in the compound 1-H is preferably pyridyl.

R⁴ in the compound 1-H is preferably a halogen atom or
30 methyl, and is more preferably methyl.

R⁵ in the compound 1-H is preferably hydroxy.

R⁶ in the compound 1-H is preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

35 R⁷ in the compound 1-H is preferably taken together

with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

[0066]

5 R¹ in the compound 1-I is preferably an optionally substituted aryl.

R² in the compound 1-I is preferably a bonding hand.

Het in the compound 1-I is preferably pyridyl.

R⁴ in the compound 1-I is preferably methyl.

R⁵ in the compound 1-I is preferably hydroxy.

10 R⁶ in the compound 1-I is preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

R⁷ in the compound 1-I is preferably taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

[0067]

R¹ in the compound 1-J is preferably an optionally substituted aryl.

R² in the compound 1-J is preferably a bonding hand.

20 Het in the compound 1-J is preferably pyridyl.

R⁴ in the compound 1-J is preferably methyl.

R⁵ in the compound 1-J is preferably hydroxy.

R⁶ in the compound 1-J is preferably taken together with R⁷ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

R⁷ in the compound 1-J is preferably taken together with R⁶ and the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl.

[0068]

30 R¹ in the compound 1-K is preferably H, a halogen atom, amino, a monoalkylamino, a dialkylamino, an optionally substituted cycloalkyl, an optionally substituted heterocycloalkyl, or an optionally substituted heteroaryl, and is more preferably a halogen atom, amino, an optionally substituted cycloalkyl, an optionally substituted heterocycloalkyl, or an

35

optionally substituted heteroaryl.

R^2 in the compound 1-K is preferably a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-(CR^aR^b)_m-O-$, $-(CR^aR^b)_m-$, or $-NR^c-$, and is more preferably a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-(CR^aR^b)_m-$, or $-NR^c-$.

5 Het in the compound 1-K is preferably pyridyl, pyrimidinyl, pyrazinyl, or imidazo[1,2-b]pyridazinyl, and is more preferably pyridyl, pyrimidinyl, or pyrazinyl.

R^4 in the compound 1-K is preferably a halogen atom or methyl.

10 L^2 in the compound 1-K is preferably $-(CR^aR^b)_m-NR^c-$.
 m of L^2 in the compound 1-K is preferably 1.

R^5 in the compound 1-K is preferably hydroxy.

R^6 in the compound 1-K is preferably a C_1 - C_6 alkyl, or is taken together with R^7 and the carbon atoms to which they are
15 bonded to form a C_3 - C_6 cycloalkyl or an optionally substituted aryl, and is more preferably taken together with R^7 and the carbon atoms to which they are bonded to form a C_3 - C_6 cycloalkyl.

R^7 in the compound 1-K is preferably a C_1 - C_6 alkyl, or is taken together with R^6 and the carbon atoms to which they are
20 bonded to form a C_3 - C_6 cycloalkyl or an optionally substituted aryl, and is more preferably taken together with R^6 and the carbon atoms to which they are bonded to form a C_3 - C_6 cycloalkyl.

[0069]

The compound of the present invention can be, for
25 example, produced from a publicly known compound or an intermediate that can be readily synthesized, according to the following method, Examples, which will be mentioned later, or a publicly known method. In the production of the compound of the present invention, in the case where a raw material has a
30 substituent that influences the reaction, it is general to carry out the reaction after protecting the raw material with an appropriate protective group in advance by a publicly known method. The protective group can be removed after the reaction by a publicly known method.

35 [0070]

The compound represented by the formula [1] may be used as it is as a medicament, but can also be made into the form of a pharmaceutically acceptable salt, solvate, or salt of the solvate for use according to a publicly known method. Examples of the pharmaceutically acceptable salt include, for example, salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid; salts with organic acids such as acetic acid, malic acid, lactic acid, citric acid, tartaric acid, maleic acid, succinic acid, fumaric acid, p-toluenesulfonic acid, benzenesulfonic acid, and methanesulfonic acid; salts with alkali metals such as lithium, potassium, and sodium; salts with alkaline earth metals such as magnesium and calcium; and salts with organic bases such as ammonium salts. These salts can be formed by a method that is normally practiced.

[0071]

For example, when the compound of the present invention is a hydrochloride salt, it can be obtained by dissolving the compound represented by the formula [1] in a solution of hydrogen chloride in an alcohol, a solution of hydrogen chloride in ethyl acetate, a solution of hydrogen chloride in 1,4-dioxane, a solution of hydrogen chloride in cyclopentyl methyl ether, or a solution of hydrogen chloride in diethyl ether.

[0072]

Among the compound of the present invention, for those having an asymmetric carbon, the respective stereoisomers and a mixture thereof are all encompassed in the present invention. Stereoisomers can be produced, for example, by optically resolving them utilizing the basicity thereof from the racemate according to a publicly known method using an optically active acid (tartaric acid, dibenzoyltartaric acid, mandelic acid, 10-camphor sulfonic acid, and the like), or by using an optically active compound prepared in advance as a raw material. In addition, stereoisomers can also be produced by optical resolution using a chiral column or by asymmetric synthesis.

[0073]

The compound of the present invention is not limited to a specific isomer, but encompasses all possible isomers and racemate.

(Method for producing the compound of the present invention)

5 [0074]

The compound of the present invention can be, for example, produced from a compound that is publicly known per se or an intermediate that can be readily prepared from the publicly known compound, according to the following method, Examples, 10 which will be mentioned later, or a publicly known method.

[0075]

If the solvents, reagents, and raw materials used in each step in the following production methods are commercially available, such commercially available products can be used as 15 they are. Also, the compounds obtained and the raw materials used in each step in the following production methods may form a salt and can be converted into another type of salt or a free form by a publicly known method. Alternatively, when the compounds obtained or the raw materials used in each step in the following 20 production methods is in a free form, they can be converted into a desired salt by a publicly known method. Examples of such a salt may include those similar to the salts to be used in the compound of the present invention, which are mentioned above.

[0076]

25 The compound of the present invention represented by the formula [1] or a pharmaceutically acceptable salt thereof may form a solvate (for example, a hydrate or the like) and/or a crystalline polymorph, and the present invention also encompasses such various types of solvates and crystalline polymorphs. For 30 the "solvate", the compound represented by the formula [1] may be coordinated with any number of solvent molecules (for example, water molecules or the like). By leaving the compound represented by the formula [1] or a pharmaceutically acceptable salt thereof to stand in the atmosphere, it absorbs water, and adsorbed water 35 may adhere thereto or a hydrate may be formed. Also, by

recrystallizing the compound represented by the formula [1] or a pharmaceutically acceptable salt thereof, a crystalline polymorph thereof may be formed.

[0077]

5 In the production of the compound of the present invention, in the case where a raw material has a substituent that may influence the reaction, a protecting group may be introduced to that substituent in advance by a publicly known method, and by removing the protecting group after the reaction
10 as necessary, the target compound can be obtained. For introduction of such a protecting group and removal of the protecting group, the conditions may be selected as appropriate for use that are shown in, for example, Wuts and Greene, "Greene's Protective Groups in Organic Synthesis", 4th edition,
15 John Wiley & Sons Inc., 2006; or P. J. Kocienski, "Protecting Groups", 3rd edition, Thieme, 2005.

[0078]

 The compounds obtained in each step of the following production methods can be isolated or purified according to a
20 conventional method such as solvent extraction, concentration, distillation, sublimation, recrystallization, reprecipitation, and chromatography. Alternatively, the compounds may be used in the subsequent step as a reaction mixture or a crude product.

[0079]

25 Unless otherwise specified, the reaction in each step in the following production methods is carried out according to publicly known methods as described in, for example, R. C. Larock, "Comprehensive Organic Transformations: A Guide to Functional Group Preparations", 2nd edition., John Wiley & Sons,
30 Inc., 1999; The Chemical Society of Japan, "Experimental Chemistry", 4th edition, Maruzen, 1992; L. Kuerti and B. Czako, "Strategic Applications of Named Reactions in Organic Synthesis", translated by Kiyoshi Tomioka, Kagaku-Dojin Publishing Company, Inc., 2006; G. S. Zweifel and M. H. Nantz, "Modern Organic
35 Synthesis: An Introduction", translated by Tamejiro Hiyama,

Kagaku-Dojin Publishing Company, Inc., 2009, or methods in the similar manner as described in the Examples, with modified or combined as appropriate.

[0080]

5 The compound of the present invention mentioned above

(1-A: a compound wherein L^1 is $-(CR^aR^b)_m-NR^c-$, and R^a and R^b are taken together with the carbon atom to which they are bonded to form $C=O$;

1-B: a compound wherein L^1 is $-C\equiv C-$;

10 1-C: a compound wherein L^1 is $-NR^c-(CR^aR^b)_m-$, and R^a and R^b are taken together with the carbon atom to which they are bonded to form $C=O$;

1-D: a compound wherein L^1 is $-NR^c-$;

1-E: a compound wherein L^1 is $-(CR^aR^b)_m-NR^c-$, and R^a and R^b are each
15 independently H, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl;

1-F: a compound wherein L^1 is $NR^c-(CR^aR^b)_m-$, and R^a and R^b are each independently H, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl;

20 1-G: a compound wherein L^1 is $-(CR^aR^b)_m-O-$, and R^a and R^b are each independently H, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl;

1-H: a compound wherein L^1 is $-O-(CR^aR^b)_m-$, and R^a and R^b are each independently H, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6
25 haloalkyl;

1-I: a compound wherein L^1 is $-CR^a=CR^b-$, and R^a and R^b are each H;

1-J: a compound wherein L^1 is $-(CR^aR^b)_m-$, and R^a and R^b are each H;
and

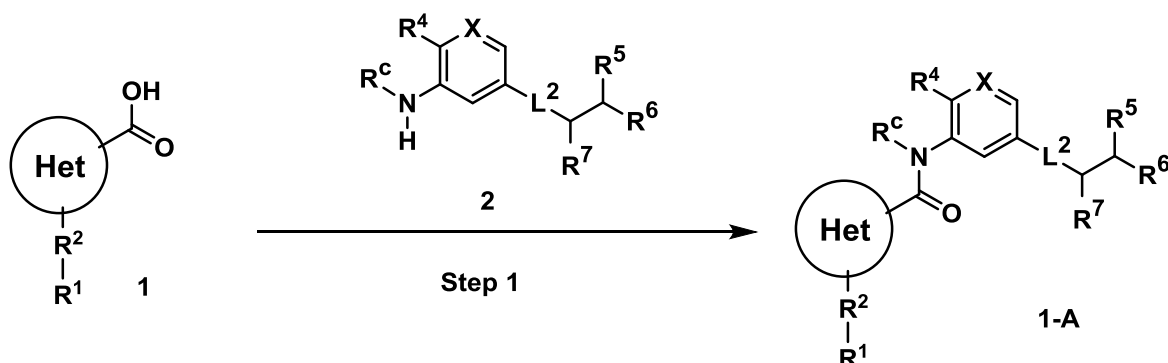
1-K: a compound wherein L^1 is $-CR^a=CR^b-$, R^a is a halogen atom, and
30 R^b is H)

can be produced by, for example, a general synthetic method, which will be shown below. For extraction, purification, and the like, treatments that are carried out in normal organic chemistry experiments may be carried out.

35 [0081]

Method for producing compound [1-A]

[Formula 2]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^c, Het, and X are as defined above.)

Step 1

The present step is a step of obtaining a compound 1-A by condensing a compound 1 or a reactive compound thereof and an amine compound 2 in the presence of a condensing agent.

[0082]

Examples of the reactive compound of the compound 1 may include, for example, those normally used in an amide condensation reaction, such as acid halides (for example, acid chloride and acid bromide), mixed acid anhydrides, imidazolides, and active amides.

[0083]

It is appropriate that the amounts to be used of the condensing agent and the amine compound 2 to be used in the present step should both be within the range of 1 molar equivalent to 3 molar equivalents with respect to the compound 1.

[0084]

Examples of the condensing agent to be used in the present step include, for example, 1,1'-carbonyldiimidazole (hereinafter, referred to as "CDI"), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (hereinafter, referred to as "EDCI"), diisopropylcarbodiimide (hereinafter, referred to as "DIC"), diethyl cyanophosphonate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (hereinafter,

referred to as "HBTU"), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (hereinafter, referred to as "HATU"), and the like.

[0085]

5 In the present step, a base can be used as necessary. Examples of the base that can be used may include, for example, organic bases such as TEA, DIPEA, N,N-dimethylaniline, and DBU.

[0086]

10 It is appropriate that the amount of such a base to be used should be within the range of 1 molar equivalent to 10 molar equivalents with respect to the compound 1.

[0087]

15 In the present step, an additive, such as 1-hydroxybenzotriazole (hereinafter, referred to as "HOBt"), N-hydroxysuccinimide, and 1-hydroxy-7-azabenzotriazole (hereinafter, referred to as "HOAt"), may also be added, as necessary.

[0088]

20 When the additive described above is used in the present step, it is appropriate that the amount of such an additive to be used should be within the range of 0.1 molar equivalents to 3 molar equivalents with respect to the compound 1.

[0089]

25 Although the solvent to be used is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, hydrocarbons such as toluene and xylene; ethers such as 1,4-dioxane, THF, and DME; amides such as DMF and DMA; halogenated hydrocarbons such as dichloromethane and chloroform; nitriles such as acetonitrile and propionitrile;
30 and a mixed solvent thereof.

[0090]

35 It is appropriate that the reaction temperature should be normally within the range of -20°C to 150°C although it varies depending on the types of raw materials and reagents to be used.

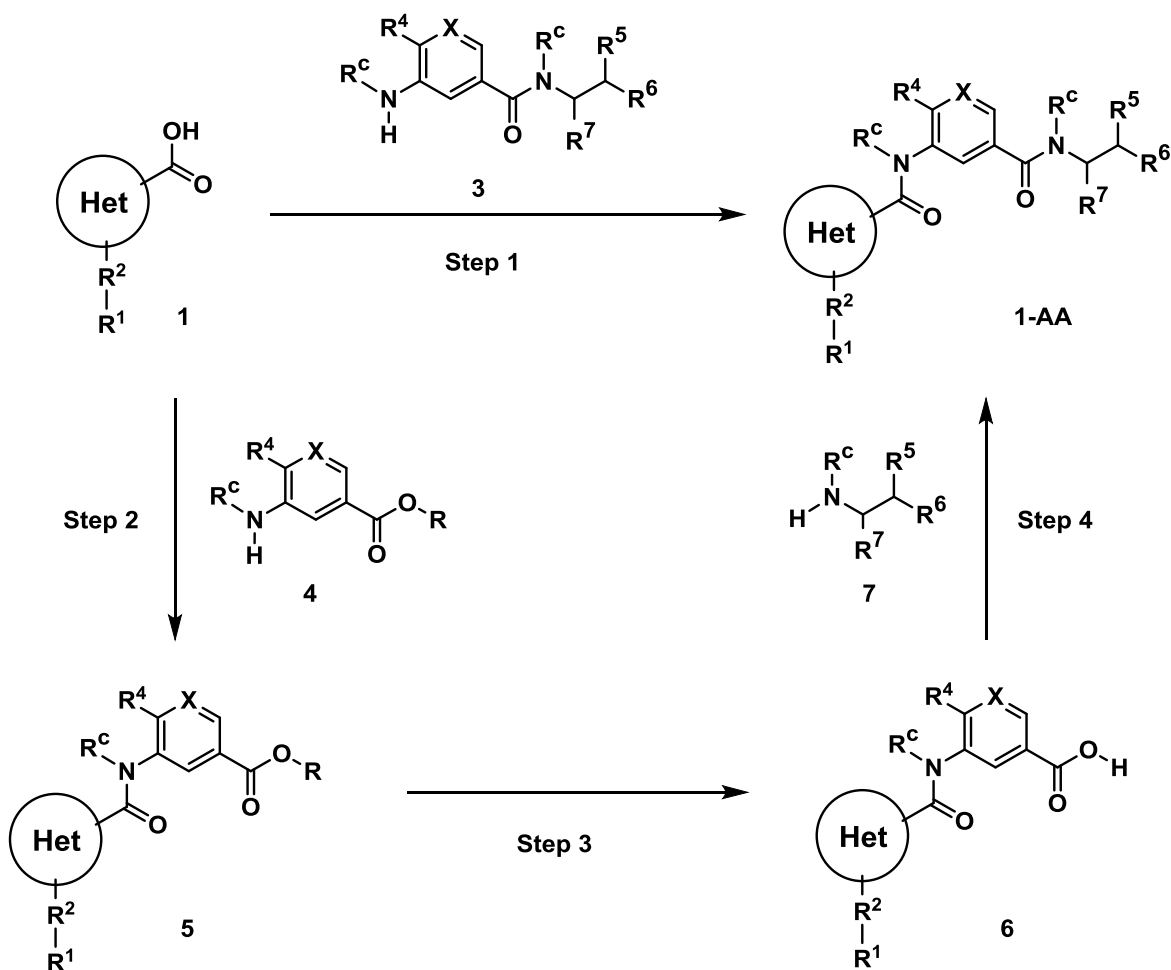
Also, a microwave reaction apparatus may be used as necessary.
[0091]

It is appropriate that the reaction time should be normally within the range of 0.1 hours to 72 hours although it varies depending on the types of raw materials to be used and the reaction temperature.
[0092]

Moreover, the compound [1] wherein L^2 is $-(CR^aR^b)_m-NR^c-$ wherein R^a and R^b are taken together with the carbon atom to which they are bonded to form $C=O$, and m and R^c are as defined above (compound 1-AA) can also be produced by the following method.
[0093]

Method for producing compound [1-AA]

[Formula 3]



for example, methyl, ethyl, and n-butyl.)

[0094]

Step 1

The present step is a step of obtaining a compound 1-AA
5 by condensing a compound 1 or a reactive compound thereof and an
amine compound 3 in the presence of a condensing agent. The
compound 1-AA can be produced by the same method as in Step 1 of
the method for producing the compound 1-A described above.

[0095]

10 Step 2

The present step is a step of obtaining a compound 5 by
condensing a compound 1 or a reactive compound thereof and an
amine compound 4 in the presence of a condensing agent. The
compound 5 can be produced by the same method as in Step 1 of the
15 method for producing the compound 1-A described above.

[0096]

Step 3

The present step is a step of obtaining a compound 6 by
hydrolyzing the ester moiety of the compound 5 described above in
20 the presence of an appropriate acid or base in an appropriate
solvent.

[0097]

Examples of the acid to be used in the present step may
include inorganic acids such as hydrochloric acid and sulfuric
25 acid; and organic acids such as trifluoroacetic acid
(hereinafter, referred to as "TFA"), methanesulfonic acid, and
toluenesulfonic acid. Examples of the base may include inorganic
bases such as sodium hydroxide, potassium hydroxide, and lithium
hydroxide.

30 [0098]

It is appropriate that the amount of the acid or the
base to be used in the present step should be within the range of
1 molar equivalent to 10 molar equivalents with respect to the
compound 5. If necessary, an excess amount of the acid or the
35 base may be used with respect to the compound 5.

[0099]

Although the solvent to be used is not limited as long as it is not involved in the reaction, examples thereof may include, for example, alcohols such as methanol, ethanol, and 2-propanol; ethers such as THF, diethyl ether, 1,4-dioxane, and DME; nitriles such as acetonitrile and propionitrile; ketones such as acetone; water; and a mixed solvent thereof.

[0100]

Although the reaction temperature varies depending on the types of raw materials and reagents to be used, the reaction can be normally carried out within the range of 20°C to 200°C, preferably 20°C to 100°C. Also, a microwave reaction apparatus may be used as necessary.

[0101]

It is appropriate that the reaction time should be normally within the range of 0.5 hours to 4 days although it varies depending on the types of raw materials to be used and the reaction temperature.

[0102]

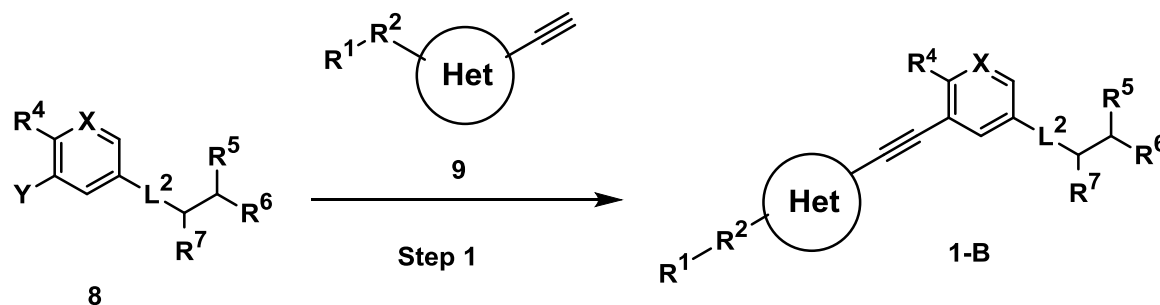
Step 4

The present step is a step of obtaining a compound 1-AA by condensing a compound 6 or a reactive compound thereof and an amine compound 7 in the presence of a condensing agent, and the compound 1-AA can be produced by the same method as in Step 1 of the method for producing the compound 1-A described above.

[0103]

Method for producing compound [1-B]

[Formula 4]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^c, Het, X, and L2 are as defined above. Y is a leaving group, and examples thereof may include, for example, a bromine atom, an iodine atom, methanesulfonate, and trifluoromethanesulfonate.)

5 Step 1

The present step is a step of obtaining a compound 1-B by subjecting a compound 8 and a compound 9 to a coupling reaction in the presence of a transition metal such as palladium. [0104]

10 For the present reaction, conditions normally used in a coupling reaction using a transition metal, specifically the Sonogashira coupling reaction, can be applied, and it can be carried out by methods described in literatures such as Sonogashira et al., J, Organomet. Chem. 2002, 653, 46-49; and
15 Negishi et al., Chem. Rev. 2003, 103, 1979-2017.
[0105]

It is appropriate that the amount of the compound 9 to be used should be within the range of 0.5 molar equivalents to 3 molar equivalents with respect to the compound 8.

20 [0106]

The organometallic catalyst to be used in the present reaction is not particularly limited. Preferable examples of the organometallic catalyst may include metal catalysts such as tris(dibenzylideneacetone)bispalladium-chloroform adduct
25 (hereinafter, referred to as "Pd₂(dba)₃CHCl₃"), tris(dibenzylideneacetone)bispalladium (hereinafter, referred to as "Pd₂(dba)₃"), tetrakis(triphenylphosphine)palladium (hereinafter, referred to as "Pd(PPh₃)₄"), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)-
30 dichloromethane adduct (hereinafter, referred to as "Pd(dppf)Cl₂·CH₂Cl₂"), bis(triphenylphosphine)palladium(II) dichloride (hereinafter, referred to as "PdCl₂(PPh₃)₂"), [1,1'-bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) (hereinafter, referred to as "Pd(dtbpf)Cl₂"),
35 bis(tricyclohexylphosphine)palladium(II) dichloride (hereinafter,

referred to as " $\text{PdCl}_2(\text{PCy}_3)_2$ "), palladium(II) acetate (hereinafter, referred to as " $\text{Pd}(\text{OAc})_2$ "), and [1,3-bis(diphenylphosphino)propane]nickel(II), and a mixture of these metal catalysts.

5 [0107]

It is appropriate that the amount of the transition metal to be used should be, for example, within the range of 0.01 molar equivalents to 0.3 molar equivalents with respect to the compound 8.

10 [0108]

In the present step, a base or a salt may be used as necessary. Examples of the base or the salt to be used may include, for example, bases or salts such as potassium carbonate, cesium carbonate, sodium carbonate, sodium bicarbonate, sodium acetate, potassium acetate, trisodium phosphate, tripotassium phosphate, and solutions thereof; as well as triethylamine (hereinafter, referred to as "TEA"), N,N-diisopropylethylamine (hereinafter, referred to as "DIPEA"), lithium chloride, and copper(I) iodide.

20 [0109]

It is appropriate that the amount of the base to be used should be, for example, within the range of 1 molar equivalent to 4 molar equivalents with respect to the compound 8.
[0110]

25 In the present step, an appropriate ligand may be used as necessary. Examples of the ligand that can be used may include, for example, 1,1'-bis(diphenylphosphino)ferrocene (hereinafter, referred to as "dppf"), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (hereinafter, referred to as "Xantphos"), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (hereinafter, referred to as "XPhos"), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter, referred to as "BINAP"), 2-dicyclohexylphosphino-2',6'-diisopropylbiphenyl (hereinafter, referred to as "RuPhos"), triphenylphosphine (hereinafter, referred to as " PPh_3 "), tricyclohexylphosphine (hereinafter,

35

referred to as "PCy₃"), and the like.

[0111]

It is appropriate that the amount of the ligand to be used should be, for example, within the range of 1 molar
5 equivalent to 5 molar equivalents with respect to the transition metal to be used.

[0112]

Although the solvent to be used in the present step is not particularly limited as long as it is not involved in the
10 reaction, examples thereof may include, for example, hydrocarbons such as toluene and xylene; ethers such as 1,4-dioxane, tetrahydrofuran (hereinafter, referred to as "THF"), and dimethoxyethane (hereinafter, referred to as "DME"); amides such as N,N-dimethylformamide (hereinafter, referred to as "DMF"),
15 N,N-dimethylacetamide (hereinafter, referred to as "DMA"), and N-methylpyrrolidone (hereinafter, referred to as "NMP"); alcohols such as ethanol, 2-propanol, and tert-butanol; water; and a mixed solvent thereof.

[0113]

20 It is appropriate that the reaction temperature should be normally within the range of 20°C to 200°C although it varies depending on the types of raw materials and reagents to be used. Also, a microwave reaction apparatus may be used as necessary.

[0114]

25 It is appropriate that the reaction time should be normally within the range of 0.1 hours to 24 hours although it varies depending on the types of raw materials to be used and the reaction temperature.

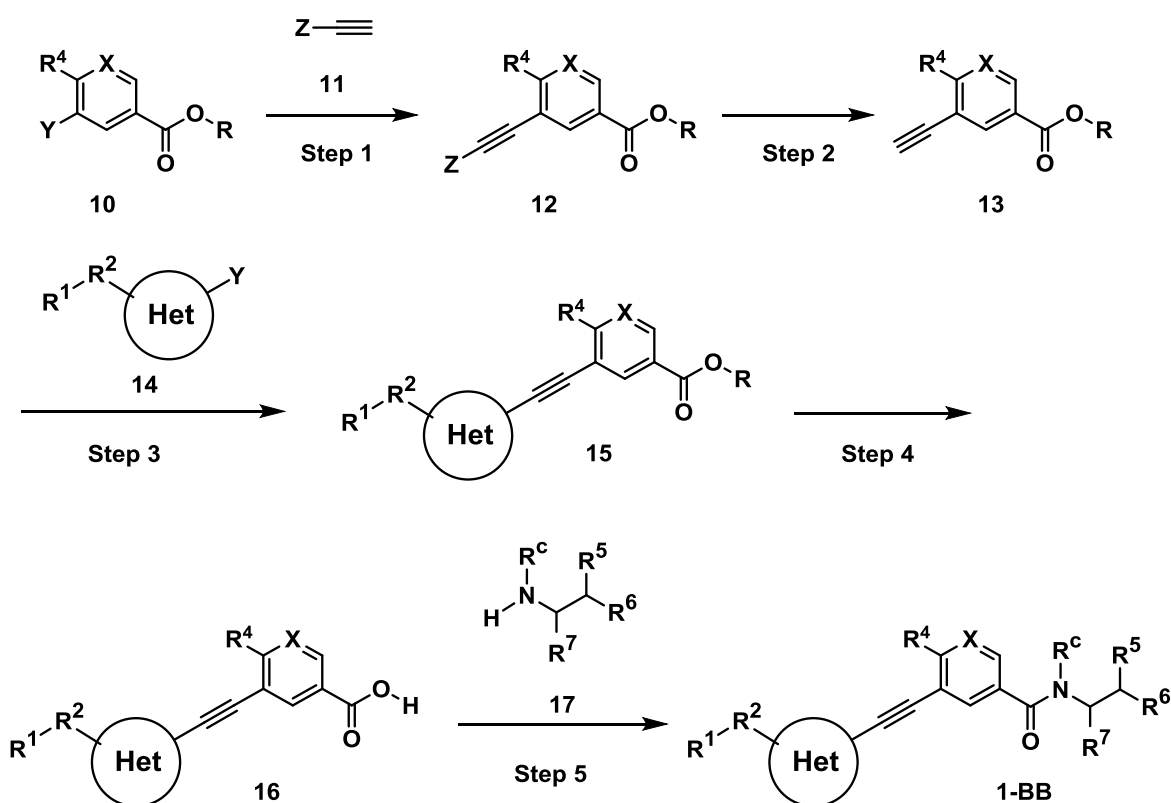
[0115]

30 A compound wherein L² is -(CR^aR^b)_m-NR^c- wherein R^a and R^b are taken together with the carbon atom to which they are bonded to form C=O (compound 1-BB) can also be produced as follows.

[0116]

Method for producing compound [1-BB]

35 [Formula 5]



(In the formula, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^c , Het, X, Y, and R are as defined above. Z is a leaving group, and examples thereof may include, for example, trimethylsilyl and triethylsilyl.)

5 [0117]

Step 1

The present step is a step of obtaining an alkyne compound 12 by subjecting a compound 10 and a compound 11 to coupling in the presence of a transition metal such as palladium, and the alkyne compound 12 can be produced by the same method as

[0118]

Step 2

The present step is a step of deprotecting Z to obtain a compound 13, and can be carried out with reference to, for example, Wuts and Greene, "Greene's Protective Groups in Organic Synthesis", 4th edition, John Wiley & Sons Inc., 2006; or P. J. Kocienski, "Protecting Groups", 3rd edition, Thieme, 2005.

[0119]

20

Step 3

The present step is a step of obtaining a compound 15 by subjecting a compound 13 and a compound 14 to coupling in the presence of a transition metal such as palladium, and the compound 15 can be produced by the same method as in Step 1 of the method for producing the compound 1-B.

[0120]

Step 4

The present step is a step of obtaining a compound 16 by hydrolyzing the ester moiety of the compound 15 in the presence of an appropriate acid or base in an appropriate solvent, and the compound 16 can be produced by the same method as in Step 3 of the method for producing the compound 1-AA.

[0121]

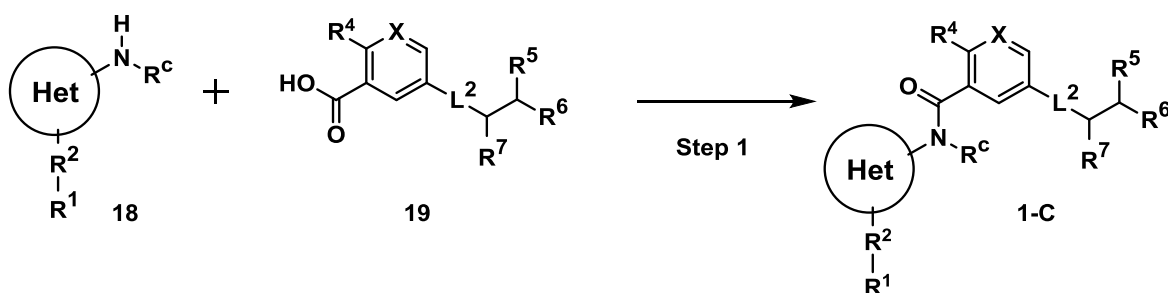
Step 5

The present step is a step of obtaining a compound 1-BB by condensing a compound 16 or a reactive compound thereof and an amine compound 17 in the presence of a condensing agent, and the compound 1-BB can be produced by the same method as in Step 1 of the method for producing the compound 1-A described above.

[0122]

Method for producing compound [1-C]

[Formula 6]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^c, Het, and X are as defined above.)

[0123]

Step 1

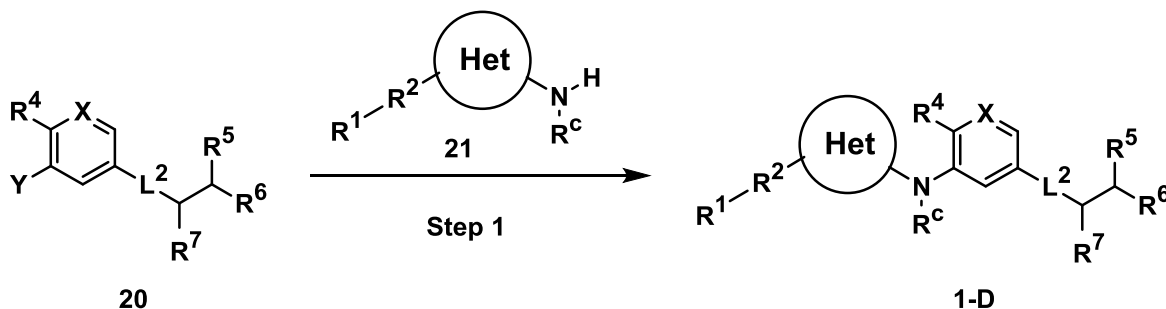
The present step is a step of obtaining a compound 1-C by condensing a compound 19 or a reactive compound thereof and an amine compound 18 in the presence of a condensing agent, and the

compound 1-C can be produced by the same method as in Step 1 of the method for producing the compound 1-A described above.

[0124]

Method for producing compound [1-D]

5 [Formula 7]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^c, L², Het, and X are as defined above. Y is a leaving group, and examples thereof may include, for example, a bromine atom, an iodine atom, and trifluoromethanesulfonate.)

10

Step 1

The present step is a step of obtaining a compound 1-D by subjecting a compound 20 and a compound 21 to a coupling reaction in the presence of a transition metal such as palladium.

15 [0125]

For the present reaction, conditions normally used in a coupling reaction using a transition metal, specifically the coupling reaction of Buchwald and others, can be applied, and it can be carried out by methods described in literatures such as Buchwald et al., J. Am. Chem. Soc. 1994, 116, 7901-7902.; Buchwald et al., Org. Synth. 2002, 78, 23-28.; and Hartwig et al., Acc. Chem. Res. 2008, 41, 1534-1544.

20

[0126]

It is appropriate that the amount of the compound 21 to be used should be within the range of 0.5 molar equivalents to 3 molar equivalents with respect to the compound 20.

25

[0127]

The organometallic catalyst to be used in the present reaction is not particularly limited. Preferable examples of the

organometallic catalyst may include metal catalysts such as tris(dibenzylideneacetone)bispalladium-chloroform adduct (hereinafter, referred to as " $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ "), tris(dibenzylideneacetone)bispalladium (hereinafter, referred to as " $\text{Pd}_2(\text{dba})_3$ "), tetrakis(triphenylphosphine)palladium (hereinafter, referred to as " $\text{Pd}(\text{PPh}_3)_4$ "), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)-dichloromethane adduct (hereinafter, referred to as " $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2$ "), bis(triphenylphosphine)palladium(II) dichloride (hereinafter, referred to as " $\text{PdCl}_2(\text{PPh}_3)_2$ "), [1,1'-bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) (hereinafter, referred to as " $\text{Pd}(\text{dtbpf})\text{Cl}_2$ "), bis(tricyclohexylphosphine)palladium(II) dichloride (hereinafter, referred to as " $\text{PdCl}_2(\text{PCy}_3)_2$ "), palladium(II) acetate (hereinafter, referred to as " $\text{Pd}(\text{OAc})_2$ "), and [1,3-bis(diphenylphosphino)propane]nickel(II), and a mixture of these metal catalysts.

[0128]

It is appropriate that the amount of the transition metal to be used should be, for example, within the range of 0.01 molar equivalents to 0.3 molar equivalents with respect to the compound 20.

[0129]

In the present step, a base or a salt may be used as necessary. Examples of the base or the salt to be used may include, for example, bases or salts such as potassium carbonate, cesium carbonate, sodium carbonate, sodium bicarbonate, sodium acetate, potassium acetate, trisodium phosphate, tripotassium phosphate, and solutions thereof; as well as triethylamine (hereinafter, referred to as "TEA"), N,N-diisopropylethylamine (hereinafter, referred to as "DIPEA"), lithium chloride, and copper(I) iodide.

[0130]

It is appropriate that the amount of the base to be used should be, for example, within the range of 1 molar

equivalent to 4 molar equivalents with respect to the compound 20.

[0131]

In the present step, an appropriate ligand may be used
5 as necessary. Examples of the ligand that can be used may include, for example, 1,1'-bis(diphenylphosphino)ferrocene (hereinafter, referred to as "dppf"), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (hereinafter, referred to as "Xantphos"), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (hereinafter,
10 referred to as "XPhos"), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter, referred to as "BINAP"), 2-dicyclohexylphosphino-2',6'-diisopropylbiphenyl (hereinafter, referred to as "RuPhos"), triphenylphosphine (hereinafter, referred to as "PPh₃"), tricyclohexylphosphine (hereinafter,
15 referred to as "PCy₃"), and the like.

[0132]

It is appropriate that the amount of the ligand to be used should be, for example, within the range of 1 molar equivalent to 5 molar equivalents with respect to the transition
20 metal to be used.

[0133]

Although the solvent to be used in the present step is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, hydrocarbons
25 such as toluene and xylene; ethers such as 1,4-dioxane, tetrahydrofuran (hereinafter, referred to as "THF"), and dimethoxyethane (hereinafter, referred to as "DME"); amides such as N,N-dimethylformamide (hereinafter, referred to as "DMF"), N,N-dimethylacetamide (hereinafter, referred to as "DMA"), and N-
30 methylpyrrolidone (hereinafter, referred to as "NMP"); alcohols such as ethanol, 2-propanol, and tert-butanol; water; and a mixed solvent thereof.

[0134]

It is appropriate that the reaction temperature should
35 be normally within the range of 20°C to 200°C although it varies

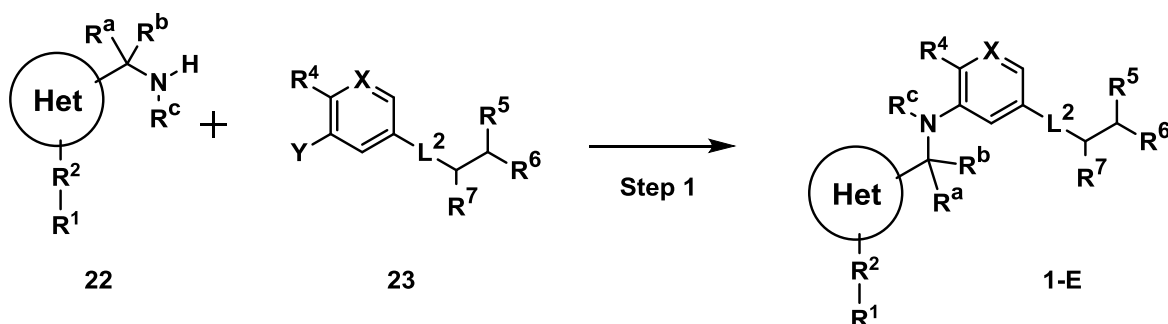
depending on the types of raw materials and reagents to be used. Also, a microwave reaction apparatus may be used as necessary.
[0135]

It is appropriate that the reaction time should be normally within the range of 0.1 hours to 24 hours although it varies depending on the types of raw materials to be used and the reaction temperature.

[0136]

Method for producing compound [1-E]

[Formula 8]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^a, R^b, R^c, L², Het, X, and Y are as defined above.)

Step 1

The present step is a step of obtaining a compound 1-E by subjecting a compound 22 and a compound 23 to a coupling reaction in the presence of a transition metal such as palladium, and the compound 1-E can be produced by the same method as in Step 1 of the method for producing the compound 1-D described above.

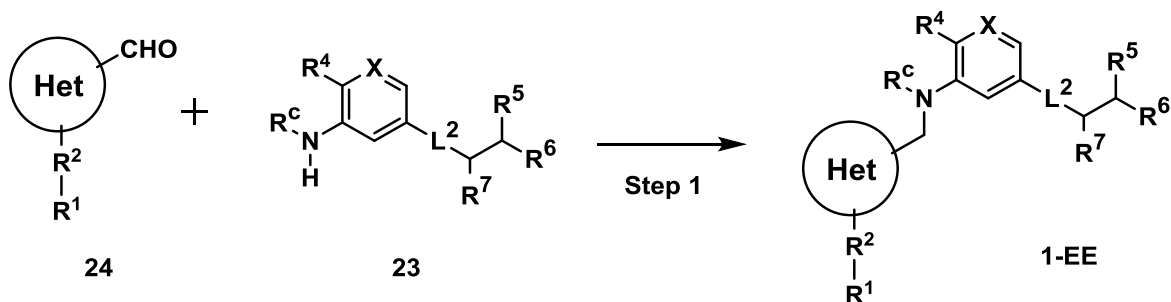
[0137]

A compound wherein L¹ is -(CR^aR^b)_m-NR^c- and R^a and R^b are each H can also be produced as follows.

[0138]

Method for producing compound [1-EE]

[Formula 9]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R⁸, L², Het, and X are as defined above.)

Step 1

5 [0139]

Step 1

The present step is a step of obtaining a compound 1-EE by a reductive amination reaction of a compound 24 and a compound 23, and can be carried out according to a method that is publicly known as a reductive amination reaction. In the present step, imine formation (first step) and reduction of the imine moiety (second step) may be carried out sequentially.

[0140]

It is appropriate that the amount of the compound 23 to be used should be within the range of 1 molar equivalent to 2.5 molar equivalents with respect to the compound 24.

[0141]

In the present step, an acid or an appropriate Lewis acid may be used as necessary. Examples of the acid that can be used in the reaction may include, for example, acetic acid and the like, and examples of the Lewis acid that can be used may include, for example, tetraisopropyl orthotitanate.

[0142]

When the acid is used in the present step, it is appropriate that the amount of the acid to be used should be within the range of 2 molar equivalents to 3 molar equivalents with respect to the amount of the compound 24.

[0143]

When the Lewis acid is used in the present step, it is appropriate that the amount of the Lewis acid to be used should

30

be within the range of 1.5 molar equivalents to 2 molar equivalents with respect to the amount of the compound 24.

[0144]

Although the solvent to be used in the present step is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, hydrocarbons such as toluene and xylene; ethers such as 1,4-dioxane, THF, and DME; halogenated hydrocarbons such as dichloromethane; and a mixed solvent thereof.

10 [0145]

In the present step, it is appropriate that the reaction temperature should be normally within the range of 0°C to 100°C although it varies depending on the types of raw materials and reagents to be used.

15 [0146]

In the present step, it is appropriate that the reaction time should be normally within the range of 0.1 hours to 48 hours although it varies depending on the types of raw materials to be used and the reaction temperature.

20 [0147]

Examples of the reducing agent to be used in the present step may include, for example, sodium triacetoxyborohydride, sodium cyanoborohydride, and the like.

[0148]

25 It is appropriate that the amount of the reducing agent to be used in the present step should be within the range of 1 molar equivalent to 2 molar equivalents with respect to the compound 24.

[0149]

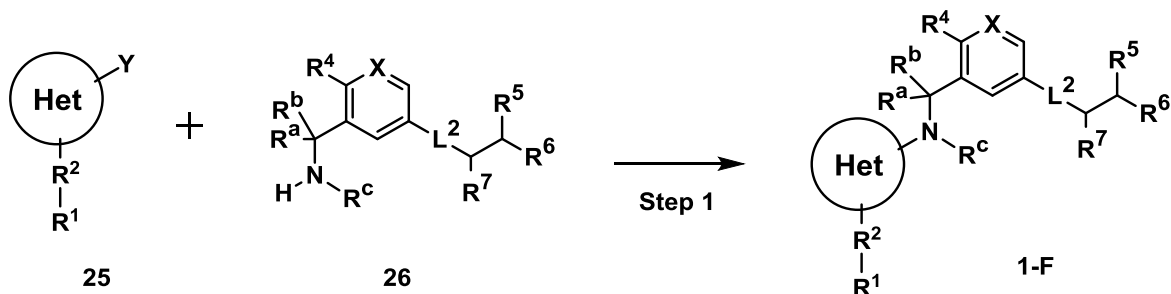
30 Although the solvent to be used in the present step is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, hydrocarbons such as toluene and xylene; ethers such as 1,4-dioxane, THF, and DME; halogenated hydrocarbons such as dichloromethane; and a mixed solvent thereof.

35

[0150]

Method for producing compound [1-F]

[Formula 10]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^a, R^b, R^c, L², Het, X, and Y are as defined above.)

Step 1

The present step is a step of obtaining a compound 1-F by allowing a compound 25 to react with a compound 26 in the presence of a base.

[0151]

It is appropriate that the amount of the compound 26 to be used should be within the range of 0.5 molar equivalents to 3 molar equivalents with respect to the compound 25.

[0152]

Examples of the base to be used in the present reaction may include pyridine, TEA, DIPEA, potassium carbonate, and sodium bicarbonate.

[0153]

It is appropriate that the amount of the base to be used should be within the range of 1 molar equivalent to 10 molar equivalents with respect to the compound 25.

[0154]

Although the solvent to be used is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, alcohols such as isopropanol, 1-butanol, and 2-methoxyethanol; ethers such as THF and 1,4-dioxane; amides such as DMF, DMA, and NMP; hydrocarbons such as benzene and toluene; dimethyl sulfoxide (hereinafter, referred to as "DMSO"); acetonitrile; and a mixed solvent thereof.

[0155]

In the present step, it is appropriate that the reaction temperature should be normally within the range of 20°C to 200°C although it varies depending on the types of raw materials and reagents to be used. Also, a microwave reaction apparatus may be used as necessary.

[0156]

It is appropriate that the reaction time should be normally within the range of 1 hour to 24 hours although it varies depending on the types of raw materials to be used and the reaction temperature.

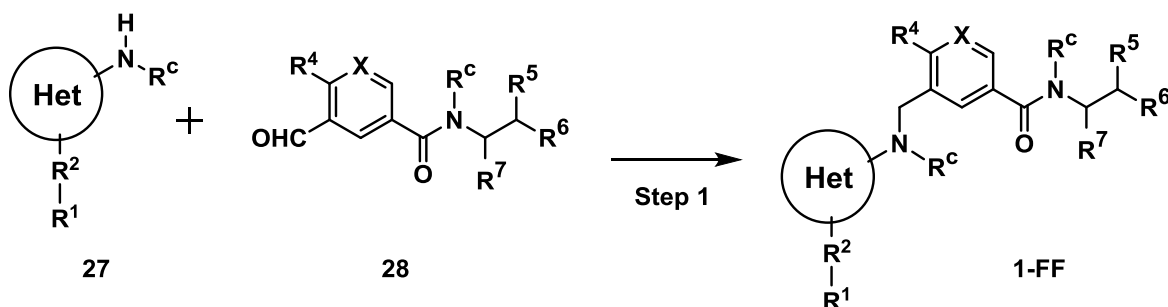
[0157]

A compound wherein L^1 is $-NR^c-(CR^aR^b)_m-$ and R^a and R^b are each H can also be produced as follows.

[0158]

Method for producing compound [1-FF]

[Formula 11]



(In the formula, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^c , L^2 , Het, and X are as defined above.)

[0159]

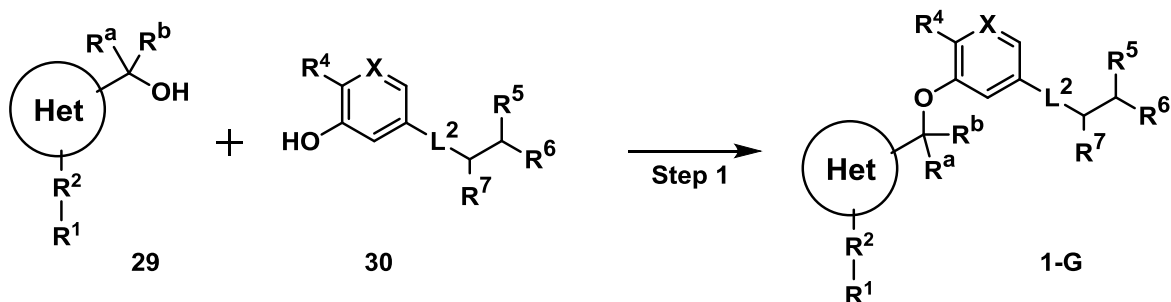
Step 1

The present step is a step of obtaining a compound 1-FF by a reductive amination reaction of a compound 27 and a compound 28, and the compound 1-FF can be produced by the same method as in Step 1 of the method for producing the compound 1-EE described above.

[0160]

Method for producing compound [1-G]

[Formula 12]



(In the formula, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^c , L^2 , Het, and X are as defined above.)

[0161]

5 Step 1

The present step is a step of obtaining an ether compound 1-G by the Mitsunobu reaction of an alcohol compound 29 and an alcohol compound 30, and can be carried out according to a publicly known method.

10 [0162]

The present step is normally carried out in an appropriate solvent in the presence of an azodicarboxylic acid ester reagent and a phosphine reagent.

[0163]

15 It is appropriate that the amount of the compound 29 to be used should be within the range of 0.5 molar equivalents to 1.5 molar equivalents with respect to the compound 30.

[0164]

20 Examples of the azodicarboxylic acid ester reagent to be used may include, for example, diethyl azodicarboxylate (hereinafter, referred to as "DEAD"), diisopropyl azodicarboxylate (hereinafter, referred to as "DIAD"), bis(2-methoxyethyl) azodicarboxylate (hereinafter, referred to as "DMEAD"), and the like.

25 [0165]

Examples of the phosphine reagent to be used may include, for example, triphenylphosphine, tributylphosphine, and the like.

[0166]

30 It is appropriate that the amount of the

azodicarboxylic acid ester reagent to be used should be within the range of 1 molar equivalent to 2 molar equivalents with respect to the compound 29.

[0167]

It is appropriate that the amount of the phosphine reagent to be used should be within the range of 1 molar equivalent to 2 molar equivalents with respect to the compound 29.

[0168]

Although the solvent to be used is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, hydrocarbons such as toluene and xylene; ethers such as 1,4-dioxane, THF, and DME; and a mixed solvent thereof.

[0169]

In the present step, it is appropriate that the reaction temperature should be normally within the range of 0°C to 100°C although it varies depending on the types of raw materials and reagents to be used.

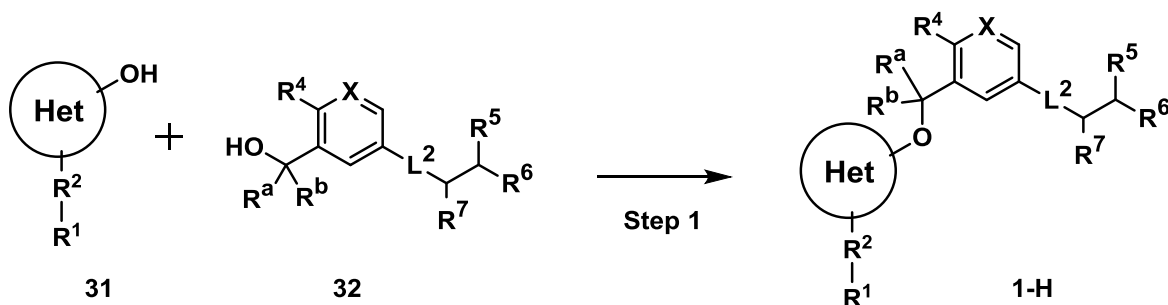
[0170]

It is appropriate that the reaction time should be normally within the range of 0.5 hours to 24 hours although it varies depending on the types of raw materials to be used and the reaction temperature.

[0171]

Method for producing compound [1-H]

[Formula 13]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^c, L², Het, and X are as defined above.)

[0172]

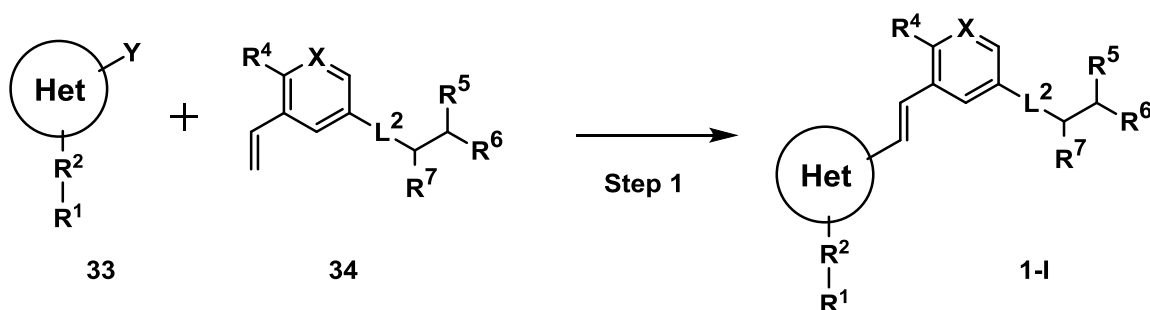
Step 1

The present step is a step of obtaining an ether compound 1-H by the Mitsunobu reaction of an alcohol compound 31 and an alcohol compound 32, and the compound 1-H can be produced by the same method as in Step 1 of the method for producing the compound 1-G described above.

[0173]

Method for producing compound [1-I]

[Formula 14]



(In the formula, R¹, R², R⁴, R⁵, R⁶, R⁷, R^c, L², Het, and X are as defined above. Y is a leaving group, and examples thereof may include, for example, a bromine atom, an iodine atom, and trifluoromethanesulfonate.)

Step 1

The present step is a step of obtaining a compound 1-I by subjecting a compound 33 and a compound 34 to a coupling reaction in the presence of a transition metal such as palladium.

[0174]

For the present reaction, conditions normally used in a coupling reaction using a transition metal, specifically the Heck reaction, can be applied, and it can be carried out by methods described in literatures such as Org. Synth. 2005, 81, 63-76.; Heck et al., J. Org. Chem. 1972, 37, 2320-2322.; and Beletskaya et al., Chem. Rev. 2000, 100, 3009-3066.

[0175]

It is appropriate that the amount of the compound 33 to be used should be within the range of 0.5 molar equivalents to 3

molar equivalents with respect to the compound 34.

[0176]

The organometallic catalyst to be used in the present reaction is not particularly limited. Preferable examples of the organometallic catalyst may include metal catalysts such as

5 tris(dibenzylideneacetone)bispalladium-chloroform adduct (hereinafter, referred to as " $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ "), tris(dibenzylideneacetone)bispalladium (hereinafter, referred to as " $\text{Pd}_2(\text{dba})_3$ "), tetrakis(triphenylphosphine)palladium (hereinafter,

10 referred to as " $\text{Pd}(\text{PPh}_3)_4$ "), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)-dichloromethane adduct (hereinafter, referred to as " $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2$ "), bis(triphenylphosphine)palladium(II) dichloride (hereinafter, referred to as " $\text{PdCl}_2(\text{PPh}_3)_2$ "), [1,1'-

15 bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) (hereinafter, referred to as " $\text{Pd}(\text{dtbpf})\text{Cl}_2$ "), bis(tricyclohexylphosphine)palladium(II) dichloride (hereinafter, referred to as " $\text{PdCl}_2(\text{PCy}_3)_2$ "), palladium(II) acetate (hereinafter, referred to as " $\text{Pd}(\text{OAc})_2$ "), and [1,3-

20 bis(diphenylphosphino)propane]nickel(II), and a mixture of these metal catalysts.

[0177]

It is appropriate that the amount of the transition metal to be used should be, for example, within the range of 0.01

25 molar equivalents to 0.3 molar equivalents with respect to the compound 33.

[0178]

In the present step, a base or a salt may be used as necessary. Examples of the base or the salt to be used may

30 include, for example, bases or salts such as potassium carbonate, cesium carbonate, sodium carbonate, sodium bicarbonate, sodium acetate, potassium acetate, trisodium phosphate, tripotassium phosphate, and solutions thereof; as well as triethylamine (hereinafter, referred to as "TEA"), N,N-diisopropylethylamine

35 (hereinafter, referred to as "DIPEA"), lithium chloride, and

copper(I) iodide.

[0179]

It is appropriate that the amount of the base to be used should be, for example, within the range of 1 molar equivalent to 4 molar equivalents with respect to the compound 33.

[0180]

In the present step, an appropriate ligand may be used as necessary. Examples of the ligand that can be used may include, for example, 1,1'-bis(diphenylphosphino)ferrocene (hereinafter, referred to as "dppf"), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (hereinafter, referred to as "Xantphos"), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (hereinafter, referred to as "XPhos"), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter, referred to as "BINAP"), 2-dicyclohexylphosphino-2',6'-diisopropylbiphenyl (hereinafter, referred to as "RuPhos"), triphenylphosphine (hereinafter, referred to as "PPh₃"), tricyclohexylphosphine (hereinafter, referred to as "PCy₃"), and the like.

[0181]

It is appropriate that the amount of the ligand to be used should be, for example, within the range of 1 molar equivalent to 5 molar equivalents with respect to the transition metal to be used.

[0182]

Although the solvent to be used in the present step is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, hydrocarbons such as toluene and xylene; ethers such as 1,4-dioxane, tetrahydrofuran (hereinafter, referred to as "THF"), and dimethoxyethane (hereinafter, referred to as "DME"); amides such as N,N-dimethylformamide (hereinafter, referred to as "DMF"), N,N-dimethylacetamide (hereinafter, referred to as "DMA"), and N-methylpyrrolidone (hereinafter, referred to as "NMP"); alcohols such as ethanol, 2-propanol, and tert-butanol; water; and a mixed

solvent thereof.

[0183]

It is appropriate that the reaction temperature should be normally within the range of 20°C to 200°C although it varies depending on the types of raw materials and reagents to be used. Also, a microwave reaction apparatus may be used as necessary.

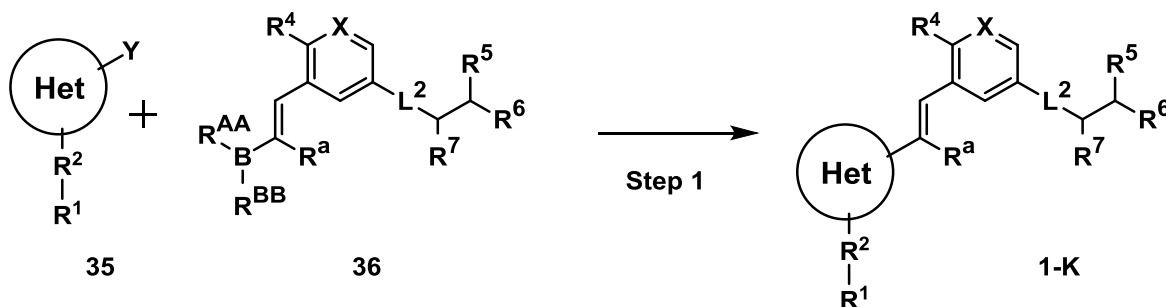
[0184]

It is appropriate that the reaction time should be normally within the range of 0.1 hours to 24 hours although it varies depending on the types of raw materials to be used and the reaction temperature.

[0185]

Method for producing compound [1-K]

[Formula 15]



(In the formula, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^a , L^2 , Het, and X are as defined above. Y is a leaving group, and examples thereof may include, for example, a bromine atom, an iodine atom, and trifluoromethanesulfonate. R^{AA} and R^{BB} each represent a hydroxy group, or R^{AA} and R^{BB} are taken together to be $-O-C(CH_3)_2-C(CH_3)_2-O-$, $-O-(CH_2)_3-O-$, or $O-CH_2-C(CH_3)_2-CH_2-O-$.)

Step 1

The present step is a step of obtaining a compound 1-K by subjecting a compound 35 and a compound 36 to a coupling reaction in the presence of a transition metal such as palladium.

[0186]

For the present reaction, conditions normally used in a coupling reaction using a transition metal, specifically the Suzuki-Miyaura coupling reaction, can be applied, and it can be

carried out by methods described in literatures such as Suzuki et al., Chem. Rev., 1995, 95, 2457-2483.

[0187]

It is appropriate that the amount of the compound 36 to be used should be within the range of 0.5 molar equivalents to 3 molar equivalents with respect to the compound 35.

[0188]

The organometallic catalyst to be used in the present reaction is not particularly limited. Preferable examples of the organometallic catalyst may include metal catalysts such as tris(dibenzylideneacetone)bispalladium-chloroform adduct (hereinafter, referred to as " $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ "), tris(dibenzylideneacetone)bispalladium (hereinafter, referred to as " $\text{Pd}_2(\text{dba})_3$ "), tetrakis(triphenylphosphine)palladium (hereinafter, referred to as " $\text{Pd}(\text{PPh}_3)_4$ "), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)-dichloromethane adduct (hereinafter, referred to as " $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2$ "), bis(triphenylphosphine)palladium(II) dichloride (hereinafter, referred to as " $\text{PdCl}_2(\text{PPh}_3)_2$ "), [1,1'-bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) (hereinafter, referred to as " $\text{Pd}(\text{dtbpf})\text{Cl}_2$ "), bis(tricyclohexylphosphine)palladium(II) dichloride (hereinafter, referred to as " $\text{PdCl}_2(\text{PCy}_3)_2$ "), palladium(II) acetate (hereinafter, referred to as " $\text{Pd}(\text{OAc})_2$ "), and [1,3-bis(diphenylphosphino)propane]nickel(II), and a mixture of these metal catalysts.

[0189]

It is appropriate that the amount of the transition metal to be used should be, for example, within the range of 0.01 molar equivalents to 0.3 molar equivalents with respect to the compound 35.

[0190]

In the present step, a base or a salt may be used as necessary. Examples of the base or the salt to be used may include, for example, bases or salts such as potassium carbonate,

cesium carbonate, sodium carbonate, sodium bicarbonate, sodium acetate, potassium acetate, trisodium phosphate, tripotassium phosphate, and solutions thereof; as well as triethylamine (hereinafter, referred to as "TEA"), N,N-diisopropylethylamine (hereinafter, referred to as "DIPEA"), lithium chloride, and copper(I) iodide.

[0191]

It is appropriate that the amount of the base to be used should be, for example, within the range of 1 molar equivalent to 4 molar equivalents with respect to the compound

[0192]

In the present step, an appropriate ligand may be used as necessary. Examples of the ligand that can be used may include, for example, 1,1'-bis(diphenylphosphino)ferrocene (hereinafter, referred to as "dppf"), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (hereinafter, referred to as "Xantphos"), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (hereinafter, referred to as "XPhos"), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter, referred to as "BINAP"), 2-dicyclohexylphosphino-2',6'-diisopropylbiphenyl (hereinafter, referred to as "RuPhos"), triphenylphosphine (hereinafter, referred to as "PPh₃"), tricyclohexylphosphine (hereinafter, referred to as "PCy₃"), and the like.

[0193]

It is appropriate that the amount of the ligand to be used should be, for example, within the range of 1 molar equivalent to 5 molar equivalents with respect to the transition metal to be used.

[0194]

Although the solvent to be used in the present step is not particularly limited as long as it is not involved in the reaction, examples thereof may include, for example, hydrocarbons such as toluene and xylene; ethers such as 1,4-dioxane, tetrahydrofuran (hereinafter, referred to as "THF"), and

dimethoxyethane (hereinafter, referred to as "DME"); amides such as N,N-dimethylformamide (hereinafter, referred to as "DMF"), N,N-dimethylacetamide (hereinafter, referred to as "DMA"), and N-methylpyrrolidone (hereinafter, referred to as "NMP"); alcohols
5 such as ethanol, 2-propanol, and tert-butanol; water; and a mixed solvent thereof.

[0195]

It is appropriate that the reaction temperature should be normally within the range of 20°C to 200°C although it varies
10 depending on the types of raw materials and reagents to be used. Also, a microwave reaction apparatus may be used as necessary.

[0196]

It is appropriate that the reaction time should be normally within the range of 0.1 hours to 24 hours although it
15 varies depending on the types of raw materials to be used and the reaction temperature.

[0197]

The compound of the present invention has an inhibitory activity against the PDGF receptor kinase, as demonstrated in
20 Test Examples mentioned below. In addition, since the compound of the present invention has an inhibitory activity against the PDGF receptor kinase, it is effective for respiratory diseases, cancers, smooth muscle proliferative diseases, vasoproliferative diseases, autoimmune/inflammatory diseases, metabolic diseases,
25 and vasoocclusive diseases.

[0198]

Moreover, the inhibitory activity against the PDGF receptor kinase of the compound of the present invention has high selectivity for the inhibitory activity against the KIT kinase,
30 as demonstrated in Test Examples mentioned below, and therefore, it can be expected that the compound of the present invention provides a PDGF receptor kinase inhibitor with suppressed undesirable actions, such as bone marrow suppression.

[0199]

35 As such, the compound of the present invention or a

pharmaceutically acceptable salt thereof can be used as, for example, a preventive or therapeutic agent for diseases in which the PDGF receptor kinase is involved.

[0200]

- 5 Examples of the respiratory disease to which the compound of the present invention or a pharmaceutically acceptable salt thereof can be applied may include pulmonary diseases and pulmonary hypertension. Above all, pulmonary hypertension is classified as follows depending on the etiology
- 10 and pathology.
- pulmonary arterial hypertension (PAH);
 - pulmonary hypertension caused by the following left heart diseases
 - left heart failure with a maintained ejection fraction,
 - 15 left heart failure with a reduced ejection fraction, valvulopathy, and
 - congenital/acquired cardiovascular conditions leading to post-capillary PH;
 - pulmonary hypertension due to pulmonary diseases and/or
 - 20 hypoxemia caused by the diseases shown below
 - chronic obstructive pulmonary disease (COPD),
 - interstitial (restrictive) pulmonary disease,
 - other pulmonary diseases involving a mixed disorder of restrictive and obstructive ones,
 - 25 hypoxic condition caused by a pulmonary disease, and developmental disorder;
 - the following pulmonary hypertensions caused by the occlusion of pulmonary artery
 - chronic thromboembolic pulmonary hypertension (CTEPH),
 - 30 and
 - pulmonary hypertension owing to the following diseases (sarcoma, angiosarcoma, malignant tumor, non-malignant tumor, vasculitis caused by a connective tissue disease, congenital pulmonary artery stenosis, parasite or the like, and pulmonary
 - 35 tumor thrombotic microangiopathy (PTTM)); and

· pulmonary hypertension caused by a multifactorial mechanism for which details are unknown, caused by the diseases shown below

blood diseases (chronic hemolytic anemia, myeloproliferative disease, and the like),

5 systemic and metabolic diseases (for example, pulmonary Langerhans cell histiocytosis, Gaucher's disease, glycogen storage disease, neurofibroma, sarcoidosis, and the like),

others (for example, chronic renal failure with/without dialysis, fibrosing mediastinitis, and the like), and

10 complex congenital heart malformation.

[0201]

For example, the pulmonary arterial hypertension (PAH) described above encompasses the followings:

idiopathic PAH;

15 hereditary PAH (in particular, with abnormality in BMPR2, TBX4, ACVRL1, ENG, SMAD9, KCNK3, SMAD1, CAV1, SMAD4, ATP13A3, SOX17, AQP1, GDF2, or unknown gene);

drug- and toxicant-induced PAH;

PAH caused by diseases (Here, the "diseases" include, 20 for example, a connective tissue disease, HIV infection, portal hypertension, congenital shunt heart disease, and schistosomiasis);

PAH long-term responders to calcium channel blockers, pulmonary veno-occlusive disease/pulmonary capillary 25 hemangiomatosis (PVOD/PCH) (including PVOD/PCH with EIF2AK4 mutation); and

persistent pulmonary hypertension of the newborn (PPHN).

[0202]

30 Examples of the inflammatory disease and autoimmune disease to which the compound of the present invention or a pharmaceutically acceptable salt thereof can be applied may include scleroderma, asthma, bronchiolitis obliterans, pulmonary fibrosis, systemic lupus erythematosus (SLE), mixed connective 35 tissue disease (MCTD), Sjogren's syndrome,

polymyositis/dermatomyositis, Crohn's disease, ulcerative colitis, cytopenia, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), allergic rhinitis, allergic sinusitis, interstitial pulmonary disease, idiopathic interstitial
5 pneumonia, chronic obstructive pulmonary disease (COPD), combined pulmonary fibrosis and emphysema (CPFE), adult respiratory distress syndrome (ARDS), psoriasis, rheumatoid arthritis, mastocytosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous vasculitis, skin
10 inflammation/diseases, urticaria, and allergic contact dermatitis.
[0203]

Examples of the cancer to which the compound of the present invention or a pharmaceutically acceptable salt thereof
15 can be applied may include acute myelogenous leukemia (AML), hypereosinophilic syndrome, T-lymphoblastic leukemia, chronic myelomonocytic leukemia (CMML), chronic myelogenous leukemia (CML), chronic eosinophilic leukemia, bone marrow fibrosis, dermatofibrosarcoma protuberans, glioma, ovarian cancer,
20 endometrial tumor, hepatocellular cancer, thyroid cancer, small cell lung cancer, non-small cell lung cancer, renal cancer, soft tissue sarcoma, neuroendocrine tumor, skin cancer, mesothelioma, bile duct cancer, head and neck squamous cell cancer, large bowel cancer, mesenchymoma, adenocarcinoma, pancreatic cancer,
25 mastocytosis, and gastrointestinal stromal tumor (GIST).
[0204]

Examples of the smooth muscle proliferative disease to which the compound of the present invention or a pharmaceutically acceptable salt thereof can be applied may include vascular
30 restenosis, atherosclerosis/arteriosclerosis obliterans, moyamoya disease (idiopathic occlusion of the circle of Willis), leiomyoma, lymphangioma, lymphangioleiomyomatosis, Williams' syndrome, tuberous sclerosis, angina pectoris, myocardial infarction, peripheral arterial disease, hypertrophic/dilated cardiomyopathy
35 cardiomyopathy, and constrictive/diastolic cardiomyopathy.

[0205]

Examples of the vasoproliferative disease to which the compound of the present invention or a pharmaceutically acceptable salt thereof can be applied may include age-related
5 macular degeneration (AMD), Osler's disease (hereditary hemorrhagic telangiectasia), hemangioma, tumor angiogenesis, and arteriovenous fistula.

[0206]

Examples of the metabolic disease to which the compound
10 of the present invention or a pharmaceutically acceptable salt thereof can be applied may include diabetes mellitus (type 1 diabetes mellitus or type 2 diabetes mellitus).

[0207]

The compound of the present invention can be used as a
15 therapeutic agent for a variety of diseases as described above in mammals such as human, mouse, rat, rabbit, dog, cat, cow, horse, pig, and monkey, as it is or as a pharmaceutical composition containing the same at, for example, 0.001% to 99.5%, preferably 0.1% to 90%, obtained by mixing the compound with a
20 pharmacologically acceptable carrier or the like.

[0208]

Although it is desirable to adjust the dose as a medicament in consideration of the conditions of the patient such as age, weight, and type and severity of disease, administration
25 route, type of the compound of the present invention, whether it is a salt or not, and the type of the salt, normally, it is appropriate that the effective amount of the compound of the present invention or a pharmaceutically acceptable salt thereof for adults, in the case of oral administration, should be within
30 the range of 0.01 mg to 5 g/adult, preferably within the range of 1 mg to 500 mg/adult, per day. In some cases, a smaller amount may be sufficient or a larger amount may be required. Normally, the dosage can be administered once a day or can be divided and administered several times a day, or in the case of intravenous
35 administration, the dosage can be administered rapidly or

persistently within 24 hours.

[0209]

One or more hydrogen, carbon, and/or other atoms in the compound of the present invention may each be replaced with an isotope of hydrogen, carbon, and/or other atoms. Examples of such an isotope include ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I , and ^{36}Cl , that is, hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine and chlorine. The compound substituted with such an isotope is also useful as a medical product and the present invention encompasses all radiolabeled products of the compound of the present invention.

[0210]

Hereinafter, the present invention will be described in further detail with reference to Comparative Examples, Examples, and Test Examples; however, the present invention is not limited to those examples.

Examples

[0211]

In Examples, the following abbreviations will be used.

TFA: Trifluoroacetic acid

Pd-C: Palladium-carbon

$\text{Pd}_2(\text{dba})_3$: Tris(dibenzylideneacetone)bispalladium

$\text{Pd}(\text{PPh}_3)_4$: Tetrakis(triphenylphosphine)palladium

$\text{PdCl}_2(\text{PPh}_3)_2$: Bis(triphenylphosphine)palladium(II) dichloride

$\text{Pd}(\text{OAc})_2$: Palladium(II) acetate

Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

PPh_3 : Triphenylphosphine

Boc_2O : Di-tert-butyl dicarbonate

HATU: O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HBTU: O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

THF: Tetrahydrofuran

DME: Dimethoxyethane

DMF: Dimethylformamide

DMSO: Dimethylsulfoxide

NMP: N-Methylpyrrolidone

5 DIPEA: N,N-Diisopropylethylamine

TEA: Triethylamine

BH₃-THF: Borane-tetrahydrofuran complex

CDCl₃: Deuterated chloroform

TLC: Thin layer chromatography

10 MS: Mass spectrometry

LCMS: High performance liquid chromatography-mass spectrometry

ESI: Electron Spray Ionization

M: Molar concentration (mol/L)

[0212]

15 MS was measured with LCMS. ESI was used as a method for ionization. Observed values of the mass spectrometry are expressed as m/z.

[0213]

The measurement conditions for LCMS were as follows:

20 Analytical instrument: ACQUITY UPLC MS/PDA system (manufactured by Waters Corporation);

Mass spectrometer: Waters 3100 MS detector;

Photodiode array detector: ACQUITY PDA detector (UV detection wavelength: 210 to 400 nm);

25 Column: Acquity BEH C18, 1.7 μ m, 2.1 $\times$ 50 mm;

Flow rate: 0.5 mL/min;

Column temperature: 40°C;

Solvent;

solution A: 0.1% formic acid/H₂O (v/v; the same hereinafter)

30 solution B: 0.1% formic acid/acetonitrile.

[0214]

The ¹H NMR spectrum was measured by using JNM-ECS400 Nuclear Magnetic Resonance Spectrometer (manufactured by JEOL RESONANCE Inc.). The observed peaks were expressed as chemical shift values δ (ppm) (s = singlet, d = doublet, t = triplet, q =

35

quartet, brs = broad singlet, m = multiplet, dd = double doublet, ddd= double double doublet, and dt = double triplet).

[0215]

In the microwave experiment, Initiator 60 (manufactured by Biotage AB) was used. This can achieve a temperature of 40 to 250°C and can reach a pressure up to 20 bar.

[0216]

The names of compounds in the present specification are given by using a naming software, ACD/NAME (registered trademark, Advanced Chemistry Development Inc.) conforming to the rules of IUPAC, by using ChemBioDraw (version 14.0, manufactured by Cambridge Soft Corporation), or in accordance with the rules of IUPAC nomenclature.

[0217]

In the names of compounds, the descriptors "r" and "s" (lower case) refer to the stereochemistry of pseudoasymmetric carbon atom according the IUPAC rules.

[0218]

Reference Example 1: 5-[(Cyclopropylmethyl)amino]pyridine-3-carboxylic acid

[Step 1] Production of methyl 5-

[(cyclopropylmethyl)amino]pyridine-3-carboxylate

To methyl 5-bromopyridine-3-carboxylate (15.0 g), 1-cyclopropylmethanamine (9.9 g), BINAP (8.6 g), cesium carbonate (45.2 g), and Pd(OAc)₂ (1.6 g), 1,4-dioxane (139 mL) was added. After degassing, the reaction mixture was stirred under argon atmosphere at 80°C overnight. Insolubles were filtered off using celite (R) and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (8.4 g). MS (m/z): 207.2 [M+H]⁺

[Step 2] Production of 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylic acid

To a solution of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate (8.4 g) obtained

in Step 1 in THF (81 mL) and methanol (81 mL), lithium hydroxide monohydrate (3.4 g) and water (81 mL) were added, and the reaction mixture was stirred at room temperature overnight. The solvent was distilled off under reduced pressure. The reaction mixture was diluted with water and then neutralized by adding 1M hydrochloric acid. The precipitated deposits were collected by filtration to afford the title compound (6.8 g). MS (m/z): 193.2 [M+H]⁺

Reference Example 2: 5-[Cyclopropyl(methyl)amino]pyridine-3-carboxylic acid

[Step 1] Production of methyl 5-[cyclopropyl(methyl)amino]pyridine-3-carboxylate

By using N-methylcyclopropanamine (9.9 g) instead of 1-cyclopropylmethanamine, the title compound (6.6 g) was obtained by the method as described in Step 1 of Reference Example 1. MS (m/z): 207.4 [M+H]⁺

[Step 2] Production of 5-[cyclopropyl(methyl)amino]pyridine-3-carboxylic acid

By using methyl 5-[cyclopropyl(methyl)amino]pyridine-3-carboxylate (6.6 g) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (4.3 g) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 193.4 [M+H]⁺

Reference Example 3: 5-[(3,3-Difluorocyclobutyl)oxy]pyridine-3-carboxylic acid

[Step 1] Production of methyl 5-[(3,3-difluorocyclobutyl)oxy]pyridine-3-carboxylate

To a solution of methyl 5-hydroxypyridine-3-carboxylate (250 mg), 3,3-difluorocyclobutan-1-ol (212 mg), and PPh₃ (599 mg) in THF (4.1 mL), diisopropyl azodicarboxylate (40% solution in toluene, 1.12 mL) was added, and the reaction mixture was stirred at 60°C for 2 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (170 mg).

MS (m/z): 244.4 [M+H]⁺

[Step 2] Production of 5-[(3,3-difluorocyclobutyl)oxy]pyridine-3-carboxylic acid

By using methyl 5-[(3,3-difluorocyclobutyl)oxy]pyridine-3-carboxylate (170 mg) obtained
5 in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (84 mg) was obtained by the method as described in Step 2 of Reference Example 1.

Reference Example 4: 5-[(4,4-Difluorocyclohexyl)oxy]pyridine-3-carboxylic acid

10 [Step 1] Production of methyl 5-[(4,4-difluorocyclohexyl)oxy]pyridine-3-carboxylate

By using 4,4-difluorocyclohexan-1-ol instead of 3,3-difluorocyclobutan-1-ol, the title compound (450 mg) was obtained by the method as described in Step 1 of Reference Example 3. MS
15 (m/z): 272.2 [M+H]⁺

[Step 2] Production of 5-[(4,4-difluorocyclohexyl)oxy]pyridine-3-carboxylic acid

By using methyl 5-[(4,4-difluorocyclohexyl)oxy]pyridine-3-carboxylate (450 mg) obtained
20 in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (350 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 258.2 [M+H]⁺

Reference Example 5: 5-[(1-Methylcyclopropyl)methoxy]pyridine-3-carboxylic acid
25

[Step 1] Production of methyl 5-[(1-methylcyclopropyl)methoxy]pyridine-3-carboxylate

By using (1-methylcyclopropyl)methanol (500 mg) instead of 3,3-difluorocyclobutan-1-ol, the title compound (540 mg) was
30 obtained by the method as described in Step 1 of Reference Example 3. MS (m/z): 222.1 [M+H]⁺

[Step 2] Production of 5-[(1-methylcyclopropyl)methoxy]pyridine-3-carboxylic acid

By using methyl 5-[(1-methylcyclopropyl)methoxy]pyridine-3-carboxylate (540 mg)
35

obtained in Step 1 instead of methyl 5-

[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (340 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 208.2 [M+H]⁺

5 [0219]

Reference Example 6: 5-[(3,3-Difluorocyclobutyl)methoxy]pyridine-3-carboxylic acid

[Step 1] Production of methyl 5-[(3,3-difluorocyclobutyl)methoxy]pyridine-3-carboxylate

10 By using (3,3-difluorocyclobutyl)methanol (500 mg) instead of 3,3-difluorocyclobutan-1-ol, the title compound (1.10 g) was obtained by the method as described in Step 1 of Reference Example 3. MS (m/z): 258.1 [M+H]⁺

[Step 2] Production of 5-[(3,3-difluorocyclobutyl)methoxy]pyridine-3-carboxylic acid

15 By using methyl 5-[(3,3-difluorocyclobutyl)methoxy]pyridine-3-carboxylate (1.10 g) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (580 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 244.2 [M+H]⁺

Reference Example 7: 3-Amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

To a suspension of 3-amino-4-methylbenzoic acid (5.00 g), (1S,2S)-2-aminocyclohexan-1-ol hydrochloride (5.52 g), and HBTU (15.1 g) in THF (165 mL), DIPEA (17.2 mL) was added, and the reaction mixture was stirred at room temperature for 2 hours. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was then distilled off under reduced pressure. Ethyl acetate was added to the obtained residue to suspend it, and the deposits were collected by filtration to afford the title compound (6.10 g). MS

25
30
35 (m/z): 249.2 [M+H]⁺

Reference Example 8: Methyl 4-chloro-3-ethynylbenzoate

[Step 1] Production of methyl 4-chloro-3-
[(trimethylsilyl)ethynyl]benzoate

To methyl 4-chloro-3-iodobenzoate (8.15 g),
5 ethynyl(trimethyl)silane (2.78 g), copper iodide (570 mg),
Pd(PPh₃)₄ (3.18 g), and TEA (55 mL), THF (27.5 mL) was added.
After degassing, the reaction mixture was stirred under argon
atmosphere at 45°C overnight. Insolubles were filtered off using
celite (R) and the solvent was then distilled off under reduced
10 pressure. The residue was purified by silica gel column
chromatography to afford the title compound (6.8 g).

[Step 2] Production of methyl 4-chloro-3-ethynylbenzoate

Methyl 4-chloro-3-[(trimethylsilyl)ethynyl]benzoate
(6.8 g) obtained in Step 1 was dissolved in THF (85 mL), TBAF (1M
15 THF solution, 31 mL) was added thereto, and the reaction mixture
was stirred at room temperature for 30 minutes. The reaction
solution was concentrated under reduced pressure, and the
obtained residue was purified by silica gel column chromatography
to afford the title compound (2.6 g).

20 Reference Example 9: 3-Ethynyl-N-[(1S,2S)-2-hydroxycyclohexyl]-4-
methylbenzamide

By using 3-ethynyl-4-methylbenzoic acid (500 mg)
instead of 3-amino-4-methylbenzoic acid, the title compound (570
mg) was obtained by the method as described in Reference Example
25 7. MS (m/z): 258.2 [M+H]⁺

Reference Example 10: 2-(5-Ethynylpyridin-3-yl)pyrimidine

[Step 1] Production of 2-[5-(methoxymethoxy)pyridin-3-
yl]pyrimidine

To 3-bromo-5-(methoxymethoxy)pyridine (4.0 g),
30 bis(pinacolato)diboron (5.6 g), potassium acetate (3.6 g), and
Pd(dppf)Cl₂·CH₂Cl₂ (1.5 g), 1,4-dioxane (73 mL) was added. After
degassing, the reaction mixture was stirred under argon
atmosphere at 80°C for 2.5 hours. Then, 2-bromopyrimidine (3.5
g), potassium carbonate (5.1 g), and water (0.5 mL) were added
35 thereto, and the reaction mixture was stirred at 85°C overnight.

The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography to afford the title compound (3.6 g). MS (m/z): 218.4 [M+H]⁺

[Step 2] Production of 5-(pyrimidin-2-yl)pyridin-3-ol

2-[5-(Methoxymethoxy)pyridin-3-yl]pyrimidine (4.11 g) obtained in Step 1 was dissolved in THF (38 mL), 35% hydrochloric acid (1.4 mL) was added thereto, and the reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure. Aqueous sodium bicarbonate solution was added to the obtained residue to neutralize it. The resulting deposits were collected by filtration to afford the title compound (2.51 g). MS (m/z): 174.4 [M+H]⁺

[Step 3] Production of 5-(pyrimidin-2-yl)pyridin-3-yl trifluoromethanesulfonate

To a solution of 5-(pyrimidin-2-yl)pyridin-3-ol (2.00 g) obtained in Step 2 and TEA (2.10 mL) in dichloromethane (38 mL), trifluoromethanesulfonic anhydride (2.27 mL) was added dropwise under ice cooling, and the reaction mixture was stirred at the same temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (770 mg). MS (m/z): 306.4 [M+H]⁺

[Step 4] Production of 2-{5-[(trimethylsilyl)ethynyl]pyridin-3-yl}pyrimidine

By using 5-(pyrimidin-2-yl)pyridin-3-yl trifluoromethanesulfonate (770 mg) obtained in Step 3 instead of methyl 4-chloro-3-iodobenzoate, the title compound (570 mg) was obtained by the method as described in Step 1 of Reference Example 8. MS (m/z): 254.5 [M+H]⁺

[Step 5] Production of 2-(5-ethynylpyridin-3-yl)pyrimidine

By using 2-{5-[(trimethylsilyl)ethynyl]pyridin-3-yl}pyrimidine (570 mg) obtained in Step 4 instead of methyl 4-

chloro-3-[(trimethylsilyl)ethynyl]benzoate, the title compound (350 mg) was obtained by the method as described in Step 2 of Reference Example 8. MS (m/z): 182.4 [M+H]⁺ [0220]

5 Reference Example 11: 3-Bromo-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

By using 3-bromo-4-chlorobenzoic acid (250 mg) instead of 3-amino-4-methylbenzoic acid, the title compound (315 mg) was obtained by the method as described in Reference Example 7. MS (m/z): 332.4 [M+H]⁺

10 Reference Example 12: 6-Bromo-N-(cyclopropylmethyl)pyrazin-2-amine

To a solution of 2,6-dibromopyrazine (500 mg) in DMF (1 mL), 1-cyclopropylmethanamine (449 mg) and potassium carbonate (871 mg) were added, and the reaction mixture was sealed in a pressure resistant stainless steel container and stirred at 120°C for 8 hours. The reaction solution was diluted with ethyl acetate. After washing it with water and saturated saline solution, the solvent was distilled off under reduced pressure.

15 The obtained residue was purified by silica gel column chromatography to afford the title compound (400 mg).

Reference Example 13: 5-Ethynyl-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

[Step 1] Production of 5-bromo-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

25 By using 5-bromo-6-methylpyridine-3-carboxylic acid (250 mg) instead of 3-amino-4-methylbenzoic acid, the title compound (380 mg) was obtained by the method as described in Reference Example 7. MS (m/z): 313.4 [M+H]⁺

30 [Step 2] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-6-methyl-5-[(trimethylsilyl)ethynyl]pyridine-3-carboxamide

By using 5-bromo-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide (100 mg) obtained in Step 1 instead of methyl 4-chloro-3-iodobenzoate, the title compound (40 mg) was obtained by the method as described in Step 1 of Reference

35

Example 8. MS (m/z): 331.5 [M+H]⁺

[Step 3] Production of 5-ethynyl-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

By using N-[(1S,2S)-2-hydroxycyclohexyl]-6-methyl-5-
5 [(trimethylsilyl)ethynyl]pyridine-3-carboxamide (40 mg) obtained in Step 2 instead of methyl 4-chloro-3-[(trimethylsilyl)ethynyl]benzoate, the title compound (23 mg) was obtained by the method as described in Step 2 of Reference

Example 8. MS (m/z): 259.5 [M+H]⁺

10 Reference Example 14: 2-(Isoquinolin-4-yl)pyrimidin-4-amine

To 2-chloropyrimidin-4-amine (200 mg), isoquinolin-4-ylboronic acid (294 mg), 1M aqueous sodium carbonate solution (3.1 mL), and Pd(dppf)Cl₂·CH₂Cl₂ (126 mg), 1,4-dioxane (5 mL) was added. After degassing and replacing with argon, the reaction
15 mixture was stirred under argon atmosphere at 90°C for 2 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (300 mg).

Reference Example 15: (1S)-1-(5-Phenylpyridin-3-yl)ethan-1-amine

20 By using (1S)-1-(5-bromopyridin-3-yl)ethan-1-amine hydrochloride (300 mg) and phenylboronic acid (185 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (280 mg) was obtained by the method as described in Reference Example 14. MS (m/z): 199.2 [M+H]⁺

25 [0221]

Reference Example 16: (1S)-1-([3,3'-Bipyridin]-5-yl)ethan-1-amine

[Step 1] Production of (SS)-N-[(1E)-1-(5-bromopyridin-3-yl)ethylidene]-2-methylpropane-2-sulfinamide

1-(5-Bromopyridin-3-yl)ethan-1-one (25 g) and (SS)-2-
30 methylpropane-2-sulfinamide (18.2 g) were dissolved in THF (500 mL), tetraethyl orthotitanate (57 g) was added thereto, and the reaction mixture was stirred at 65°C overnight. The reaction solution was diluted with ethyl acetate, and water was added thereto. The reaction solution was filtered through celite (R),
35 and the solvent was distilled off under reduced pressure. The

residue was purified by silica gel column chromatography to afford the title compound (34 g). MS (m/z): 303.0 [M+H]⁺

[Step 2] Production of (SS)-N-[(1S)-1-(5-bromopyridin-3-yl)ethyl]-2-methylpropane-2-sulfinamide

5 A suspension of dichloro(p-cymene)ruthenium(II) dimer (6.86 g), 2-amino-2-methyl-1-propanol (2.14 mL), and Molecular Sieve 4A (34 g) in 2-propanol (560 mL) was stirred under argon atmosphere at 80°C for 30 minutes. Then, while stirring the reaction solution at 50°C, a solution of (SS)-N-[(1E)-1-(5-bromopyridin-3-yl)ethylidene]-2-methylpropane-2-sulfinamide (34
10 g) obtained in Step 1 in 2-propanol (9 mL) and potassium tert-butoxide (6.29 g) were added thereto, and the reaction mixture was stirred at the same temperature for 6 hours. The reaction solution was filtered through celite (R), and the solvent was
15 distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (24.2 g). MS (m/z): 305.1 [M+H]⁺

[Step 3] Production of (SS)-N-[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]-2-methylpropane-2-sulfinamide

20 By using (SS)-N-[(1S)-1-(5-bromopyridin-3-yl)ethyl]-2-methylpropane-2-sulfinamide (23.2 g) obtained in Step 2 and pyridin-3-ylboronic acid (11.2 g) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (22.7 g) was obtained by the method as described in Reference Example
25 14. MS (m/z): 304.2 [M+H]⁺

[Step 4] Production of (1S)-1-([3,3'-bipyridin]-5-yl)ethan-1-amine

 To a solution of (SS)-N-[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]-2-methylpropane-2-sulfinamide (22.7 g) obtained in Step
30 3 in methanol (150 mL), hydrogen chloride (2M methanol solution, 5.46 mL) was added under ice cooling, and the reaction mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by column chromatography using
35 amino modified spherical silica gel to afford the title compound

(12.9 g). MS (m/z): 200.2 [M+H]⁺

Reference Example 17: (1S)-1-[5-(Phenylethynyl)pyridin-3-yl]ethan-1-amine dihydrochloride

[Step 1] Production of (SS)-2-methyl-N-{(1S)-1-[5-

5 (phenylethynyl)pyridin-3-yl]ethyl}propane-2-sulfinamide

By using (SS)-N-[(1S)-1-(5-bromopyridin-3-yl)ethyl]-2-methylpropane-2-sulfinamide (500 mg) obtained in Step 2 of Reference Example 16 and ethynylbenzene (335 mg) instead of methyl 4-chloro-3-iodobenzoate and ethynyl(trimethyl)silane, the
10 title compound (530 mg) was obtained by the method as described in Step 1 of Reference Example 8. MS (m/z): 327.2 [M+H]⁺

[Step 2]: Production of (1S)-1-[5-(phenylethynyl)pyridin-3-yl]ethan-1-amine dihydrochloride

To a solution of (SS)-2-methyl-N-{(1S)-1-[5-
15 (phenylethynyl)pyridin-3-yl]ethyl}propane-2-sulfinamide (530 mg) obtained in Step 1 in methanol (8.1 mL), hydrogen chloride (2M methanol solution, 0.18 mL) was added under ice cooling, and the reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and
20 ethyl acetate was added to the obtained residue to suspend it. The deposits were collected by filtration to afford the title compound (500 mg). MS (m/z): 223.2 [M+H]⁺

Reference Example 18: (1S)-1-[5-(Pyrimidin-2-yl)pyridin-3-yl]ethan-1-amine

25 [Step 1] Production of (SS)-2-methyl-N-{(1S)-1-[5-(pyrimidin-2-yl)pyridin-3-yl]ethyl}propane-2-sulfinamide

By using (SS)-N-[(1S)-1-(5-bromopyridin-3-yl)ethyl]-2-methylpropane-2-sulfinamide (600 mg) obtained in Step 2 of Reference Example 16 instead of 3-bromo-5-

30 (methoxymethoxy)pyridine, the title compound (420 mg) was obtained by the method as described in Step 1 of Reference Example 10. MS (m/z): 305.4 [M+H]⁺

[Step 2]: Production of (1S)-1-[5-(pyrimidine-2-yl)pyridin-3-yl]ethan-1-amine

35 By using (SS)-2-methyl-N-{(1S)-1-[5-(pyrimidin-2-

yl)pyridin-3-yl]ethyl}propane-2-sulfinamide (420 mg) obtained in Step 1 instead of (SS)-N-[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]-2-methylpropane-2-sulfinamide, the title compound (200 mg) was obtained by the method as described in Step 4 of Reference

5 Example 16. MS (m/z): 201.3 [M+H]⁺

Reference Example 19: Pyrazolo[5,1-b][1,3]thiazole-7-carbaldehyde [Step 1] Production of (pyrazolo[5,1-b][1,3]thiazol-7-yl)methanol

To a solution of pyrazolo[5,1-b][1,3]thiazole-7-carboxylic acid (100 mg) in THF (2 mL), lithium aluminum hydride
10 (1M hexane solution, 1.5 mL) was added, and the reaction mixture was stirred at 50°C for 5 hours. To the reaction solution, methanol and potassium sodium L-(+)-tartrate tetrahydrate were added at 0°C, and the reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated
15 under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (57 mg). MS (m/z): 155.3 [M+H]⁺

[Step 2] Production of pyrazolo[5,1-b][1,3]thiazole-7-carbaldehyde

20 To a solution of (pyrazolo[5,1-b][1,3]thiazol-7-yl)methanol (57 mg) obtained in Step 1 in THF (1.2 mL), manganese dioxide (160 mg) was added, and the reaction mixture was stirred at room temperature overnight. After filtering the reaction solution to remove insolubles, the filtrate was concentrated
25 under reduced pressure to afford to the title compound (42 mg).

Reference Example 20: 5-Amino-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

By using 5-amino-6-methylpyridine-3-carboxylic acid (915 mg) instead of 3-amino-4-methylbenzoic acid, the title compound (1.17
30 g) was obtained by the method as described in Reference Example 7. MS (m/z): 250.2 [M+H]⁺

[0222]

Reference Example 21: N-(5-Formylpyridin-2-yl)morpholine-4-carboxamide

35 [Step 1] Production of phenyl (5-formylpyridin-2-yl)carbamate

To a solution of 6-aminopyridine-3-carbaldehyde (250 mg) in THF (5.1 mL), TEA (0.57 mL) and phenyl chloroformate (304 mg) were added, and the reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (246 mg). MS (m/z): 243.2 [M+H]⁺

[Step 2] Production of N-(5-formylpyridin-2-yl)morpholine-4-carboxamide

To a solution of phenyl (5-formylpyridin-2-yl)carbamate (40 mg) obtained in Step 1 in NMP (0.34 mL), morpholine (43 mg) and TEA (0.072 mL) were added, and the reaction mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (246 mg). MS (m/z): 236.1 [M+H]⁺

Reference Example 22: N-Cyclopropyl-N'-(5-formylpyridin-2-yl)-N-methylurea

By using N-methylcyclopropanamine (94 mg) instead of morpholine, the title compound (21 mg) was obtained by the method as described in Step 2 of Reference Example 21. MS (m/z): 220.1 [M+H]⁺

Reference Example 23: tert-Butyl 7-formyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate

[Step 1] Production of tert-butyl 7-bromo-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate

To a solution of 7-bromo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (160 mg) in THF (2.5 mL), TEA (0.01 mL), Boc₂O (0.19 mL), and DMAP (4.5 mg) were added, and the reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (177 mg). MS (m/z): 315.1 [M+H]⁺

[Step 2] Production of tert-butyl 7-ethenyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate

By using tert-butyl 7-bromo-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate (177 mg) obtained in Step 1 and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (172 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (118 mg) was obtained by the method as described in Reference Example 14. MS (m/z): 263.2 [M+H]⁺
[Step 3] Production of tert-butyl 7-formyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate

In a solution of tert-butyl 7-ethenyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate (118 mg) obtained in Step 2 in dichloromethane (2 mL), bubbling with O₃ was carried out at -78°C over 30 minutes. Then, argon gas was bubbled into the solution until it became colorless. Triphenylphosphine (142 mg) was added thereto, and the reaction mixture was stirred at room temperature overnight. Water was added to the reaction solution, and the reaction mixture was extracted with dichloromethane. After drying the organic layer over anhydrous sodium sulfate, the solvent was removed under reduced pressure to afford the title compound as a crude product.

Reference Example 24: 6-(1H-1,2,3-Triazol-1-yl)pyridine-3-carbaldehyde
[Step 1] Production of 5-ethenyl-2-(1H-1,2,3-triazol-1-yl)pyridine

By using 5-bromo-2-(1H-1,2,3-triazol-1-yl)pyridine (142 mg) (for example, synthesized by the method as described in WO 2006/038100) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (117 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (90 mg) was obtained by the method as described in Reference Example 14. MS (m/z): 173.1 [M+H]⁺
[Step 2] Production of 6-(1H-1,2,3-triazol-1-yl)pyridine-3-carbaldehyde

By using 5-ethenyl-2-(1H-1,2,3-triazol-1-yl)pyridine (90 mg) obtained in Step 1 instead of tert-butyl 7-ethenyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate, the title

compound (306 mg) was obtained as a crude product by the method as described in Step 3 of Reference Example 23. MS (m/z): 175.1 [M+H]⁺

Reference Example 25: 5-(2H-1,2,3-Triazol-2-yl)pyridine-3-carbaldehyde

[Step 1] Production of [5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl]methanol

To a solution of methyl 5-(2H-1,2,3-triazol-2-yl)pyridine-3-carboxylate (44 mg) (for example, synthesized by the method as described in Angew. Chem. Int. Ed. 2011, 50, 8944-8947.) in methanol (2.2 mL), sodium borohydride (41 mg) was added, and the reaction mixture was stirred at room temperature overnight. Water was added to the reaction solution, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound.

[Step 2] Production of 5-(2H-1,2,3-triazol-2-yl)pyridine-3-carbaldehyde

By using [5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl]methanol obtained in Step 1 instead of pyrazolo[5,1-b][1,3]thiazol-7-yl)methanol, the title compound (22 mg) was obtained by the method as described in Step 2 of Reference Example 19.

[0223]

Reference Example 26: 3-Formyl-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-formyl-4-methylbenzoic acid (100 mg) instead of 3-amino-4-methylbenzoic acid, the title compound (134 mg) was obtained by the method as described in Reference Example 7. MS (m/z): 262.5 [M+H]⁺

Reference Example 27: 5-(Pyrimidin-2-yl)pyridin-3-amine dihydrochloride

[Step 1] Production of di-tert-butyl (5-bromopyridin-3-yl)-2-imidodicarbonate

By using 5-bromopyridin-3-amine (25.0 g) instead of 7-

bromo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine, the title compound (40.0 g) was obtained by the method as described in Step 1 of Reference Example 23. MS (m/z): 373.4 [M+H]⁺

[Step 2] Production of di-tert-butyl [5-(pyrimidin-2-yl)pyridin-3-yl]-2-imidodicarbonate

By using di-tert-butyl (5-bromopyridin-3-yl)-2-imidodicarbonate (30.0 g) obtained in Step 1 instead of 3-bromo-5-(methoxymethoxy)pyridine, the title compound (14.3 g) was obtained by the method as described in Step 1 of Reference

Example 10. MS (m/z): 373.5 [M+H]⁺

[Step 3] Production of 5-(pyrimidin-2-yl)pyridin-3-amine dihydrochloride

To a solution of di-tert-butyl [5-(pyrimidin-2-yl)pyridin-3-yl]-2-imidodicarbonate (14.3 g) obtained in Step 2 in ethanol (128 mL), hydrogen chloride (4M ethyl acetate solution, 14 mL) was added, and the reaction mixture was stirred at 60°C for 3 hours. The reaction solution was concentrated under reduced pressure, and the residue was suspended in ethyl acetate to collect the deposits by filtration. The deposits were washed with ethyl acetate and then dried to afford the title compound (3.5 g). MS (m/z): 173.4 [M+H]⁺

Reference Example 28: 3-Formyl-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

By using 3-formylbenzoic acid (500 mg) instead of 3-amino-4-methylbenzoic acid, the title compound (590 mg) was obtained by the method as described in Reference Example 7. MS (m/z): 248.5 [M+H]⁺

Reference Example 29: 4-Fluoro-3-formyl-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

By using 4-fluoro-3-formylbenzoic acid (300 mg) instead of 3-amino-4-methylbenzoic acid, the title compound (300 mg) was obtained by the method as described in Reference Example 7. MS (m/z): 266.5 [M+H]⁺

Reference Example 30: 5-Formyl-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

[Step 1] Production of 5-ethenyl-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

By using 5-bromo-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide (750 mg) obtained in Step 1 of Reference Example 13 and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (479 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (614 mg) was obtained by the method as described in Reference Example 14. MS (m/z): 261.2 [M+H]⁺

[Step 2] Production of 5-formyl-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

By using 5-ethenyl-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide (614 mg) obtained in Step 1 instead of tert-butyl 7-ethenyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate, the title compound (360 mg) was obtained by the method as described in Step 3 of Reference Example 23. MS (m/z): 263.2 [M+H]⁺
[0224]

Reference Example 31: Methyl 4-chloro-3-(hydroxymethyl)benzoate

To a solution of methyl 4-chloro-3-formylbenzoate (200 mg) in methanol (3.4 mL) and THF (3.4 mL), sodium borohydride (38 mg) was added at 0°C, and the reaction mixture was stirred at room temperature overnight. Water was added to the reaction solution, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (130 mg).

Reference Example 32: Methyl 3-[(ethylamino)methyl]-4-methylbenzoate

To a solution of methyl 3-formyl-4-methylbenzoate (500 mg) in methanol (11 mL), ethylamine (2M methanol solution, 2.8 mL) was added, and the reaction mixture was stirred at room temperature for 30 minutes. Then, sodium borohydride (159 mg) was added thereto, and the reaction mixture was stirred at room temperature for 2 hours. Water was added to the reaction solution, and the solvent was distilled off under reduced

pressure. The residue was purified by silica gel column chromatography to afford the title compound (423 mg). MS (m/z): 208.2 [M+H]⁺

Reference Example 33: Ethyl 5-formyl-6-methylpyridine-3-carboxylate

[Step 1] Production of ethyl 5-ethenyl-6-methylpyridine-3-carboxylate

By using ethyl 5-bromo-6-methylpyridine-3-carboxylate (4.2 g) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.7 g) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (3.0 g) was obtained by the method as described in Reference Example 14. MS (m/z): 192.1 [M+H]⁺

[Step 2] Production of ethyl 5-formyl-6-methylpyridine-3-carboxylate

By using ethyl 5-ethenyl-6-methylpyridine-3-carboxylate (3.0 g) obtained in Step 1 instead of tert-butyl 7-ethenyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate, the title compound (2.7 g) was obtained by the method as described in Step 3 of Reference Example 23. MS (m/z): 194.1 [M+H]⁺

Reference Example 34: 1-[(5-Bromopyridin-3-yl)methyl]-4-methylpiperazine

To a solution of 5-bromopyridine-3-carbaldehyde (500 mg) in dichloromethane (11 mL), acetic acid (0.15 mL) and 1-methylpiperazine (808 mg) were added, and the reaction mixture was stirred at room temperature for 1 hour. Then, sodium triacetoxyborohydride (1.14 g) was added thereto, and the reaction mixture was stirred at room temperature for 2 hours. Water was added to the reaction solution, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (700 mg). MS (m/z): 270.1 [M+H]⁺

Reference Example 35: 4-[(5-Bromopyridin-3-yl)methyl]morpholine

By using morpholine (703 mg) instead of 1-methylpiperazine, the title compound (570 mg) was obtained by the

method as described in Reference Example 34. MS (m/z): 257.1
[M+H]⁺
[0225]

Reference Example 36: 5-Bromo-N-(oxan-4-yl)pyridin-3-amine

5 By using 3,5-dibromopyridine and oxan-4-amine (256 mg) instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (230 mg) was obtained by the method as described in Step 1 of Reference Example 1. MS (m/z): 257.0 [M+H]⁺

10 Reference Example 37: 5-Bromo-N-(1-methylpiperidin-4-yl)pyridin-3-amine

By using 3,5-dibromopyridine and 1-methylpiperidin-4-amine (304 mg) instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (300 mg) was
15 obtained by the method as described in Step 1 of Reference Example 1. MS (m/z): 270.1 [M+H]⁺

Reference Example 38: 1-[(5-Bromopyridin-3-yl)methyl]-4-ethylpiperazine

By using 1-ethylpiperazine (921 mg) instead of 1-methylpiperazine, the title compound (680 mg) was obtained by the method as described in Reference Example 34. MS (m/z): 284.1
20 [M+H]⁺

Reference Example 39: 5-Bromo-N-(oxetan-3-yl)pyridin-3-amine

By using 3,5-dibromopyridine (1.00 g) and oxetan-3-amine (309 mg) instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (410 mg) was
25 obtained by the method as described in Step 1 of Reference Example 1. MS (m/z): 229.3 [M+H]⁺

Reference Example 40: Di-tert-butyl 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl-2-imidodicarbonate

[Step 1] Production of benzyl 2-[bis(tert-butoxycarbonyl)amino]-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

By using benzyl 2-amino-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (600 mg) instead of 7-bromo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine, the title compound (960 mg)
35

was obtained by the method as described in Step 1 of Reference Example 23.

[Step 2] Production of di-tert-butyl 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl-2-imidodicarbonate

5 To a solution of benzyl 2-[bis(tert-butoxycarbonyl)amino]-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (960 mg) obtained in Step 1 in methanol (100 mL), after degassing, 5% Pd-C (400 mg) was added under argon atmosphere while stirring the solution at room temperature. The
10 reaction mixture was stirred under hydrogen atmosphere at room temperature for 4 hours. The reaction solution was filtered through celite (R), and then the solvent was distilled off under reduced pressure to afford the title compound (700 mg).
[0226]

15 Reference Example 41: 3-Amino-N-[(1S,2S)-2-{[tert-butyl(dimethyl)silyl]oxy}cyclohexyl]-4-methylbenzamide

 To a solution of 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (800 mg) obtained in Reference Example 7 in dichloromethane (16 mL), tert-
20 butyldimethylsilyl triflate (1.11 g) and 2,6-lutidine (690 mg) were added, and the reaction mixture was stirred at room temperature overnight. The reaction solution was diluted with ethyl acetate. After washing it with water and saturated saline solution, the solvent was distilled off under reduced pressure.
25 The obtained residue was purified by silica gel column chromatography to afford the title compound (661 mg). MS (m/z): 363.3 [M+H]⁺

Reference Example 42: Methyl 3-(aminomethyl)-4-methylbenzoate
[Step 1] Production of methyl 3-(hydroxyimino)methyl-4-methylbenzoate
30 methylbenzoate

 To a solution of methyl 3-formyl-4-methylbenzoate (1.00 g) in methanol (20 mL), 50% aqueous hydroxylamine solution (1.32 mL) was added, and the reaction mixture was stirred at 50°C for 2 hours. The reaction solution was concentrated under reduced
35 pressure, and ethyl acetate was added to the obtained residue.

The organic layer was washed with water and saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was then distilled off under reduced pressure to afford the title compound (1.02 g). MS (m/z): 194.4

5 [M+H]⁺

[Step 2] Production of methyl 3-(aminomethyl)-4-methylbenzoate

To methyl 3-[(hydroxyimino)methyl]-4-methylbenzoate (1.02 g) obtained in Step 1, hydrogen chloride (2M methanol solution, 15 mL) was added. After degassing, 5% Pd-C (500 mg) was
10 added under argon atmosphere while stirring the reaction mixture at room temperature. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 3 hours. The reaction solution was filtered through celite (R), and then the solvent was distilled off under reduced pressure. To the obtained
15 residue, aqueous sodium hydroxide solution was added to basify it, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline solution and dried over anhydrous magnesium sulfate, and the solvent was then distilled off under reduced pressure to afford the title compound
20 (820 mg). MS (m/z): 180.4 [M+H]⁺

Reference Example 43: 3-Bromo-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-bromo-4-methylbenzoic acid (16.6 g) instead of 3-amino-4-methylbenzoic acid, the title compound (23.0 g) was
25 obtained by the method as described in Reference Example 7. MS (m/z): 312.0 [M+H]⁺

[0227]

Example 1: 2-(Cyclopropylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbonyl}-2-methylphenyl)-1,3-thiazole-5-
30 carboxamide

[Step 1] Production of methyl 3-[(2-bromo-1,3-thiazole-5-carbonyl)amino]-4-methylbenzoate

To a solution of 2-bromo-1,3-thiazole-5-carboxylic acid (2.20 g) in DMF (20 mL), methyl 3-amino-4-methylbenzoate (1.75 g), HATU
35 (4.83 g), and DIPEA (3.66 mL) were added sequentially, and the

reaction mixture was stirred at room temperature for 6 hours. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated saline solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (1.02 g).

[Step 2] Production of methyl 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoate

To a solution of methyl 3-[(2-bromo-1,3-thiazole-5-carbonyl)amino]-4-methylbenzoate (150 mg) obtained in Step 1 in NMP (0.5 mL), cyclopropanamine (121 mg) was added, and the reaction mixture was stirred at 80°C for 6 hours. After allowing the reaction solution to be cooled, it was purified by silica gel column chromatography to afford the title compound (105 mg).

[Step 3] Production of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid

By using methyl 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoate (103 mg) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (90 mg) was obtained by the method as described in Step 2 of Reference Example 1.

[Step 4] Production of 2-(cyclopropylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide

To a solution of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid (30 mg) obtained in Step 3 in DMF (1 mL), HATU (54 mg) and DIPEA (0.065 mL) were added sequentially, and the reaction mixture was stirred at room temperature for 10 minutes. Then, (1S,2S)-2-aminocyclohexan-1-ol hydrochloride (22 mg) was added thereto, and the reaction mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated

saline solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (16 mg).

5 Example 2: N-(5-{[(1S,2S)-2-Hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide

[Step 1] Production of methyl 3-[(5-bromopyridine-3-carbonyl)amino]-4-methylbenzoate

By using 5-bromopyridine-3-carboxylic acid (1.00 g)
10 instead of 2-bromo-1,3-thiazole-5-carboxylic acid, the title compound (1.70 g) was obtained by the method as described in Step 1 of Example 1. MS (m/z): 349.0 [M+H]⁺

[Step 2] Production of 3-[(5-bromopyridine-3-carbonyl)amino]-4-methylbenzoic acid

15 By using methyl 3-[(5-bromopyridine-3-carbonyl)amino]-4-methylbenzoate (650 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (505 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 335.0 [M+H]⁺

20 [Step 3] Production of 5-bromo-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide

By using 3-[(5-bromopyridine-3-carbonyl)amino]-4-methylbenzoic acid (505 mg) obtained in Step 2 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic
25 acid, the title compound (650 mg) was obtained by the method as described in Step 4 of Example 1. MS (m/z): 432.1 [M+H]⁺

[Step 4] Production of N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide
30

By using 5-bromo-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide (50 mg) obtained in Step 3 and phenylboronic acid (17 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (40 mg) was obtained by the
35

method as described in Reference Example 14.

Example 3: 2-(Cyclopropylmethyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide

5 [Step 1] Production of methyl 3-{[2-(cyclopropylmethyl)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoate

By using 2-(cyclopropylmethyl)-1,3-thiazole-5-carboxylic acid (100 mg) instead of 2-bromo-1,3-thiazole-5-carboxylic acid, the title compound (160 mg) was obtained by the
10 method as described in Step 1 of Example 1. MS (m/z): 331.5 [M+H]⁺

[Step 2] Production of 3-{[2-(cyclopropylmethyl)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid

By using methyl 3-{[2-(cyclopropylmethyl)-1,3-thiazole-
15 5-carbonyl]amino}-4-methylbenzoate (160 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (145 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 317.4 [M+H]⁺

20 [Step 3] Production of 2-(cyclopropylmethyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide

By using 3-{[2-(cyclopropylmethyl)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid (40 mg) obtained in Step 2
25 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (38 mg) was obtained by the method as described in Step 4 of Example 1.
Example 5: N-(5-{[(1S,2S)-2-Hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-phenyl-1,3-oxazole-5-carboxamide

30 By using 2-phenyl-1,3-oxazole-5-carboxylic acid (30 mg) and 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (43 mg) obtained in Reference Example 7 instead of 2-bromo-1,3-thiazole-5-carboxylic acid and methyl 3-amino-4-methylbenzoate, the title compound (53 mg) was obtained by the method as
35 described in Step 1 of Example 1.

[0228]

Example 6: N-(5-{[(1S)-2-Hydroxy-1-phenylethyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide

[Step 1] Production of methyl 4-methyl-3-[(5-phenylpyridine-3-carbonyl)amino]benzoate

By using methyl 3-[(5-bromopyridine-3-carbonyl)amino]-4-methylbenzoate (1.00 g) obtained in Step 1 of Example 2 and phenylboronic acid (419 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (1.00 g) was obtained by the method as described in Reference Example 14. MS (m/z): 347.2 [M+H]⁺

[Step 2] Production of 4-methyl-3-[(5-phenylpyridine-3-carbonyl)amino]benzoic acid

By using methyl 4-methyl-3-[(5-phenylpyridine-3-carbonyl)amino]benzoate (1.00 g) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (910 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 333.2 [M+H]⁺

[Step 3] Production of N-(5-{[(1S)-2-hydroxy-1-phenylethyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide

By using 4-methyl-3-[(5-phenylpyridine-3-carbonyl)amino]benzoic acid (40 mg) obtained in Step 2 and (2S)-2-amino-2-phenylethan-1-ol (25 mg) instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid and (1S,2S)-2-aminocyclohexan-1-ol hydrochloride, the title compound (38 mg) was obtained by the method as described in Step 4 of Example 1.

Example 17: 5-[Cyclopropyl(methyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide

By using 5-[cyclopropyl(methyl)amino]pyridine-3-carboxylic acid (70 mg) obtained in Reference Example 2 and 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (90 mg) obtained in Reference Example 7 instead of 2-bromo-1,3-thiazole-5-carboxylic acid and methyl 3-amino-4-methylbenzoate, the title

compound (43 mg) was obtained by the method as described in Step 1 of Example 1.

Example 20: 5-(3-Fluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide

By using 5-bromo-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide (61 mg) obtained in Step 3 of Example 2 and (3-fluorophenyl)boronic acid (28 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (43 mg) was obtained by the method as described in Reference Example 14.

Example 24: 5-(Cyclopropylmethoxy)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide

By using 5-(cyclopropylmethoxy)pyridine-3-carboxylic acid (40 mg) and 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (57 mg) obtained in Reference Example 7 instead of 2-bromo-1,3-thiazole-5-carboxylic acid and methyl 3-amino-4-methylbenzoate, the title compound (58 mg) was obtained by the method as described in Step 1 of Example 1.

Example 26: 2-[(2-Cyclopropylethyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide

[Step 1] Production of methyl 3-[(2-chloro-1,3-thiazole-5-carbonyl)amino]-4-methylbenzoate

To a stirred solution of methyl 3-amino-4-methylbenzoate (6.89 g) in THF (80 mL), a solution of 2-chloro-1,3-thiazole-5-carbonyl chloride (8.31 g) in THF (80 mL) was added dropwise under ice cooling, and the reaction mixture was stirred at the same temperature for 30 minutes. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated saline solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off

under reduced pressure. Water was added to the obtained residue to suspend it, and the deposits were collected by filtration to afford the title compound (12.5 g). MS (m/z): 311.4 [M+H]⁺

[Step 2] Production of 3-[(2-chloro-1,3-thiazole-5-carbonyl)amino]-4-methylbenzoic acid

By using methyl 3-[(2-chloro-1,3-thiazole-5-carbonyl)amino]-4-methylbenzoate (12.5 g) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (10.4 g) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 297.4 [M+H]⁺

[Step 3] Production of 2-chloro-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide

By using 3-[(2-chloro-1,3-thiazole-5-carbonyl)amino]-4-methylbenzoic acid (7.5 g) obtained in Step 2 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (9.8 g) was obtained by the method as described in Step 4 of Example 1. MS (m/z): 394.2 [M+H]⁺

[Step 4] Production of N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide

By using 2-chloro-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide (90 mg) obtained in Step 3 and 2-cyclopropylethan-1-amine (249 mg) instead of methyl 3-[(2-bromo-1,3-thiazole-5-carbonyl)amino]-4-methylbenzoate and cyclopropanamine, the title compound (72 mg) was obtained by the method as described in Step 2 of Example 1.

[0229]

Example 57: 3-[(5-Bromopyridin-3-yl)ethynyl]-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

[Step 1] Production of methyl 3-[(5-bromopyridin-3-yl)ethynyl]-4-chlorobenzoate

By using methyl 4-chloro-3-ethynylbenzoate (1.01 g)

obtained in Reference Example 8 and 3-bromo-5-iodopyridine (1.47 g) instead of ethynyl(trimethyl)silane and methyl 4-chloro-3-iodobenzoate, the title compound (1.60 g) was obtained by the method as described in Step 1 of Reference Example 8. MS (m/z):

5 350.0 [M+H]⁺

[Step 2] Production of 3-[(5-bromopyridin-3-yl)ethynyl]-4-chlorobenzoic acid

By using methyl 3-[(5-bromopyridin-3-yl)ethynyl]-4-chlorobenzoate (600 mg) obtained in Step 1 instead of methyl 5-
10 [(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (360 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 335.9 [M+H]⁺

[Step 3] Production of 3-[(5-bromopyridin-3-yl)ethynyl]-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

15 By using 3-[(5-bromopyridin-3-yl)ethynyl]-4-chlorobenzoic acid (370 mg) obtained in Step 2 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (170 mg) was obtained by the method as described in Step 4 of Example 1.

20 Example 58: 4-Chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(5-phenylpyridin-3-yl)ethynyl]benzamide

By using 3-[(5-bromopyridin-3-yl)ethynyl]-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide (50 mg) obtained in Example 57 and phenylboronic acid (15 mg) instead of 2-
25 chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (5 mg) was obtained by the method as described in Reference Example 14.

Example 59: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-[(5-methylpyridin-3-yl)ethynyl]benzamide

30 By using 3-ethynyl-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (30 mg) obtained in Reference Example 9 and 3-bromo-5-methylpyridine (30 mg) instead of ethynyl(trimethyl)silane and methyl 4-chloro-3-iodobenzoate, the title compound (14 mg) was obtained by the method as described in
35 Step 1 of Reference Example 8.

Example 61: 3-[(5-Bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-ethynyl-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (20.5 g) obtained in Reference Example 9 and 3-bromo-5-iodopyridine (24.8 g) instead of ethynyl(trimethyl)silane and methyl 4-chloro-3-iodobenzoate, the title compound (14.5 g) was obtained by the method as described in Step 1 of Reference Example 8.

Example 62: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]ethynyl}benzamide

To 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (30 mg) obtained in Example 61, 2-(tributylstannyl)pyrimidine (54 mg), Pd(PPh₃)₄ (17 mg), copper iodide (7 mg), and cesium fluoride (22 mg), DMF (0.5 mL) was added, and that mixture was allowed to react at 150°C for 30 minutes, using a microwave reaction apparatus. After allowing the reaction solution to be cooled, it was purified by silica gel column chromatography to afford the title compound (15 mg).
[0230]

Example 67: 3-[(5-Cyclopropylpyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (400 mg) obtained in Example 61 and cyclopropylboronic acid (249 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (250 mg) was obtained by the method as described in Reference Example 14.

Example 76: 3-[(5-Bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

[Step 1] Production of 3-[(5-bromopyridin-3-yl)ethynyl]-4-methylbenzoic acid

By using 3-ethynyl-4-methylbenzoic acid (40 mg) and 3-bromo-5-iodopyridine (71 mg) instead of ethynyl(trimethyl)silane and methyl 4-chloro-3-iodobenzoate, the title compound (47 mg) was obtained by the method as described in Step 1 of Reference

Example 8. MS (m/z): 316.2 [M+H]⁺

[Step 2] Production of 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

By using 3-[(5-bromopyridin-3-yl)ethynyl]-4-methylbenzoic acid (25 mg) obtained in Step 1 and (1S,2S)-2-amino-1-phenylpropan-1,3-diol (16 mg) instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid and (1S,2S)-2-aminocyclohexan-1-ol hydrochloride, the title compound (28 mg) was obtained by the method as described in Step 4 of Example 1.

Example 77: N¹-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-N³-(5-phenylpyridin-3-yl)benzene-1,3-dicarboxamide

[Step 1] Production of methyl 5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylbenzoate

By using 3-(methoxycarbonyl)-4-methylbenzoic acid (500 mg) instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (600 mg) was obtained by the method as described in Step 4 of Example 1. MS (m/z): 292.3 [M+H]⁺

[Step 2] Production of 5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylbenzoic acid

By using methyl 5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylbenzoate (600 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (430 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 278.3 [M+H]⁺

[Step 3] Production of N³-(5-bromopyridin-3-yl)-N¹-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzene-1,3-dicarboxamide

By using 5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylbenzoic acid (200 mg) obtained in Step 2 and 5-bromopyridin-3-amine (137 mg) instead of 2-bromo-1,3-thiazole-5-carboxylic acid and methyl 3-amino-4-methylbenzoate, the title compound (166 mg) was obtained by the method as described in Step 1 of Example 1. MS (m/z): 432.3 [M+H]⁺

[Step 4] Production of N¹-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-N³-(5-phenylpyridin-3-yl)benzene-1,3-dicarboxamide

By using N³-(5-bromopyridin-3-yl)-N¹-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzene-1,3-dicarboxamide (50 mg) obtained in Step 3 and phenylboronic acid (17 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (40 mg) was obtained by the method as described in Reference Example 14.

Example 78: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzamide

[Step 1] Production of methyl 4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzoate

By using methyl 3-bromo-4-methylbenzoate (350 mg) and 2-(pyridin-3-yl)pyrimidin-4-amine (263 mg) instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (280 mg) was obtained by the method as described in Step 1 of Reference Example 1.

[Step 2] Production of 4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzoic acid

By using methyl 4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzoate (280 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (180 mg) was obtained by the method as described in Step 2 of Reference Example 1.

[Step 3] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzamide

By using 4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzoic acid (50 mg) instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (50 mg) was obtained by the method as described in Step 4 of Example 1.

Example 83: 3-(2-Amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

[Step 1] Production of methyl 3-{2-[bis(tert-

butoxycarbonyl) amino]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}-4-methylbenzoate

By using methyl 3-bromo-4-methylbenzoate (84 mg) and di-tert-butyl 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl-2-imidodicarbonate (86 mg) obtained in Reference Example 40 instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (54 mg) was obtained by the method as described in Step 1 of Reference Example 1. MS (m/z): 499.6 [M+H]⁺

[Step 2] Production of methyl 3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylbenzoate

To methyl 3-{2-[bis(tert-butoxycarbonyl) amino]-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl}-4-methylbenzoate (70 mg) obtained in Step 1, hydrogen chloride (2M methanol solution, 2.1 mL) was added, and the reaction mixture was stirred at 50°C for 5 hours. After allowing the reaction solution to be cooled, it was purified by silica gel column chromatography to afford the title compound (10 mg). MS (m/z): 299.5 [M+H]⁺

[Step 3] Production of 3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylbenzoic acid

By using methyl 3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylbenzoate (10 mg) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl) amino]pyridine-3-carboxylate, the title compound was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 285.3 [M+H]⁺

[Step 4] Production of 3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

By using 3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-4-methylbenzoic acid obtained in Step 3 and (1S,2S)-2-amino-1-phenylpropan-1,3-diol (11 mg) instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl] amino}-4-methylbenzoic acid and (1S,2S)-2-aminocyclohexan-1-ol hydrochloride, the title compound (6 mg) was obtained by the method as described in Step 4

of Example 1.

[0231]

Example 84: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzamide

5 [Step 1] Production of methyl 4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzoate

By using methyl 3-bromo-4-methylbenzoate (324 mg) and (1S)-1-(5-phenylpyridin-3-yl)ethan-1-amine (280 mg) obtained in Reference Example 15 instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (220 mg) was obtained by the method as described in Step 1 of Reference Example 1. MS (m/z): 347.3 [M+H]⁺

[Step 2] Production of 4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzoic acid

15 By using methyl 4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzoate (220 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (180 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 333.3 [M+H]⁺

20 [Step 3] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzamide

By using 4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzoic acid (50 mg) obtained in Step 2 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (60 mg) was obtained by the method as described in Step 4 of Example 1.

Example 85: 3-{[(1S)-1-([3,3'-Bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

30 [Step 1] Production of methyl 3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-4-methylbenzoate

By using methyl 3-bromo-4-methylbenzoate (13.9 g) and (1S)-1-([3,3'-bipyridin]-5-yl)ethan-1-amine (11.0 g) obtained in Reference Example 16 instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (10.3 g) was obtained by the method as described in Step 1 of

Reference Example 1. MS (m/z): 348.3 [M+H]⁺

[Step 2] Production of 3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-4-methylbenzoic acid

By using methyl 3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-4-methylbenzoate (10.3 g) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (8.7 g) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 334.4 [M+H]⁺

[Step 3] Production of 3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-4-methylbenzoic acid (8.7 g) obtained in Step 2 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (9.4 g) was obtained by the method as described in Step 4 of Example 1.

Example 87: 3-{[(1S)-1-([3,4'-Bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of methyl 3-{[(1R)-1-(5-bromopyridin-3-yl)ethyl]amino}-4-methylbenzoate

By using methyl 3-iodo-4-methylbenzoate (6.49 g) and (1S)-1-(5-bromopyridin-3-yl)ethan-1-amine (3.78 g) instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (1.80 g) was obtained by the method as described in Step 1 of Reference Example 1. MS (m/z): 349.0 [M+H]⁺

[Step 2] Production of 3-{[(1R)-1-(5-bromopyridin-3-yl)ethyl]amino}-4-methylbenzoic acid

By using methyl 3-{[(1R)-1-(5-bromopyridin-3-yl)ethyl]amino}-4-methylbenzoate (1.00 g) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (820 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 335.1 [M+H]⁺

[Step 3] Production of 3-{[(1S)-1-(5-bromopyridin-3-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-{[(1R)-1-(5-bromopyridin-3-yl)ethyl]amino}-

4-methylbenzoic acid (820 mg) obtained in Step 2 instead of 3-
{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-
methylbenzoic acid, the title compound (920 mg) was obtained by
the method as described in Step 4 of Example 1. MS (m/z): 432.3
5 [M+H]⁺

[Step 4] Production of 3-{[(1S)-1-([3,4'-bipyridin]-5-
yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-{[(1S)-1-(5-bromopyridin-3-yl)ethyl]amino}-
N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (30 mg)

10 obtained in Step 3 and pyridin-4-ylboronic acid (10 mg) instead
of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid,
the title compound (9 mg) was obtained by the method as described
in Reference Example 14.

Example 89: 3-{[(1S)-1-([2,3'-Bipyridin]-5'-yl)ethyl]amino}-N-
15 [(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of methyl 3-{[(1S)-1-([2,3'-bipyridin]-5'-
yl)ethyl]amino}-4-methylbenzoate

By using methyl 3-{[(1R)-1-(5-bromopyridin-3-
yl)ethyl]amino}-4-methylbenzoate (150 mg) obtained in Step 1 of
20 Example 87 and 2-bromopyridine (170 mg) instead of 3-bromo-5-
(methoxymethoxy)pyridine and 2-bromopyrimidine, the title
compound (90 mg) was obtained by the method as described in Step
1 of Reference Example 10. MS (m/z): 348.2 [M+H]⁺

[Step 2] Production of 3-{[(1S)-1-([2,3'-bipyridin]-5'-
25 yl)ethyl]amino}-4-methylbenzoic acid

By using methyl 3-{[(1S)-1-([2,3'-bipyridin]-5'-
yl)ethyl]amino}-4-methylbenzoate (90 mg) obtained in Step 1
instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-
carboxylate, the title compound (86 mg) was obtained by the

30 method as described in Step 2 of Reference Example 1. MS (m/z):
334.2 [M+H]⁺

[Step 3] Production of 3-{[(1S)-1-([2,3'-bipyridin]-5'-
yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-{[(1S)-1-([2,3'-bipyridin]-5'-

35 yl)ethyl]amino}-4-methylbenzoic acid (70 mg) obtained in Step 2

instead of 3-{{2-(cyclopropylamino)-1,3-thiazole-5-carbonyl}amino}-4-methylbenzoic acid, the title compound (10 mg) was obtained by the method as described in Step 4 of Example 1.

Example 91: 3-{{(5-Bromopyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (1.6 g) obtained in Reference Example 7 instead of 1-methylpiperazine, the title compound (2.0 g) was obtained by the method as described in Reference Example 34.

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Example 92: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{{(5-phenylpyridin-3-yl)methyl}amino}benzamide

By using 3-{{(5-bromopyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (30 mg) obtained in Example 91 and phenylboronic acid (10 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (23 mg) was obtained by the method as described in Reference Example 14.

Example 94: 3-{{[5-(Cyclopropylethynyl)pyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using ethynylcyclopropane (63 mg) and 3-{{(5-bromopyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (100 mg) obtained in Example 91 instead of ethynyl(trimethyl)silane and methyl 4-chloro-3-iodobenzoate, the title compound (64 mg) was obtained by the method as described in Step 1 of Reference Example 8.

Example 95: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl)methyl}amino}benzamide

[Step 1] Production of methyl 3-{{(5-bromopyridin-3-yl)methyl}amino}-4-methylbenzoate

By using methyl 3-amino-4-methylbenzoate (9.0 g) instead of 1-methylpiperazine, the title compound (13.0 g) was obtained by the method as described in Reference Example 34. MS (m/z): 335.3 [M+H]⁺

[Step 2] Production of methyl 4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzoate

By using methyl 3-([5-bromopyridin-3-yl)methyl]amino)-4-

methylbenzoate (13.0 g) obtained in Step 1 instead of 3-bromo-5-

5 (methoxymethoxy)pyridine, the title compound (9.0 g) was obtained by the method as described in Step 1 of Reference Example 10. MS (m/z): 335.5 [M+H]⁺

[Step 3] Production of 4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzoic acid

10 By using methyl 4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzoate (9.0 g) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (6.6 g) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z):
15 321.5 [M+H]⁺

[Step 4] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzamide

By using 4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzoic acid (6.0 g) obtained in Step 3 instead
20 of 3-([2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino)-4-methylbenzoic acid, the title compound (5.5 g) was obtained by the method as described in Step 4 of Example 1.

Example 96: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzamide

25 [Step 1] Production of methyl 4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzoate

By using methyl 3-amino-4-methylbenzoate (210 mg) and quinolin-3-carbaldehyde (200 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (230 mg)
30 was obtained by the method as described in Reference Example 34.

[Step 2] Production of 4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzoic acid

By using methyl 4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl)methyl]amino)benzoate (230 mg) obtained in Step 1 instead of
35 methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the

title compound (200 mg) was obtained by the method as described in Step 2 of Reference Example 1.

[Step 3] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[[quinolin-3-yl)methyl]amino}benzamide

5 By using 4-methyl-3-[[quinolin-3-yl)methyl]amino}benzoic acid (40 mg) obtained in Step 2 instead of 3-[[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (43 mg) was obtained by the method as described in Step 4 of Example 1.

10 Example 98: 3-[(5-[4-(2-Aminopropan-2-yl)phenyl]pyridin-3-yl)methyl]amino]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-[(5-bromopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (80 mg) obtained in Example 91 and 2-(4-bromophenyl)propan-2-amine (49 mg) instead of 3-bromo-5-(methoxymethoxy)pyridine and 2-bromopyrimidine, the title compound (41 mg) was obtained by the method as described in Step 1 of Reference Example 10.

[0233]

20 Example 101: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-[(6-phenylpyrazin-2-yl)methyl]amino}benzamide

[Step 1] Production of methyl 3-[(6-chloropyrazin-2-yl)methyl]amino}-4-methylbenzoate

By using methyl 3-amino-4-methylbenzoate (449 mg) and 6-chloropyrazine-2-carbaldehyde (774 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (150 mg) was obtained by the method as described in Reference Example 34.

[Step 2] Production of methyl 4-methyl-3-[(6-phenylpyrazin-2-yl)methyl]amino}benzoate

30 By using methyl 3-[(6-chloropyrazin-2-yl)methyl]amino}-4-methylbenzoate (70 mg) obtained in Step 1 and phenylboronic acid (35 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (66 mg) was obtained by the method as described in Reference Example 14.

[Step 3] Production of 4-methyl-3-{[(6-phenylpyrazin-2-yl)methyl]amino}benzoic acid

By using methyl 4-methyl-3-{[(6-phenylpyrazin-2-yl)methyl]amino}benzoate (66 mg) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (55 mg) was obtained by the method as described in Step 2 of Reference Example 1.

[Step 4] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(6-phenylpyrazin-2-yl)methyl]amino}benzamide

By using 4-methyl-3-{[(6-phenylpyrazin-2-yl)methyl]amino}benzoic acid (25 mg) obtained in Step 3 instead of 3-[[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino]-4-methylbenzoic acid, the title compound (19 mg) was obtained by the method as described in Step 4 of Example 1.

Example 109: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[(1H-pyrazolo[3,4-b]pyridin-5-yl)methyl]amino}benzamide

By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (73 mg) obtained in Reference Example 7 and 1H-pyrazolo[3,4-b]pyridine-5-carbaldehyde (43 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (84 mg) was obtained by the method as described in Reference Example 34.

Example 110: N-[(1S,2S)-2-Hydroxycyclohexyl]-3-{[(imidazo[1,2-b]pyridazin-3-yl)methyl]amino}-4-methylbenzamide

By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (24 mg) obtained in Reference Example 7 and imidazo[1,2-b]pyridazine-3-carbaldehyde (15 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (18 mg) was obtained by the method as described in Reference Example 34.

Example 113: 3-{[(2-Aminopyrimidin-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of 3-{[(2-chloropyrimidin-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-

methylbenzamide (513 mg) obtained in Reference Example 7 and 2-chloropyrimidine-5-carbaldehyde (310 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (320 mg) was obtained by the method as described in

5 Reference Example 34. MS (m/z): 375.5 [M+H]⁺

[Step 2] Production of 3-{[(2-aminopyrimidin-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

To 3-{[(2-chloropyrimidin-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (320 mg) obtained
10 in Step 1, 1,4-dioxane (8 mL) and 28% aqueous ammonia solution (4 mL) were added, and the reaction mixture was sealed in a pressure resistant stainless steel container and stirred at 100°C for 8 hours. After allowing the reaction solution to be cooled, it was purified by silica gel column chromatography to afford the title
15 compound (173 mg).

Example 116: 3-{[(6-Acetamidopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of 3-{[(6-bromopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

20 By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (380 mg) obtained in Reference Example 7 and 6-bromopyridine-3-carbaldehyde (300 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (370 mg) was obtained by the method as described in

25 Reference Example 34. MS (m/z): 418.5 [M+H]⁺

[Step 2] Production of 3-{[(6-acetamidopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-{[(6-bromopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (50 mg) obtained
30 in Step 1 and acetamide (18 mg) instead of methyl 5-bromopyridine-3-carboxylate and 1-cyclopropylmethanamine, the title compound (22 mg) was obtained by the method as described in Step 1 of Reference Example 1.

35 [0234]

Example 118: 3-{[(2,2'-Bipyridin]-5-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-{[(6-bromopyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (60 mg) obtained in Step 1 of Example 116 and 2-(tributylstannyl)pyridine (79 mg) instead of 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide and 2-(tributylstannyl)pyrimidine, the title compound (23 mg) was obtained by the method as described in Example 62.

Example 122: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl}amino}benzamide

A mixture of 3-{[(6-bromopyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (60 mg) obtained in Step 1 of Example 116, 1H-pyrazole (20 mg), copper iodide (11 mg), potassium phosphate (91 mg), trans-N,N'-dimethylcyclohexane-1,2-diamine (0.014 mL), and DMF (0.36 mL) was allowed to react at 100°C for 30 minutes, using a microwave reaction apparatus. To the reaction solution, 1H-pyrazole (20 mg), copper iodide (11 mg), and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.014 mL) were added, and the reaction mixture was allowed to react at 100°C for additional 30 minutes, using the microwave reaction apparatus. After allowing the reaction solution to be cooled, it was purified by silica gel column chromatography to afford the title compound (34 mg).

Example 129: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[(6-[(pyridin-3-yl)carbamoyl]amino}pyridin-3-yl)methyl}amino}benzamide

[Step 1] Production of 3-{[(6-aminopyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (203 mg) obtained in Reference Example 7 and 6-aminopyridine-3-carbaldehyde (100 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (149 mg) was obtained by the method as described in

Reference Example 34. MS (m/z): 355.6 [M+H]⁺

[Step 2] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[[[6-[(pyridin-3-yl)carbamoyl]amino]pyridin-3-yl)methyl]amino}benzamide

A mixture of 3-[[[6-aminopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (35 mg) obtained in Step 1, 3-isocyanatopyridine (14 mg), potassium carbonate (20 mg), and DMF (0.33 mL) was allowed to react at 80°C for 30 minutes, using a microwave reaction apparatus. After allowing the reaction solution to be cooled, it was purified by silica gel column chromatography to afford the title compound (5.8 mg).

Example 131: 3-[[[5-Aminopyrazin-2-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of methyl 3-[[[5-[(tert-butoxycarbonyl)amino]pyrazin-2-yl)methyl]amino]-4-methylbenzoate

To a solution of tert-butyl [5-(bromomethyl)pyrazin-2-yl]carbamate (1.44 g) and methyl 3-amino-4-methylbenzoate (561 mg) in DMF (12 mL), potassium carbonate (1.76 g) was added, and the reaction mixture was stirred at room temperature overnight. The reaction solution was diluted with ethyl acetate. After washing it with water and saturated saline solution, the solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography to afford the title compound (360 mg). MS (m/z): 373.5 [M+H]⁺

[Step 2] Production of 3-[[[5-[(tert-butoxycarbonyl)amino]pyrazin-2-yl)methyl]amino]-4-methylbenzoic acid

By using methyl 3-[[[5-[(tert-butoxycarbonyl)amino]pyrazin-2-yl)methyl]amino]-4-methylbenzoate (160 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (125 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 359.3 [M+H]⁺

[Step 3] Production of tert-butyl {5-[5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl]-2-methylanilino)methyl}pyrazin-2-yl}carbamate

By using 3-[(5-[(tert-butoxycarbonyl)amino]pyrazin-2-yl)methyl]amino]-4-methylbenzoic acid (125 mg) obtained in Step 2 instead of 3-[[2-(cyclopropylamino)-1,3-thiazole-5-

carbonyl]amino]-4-methylbenzoic acid, the title compound (105 mg)

5 was obtained by the method as described in Step 4 of Example 1.

MS (m/z): 456.6 [M+H]⁺

[Step 4] Production of 3-[[5-aminopyrazin-2-yl)methyl]amino]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

To a solution of tert-butyl {5-[(5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl)-2-methylanilino)methyl]pyrazin-2-yl}carbamate (95 mg) obtained in step 3 in dichloromethane (2 mL), trifluoroacetic acid (0.16 mL) was added, and the reaction mixture was stirred at room temperature for 2 hours. To the residue obtained by concentrating the reaction solution under reduced pressure, methanol (2 mL) and 2M aqueous sodium hydroxide solution (2 mL) were added, and the reaction mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with water, and the reaction mixture was extracted with chloroform. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (40 mg).

Example 138: N-[(1S,2S)-2-Hydroxycyclohexyl]-3-[(6-[(1R,3R)-3-methoxycyclobutane-1-carbonyl]amino)pyridin-3-yl)methyl]amino]-4-methylbenzamide

25 [Step 1] Production of 3-[(6-aminopyridin-3-yl)methyl]amino]-N-[(1S,2S)-2-[[tert-butyl(dimethyl)silyl]oxy]cyclohexyl]-4-methylbenzamide

By using 3-amino-N-[(1S,2S)-2-[[tert-butyl(dimethyl)silyl]oxy]cyclohexyl]-4-methylbenzamide (468 mg)

30 obtained in Reference Example 41 and 6-aminopyridine-3-carbaldehyde (150 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (223 mg) was obtained by the method as described in Reference Example 34. MS (m/z): 469.4 [M+H]⁺

35 [Step 2] Production of N-[(1S,2S)-2-[[tert-

butyl(dimethyl)silyloxy)cyclohexyl]-3-{{(6-{{(1r,3r)-3-methoxycyclobutane-1-carbonyl}amino}pyridin-3-yl)methyl}amino}-4-methylbenzamide

By using (1r,3r)-3-methoxycyclobutane-1-carboxylic acid
5 (36 mg) and 3-{{(6-aminopyridin-3-yl)methyl}amino}-N-[(1S,2S)-2-{{tert-butyl(dimethyl)silyloxy)cyclohexyl]-4-methylbenzamide (30 mg) obtained in Step 1 instead of 2-bromo-1,3-thiazole-5-carboxylic acid and methyl 3-amino-4-methylbenzoate, the title compound (60 mg) was obtained by the method as described in Step
10 1 of Example 1.

[Step 3] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-3-{{(6-{{(1r,3r)-3-methoxycyclobutane-1-carbonyl}amino}pyridin-3-yl)methyl}amino}-4-methylbenzamide

By using N-[(1S,2S)-2-{{tert-
15 butyl(dimethyl)silyloxy)cyclohexyl]-3-{{(6-{{(1r,3r)-3-methoxycyclobutane-1-carbonyl}amino}pyridin-3-yl)methyl}amino}-4-methylbenzamide (60 mg) obtained in Step 2 instead of methyl 4-chloro-3-[(trimethylsilyl)ethynyl]benzoate, the title compound (8 mg) was obtained by the method as described in Step 2 of
20 Reference Example 8.

[0235]

Example 140: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{{[6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl}amino}benzamide

By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-
25 methylbenzamide (136 mg) obtained in Reference Example 7 and 6-(1H-1,2,3-triazol-1-yl)pyridine-3-carbaldehyde (306 mg) obtained in Reference Example 24 instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (74 mg) was obtained by the method as described in Reference Example 34.

30 Example 142: 3-{{(2-Aminopyrimidin-5-yl)methyl}amino}-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

[Step 1] Production of methyl 4-chloro-3-{{(2-chloropyrimidin-5-yl)methyl}amino}benzoate

By using methyl 3-amino-4-chlorobenzoate (1.00 g) and
35 2-chloropyrimidine-5-carbaldehyde (806 mg) instead of 1-

methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (376 mg) was obtained by the method as described in Reference Example 34. MS (m/z): 312.3 [M+H]⁺

[Step 2] Production of 3-{[(2-aminopyrimidin-5-yl)methyl]amino}-4-chlorobenzoic acid

To methyl 4-chloro-3-{[(2-chloropyrimidin-5-yl)methyl]amino}benzoate (199 mg) obtained in Step 1, 1,4-dioxane (0.86 mL) and 28% aqueous ammonia solution (0.86 mL) were added, and the reaction mixture was sealed in a pressure resistant stainless steel container and stirred at 100°C for 2 days. To the residue obtained by concentrating the reaction solution under reduced pressure, ethanol (3.2 mL) and 2M aqueous sodium hydroxide solution (3.2 mL) were added, and the reaction mixture was stirred at 90°C overnight. The solvent was distilled off under reduced pressure. The reaction mixture was diluted with water and then neutralized by adding hydrochloric acid. The precipitated deposits were collected by filtration to afford the title compound (102 mg). MS (m/z): 279.4 [M+H]⁺

[Step 3] Production of 3-{[(2-aminopyrimidin-5-yl)methyl]amino}-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

By using 3-{[(2-aminopyrimidin-5-yl)methyl]amino}-4-chlorobenzoic acid (50 mg) obtained in Step 2 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (36 mg) was obtained by the method as described in Step 4 of Example 1.

Example 144: 3-{[(3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of tert-butyl 7-[(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylanilino)methyl]-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate

By using 3-amino-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (134 mg) obtained in Reference Example 7 and tert-butyl 7-formyl-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate obtained in Reference Example 23 instead of 1-

methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (124 mg) was obtained by the method as described in Reference Example 34. MS (m/z): 497.3 [M+H]⁺

[Step 2] Production of 3-{[(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

To a solution of tert-butyl 7-[(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylanilino)methyl]-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazine-4-carboxylate (59 mg) obtained in step 1 in dichloromethane (1.4 mL), trifluoroacetic acid (0.7 mL) was added, and the reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (37 mg).

Example 147: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide

[Step 1] Production of methyl 3-{[(5-bromopyridin-3-yl)amino]methyl}-4-methylbenzoate

By using 5-bromopyridin-3-amine (1.5 g) and methyl 3-formyl-4-methylbenzoate (1.5 g) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (2.3 g) was obtained by the method as described in Reference Example 34. MS (m/z): 335.4 [M+H]⁺

[Step 2] Production of methyl 4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzoate

By using methyl 3-{[(5-bromopyridin-3-yl)amino]methyl}-4-methylbenzoate (170 mg) obtained in Step 1 instead of 3-bromo-5-(methoxymethoxy)pyridine, the title compound (35 mg) was obtained by the method as described in Step 1 of Reference Example 10. MS (m/z): 335.5 [M+H]⁺

[Step 3] Production of 4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzoic acid

By using methyl 4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzoate (35 mg) obtained in Step 2

instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (33 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 321.5 [M+H]⁺

5 [Step 4] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide

By using 4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzoic acid (33 mg) obtained in Step 3 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (6 mg) was obtained by the method as described in Step 4 of Example 1.

Example 148: 3-{[([2,3'-Bipyridin]-5'-yl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of 3-{[(5-bromopyridin-3-yl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 5-bromopyridin-3-amine (437 mg) and 3-formyl-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (600 mg) obtained in Reference Example 26 instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (560 mg) was obtained by the method as described in Reference Example 34. MS (m/z): 418.6 [M+H]⁺

[Step 2] Production of 3-{[([2,3'-bipyridin]-5'-yl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-{[(5-bromopyridin-3-yl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (80 mg) obtained in Step 1 and 2-bromopyridine (36 mg) instead of 3-bromo-5-(methoxymethoxy)pyridine and 2-bromopyrimidine, the title compound (10 mg) was obtained by the method as described in Step 1 of Reference Example 10.

30 [0236]

Example 152: 3-{[(5-Bromopyridin-3-yl)amino]methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

[Step 1] Production of 3-{[(5-bromopyridin-3-yl)amino]methyl}-4-methylbenzoic acid

35 By using methyl 3-{[(5-bromopyridin-3-yl)amino]methyl}-

4-methylbenzoate (1.0 g) obtained in Step 1 of Example 147 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (950 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z):

5 321.4 [M+H]⁺

[Step 2] Production of 3-{[(5-bromopyridin-3-yl)amino]methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

By using 3-{[(5-bromopyridin-3-yl)amino]methyl}-4-methylbenzoic acid (350 mg) obtained in Step 1 and (1S,2S)-2-amino-1-phenylpropan-1,3-diol (219 mg) instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid and (1S,2S)-2-aminocyclohexan-1-ol hydrochloride, the title compound (500 mg) was obtained by the method as described in Step 4 of Example 1.

15 Example 153: N-[(1S,2S)-1,3-Dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-{[(5-phenylpyridin-3-yl)amino]methyl}benzamide

By using 3-{[(5-bromopyridin-3-yl)amino]methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide (50 mg) obtained in Example 152 and phenylboronic acid (16 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (29 mg) was obtained by the method as described in Reference Example 14.

Example 155: 3-{[([2,3'-Bipyridin]-5'-yl)amino]methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

25 By using 3-{[(5-bromopyridin-3-yl)amino]methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide (50 mg) obtained in Example 152 and 2-(tributylstannyl)pyridine (51 mg) instead of 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide and 2-(tributylstannyl)pyrimidine, the title compound (20 mg) was obtained by the method as described in Example 62.

Example 156: N-[(1S,2S)-1,3-Dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-{[(6-phenylpyrazin-2-yl)amino]methyl}benzamide

[Step 1] Production of methyl 3-{[(6-chloropyrazin-2-yl)amino]methyl}-4-methylbenzoate

35

A mixture of 2,6-dichloropyrazine (300 mg), methyl 3-(aminomethyl)-4-methylbenzoate (397 mg) obtained in Reference Example 42, NMP (4 mL), and DIPEA (1.05 mL) was stirred at 100°C for 4 hours. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water and saturated saline solution. The solvent was distilled off under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (423 mg). MS (m/z): 292.5 [M+H]⁺

[Step 2] Production of 3-{[(6-chloropyrazin-2-yl)amino]methyl}-4-methylbenzoic acid

By using methyl 3-{[(6-chloropyrazin-2-yl)amino]methyl}-4-methylbenzoate (580 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (520 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 278.4 [M+H]⁺

[Step 3] Production of 3-{[(6-chloropyrazin-2-yl)amino]methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

By using 3-{[(6-chloropyrazin-2-yl)amino]methyl}-4-methylbenzoic acid (300 mg) obtained in Step 2 and (1S,2S)-2-amino-1-phenylpropan-1,3-diol (217 mg) instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid and (1S,2S)-2-aminocyclohexan-1-ol hydrochloride, the title compound (420 mg) was obtained by the method as described in Step 4 of Example 1. MS (m/z): 427.6 [M+H]⁺

[Step 4] Production of N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-{[(6-phenylpyrazin-2-yl)amino]methyl}benzamide

By using 3-{[(6-chloropyrazin-2-yl)amino]methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide (50 mg) obtained in Step 3 and phenylboronic acid (17 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (36 mg) was obtained by the method as described in Reference Example 14.

Example 158: N-[3-({[6-(3,4-Dimethoxyphenyl)pyrazin-2-

yl]amino}methyl)phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea

[Step 1] Production of N-[(3-aminophenyl)methyl]-6-chloropyrazin-2-amine

By using 3-(aminomethyl)aniline (1.23 g) instead of methyl 3-(aminomethyl)-4-methylbenzoate, the title compound (1.22 g) was obtained by the method as described in Step 3 of Example 156.

[Step 2] Production of N-[(3-aminophenyl)methyl]-6-(3,4-dimethoxyphenyl)pyrazin-2-amine

By using N-[(3-aminophenyl)methyl]-6-chloropyrazin-2-amine (160 mg) obtained in Step 1 and (3,4-dimethoxyphenyl)boronic acid (149 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (190 mg) was obtained by the method as described in Reference Example 14.

[Step 3] Production of N-[3-({[6-(3,4-dimethoxyphenyl)pyrazin-2-yl]amino}methyl)phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea To N-[(3-aminophenyl)methyl]-6-(3,4-dimethoxyphenyl)pyrazin-2-amine (40 mg) obtained in Step 2, THF (1 mL), TEA (0.20 mL), and triphosgene (18 mg) were added, and the reaction mixture was stirred at room temperature for 10 minutes. Then, (1S,2R)-2-aminocyclohexan-1-ol hydrochloride (180 mg) was added thereto, and the reaction mixture was stirred at the same temperature for 2 hours. The reaction solution was purified by silica gel column chromatography to afford the title compound (37 mg).

[0237]

Example 159: N-[(1R,2S)-2-Hydroxycyclohexyl]-N'-[3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]urea

[Step 1] Production of N-[(3-nitrophenyl)methyl]-5-(pyrimidin-2-yl)pyridin-3-amine

By using 5-(pyrimidin-2-yl)pyridin-3-amine (100 mg) obtained in Reference Example 27 and 3-nitrobenzaldehyde (88 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (40 mg) was obtained by the method as described in Reference Example 34.

[Step 2] Production of N-[(3-aminophenyl)methyl]-5-(pyrimidin-2-yl)pyridin-3-amine

To a solution of N-[(3-nitrophenyl)methyl]-5-(pyrimidin-2-yl)pyridin-3-amine (40 mg) obtained in Step 1 in
5 methanol (5 mL) and THF (5 mL), after degassing, 10% Pd-C (50 mg) was added under argon atmosphere while stirring the solution at room temperature. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 4 hours. The reaction solution was filtered through celite (R), and the solvent was distilled
10 off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (20 mg).

[Step 3] Production of N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]urea

By using N-[(3-aminophenyl)methyl]-5-(pyrimidin-2-yl)pyridin-3-amine (20 mg) obtained in Step 2 instead of N-[(3-aminophenyl)methyl]-6-(3,4-dimethoxyphenyl)pyrazin-2-amine, the title compound (13 mg) was obtained by the method as described in Step 3 of Example 158.

Example 161: N-[4-Fluoro-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea
20

[Step 1] Production of N-[(2-fluoro-5-nitrophenyl)methyl]-5-(pyrimidin-2-yl)pyridin-3-amine

By using 5-(pyrimidin-2-yl)pyridin-3-amine (133 mg) obtained in Reference Example 27 and 2-fluoro-5-nitrobenzaldehyde (196 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (150 mg) was obtained by the method as described in Reference Example 34.

[Step 2] Production of tert-butyl [(2-fluoro-5-nitrophenyl)methyl][5-(pyrimidin-2-yl)pyridin-3-yl]carbamate

By using N-[(2-fluoro-5-nitrophenyl)methyl]-5-(pyrimidin-2-yl)pyridin-3-amine (150 mg) obtained in Step 1 instead of 7-bromo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine, the title compound (105 mg) was obtained by the method as described in Step 1 of Reference Example 23.

35 [Step 3] Production of tert-butyl [(5-amino-2-

fluorophenyl)methyl][5-(pyrimidin-2-yl)pyridin-3-yl]carbamate

To a solution of tert-butyl [(2-fluoro-5-nitrophenyl)methyl][5-(pyrimidin-2-yl)pyridin-3-yl]carbamate (104 mg) obtained in Step 2 in ethanol (2 mL) and water (0.2 mL),
5 tin(II) chloride dihydrate (221 mg) was added, and the reaction mixture was stirred at 65°C for 2 hours. To the reaction solution, aqueous sodium hydroxide solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline solution, and the solvent was
10 distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (72 mg).

[Step 4] Production of tert-butyl {[2-fluoro-5-({[(1R,2S)-2-hydroxycyclohexyl]carbamoyl}amino)phenyl)methyl}[5-(pyrimidin-2-yl)pyridin-3-yl]carbamate
15

By using tert-butyl [(5-amino-2-fluorophenyl)methyl][5-(pyrimidin-2-yl)pyridin-3-yl]carbamate (70 mg) obtained in Step 3 instead of N-[(3-aminophenyl)methyl]-6-(3,4-dimethoxyphenyl)pyrazin-2-amine, the title compound (82 mg) was
20 obtained by the method as described in Step 3 of Example 158.

[Step 5] Production of N-[4-fluoro-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea

To a solution of tert-butyl {[2-fluoro-5-({[(1R,2S)-2-hydroxycyclohexyl]carbamoyl}amino)phenyl)methyl}[5-(pyrimidin-2-yl)pyridin-3-yl]carbamate (80 mg) obtained in Step 4 in methanol
25 (0.3 mL), hydrogen chloride (4M 1,4-dioxane solution, 1 mL) was added, and the reaction mixture was stirred at room temperature for 2 hours. The reaction solution was purified by silica gel
30 column chromatography to afford the title compound (50 mg).

Example 164: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{1-[(6-phenylpyrazin-2-yl)amino]ethyl}benzamide

[Step 1] Production of methyl 3-{1-[(6-chloropyrazin-2-yl)amino]ethyl}-4-methylbenzoate

35 By using methyl 3-(1-aminoethyl)-4-methylbenzoate (218

mg) instead of methyl 3-(aminomethyl)-4-methylbenzoate, the title compound (75 mg) was obtained by the method as described in Step 3 of Example 156.

[Step 2] Production of methyl 4-methyl-3-{1-[(6-phenylpyrazin-2-yl)amino]ethyl}benzoate

By using methyl 3-{1-[(6-chloropyrazin-2-yl)amino]ethyl}-4-methylbenzoate (75 mg) obtained in Step 1 and phenylboronic acid (36 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (80 mg) was obtained by the method as described in Reference Example 14.

[Step 3] Production of 4-methyl-3-{1-[(6-phenylpyrazin-2-yl)amino]ethyl}benzoic acid

By using methyl 4-methyl-3-{1-[(6-phenylpyrazin-2-yl)amino]ethyl}benzoate (77 mg) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (67 mg) was obtained by the method as described in Step 2 of Reference Example 1.

[Step 4] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{1-[(6-phenylpyrazin-2-yl)amino]ethyl}benzamide

By using 4-methyl-3-{1-[(6-phenylpyrazin-2-yl)amino]ethyl}benzoic acid (30 mg) obtained in Step 3 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (17 mg) was obtained by the method as described in Step 4 of Example 1.

Example 165: 3-[[[3,3'-Bipyridin]-5-yl)methoxy]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of methyl 3-[(5-bromopyridin-3-yl)methoxy]-4-methylbenzoate

By using methyl 3-hydroxy-4-methylbenzoate (750 mg) and (5-bromopyridin-3-yl)methanol (933 mg) instead of methyl 5-hydroxypyridine-3-carboxylate and 3,3-difluorocyclobutan-1-ol, the title compound (1.16 g) was obtained by the method as described in Step 1 of Reference Example 3. MS (m/z): 336.4 [M+H]⁺

[Step 2] Production of methyl 3-[[[3,3'-bipyridin]-5-yl)methoxy]-

4-methylbenzoate

By using methyl 3-[(5-bromopyridin-3-yl)methoxy]-4-methylbenzoate (150 mg) obtained in Step 1 and pyridin-3-ylboronic acid (66 mg) instead of 2-chloropyrimidin-4-amine and
5 isoquinolin-4-ylboronic acid, the title compound (103 mg) was obtained by the method as described in Reference Example 14. MS (m/z): 335.5 [M+H]⁺

[Step 3] Production of 3-([(3,3'-bipyridin]-5-yl)methoxy]-4-methylbenzoic acid

10 By using methyl 3-([(3,3'-bipyridin]-5-yl)methoxy]-4-methylbenzoate (103 mg) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (100 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 321.6 [M+H]⁺

15 [Step 4] Production of 3-([(3,3'-bipyridin]-5-yl)methoxy)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-([(3,3'-bipyridin]-5-yl)methoxy)-4-methylbenzoic acid (50 mg) obtained in Step 3 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic
20 acid, the title compound (47 mg) was obtained by the method as described in Step 4 of Example 1.

[0238]

Example 166: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzamide

25 [Step 1] Production of methyl 4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzoate

By using methyl 3-[(5-bromopyridin-3-yl)methoxy]-4-methylbenzoate (250 mg) obtained in Step 1 of Example 165 instead of 3-bromo-5-(methoxymethoxy)pyridine, the title compound (127
30 mg) was obtained by the method as described in Step 1 of Reference Example 10. MS (m/z): 336.4 [M+H]⁺

[Step 2] Production of 4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzoic acid

By using methyl 4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzoate (127 mg) obtained in Step 1 instead of
35

methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (101 mg) was obtained by the method as described in Step 2 of Reference Example 1.

[Step 3] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzamide

By using 4-methyl-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzoic acid (60 mg) obtained in Step 2 instead of 3-{{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (76 mg) was obtained by the method as described in Step 4 of Example 1.

Example 170: 4-Chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl)benzamide

[Step 1] Production of methyl 4-chloro-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl)benzoate

By using 5-(pyrimidin-2-yl)pyridin-3-ol (123 mg) obtained in Step 2 of Reference Example 10 and methyl 4-chloro-3-(hydroxymethyl)benzoate (130 mg) obtained in Reference Example 31 instead of methyl 5-hydroxypyridine-3-carboxylate and 3,3-difluorocyclobutan-1-ol, the title compound (50 mg) was obtained by the method as described in Step 1 of Reference Example 3. MS (m/z): 356.4 [M+H]⁺

[Step 2] Production of 4-chloro-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl)benzoic acid

By using methyl 4-chloro-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl)benzoate (50 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (43 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 342.4 [M+H]⁺

[Step 3] Production of 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl)benzamide

By using 4-chloro-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl)benzoic acid (43 mg) obtained in Step 2 instead of 3-{{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (39 mg) was obtained by

the method as described in Step 4 of Example 1.

Example 172: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-[1-(5-phenylpyridin-3-yl)ethoxy]benzamide

[Step 1] Production of methyl 3-[1-(5-bromopyridin-3-yl)ethoxy]-4-methylbenzoate

By using methyl 3-hydroxy-4-methylbenzoate (432 mg) and 1-(5-bromopyridin-3-yl)ethan-1-ol (500 mg) instead of methyl 5-hydroxypyridine-3-carboxylate and 3,3-difluorocyclobutan-1-ol, the title compound (650 mg) was obtained by the method as

described in Step 1 of Reference Example 3. MS (m/z): 350.3 [M+H]⁺

[Step 2] Production of 3-[1-(5-bromopyridin-3-yl)ethoxy]-4-methylbenzoic acid

By using methyl 3-[1-(5-bromopyridin-3-yl)ethoxy]-4-methylbenzoate (450 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (350 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 336.3 [M+H]⁺

[Step 3] Production of 3-[1-(5-bromopyridin-3-yl)ethoxy]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-[1-(5-bromopyridin-3-yl)ethoxy]-4-methylbenzoic acid (350 mg) obtained in Step 2 instead of 3-[[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino]-4-methylbenzoic acid, the title compound (350 mg) was obtained by the method as described in Step 4 of Example 1. MS (m/z): 433.5 [M+H]⁺

[Step 4] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[1-(5-phenylpyridin-3-yl)ethoxy]benzamide

By using 3-[1-(5-bromopyridin-3-yl)ethoxy]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (50 mg) obtained in Step 3 and phenylboronic acid (17 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (30 mg) was obtained by the method as described in Reference Example 14.

Example 173: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-[(E)-2-(5-phenylpyridin-3-yl)ethenyl]benzamide

[Step 1] Production of 3-ethenyl-N-[(1R,2R)-2-hydroxycyclohexyl]-4-methylbenzamide

By using 3-bromo-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (20.0 g) obtained in Reference Example 43 and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11.8 g) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (13.0 g) was obtained by the method as described in Reference Example 14. MS (m/z): 260.2 [M+H]⁺

[Step 2] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(E)-2-(5-phenylpyridin-3-yl)ethenyl]benzamide

A mixture of 3-ethenyl-N-[(1R,2R)-2-hydroxycyclohexyl]-4-methylbenzamide (30 mg) obtained in Step 1, 3-bromo-5-phenylpyridine (27 mg), TEA (0.024 mL), tris(2-methylphenyl)phosphine (11 mg), Pd(OAc)₂ (3.9 mg), and acetonitrile (0.58 mL) was allowed to react at 100°C for 80 minutes, using a microwave reaction apparatus. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (24 mg).

Example 174: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-[2-(5-phenylpyridin-3-yl)ethyl]benzamide

To a solution of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(E)-2-(5-phenylpyridin-3-yl)ethenyl]benzamide (15 mg) obtained in Example 173 in ethanol (5 mL), after degassing, 10% Pd-C (7.7 mg) was added under argon atmosphere while stirring the solution at room temperature. The reaction mixture was stirred under hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through celite (R), and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (7 mg).

[0239]

Example 175: N-[(1S,2S)-2-Hydroxycyclohexyl]-4-methyl-3-{[methyl(5-phenylpyridin-3-yl)amino]methyl}benzamide

[Step 1] Production of methyl 3-{[(5-bromopyridin-3-

yl) (methyl)amino]methyl}-4-methylbenzoate

To a solution of methyl 3-{[(5-bromopyridin-3-yl)amino]methyl}-4-methylbenzoate (850 mg) obtained in Step 1 of Example 147 in THF (10 mL), 60% sodium hydride (79 mg) was added
5 under ice cooling, and the reaction mixture was stirred at room temperature for 20 minutes. Then, iodomethane (720 mg) was added thereto, and the reaction mixture was stirred at the same temperature overnight. To the reaction solution, water was added under ice cooling, and the mixture was extracted with ethyl
10 acetate. The organic layer was washed with saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (200 mg). MS (m/z): 349.4 [M+H]⁺

15 [Step 2] Production of 3-{[(5-bromopyridin-3-yl) (methyl)amino]methyl}-4-methylbenzoic acid

By using methyl 3-{[(5-bromopyridin-3-yl) (methyl)amino]methyl}-4-methylbenzoate (200 mg) obtained in Step 1 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title
20 compound (170 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 335.4 [M+H]⁺

[Step 3] Production of 3-{[(5-bromopyridin-3-yl) (methyl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

25 By using 3-{[(5-bromopyridin-3-yl) (methyl)amino]methyl}-4-methylbenzoic acid (170 mg) obtained in Step 2 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (147 mg) was obtained by the method as described in Step 4 of Example 1.

30 MS (m/z): 432.6 [M+H]⁺

[Step 4] Production of N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[methyl(5-phenylpyridin-3-yl)amino]methyl}benzamide

By using 3-{[(5-bromopyridin-3-yl) (methyl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide (30 mg) obtained in Step 3 and phenylboronic acid
35

(9.3 mg) instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (24 mg) was obtained by the method as described in Reference Example 14.

Example 177: 3-[(Z)-2-([2,3'-Bipyridin]-5'-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

[Step 1] Production of 3-(2,2-difluoroethenyl)-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

To a solution of 4-fluoro-3-formyl-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide (500 mg) obtained in Reference Example 29 and triphenylphosphine (593 mg) in DMF (3.8 mL), a solution of sodium chlorodifluoroacetate (431 mg) in DMF (0.94 mL) was added dropwise at 100°C over 30 minutes, and the reaction mixture was stirred at the same temperature for 30 minutes. To the reaction solution, water was added under ice cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (200 mg). MS (m/z): 300.1 [M+H]⁺

[Step 2] Production of 4-fluoro-3-[(Z)-2-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

To 3-(2,2-difluoroethenyl)-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide (100 mg) obtained in Step 1, bis(pinacolato)diboron (170 mg), potassium acetate (39 mg), tricyclohexylphosphine (19 mg), and copper(I) chloride (3.3 mg), THF (2.2 mL) was added, and after degassing, the reaction mixture was stirred under argon atmosphere at 40°C overnight. To the reaction solution, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure to afford the title compound (130 mg). [Step 3] Production of 3-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-

fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

By using 5'-bromo-2,3'-bipyridine (45 mg) and 4-fluoro-3-[(Z)-2-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide (65 mg)

5 obtained in Step 2 instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (10 mg) was obtained by the method as described in Reference Example 14.

Example 180: 5-[(Z)-2-([2,3'-Bipyridin]-5'-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

10 [Step 1] Production of ethyl 5-(2,2-difluoroethenyl)-6-methylpyridine-3-carboxylate

By using ethyl 5-formyl-6-methylpyridine-3-carboxylate (2.65 g) obtained in Reference Example 33 instead of 4-fluoro-3-formyl-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide, the title
15 compound (2.80 g) was obtained by the method as described in Step 1 of Example 177. MS (m/z): 228.1 [M+H]⁺

[Step 2] Production of ethyl 5-[(Z)-2-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-6-methylpyridine-3-carboxylate

20 By using ethyl 5-(2,2-difluoroethenyl)-6-methylpyridine-3-carboxylate (200 mg) obtained in Step 1 instead of 3-(2,2-difluoroethenyl)-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide, the title compound (280 mg) was obtained by the method as described in Step 2 of Example 177.

25 [Step 3] Production of ethyl 5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-6-methylpyridine-3-carboxylate

By using 5'-bromo-2,3'-bipyridine (196 mg) and ethyl 5-[(Z)-2-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-6-methylpyridine-3-carboxylate (280 mg) obtained in
30 Step 2 instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (230 mg) was obtained by the method as described in Reference Example 14. MS (m/z): 364.2 [M+H]⁺

[Step 4] Production of 5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-6-methylpyridine-3-carboxylic acid
35

By using ethyl 5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-6-methylpyridine-3-carboxylate (230 mg) obtained in Step 3 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (165 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 336.1 [M+H]⁺

[Step 5] Production of 5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

By using 5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-6-methylpyridine-3-carboxylic acid (120 mg) obtained in Step 4 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (77 mg) was obtained by the method as described in Step 4 of Example 1.

Example 192: 3-[(Z)-2-(2-Aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

[Step 1] Production of methyl 3-(2,2-difluoroethenyl)-4-fluorobenzoate

By using methyl 4-fluoro-3-formylbenzoate (1.27 g) instead of 4-fluoro-3-formyl-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide, the title compound (1.30 g) was obtained by the method as described in Step 1 of Example 177.

[Step 2] Production of methyl 3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluorobenzoate

To methyl 3-(2,2-difluoroethenyl)-4-fluorobenzoate (130 mg) obtained in Step 1, bis(pinacolato)diboron (305 mg), potassium acetate (118 mg), tricyclohexylphosphine (34 mg), and copper(I) chloride (22 mg), THF (4 mL) was added, and after degassing, the reaction mixture was stirred under argon atmosphere at 40°C for 8 hours. To the reaction solution, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was then distilled off under

reduced pressure. To the obtained residue, 5-bromopyrimidin-2-amine (105 mg), potassium carbonate (166 mg), Pd(dppf)Cl₂·CH₂Cl₂ (49 mg), 1,4-dioxane (2 mL), and water (0.2 mL) were added, and after degassing, the reaction mixture was stirred under argon atmosphere at 85°C overnight. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to afford the title compound (200 mg). MS (m/z): 292.1 [M+H]⁺

[Step 3] Production of 3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluorobenzoic acid

By using methyl 3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluorobenzoate (200 mg) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (36 mg) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 278.1 [M+H]⁺

[Step 4] Production of 3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

By using 3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluorobenzoic acid (36 mg) obtained in Step 3 instead of 3-[[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino]-4-methylbenzoic acid, the title compound (4 mg) was obtained by the method as described in Step 4 of Example 1. Example 194: 3-[(Z)-2-{5-[(4-Ethylpiperazin-1-yl)methyl]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[Step 1] Production of methyl 3-(2,2-difluoroethenyl)-4-methylbenzoate

By using methyl 3-formyl-4-methylbenzoate (13.4 g) instead of 4-fluoro-3-formyl-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide, the title compound (15.0 g) was obtained by the method as described in Step 1 of Example 177. MS (m/z): 213.1 [M+H]⁺

[Step 2] Production of methyl 3-[(Z)-2-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-4-methylbenzoate

By using methyl 3-(2,2-difluoroethenyl)-4-methylbenzoate (6.0 g) obtained in Step 1 instead of 3-(2,2-difluoroethenyl)-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide, the title compound (8.6 g) was
5 obtained by the method as described in Step 2 of Example 177.

[Step 3] Production of methyl 3-[(Z)-2-fluoro-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-4-methylbenzoate

By using 1-[(5-bromopyridin-3-yl)methyl]-4-ethylpiperazine (6.3 g) obtained in Reference Example 38 and
10 methyl 3-[(Z)-2-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-4-methylbenzoate (8.5 g) obtained in Step 2 instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (7.5 g) was obtained by the method as described in Reference Example 14. MS (m/z): 398.3 [M+H]⁺

15 [Step 4] Production of 3-[(Z)-2-fluoro-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-4-methylbenzoic acid

By using methyl 3-[(Z)-2-fluoro-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-4-methylbenzoate (7.5 g) obtained in Step 3 instead of methyl 5-
20 [(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (4.7 g) was obtained by the method as described in Step 2 of Reference Example 1. MS (m/z): 384.5 [M+H]⁺

[Step 5] Production of 3-[(Z)-2-{5-[(4-Ethylpiperazin-1-yl)methyl]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-
25 hydroxycyclohexyl]-4-methylbenzamide

By using 3-[(Z)-2-fluoro-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-4-methylbenzoic acid (4.7 g) obtained in Step 4 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title
30 compound (3.4 g) was obtained by the method as described in Step 4 of Example 1.

[0240]

Example 199: 5-[(Z)-2-{6-[(Cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-
35 methylpyridine-3-carboxamide

[Step 1] Production of ethyl 5-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-6-methylpyridine-3-carboxylate

By using 5-bromopyridin-2-amine (114 mg) and ethyl 5-[(Z)-2-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]-6-methylpyridine-3-carboxylate obtained in Step 2 of Example 180 instead of 2-chloropyrimidin-4-amine and isoquinolin-4-ylboronic acid, the title compound (40 mg) was obtained by the method as described in Reference Example 14. MS (m/z): 302.1 [M+H]⁺

[Step 2] Production of ethyl 5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-6-methylpyridine-3-carboxylate

By using ethyl 5-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-6-methylpyridine-3-carboxylate (60 mg) obtained in Step 1 and cyclopropanecarbaldehyde (19 mg) instead of 1-methylpiperazine and 5-bromopyridine-3-carbaldehyde, the title compound (12 mg) was obtained by the method as described in Reference Example 34. MS (m/z): 356.5 [M+H]⁺

[Step 3] Production of 5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-6-methylpyridine-3-carboxylic acid

By using ethyl 5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-6-methylpyridine-3-carboxylate (12 mg) obtained in Step 2 instead of methyl 5-[(cyclopropylmethyl)amino]pyridine-3-carboxylate, the title compound (11 mg) was obtained by the method as described in Step 2 of Reference Example 1.

[Step 4] Production of 5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-N-

[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

By using 5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-6-methylpyridine-3-carboxylic acid (11 mg) obtained in Step 3 instead of 3-{[2-(cyclopropylamino)-1,3-thiazole-5-carbonyl]amino}-4-methylbenzoic acid, the title compound (10 mg) was obtained by the method as described in Step

4 of Example 1.

[0241]

The compounds of Reference Examples and Examples are shown in Table 3 to Table 29 described below.

5 [0242]

In the tables, Referenced Reference Example means that the compound in question was produced using the corresponding raw materials by the method as described in the method for producing the compound with the Reference Example number corresponding to that number, and for example, a Reference Example compound with a Referenced Reference Example number of 1 means that it was produced by the method as described in Reference Example 1.

[0243]

In the tables, Referenced Example means that the compound in question was produced using the corresponding raw materials by the method as described in the method for producing the compound with the Example number corresponding to that number, and for example, an Example compound with a Referenced Example number of 1 means that it was produced by the method as described in Example 1.

[0244]

In the tables, Chemical Name refers to the name of the compound corresponding to the Reference Example number and the Example number. In addition, Data means the instrumental analytical data, such as mass spectrometric data (m/z values), ¹H NMR data (δ (ppm) of peaks), and elemental analytical data (composition (%) of C, H and N).

[0245]

[Table 3]

Example	Referenced Example	Chemical Name
1	1	2-(cyclopropylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide

2	2	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide
3	3	2-(cyclopropylmethyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide
4	3	5-(cyclopropylamino)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
5	5	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-2-phenyl-1,3-oxazole-5-carboxamide
6	6	N-(5-{{(1S)-2-hydroxy-1-phenylethyl}carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide
7	5	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-5-[(propan-2-yl)oxy]pyridine-3-carboxamide
8	1	2-[(cyclopropylmethyl)amino]-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide
9	2	5-(4-chlorophenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
10	5	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-2-propyl-1,3-thiazole-5-carboxamide
11	2	5-(3-chlorophenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
12	2	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-5-(2-methylphenyl)pyridine-3-carboxamide
13	2	5-(2-chlorophenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide

[0246]

[Table 4]

Example	Referenced Example	Chemical Name
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14	6	N-(5-{[(2S)-1-hydroxypentan-2-yl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide
15	2	5-[(E)-2-cyclopropylethenyl]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
16	3	5-[(cyclopropylmethyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
17	17	5-[cyclopropyl(methyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
18	2	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-(4-methoxyphenyl)pyridine-3-carboxamide
19	2	5-(4-fluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
20	20	5-(3-fluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
21	2	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[4-(trifluoromethyl)phenyl]pyridine-3-carboxamide
22	2	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[3-(trifluoromethyl)phenyl]pyridine-3-carboxamide
23	2	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-(2-methylprop-1-en-1-yl)pyridine-3-carboxamide
24	24	5-(cyclopropylmethoxy)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
25	1	2-[(3,3-difluorocyclobutyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide

[0247]

[Table 5]

Example	Referenced Example	Chemical Name
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26	26	2-[(2-cyclopropylethyl)amino]-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide
27	26	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-2-[(propan-2-yl)amino]-1,3-thiazole-5-carboxamide
28	3	5-[(4,4-difluorocyclohexyl)oxy]-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
29	2	5-(2-fluorophenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
30	2	5-(2,3-difluorophenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
31	2	5-(2,4-difluorophenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
32	2	5-(3,5-difluorophenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
33	2	5-(2-fluoro-4-methoxyphenyl)-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
34	2	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-5-[3-(trifluoromethoxy)phenyl]pyridine-3-carboxamide
35	2	N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)-5-[2-(trifluoromethoxy)phenyl]pyridine-3-carboxamide
36	2	5-[2-fluoro-4-(trifluoromethyl)phenyl]-N-(5-{{(1S,2S)-2-hydroxycyclohexyl}carbamoyl}-2-methylphenyl)pyridine-3-carboxamide

[0248]

[Table 6]

Example	Referenced Example	Chemical Name
37	2	5-(2,6-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
38	26	2-(tert-butylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide
39	26	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-[(1-methylcyclopropyl)amino]-1,3-thiazole-5-carboxamide
40	26	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-[(1-methylcyclobutyl)amino]-1,3-thiazole-5-carboxamide
41	26	2-[(2,2-dimethylpropyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide
42	2	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-(3,4,5-trifluorophenyl)pyridine-3-carboxamide
43	2	5-(4-cyclopropylphenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
44	3	N-(2-chloro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)-5-(cyclopropylmethoxy)pyridine-3-carboxamide
45	5	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)imidazo[2,1-b][1,3]thiazole-5-carboxamide
46	3	5-(cyclopropylmethoxy)-N-(3-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
47	5	5-[(3,3-difluorocyclobutyl)oxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide

[0249]

[Table 7]

Example	Referenced Example	Chemical Name
48	3	2-(cyclopropylmethyl)-N-(3-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide
49	5	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-methoxypyridine-3-carboxamide
50	5	5-ethoxy-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
51	5	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(pyridin-2-yl)oxy]pyridine-3-carboxamide
52	5	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(pyrimidin-2-yl)oxy]pyridine-3-carboxamide
53	5	N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(1-methylcyclopropyl)methoxy]pyridine-3-carboxamide
54	5	5-[(3,3-difluorocyclobutyl)methoxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide
55	3	N-(2-chloro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)-2-(cyclopropylmethyl)-1,3-thiazole-5-carboxamide
56	3	5-(cyclopropylmethoxy)-N-(2-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)pyridine-3-carboxamide
57	57	3-[(5-bromopyridin-3-yl)ethynyl]-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
58	58	4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(5-phenylpyridin-3-yl)ethynyl]benzamide
59	59	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(5-methylpyridin-3-yl)ethynyl]benzamide

[Table 8]

Example	Referenced Example	Chemical Name
60	59	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(5-phenylpyridin-3-yl)ethynyl]benzamide
61	61	3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
62	62	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]ethynyl}benzamide
63	62	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrazin-2-yl)pyridin-3-yl]ethynyl}benzamide
64	59	4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]ethynyl}benzamide
65	59	3-[(6-aminopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
66	62	3-{[2,3'-bipyridin]-5'-yl}ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
67	67	3-[(5-cyclopropylpyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
68	67	3-[(6-cyclopropylpyrazin-2-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
69	67	3-{[6-(2-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
70	67	3-{[6-(3-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
71	67	3-{[6-(4-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
72	59	3-(6-{[(cyclopropylmethyl)amino]pyrazin-2-yl}ethynyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[0251]

[Table 9]

Example	Referenced Example	Chemical Name
73	59	5-[(5-cyclopropylpyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
74	59	3-[(6-bromopyrazin-2-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
75	67	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-phenylpyrazin-2-yl)ethynyl]benzamide
76	76	3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide
77	77	N1-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-N3-(5-phenylpyridin-3-yl)benzene-1,3-dicarboxamide
78	78	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzamide
79	78	N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[2-(isoquinolin-4-yl)pyrimidin-4-yl]amino}-4-methylbenzamide
80	78	N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-3-{[2-(isoquinolin-4-yl)pyrimidin-4-yl]amino}-4-methylbenzamide
81	78	3-[[2,3'-bipyridin]-6-yl]amino]-5-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
82	78	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[2-(methylamino)quinazolin-5-yl]amino}benzamide
83	83	3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide
84	84	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzamide

[0252]

[Table 10]

Example	Referenced Example	Chemical Name
85	85	3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
86	84	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({(1S)-1-[5-(phenylethynyl)pyridin-3-yl]ethyl} amino)benzamide
87	87	3-{[(1S)-1-([3,4'-bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
88	84	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({(1S)-1-[5-(pyrimidin-2-yl)pyridin-3-yl]ethyl} amino)benzamide
89	89	3-{[(1S)-1-([2,3'-bipyridin]-5'-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
90	84	3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
91	91	3-{[(5-bromopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
92	92	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(5-phenylpyridin-3-yl)methyl}amino} benzamide
93	92	3-{[(2,2'-bipyridin]-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
94	94	3-({[5-(cyclopropylethynyl)pyridin-3-yl]methyl} amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
95	95	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]methyl} amino)benzamide
96	96	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(quinolin-3-yl)methyl}amino} benzamide

[0253]

5 [Table 11]

Example	Referenced Example	Chemical Name
97	94	N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(5-[(1-hydroxycyclopropyl)ethynyl]pyridin-3-yl)methyl]amino]-4-methylbenzamide
98	98	3-[(5-[4-(2-aminopropan-2-yl)phenyl]pyridin-3-yl)methyl]amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
99	92	3-({5-(4-aminophenyl)pyridin-3-yl)methyl} amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
100	92	3-({5-(3,5-difluorophenyl)pyridin-3-yl)methyl} amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
101	101	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(6-phenylpyrazin-2-yl)methyl}amino} benzamide
102	92	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({5-(thiophen-2-yl)pyridin-3-yl)methyl} amino)benzamide
103	92	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({5-(thiophen-3-yl)pyridin-3-yl)methyl} amino)benzamide
104	95	4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-({5-(pyrimidin-2-yl)pyridin-3-yl)methyl} amino)benzamide
105	91	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(pyrazolo[5,1-b][1,3]thiazol-7-yl)methyl}amino} benzamide
106	95	3-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-5-({5-(pyrimidin-2-yl)pyridin-3-yl)methyl} amino)benzamide
107	98	3-({5-(5-fluoropyrimidin-2-yl)pyridin-3-yl)methyl} amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[0254]

[Table 12]

Example	Referenced Example	Chemical Name
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108	91	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3- {[(thieno[3,2-b]pyridin-6-yl)methyl]amino} benzamide
109	109	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3- {[(1H-pyrazolo[3,4-b]pyridin-5-yl)methyl]amino} benzamide
110	110	N-[(1S,2S)-2-hydroxycyclohexyl]-3- {[(imidazo[1,2-b]pyridazin-3-yl)methyl]amino} -4-methylbenzamide
111	98	N-[(1S,2S)-2-hydroxycyclohexyl]-3- ({[5-(imidazo[1,2-a]pyrazin-6-yl)pyridin-3-yl]methyl} amino) -4-methylbenzamide
112	91	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3- ({[1-(pyridin-2-yl)-1H-pyrazol-4-yl]methyl} amino) benzamide
113	113	3- {[(2-aminopyrimidin-5-yl)methyl]amino} -N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
114	113	3- ({[2-(cyclopropylamino)pyrimidin-5-yl]methyl} amino) -N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
115	98	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3- ({[5-(pyrazin-2-yl)pyridin-3-yl]methyl} amino) benzamide
116	116	3- {[(6-acetamidopyridin-3-yl)methyl]amino} -N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
117	113	3- ({[6-[(cyclopropylmethyl)amino]pyridin-3-yl} methyl) amino] -N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
118	118	3- {[([2,2'-bipyridin]-5-yl)methyl]amino} -N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
119	91	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3- {[(pyrazolo[1,5-a]pyrimidin-3-yl)methyl]amino} benzamide

[0255]

[Table 13]

Example	Referenced Example	Chemical Name
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120	116	3-[(6-[(cyclopropanecarbonyl)amino]pyridin-3-yl)methyl]amino]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
121	92	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-phenylpyrimidin-5-yl)methyl]amino} benzamide
122	122	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl]amino} benzamide
123	91	N-[(1S,2S)-2-hydroxycyclohexyl]-6-methyl-5-[(pyrazolo[1,5-a]pyridin-3-yl)methyl]amino} pyridine-3-carboxamide
124	116	methyl {5-[(5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylanilino)methyl]pyridin-2-yl} carbamate
125	116	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(oxan-4-yl)amino]pyridin-3-yl)methyl]amino} benzamide
126	116	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(pyridin-2-yl)amino]pyrimidin-5-yl)methyl]amino} benzamide
127	91	N-{5-[(5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylanilino)methyl]pyridin-2-yl} morpholine-4-carboxamide
128	92	N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(2-(4-methoxyphenyl)pyrimidin-5-yl)methyl]amino)-4-methylbenzamide
129	129	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(pyridin-3-yl)carbamoyl]amino}pyridin-3-yl)methyl]amino} benzamide
130	116	3-[(6-(cyclobutylamino)pyridin-3-yl)methyl]amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
131	131	3-[(5-aminopyrazin-2-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[0256]

[Table 14]

Example	Referenced Example	Chemical Name
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132	113	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(oxan-4-yl)amino]pyrimidin-5-yl)methyl]amino]benzamide
133	91	3-[[6-[[cyclopropyl(methyl)carbamoyl]amino]pyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
134	116	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(propan-2-yl)amino]pyridin-3-yl)methyl]amino]benzamide
135	113	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(3R)-oxolan-3-yl]amino]pyrimidin-5-yl)methyl]amino} benzamide
136	113	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(3S)-oxolan-3-yl]amino]pyrimidin-5-yl)methyl]amino} benzamide
137	116	N-{5-[(5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl)-2-methylanilino)methyl]pyridin-2-yl} oxane-4-carboxamide
138	138	N-[(1S,2S)-2-hydroxycyclohexyl]-3-[[6-[[1r,3r)-3-methoxycyclobutane-1-carbonyl]amino]pyridin-3-yl)methyl]amino}-4-methylbenzamide
139	138	N-{5-[(5-[(1S,2S)-2-hydroxycyclohexyl]carbamoyl)-2-methylanilino)methyl]pyridin-2-yl} oxolane-3-carboxamide
140	140	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl]amino}benzamide
141	116	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(oxetan-3-yl)amino]pyridin-3-yl)methyl]amino]benzamide
142	142	3-[(2-aminopyrimidin-5-yl)methyl]amino}-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

[0257]

[Table 15]

Example	Referenced Example	Chemical Name
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143	142	3-{{(2-aminopyrimidin-5-yl)methyl}amino}-5-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
144	144	3-{{(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
145	91	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl]methyl}amino)benzamide
146	101	3-{{([3,3'-bipyridin]-5-yl)amino}methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
147	147	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide
148	148	3-{{([2,3'-bipyridin]-5'-yl)amino}methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
149	95	N-[(1R,2R)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide
150	91	N-[(1S,2S)-2-hydroxycyclohexyl]-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide
151	91	4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide
152	152	3-{{(5-bromopyridin-3-yl)amino}methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide
153	153	N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-{{(5-phenylpyridin-3-yl)amino}methyl}benzamide
154	153	3-{{(5-cyclopropylpyridin-3-yl)amino}methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide

[0258]

[Table 16]

Example	Referenced Example	Chemical Name
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155	155	3-([(2,3'-bipyridin]-5'-yl)amino)methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide
156	156	N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-([(6-phenylpyrazin-2-yl)amino)methyl}benzamide
157	94	5-([5-(cyclopropylethynyl)pyridin-3-yl]amino)methyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
158	158	N-[3-([6-(3,4-dimethoxyphenyl)pyrazin-2-yl]amino)methyl]phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea
159	159	N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[3-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]urea
160	159	N-[2-fluoro-5-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea
161	161	N-[4-fluoro-3-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea
162	161	N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[4-methyl-3-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]urea
163	161	N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[2-methyl-5-([5-(pyrimidin-2-yl)pyridin-3-yl]amino)methyl]phenyl]urea
164	164	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{1-[(6-phenylpyrazin-2-yl)amino]ethyl}benzamide
165	165	3-([(3,3'-bipyridin]-5-yl)methoxy]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
166	166	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzamide

[0259]

[Table 17]

Example	Referenced Example	Chemical Name
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167	166	4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzamide
168	165	3-{[(3,3'-bipyridin)-5-yl]oxy}methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
169	166	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl}benzamide
170	170	4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl}benzamide
171	166	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{1-[5-(pyrimidin-2-yl)pyridin-3-yl]ethoxy}benzamide
172	172	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[1-(5-phenylpyridin-3-yl)ethoxy]benzamide
173	173	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(E)-2-(5-phenylpyridin-3-yl)ethenyl]benzamide
174	174	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[2-(5-phenylpyridin-3-yl)ethyl]benzamide
175	175	N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[methyl(5-phenylpyridin-3-yl)amino]methyl}benzamide
176	84	3-{[ethyl(5-phenylpyridin-3-yl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
177	177	3-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
178	177	4-fluoro-3-{(Z)-2-fluoro-2-[5-(pyrimidin-2-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

[0260]

[Table 18]

Example	Referenced Example	Chemical Name
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179	177	3-[(Z)-2-fluoro-2-(imidazo[1,2-b]pyridazin-3-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
180	180	5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
181	177	3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
182	177	3-[(Z)-2-fluoro-2-{5-[(morpholin-4-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
183	177	3-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
184	180	4-fluoro-3-{(Z)-2-fluoro-2-[5-(morpholin-4-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
185	180	4-fluoro-3-[(Z)-2-fluoro-2-{5-[(oxan-4-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
186	180	4-fluoro-3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
187	180	5-{(Z)-2-[5-(cyclopropylmethoxy)pyridin-3-yl]-2-fluoroethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
188	180	5-{(Z)-2-fluoro-2-[5-(morpholin-4-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide

[0261]

[Table 19]

Example	Referenced Example	Chemical Name
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189	180	5-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
190	180	5-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
191	180	3-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
192	192	3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
193	177	3-[(Z)-2-fluoro-2-{5-[(1-methylpiperidin-4-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
194	194	3-[(Z)-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
195	180	5-[(Z)-2-fluoro-2-{5-[(oxetan-3-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
196	180	4-fluoro-3-[(Z)-2-fluoro-2-{5-[(oxetan-3-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
197	177	3-[(Z)-2-(6-{[2-(dimethylamino)ethyl]amino}pyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
198	177	3-[(Z)-2-(5-{[2-(dimethylamino)ethyl]amino}pyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide

[0262]

[Table 20]

Example	Referenced Example	Chemical Name
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199	199	5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide
200	180	3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-4-methylbenzamide
201	180	3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-(2-hydroxy-3,3-dimethylbutyl)-4-methylbenzamide
202	180	3-[(Z)-2-{2-[(cyclopropylmethyl)amino]pyrimidin-5-yl}-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
203	180	3-{(Z)-2-[2-(cyclopropylamino)pyrimidin-5-yl]-2-fluoroethenyl}-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
204	180	3-[(Z)-2-(2-amino-4-methylpyrimidin-5-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
205	180	4-fluoro-3-{(Z)-2-fluoro-2-[2-(methylamino)pyrimidin-5-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide
206	177	3-[(Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
207	177	4-fluoro-3-[(Z)-2-fluoro-2-(5-fluoropyridin-3-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

[0263]

[Table 21]

Example	Data
1	MS(ESI+)m/z 415.5(M+H) ⁺
2	MS(ESI+)m/z 430.3(M+H) ⁺
3	MS(ESI+)m/z 414.3(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:10.18(s,1H), 8.45(s,1H), 8.09(d,1H), 7.82-7.80(m,1H), 7.72(dd,1H), 7.36(d,1H), 4.61(d,1H), 3.67-3.55(m,1H), 3.46-3.36(m,1H), 2.92(d,2H), 2.26(s,3H), 1.94-1.78(m,2H), 1.70-1.55(m,2H), 1.30-1.08(m,5H), 0.63-0.56(m,2H), 0.36-0.30(m,2H)

4	MS(ESI+)m/z 409.3(M+H) ⁺
5	MS(ESI+)m/z 420.4(M+H) ⁺
6	MS(ESI+)m/z 452.4(M+H) ⁺
7	MS(ESI+)m/z 412.3(M+H) ⁺
8	MS(ESI+)m/z 429.5(M+H) ⁺
9	MS(ESI+)m/z 464.3(M+H) ⁺
10	MS(ESI+)m/z 402.4(M+H) ⁺
11	MS(ESI+)m/z 464.3(M+H) ⁺
12	MS(ESI+)m/z 444.4(M+H) ⁺
13	MS(ESI+)m/z 464.3(M+H) ⁺
14	MS(ESI+)m/z 418.5(M+H) ⁺
15	MS(ESI+)m/z 420.4(M+H) ⁺
16	MS(ESI+)m/z 423.4(M+H) ⁺
17	MS(ESI+)m/z 423.4(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆)δ:10.09(s,1H), 8.52(d,1H), 8.49(d,1H), 8.08(d,1H), 7.85(d,1H), 7.74-7.70(m,2H), 7.36(d,1H), 4.58(d,1H), 3.64-3.60(m,1H), 3.43-3.39(m,1H), 3.02(s,1H), 2.28(s,3H), 1.89-1.83(m,2H), 1.66-1.62(m,2H), 1.26-1.17(m,4H), 0.93-0.88(m,2H), 0.63-0.59(m,2H)
18	MS(ESI+)m/z 460.4(M+H) ⁺
19	MS(ESI+)m/z 448.3(M+H) ⁺
20	MS(ESI+)m/z 448.3(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:10.31(s,1H), 9.15(d,1H), 9.13(d,1H), 8.66(dd,1H), 8.09(d,1H), 7.88(d,1H), 7.80-7.70(m,3H), 7.65-7.57(m,1H), 7.38(d,1H), 7.36-7.28(m,1H), 4.59(d,1H), 3.69-3.57(m,1H), 3.46-3.37(m,1H), 2.31(s,3H), 1.94-1.80(m,2H), 1.69-1.57(m,2H), 1.31-1.15(m,4H)
21	MS(ESI+)m/z 498.3(M+H) ⁺

[0264]

[Table 22]

Example	Data
22	MS(ESI+)m/z 498.3(M+H) ⁺
23	MS(ESI+)m/z 408.3(M+H) ⁺
24	MS(ESI+)m/z 424.3(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:10.16(s,1H), 8.74(d,1H), 8.48(d,1H), 8.07(d,1H), 7.86-7.85(m,2H), 7.72(dd,1H), 7.37(d,1H), 4.57(d,1H), 4.00(d,2H), 3.64-3.60(m,1H), 3.44-3.38(m,1H), 2.28(s,3H), 1.91-1.83(m,2H), 1.66-1.61(m,2H), 1.28-1.18(m,5H), 0.63-0.59(m,2H), 0.39-0.35(m,2H)
25	MS(ESI+)m/z 465.3(M+H) ⁺
26	MS(ESI+)m/z 443.6(M+H) ⁺

27	MS(ESI+)m/z 417.6(M+H) ⁺
28	MS(ESI+)m/z 488.5(M+H) ⁺
29	MS(ESI+)m/z 448.5(M+H) ⁺
30	MS(ESI+)m/z 466.5(M+H) ⁺
31	MS(ESI+)m/z 466.5(M+H) ⁺
32	MS(ESI+)m/z 466.5(M+H) ⁺
33	MS(ESI+)m/z 478.4(M+H) ⁺
34	MS(ESI+)m/z 514.6(M+H) ⁺
35	MS(ESI+)m/z 514.5(M+H) ⁺
36	MS(ESI+)m/z 516.6(M+H) ⁺
37	MS(ESI+)m/z 466.4(M+H) ⁺
38	MS(ESI+)m/z 431.6(M+H) ⁺
39	MS(ESI+)m/z 429.8(M+H) ⁺
40	MS(ESI+)m/z 443.8(M+H) ⁺
41	MS(ESI+)m/z 445.7(M+H) ⁺
42	MS(ESI+)m/z 484.6(M+H) ⁺
43	MS(ESI+)m/z 470.7(M+H) ⁺
44	MS(ESI+)m/z 444.6(M+H) ⁺
45	MS(ESI+)m/z 399.6(M+H) ⁺
46	MS(ESI+)m/z 442.6(M+H) ⁺
47	MS(ESI+)m/z 460.8(M+H) ⁺
48	MS(ESI+)m/z 432.5(M+H) ⁺
49	MS(ESI+)m/z 384.3(M+H) ⁺

[0265]

[Table 23]

Example	Data
50	MS(ESI+)m/z 398.3(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:10.19(s,1H), 8.75(d,1H), 8.48(d,1H), 8.09(d,1H), 7.86-7.84(m,2H), 7.72(dd,1H), 7.37(d,1H), 4.59(d,1H), 4.2(q,2H), 3.64-3.61(m,1H), 3.43-3.37(m,1H), 2.28(s,3H), 1.91-1.82(m,2H), 1.66-1.61(m,2H), 1.38(t,3H), 1.28-1.21(m,4H)
51	MS(ESI+)m/z 447.3(M+H) ⁺
52	MS(ESI+)m/z 448.3(M+H) ⁺
53	MS(ESI+)m/z 438.4(M+H) ⁺
54	MS(ESI+)m/z 474.4(M+H) ⁺
55	MS(ESI+)m/z 434.2(M+H) ⁺
56	MS(ESI+)m/z 428.3(M+H) ⁺

57	MS(ESI+)m/z 433.1(M+H) ⁺
58	MS(ESI+)m/z 431.3(M+H) ⁺
59	MS(ESI+)m/z 349.5(M+H) ⁺
60	MS(ESI+)m/z 411.6(M+H) ⁺
61	MS(ESI+)m/z 413.4(M+H) ⁺
62	MS(ESI+)m/z 413.5(M+H) ⁺
63	MS(ESI+)m/z 413.5(M+H) ⁺
64	MS(ESI+)m/z 433.5(M+H) ⁺
65	MS(ESI+)m/z 350.6(M+H) ⁺
66	MS(ESI+)m/z 412.5(M+H) ⁺
67	MS(ESI+)m/z 375.7(M+H) ⁺
68	MS(ESI+)m/z 376.5(M+H) ⁺
69	MS(ESI+)m/z 430.5(M+H) ⁺
70	MS(ESI+)m/z 430.5(M+H) ⁺
71	MS(ESI+)m/z 430.5(M+H) ⁺
72	MS(ESI+)m/z 405.5(M+H) ⁺
73	MS(ESI+)m/z 376.6(M+H) ⁺
74	MS(ESI+)m/z 414.4(M+H) ⁺
75	MS(ESI+)m/z 412.6(M+H) ⁺
76	MS(ESI+)m/z 465.4(M+H) ⁺
77	MS(ESI+)m/z 430.5(M+H) ⁺
78	MS(ESI+)m/z 404.6(M+H) ⁺
79	MS(ESI+)m/z 454.6(M+H) ⁺

[0266]

[Table 24]

Example	Data
80	MS(ESI+)m/z 506.6(M+H) ⁺
81	MS(ESI+)m/z 421.7(M+H) ⁺
82	MS(ESI+)m/z 406.3(M+H) ⁺
83	MS(ESI+)m/z 434.6(M+H) ⁺
84	MS(ESI+)m/z 430.5(M+H) ⁺
85	MS(ESI+)m/z 431.4(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.93(d,1H), 8.78(d,1H), 8.68(d,1H), 8.62(d,1H), 8.24(dd,1H), 8.14-8.11(m,1H), 7.68(d,1H), 7.54-7.50(m,1H), 7.03-6.99(m,2H), 6.95(s,1H), 5.33(d,1H), 4.85-4.81(m,1H), 4.47(d,1H), 3.53-3.48(m,1H), 3.39-3.33(m,1H), 2.25(s,3H), 1.86-1.76(m,2H), 1.61(d,3H), 1.78-1.74(m,2H), 1.24-1.16(m,4H)
86	MS(ESI+)m/z 454.4(M+H) ⁺

87	MS(ESI+)m/z 431.4(M+H) ⁺
88	MS(ESI+)m/z 432.4(M+H) ⁺
89	MS(ESI+)m/z 431.4(M+H) ⁺
90	MS(ESI+)m/z 451.3(M+H) ⁺
91	MS(ESI+)m/z 418.6(M+H) ⁺
92	MS(ESI+)m/z 416.7(M+H) ⁺
93	MS(ESI+)m/z 417.4(M+H) ⁺
94	MS(ESI+)m/z 404.4(M+H) ⁺
95	MS(ESI+)m/z 418.7(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:9.37(d,1H), 8.94(d,2H), 8.73(d,1H), 8.68(dd,1H), 7.75(d,1H), 7.51(dd,1H), 7.06-7.01(m,2H), 6.95(s,1H), 5.91(dd,1H), 4.55(d,2H), 4.49(d,1H), 3.52-3.48(m,1H), 3.39-3.36(m,1H), 2.21(s,3H), 1.86-1.74(m,2H), 1.62-1.56(m,2H), 1.17-1.16(m,4H)
96	MS(ESI+)m/z 390.4(M+H) ⁺
97	MS(ESI+)m/z 420.7(M+H) ⁺
98	MS(ESI+)m/z 473.5(M+H) ⁺
99	MS(ESI+)m/z 431.7(M+H) ⁺
100	MS(ESI+)m/z 452.7(M+H) ⁺
101	MS(ESI+)m/z 417.4(M+H) ⁺
102	MS(ESI+)m/z 422.6(M+H) ⁺
103	MS(ESI+)m/z 422.6(M+H) ⁺
104	MS(ESI+)m/z 438.6(M+H) ⁺

[0267]

[Table 25]

Example	Data
105	MS(ESI+)m/z 385.5(M+H) ⁺
106	MS(ESI+)m/z 436.6(M+H) ⁺
107	MS(ESI+)m/z 436.6(M+H) ⁺
108	MS(ESI+)m/z 396.6(M+H) ⁺
109	MS(ESI+)m/z 380.6(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:13.56(brs,1H), 8.58(s,1H), 8.15(s,1H), 8.09(s,1H), 7.78(d,1H), 7.05-7.01(m,2H), 7.00(s,1H), 5.74(t,1H), 4.59-4.46(m,3H), 3.59-3.35(m,2H), 2.19(s,3H), 1.93-1.72(m,2H), 1.67-1.50(m,2H), 1.27-1.09(m,4H)
110	MS(ESI+)m/z 380.6(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.59(dd,1H), 8.12(dd,1H), 7.81(d,1H), 7.67(s,1H), 7.23(dd,1H), 7.14(d,1H), 7.09-7.01(m,2H), 5.50(t,1H), 4.78(d,2H), 4.55(d,1H), 3.62-3.48(m,1H), 3.47-3.31(m,1H), 2.15(s,3H), 1.93-1.75(m,2H), 1.70-1.55(m,2H), 1.29-1.12(m,4H)
111	MS(ESI+)m/z 457.7(M+H) ⁺

112	MS(ESI+)m/z 406.6(M+H) ⁺
113	MS(ESI+)m/z 356.6(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.23(s,2H), 7.82(d,1H), 7.07-7.00(m,3H), 6.49(s,2H), 5.42(t,1H), 4.56(d,1H), 4.17(d,2H), 3.63-3.51(m,1H), 3.45-3.35(m,1H), 2.14(s,3H), 1.93-1.78(m,2H), 1.69-1.55(m,2H), 1.28-1.14(m,4H)
114	MS(ESI+)m/z 396.6(M+H) ⁺
115	MS(ESI+)m/z 418.8(M+H) ⁺
116	MS(ESI+)m/z 397.8(M+H) ⁺
117	MS(ESI+)m/z 409.6(M+H) ⁺
118	MS(ESI+)m/z 417.7(M+H) ⁺
119	MS(ESI+)m/z 380.5(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:9.06(dd,1H), 8.56(dd,1H), 8.20(s,1H), 7.78(d,1H), 7.16(s,1H), 7.06-7.01(m,3H), 5.37(t,1H), 4.61-4.54(m,3H), 3.61-3.52(m,2H), 2.14(s,3H), 1.92-1.78(m,2H), 1.67-1.57(m,2H), 1.27-1.16(m,4H)
120	MS(ESI+)m/z 423.7(M+H) ⁺
121	MS(ESI+)m/z 417.5(M+H) ⁺
122	MS(ESI+)m/z 406.3(M+H) ⁺
123	MS(ESI+)m/z 380.2(M+H) ⁺
124	MS(ESI+)m/z 413.3(M+H) ⁺
125	MS(ESI+)m/z 439.4(M+H) ⁺

[0268]

[Table 26]

Example	Data
126	MS(ESI+)m/z 433.5(M+H) ⁺
127	MS(ESI+)m/z 468.5(M+H) ⁺
128	MS(ESI+)m/z 447.5(M+H) ⁺
129	MS(ESI+)m/z 475.4(M+H) ⁺
130	MS(ESI+)m/z 409.4(M+H) ⁺
131	MS(ESI+)m/z 356.6(M+H) ⁺
132	MS(ESI+)m/z 440.2(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.28(s,2H), 7.81(d,1H), 7.06-7.00(m,4H), 5.42(t,1H), 4.56(d,1H), 4.17(d,2H), 3.93-3.81(m,3H), 3.62-3.52(m,1H), 2.13(s,3H), 1.92-1.75(m,4H), 1.68-1.54(m,2H), 1.54-1.41(m,2H), 1.29-1.14(m,4H)
133	MS(ESI+)m/z 452.4(M+H) ⁺
134	MS(ESI+)m/z 397.3(M+H) ⁺
135	MS(ESI+)m/z 426.3(M+H) ⁺
136	MS(ESI+)m/z 426.3(M+H) ⁺
137	MS(ESI+)m/z 467.4(M+H) ⁺

138	MS(ESI+)m/z 467.4(M+H) ⁺
139	MS(ESI+)m/z 453.4(M+H) ⁺
140	MS(ESI+)m/z 407.3(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.83(d,1H), 8.59(s,1H), 8.10-8.06(m,2H), 7.98(d,1H), 7.80(d,1H), 7.07-7.03(m,2H), 6.96(s,1H), 5.86(t,1H), 4.53(m,3H), 3.58-3.30(m,2H), 2.21(s,3H), 1.91-1.72(m,2H), 1.68-1.52(m,2H),1.27-1.09(m,4H)
141	MS(ESI+)m/z 411.3(M+H) ⁺
142	MS(ESI+)m/z 376.1(M+H) ⁺
143	MS(ESI+)m/z 374.4(M+H) ⁺
144	MS(ESI+)m/z 397.3(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:7.78(d,1H), 7.58(d,1H),7.05-6.97(m,3H),6.94(d,1H),6.54(s,1H),5.42(t,1H),4.54(d,1H),4.19(d,2H),4.07(d,2H),3.61-3.30(m,4H),2.14(s,3H),1.94-1.74(m,2H),1.70-1.52(m,2H),1.32-1.10(m,4H)
145	MS(ESI+)m/z 407.3(M+H) ⁺
146	MS(ESI+)m/z 417.6(M+H) ⁺

[0269]

[Table 27]

Example	Data
147	MS(ESI+)m/z 418.6(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.90(d,2H), 8.75(d,1H), 8.13(d,1H), 7.97(d,1H), 7.88(dd,1H), 7.85(d,1H), 7.71(dd,1H), 7.47(dd,1H), 7.29(d,1H), 6.57(dd,1H), 4.54(d,1H), 4.35(d,2H), 3.60-3.55(m,1H), 3.42-3.36(m,1H), 2.41(s,3H), 1.87-1.79(m,2H), 1.63-1.59(m,2H), 1.25-1.44(m,4H)
148	MS(ESI+)m/z 417.8(M+H) ⁺ ¹ H-NMR(400MHz,CD ₃ OD) δ:8.63-8.62(m,1H), 8.33(s,1H), 8.02(dd,1H), 7.93-7.83(m,3H), 7.70-7.67(m,1H), 7.58-7.57(m,1H), 7.41-7.38(m,1H), 7.31(dd,1H), 4.45(d,1H), 3.78-3.71(m,1H), 3.51-3.44(m,1H), 2.47(d,1H), 2.04-1.97(m,2H), 1.76-1.70(m,2H), 1.37-1.29(m,4H)
149	MS(ESI+)m/z 418.5(M+H) ⁺
150	MS(ESI+)m/z 404.6(M+H) ⁺
151	MS(ESI+)m/z 422.6(M+H) ⁺
152	MS(ESI+)m/z 470.6(M+H) ⁺
153	MS(ESI+)m/z 468.7(M+H) ⁺
154	MS(ESI+)m/z 432.7(M+H) ⁺
155	MS(ESI+)m/z 469.7(M+H) ⁺
156	MS(ESI+)m/z 469.7(M+H) ⁺
157	MS(ESI+)m/z 405.7(M+H) ⁺
158	MS(ESI+)m/z 478.5(M+H) ⁺
159	MS(ESI+)m/z 419.7(M+H) ⁺
160	MS(ESI+)m/z 437.5(M+H) ⁺

161	MS(ESI+)m/z 437.5(M+H) ⁺
162	MS(ESI+)m/z 433.5(M+H) ⁺
163	MS(ESI+)m/z 433.5(M+H) ⁺
164	MS(ESI+)m/z 431.6(M+H) ⁺
165	MS(ESI+)m/z 418.8(M+H) ⁺
166	MS(ESI+)m/z 419.8(M+H) ⁺
167	MS(ESI+)m/z 439.6(M+H) ⁺
168	MS(ESI+)m/z 418.7(M+H) ⁺
169	MS(ESI+)m/z 419.8(M+H) ⁺
170	MS(ESI+)m/z 439.6(M+H) ⁺
171	MS(ESI+)m/z 433.6(M+H) ⁺
172	MS(ESI+)m/z 431.7(M+H) ⁺

[0270]

[Table 28]

Example	Data
173	MS(ESI+)m/z 413.6(M+H) ⁺
174	MS(ESI+)m/z 415.6(M+H) ⁺
175	MS(ESI+)m/z 430.7(M+H) ⁺
176	MS(ESI+)m/z 444.4(M+H) ⁺
177	MS(ESI+)m/z 436.3(M+H) ⁺ ¹ H-NMR(400MHz, DMSO-d ₆) δ:9.35(d,1H), 9.08(d,1H), 8.78-8.76(m,2H), 8.38(dd,1H), 8.25-8.22(m,2H), 7.97-7.92(m,1H), 7.90-7.85(m,1H), 7.48(ddd,1H), 7.41(dd,1H), 7.11(d,1H), 4.64(d,1H), 3.61-3.59(m,1H), 3.40-3.36(m,1H), 1.92-1.84(m,2H), 1.67-1.65(m,2H), 1.26-1.15(m,4H)
178	MS(ESI+)m/z 437.2(M+H) ⁺
179	MS(ESI+)m/z 395.3(M+H) ⁺
180	MS(ESI+)m/z 433.3(M+H) ⁺
181	MS(ESI+)m/z 467.5(M+H) ⁺
182	MS(ESI+)m/z 454.4(M+H) ⁺
183	MS(ESI+)m/z 424.4(M+H) ⁺
184	MS(ESI+)m/z 444.3(M+H) ⁺
185	MS(ESI+)m/z 458.3(M+H) ⁺
186	MS(ESI+)m/z 471.4(M+H) ⁺
187	MS(ESI+)m/z 426.3(M+H) ⁺
188	MS(ESI+)m/z 441.3(M+H) ⁺
189	MS(ESI+)m/z 371.2(M+H) ⁺

	¹ H-NMR(400MHz,DMSO-d ₆) δ:8.76(d,1H), 8.36-8.29(m,3H), 7.78(dd,1H), 6.53-6.43(m,4H), 4.66(d,1H), 3.64-3.62(m,1H), 3.43-3.37(m,1H), 2.59(s,3H), 1.91-1.82(m,2H), 1.66-1.62(m,2H), 1.27-1.21(m,4H)
190	MS(ESI+)m/z 372.2(M+H) ⁺
191	MS(ESI+)m/z 374.2(M+H) ⁺
192	MS(ESI+)m/z 375.2(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.64(s,2H), 8.27(dd,1H), 8.21(d,1H), 7.84-7.80(m,1H), 7.33(dd,1H), 7.23(s,2H), 6.57(d,1H), 4.67(brs,1H), 3.62-3.60(m,1H), 3.48-3.40(m,1H), 1.91-1.82(m,2H), 1.66-1.63(m,2H), 1.26-1.14(m,4H)
193	MS(ESI+)m/z 467.4(M+H) ⁺

[0271]

[Table 29]

Example	Data
194	MS(ESI+)m/z 481.4(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.93(d,1H), 8.54(d,1H), 8.16(d,1H), 8.08(d,1H), 8.03(dd,1H), 7.73(dd,1H), 7.34(d,1H), 6.96(d,1H), 4.60(d,1H), 3.63-3.61(m,1H), 3.57(s,2H), 3.44-3.40(m,1H), 2.49-2.33(m,8H), 2.43(s,3H), 2.30(q,2H), 1.91-1.84(m,2H), 1.66-1.63(m,2H), 1.26-1.19(m,4H), 0.97(t,3H)
195	MS(ESI+)m/z 427.5(M+H) ⁺
196	MS(ESI+)m/z 430.5(M+H) ⁺
197	MS(ESI+)m/z 441.6(M+H) ⁺
198	MS(ESI+)m/z 441.6(M+H) ⁺
199	MS(ESI+)m/z 425.5(M+H) ⁺
200	MS(ESI+)m/z 501.3(M+H) ⁺
201	MS(ESI+)m/z 469.4(M+H) ⁺
202	MS(ESI+)m/z 429.6(M+H) ⁺
203	MS(ESI+)m/z 415.3(M+H) ⁺
204	MS(ESI+)m/z 389.2(M+H) ⁺
205	MS(ESI+) m/z 389.2(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.69(s,2H), 8.28(dd,1H), 8.18(d,1H), 7.84-7.80(m,1H), 7.69(dd,1H), 7.33(dd,1H), 6.57(d,1H), 4.62(d,1H), 3.65-3.59(m,1H), 3.45-3.38(m,1H), 2.86(d,3H), 1.89-1.83(m,2H), 1.66-1.61(m,2H), 1.27-1.18(m,4H)
206	MS(ESI+) m/z 371.2(M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.16(d,2H), 8.03(d,1H), 7.93(s,1H), 7.64(dd,1H), 7.28(d,1H), 6.94(s,2H), 6.73(d,1H), 4.56(d,1H), 3.61-3.54(m,1H), 3.42-3.33(m,1H), 2.34(s,3H), 1.87-1.78(m,2H), 1.62-1.57(m,2H), 1.25-1.13(m,4H)
207	MS(ESI+) m/z 377.0 (M+H) ⁺ ¹ H-NMR(400MHz,DMSO-d ₆) δ:8.87(s,1H), 8.64(d,1H), 8.30(dd,1H), 8.19-8.17(m,2H), 7.90-7.86(m,1H), 7.36(dd,1H), 7.03(d,1H), 4.57(d,1H), 3.60-3.55(m,1H), 3.40-3.32(m,1H), 1.89-1.79(m,2H), 1.63-1.56(m,2H), 1.25-1.14(m,4H)

[0272]

Hereinafter, biological test examples for the compounds used in the present invention will be shown.

[0273]

5 <Test Example 1: PDGFR- β Tyrosine kinase inhibitory action>

1. Preparation of test substance

The test substance was prepared with dimethyl sulfoxide (DMSO) to 10 mM and diluted with DMSO so as to reach a concentration of 0.001 to 1000 μ M. This DMSO solution was diluted
10 by 8 times with an assay buffer 1 (50 mM HEPES (pH 7.0), 0.02% NaN₃, 0.01% Bovine Serum Albumin, 0.1 mM orthovanadate, 1 mM Dithiothreitol, 5 mM MgCl₂, and 1 mM MnCl₂) and further diluted by 5 times with an assay buffer 2 (50 mM HEPES (pH 7.0), 0.02% NaN₃, 0.01% Bovine Serum Albumin, 0.1 mM orthovanadate, 1 mM
15 Dithiothreitol, 5 mM MgCl₂, 1 mM MnCl₂, and 40 nM Supplemented Enzymatic Buffer (cisbio)).

[0274]

2. Measurement of PDGFR- β tyrosine kinase inhibitory action

For the measurement, the HTRF KinEASE-TK kit from
20 Cisbio Bioassays SAS was used. To a 384 well plate, the test substance solution was added at 4 μ L each, then 2 μ L of a PDGFR- β enzyme solution (final concentration of 1 ng/ μ L, Carna Biosciences, Inc.) and 4 μ L of a substrate solution obtained by adding 0.6 μ M ATP to TK substrate-3-biotin (cisbio) were added,
25 and the solution was allowed to react at 30°C for 30 minutes at a final concentration of the test substance being 0.01 to 10,000 nM.

Thereafter, 10 μ L of a detection solution (cisbio) was added to each well and allowed to react at 30°C for 1 hour. The
30 fluorescence intensity was measured with a microplate reader (Spectra Max M5, Molecular device).

[0275]

3. Analysis of measurement results

Using the ratio of fluorescence intensity for each
35 condition, the inhibition rate was calculated when the values for

the positive control (1% DMSO solution) and the negative control (enzyme (-)) were defined as 0% and 100%, respectively.

Subsequently, a nonlinear regression analysis with a two parameter logistic model for the log concentration and inhibition rate was carried out using the SAS system (SAS Institute Inc.) to estimate the concentration of the test substance that inhibits the PDGFR- β tyrosine kinase activity by 50% (IC₅₀ value).

The results are shown in the following Table 30 to Table 33.

10 [Table 30]

Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)	Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)
1	5.9	31	73
2	22	32	47
3	82	33	19
4	4.9	34	19
5	6.1	35	160
6	12	36	130
7	170	37	33
8	6.0	38	79
9	26	39	100
10	220	40	43
11	17	41	130
12	170	42	230
13	140	43	23
14	40	44	190
15	11	45	15
16	22	46	77
17	42	47	390
18	39	48	120
19	13	49	120
20	13	50	61
21	73	51	61
22	14	52	77
23	26	53	12
24	64	54	40

25	39	55	83
26	4.6	56	120
27	8.3	57	51
28	170	58	12
29	35	59	210
30	44	60	46

[0276]

[Table 31]

Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)	Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)
61	41	91	150
62	6.5	92	46
63	15	93	360
64	260	94	49
65	94	95	120
66	5.4	96	200
67	43	97	100
68	80	98	140
69	25	99	13
70	20	100	32
71	42	101	170
72	10	102	23
73	220	103	50
74	180	104	260
75	15	105	230
76	49	106	67
77	38	107	190
78	51	108	51
79	120	109	46
80	120	110	350
81	190	111	150
82	27	112	39
83	5.0	113	83
84	19	114	270
85	180	115	260
86	230	116	66

87	250	117	79
88	230	118	390
89	78	119	330
90	310	120	20

[0277]

[Table 32]

Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)	Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)
121	160	151	170
122	150	152	50
123	210	153	88
124	22	154	340
125	130	155	36
126	45	156	25
127	63	157	180
128	180	158	26
129	17	159	26
130	80	160	46
131	490	161	16
132	72	162	2.6
133	170	163	260
134	170	164	110
135	120	165	390
136	32	166	49
137	41	167	210
138	16	168	350
139	30	169	52
140	330	170	200
141	69	171	260
142	210	172	190
143	97	173	54
144	65	174	27
145	100	175	24
146	210	176	50
147	24	177	15
148	16	178	26

149	220	179	5.9
150	360	180	16

[0278]

[Table 33]

Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)	Test Compound (Compound of Example)	PDGF- β IC ₅₀ (nM)
181	100	195	19
182	33	196	26
183	30	197	120
184	51	198	7.2
185	5.1	199	52
186	150	200	16
187	14	201	38
188	68	202	77
189	200	203	61
190	110	204	21
191	35	205	130
192	29	206	31
193	1.0	207	100
194	35		

5 [0279]

[0280]

<Test Example 2: Suppression action against proliferation of TEL-PDGFR β and TEL-KIT fusion gene transfected cells>

[0281]

10 1. Fabrication of TEL-PDGFR β and TEL-KIT fusion gene transfected cells

A human TEL-PDGFR β fusion gene (see, for example, CELL, 1994, 77, 307-316) or a human TEL-KIT fusion gene was inserted into the multicloning site of the retroviral expression vector pMYs-IRES-GFP to fabricate a vector for gene transfection. As for the human TEL-KIT fusion gene, an amino sequence that is important for the enzymatic activity of the KIT gene (Accession No. NP_000213.1, 521 to 928th amino acids) was identified and

properly combined with the amino acid sequence of the TEL gene, thereby creating a sequence that exhibits activation in the absence of a ligand factor. Subsequently, the vectors for gene transfection were introduced using a transfection reagent

5 (FuGENE6, Promega Corporation) into packaging cells derived from a human fetal kidney cell line, PLAT-E, in the logarithmic growth phase. Since the culture supernatant of PLAT-E after the gene transfection contained virus particles for gene transfection, it was collected and used as a medium for gene transfection. The
10 medium for gene transfection was added to a plate coated with RetroNectin and incubated, and the virus particles were allowed to adhere to the plate. Thereafter, the mouse pro-B cell line Ba/F3 in the logarithmic growth phase was seeded onto the plate and infected with the virus to fabricate cells that proliferate
15 in a PDGFR β or KIT dependent manner.

[0282]

2. Preparation of test substance

The test substance was prepared with dimethyl sulfoxide (DMSO) to 10 mM and diluted with DMSO so as to reach a
20 concentration of 0.0001 to 3 mM. Furthermore, it was diluted by 100 times with distilled water.

[0283]

3. Measurement of suppression action against proliferation of TEL-PDGFR β or TEL-KIT expressing cells

25 The day after TEL-PDGFR β and TEL-KIT expressing cells were seeded onto 96 well plates, the prepared test substance solution was added thereto with a final concentration being 0.1 to 10,000 nM. After 72 hours, the viable cell count was measured using the amount of formazan generated from the reduction of a
30 tetrazolium salt compound by the mitochondrial dehydrogenase of viable cells as an indicator.

[0284]

4. Analysis of measurement results

Based on the amount of formazan in each condition, the
35 suppression rate against cell proliferation was calculated when

the amounts of formazan in the negative control (0.1% DMSO solution) and Blank (medium only) were defined as 0% and 100%, respectively. Subsequently, a nonlinear regression analysis with a two parameter logistic model for the log dose and suppression rate against cell proliferation was carried out using the SAS system (SAS Institute Inc.) to estimate the IC₅₀ value.

The results are shown in the following Table 34 to Table 38.

[0285]

10 [Table 34]

Test Compound (Compound of Example)	PDGFR β /BaF3 proliferation inhibition (IC ₅₀)	KIT/BaF3 proliferation inhibition (IC ₅₀)
1	17	480
2	3.6	200
3	1.4	620
4	26	1500
5	5.8	170
6	14	170
7	43	1900
8	9.7	650
9	22	530
10	25	660
11	13	310
12	35	800
13	17	790
14	11	330
15	3.9	330
16	130	1300
17	10	800
18	20	530
19	30	1000
20	24	900
21	60	2000

22	59	900
23	4.9	620
24	11	1200
25	50	>10000
26	9.3	460
27	8.7	1000
28	50	5800
29	7.5	290

[0286]

[Table 35]

Test Compound (Compound of Example)	PDGFR β /BaF3 proliferation inhibition (IC ₅₀)	KIT/BaF3 proliferation inhibition (IC ₅₀)
30	22	1300
31	8.0	1000
32	17	920
33	80	880
34	8.0	540
35	17	2200
36	25	3500
37	5.1	470
38	7.3	1200
39	13	1000
40	4.6	1200
41	35	2100
42	41	7900
43	17	640
44	21	940
45	0.8	92
46	17	410
47	75	7000
48	16	650

57	440	6900
58	110	1800
59	27	500
60	5.9	410
61	18	840
62	1.7	87
63	0.8	240
64	5.9	230
65	14	270

[0287]

[Table 36]

Test Compound (Compound of Example)	PDGFR β /BaF3 proliferation inhibition (IC ₅₀)	KIT/BaF3 proliferation inhibition (IC ₅₀)
66	2.5	100
67	5.2	300
68	16	2000
69	5.8	330
70	1.8	300
71	6.0	570
75	4.5	300
77	79	600
78	27	570
79	46	2000
80	80	>10000
81	140	3300
84	50	500
85	19	4600
86	42	1700
87	27	9900
88	43	6000
89	20	610

90	35	8300
91	26	2700
92	20	1400
93	45	6200
94	10	260
95	5.7	1000
96	12	310
97	20	1900
98	40	>10000
99	0.5	480

[0288]

[Table 37]

Test Compound (Compound of Example)	PDGFR β /BaF3 proliferation inhibition (IC ₅₀)	KIT/BaF3 proliferation inhibition (IC ₅₀)
100	17	8900
101	56	9000
102	2.0	620
103	4.1	2500
104	3.4	3400
105	4.7	920
106	2.1	1300
107	19	1200
108	2.3	300
112	1.3	250
113	0.2	700
114	2.7	960
115	1.4	1700
146	22	730
147	5.6	100
148	2.4	170
149	58	670

152	100	>10000
153	27	7000
154	230	>10000
155	69	10000
156	22	>10000
158	41	3000
159	1.7	380
160	5.9	1200
161	4.8	>10000
162	1.1	270
163	200	2600
164	180	1400

[0289]

[Table 38]

Test Compound (Compound of Example)	PDGFR β /BaF3 proliferation inhibition (IC ₅₀)	KIT/BaF3 proliferation inhibition (IC ₅₀)
165	9.0	2900
166	2.5	1200
168	18	4100
169	4.0	400
171	12	2400
173	4.6	700
174	50	870

5 [0290]

<Test Example 3: Suppression action against proliferation of pulmonary arterial smooth muscle cells>

[0291]

1. Preparation of test substance

10 The test substance was prepared with dimethyl sulfoxide (DMSO) to 10 mM and diluted with DMSO so as to reach a concentration of 0.003 to 3 mM. Furthermore, it was diluted by 50

times with distilled water.

[0292]

2. Measurement of suppression action against proliferation of pulmonary arterial smooth muscle cells

5 The day after healthy human derived pulmonary arterial smooth muscle cells were seeded onto a 96 well plate using a smooth muscle cell proliferation medium, the proliferation medium was replaced with a 0.1% FBS medium, and the cells were cultured for an additional day. A test substance solution was diluted by
10 10 times with a medium containing BrdU and human PDGF-BB (final concentration of 10 ng/mL, Sigma-Aldrich) and added to cells in equal amounts so as to reach a final concentration of 3 to 10,000 nM. Also, to the human PDGF-BB negative control, BrdU and 0.1% DMSO solution were added. After culturing for 1 day, the amount
15 of BrdU taken up by the proliferating cells was measured using an anti-BrdU antibody.

[0293]

3. Analysis of measurement results

 Based on the amount of BrdU in each condition, the
20 suppression rate against cell proliferation was calculated when the amounts of BrdU in the positive control (human PDGF-BB (+)) and the negative control (human PDGF-BB (-)) were defined as 0% and 100%, respectively. Subsequently, a nonlinear regression analysis with a two parameter logistic model for the log dose and
25 suppression rate against cell proliferation was carried out using the SAS system (SAS Institute Inc.) to estimate the IC₅₀ value.

 The results are shown in the following Table 39 to Table 46.

[0294]

30 [Table 39]

Test Compound (Compound of Example)	Human normal PASMC proliferation suppression (PDGF stimulation IC ₅₀)
1	110
2	23

3	30
4	220
5	48
6	23
7	150
8	110
9	46
10	140
11	49
12	65
13	100
14	48
15	18
16	81
17	130
18	47
19	81
20	77
21	140
22	100
23	64
24	110
25	230
26	25
27	70
28	280

[0295]

[Table 40]

Test Compound (Compound of Example)	Human normal PASMC proliferation suppression (PDGF stimulation IC ₅₀)
29	130
30	52

31	100
32	190
33	67
34	130
35	320
36	92
37	46
38	210
39	150
40	75
41	210
42	95
43	72
44	140
45	56
46	370
47	350
48	310
49	250
50	270
51	180
52	420
53	71
54	340
55	69
56	240

[0296]

[Table 41]

Test Compound (Compound of Example)	Human normal PASMC proliferation suppression (PDGF stimulation IC ₅₀)
57	420
58	57

59	93
60	26
61	18
62	34
63	10
64	92
65	60
66	30
67	120
68	72
69	61
70	50
71	43
72	70
73	80
74	18
75	13
76	27
78	150
79	170
80	280
81	110
82	72
83	48
84	160
85	130
86	280

[0297]

[Table 42]

Test Compound (Compound of Example)	Human normal PSMC proliferation suppression (PDGF stimulation IC ₅₀)
87	350

88	210
89	190
90	360
91	150
92	66
93	260
94	90
95	96
96	72
97	160
98	160
99	27
100	71
101	71
102	30
103	40
104	38
105	28
106	140
107	110
108	85
109	170
110	240
111	380
112	26
113	51
114	190

[0298]

[Table 43]

Test Compound (Compound of Example)	Human normal PSMC proliferation suppression (PDGF stimulation IC ₅₀)
115	290

116	120
117	230
118	140
119	93
120	34
121	300
122	300
123	290
124	25
125	30
126	64
127	45
128	79
129	20
130	53
131	340
132	73
133	110
134	60
135	390
136	150
137	60
138	51
139	100
140	43
141	190
142	130

[0299]

[Table 44]

Test Compound (Compound of Example)	Human normal PSMC proliferation suppression (PDGF stimulation IC ₅₀)
143	90

144	39
145	47
146	44
147	52
148	110
149	150
150	300
151	250
152	82
153	62
154	98
155	160
156	79
157	52
158	22
159	21
160	44
161	110
162	36
163	150
164	110
165	46
166	65
167	210
168	110
169	43
170	130

[0300]

[Table 45]

Test Compound (Compound of Example)	Human normal PASMC proliferation suppression (PDGF stimulation IC ₅₀)
177	11

178	44
179	20
180	32
181	500
182	190
183	24
184	82
185	28
186	220
187	20
188	60
189	90
190	110
191	29
192	24
193	18
194	74
195	26
196	31
197	110
198	39
199	70
200	120
201	120
202	33
203	200
204	52
205	160

[0301]

[Table 46]

Test Compound (Compound of Example)	Human normal PASMC proliferation suppression (PDGF stimulation IC ₅₀)
--	---

206	92
207	99

[0302]

<Test Example 4: Suppression action against formation of erythroid colonies>

5 [0303]

1. Preparation of test substance

The test substance was prepared with dimethyl sulfoxide (DMSO) to 10 mM and diluted with DMSO so as to reach a concentration of 0.1 to 3 mM, thereby preparing a test substance solution with a concentration 1000 times the final concentration.

10

[0304]

2. Measurement of suppression action against formation of erythroid colonies

Human bone marrow CD34 positive hematopoietic stem cells were thawed and the cells were suspended in the MethoCult medium. Then, the test substance solution was added thereto so as to reach a final concentration of 0.1 to 10 μ M. The cells were seeded onto a 35 mm dish and cultured for 14 days. The number of erythroid progenitor cell derived cell colonies was measured under microscope.

20

[0305]

3. Analysis of measurement results

Based on the number of colonies in each condition, the suppression rate against colony formation was calculated when the negative control (0.1% DMSO solution) was defined as 100%, and a nonlinear regression analysis with a two parameter logistic model for the log dose and suppression rate against colony formation was carried out using the SAS system (SAS Institute Inc.) to estimate the IC₅₀ value. The results are shown in the following Table 47.

30

[0306]

[Table 47]

Test Compound (Compound of Example)	Suppression rate against erythroid colony formation (IC ₅₀)
1	3000
2	890
3	>3000
5	470
6	250
7	5500
8	2800
14	360
16	6700
17	1800
20	3200
24	3000
29	>3000
61	>3000
62	180
65	2000
68	5000
71	2000
75	600
85	>10000
95	1900
105	1400
109	2000
110	3200
112	1200
113	4500
114	7500
147	320
148	1000
159	>10000
169	530

Formulation Example

The following Formulation Example is only illustrative and is not intended to limit the scope of the present invention in any way.

5 Formulation Example 1: Tablet (Oral)

In 80 mg of one formulated tablet

	Example 1 compound of the present invention	5.0 mg
	Corn starch	46.6 mg
	Crystalline cellulose	24.0 mg
10	Methylcellulose	4.0 mg
	Magnesium stearate	0.4 mg

Mixed powder of the components in the above percentage is compressed to form an oral tablet by a conventional method.

15 Industrial Applicability

[0308]

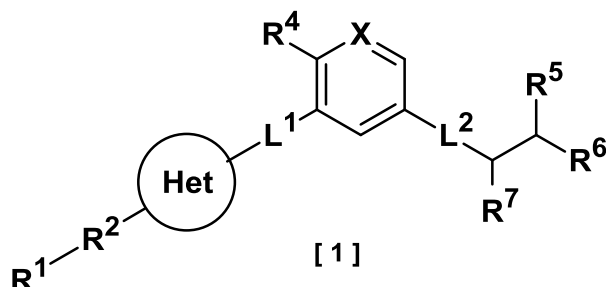
Since the compound of the present invention has an inhibitory activity against the PDGF receptor kinase, it is useful as a therapeutic agent for respiratory diseases, cancers, smooth muscle proliferative diseases, vasoproliferative diseases, autoimmune/inflammatory diseases, metabolic diseases, vasoocclusive diseases, and the like.

CLAIMS

[Claim 1]

A compound represented by the following formula [1]:

[Formula 1]



5

wherein

R^1 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, a C_1 - C_6 haloalkyl, a C_2 - C_6 alkenyl, a C_2 - C_6 haloalkenyl, a C_2 - C_6 alkynyl, a C_2 - C_6 haloalkynyl, a C_1 - C_6 alkoxy, hydroxy, carboxy, an alkylcarbonyloxy, amino, a monoalkylamino, a dialkylamino, an aminoalkyl, an alkylcarbonylamino, nitro, an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted C_3 - C_6 cycloalkenyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl;

15

R^2 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, $-CR^a=CR^b-$, or $-C\equiv C-$, wherein

R^a in R^2 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl and

20

R^b in R^2 is a hydrogen atom, a halogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl, or

R^a and R^b in R^2 are taken together with the carbon atom to which they are bonded to form $C=O$,

each R^c in R^2 is independently a hydrogen atom, a C_1 - C_6 alkyl, or a C_1 - C_6 haloalkyl, and

25

m is an integer of 0 to 3;

Het is a 5- to 10-membered heteroaryl;

L^1 is a bonding hand, $-(CR^aR^b)_m-NR^c-$, $-NR^c-(CR^aR^b)_m-$, $-(CR^aR^b)_m-O-$, $-O-(CR^aR^b)_m-$, $-(CR^aR^b)_m-$, $-NR^c-$, $-O-$, $-NR^c-CO-NR^c-$, -

30

$\text{CR}^{\text{a}}=\text{CR}^{\text{b}}-$, or $-\text{C}\equiv\text{C}-$, wherein

R^{a} in L^1 is a hydrogen atom, a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl, or a $\text{C}_1\text{-C}_6$ haloalkyl and

R^{b} in L^1 is a hydrogen atom, a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl, or a $\text{C}_1\text{-C}_6$ haloalkyl, or

R^{a} and R^{b} in L^1 are taken together with the carbon atom to which they are bonded to form $\text{C}=\text{O}$,

each R^{c} in L^1 is independently a hydrogen atom, a $\text{C}_1\text{-C}_6$ alkyl, or a $\text{C}_1\text{-C}_6$ haloalkyl, and

m in L^1 is an integer of 0 to 3;

X is N or C-R^3 , wherein

R^3 is a hydrogen atom, a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl, or a $\text{C}_1\text{-C}_6$ haloalkyl;

R^4 is a hydrogen atom, a halogen atom, or methyl;

L^2 is a bonding hand, $-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_m\text{-NR}^{\text{c}}-$, $-\text{NR}^{\text{c}}-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_m-$, $-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_m\text{-O-}$, $-\text{O}-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_m-$, $-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_m-$, $-\text{NR}^{\text{c}}-$, $-\text{O-}$, $-\text{NR}^{\text{c}}\text{-CO-NR}^{\text{c}}-$, $-\text{CR}^{\text{a}}=\text{CR}^{\text{b}}-$, or $-\text{C}\equiv\text{C}-$, wherein

R^{a} in L^2 is a hydrogen atom, a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl, or a $\text{C}_1\text{-C}_6$ haloalkyl and

R^{b} in L^2 is a hydrogen atom, a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl, or a $\text{C}_1\text{-C}_6$ haloalkyl, or

R^{a} and R^{b} in L^2 are taken together with the carbon atom to which they are bonded to form $\text{C}=\text{O}$,

each R^{c} in L^2 is independently a hydrogen atom, a $\text{C}_1\text{-C}_6$ alkyl, or a $\text{C}_1\text{-C}_6$ haloalkyl, and

m in L^2 is an integer of 0 to 3;

R^5 is a hydrogen atom, a halogen atom, hydroxy, amino, a $\text{C}_1\text{-C}_6$ alkyl, a $\text{C}_1\text{-C}_6$ haloalkyl, a $\text{C}_1\text{-C}_6$ alkoxy, or a $\text{C}_1\text{-C}_6$ haloalkoxy; and

R^6 is a hydrogen atom, a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl, a $\text{C}_1\text{-C}_6$ haloalkyl, or an optionally substituted phenyl and

R^7 is a hydrogen atom, a halogen atom, a $\text{C}_1\text{-C}_6$ alkyl, a $\text{C}_1\text{-C}_6$ haloalkyl, a hydroxyalkyl, an optionally substituted phenyl, or an optionally substituted $\text{C}_3\text{-C}_6$ cycloalkyl, or

R^6 and R^7 are taken together with the carbon atoms to

which they are bonded to form a C₃-C₆ cycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl or a pharmaceutically acceptable salt thereof, or a solvate thereof.

5

[Claim 2]

The compound according to claim 1, wherein:

R¹ is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl, a C₂-C₆ alkenyl, a C₁-C₆ alkoxy, amino, a monoalkylamino, a
10 dialkylamino, an aminoalkyl, an alkylcarbonylamino, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl;

R² is a bonding hand, -(CR^aR^b)_m-NR^c-, -(CR^aR^b)_m-O-, -
15 (CR^aR^b)_m-, -NR^c-, -O-, -NR^c-CO-NR^c-, -CR^a=CR^b-, or -C≡C-;

L¹ is a bonding hand, -(CR^aR^b)_m-NR^c-, -NR^c-(CR^aR^b)_m-, -
(CR^aR^b)_m-O-, -O-(CR^aR^b)_m-, -(CR^aR^b)_m-, -NR^c-, -CR^a=CR^b-, or -C≡C-,
wherein

R^a in L¹ is a hydrogen atom, a halogen atom, or a C₁-
20 C₆ alkyl and

R^b in L¹ is a hydrogen atom, a halogen atom, or a C₁-
C₆ alkyl, or

R^a in L¹ and R^b in L¹ are taken together with the
carbon atom to which they are bonded to form C=O,

25 each R^c in L¹ is independently a hydrogen atom, a C₁-
C₆ alkyl, or a C₁-C₆ haloalkyl, and

m in L¹ is an integer of 0 to 2;

X is N or C-R³, wherein

R³ is a hydrogen atom, a halogen atom, a C₁-C₆ alkyl,
30 or a C₁-C₆ haloalkyl;

R⁴ is a hydrogen atom, a halogen atom, or methyl;

L² is -(CR^aR^b)_m-NR^c- or -NR^c-CO-NR^c-, wherein

R^a and R^b in L² are taken together with the carbon
atom to which they are bonded to form C=O,

35 each R^c in L² is independently a hydrogen atom, and

m in L² is 1;

R⁵ is hydroxy; and

R⁶ is a hydrogen atom, a C₁-C₆ alkyl, or an optionally substituted phenyl and

5 R⁷ is a hydrogen atom, a C₁-C₆ alkyl, a hydroxyalkyl, or an optionally substituted phenyl, or

R⁶ and R⁷ are taken together with the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl or an optionally substituted aryl

10 or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 3]

The compound according to claim 1, wherein:

15 R¹ is a hydrogen atom, a C₁-C₆ alkoxy, amino, a monoalkylamino, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, or an optionally substituted heteroaryl;

R² is a bonding hand, -(CR^aR^b)_m-O-, -(CR^aR^b)_m-, or -NR^c-;

20 L¹ is -(CR^aR^b)_m-NR^c-, -NR^c-(CR^aR^b)_m-, or -CR^a=CR^b-,
wherein

R^a in L¹ is a hydrogen atom or a halogen atom and

R^b in L¹ is a hydrogen atom, or

25 R^a and R^b in L¹ are taken together with the carbon atom to which they are bonded to form C=O,

each R^c in L¹ is independently a hydrogen atom, and
m in L¹ is 0 or 1;

X is N or C-R³, wherein

R³ is a hydrogen atom;

30 R⁴ is a halogen atom or methyl;

L² is -(CR^aR^b)_m-NR^c-, wherein

R^a and R^b in L² are taken together with the carbon atom to which they are bonded to form C=O,

35 each R^c in L² is independently a hydrogen atom, and
m in L² is 1;

R⁵ is hydroxy; and

R⁶ and R⁷ are taken together with the carbon atoms to which they are bonded to form a C₃-C₆ cycloalkyl or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 4]

The compound according to claim 1, selected from the group consisting of the following (1) to (207):

- 10 (1) 2-(cyclopropylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- (2) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide,
- 15 (3) 2-(cyclopropylmethyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- (4) 5-(cyclopropylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-
- 20 carboxamide,
- (5) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-phenyl-1,3-oxazole-5-carboxamide,
- (6) N-(5-{[(1S)-2-hydroxy-1-phenylethyl]carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide,
- 25 (7) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(propan-2-yl)oxy]pyridine-3-carboxamide,
- (8) 2-[(cyclopropylmethyl)amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,
- 30 (9) 5-(4-chlorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,
- (10) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-2-propyl-1,3-thiazole-5-carboxamide,
- 35 (11) 5-(3-chlorophenyl)-N-(5-{[(1S,2S)-2-

hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(12) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-(2-methylphenyl)pyridine-3-carboxamide,

5 (13) 5-(2-chlorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(14) N-(5-{[(2S)-1-hydroxypentan-2-yl] carbamoyl}-2-methylphenyl)-5-phenylpyridine-3-carboxamide,

10 (15) 5-[(E)-2-cyclopropylethenyl]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(16) 5-[(cyclopropylmethyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-

15 carboxamide,

(17) 5-[cyclopropyl (methyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(18) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-

20 methylphenyl)-5-(4-methoxyphenyl)pyridine-3-carboxamide,

(19) 5-(4-fluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(20) 5-(3-fluorophenyl)-N-(5-{[(1S,2S)-2-

25 hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(21) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-[4-(trifluoromethyl)phenyl]pyridine-3-carboxamide,

30 (22) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-[3-(trifluoromethyl)phenyl]pyridine-3-carboxamide,

(23) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-(2-methylprop-1-en-1-yl)pyridine-3-carboxamide,

35 (24) 5-(cyclopropylmethoxy)-N-(5-{[(1S,2S)-2-

hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(25) 2-[(3,3-difluorocyclobutyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,

(26) 2-[(2-cyclopropylethyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,

(27) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-

10 methylphenyl)-2-[(propan-2-yl) amino]-1,3-thiazole-5-carboxamide,

(28) 5-[(4,4-difluorocyclohexyl) oxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(29) 5-(2-fluorophenyl)-N-(5-{[(1S,2S)-2-

15 hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(30) 5-(2,3-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

20 (31) 5-(2,4-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(32) 5-(3,5-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

25 (33) 5-(2-fluoro-4-methoxyphenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(34) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-

30 methylphenyl)-5-[3-(trifluoromethoxy)phenyl]pyridine-3-carboxamide,

(35) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-[2-(trifluoromethoxy)phenyl]pyridine-3-carboxamide,

35 (36) 5-[2-fluoro-4-(trifluoromethyl)phenyl]-N-(5-{[(1S,2S)-2-

hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(37) 5-(2,6-difluorophenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-

5 carboxamide,

(38) 2-(tert-butylamino)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,

(39) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-2-[(1-methylcyclopropyl) amino]-1,3-thiazole-5-carboxamide,

(40) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-2-[(1-methylcyclobutyl) amino]-1,3-thiazole-5-carboxamide,

15 (41) 2-[(2,2-dimethylpropyl) amino]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-1,3-thiazole-5-carboxamide,

(42) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-5-(3,4,5-trifluorophenyl)pyridine-3-carboxamide,

20 (43) 5-(4-cyclopropylphenyl)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(44) N-(2-chloro-5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}phenyl)-5-

25 (cyclopropylmethoxy)pyridine-3-carboxamide,

(45) N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)imidazo[2,1-b][1,3]thiazole-5-carboxamide,

(46) 5-(cyclopropylmethoxy)-N-(3-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-

30 carboxamide,

(47) 5-[(3,3-difluorocyclobutyl) oxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(48) 2-(cyclopropylmethyl)-N-(3-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl] carbamoyl}-2-methylphenyl)-1,3-thiazole-5-

35

carboxamide,

(49) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-methoxypyridine-3-carboxamide,

(50) 5-ethoxy-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(51) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(pyridin-2-yl)oxy]pyridine-3-carboxamide,

(52) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(pyrimidin-2-yl)oxy]pyridine-3-carboxamide,

(53) N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-5-[(1-methylcyclopropyl)methoxy]pyridine-3-carboxamide,

(54) 5-[(3,3-difluorocyclobutyl)methoxy]-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-

carboxamide,

(55) N-(2-chloro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)-2-(cyclopropylmethyl)-1,3-thiazole-5-carboxamide,

(56) 5-(cyclopropylmethoxy)-N-(2-fluoro-5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}phenyl)pyridine-3-carboxamide,

(57) 3-[(5-bromopyridin-3-yl)ethynyl]-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(58) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(5-phenylpyridin-3-yl)ethynyl]benzamide,

(59) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(5-methylpyridin-3-yl)ethynyl]benzamide,

(60) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(5-phenylpyridin-3-yl)ethynyl]benzamide,

(61) 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(62) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]ethynyl}benzamide,

(63) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrazin-2-yl)pyridin-3-yl]ethynyl}benzamide,

(64) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[5-(pyrimidin-2-

- yl)pyridin-3-yl]ethynyl}benzamide,
(65) 3-[(6-aminopyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(66) 3-[[2,3'-bipyridin]-5'-yl]ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
5 (67) 3-[(5-cyclopropylpyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(68) 3-[(6-cyclopropylpyrazin-2-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
10 (69) 3-{[6-(2-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(70) 3-{[6-(3-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(71) 3-{[6-(4-fluorophenyl)pyrazin-2-yl]ethynyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
15 (72) 3-({6-[(cyclopropylmethyl)amino]pyrazin-2-yl}ethynyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(73) 5-[(5-cyclopropylpyridin-3-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
20 (74) 3-[(6-bromopyrazin-2-yl)ethynyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(75) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-phenylpyrazin-2-yl)ethynyl]benzamide,
(76) 3-[(5-bromopyridin-3-yl)ethynyl]-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,
25 (77) N¹-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-N³-(5-phenylpyridin-3-yl)benzene-1,3-dicarboxamide,
(78) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[2-(pyridin-3-yl)pyrimidin-4-yl]amino}benzamide,
30 (79) N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[2-(isoquinolin-4-yl)pyrimidin-4-yl]amino}-4-methylbenzamide,
(80) N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-3-{[2-(isoquinolin-4-yl)pyrimidin-4-yl]amino}-4-methylbenzamide,
(81) 3-[[2,3'-bipyridin]-6-yl]amino]-5-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
35

- (82) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[2-(methylamino)quinazolin-5-yl]amino}benzamide,
- (83) 3-(2-amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,
- 5 (84) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(1S)-1-(5-phenylpyridin-3-yl)ethyl]amino}benzamide,
- (85) 3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (86) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({(1S)-1-[5-(phenylethynyl)pyridin-3-yl]ethyl}amino)benzamide,
- 10 (87) 3-{[(1S)-1-([3,4'-bipyridin]-5-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (88) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({(1S)-1-[5-(pyrimidin-2-yl)pyridin-3-yl]ethyl}amino)benzamide,
- 15 (89) 3-{[(1S)-1-([2,3'-bipyridin]-5'-yl)ethyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (90) 3-{[(1S)-1-([3,3'-bipyridin]-5-yl)ethyl]amino}-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- (91) 3-{[(5-bromopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-
- 20 hydroxycyclohexyl]-4-methylbenzamide,
- (92) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(5-phenylpyridin-3-yl)methyl]amino}benzamide,
- (93) 3-{[(3,3'-bipyridin]-5-yl)methyl}amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 25 (94) 3-({[5-(cyclopropylethynyl)pyridin-3-yl]methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (95) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]methyl}amino)benzamide,
- (96) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(quinolin-3-
- 30 yl)methyl]amino}benzamide,
- (97) N-[(1S,2S)-2-hydroxycyclohexyl]-3-({[5-[(1-hydroxycyclopropyl)ethynyl]pyridin-3-yl]methyl}amino)-4-methylbenzamide,
- (98) 3-({[5-[4-(2-aminopropan-2-yl)phenyl]pyridin-3-yl]methyl}amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-
- 35

methylbenzamide,

(99) 3-([5-(4-aminophenyl)pyridin-3-yl]methyl)amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(100) 3-([5-(3,5-difluorophenyl)pyridin-3-yl]methyl)amino)-N-
5 [(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(101) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(6-phenylpyrazin-2-yl)methyl]amino}benzamide,

(102) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([5-(thiophen-2-yl)pyridin-3-yl]methyl)amino)benzamide,

10 (103) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([5-(thiophen-3-yl)pyridin-3-yl]methyl)amino)benzamide,

(104) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-([5-(pyrimidin-2-yl)pyridin-3-yl]methyl)amino)benzamide,

(105) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(pyrazolo[5,1-
15 b][1,3]thiazol-7-yl)methyl]amino}benzamide,

(106) 3-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-5-([5-(pyrimidin-2-yl)pyridin-3-yl]methyl)amino)benzamide,

(107) 3-([5-(5-fluoropyrimidin-2-yl)pyridin-3-yl]methyl)amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

20 (108) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(thieno[3,2-b]pyridin-6-yl)methyl]amino}benzamide,

(109) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(1H-pyrazolo[3,4-b]pyridin-5-yl)methyl]amino}benzamide,

(110) N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(imidazo[1,2-
25 b]pyridazin-3-yl)methyl]amino)-4-methylbenzamide,

(111) N-[(1S,2S)-2-hydroxycyclohexyl]-3-([5-(imidazo[1,2-a]pyrazin-6-yl)pyridin-3-yl]methyl)amino)-4-methylbenzamide,

(112) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([1-(pyridin-2-yl)-1H-pyrazol-4-yl]methyl)amino)benzamide,

30 (113) 3-[(2-aminopyrimidin-5-yl)methyl]amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(114) 3-([2-(cyclopropylamino)pyrimidin-5-yl]methyl)amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(115) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([5-(pyrazin-2-yl)pyridin-3-yl]methyl)amino)benzamide,
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- (116) 3-{[(6-acetamidopyridin-3-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (117) 3-[(6-[(cyclopropylmethyl)amino]pyridin-3-yl)methyl]amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 5 (118) 3-{[(2,2'-bipyridin]-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (119) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(pyrazolo[1,5-a]pyrimidin-3-yl)methyl]amino}benzamide,
- 10 (120) 3-[(6-[(cyclopropanecarbonyl)amino]pyridin-3-yl)methyl]amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (121) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(2-phenylpyrimidin-5-yl)methyl]amino}benzamide,
- 15 (122) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[6-(1H-pyrazol-1-yl)pyridin-3-yl)methyl]amino}benzamide,
- (123) N-[(1S,2S)-2-hydroxycyclohexyl]-6-methyl-5-{[(pyrazolo[1,5-a]pyridin-3-yl)methyl]amino}pyridine-3-carboxamide,
- (124) methyl {5-[(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylanilino)methyl]pyridin-2-yl}carbamate,
- 20 (125) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-[(oxan-4-yl)amino]pyridin-3-yl)methyl]amino}benzamide,
- (126) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(pyridin-2-yl)amino]pyrimidin-5-yl)methyl]amino}benzamide,
- 25 (127) N-{5-[(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylanilino)methyl]pyridin-2-yl}morpholine-4-carboxamide,
- (128) N-[(1S,2S)-2-hydroxycyclohexyl]-3-[(2-(4-methoxyphenyl)pyrimidin-5-yl)methyl]amino)-4-methylbenzamide,
- (129) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(6-{[(pyridin-3-yl)carbamoyl]amino}pyridin-3-yl)methyl]amino}benzamide,
- 30 (130) 3-[(6-(cyclobutylamino)pyridin-3-yl)methyl]amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide
- (131) 3-{[(5-aminopyrazin-2-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 35 (132) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-[(oxan-4-

yl) amino]pyrimidin-5-yl)methyl) amino]benzamide,

(133) 3-{{(6-{{(cyclopropyl(methyl) carbamoyl) amino}pyridin-3-yl)methyl} amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

5 (134) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(6-{{(propan-2-yl) amino]pyridin-3-yl)methyl) amino]benzamide,

(135) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(2-{{(3R)-oxolan-3-yl} amino}pyrimidin-5-yl)methyl} amino}benzamide,

(136) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(2-{{(3S)-oxolan-3-yl} amino}pyrimidin-5-yl)methyl} amino}benzamide

(137) N-{5-[(5-{{(1S,2S)-2-hydroxycyclohexyl} carbamoyl)-2-methylanilino)methyl]pyridin-2-yl}oxane-4-carboxamide,

(138) N-[(1S,2S)-2-hydroxycyclohexyl]-3-{{(6-{{(1r,3r)-3-methoxycyclobutane-1-carbonyl} amino}pyridin-3-yl)methyl} amino)-4-methylbenzamide,

(139) N-{5-[(5-{{(1S,2S)-2-hydroxycyclohexyl} carbamoyl)-2-methylanilino)methyl]pyridin-2-yl}oxolane-3-carboxamide,

(140) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)methyl} amino}benzamide,

20 (141) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{(6-{{(oxetan-3-yl) amino]pyridin-3-yl)methyl) amino]benzamide,

(142) 3-{{(2-aminopyrimidin-5-yl)methyl} amino)-4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(143) 3-{{(2-aminopyrimidin-5-yl)methyl} amino)-5-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(144) 3-{{(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)methyl} amino)-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(145) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methyl} amino}benzamide,

(146) 3-{{[[3,3'-bipyridin]-5-yl) amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(147) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{{[5-(pyrimidin-2-yl)pyridin-3-yl] amino}methyl}benzamide,

35 (148) 3-{{[[2,3'-bipyridin]-5'-yl) amino]methyl}-N-[(1S,2S)-2-

hydroxycyclohexyl]-4-methylbenzamide,

(149) N-[(1R,2R)-2-hydroxycyclohexyl]-4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide,

(150) N-[(1S,2S)-2-hydroxycyclohexyl]-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide,

(151) 4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)benzamide,

(152) 3-{{[5-bromopyridin-3-yl]amino}methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,

(153) N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-{{[5-phenylpyridin-3-yl]amino}methyl}benzamide,

(154) 3-{{[5-cyclopropylpyridin-3-yl]amino}methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,

(155) 3-{{[2,3'-bipyridin]-5'-yl]amino}methyl}-N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methylbenzamide,

(156) N-[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]-4-methyl-3-{{[6-phenylpyrazin-2-yl]amino}methyl}benzamide,

(157) 5-({[5-(cyclopropylethynyl)pyridin-3-yl]amino}methyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,

(158) N-[3-({[6-(3,4-dimethoxyphenyl)pyrazin-2-yl]amino}methyl)phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea,

(159) N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]urea,

(160) N-[2-fluoro-5-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea,

(161) N-[4-fluoro-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]-N'-[(1R,2S)-2-hydroxycyclohexyl]urea,

(162) N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[4-methyl-3-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]urea,

(163) N-[(1R,2S)-2-hydroxycyclohexyl]-N'-[2-methyl-5-({[5-(pyrimidin-2-yl)pyridin-3-yl]amino}methyl)phenyl]urea,

(164) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{1-[6-phenylpyrazin-2-yl]amino}ethyl}benzamide,

(165) 3-{{[3,3'-bipyridin]-5-yl}methoxy}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

- (166) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzamide,
(167) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]methoxy}benzamide,
5 (168) 3-{[(3,3'-bipyridin]-5-yl)oxy}methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(169) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl}benzamide,
(170) 4-chloro-N-[(1S,2S)-2-hydroxycyclohexyl]-3-{[5-(pyrimidin-2-yl)pyridin-3-yl]oxy}methyl}benzamide,
10 (171) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{1-[5-(pyrimidin-2-yl)pyridin-3-yl]ethoxy}benzamide,
(172) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[1-(5-phenylpyridin-3-yl)ethoxy]benzamide,
15 (173) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(E)-2-(5-phenylpyridin-3-yl)ethenyl]benzamide,
(174) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[2-(5-phenylpyridin-3-yl)ethyl]benzamide,
(175) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[methyl(5-phenylpyridin-3-yl)amino]methyl}benzamide,
20 (176) 3-{[ethyl(5-phenylpyridin-3-yl)amino]methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(177) 3-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
25 (178) 4-fluoro-3-{(Z)-2-fluoro-2-[5-(pyrimidin-2-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
(179) 3-[(Z)-2-fluoro-2-(imidazo[1,2-b]pyridazin-3-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(180) 5-[(Z)-2-([2,3'-bipyridin]-5'-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
30 (181) 3-[(Z)-2-fluoro-2-{5-[4-methylpiperazin-1-yl]methyl}pyridin-3-yl]ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(182) 3-[(Z)-2-fluoro-2-{5-[morpholin-4-yl]methyl}pyridin-3-yl]ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
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- (183) 3-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (184) 4-fluoro-3-{(Z)-2-fluoro-2-[5-(morpholin-4-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- 5 (185) 4-fluoro-3-[(Z)-2-fluoro-2-{5-[(oxan-4-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- (186) 4-fluoro-3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- 10 (187) 5-{(Z)-2-[5-(cyclopropylmethoxy)pyridin-3-yl]-2-fluoroethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
- (188) 5-{(Z)-2-fluoro-2-[5-(morpholin-4-yl)pyridin-3-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
- 15 (189) 5-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
- (190) 5-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
- (191) 3-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- 20 (192) 3-[(Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- (193) 3-[(Z)-2-fluoro-2-{5-[(1-methylpiperidin-4-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 25 (194) 3-[(Z)-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- (195) 5-[(Z)-2-fluoro-2-{5-[(oxetan-3-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,
- 30 (196) 4-fluoro-3-[(Z)-2-fluoro-2-{5-[(oxetan-3-yl)amino]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,
- (197) 3-[(Z)-2-(6-{[2-(dimethylamino)ethyl]amino}pyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
- 35 (198) 3-[(Z)-2-(5-{[2-(dimethylamino)ethyl]amino}pyridin-3-yl)-2-

fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,
(199) 5-[(Z)-2-{6-[(cyclopropylmethyl)amino]pyridin-3-yl}-2-
fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-
3-carboxamide,

5 (200) 3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-
yl)methyl]pyridin-3-yl}ethenyl]-N-[(1S,2S)-2-hydroxy-2,3-dihydro-
1H-inden-1-yl]-4-methylbenzamide,

(201) 3-[(Z)-2-fluoro-2-{5-[(4-methylpiperazin-1-
yl)methyl]pyridin-3-yl}ethenyl]-N-(2-hydroxy-3,3-dimethylbutyl)-

10 4-methylbenzamide,

(202) 3-[(Z)-2-{2-[(cyclopropylmethyl)amino]pyrimidin-5-yl}-2-
fluoroethenyl]-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(203) 3-{(Z)-2-[2-(cyclopropylamino)pyrimidin-5-yl]-2-
fluoroethenyl}-4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

15 (204) 3-[(Z)-2-(2-amino-4-methylpyrimidin-5-yl)-2-fluoroethenyl]-
4-fluoro-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(205) 4-fluoro-3-{(Z)-2-fluoro-2-[2-(methylamino)pyrimidin-5-
yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(206) 3-[(Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-N-[(1S,2S)-
20 2-hydroxycyclohexyl]-4-methylbenzamide, and

(207) 4-fluoro-3-[(Z)-2-fluoro-2-(5-fluoropyridin-3-yl)ethenyl]-
N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

or a pharmaceutically acceptable salt thereof, or a solvate
thereof.

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[Claim 5]

The compound according to claim 1, selected from the
group consisting of the following (1) to (15):

(1) 2-(cyclopropylmethyl)-N-(5-{[(1S,2S)-2-
30 hydroxycyclohexyl]carbamoyl}-2-methylphenyl)-1,3-thiazole-5-
carboxamide,

(2) 5-[cyclopropyl(methyl)amino]-N-(5-{[(1S,2S)-2-
hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-
carboxamide,

35 (3) 5-(3-fluorophenyl)-N-(5-{[(1S,2S)-2-

hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(4) 5-(cyclopropylmethoxy)-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-

5 carboxamide,

(5) 5-ethoxy-N-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-methylphenyl)pyridine-3-carboxamide,

(6) 3-{[(2-aminopyrimidin-5-yl)methyl]amino}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

10 (7) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-{[(pyrazolo[1,5-a]pyrimidin-3-yl)methyl]amino}benzamide,

(8) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-[(2-{(oxan-4-yl)amino}pyrimidin-5-yl)methyl]amino}benzamide,

(9) N-[(1S,2S)-2-hydroxycyclohexyl]-4-methyl-3-([6-(1H-1,2,3-
15 triazol-1-yl)pyridin-3-yl)methyl]amino}benzamide,

(10) 3-{[(2,3'-bipyridin]-5'-yl)amino}methyl}-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(11) 5-[(Z)-2-(6-aminopyridin-3-yl)-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-6-methylpyridine-3-carboxamide,

20 (12) 3-[(Z)-2-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-3-yl}-2-fluoroethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]-4-methylbenzamide,

(13) 4-fluoro-3-{(Z)-2-fluoro-2-[2-(methylamino)pyrimidin-5-yl]ethenyl}-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(14) 3-[(Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-N-[(1S,2S)-
25 2-hydroxycyclohexyl]-4-methylbenzamide, and

(15) 4-fluoro-3-[(Z)-2-fluoro-2-(5-fluoropyridin-3-yl)ethenyl]-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

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[Claim 6]

A pharmaceutical composition comprising the compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active
35 ingredient.

[Claim 7]

A PDGF receptor kinase inhibitor comprising the compound according to any one of claims 1 to 5 or a
5 pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.

[Claim 8]

A therapeutic agent for pulmonary hypertension,
10 scleroderma, asthma, bronchiolitis obliterans, pulmonary fibrosis, acute myelogenous leukemia (AML), hypereosinophilic syndrome, T-lymphoblastic leukemia, chronic myelomonocytic leukemia (CMML), chronic myelogenous leukemia (CML), chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, glioma,
15 ovarian cancer, vascular restenosis, atherosclerosis/arteriosclerosis obliterans, moyamoya disease (idiopathic occlusion of the circle of Willis), leiomyoma, lymphangiioleiomyomatosis, or age-related macular degeneration (AMD), in which a PDGF receptor kinase is involved, the
20 therapeutic agent comprising the compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient.