

AMIDE DERIVATIVE HAVING ANTIVIRAL ACTIVITY

Technical Field

[0001]

The present invention relates to compounds useful for the treatment and/or prevention of respiratory syncytial virus (hereinafter referred to as "RSV") infection and related diseases caused by the infection and also to pharmaceutical compositions containing the same. In particular, the present invention relates to amide derivatives having RSV inhibitory activity.

Background Art

[0002]

Human respiratory syncytial virus (RSV) is a negative-sense single-stranded RNA virus, which belongs to the genus Pneumovirus of the Paramyxoviridae family, and is the most common cause of bronchiolitis and pneumonia in infants under 1 year of age. Most children become infected with RSV before their second birthday, and about 1-3% of those infected require hospitalization. The elderly and adults with heart, lung or immune system disorders are particularly susceptible and at high risk for severe illness and complications (Non-Patent Document 1).

[0003]

There are two antigenic subtypes A and B of RSV. These two types co-circulate generally in RSV outbreaks. However, the ratio of these types varies geographically and seasonally, and this is considered as one of the reasons for different clinical impact in each outbreak. Therefore, in view of the treatment for RSV, agents effective against both subtypes A and B are desirable (Non-Patent Document 1).

[0004]

To date, there has been no vaccine that can prevent RSV infection. Palivizumab is a monoclonal antibody used prophylactically to prevent RSV infection in high-risk infants,

e.g., preterm infants, and infants with heart or lung disease. The high cost of treatment with palivizumab has limited the use of this drug. A nucleic acid analog, ribavirin, was approved in the United States as the only antiviral agent to treat RSV infection, but its efficacy is limited and there is a concern of side effect profile. Therefore, there is a need for a safe and effective RSV treatment that can be widely used for all types of RSV and age groups from infants to the elderly (Non-Patent Document 1).

[0005]

Inhibitors targeting on the F protein involved in RSV membrane fusion, such as Ziresovir, JNJ-53718678 and RV-521, inhibitors targeting on the N protein involved in genome stabilization, such as EDP-938, and inhibitors targeting on polymerase of L protein, such as PC786, are in clinical development for RSV therapy (Non-Patent Document 2).

To date, no amide derivative having RSV inhibitory activity, such as those described in this application, are known.

Prior Art Document

Non-patent Document

[0006]

Non-Patent Document 1: Cellular and Molecular Life Sciences, 2020, Jun 16, 1-14

Non-Patent Document 2: Expert Opinion on Investigational Drugs, 2020, Mar 29, 3, 285-294

Summary of the Invention

Problem to be solved by the Invention

[0007]

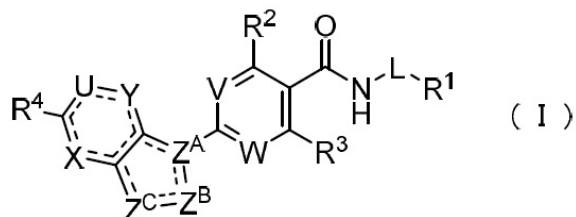
The purpose of the present invention is to provide novel compounds having RSV inhibitory activity. More preferably, the present invention provides compounds useful for the treatment and/or prevention of RSV infection and related diseases caused by the infection, and medicaments containing the same.

Means for solving the Problem

[0008]

The present invention relates to the following items (1) to (17).

(1) A compound of the formula (I):



wherein:

the dashed line indicates the presence or absence of a bond;

R^1 is carboxy, cyano, substituted or unsubstituted aromatic heterocyclyl, $-C(=O)-NR^{1B}R^{1C}$ or $-CH=CHC(=O)-OH$;

R^{1B} and R^{1C} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted aminosulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl;

L is substituted or unsubstituted non-aromatic carbocyclyldiyl, substituted or unsubstituted non-aromatic heterocyclyldiyl or substituted or unsubstituted alkylene;

R^2 is substituted or unsubstituted alkyl;

R^3 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted amino or substituted or unsubstituted carbamoyl;

X is $=CR^X-$ or $=N-$;

Y is $=CR^Y-$ or $=N-$;

U is $-CR^U=$ or $-N=$;

V is $-CR^V=$ or $-N=$;

W is $=CR^W-$ or $=N-$;

Z^A is $-C=$ or $-N-$;

Z^B is $-CR^5R^6-$, $-CR^5=$, $-NR^5-$ or $-N=$;

Z^C is $-CR^7R^8-$, $-CR^7=$, $-NR^7-$ or $=N-$;

R^X , R^Y , R^V and R^W are each independently a hydrogen atom, cyano,

halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl;

R^U is a hydrogen atom, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl or substituted or unsubstituted non-aromatic carbocyclyl;

R^5 and R^6 are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl, or R^5 and R^6 are taken together to form oxo;

R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted alkylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring; or

R^5 and R^7 are taken together with the carbon atoms to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted aromatic carbon ring; or

R^4 is a hydrogen atom, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted aromatic heterocyclyloxy, substituted or

unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyl or substituted or unsubstituted non-aromatic heterocyclylcarbonyl, or R^4 and R^U are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic heterocyclic ring, or a pharmaceutically acceptable salt thereof.

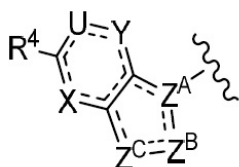
(2) The compound of item (1), wherein R^1 is carboxy, or a pharmaceutically acceptable salt thereof.

(3) The compound of item (1) or (2), wherein L is substituted or unsubstituted non-aromatic carbocyclldiyl, or a pharmaceutically acceptable salt thereof.

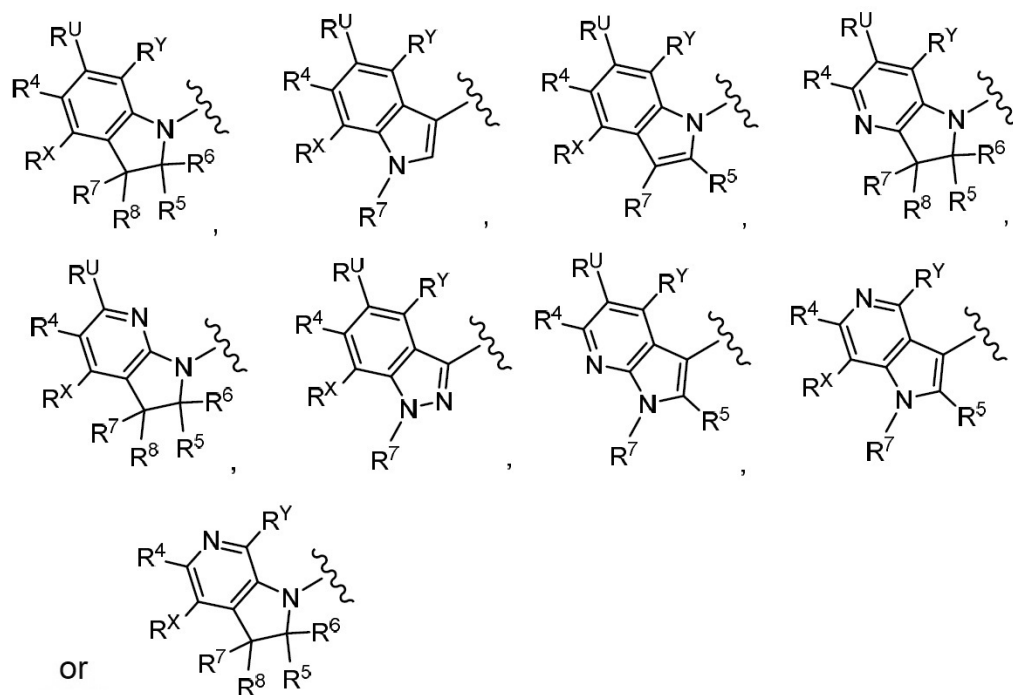
(4) The compound of any one of items (1) to (3), wherein R^3 is a hydrogen atom, or a pharmaceutically acceptable salt thereof.

(5) The compound of any one of items (1) to (4), wherein V is $-N=$ and W is $=N-$, or a pharmaceutically acceptable salt thereof.

(6) The compound of any one of items (1) to (5), wherein the group of the formula:

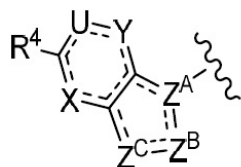


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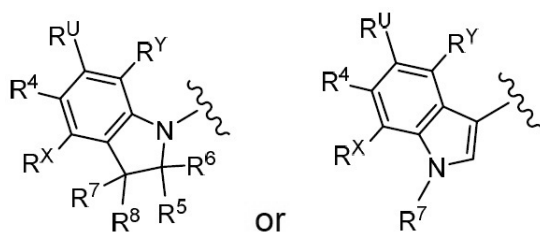


wherein each symbol is as defined in item (1),
or a pharmaceutically acceptable salt thereof.

(7) The compound of any one of items (1) to (6), wherein the group
of the formula:

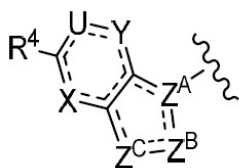


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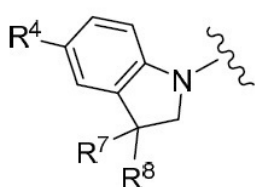


wherein each symbol is as defined in item (1),
or a pharmaceutically acceptable salt thereof.

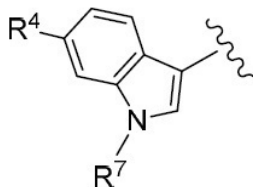
(8) The compound of any one of items (1) to (7), wherein the group
of the formula:



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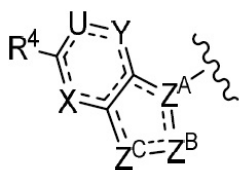


or

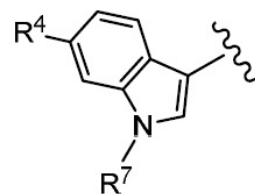


wherein each symbol is as defined in item (1),
or a pharmaceutically acceptable salt thereof.

(9) The compound of any one of items (1) to (8), wherein the group
of the formula:



is

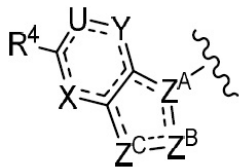


wherein

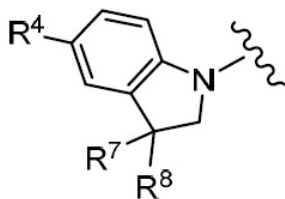
R⁴ is as defined in item (1); and

R⁷ is substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocycloxyloxycarbonyl, substituted or unsubstituted non-aromatic heterocycloxyloxycarbonyl or substituted or unsubstituted non-aromatic carbocyclylsulfonyl,
or a pharmaceutically acceptable salt thereof.

(10) The compound of any one of items (1) to (8), wherein the group of the formula:



is



wherein

R^4 is as defined in item (1); and

R^7 and R^8 are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring, or a pharmaceutically acceptable salt thereof.

(11) The compound of any one of items (1) to (10), wherein R^4 is substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl or substituted or unsubstituted non-aromatic carbocyclyl, or a pharmaceutically acceptable salt thereof.

(12) The compound of any one of items (1) to (11), wherein R^4 is substituted or unsubstituted non-aromatic heterocyclyloxy or

substituted or unsubstituted non-aromatic carbocycloxy,
or a pharmaceutically acceptable salt thereof.

(13) The compound of item (1) selected from the group consisting of compounds I-082, I-162, I-481, I-496, I-503, I-506, I-549, I-552, I-568, I-569, I-570, I-571, I-591, I-613, I-617 and I-618, or a pharmaceutically acceptable salt thereof.

(14) A pharmaceutical composition comprising the compound of any one of items (1) to (13) or a pharmaceutically acceptable salt thereof.

(15) The pharmaceutical composition of item (14) having an anti-RS virus activity.

(16) A method for the treatment and/or prevention of RSV infection, characterized in that the compound of any of the items (1) to (13) or a pharmaceutically acceptable salt thereof is administered.

(17) The compound of any one of items (1) to (13) or a pharmaceutically acceptable salt thereof for the treatment and/or prevention of RSV infection.

(18) Use of the compound of any one of items (1) to (13), or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of RSV infection.

Effect of the Invention

[0009]

The compounds of the present invention have RSV inhibitory activity and are useful as therapeutic and/or prophylactic agents for RSV infection and related diseases caused by the infection.

Mode for Carrying out the Invention

[0010]

Hereinafter, the meaning of each term used in the present

specification will be described. Unless particularly stated otherwise, each term is used in the same sense, either alone or in combination with other terms.

The term "consist of" means having only the constituent elements.

The term "comprise" means that elements are not limited to the constituent elements, and elements that are not described are not excluded.

Hereinafter, the present invention will be described while showing exemplary embodiments. Throughout the present specification, it should be understood that, unless particularly stated otherwise, an expression of a singular form also includes the concept of a plural form thereof. Therefore, it should be understood that, unless particularly stated otherwise, an article for a singular form (for example, in the case of English, "a", "an", "the", or the like) also includes the concept of a plural form thereof.

Furthermore, it should be understood that, unless particularly stated otherwise, the terms used in the present specification are used in the meanings normally used in the above-described art. Accordingly, unless otherwise defined, all terminologies and scientific and technical terms used in the present specification have the same meanings as commonly understood by those having ordinary skill in the art to which the present invention belongs. In a case of contradiction, priority is given to the present specification (including definitions).

[0011]

"Halogen" includes a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom. Particularly, fluorine atom and chlorine atom are preferred.

[0012]

"Alkyl" includes linear or branched hydrocarbon groups each having 1 to 15 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms, and even more preferably 1 to 4

carbon atoms. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, isooctyl, n-nonyl, and n-decyl.

Preferred embodiments of "alkyl" include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and n-pentyl. More preferred embodiments include methyl, ethyl, n-propyl, isopropyl, and tert-butyl.

[0013]

"Alkenyl" includes linear or branched hydrocarbon groups each having one or more double bond(s) at any position and having 2 to 15 carbon atoms, preferably 2 to 10 carbon atoms, more preferably 2 to 6 carbon atoms, and even more preferably 2 to 4 carbon atoms. Examples include vinyl, allyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, and pentadecenyl.

Preferred embodiments of "alkenyl" include vinyl, allyl, propenyl, isopropenyl, and butenyl. More preferred embodiments include ethenyl and n-propenyl.

[0014]

"Alkynyl" includes linear or branched hydrocarbon groups each having one or more triple bond(s) at any position and having 2 to 10 carbon atoms, preferably 2 to 8 carbon atoms, more preferably 2 to 6 carbon atoms, and even more preferably 2 to 4 carbon atoms. Alkynyl may further have a double bond at any position. Examples include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, and decynyl.

Preferred embodiments of "alkynyl" include ethynyl, propynyl, butynyl, and pentynyl. More preferred embodiments include ethynyl and propynyl.

[0015]

"Alkylene" includes linear or branched divalent hydrocarbon groups each having 1 to 15 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms, and even more preferably 1 to 4 carbon atoms. Examples include methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, and hexamethylene.

[0016]

"Aromatic carbocyclyl" means a cyclic aromatic hydrocarbon group having a single ring or two or more rings. Examples include phenyl, naphthyl, anthryl, and phenanthryl.

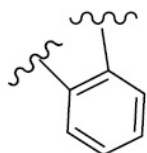
Preferred embodiments of "aromatic carbocyclyl" include phenyl.

[0017]

"Aromatic carbon ring" means a ring derived from the above "aromatic carbocyclyl".

[0018]

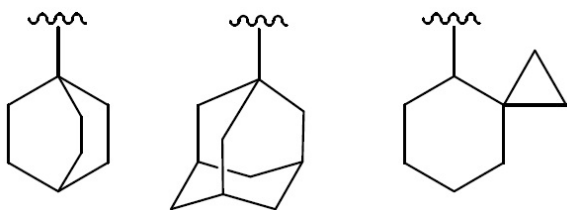
"R⁵ and R⁷ are taken together with the carbon atoms to which they are attached to form a substituted or unsubstituted aromatic carbon ring" includes, for example, the following rings.



[0019]

"Non-aromatic carbocyclyl" means a cyclic saturated hydrocarbon group or a cyclic non-aromatic unsaturated hydrocarbon group, both having a single ring or two or more rings. The "non-aromatic carbocyclyl" having two or more rings also includes a non-aromatic carbocyclyl having a single ring or two or more rings, to which the ring in the above "aromatic carbocyclyl" is fused.

Furthermore, the "non-aromatic carbocyclyl" also includes a bridged group or a group forming a spiro ring, such as follows.



A non-aromatic carbocyclyl having a single ring preferably has 3 to 16 carbon atoms, more preferably 3 to 12 carbon atoms, and even more preferably 4 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclohexadienyl.

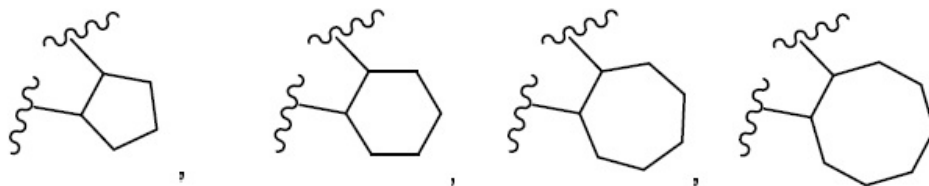
A non-aromatic carbocyclyl having two or more rings preferably has 8 to 20 carbon atoms, and more preferably 8 to 16 carbon atoms. Examples include indanyl, indenyl, acenaphthyl, tetrahydronaphthyl, and fluorenyl.

[0020]

"Non-aromatic carbon ring" means a ring derived from the above "non-aromatic carbocyclyl".

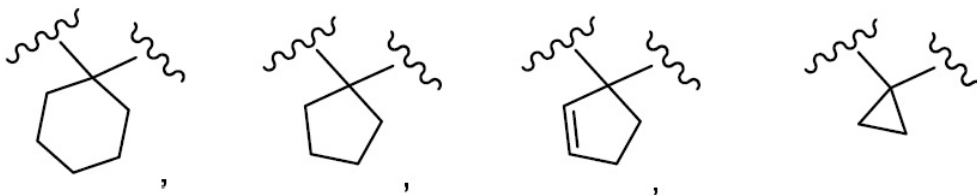
[0021]

Examples of R^5 and R^7 are taken together with the carbon atoms to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring" include the following rings.



[0022]

Examples of R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring" include the following rings.



[0023]

"Non-aromatic carbocyclyldiyl" means a divalent group derived from the above "non-aromatic carbon ring". Examples include cyclopropanediyl, cyclobutanediyl, cyclopentanediiyl, cyclohexanediiyl, cycloheptanediiyl, cyclooctanediiyl, bicyclo[2.2.2]octanediiyl, bicyclo[2.2.1]heptanediiyl, adamantanediiyl. One carbon atom may have two bonding hands. Examples include cyclohexane-1,1-diyl and adamantane-2,2-diyl.

[0024]

"Aromatic heterocyclyl" means an aromatic cyclic group having a single ring or two or more rings, which has one or more identical or different heteroatom(s) optionally selected from O, S, and N in the ring(s).

An aromatic heterocyclyl having two or more rings also includes an aromatic heterocyclyl having a single ring or two or more rings, to which a ring in the above "aromatic carbocyclyl" is fused, and the bonding hand may be carried by any of the rings.

The aromatic heterocyclyl having a single ring is preferably a 5- to 8-membered ring, and more preferably a 5-membered or 6-membered ring. Examples of 5-membered aromatic heterocyclyl include pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furyl, thienyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, and thiadiazolyl. Examples of 6-membered aromatic heterocyclyl include pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

The aromatic heterocyclyl having two rings is preferably a 8- to 10-membered ring, and more preferably a 9-membered or 10-membered ring. Examples include indolyl, isoindolyl, indazolyl, indolizinyll, quinolinyl, isoquinolinyl, cinolinyl, phthalazinyl,

quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, oxazolopyridyl, and thiazolopyridyl.

The aromatic heterocyclyl having three or more rings is preferably 13- to 15-membered ring. Examples include carbazolyl, acridinyl, xanthenyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, and dibenzofuryl.

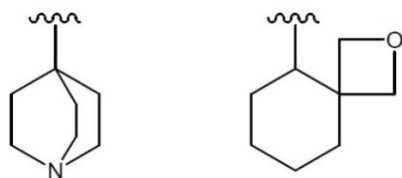
[0025]

"Aromatic heterocyclic ring" means a ring derived from the above "aromatic heterocyclyl".

[0026]

"Non-aromatic heterocyclyl" means a non-aromatic cyclic group having a single ring or two or more rings, which has one or more identical or different heteroatom(s) optionally selected from O, S, and N in the ring(s). A non-aromatic heterocyclyl having two or more rings also includes a non-aromatic heterocyclyl having a single ring or two or more rings, to which a ring in each of the above "aromatic carbocyclyl", "non-aromatic carbocyclyl", and/or "aromatic heterocyclyl" is fused, as well as a non-aromatic carbocyclyl having a single ring or two or more rings, to which a ring in the above "aromatic heterocyclyl" is fused, and the bonding hand may be carried by any of the rings.

Furthermore, the "non-aromatic heterocyclyl" also includes a bridged group or a group forming a spiro ring, such as follows.



The non-aromatic heterocyclyl having a single ring is preferably a 3- to 8-membered ring, and more preferably a 5-membered or 6-membered ring.

Examples of 3-membered non-aromatic heterocyclyl include thiiranyl, oxiranyl, and aziridinyl. Examples of 4-membered non-aromatic heterocyclyl include oxetanyl and azetidiny. Examples of 5-membered non-aromatic heterocyclyl include oxathiolanyl, thiazolidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, tetrahydrofuryl, dihydrothiazolyl, tetrahydroisothiazolyl, dioxolanyl, dioxolyl, and thiolanyl. Examples of 6-membered non-aromatic heterocyclyl include dioxanyl, thianyl, piperidyl, piperazinyl, morpholiny, morpholino, thiomorpholiny, thiomorpholino, dihydropyridyl, tetrahydropyridyl, tetrahydropyranyl, dihydroxazinyl, tetrahydropyridazinyl, hexahydropyrimidinyl, dioxazinyl, thiinyl, and thiazinyl. Examples of 7-membered non-aromatic heterocyclyl include hexahydroazepinyl, tetrahydrodiazepinyl, and oxepanyl.

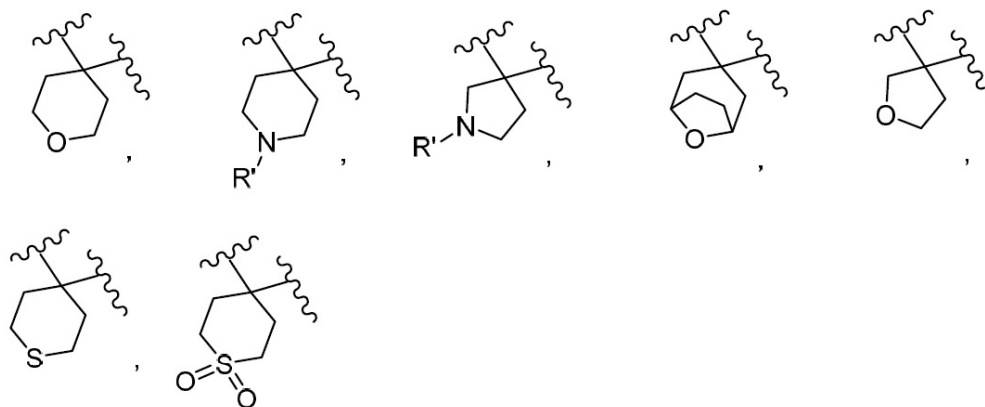
The non-aromatic heterocyclyl having two or more rings is preferably an 8- to 20-membered ring, and more preferably an 8- to 10-membered ring. Examples include indolinyl, isoindolinyl, chromanyl, and isochromanyl.

[0027]

"Non-aromatic heterocyclic ring" means a ring derived from the above "non-aromatic heterocyclyl".

[0028]

Examples of "R⁷ and R⁸ are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic heterocyclic ring" include the following rings.

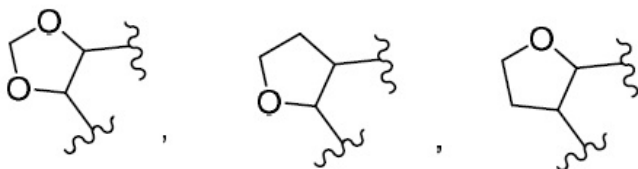


wherein

R' is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted non-aromatic heterocyclyl, or substituted or unsubstituted alkylcarbonyl.

[0029]

Examples of "R⁴ and R^U are taken together with the carbon atom to which they are attached to form a substituted non-aromatic heterocyclic ring" include the following rings.



[0030]

"Non-aromatic heterocyclyldiyl" means a divalent group derived from the above "non-aromatic heterocyclic ring". "Non-aromatic heterocyclyldiyl" include non-aromatic ring diyl of 1 to 9 carbons containing 1 to 4 nitrogen, oxygen and/or sulfur atoms. Examples include pyrrolindiyl, pyrrolidinediyl, imidazolidinediyl, imidazolidinediyl, pyrazolinediyl, pyrazolidinediyl, piperidinediyl, piperazinediyl, morpholindiyl, tetrahydropyranediyl. One carbon atom may have two bonding hands. Examples include tetrahydropyran-4,4-diyl, and piperidine-4,4-diyl.

[0031]

"Trialkylsilyl" means a group having three of the above "alkyls" bonded to a silicon atom. The three alkyl groups may be the same or different. Examples include trimethylsilyl, triethylsilyl, and tert-butyldimethylsilyl.

[0032]

In the present specification, the phrase "may be substituted with Substituent Group α " means that "may be substituted with one or more group(s) selected from Substituent Group α ". The same also applies to substituent groups β , γ , and γ' .

[0033]

Examples of substituents for "substituted alkyl", "substituted alkenyl", "substituted alkynyl", "substituted alkyloxy", "substituted alkenyloxy", "substituted alkynyloxy", "substituted alkylcarbonyloxy", "substituted alkenylcarbonyloxy", "substituted alkynylcarbonyloxy", "substituted alkylcarbonyl", "substituted alkenylcarbonyl", "substituted alkynylcarbonyl", "substituted alkyloxycarbonyl", "substituted alkenyloxycarbonyl", "substituted alkynyloxycarbonyl", "substituted alkylsulfanyl", "substituted alkenylsulfanyl", "substituted alkynylsulfanyl", "substituted alkylsulfinyl", "substituted alkenylsulfinyl", "substituted alkynylsulfinyl", "substituted alkylsulfonyl", "substituted alkenylsulfonyl", and "substituted alkynylsulfonyl" include the following Substituent Group A. One or more group(s) selected from the following Substituent Group A may be attached to a carbon atom at any position.

Substituent Group A: halogen, hydroxy, carboxy, formyl, formyloxy, sulfanyl, sulfinyl, sulfo, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, cyano, nitro, nitroso, azido, hydrazino, ureido, amidino, guanidino, pentafluorothio, trialkylsilyl,

alkyloxy which may be substituted with Substituent Group α , alkenyloxy which may be substituted with Substituent Group α , alkynyloxy which may be substituted with Substituent Group α , alkylcarbonyloxy which may be substituted with Substituent Group α , alkenylcarbonyloxy which may be substituted with Substituent Group α , alkynylcarbonyloxy which may be substituted with Substituent Group α , alkylcarbonyl which may be substituted with Substituent Group α , alkenylcarbonyl which may be substituted with Substituent Group α , alkynylcarbonyl which may be substituted with

Substituent Group α , alkyloxycarbonyl which may be substituted with Substituent Group α , alkenyloxycarbonyl which may be substituted with Substituent Group α , alkynyloxycarbonyl which may be substituted with Substituent Group α , alkylsulfanyl which may be substituted with Substituent Group α , alkenylsulfanyl which may be substituted with Substituent Group α , alkynylsulfanyl which may be substituted with Substituent Group α , alkylsulfinyl which may be substituted with Substituent Group α , alkenylsulfinyl which may be substituted with Substituent Group α , alkynylsulfinyl which may be substituted with Substituent Group α , alkylsulfonyl which may be substituted with Substituent Group α , alkenylsulfonyl which may be substituted with Substituent Group α , alkynylsulfonyl which may be substituted with Substituent Group α ,

amino which may be substituted with Substituent Group β , imino which may be substituted with Substituent Group β , carbamoyl which may be substituted with Substituent Group β , sulfamoyl which may be substituted with Substituent Group β ,

aromatic carbocyclyl which may be substituted with Substituent Group γ , non-aromatic carbocyclyl which may be substituted with Substituent Group γ' , aromatic heterocyclyl which may be substituted with Substituent Group γ , non-aromatic heterocyclyl which may be substituted with Substituent Group γ' , aromatic carbocyclyloxy which may be substituted with Substituent Group γ , non-aromatic carbocyclyloxy which may be substituted with Substituent Group γ' , aromatic heterocyclyloxy which may be substituted with Substituent Group γ , non-aromatic heterocyclyloxy which may be substituted with Substituent Group γ' , aromatic carbocyclylcarbonyloxy which may be substituted with Substituent Group γ , non-aromatic carbocyclylcarbonyloxy which may be substituted with Substituent Group γ' , aromatic heterocyclylcarbonyloxy which may be substituted with Substituent Group γ , non-aromatic heterocyclylcarbonyloxy which may be substituted with Substituent Group γ' , aromatic carbocyclylcarbonyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylcarbonyl which may be substituted with Substituent Group γ' , aromatic heterocyclylcarbonyl which

may be substituted with Substituent Group γ , non-aromatic heterocyclylcarbonyl which may be substituted with Substituent Group γ' , aromatic carbocyclyloxy carbonyl which may be substituted with Substituent Group γ , non-aromatic carbocyclyloxy carbonyl which may be substituted with Substituent Group γ' , aromatic heterocyclyloxy carbonyl which may be substituted with Substituent Group γ , non-aromatic heterocyclyloxy carbonyl which may be substituted with Substituent Group γ' , aromatic carbocyclylalkyloxy which may be substituted with Substituent Group γ , non-aromatic carbocyclylalkyloxy which may be substituted with Substituent Group γ' , aromatic heterocyclylalkyloxy which may be substituted with Substituent Group γ , non-aromatic heterocyclylalkyloxy which may be substituted with Substituent Group γ' , aromatic carbocyclylalkyloxy carbonyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylalkyloxy carbonyl which may be substituted with Substituent Group γ' , aromatic heterocyclylalkyloxy carbonyl which may be substituted with Substituent Group γ , non-aromatic heterocyclylalkyloxy carbonyl which may be substituted with Substituent Group γ' , aromatic carbocyclylsulfanyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylsulfanyl which may be substituted with Substituent Group γ' , aromatic heterocyclylsulfanyl which may be substituted with Substituent Group γ , non-aromatic heterocyclylsulfanyl which may be substituted with Substituent Group γ' , aromatic carbocyclylsulfinyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylsulfinyl which may be substituted with Substituent Group γ' , aromatic heterocyclylsulfinyl which may be substituted with Substituent Group γ , non-aromatic heterocyclylsulfinyl which may be substituted with Substituent Group γ' , aromatic carbocyclylsulfonyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylsulfonyl which may be substituted with Substituent Group γ' , aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ , and non-aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ' .

[0034]

Substituent Group α : halogen, hydroxy, carboxy, alkyloxy, haloalkyloxy, alkenyloxy, alkynyloxy, sulfanyl, and cyano.

[0035]

Substituent Group β : halogen, hydroxy, carboxy, cyano, alkyl which may be substituted with Substituent Group α , alkenyl which may be substituted with Substituent Group α , alkynyl which may be substituted with Substituent Group α , alkylcarbonyl which may be substituted with Substituent Group α , and alkenylcarbonyl which may be substituted with group α , alkynylcarbonyl which may be substituted with group α , alkylsulfanyl which may be substituted with group α , alkenylsulfanyl which may be substituted with group α , alkynylsulfanyl which may be substituted with group α , alkylsulfinyl which may be substituted with Substituent Group α , alkenylsulfinyl which may be substituted with Substituent Group α , alkynylsulfinyl which may be substituted with Substituent Group α , alkylsulfonyl which may be substituted with Substituent Group α , alkenylsulfonyl which may be substituted with Substituent Group α , alkynylsulfonyl which may be substituted with Substituent Group α ,

aromatic carbocyclyl which may be substituted with Substituent Group γ , non-aromatic carbocyclyl which may be substituted with Substituent Group γ' , aromatic heterocyclyl which may be substituted with Substituent Group γ , non-aromatic heterocyclyl which may be substituted with Substituent Group γ' , aromatic carbocyclylalkyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylalkyl which may be substituted with Substituent Group γ' , aromatic heterocyclylalkyl which may be substituted with Substituent Group γ , non-aromatic heterocyclylalkyl which may be substituted with Substituent Group γ' , aromatic carbocyclylcarbonyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylcarbonyl which may be substituted with Substituent Group γ' , aromatic heterocyclylcarbonyl which may be substituted with Substituent

Group γ , non-aromatic heterocyclylcarbonyl which may be substituted with group γ' , aromatic carbocyclyloxy carbonyl which may be substituted with group γ , non-aromatic carbocyclyloxy carbonyl which may be substituted with group γ' , aromatic heterocyclyloxy carbonyl which may be substituted with group γ , non-aromatic heterocyclyloxy carbonyl which may be substituted with group γ' , aromatic carbocyclylsulfanyl which may be substituted with group γ , non-aromatic carbocyclylsulfanyl which may be substituted with Substituent Group γ' , aromatic heterocyclylsulfanyl which may be substituted with group γ , non-aromatic heterocyclylsulfanyl which may be substituted with Substituent Group γ' , aromatic carbocyclylsulfinyl which may be substituted with Substituent Group γ , non-aromatic carbocyclylsulfinyl which may be substituted with Substituent Group γ' , aromatic heterocyclylsulfinyl which may be substituted with Substituent Group γ , non-aromatic heterocyclylsulfinyl which may be substituted with group γ' , aromatic carbocyclylsulfonyl which may be substituted with group γ , non-aromatic carbocyclylsulfonyl which may be substituted with group γ' , aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ , and non-aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ' .

[0036]

Substituent Group γ : Substituent Group α , alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, alkylcarbonyl, haloalkylcarbonyl, alkenylcarbonyl, and alkynylcarbonyl.

[0037]

Substituent Group γ' : Substituent Group γ and oxo.

[0038]

Examples of substituents on the ring of "substituted aromatic carbon ring" and "aromatic heterocyclic ring" for "substituted aromatic carbocyclyl", "substituted aromatic heterocyclyl", "substituted aromatic carbocyclyloxy", "substituted aromatic

heterocyclyloxy", "substituted aromatic carbocyclylcarbonyloxy", "substituted aromatic heterocyclylcarbonyloxy", "substituted aromatic carbocyclylcarbonyl", "substituted aromatic heterocyclylcarbonyl", "substituted aromatic carbocyclyloxy carbonyl", "substituted aromatic heterocyclyloxy carbonyl", "substituted aromatic carbocyclylsulfanyl", "substituted aromatic heterocyclylsulfanyl", "substituted aromatic carbocyclylsulfinyl", "substituted aromatic heterocyclylsulfinyl", "substituted aromatic carbocyclylsulfonyl", "substituted aromatic heterocyclylsulfonyl", "substituted aromatic carbon ring formed by R⁵ and R⁷ together with the carbon atom to which they are attached" include the following Substituent Group B. One or more group(s) selected from the following Substituent Group B may be attached to an atom at any position on the ring.

Substituent Group B: halogen, hydroxy, carboxy, formyl, formyloxy, sulfanyl, sulfinyloxy, sulfo, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, cyano, nitro, nitroso, azido, hydrazino, ureido, amidino, guanidino, pentafluorothio, trialkylsilyl, alkyl substituted with Substituent Group α , alkenyl substituted with Substituent Group α , alkynyl substituted with Substituent Group α , alkyloxy substituted with Substituent Group α , alkenyloxy substituted with Substituent Group α , alkynyloxy substituted with Substituent Group α , alkylcarbonyloxy which may be substituted with Substituent Group α , alkenylcarbonyloxy which may be substituted with Substituent Group α , alkynylcarbonyloxy which may be substituted with Substituent Group α , alkylcarbonyl which may be substituted with group α , alkenylcarbonyl which may be substituted with group α , alkynylcarbonyl which may be substituted with group α , alkyloxycarbonyl which may be substituted with group α , alkenyloxycarbonyl which may be substituted with group α , alkynyloxycarbonyl which may be substituted with group α , alkylsulfanyl which may be substituted with Substituent Group α , alkenylsulfanyl which may be substituted with Substituent Group α , alkynylsulfanyl which may be substituted with Substituent Group α .

α , alkylsulfinyl which may be substituted with Substituent Group α ,
 α , alkenylsulfinyl which may be substituted with group α ,
 alkynylsulfinyl which may be substituted with group α ,
 alkylsulfonyl which may be substituted with group α ,
 alkenylsulfonyl which may be substituted with group α ,
 alkynylsulfonyl which may be substituted with group α ,
 amino which may be substituted with Substituent Group β , imino
 which may be substituted with Substituent Group β , carbamoyl which
 may be substituted with Substituent Group β , sulfamoyl which may
 be substituted with Substituent Group β ,
 aromatic carbocyclyl which may be substituted with Substituent
 Group γ , non-aromatic carbocyclyl which may be substituted with
 Substituent Group γ' , aromatic heterocyclyl which may be
 substituted with Substituent Group γ , non-aromatic heterocyclyl
 which may be substituted with Substituent Group γ' , aromatic
 carbocyclyloxy which may be substituted with Substituent Group γ ,
 non-aromatic carbocyclyloxy which may be substituted with
 Substituent Group γ' , aromatic heterocyclyloxy which may be
 substituted with Substituent Group γ , non-aromatic
 heterocyclyloxy which may be substituted with Substituent Group
 γ' , aromatic carbocyclylcarbonyloxy which may be substituted with
 Substituent Group γ , non-aromatic carbocyclylcarbonyloxy which
 may be substituted with Substituent Group γ' , aromatic
 heterocyclylcarbonyloxy which may be substituted with Substituent
 Group γ , non-aromatic heterocyclylcarbonyloxy which may be
 substituted with Substituent Group γ' , aromatic
 carbocyclylcarbonyl which may be substituted with group γ , non-
 aromatic carbocyclylcarbonyl which may be substituted with group
 γ' , aromatic heterocyclylcarbonyl which may be substituted with
 group γ , non-aromatic heterocyclylcarbonyl which may be
 substituted with Substituent Group γ' , aromatic
 carbocyclyloxy carbonyl which may be substituted with Substituent
 Group γ , non-aromatic carbocyclyloxy carbonyl which may be
 substituted with Substituent Group γ' , aromatic
 heterocyclyloxy carbonyl which may be substituted with Substituent
 Group γ , non-aromatic heterocyclyloxy carbonyl which may be

substituted with Substituent Group γ' , aromatic carbocyclalkyl which may be substituted with Substituent Group γ , non-aromatic carbocyclalkyl which may be substituted with Substituent Group γ' , aromatic heterocyclalkyl which may be substituted with Substituent Group γ , non-aromatic heterocyclalkyl which may be substituted with Substituent Group γ' , aromatic carbocyclalkyloxy which may be substituted with Substituent Group γ , non-aromatic carbocyclalkyloxy which may be substituted with Substituent Group γ' , aromatic heterocyclalkyloxy which may be substituted with Substituent Group γ , non-aromatic heterocyclalkyloxy which may be substituted with Substituent Group γ' , aromatic carbocyclalkyloxycarbonyl which may be substituted with Substituent Group γ , non-aromatic carbocyclalkyloxycarbonyl which may be substituted with group γ' , aromatic heterocyclalkyloxycarbonyl which may be substituted with Substituent Group γ , non-aromatic heterocyclalkyloxycarbonyl which may be substituted with Substituent Group γ' , aromatic carbocyclalkyloxyalkyl, which may be substituted with Substituent Group γ , non-aromatic carbocyclalkyloxyalkyl which may be substituted with Substituent Group γ' , aromatic heterocyclalkyloxyalkyl which may be substituted with Substituent Group γ , non-aromatic heterocyclalkyloxyalkyl which may be substituted with Substituent Group γ' , aromatic carbocyclalsulfanyl which may be substituted with Substituent Group γ , non-aromatic carbocyclalsulfanyl which may be substituted with Substituent Group γ' , aromatic heterocyclalsulfanyl which may be substituted with Substituent Group γ , non-aromatic heterocyclalsulfanyl which may be substituted with group γ' , aromatic carbocyclalsulfinyl which may be substituted with group γ , non-aromatic carbocyclalsulfinyl which may be substituted with group γ' , aromatic heterocyclalsulfinyl which may be substituted with Substituent Group γ , non-aromatic heterocyclalsulfinyl which may be substituted with Substituent Group γ' , aromatic carbocyclalsulfonyl which may be substituted with Substituent Group γ , non-aromatic carbocyclalsulfonyl which may be substituted

with Substituent Group γ' , aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ , and non-aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ' .

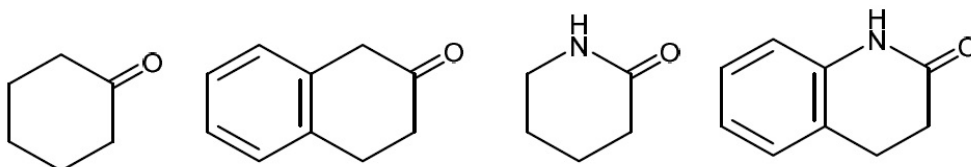
[0039]

Examples of substituents on the ring of "non-aromatic carbon ring" or "non-aromatic heterocyclic ring" for "substituted non-aromatic carbocyclyl", "substituted non-aromatic heterocyclyl", "substituted non-aromatic carbocyclyloxy", "substituted non-aromatic heterocyclyloxy", "substituted non-aromatic carbocyclylcarbonyloxy", "substituted non-aromatic heterocyclylcarbonyloxy", "substituted non-aromatic carbocyclylcarbonyl", "substituted non-aromatic heterocyclylcarbonyl", "substituted non-aromatic carbocyclyloxycarbonyl", "substituted non-aromatic heterocyclyloxycarbonyl", "substituted non-aromatic carbocyclylsulfanyl", "substituted non-aromatic heterocyclylsulfanyl", "substituted non-aromatic carbocyclylsulfinyl", "substituted non-aromatic heterocyclylsulfinyl", "substituted non-aromatic carbocyclylsulfonyl", "substituted non-aromatic heterocyclylsulfonyl", "substituted non-aromatic carbocyclyldiyl", "substituted non-aromatic heterocyclyldiyl", "substituted non-aromatic carbocyclyloxyimino", "substituted non-aromatic carbocyclyliminoxy", "substituted non-aromatic carbon ring formed by R^5 and R^7 together with the carbon atom to which they are attached", "substituted non-aromatic carbon ring formed by R^7 and R^8 together with the carbon atom to which they are attached", "substituted non-aromatic heterocyclic ring formed by R^7 and R^8 together with the carbon atom to which they are attached" and "substituted non-aromatic heterocyclic ring formed by R^4 and R^U together with the carbon atom to which they are attached" include the following Substituent Group C. One or more group(s) selected from the following Substituent Group C may be attached to an atom at any position of the ring.

Substituent Group C: Substituent Group B and oxo.

[0040]

When "non-aromatic carbon ring" or "non-aromatic heterocyclic ring" is substituted with "oxo", it means a ring in which two hydrogen atoms on a carbon atom are substituted, as follows.



[0041]

Examples of the substituent group for "substituted amino", "substituted imino", "substituted carbamoyl" and "substituted sulfamoyl" are as listed in Substituent Group D, as follows, and may be one or two groups selected from Substituent Group D.

Substituent Group D: halogen, hydroxy, carboxy, cyano, alkyl which may be substituted with Substituent Group α , alkenyl which may be substituted with Substituent Group α , alkynyl which may be substituted with Substituent Group α , alkylcarbonyl which may be substituted with Substituent Group α , and alkenylcarbonyl which may be substituted with Substituent Group α , alkynylcarbonyl which may be substituted with Substituent Group α , alkylsulfanyl which may be substituted with Substituent Group α , alkenylsulfanyl which may be substituted with Substituent Group α , alkynylsulfanyl, alkylsulfinyl which may be substituted with Substituent Group α , alkenylsulfinyl which may be substituted with Substituent Group α , alkynylsulfinyl which may be substituted with Substituent Group α , alkylsulfonyl which may be substituted with Substituent Group α , alkenylsulfonyl which may be substituted with Substituent Group α , alkynylsulfonyl which may be substituted with Substituent Group α , amino which may be substituted with Substituent Group β , imino which may be substituted with Substituent Group β , carbamoyl which may be substituted with Substituent Group β , sulfamoyl which may be substituted with Substituent Group β , sulfamoyl which may be

substituted with substituent group,
aromatic carbocyclyl which may be substituted with Substituent
Group γ , non-aromatic carbocyclyl which may be substituted with
Substituent Group γ' , aromatic heterocyclyl which may be
substituted with Substituent Group γ , non-aromatic heterocyclyl
which may be substituted with Substituent Group γ' , aromatic
carbocyclylalkyl which may be substituted with Substituent Group
 γ , non-aromatic carbocyclylalkyl which may be substituted with
Substituent Group γ' , aromatic heterocyclylalkyl which may be
substituted with Substituent Group γ , non-aromatic
heterocyclylalkyl which may be substituted with Substituent Group
 γ' , aromatic carbocyclylcarbonyl which may be substituted with
Substituent Group γ , non-aromatic carbocyclylcarbonyl which may
be substituted with Substituent Group γ' , aromatic
heterocyclylcarbonyl which may be substituted with Substituent
Group γ , non-aromatic heterocyclylcarbonyl which may be
substituted with Substituent Group γ' , aromatic
carbocyclylloxycarbonyl which may be substituted with Substituent
Group γ , non-aromatic carbocyclylloxycarbonyl which may be
substituted with Substituent Group γ' , aromatic
heterocyclylloxycarbonyl which may be substituted with Substituent
Group γ , non-aromatic heterocyclylloxycarbonyl which may be
substituted with Substituent Group γ' , aromatic
carbocyclylsulfanyl which may be substituted with Substituent
Group γ , non-aromatic carbocyclylsulfanyl which may be substituted
with Substituent Group γ' , aromatic heterocyclylsulfanyl which
may be substituted with Substituent Group γ , non-aromatic
heterocyclylsulfanyl which may be substituted with Substituent
Group γ' , aromatic carbocyclylsulfinyl which may be substituted
with Substituent Group γ , non-aromatic carbocyclylsulfinyl which
may be substituted with Substituent Group γ' , aromatic
heterocyclylsulfinyl which may be substituted with Substituent
Group γ , non-aromatic heterocyclylsulfinyl which may be
substituted with Substituent Group γ' , aromatic
carbocyclylsulfonyl which may be substituted with Substituent
Group γ , non-aromatic carbocyclylsulfonyl which may be substituted

with Substituent Group γ' , aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ , and non-aromatic heterocyclylsulfonyl which may be substituted with Substituent Group γ' .

[0042]

In the compound of the formula (I), preferred embodiments for R^1 , R^{1B} , R^{1C} , L, R^2 , R^3 , X, Y, U, V, W, Z^A , Z^B , Z^C , R^5 , R^6 , R^7 , R^8 , R^X , R^Y , R^V , R^W , R^U and R^4 are shown below. Embodiments of the compound of the formula (I) include any combination of the following specific examples.

[0043]

R^1 is carboxy, cyano, substituted or unsubstituted aromatic heterocyclyl, $-C(=O)-NR^{1B}R^{1C}$ or $-CH=CHC(=O)-OH$; wherein R^{1B} and R^{1C} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted aminosulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl (hereinafter referred to as a-1).

R^1 is carboxy or $-C(=O)-NR^{1B}R^{1C}$; wherein R^{1B} and R^{1C} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted aminosulfonyl, or substituted or unsubstituted non-aromatic heterocyclylsulfonyl (hereinafter referred to as a-2).

R^1 is carboxy (hereinafter referred to as a-3).

[0044]

L is substituted or unsubstituted non-aromatic carbocyclyldiyl, substituted or unsubstituted non-aromatic heterocyclyldiyl or substituted or unsubstituted alkylene (hereinafter referred to as b-1).

L is substituted or unsubstituted non-aromatic carbocyclyldiyl or substituted or unsubstituted non-aromatic heterocyclyldiyl (hereinafter referred to as b-2).

L is substituted or unsubstituted non-aromatic carbocyclyldiyl (hereinafter referred to as b-3).

L is substituted or unsubstituted adamantanediyl or substituted or unsubstituted cyclohexanediyl (hereinafter referred to as b-4).

L is substituted or unsubstituted adamantane-2,2-diyl or substituted or unsubstituted cyclohexane-1,1-diyl (hereinafter referred to as b-5).

L is non-aromatic carbocyclyldiyl substituted with one or more substituent(s) selected from Substituent Group a (Substituent Group a: cyano, alkyloxy, hydroxy and halogen) or unsubstituted non-aromatic carbocyclyldiyl (hereinafter referred to as b-6).

L is adamantanediyl substituted with one or more substituent(s) selected from Substituent Group a, or unsubstituted adamantanediyl (hereinafter referred to as b-7).

L is adamantane-2,2-diyl substituted with one or more substituent(s) selected from Substituent Group a, or unsubstituted adamantane-2,2-diyl (hereinafter referred to as b-8).

L is cyclohexanediyl substituted with halogen or unsubstituted cyclohexanediyl (hereinafter referred to as b-9).

L is cyclohexane-1,1-diyl substituted with halogen or unsubstituted cyclohexane-1,1-diyl (hereinafter referred to as b-10).

L is adamantanediyl substituted with one or more substituent(s) selected from Substituent Group a, unsubstituted adamantanediyl, cyclohexanediyl substituted with halogen or unsubstituted cyclohexanediyl (hereinafter referred to as b-11).

L is adamantane-2,2-diyl substituted with one or more substituent(s) selected from Substituent Group a, unsubstituted adamantane-2,2-diyl, cyclohexane-1,1-diyl substituted with halogen or unsubstituted cyclohexane-1,1-diyl (hereinafter referred to as b-12).

L is adamantane-2,2-diyl substituted with one or more substituent(s) selected from Substituent Group a (hereinafter referred to as b-13).

L is unsubstituted adamantane-2,2-diyl (hereinafter referred to as b-14).

L is cyclohexane-1,1-diyl substituted with halogen

(hereinafter referred to as b-15).

L is unsubstituted cyclohexane-1,1-diyl (hereinafter referred to as b-16).

[0045]

R² is substituted or unsubstituted alkyl (hereinafter referred to as c-1).

R² is alkyl substituted with halogen or unsubstituted alkyl (hereinafter referred to as c-2).

R² is alkyl substituted with halogen (hereinafter referred to as c-3).

[0046]

R³ is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted amino, or substituted or unsubstituted carbamoyl (hereinafter referred to as d-1).

R³ is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy or substituted or unsubstituted amino (hereinafter referred to as d-2).

R³ is a hydrogen atom or substituted or unsubstituted alkyl (hereinafter referred to as d-3).

R³ is a hydrogen atom or alkyl substituted with one or more substituent(s) selected from Substituent Group b (Substituent Group b: dialkylamino, amino and hydroxy) or unsubstituted alkyl (hereinafter referred to as d-4).

R³ is a hydrogen atom (hereinafter referred to as d-5).

[0047]

X is =CR^x- or =N-, wherein R^x is a hydrogen atom, cyano, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl (hereinafter referred to as e-1).

X is =CR^x- or =N-, wherein R^x is a hydrogen atom, halogen or substituted or unsubstituted alkyl (hereinafter referred to as e-2).

X is =CR^x- or =N-, wherein R^x is a hydrogen atom, halogen or

unsubstituted alkyl (hereinafter referred to as e-3).

X is =CH- or =N- (hereinafter referred to as e-4).

X is =CH- (hereinafter referred to as e-5).

X is =N- (hereinafter referred to as e-6).

[0048]

Y is =CR^Y- or =N-, wherein R^Y is a hydrogen atom, cyano, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl (hereinafter referred to as f-1).

Y is =CR^Y- or =N-, wherein R^Y is a hydrogen atom or halogen (hereinafter referred to as f-2).

Y is =CH- or =N- (hereinafter referred to as f-3).

Y is =CH- (hereinafter referred to as f-4).

Y is =N- (hereinafter referred to as f-5).

[0049]

U is -CR^U= or -N=, wherein R^U is a hydrogen atom, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl or substituted or unsubstituted non-aromatic carbocyclyl (hereinafter referred to as g-1).

U is -CR^U= or -N=, wherein R^U is a hydrogen atom, halogen, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted non-aromatic heterocycloxy or substituted or unsubstituted alkyloxy (hereinafter referred to as g-2).

U is -CR^U= or -N=, wherein R^U is a hydrogen atom, halogen, non-aromatic carbocycloxy substituted with pyrazolyl or unsubstituted non-aromatic carbocycloxy, non-aromatic heterocycloxy substituted with oxetanyl or unsubstituted non-aromatic heterocycloxy, or unsubstituted alkyloxy (hereinafter

referred to as g-3).

U is $-\text{CH}=\text{}$ or $-\text{N}=\text{}$ (hereinafter referred to as g-4).

U is $-\text{CH}=\text{}$ (hereinafter referred to as g-5).

U is $-\text{N}=\text{}$ (hereinafter referred to as g-6).

[0050]

V is $-\text{CR}^{\text{V}}=\text{}$ or $-\text{N}=\text{}$, wherein R^{V} is a hydrogen atom, cyano, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl (hereinafter referred to as h-1).

V is $-\text{CR}^{\text{V}}=\text{}$ or $-\text{N}=\text{}$, wherein R^{V} is a hydrogen atom, cyano or substituted or unsubstituted carbamoyl (hereinafter referred to as h-2).

V is $-\text{CR}^{\text{V}}=\text{}$ or $-\text{N}=\text{}$, wherein R^{V} is a hydrogen atom, cyano or unsubstituted carbamoyl (hereinafter referred to as h-3).

V is $-\text{CH}=\text{}$ or $-\text{N}=\text{}$ (hereinafter referred to as h-4).

V is $-\text{CH}=\text{}$ (hereinafter referred to as h-5).

V is $-\text{N}=\text{}$ (hereinafter referred to as h-6).

[0051]

W is $=\text{CR}^{\text{W}}-\text{}$ or $=\text{N}-\text{}$, wherein R^{W} is a hydrogen atom, cyano, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl (hereinafter referred to as i-1).

W is $=\text{CH}-\text{}$ or $=\text{N}-\text{}$ (hereinafter referred to as i-2).

W is $=\text{CH}-\text{}$ (hereinafter referred to as i-3).

W is $=\text{N}-\text{}$ (hereinafter referred to as i-4).

[0052]

Z^{A} is $-\text{C}=\text{}$ or $-\text{N}-\text{}$ (hereinafter referred to as j-1).

Z^{A} is $-\text{C}=\text{}$ (hereinafter referred to as j-2).

Z^{A} is $-\text{N}-\text{}$ (hereinafter referred to as j-3).

[0053]

Z^{B} is $-\text{CR}^5\text{R}^6-\text{}$, $-\text{CR}^5=\text{}$, $-\text{NR}^5-\text{}$ or $-\text{N}=\text{}$, wherein R^5 and R^6 are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl, or R^5 and R^6 are taken together to form oxo (hereinafter

referred to as k-1).

Z^B is $-CR^5R^6-$, $-CR^5=$ or $-NR^5-$, wherein R^5 and R^6 are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl, or R^5 and R^6 are taken together to form oxo (hereinafter referred to as k-2).

Z^B is $-CR^5R^6-$ or $-CR^5=$, wherein R^5 and R^6 are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl, or R^5 and R^6 are taken together to form oxo (hereinafter referred to as k-3).

Z^B is $-CR^5R^6-$, wherein R^5 and R^6 are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl, or R^5 and R^6 are taken together to form oxo (hereinafter referred to as k-4).

Z^B is $-CR^5=$, wherein R^5 is a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl (hereinafter referred to as k-5).

Z^B is $-CR^5R^6-$ or $-CR^5=$, wherein R^5 and R^6 are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, or R^5 and R^6 are taken together to form oxo (hereinafter referred to as k-6).

Z^B is $-CR^5R^6-$, wherein R^5 and R^6 are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, or R^5 and R^6 are taken together to form oxo (hereinafter referred to as k-7).

Z^B is $-CR^5=$, wherein R^5 is a hydrogen atom or substituted or unsubstituted non-aromatic heterocyclyl (hereinafter referred to as k-8).

Z^B is $-CR^5R^6-$ or $-CR^5=$, wherein R^5 and R^6 are each independently a hydrogen atom (hereinafter referred to as k-9).

Z^B is $-CR^5R^6-$, wherein R^5 and R^6 are each independently a hydrogen atom (hereinafter referred to as k-10).

Z^B is $-CR^5=$, wherein R^5 is a hydrogen atom (hereinafter referred to as k-11).

Z^B is $-CR^5R^6-$ or $-CR^5=$, wherein R^5 and R^6 are each independently a hydrogen atom or unsubstituted non-aromatic heterocyclyl, or R^5 and R^6 are taken together to form oxo (hereinafter referred to as k-12).

Z^B is $-CR^5R^6-$, wherein R^5 and R^6 are each independently a hydrogen atom or unsubstituted non-aromatic heterocyclyl, or R^5 and R^6 are taken together to form oxo (hereinafter referred to as k-13).

Z^B is $-CR^5=$, wherein R^5 is a hydrogen atom or unsubstituted non-aromatic heterocyclic (hereinafter referred to as k-14).

Z^B is $-CH_2-$ (hereafter referred to as k-15).

Z^B is $-CH=$ (hereafter referred to as k-16).

[0054]

Z^C is $-CR^7R^8-$, $-CR^7=$, $-NR^7-$ or $=N-$, wherein R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted alkylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as l-1).

Z^C is $-CR^7R^8-$, $-CR^7=$ or $-NR^7-$, wherein R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or

unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted alkylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 1-2).

Z^C is $-CR^7R^8-$ or $-NR^7-$, wherein R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted alkylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 1-3).

Z^C is $-CR^7R^8-$, wherein R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted alkylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 1-4).

Z^C is $-NR^7-$, wherein R^7 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic

carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl or substituted or unsubstituted alkylsulfonyl (hereinafter referred to as 1-5).

Z^C is $-CR^7R^8-$ or $-NR^7-$, wherein R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 1-6).

Z^C is $-CR^7R^8-$, wherein R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 1-7).

Z^C is $-NR^7-$, wherein R^7 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, or

substituted or unsubstituted non-aromatic carbocyclylsulfonyl (hereinafter referred to as 1-8).

Z^c is $-CR^7R^8-$ or $-NR^7-$, wherein R^7 and R^8 are each independently a hydrogen atom, alkyl substituted with one or more substituent(s) selected from Substituent Group c (Substituent Group c: halogen, hydroxy, alkyloxy, non-aromatic carbocyclyl, non-aromatic carbocyclyl substituted with halogen, non-aromatic heterocyclyl, non-aromatic heterocyclylcarbonyl and aromatic carbocyclyl) or unsubstituted alkyl, non-aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group d (Substituent Group d: halogen, alkyloxy, cyano, hydroxy, haloalkyl and alkyloxy substituted with phenyl) or unsubstituted non-aromatic carbocyclyl, non-aromatic heterocyclyl substituted with haloalkyl or unsubstituted non-aromatic heterocyclyl, aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group e (Substituent Group e: halogen, alkyl, haloalkyl, alkyloxy and cyano) or unsubstituted aromatic carbocyclyl, aromatic heterocyclyl substituted with one or more substituent(s) selected from Substituent Group f (Substituent Group group f: alkyl, halogen, haloalkyl, alkyloxy, hydroxy and cyano) or unsubstituted aromatic heterocyclyl, unsubstituted non-aromatic carbocyclyloxycarbonyl, unsubstituted non-aromatic heterocyclyloxycarbonyl, unsubstituted non-aromatic carbocyclylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a non-aromatic carbon ring substituted with halogen or a unsubstituted non-aromatic carbon ring or to form a non-aromatic heterocyclic ring substituted with one or more substituent(s) selected from Substituent Group g (Substituent Group g: alkyl, haloalkyl, alkylcarbonyl, alkyloxycarbonyl substituted with phenyl, alkyloxycarbonyl, non-aromatic heterocyclyl, alkylcarbamoyl, non-aromatic carbocyclyl, aromatic heterocyclyl and aromatic heterocyclyl substituted with halogen) or a unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as referred to as 1-9).

Z^c is $-CR^7R^8-$, wherein R^7 and R^8 are each independently a

hydrogen atom, unsubstituted alkyl, unsubstituted non-aromatic carbocyclyl, unsubstituted non-aromatic heterocyclyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a non-aromatic carbon ring substituted with halogen or a unsubstituted non-aromatic carbon ring or to form a non-aromatic heterocyclic ring substituted with one or more substituent(s) selected from Substituent Group g or a unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 1-10).

Z^c is $-NR^7-$, wherein R^7 is a hydrogen atom, alkyl substituted with one or more substituent(s) selected from Substituent Group c or unsubstituted alkyl, non-aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group d or unsubstituted non-aromatic carbocyclyl, non-aromatic heterocyclyl substituted with haloalkyl or unsubstituted non-aromatic heterocyclyl, aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group e or unsubstituted aromatic carbocyclyl, aromatic heterocyclyl substituted with one or more substituent(s) selected from Substituent Group f or unsubstituted aromatic heterocyclyl, unsubstituted non-aromatic carbocyclyloxycarbonyl, unsubstituted non-aromatic heterocyclyloxycarbonyl, or unsubstituted non-aromatic carbocyclylsulfonyl (hereinafter referred to as 1-11).

Z^c is $-CR^7R^8-$, wherein R^7 and R^8 are each independently unsubstituted alkyl (hereinafter referred to as 1-12).

Z^c is $-NR^7-$, wherein R^7 is unsubstituted alkyl (hereinafter referred to as 1-13).

[0055]

R^4 is a hydrogen atom, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted aromatic heterocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, substituted or unsubstituted

carbamoyl, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyl or substituted or unsubstituted non-aromatic heterocyclylcarbonyl, or R^4 and R^U are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as m-1).

R^4 is substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted aromatic heterocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclylcarbonyl, or R^4 and R^U are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as m-2).

R^4 is substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic

heterocyclylcarbonyl, or R^4 and R^U are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as m-3).

R^4 is alkyloxy substituted with one or more substituent(s) selected from Substituent Group h (Substituent Group h: halogen, hydroxy, alkyloxy, cyano, alkylcarbonyloxy, substituted aromatic heterocyclyl (substituents: alkyl or alkyloxy), non-aromatic heterocyclyl, substituted non-aromatic heterocyclyl (substituents: aromatic heterocyclyl, alkyl or halogen), aromatic heterocyclylamino, aromatic carbocyclyl, and aromatic carbocyclyl substituted with alkyloxy) or unsubstituted alkyloxy;

non-aromatic heterocyclyloxy substituted with one or more substituent(s) selected from Substituent Group j (Substituent Group j: alkyl, halogen, haloalkyl, cyanoalkyl, alkylcarbonyl, alkylcarbamoyle, alkyloxy carbonyl, alkyloxyalkyl, alkylsulfonylalkyl, non-aromatic heterocyclyl, substituted aromatic heterocyclyl (substituents: alkyl, alkyloxy, halogen, haloalkyl or cyano), aromatic heterocyclyl, non-aromatic carbocyclyl, non-aromatic carbocyclyl substituted with halogen, substituted non-aromatic heterocyclyl (substituents: halogen or alkylcarbonyl), non-aromatic heterocyclylalkyl, non-aromatic carbocyclylalkyl, non-aromatic carbocyclylalkyl substituted with halogen, aromatic heterocyclylalkyl substituted with alkyl, non-aromatic heterocyclylcarbonyl, non-aromatic carbocyclylcarbonyl, aromatic heterocyclylcarbonyl, aromatic carbocyclylalkyloxy carbonyl, and non-aromatic carbocyclylsulfonyl) or unsubstituted non-aromatic heterocyclyloxy;

non-aromatic carbocyclyloxy substituted with one or more substituent(s) selected from Substituent Group k (Substituent Group k: alkyl, halogen, haloalkyl, alkyloxy, alkylsulfonyl, haloalkylamino, alkylamino, aromatic heterocyclyl, non-aromatic heterocyclyl substituted with halogen, non-aromatic heterocyclyl, aromatic heterocyclyl substituted with halogen, aromatic heterocyclylamino substituted with halogen, non-aromatic

heterocyclylalkyl substituted with halogen, non-aromatic carbocyclyloxy, and non-aromatic carbocyclyliminoxy substituted with halogen) or unsubstituted non-aromatic carbocyclyloxy;

aromatic carbocyclyloxy;

alkyl or substituted with one or more substituent(s) selected from Substituent Group l (Substituent Group l: halogen, aromatic carbocyclyl, aromatic carbocyclyl substituted with alkyloxy, non-aromatic heterocyclyl, and substituted non-aromatic heterocyclyl (substituents: aromatic heterocyclyl, non-aromatic heterocyclyl substituted with alkyl or halogen), and non-aromatic carbocyclyloxyimino substituted with halogen) or unsubstituted alkyl;

alkenyl substituted with one or more substituent(s) selected from Substituent Group m (Substituent Group m: aromatic carbocyclyl substituted with alkyloxy, non-aromatic heterocyclyl, and non-aromatic heterocyclyl substituted with aromatic carbocyclylalkyloxycarbonyl) or unsubstituted alkenyl;

amino substituted with one or more substituent(s) selected from Substituent Group n (Substituent Group n: aromatic carbocyclylalkyl substituted with alkyloxy, aromatic carbocyclylcarbonyl substituted with alkyloxy, non-aromatic heterocyclyl substituted with aromatic heterocyclyl, aromatic heterocyclyl, aromatic carbocyclylsulfonyl, aromatic carbocyclylcarbonyl, alkyl, and aromatic heterocyclyl substituted with haloalkyl) or unsubstituted amino;

carbamoyl substituted with haloalkyl or unsubstituted carbamoyl;

hydroxy;

halogen;

aromatic carbocyclyl substituted with alkyloxyalkyl or unsubstituted aromatic carbocyclyl;

unsubstituted aromatic heterocyclyl;

non-aromatic heterocyclyl substituted with one or more substituent(s) selected from Substituent Group o (Substituent Group o: aromatic heterocyclyl, aromatic carbocyclylalkyl, aromatic heterocyclylalkyl, and haloalkyl) or unsubstituted non-

aromatic heterocyclyl;

non-aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group p (Substituent Group p: carbamoyl and dialkylcarbamoyl) or unsubstituted non-aromatic carbocyclyl;

non-aromatic heterocyclylcarbonyl substituted with one or more substituent(s) selected from Substituent Group q (Substituent Group q: aromatic heterocyclyl, haloalkyl, non-aromatic heterocyclyl substituted with halogen, aromatic heterocyclyl substituted with halogen, halogen, and alkyloxy) or unsubstituted non-aromatic heterocyclylcarbonyl;

non-aromatic carbocyclyloxyimino substituted with halogen; or

R^4 and R^U are taken together with the carbon atom to which they are attached to form a non-aromatic heterocyclic ring substituted with halogen or a unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as m-4).

R^4 is substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted carbamoyl, or substituted or unsubstituted non-aromatic heterocyclylcarbonyl (hereinafter referred to as m-5).

R^4 is alkyloxy substituted with one or more substituent(s) selected from Substituent Group h or unsubstituted alkyloxy, non-aromatic heterocyclyloxy substituted with one or more substituent(s) selected from Substituent Group j or unsubstituted non-aromatic heterocyclyloxy, non-aromatic carbocyclyloxy substituted with one or more substituent(s) selected from Substituent Group k or unsubstituted non-aromatic carbocyclyloxy, carbamoyl substituted with haloalkyl or unsubstituted carbamoyl, or non-aromatic heterocyclylcarbonyl substituted with one or more substituent(s) selected from Substituent Group q or unsubstituted non-aromatic heterocyclylcarbonyl (hereinafter referred to as m-6).

R^4 is substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, or substituted or

unsubstituted non-aromatic carbocycloxyloxy (hereinafter referred to as m-7).

R⁴ is alkyloxy substituted with one or more substituent(s) selected from Substituent Group h or unsubstituted alkyloxy, non-aromatic heterocycloxyloxy substituted with one or more substituent(s) selected from Substituent Group j or unsubstituted non-aromatic heterocycloxyloxy, or non-aromatic carbocycloxyloxy substituted with one or more substituent(s) selected from Substituent Group k or unsubstituted non-aromatic carbocycloxyloxy (hereinafter referred to as m-8).

R⁴ is substituted or unsubstituted alkyloxy (hereinafter referred to as m-9).

R⁴ is alkyloxy substituted with one or more substituent(s) selected from Substituent Group h or unsubstituted alkyloxy (hereinafter referred to as m-10).

R⁴ is substituted or unsubstituted non-aromatic heterocycloxyloxy (hereinafter referred to as m-11).

R⁴ is non-aromatic heterocycloxyloxy substituted with one or more substituent(s) selected from Substituent Group j or unsubstituted non-aromatic heterocycloxyloxy (hereinafter referred to as m-12).

R⁴ is substituted or unsubstituted non-aromatic carbocycloxyloxy (hereinafter referred to as m-13).

R⁴ is non-aromatic carbocycloxyloxy substituted with one or more substituent(s) selected from Substituent Group k or unsubstituted non-aromatic carbocycloxyloxy (hereinafter referred to as m-14).

R⁴ is non-aromatic carbocycloxyloxy substituted with one or more substituent(s) selected from Substituent Group k (hereinafter referred to as m-15).

R⁴ is substituted non-aromatic carbocycloxyloxy (substituent: non-aromatic heterocyclyl substituted with halogen) (hereinafter referred to as m-16).

R⁴ is substituted non-aromatic heterocycloxyloxy (substituents: aromatic heterocyclyl) (hereinafter referred to as m-17).

R⁴ is substituted non-aromatic heterocycloxyloxy (substituents: aromatic heterocyclyl substituted with halogen) (hereinafter referred to as m-18).

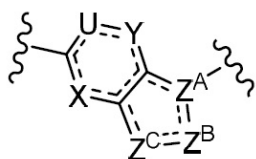
R⁴ is substituted non-aromatic heterocyclyloxy (substituents: haloalkyl) (hereinafter referred to as m-19).

R⁴ is substituted non-aromatic carbocyclyloxy (substituent: haloalkylamino) (hereinafter referred to as m-20).

[0056]

Furthermore, examples of the compound of formula (I) encompass all combination of the specific examples as shown below.

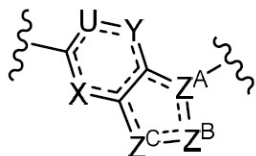
Preferred embodiments of the group of the formula:



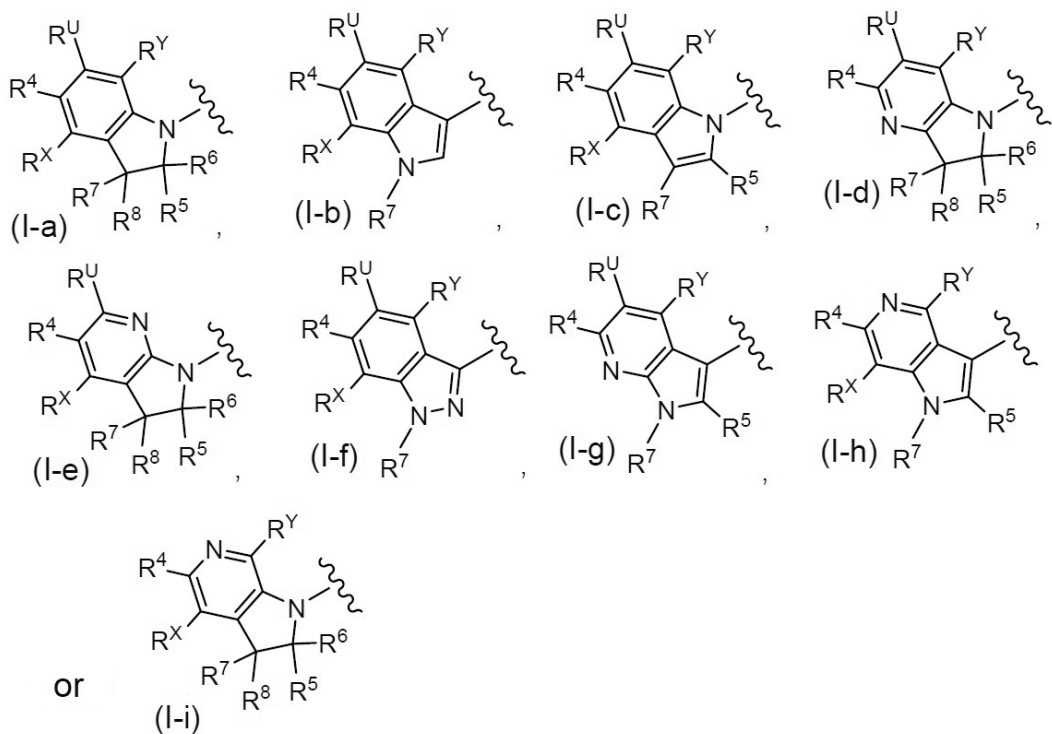
and R¹, R^{1B}, R^{1C}, L, R², R³, V, W, R⁵, R⁶, R⁷, R⁸, R^X, R^Y, R^V, R^W, R^U and R⁴ are shown below.

[0057]

The group of the formula:

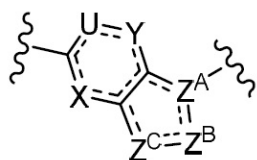


is one represented by the formula (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h) or (I-i) as follows.



[0058]

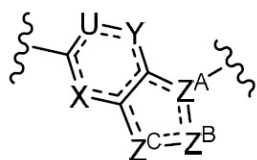
The group of the formula:



is one represented by the formula (I-a), (I-b), (I-h) or (I-i).

[0059]

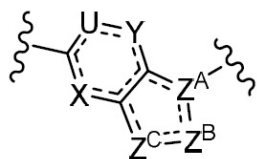
The group of the formula:



is one represented by the formula (I-a), (I-b) or (I-i).

[0060]

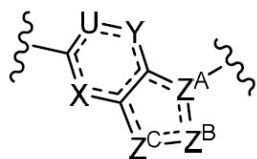
The group of the formula:



is one represented by the formula (I-a) or (I-b).

[0061]

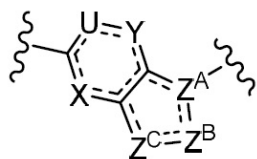
The group of the formula:



is one represented by the formula (I-a).

[0062]

The group of the formula:



is one represented by the formula (I-b).

[0063]

R^x is a hydrogen atom, cyano, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl (hereinafter referred to as ee-1).

R^x is a hydrogen atom, halogen or substituted or unsubstituted alkyl (hereinafter referred to as ee-2).

R^x is a hydrogen atom, halogen or unsubstituted alkyl (hereinafter referred to as ee-3)

R^x is a hydrogen atom (hereinafter referred to as ee-4).

[0064]

R^y is a hydrogen atom, cyano, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl (hereinafter referred to as ff-1).

R^y is a hydrogen atom or halogen (hereinafter referred to as ff-2).

R^y is a hydrogen atom (hereinafter referred to as ff-3).

[0065]

R^U is a hydrogen atom, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl or substituted or unsubstituted non-aromatic carbocyclyl (hereinafter referred to as gg-1).

R^U is a hydrogen atom, halogen, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy or substituted or unsubstituted alkyloxy (hereinafter referred to as gg-2).

R^U is a hydrogen atom, halogen, non-aromatic carbocyclyloxy substituted with pyrazolyl or unsubstituted non-aromatic carbocyclyloxy, non-aromatic heterocyclyloxy substituted with oxetanyl or unsubstituted non-aromatic heterocyclyloxy, or unsubstituted alkyloxy (hereinafter referred to as gg-3).

R^U is a hydrogen atom (hereinafter referred to as gg-4).

[0066]

R⁵ and R⁶ are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl, or R⁵ and R⁶ are taken together to form oxo (hereinafter referred to as kk-1).

R⁵ is a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl (hereinafter referred to as kk-5).

R⁵ and R⁶ are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, or R⁵ and R⁶ are taken together to form oxo (hereinafter referred to as kk-6).

R⁵ is a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl (hereinafter referred to as kk-8).

R⁵ and R⁶ are each independently a hydrogen atom (hereinafter referred to as kk-9).

R⁵ is a hydrogen atom (hereinafter referred to as kk-10).

R⁵ and R⁶ are each independently a hydrogen atom, unsubstituted non-aromatic heterocyclyl, or R⁵ and R⁶ are taken together to form oxo (hereinafter referred to as kk-12).

R⁵ is a hydrogen atom or unsubstituted non-aromatic heterocyclyl (hereinafter referred to as kk-14).

[0067]

R⁷ and R⁸ are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted alkylsulfonyl, or R⁷ and R⁸ are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as ll-1).

R⁷ is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl or substituted or unsubstituted alkylsulfonyl (hereinafter referred to as ll-5).

R⁷ and R⁸ are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic

carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 11-6).

R^7 and R^8 are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 11-7).

R^7 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxy carbonyl, substituted or unsubstituted non-aromatic heterocyclyloxy carbonyl, or substituted or unsubstituted non-aromatic carbocyclylsulfonyl (hereinafter referred to as 11-8).

R^7 and R^8 are each independently a hydrogen atom, alkyl substituted with one or more substituent(s) selected from Substituent Group c or unsubstituted alkyl, non-aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group d or unsubstituted non-aromatic carbocyclyl, non-aromatic heterocyclyl substituted with haloalkyl or unsubstituted non-aromatic heterocyclyl, aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group e or unsubstituted aromatic carbocyclyl, aromatic heterocyclyl substituted with one or more substituent(s)

selected from Substituent Group f or unsubstituted aromatic heterocyclyl, unsubstituted non-aromatic carbocyclyloxycarbonyl, unsubstituted non-aromatic heterocyclyloxycarbonyl, unsubstituted non-aromatic carbocyclylsulfonyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a non-aromatic carbon ring substituted with halogen or a unsubstituted non-aromatic carbon ring or non-aromatic heterocyclic ring substituted with one or more substituent(s) selected from Substituent Group g or unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 11-9).

R^7 and R^8 are each independently a hydrogen atom, unsubstituted alkyl, unsubstituted non-aromatic carbocyclyl, unsubstituted non-aromatic heterocyclyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a non-aromatic carbon ring substituted with halogen or a unsubstituted non-aromatic carbon ring or a non-aromatic heterocyclic ring substituted with one or more substituent(s) selected from Substituent Group g or a unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 11-10).

R^7 and R^8 are each independently unsubstituted alkyl (hereinafter referred to as 11-11).

R^7 is a hydrogen atom, alkyl substituted with one or more substituent(s) selected from Substituent Group c or unsubstituted alkyl, non-aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group d or unsubstituted non-aromatic carbocyclyl, non-aromatic heterocyclyl substituted with haloalkyl or unsubstituted non-aromatic heterocyclyl, aromatic carbocyclyl substituted with one or more substituent(s) selected from Substituent Group e or unsubstituted aromatic carbocyclyl, aromatic heterocyclyl substituted with one or more substituent(s) selected from Substituent Group f or unsubstituted aromatic heterocyclyl, unsubstituted non-aromatic carbocyclyloxycarbonyl, unsubstituted non-aromatic heterocyclyloxycarbonyl or unsubstituted non-aromatic carbocyclylsulfonyl (hereinafter referred to as 11-12).

R^7 is unsubstituted alkyl (hereinafter referred to as 11-13).

R⁷ and R⁸ are taken together with the carbon atom to which they are attached to form a unsubstituted non-aromatic heterocyclic ring (hereinafter referred to as 11-14).

R⁷ and R⁸ are taken together with the carbon atom to which they are attached to form a non-aromatic carbon ring substituted with halogen (hereinafter referred to as 11-15).

R⁷ is substituted non-aromatic carbon ring (substituent: halogen) (hereinafter referred to as 11-16).

R⁷ is substituted alkyl (substituent: alkyloxy) (hereinafter referred to as 11-17).

[0068]

R¹ is as defined in the above (a-1), (a-2) or (a-3).

[0069]

L is as defined in the above (b-1), (b-2), (b-3), (b-4), (b-5), (b-6), (b-7), (b-8), (b-9), (b-10), (b-11), (b-12), (b-13), (b-14), (b-15) or (b-16).

[0070]

R² is as defined in the above (c-1), (c-2) or (c-3).

[0071]

R³ is as defined in the above (d-1), (d-2), (d-3), (d-4) or (d-5).

[0072]

V is as defined in the above (h-1), (h-2), (h-3), (h-4), (h-5) or (h-6).

[0073]

W is as defined in the above (i-1), (i-2), (i-3) or (i-4).

[0074]

R⁴ is as defined in the above (m-1), (m-2), (m-3), (m-4), (m-5), (m-6), (m-7), (m-8), (m-9), (m-10), (m-11), (m-12), (m-13),

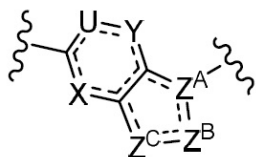
(m-14), (m-15), (m-16), (m-17), (m-18), (m-19) or (m-20).

[0075]

(1-A)

In one embodiment, a compound of the formula (I) is a compound, wherein

the group of the formula:



is as defined in (I-a),

R^X is as defined in (ee-4),

R^Y is as defined in (ff-3),

R^U is as defined in (gg-4),

R^5 and R^6 are as defined in (kk-9),

R^7 and R^8 are as defined in (ll-14),

R^1 is as defined in (a-3),

L is as defined in (b-14),

R^2 is as defined in (c-3),

R^3 is as defined in (d-5),

V is as defined in (h-6),

W is as defined in (i-4), and

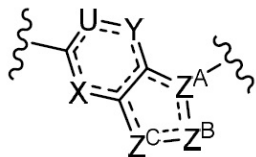
R^4 is as defined in (m-17).

[0076]

(1-B)

In one embodiment, a compound of formula (I) is a compound, wherein

the group of the formula:



is as defined in (I-b),

R^X is as defined in (ee-4),

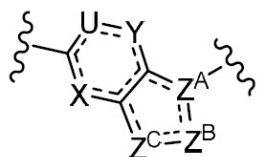
R^y is as defined in (ff-3),
 R^u is as defined in (gg-4),
 R^7 is as defined in (ll-15),
 R^1 is as defined in (a-3),
 L is as defined in (b-14),
 R^2 is as defined in (c-3),
 R^3 is as defined in (d-5),
 V is as defined in (h-6),
 W is as defined in (i-3), and
 R^4 is as defined in (m-17).

[0077]

(1-C)

In one embodiment, a compound of formula (I) is a compound, wherein

the group of the formula:



is as defined in (I-b),

R^x is as defined in (ee-4),
 R^y is as defined in (ff-3),
 R^u is as defined in (gg-4),
 R^7 is as defined in (ll-15),
 R^1 is as defined in (a-3),
 L is as defined in (b-14),
 R^2 is as defined in (c-3),
 R^3 is as defined in (d-5),
 V is as defined in (h-6),
 W is as defined in (i-4), and
 R^4 is as defined in (m-16).

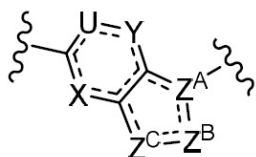
[0078]

(1-D)

In one embodiment, a compound of formula (I) is a compound,

wherein

the group of the formula:



is as defined in (I-b),

R^x is as defined in (ee-4),

R^y is as defined in (ff-3),

R^u is as defined in (gg-4),

R^7 is as defined in (ll-13),

R^1 is as defined in (a-3),

L is as defined in (b-14),

R^2 is as defined in (c-3),

R^3 is as defined in (d-5),

V is as defined in (h-6),

W is as defined in (i-4), and

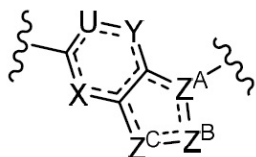
R^4 is as defined in (m-16).

[0079]

(1-E)

In one embodiment, a compound of formula (I) is a compound,
wherein

the group of the formula:



is as defined in (I-i),

R^x is as defined in (ee-4),

R^y is as defined in (ff-3),

R^5 and R^6 are as defined in (kk-9),

R^7 and R^8 are as defined in (ll-14),

R^1 is as defined in (a-3),

L is as defined in (b-14),

R^2 is as defined in (c-3),

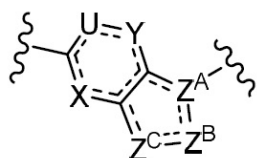
R³ is as defined in (d-5),
V is as defined in (h-6),
W is as defined in (i-4), and
R⁴ is as defined in (m-18).

[0080]

(1-F)

In one embodiment, a compound of formula (I) is a compound,
wherein

the group of the formula:



is as defined in (I-a),

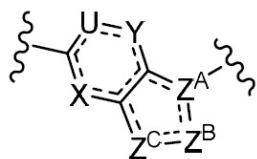
R^x is as defined in (ee-4),
R^y is as defined in (ff-3),
R^u is as defined in (gg-4),
R⁵ and R⁶ are as defined in (kk-9),
R⁷ and R⁸ are as defined in (ll-14),
R¹ is as defined in (a-3),
L is as defined in (b-14),
R² is as defined in (c-3),
R³ is as defined in (d-5),
V is as defined in (h-6),
W is as defined in (i-4), and
R⁴ is as defined in (m-16).

[0081]

(1-G)

In one embodiment, a compound of formula (I) is a compound,
wherein

the group of the formula:



is as defined in (I-a),

R^X is as defined in (ee-4),

R^Y is as defined in (ff-3),

R^U is as defined in (gg-4),

R^5 and R^6 are as defined in (kk-9),

R^7 and R^8 are as defined in (ll-14),

R^1 is as defined in (a-3),

L is as defined in (b-14),

R^2 is as defined in (c-3),

R^3 is as defined in (d-5),

V is as defined in (h-6),

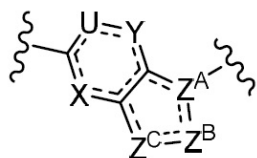
W is as defined in (i-4), and

R^4 is as defined in (m-19).

(1-H)

In one embodiment, a compound of formula (I) is a compound, wherein

the group of the formula:



is as defined in (I-a),

R^X is as defined in (ee-4),

R^Y is as defined in (ff-3),

R^U is as defined in (gg-4),

R^5 and R^6 are as defined in (kk-9),

R^7 and R^8 are as defined in (ll-14),

R^1 is as defined in (a-3),

L is as defined in (b-14),

R^2 is as defined in (c-3),

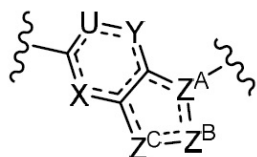
R^3 is as defined in (d-5),

V is as defined in (h-6),
W is as defined in (i-4), and
R⁴ is as defined in (m-20).

(1-I)

In one embodiment, a compound of formula (I) is a compound,
wherein

the group of the formula:



is as defined in (I-b),

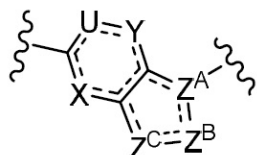
R^x is as defined in (ee-4),
R^y is as defined in (ff-3),
R^u is as defined in (gg-4),
R⁷ is as defined in (ll-17),
R¹ is as defined in (a-3),
L is as defined in (b-14),
R² is as defined in (c-3),
R³ is as defined in (d-5),
V is as defined in (h-6),
W is as defined in (i-4), and
R⁴ is as defined in (m-16).

[0082]

(1-J)

In one embodiment, a compound of formula (I) is a compound,
wherein

the group of the formula:



is as defined in (I-a),

R^x is as defined in (ee-4),

R^y is as defined in (ff-3),
R^u is as defined in (gg-4),
R⁵ and R⁶ are as defined in (kk-9),
R⁷ and R⁸ are as defined in (ll-11),
R¹ is as defined in (a-3),
L is as defined in (b-14),
R² is as defined in (c-3),
R³ is as defined in (d-5),
V is as defined in (h-6),
W is as defined in (i-4), and
R⁴ is as defined in (m-16).

[0083]

Compounds of formula (I) are not limited to specific isomers, but include all possible isomers (e.g., keto-enol isomers, imine-enamin isomers, diastereoisomers, optical isomers, rotational isomers, etc.), racemates or mixtures thereof.

[0084]

One or more hydrogen, carbon, and/or other atom(s) of the compounds of formula (I) may be substituted by isotope(s) of hydrogen, carbon, and/or other atom(s), respectively. Examples of such isotopes include hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine, and chlorine, as in the cases of ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, ¹²³I, and ³⁶Cl, respectively. The compounds of formula (I) also include compounds substituted with such isotopes. The compounds substituted with the isotopes are also useful as pharmaceutical products and include all radiolabeled forms of the compounds of formula (I). Furthermore, a "radiolabeling method" for producing the "radiolabeled forms" is also included in the present invention, and the "radiolabeled forms" are useful as tools for metabolic pharmacokinetics studies, studies on binding assay, and/or diagnostics.

[0085]

Radiolabeled entities of the compound of formula (I) can be prepared by methods well known in the art. For example, tritium-labeled compounds of formula (I) can be prepared by introducing tritium into certain compounds of formula (I) by a catalytic dehalogenation reaction using tritium. This method involves reacting a compound indicated by formula (I) with an appropriately halogen-substituted precursor and tritium gas in the presence or absence of a base, in the presence of a suitable catalyst, e.g. Pd/C. The process includes other suitable methods for preparing tritium-labeled compounds described in "Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A), Chapter 6 (1987). ¹⁴C-Labeled compounds can be prepared by using raw materials having ¹⁴C carbons.

[0086]

Examples of pharmaceutically acceptable salts of the compounds of formula (I) include salts of compounds of formula (I) with alkali metals (for example, lithium, sodium, and potassium), alkaline earth metals (for example, calcium and barium), magnesium, transition metals (for example, zinc and iron), ammonia, organic bases (for example, trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, pyridine, picoline, and quinoline), and amino acids, or salts with inorganic acids (for example, hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, hydrobromic acid, phosphoric acid, and hydroiodic acid) and organic acids (for example, formic acid, acetic acid, propionic acid, trifluoroacetic acid, citric acid, lactic acid, tartaric acid, oxalic acid, maleic acid, fumaric acid, succinic acid, mandelic acid, glutaric acid, malic acid, benzoic acid, phthalic acid, ascorbic acid, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoroacetic acid). These salts can be formed according to methods that are conventionally carried out.

[0087]

The compounds of formula (I) or pharmaceutically acceptable salts thereof may form solvates (e.g., hydrate and the like), co-crystals and/or crystal polymorphs. The present invention encompasses those various solvates co-crystals and crystal polymorphs. The "solvates" may be those wherein any numbers of solvent molecules (e.g. water molecules and the like) are coordinated with the compounds of formula (I). When the compounds of formula (I) or pharmaceutically acceptable salts thereof are allowed to stand in the atmosphere, the compounds may absorb water, resulting in attachment of adsorbed water or formation of hydrates. Recrystallization of the compounds of formula (I) or pharmaceutically acceptable salts thereof may produce crystal polymorphs. The "co-crystal" means that a compound of formula (I) or a salt thereof and a counter molecule exist in the same crystal lattice, which may contain any number of counter molecules.

[0088]

The compounds of formula (I) of the present invention or pharmaceutically acceptable salts thereof may form prodrugs, and the present invention also includes such various prodrugs. A prodrug is a derivative of a compound of the present invention having a group that can be chemically or metabolically degraded, and is a compound which becomes a pharmaceutically active compound of the present invention in vivo as a result of solvolysis or under physiological conditions. Prodrugs include compounds that are subjected to enzymatic oxidation, reduction, hydrolysis, and the like under physiological conditions in the living body and are converted to the compounds of formula (I); compounds that are hydrolyzed by gastric acid or the like and are converted to the compounds of formula (I); and the like. Methods for selecting and producing an appropriate prodrug derivative are described in, for example, "Design of Prodrugs, Elsevier, Amsterdam, 1985". A prodrug may have activity per se.

[0089]

When the compound of formula (I) or its pharmaceutically

acceptable salt has hydroxyl group(s), the prodrugs may be acyloxy derivatives and sulfonyloxy derivatives that are prepared by, for example, reacting a compound having hydroxyl group(s) with suitable acyl halide, suitable acid anhydride, suitable sulfonyl chloride, suitable sulfonyl anhydride or mixed anhydride, or by reacting with a condensing agent. Examples include $\text{CH}_3\text{COO}-$, $\text{C}_2\text{H}_5\text{COO}-$, $\text{tert-BuCOO}-$, $\text{C}_{15}\text{H}_{31}\text{COO}-$, $\text{PhCOO}-$, $(\text{m-NaOOCPh})\text{COO}-$, $\text{NaOOCCH}_2\text{CH}_2\text{COO}-$, $\text{CH}_3\text{CH}(\text{NH}_2)\text{COO}-$, $\text{CH}_2\text{N}(\text{CH}_3)_2\text{COO}-$, CH_3SO_3- , $\text{CH}_3\text{CH}_2\text{SO}_3-$, CF_3SO_3- , CH_2FSO_3- , $\text{CF}_3\text{CH}_2\text{SO}_3-$, $\text{p-CH}_3\text{-O-PhSO}_3-$, PhSO_3- and $\text{p-CH}_3\text{PhSO}_3-$.

[0090]

The following examples of formulations are only exemplified and not intended to limit the scope of the invention.

The compound of the present invention can be administered as a pharmaceutical composition by any conventional route, particularly enterally, for example, orally, for example, in the form of a tablet or a capsule; parenterally, for example, in the form of an injectable preparation or a suspension; and topically, for example, in the form of a lotion, a gel, an ointment or a cream, or as a pharmaceutical composition in a transnasal form or a suppository form. A pharmaceutical composition comprising the compound of the present invention in a free form or in the form of a pharmaceutically acceptable salt together with at least one pharmaceutically acceptable carrier or diluent can be produced by a mixing, granulating, or coating method in a conventional manner. For example, the oral composition can be a tablet, a granular preparation, or a capsule, each containing an excipient, a disintegrating agent, a binder, a lubricating agent, and the like, as well as an active ingredient and the like. Furthermore, the composition for injection can be prepared as a solution or a suspension, may be sterilized, and may contain a preservative, a stabilizer, a buffering agent, and the like.

[0091]

The compounds of the invention are useful for the following symptoms caused by RSV, and such symptoms caused by RSV vary from

mild common cold-like symptoms to severe lower respiratory tract diseases such as bronchiolitis and pneumonia. In other words, it is useful for common cold symptoms such as cough, runny nose, and fever, as well as for symptoms such as wheezing and trapped breathing that occur in more severe cases, and for diseases such as bronchitis and pneumonia that occur as a result of worsening of these symptoms.

[0092]

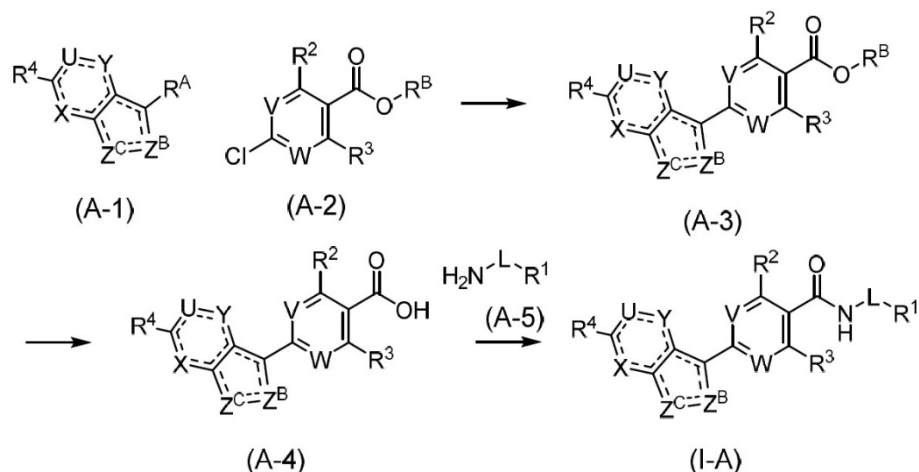
(Method for producing the compounds of the invention)

The compounds of formula (I) according to the present invention can be produced by, for example, the general synthesis method described below. Regarding extraction, purification, and the like, the treatments carried out in ordinary experiments of organic chemistry may be carried out.

The compounds of the present invention can be produced with reference to techniques known in the art.

[0093]

(Method A)



wherein each symbol is as defined above, and R^A is $-B(OH)_2$, $-Sn(C1-C6 \text{ alkyl})_3$, etc., and R^B is C1-C6 alkyl, etc.

Step 1

Compound (A-3) can be obtained by reacting Compound (A-1) with

Compound (A-2) in a solvent (e.g., tetrahydrofuran, toluene, dimethylformamide, 1,4-dioxane, ethanol, water, etc.) or a mixed solvent thereof, in the presence of a metal catalyst (e.g., tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium(II) dichloride, bis(tri-tert-butylphosphine)palladium, etc.) and a base (e.g., potassium carbonate, sodium hydrogen carbonate, sodium phosphate, sodium hydrogen phosphate, potassium phosphate, potassium hydrogen phosphate, lithium hydroxide, sodium hydroxide, potassium hydroxide, potassium tert-butoxide, etc.) at 20°C to a reflux temperature of the solvent for 0.1 to 48 hours, preferably 0.5 to 12 hours.

[0094]

Step 2

Deprotection reaction for the carboxyl protecting group of Compound (A-3) can be carried out by conventional method, for example, as described in Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons).

[0095]

Step 3

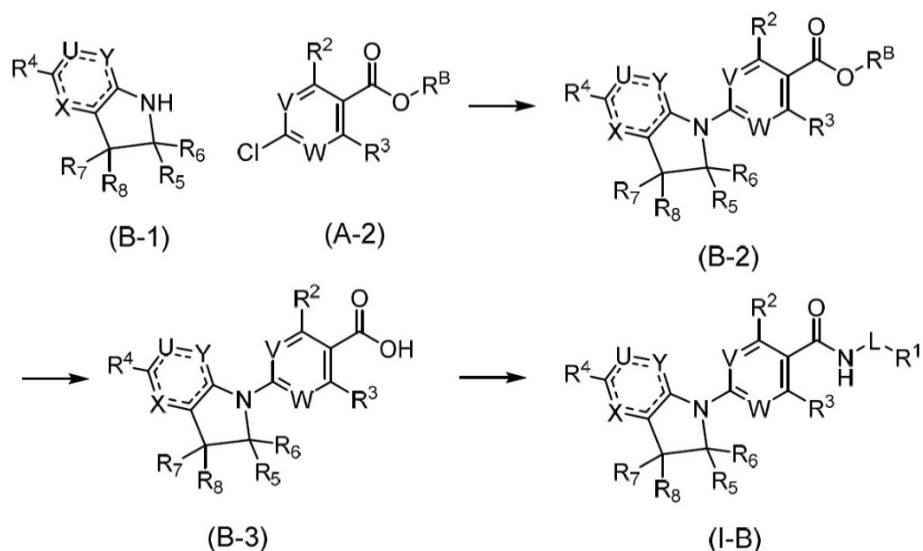
Compound (I-A) can be obtained by reacting Compound (A-4) with compound (A-5) in a solvent (e.g., dimethylformamide, tetrahydrofuran, dichloromethane, acetonitrile, water, etc.) or a mixed solvent thereof, in the presence or absence of a base (e.g., triethylamine, pyridine, diisopropylamine, 1-methylimidazole, etc.) using a dehydration-condensation agent (e.g., dicyclohexylcarbodiimide, carbonyldiimidazole, EDC · HCl, HATU, etc.).

Alternatively, an acylating reagent (e.g., thionyl chloride, oxalyl chloride, etc.) is added to Compound (A-4) in a solvent (e.g., tetrahydrofuran, 1,4-dioxane, dichloromethane, dimethylformamide, etc.) in the presence or absence of a base (e.g., pyridine, triethylamine, diisopropylamine, 1-methylimidazole, etc.) to form acid chloride, which is then added

with Compound (A-5) and the reaction is carried out at -20°C to 60°C, preferably -10°C to 30°C for 0.1 hour to 24 hours, preferably 0.5 hours to 12 hours to afford Compound (I-A).

[0096]

(Method B)



wherein each symbol is as defined above.

Step 1

Compound (B-2) can be obtained by reacting Compound (B-1) with Compound (A-2) in a solvent (e.g., 1,4-dioxane, toluene, tetrahydrofuran, dimethylformamide, N-methylpyrrolidone, etc.) in the presence or absence of a base (e.g., triethylamine, diisopropylamine, cesium carbonate, potassium carbonate, sodium hydride, etc.) or an acid (e.g., toluenesulfonic acid, acetic acid, hydrogen chloride, sulfuric acid, etc.) at 20°C to a reflux temperature of the solvent, preferably 40°C to 120°C, for 0.1 hour to 48 hours, preferably 0.5 hours to 12 hours.

Alternatively, Compound (B-2) can be obtained by reacting Compound (B-1) with Compound (A-2) in a solvent (e.g., 1,4-dioxane, toluene, tetrahydrofuran, dimethylformamide, N-methylpyrrolidone, butanol, water, etc.) or a mixed solvent thereof, in the presence or absence of a ligand (e.g., Xantphos, diphenylphosphinoferrocene, X-phos, etc.) and in the presence of a metal catalyst (e.g.,

palladium acetate, bis(dibenzylideneacetone)palladium, tetrakis (triphenylphosphine)palladium, bis(triphenylphosphine)palladium(II) dichloride, bis(tri-tert-butylphosphine, etc.), and a base (e.g., potassium tert-butoxide, sodium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium phosphate, sodium hydrogen phosphate, lithium hydroxide, sodium hydroxide, etc.) for 0.1 to 48 hours, preferably 0.5 to 12 hours, at 20°C to a reflux temperature of the solvent, or in some cases a temperature under microwave irradiation.

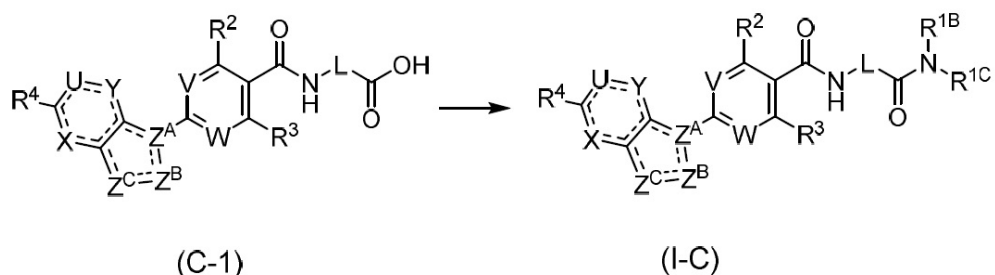
[0097]

Step 2 and Step 3

Compound (I-B) can be obtained by carrying out Step 2 and Step 3 of Method A, using Compound (B-2).

[0098]

(Method C)



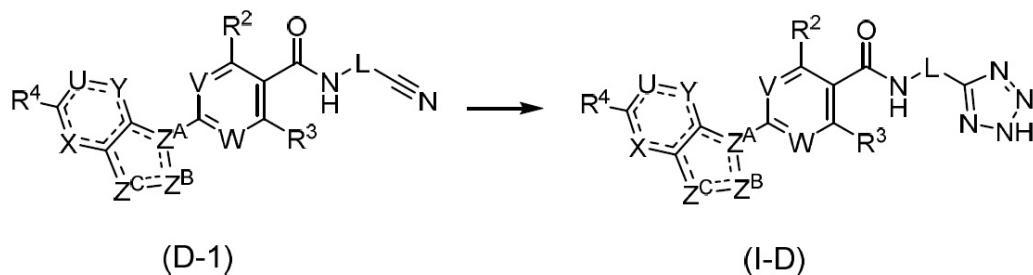
wherein each symbol is as defined above

Step 1

Compound (I-C) can be obtained by reacting Compound (C-1) with $\text{NHR}^{1\text{B}}\text{R}^{1\text{C}}$ in a solvent (e.g., dimethylformamide, tetrahydrofuran, dichloromethane, acetonitrile, water, etc.) or a mixed solvent thereof, in the presence of a dehydration-condensation agent (e.g., dicyclohexylcarbodiimide, carbonyldiimidazole, EDC · HCl, HATU, etc.) and a base (e.g., triethylamine, pyridine, diisopropylamine, 1-methylimidazole, sodium hydride, etc.).

[0099]

(Method D)



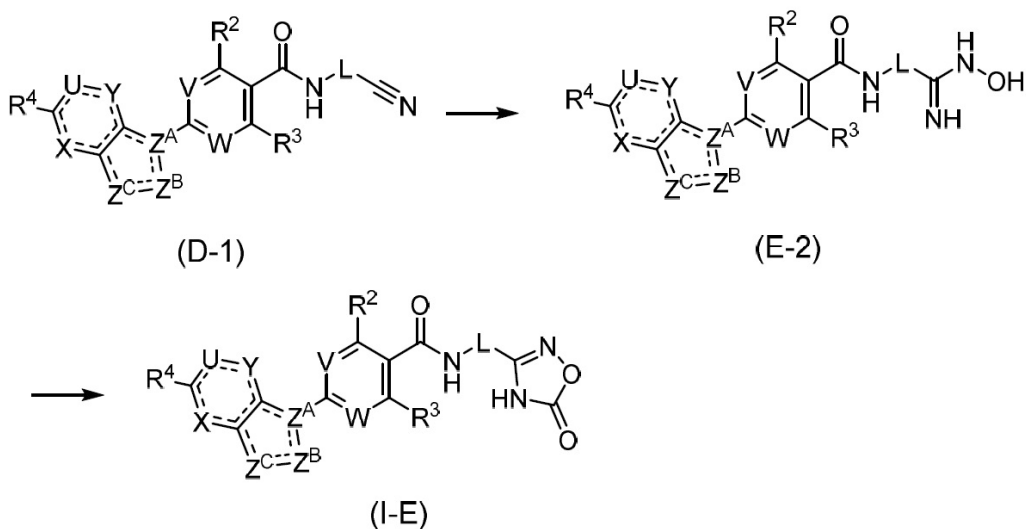
wherein each symbol is as defined above.

Step 1

Compound (I-D) can be obtained by reacting Compound (D-1) with an azide compound (e.g., azidotrimethylsilane, sodium azide, tributyltin azide, etc.) in a solvent (e.g., 1,4-dioxane, dimethylformamide, water, etc.) or a mixed solvent thereof, in the presence of an additive (e.g., dibutylstannane, zinc chloride, ammonium chloride, etc.) at 60°C to a reflux temperature of the solvent, or in some cases a temperature under microwave irradiation, for 0.5 to 48 hours, preferably 1 to 4 hours.

[0100]

(Method E)



wherein each symbol is as defined above.

Step 1

Compound (E-2) can be obtained by reacting Compound (D-1) with hydroxyamine, etc., in a solvent (e.g., methanol, ethanol, tetrahydrofuran, water, etc.) or a mixed solvent thereof, in the presence or absence of a base (e.g., potassium carbonate, triethylamine, etc.) at room temperature to a reflux temperature of the solvent or in some case a temperature under microwave irradiation.

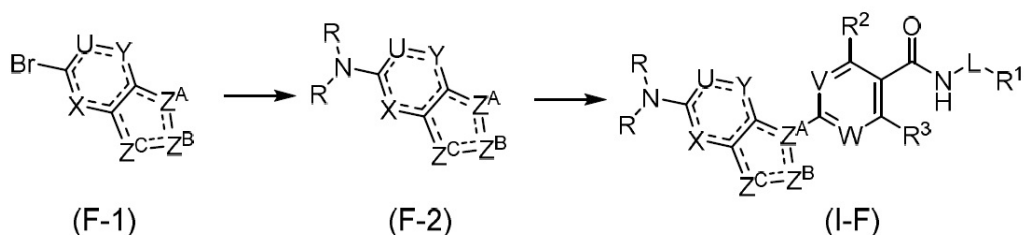
[0101]

Step 2

Compound (I-E) can be obtained by reacting Compound (E-2) with 1,1'-carbonyldiimidazole or ethyl chloroformate in a solvent (e.g., dimethylformamide, chloroform, dichloromethane, tetrahydrofuran, toluene, etc.) or a mixed solvent thereof, in the presence of a base (e.g., triethylamine, DBU, potassium carbonate, etc.) at room temperature to a reflux temperature of the solvent.

[0102]

(Method F)



wherein R is a group independently selected from Substituent Group n, and the other symbols are as defined above.

Step 1

Compound (F-2) can be obtained by reacting Compound (F-1) with amine in a solvent (e.g., 1,4-dioxane, toluene, tetrahydrofuran, dimethylformamide, N-methylpyrrolidone, butanol, water, etc.) or a mixed solvent thereof, in the presence or absence of a ligand (e.g., Xantphos, diphenylphosphinoferrocene, X-Phos, BINAP, etc.) and in the presence of a metal catalyst (e.g., palladium acetate, bis(dibenzylideneacetone)palladium, tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium(II) dichloride, bis(tri-tert-butylphosphine), etc.) and a base (e.g., potassium tert-butoxide, sodium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium phosphate, sodium hydrogen phosphate, lithium hydroxide, sodium hydroxide, etc.) at 20°C to a reflux temperature of the solvent or in some cases a temperature under microwave irradiation for 0.1 to 48 hours, preferably for 0.5 to 12 hours.

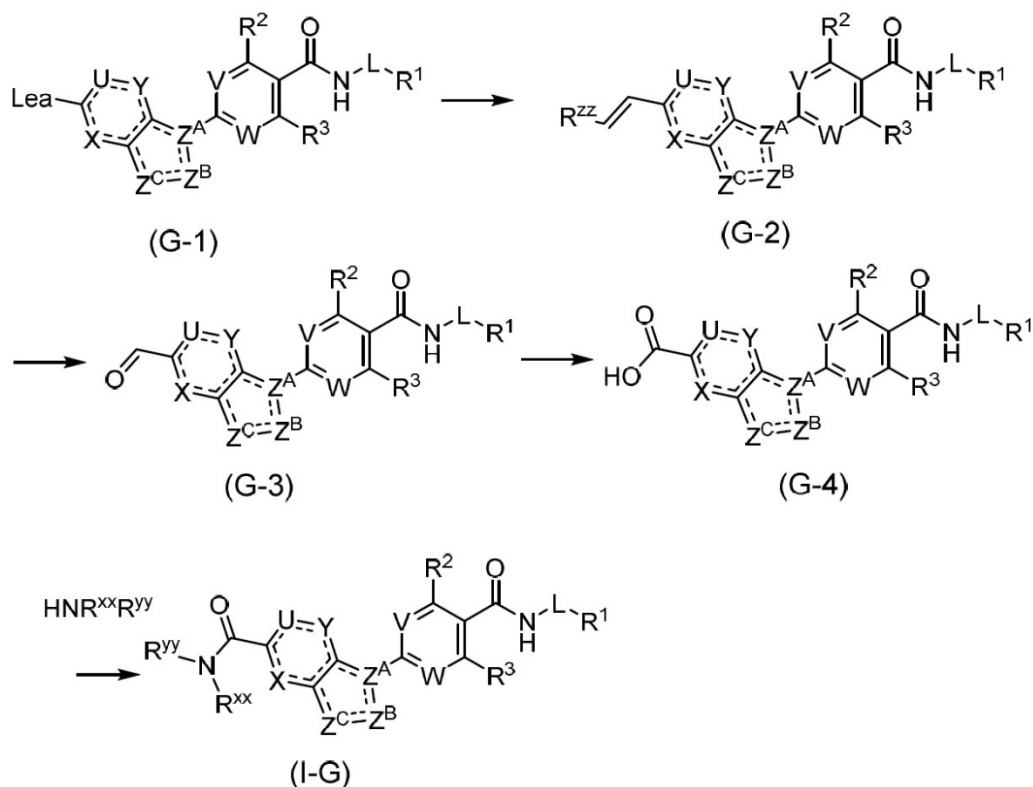
[0103]

Step 2

Compound (I-F) can be obtained by carrying out Step 1 of Method A or Step 1 of Method B, using Compound (F-2).

[0104]

(Method G)



wherein each symbol is as defined above, Lea is a leaving group, R^{ZZ} is a hydrogen atom, C1-C6 alkyl, etc., R^{XX} and R^{YY} are each independently a hydrogen atom, C1-C6 alkyl, etc., or R^{XX} and R^{YY} are taken together with the adjacent nitrogen atom to form a ring.

Step 1

Compound (G-2) can be obtained by carrying out Step 1 of Method A, using Compound (G-1).

[0105]

Step 2

Compound (G-3) can be obtained by reacting Compound (G-2) in a solvent (e.g., 1,4-dioxane, tetrahydrofuran, or water, etc.) or a mixed solvent thereof, adding with sodium periodate or oxon and ruthenium chloride or potassium osmite. Alternatively, ozonide is obtained by ozone oxidation, followed by treatment with a reducing

agent (e.g., zinc, dimethyl sulfide, triphenylphosphine, etc.) to obtain Compound (G-3).

[0106]

Step 3

Compound (G-4) can be obtained by reacting Compound (G-3) in a solvent (e.g., tetrahydrofuran, tert-butanol, water, etc.) or a mixed solvent thereof, adding with sodium dihydrogen phosphate and sodium chlorite in the presence of 2-methyl-2-butene, sulfamic acid, etc.

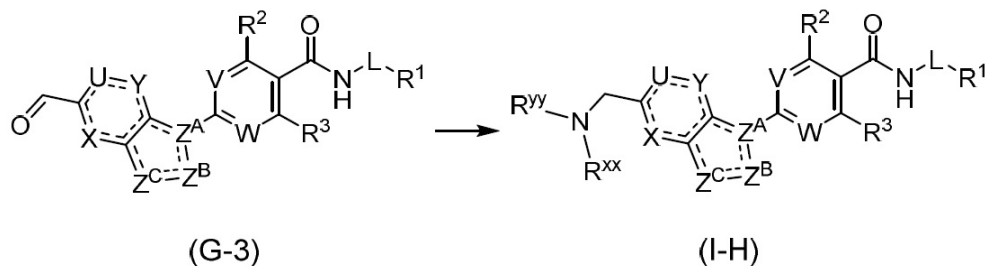
[0107]

Step 4

Compound (I-G) can be obtained by carrying out Step 1 of Method C, using Compound (G-4).

[0108]

(Method H)



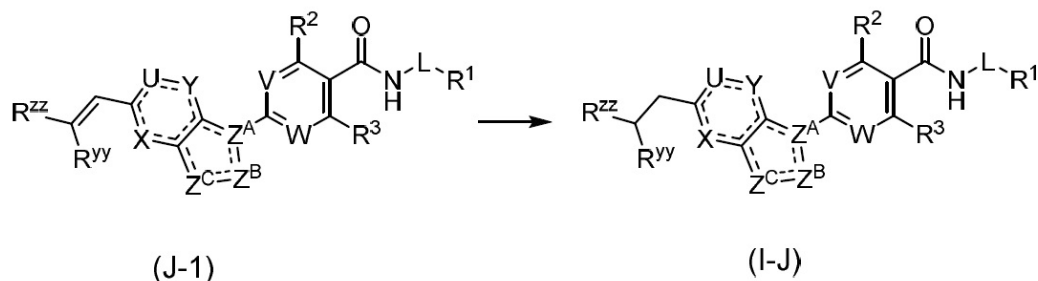
wherein each symbol is as defined above, and R^{xx} and R^{yy} are hydrogen atoms, C1-C6 alkyl, or R^{xx} and R^{yy} are taken together with the adjacent nitrogen atom to form a ring.

Step 1

Compound (I-H) can be obtained by reacting Compound (G-3) with $NHR^{yy}R^{xx}$ in a solvent (e.g., chloroform, tetrahydrofuran, acetonitrile, acetic acid, etc.) or a mixed solvent thereof, in the presence of a reducing agent (e.g., sodium triacetoxyborohydride, 2-picoline borane, etc.) at room temperature to a reflux temperature of the solvent for 0.1 to 48 hours, preferably for 0.5 to 8 hours.

[0109]

(Method J)



wherein each symbol is as defined above, and R^{ZZ} and R^{YY} are hydrogen atoms, C1-C6 alkyl, aromatic carbocyclyl, aromatic heterocyclyl, etc.

Step 1

Compound (I-J) can be obtained by catalytic hydrogenation of Compound (J-1) in a solvent (e.g., tetrahydrofuran, methanol, toluene, chloroform, etc.) or a mixed solvent thereof, in the presence of a heterogeneous catalyst (e.g., palladium on carbon, palladium hydroxide, Raney nickel, platinum oxide, etc.).

[0110]

Since the compound of the present invention has an anti-RSV action, i.e., CPE (CytoPathic Effect) inhibiting action, the compound is useful as a therapeutic and/or prophylactic agent for diseases such as bronchiolitis and pneumonia.

Furthermore, the compound of the present invention has utility as a medicine, and preferably, the compound of the present invention has any one or a plurality of the following excellent features.

a) Inhibitory activity against CYP enzymes (for example, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) is weak.

b) Satisfactory pharmacokinetics such as high bioavailability and adequate clearance are exhibited.

c) Metabolic stability is high.

d) Irreversible inhibitory activity is not exhibited against

CYP enzymes (for example, CYP3A4) within the concentration range of the measurement conditions described in the present specification.

e) Mutagenicity is not exhibited.

f) The cardiovascular risk is low.

g) High solubility is exhibited.

h) High RSV type A CPE inhibiting action and high RSV type B inhibiting action are exhibited.

i) The amount of virus in the lungs is reduced.

[0111]

The pharmaceutical compositions of the present invention can be administered either orally or parenterally. Examples of a parenteral administration include transdermal, subcutaneous, intravenous, intra-arterial, intramuscular, intraperitoneal, transmucosal, inhalation, transnasal, ocular instillation, ear instillation, and intravaginal administration.

[0112]

For oral administration, the pharmaceutical composition may be prepared into any dosage form that is commonly used, such as a solid preparation for internal use (for example, tablet, powder, granule, capsule, pill, or film), or a liquid preparation for internal use (for example, suspension, emulsion, elixir, syrup, limonade, spirit preparation, aromatic water preparation, extract, decoction, tincture, etc.) and administered. The tablet may be a dragee, a film-coated tablet, an enteric-coated tablet, a sustained release tablet, a troche, a sublingual tablet, a buccal tablet, a chewable tablet, or an orally disintegrating tablet; the powder preparation and granular preparation may be dry syrups; and the capsule may be a soft capsule, a microcapsule, or a sustained release capsule.

[0113]

For parenteral administration, a pharmaceutical composition can be suitably administered in any dosage form that is commonly

used, such as an injectable preparation, an infusion, or a preparation for external use (for example, an eye drop, a nasal drop, an ear drop, an aerosol, an inhalant, a lotion, an impregnating agent, a liniment, a gargling agent, an enema, an ointment, a plaster, a jelly, a cream, a patch, a poultice, a powder preparation for external use, or a suppository). The injectable preparation may be an O/W, W/O, O/W/O, or W/O/W type emulsion, or the like.

[0114]

A pharmaceutical composition can be obtained by mixing an effective amount of the compound of the present invention with various pharmaceutical additives appropriate for the dosage form, such as an excipient, a binder, a disintegrating agent, and a lubricating agent, as necessary. Furthermore, the pharmaceutical composition can be prepared into a pharmaceutical composition for use for a child, an elderly, a patient with a serious case, or a surgical operation, by appropriately changing the effective amount of the compound of the present invention, the dosage form, and/or various pharmaceutical additives. For example, a pharmaceutical composition for use for a child may be administered to a neonate (less than 4 weeks after birth), an infant (from 4 weeks after birth to less than 1 year), a preschool child (from 1 year to less than 7 years), a child (from 7 years to less than 15 years), or a patient 15 year to 18 years of age. For example, a pharmaceutical composition for an elderly may be administered to a patient 65 years of age or older.

[0115]

It is desirable to set the amount of administration of the pharmaceutical composition of the present invention after considering the age and body weight of the patient, the type and degree of the disease, the route of administration, and the like; however, in the case of oral administration, the amount of administration is usually 0.05 to 100 mg/kg/day and is preferably in the range of 0.1 to 10 mg/kg/day. In the case of parenteral

administration, the amount of administration may vary greatly depending on the route of administration; however, the amount of administration is usually 0.005 to 10 mg/kg/day and is preferably in the range of 0.01 to 1 mg/kg/day. This may be administered once a day or several times a day.

[0116]

The compound of the present invention may be used in combination with L-protein inhibitors, F-protein inhibitors, N-protein enzyme inhibitors, etc. (hereinafter referred to as concomitant drug), for the purpose of enhancing the action of the compound, reducing the amount of administration of the compound, or the like. At this time, the timing of administration for the compound of the present invention and the concomitant drug is not limited, and these may be administered simultaneously to the target of administration or may be administered with a time difference. Furthermore, the compound of the present invention and the concomitant drug may be administered as two or more kinds of preparations each including active ingredients, or may be administered as a single preparation including those active ingredients.

[0117]

The amount of administration of the concomitant drug can be appropriately selected based on the clinically used dosage. Furthermore, the blending ratio of the compound of the present invention and the concomitant drug can be appropriately selected according to the target of administration, the route of administration, the target disease, symptoms, combination, and the like. For example, when the target of administration is a human being, 0.01 to 100 parts by weight of the concomitant drug may be used with respect to 1 part by weight of the compound of the present invention.

EXAMPLES

[0118]

Hereinafter, the present invention will be described in more detail by way of Examples, Reference Examples, and Test Examples; however, the present invention is not intended to be limited by these.

[0119]

Abbreviations as used herein have the following meanings.

Boc₂O: di-tert-butyl dicarbonate

DIAD: diisopropyl azodicarboxylate

DMEAD: bis(2-methoxyethyl) azodicarboxylate

DMAP: 4-dimethylaminopyridine

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

Me₄tBuXphos: 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl

TolBINAP: 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl

Ts: tosyl

Pd₂(dba)₃: tris(dibenzylideneacetone)bispalladium

PdCl₂(dppf): 1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane adduct

Pd(PPh₃)₄: tetrakis(triphenylphosphine)palladium

Xantphos Pd G3: [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

Xantphos Pd G2: chloro[(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II)

X-Phos: 2,4,6-triisopropyl-2'-(dicyclohexylphosphino)biphenyl

[0120]

(Method for identifying compound)

The NMR analysis obtained in each Example was performed at 400 MHz, and measurement was made using DMSO-d₆ and CDCl₃. Furthermore, when NMR data are shown, there are occasions in which all the

measured peaks are not described.

The term RT in the specification indicates retention time in a LC/MS: liquid chromatography / mass analysis, and the retention time was measured under the following conditions.

(Method 1)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm (detection range 190-500nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution.

Gradient: A linear gradient of 5% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Method 2)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm (detection range 190-400nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution.

Gradient: A linear gradient of 5% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Method 3)

Column: Shim-pack XR-ODS (2.2 μ m, i.d. 50 x 3.0 mm) (Shimadzu)

Flow rate: 1.6 mL/min

UV detection wavelength: 254 nm (detection range 190-800nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution

Gradient: A linear gradient of 10% to 100% solvent [B] was carried out for 3 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Method 4)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m) i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm (detection range 210-500nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution

Gradient: A linear gradient of 5% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Method 5)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m) i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm (detection range 190-500nm)

Mobile phase: [A] was 10 mM ammonium carbonate-containing aqueous solution, and [B] was acetonitrile

Gradient: A linear gradient of 5% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Method 6)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m) i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm (detection range 190-400nm)

Mobile phase: [A] was 10 mM ammonium carbonate-containing aqueous solution, and [B] was acetonitrile

Gradient: A linear gradient of 5% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was

maintained for 0.5 minutes.

(Method 7)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m)
i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm (detection range 190-500nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution

Gradient: A linear gradient of 70% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Method 8)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m)
i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm (detection range 190-500nm)

Mobile phase: [A] was 10 mM ammonium carbonate-containing aqueous solution, and [B] was acetonitrile

Gradient: A linear gradient of 50% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Method 9)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m)
i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.6 mL/min

UV detection wavelength: 254 nm (detection range 190-500nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution

Gradient: A linear gradient of 25% to 95% solvent [B] was carried out for 1.5 minutes, and then 95% solvent [B] was maintained for 1.5 minutes.

(Method 10)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m)
i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.6 mL/min

UV detection wavelength: 254 nm (detection range 190-500nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution

Gradient: A linear gradient of 25% to 95% solvent [B] was carried out for 1.5 minutes, and then 95% solvent [B] was maintained for 1.5 minutes.

(Method 11)

Column: ACQUITY UPLC (registered trademark) CSH C18 (1.7 μ m
i.d. 2.1 x 50 mm) (Waters)

Flow rate: 0.6 mL/min

UV detection wavelength: 254 nm (detection range 190-500nm)

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution

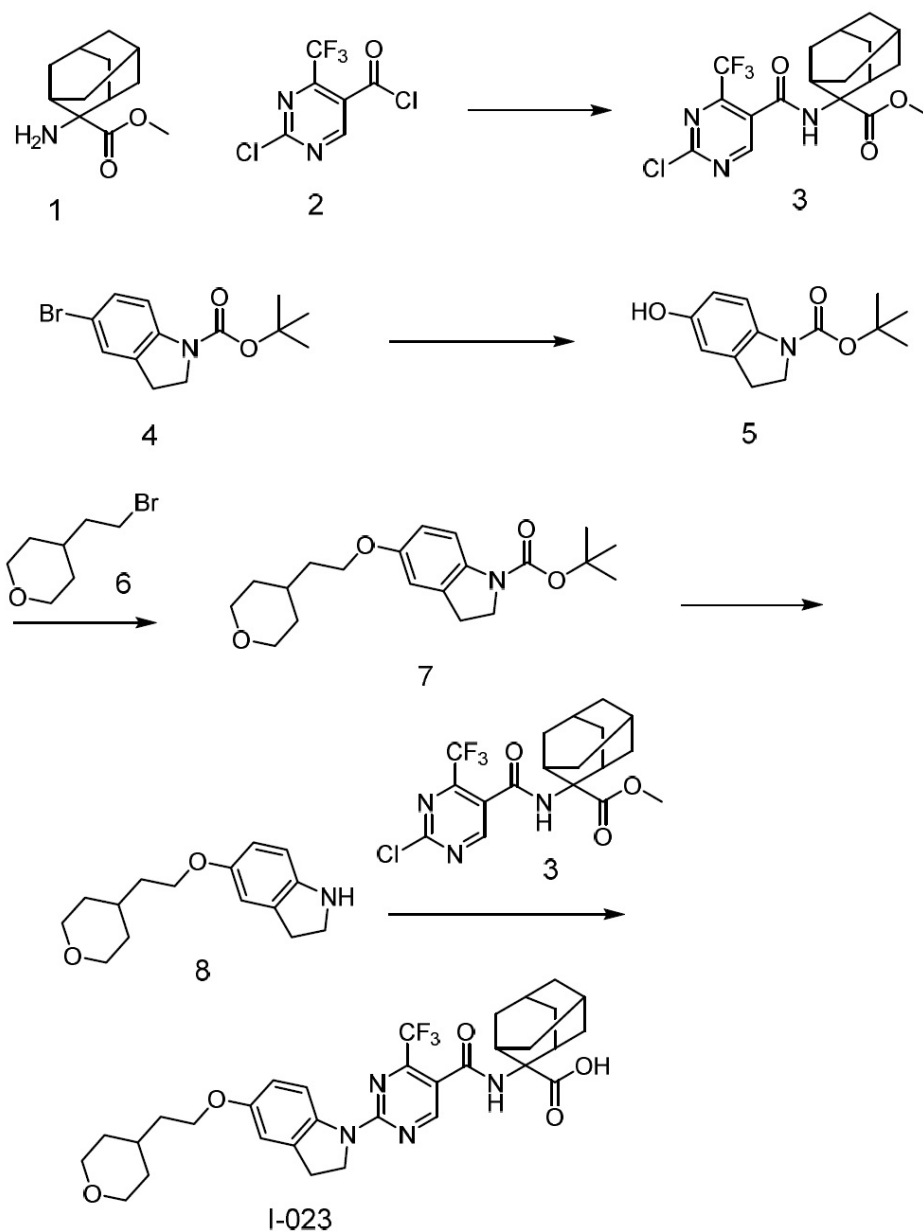
Gradient: A linear gradient of 25% to 95% solvent [B] was carried out for 1.5 minutes, and then 95% solvent [B] was maintained for 1.5 minutes.

In the specification, the mention of MS (m/z) indicates the value observed by mass spectrometry.

[0121]

Example 1

Synthesis of Compound (I-023)



Step 1 Synthesis of Compound 3

To Compound 1 (910 mg, 3.62 mmol) were added chloroform (20 mL) and diisopropylethylamine (0.76 mL, 4.34 mmol), and then Compound 2 (887 mg, 3.62 mmol) under ice-cooling. The mixture was warmed to room temperature and stirred for 2 hours, and then water

was added. The mixture was extracted with chloroform, and the two layers were separated. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was added with ethyl acetate-hexane. The solid was filtered to obtain Compound 3 (1.34 g, yield 81%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.75-1.82 (m, 6H), 1.87-1.97 (m, 4H), 2.15 (m, 2H), 2.60 (s, 2H), 3.78 (s, 3H), 6.00 (s, 1H), 8.98 (s, 1H).

[0122]

Step 2 Synthesis of Compound 5

To Compound 4 (22.6 g, 76 mmol) were added 1,4-dioxane (158mL), bis(pinacolato)diborane (25g, 98 mmol), $\text{PdCl}_2(\text{dppf})$ (6.2 g, 7.6 mmol) and potassium acetate (11.1 g, 114 mmol), and the mixture was stirred at 100°C . After 3 hours, the mixture was cooled to room temperature and filtered through Celite (registered trademark). The filtrate was concentrated under reduced pressure, and the residue was added with diisopropyl ether to precipitate a solid. The precipitated solid was removed by filtration, and the filtrate was concentrated under reduced pressure.

The concentrated residue was dissolved in tetrahydrofuran (226 mL) and mixed with 1 mol/L aqueous sodium hydroxide solution (114 mL, 114 mmol), and 30% aqueous hydrogen peroxide solution (11.6 mL, 114 mmol) were added. After stirring at room temperature for 1 hour, the reaction was quenched by adding aqueous sodium thiosulfate. The two layers were separated by extraction with ethyl acetate, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 5 (7.7 g, yield 43%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.57 (s, 9H), 3.04 (t, $J = 8.8\text{Hz}$, 2H), 3.96 (m, 2H), 4.58 (s, 1H), 6.61 (d, $J = 8.8\text{Hz}$, 1H), 6.64 (s, 1H), 7.34 (brs, 0.4H), 7.73 (brs, 0.6H).

[0123]

Step 3 Synthesis of Compound 7

To Compound 5 (2.5 g, 10.6 mmol) were added dimethylformamide (25 mL), Compound 6 (3.08 g, 15.9 mmol) and potassium carbonate (2.94 g, 21.3 mmol), and the mixture was stirred at 60°C for 5 hours. The reaction solution was added with water and extracted with ethyl acetate. The two layers were separated, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 7 (2.55 g, yield 69%).

¹H-NMR (CDCl₃) δ: 1.35 (m, 2H), 1.57 (s, 9H), 1.60-1.82 (m, 5H), 3.05 (t, J = 8.8Hz, 2H), 3.40 (td, J = 12.0, 1.6Hz, 2H), 3.90-4.00 (m, 6H), 6.68 (d, J = 8.8Hz, 1H), 6.72 (s, 1H), 7.34 (brs, 0.4H), 7.73 (brs, 0.6H).

[0124]

Step 4 Synthesis of Compound 8

To Compound 7 (2.55 g, 7.34 mmol) were added dichloromethane (20 mL) and trifluoroacetic acid (10mL, 130mmol). After stirring at room temperature for 1 hour, aqueous sodium bicarbonate solution was added to neutralize the mixture. The two layers were separated by extraction with chloroform, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to afford Compound 8 (1.95 g) as a crude product.

¹H-NMR (CDCl₃) δ: 1.35 (m, 2H), 1.61-1.84 (m, 5H), 2.78 (brs, 1H), 3.01 (t, J = 8.4Hz, 2H), 3.40 (td, J = 12.0, 1.6Hz, 2H), 3.54 (t, J = 8.4Hz, 2H), 3.91-4.00 (m, 4H), 6.57-6.61 (m, 2H), 6.76 (s, 1H).

[0125]

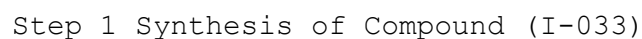
Step 5 Synthesis of Compound (I-023)

To Compound 8 (107 mg, 0.43 mmol) were added 1,4-dioxane (3 mL), triethylamine (0.149 mL, 1.08 mmol) and Compound 3 (150 mg, 0.36 mmol), and the mixture was stirred at 50°C for 2 hours. The mixture was added with water and extracted with chloroform. The

To the residue were added tetrahydrofuran (2 mL), ethanol (2 mL) and 4 mol/L aqueous lithium hydroxide solution (0.90 mL, 3.6 mmol). The mixture was stirred at 90°C for 8 hours and 10% aqueous citric acid solution was added. The mixture was extracted with chloroform, and the two layers were separated. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform-methanol) to afford Compound (I-023) (90 mg, yield 41%).

[0126]

Synthesis of Compound (I-033)



Compound 8 (41 mg, 0.16 mmol) and Compound 9 (40 mg, 0.11 mmol), which was synthesized in the same manner as Compound 3, were dissolved in 1,4-dioxane (0.5 mL), and Xantphos Pd G3 (10 mg, 0.01 mmol) and potassium carbonate (38 mg, 0.27 mmol) were added. After stirring at 100°C for 3 hours, water was added. The mixture was extracted with chloroform, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure.

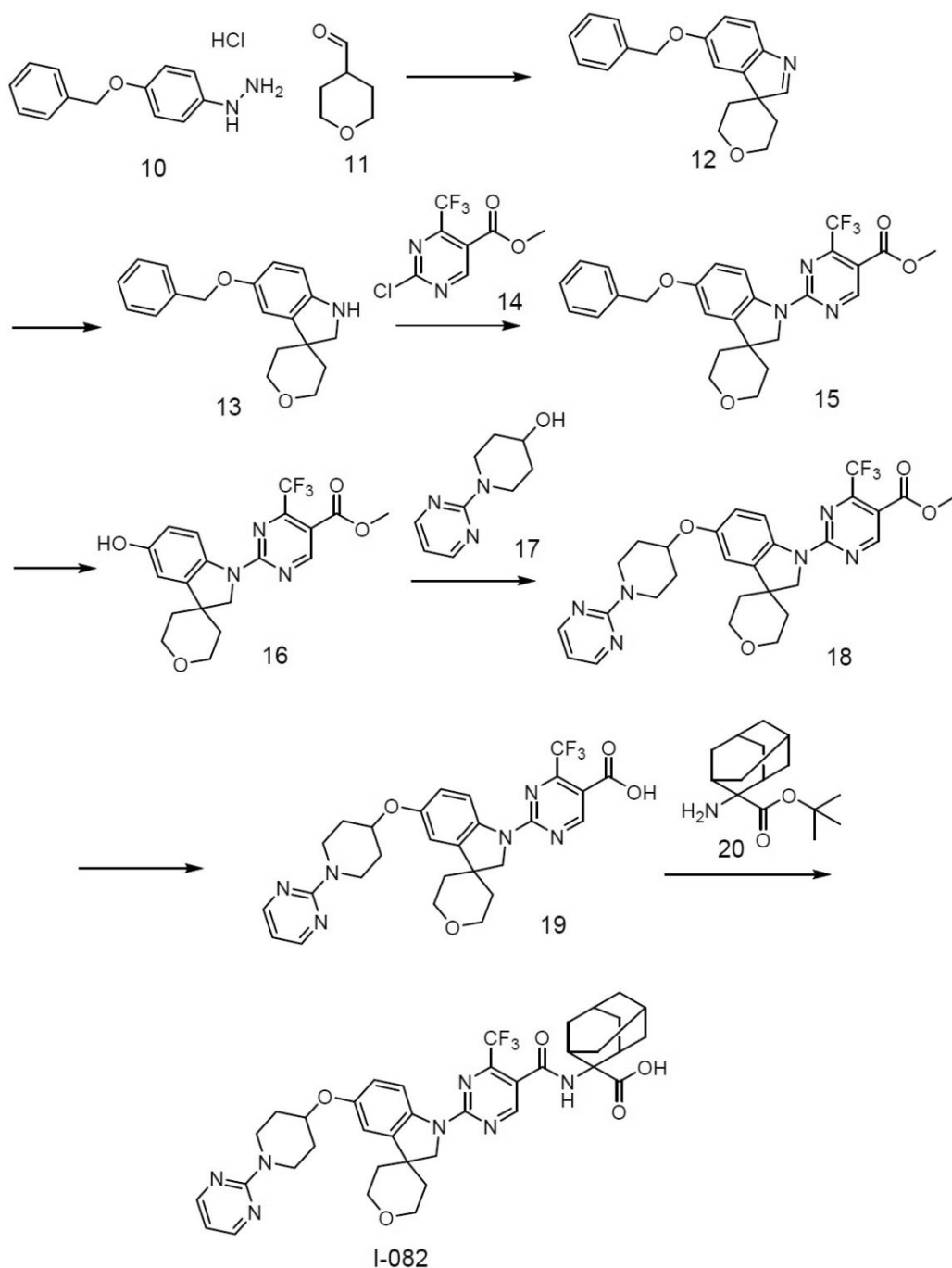
To the residue were added ethanol (0.5 mL) and tetrahydrofuran (0.5 mL) to dissolve, and 4 mol/L aqueous lithium hydroxide solution (0.27 mL) was added. The mixture was stirred at 50°C for 4 hours. Aqueous citric acid solution was added, and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol) to afford Compound (I-033) (20 mg, yield 33%).

¹H-NMR (DMSO-d₆) δ: 1.15-1.30 (m, 3H), 1.50-1.78 (m, 12H), 2.03-2.10 (m, 2H), 3.22 (m, 2H), 3.29 (m, 2H), 3.83 (dd, J = 10.8, 3.2 Hz, 2H), 3.98 (t, J = 6.4 Hz, 2H), 4.06 (t, J = 8.0 Hz, 2H), 6.77 (dd, J = 8.8, 3.5 Hz, 1H), 6.89 (s, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.44 (s, 1H), 12.2 (s, 1H).

[0127]

Example 3

Synthesis of Compound (I-082)



Step 1: Synthesis of Compound 12

Compound 10 (31g, 124 mmol) and compound 11 (16.9 g, 148 mmol) were suspended in dichloromethane (600 mL) and cooled under ice bath. Trifluoroacetic acid (19 mL, 247 mmol) was added. After 30 minutes, the mixture was warmed to 45°C, and stirred for 3 hours. The mixture was added with aqueous sodium carbonate solution to neutralize under ice-cooling and filtered through Celite

(registered trademark). The two layers of filtrate was separated, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and diethyl ether was added to the residue. The solid was filtered to obtain Compound 12 (9.04 g, yield 25%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.63 (m, 2H), 1.93 (ddd, $J = 13.6, 10.0, 4.0\text{Hz}$, 2H), 3.90 (m, 2H), 4.10 (m, 2H), 5.10 (s, 2H), 6.97 (dd, $J = 8.4, 2.4\text{Hz}$, 1H), 7.06 (d, $J = 2.4\text{Hz}$, 1H), 7.34 (m, 1H), 7.40 (m, 2H), 7.45 (m, 2H), 7.56 (d, $J = 8.4\text{Hz}$, 1H), 8.32 (s, 1H).

LC/MS (ESI): $m/z = 294$ $[\text{M}+\text{H}]^+$, RT=1.96 min, LC/MS Method 1

[0128]

Step 2 Synthesis of Compound 13

Compound 12 (18 g, 61.4 mmol) was suspended in methanol (180 mL), and sodium borohydride (2.55 g, 67.5 mmol) was added under ice-cooling. After 10 minutes, the mixture was warmed to room temperature, and stirred for 2 hours. Aqueous ammonium chloride was added under ice-cooling, and the mixture was extracted with chloroform. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The residue was added with diisopropyl ether, and the solvent was removed under reduced pressure. The solid was filtered to obtain Compound 13 (16.1 g, yield 89%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.65 (d, $J = 13.6\text{Hz}$, 2H), 1.94 (m, 2H), 3.52 (m, 2H), 3.55 (m, 2H), 3.96 (m, 2H), 4.99 (s, 2H), 6.59 (d, $J = 8.4\text{Hz}$, 1H), 6.70 (d, $J = 8.4, 2.4\text{Hz}$, 1H), 6.79 (d, $J = 2.4\text{Hz}$, 1H), 7.26 (s, 1H), 7.31 (m, 1H), 7.38 (m, 2H), 7.43 (m, 2H).

LC/MS (ESI): $m/z = 296$ $[\text{M}+\text{H}]^+$, RT=1.67 min, LC/MS Method 1

[0129]

Step 3 Synthesis of Compound 15

Compound 13 (16.1 g, 54.5 mmol) was dissolved in 1,4-dioxane (242 mL), and triethylamine (17.4 mL, 125 mmol) and Compound 14 (14.4 g, 60 mmol) were added, and the mixture was stirred at 50°C for 3 hours. After cooling, water was added and the mixture was extracted with chloroform. The organic layer was washed with water

and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and ethyl acetate-hexane was added to the residue. The solid was filtered to obtain Compound 15 (25.3 g, yield 93%).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.58 (m, 2H), 1.98 (m, 2H), 3.52 (m, 2H), 3.86 (s, 3H), 3.90 (m, 2H), 4.27 (m, 2H), 5.12 (s, 2H), 6.98 (m, 1H), 7.13 (d, $J = 2.4\text{Hz}$, 1H), 7.34 (m, 1H), 7.40 (m, 2H), 7.47 (m, 2H), 8.21 (m, 1H), 9.11 (s, 1H).

LC/MS (ESI): $m/z = 500$ $[\text{M}+\text{H}]^+$, $\text{RT} = 3.10$ min, LC/MS Method 1

[0130]

Step 4 Synthesis of Compound 16

To Compound 15 (25.3 g, 50.7 mmol) were added chloroform (253 mL) and tetrahydrofuran (127 mL) to dissolve, and 5wt% Palladium hydroxide (5 g, 1.78 mmol) was added. The mixture was stirred for 2 hours at room temperature under hydrogen atmosphere. The mixture was filtered through Celite (registered trademark), and the filtrate was concentrated under reduced pressure. Ethyl acetate-hexane was added to the residue, and the solid was filtered to obtain Compound 16 (19.6 g, yield 95%).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.58 (m, 2H), 1.88 (m, 2H), 3.52 (m, 2H), 3.86 (s, 3H), 3.89 (m, 2H), 4.24 (m, 2H), 6.71 (dd, $J = 8.8, 2.4\text{Hz}$, 1H), 6.76 (d, $J = 2.4\text{Hz}$, 1H), 8.13 (m, 1H), 9.09 (s, 1H), 9.42 (s, 1H).

LC/MS (ESI): $m/z = 410$ $[\text{M}+\text{H}]^+$, $\text{RT} = 2.20$ min, LC/MS Method 1

[0131]

Step 5 Synthesis of Compound 18

Compound 16 (16.1 g, 39.3 mmol), Compound 17 (10.6 g, 59.0 mmol), triphenylphosphine (16.5 g, 62.9 mmol) were dissolved in tetrahydrofuran (217 mL) and cooled under ice bath, and DIAD (11.47 mL, 59.0 mmol) was added dropwise. After the addition, the mixture was warmed to 40°C , and stirred for 2 hours. The reaction mixture was allowed to room temperature and concentrated under reduced pressure. Ethyl acetate-diisopropyl ether was added, and the solid was filtered to obtain Compound 18 (20.3 g, yield

91%).

¹H-NMR (DMSO-d₆) δ: 1.52-1.63 (m, 4H), 1.97-2.05 (m, 4H), 3.46-3.58 (m, 4H), 3.87 (s, 3H), 3.90 (m, 2H), 4.20-4.28 (m, 4H), 4.69 (m, 1H), 6.61 (t, J = 4.8Hz, 1H), 6.96 (m, 1H), 7.11 (d, J = 2.0Hz, 1H), 8.22 (m, 1H), 8.36 (d, J = 4.8Hz, 2H), 9.12 (s, 1H).

LC/MS (ESI): m/z = 571 [M+H]⁺, RT = 2.95 min, LC/MS Method 1

[0132]

Step 6 Synthesis of Compound 19

To Compound 18 (20.3 g, 35.6 mmol) were added tetrahydrofuran (203 mL), ethanol (203 mL) and 4 mol/L aqueous lithium hydroxide solution (44.5 mL, 178 mmol). After stirring at 50°C for 4 hours, the mixture was allowed to room temperature, and 10% aqueous citric acid solution was added. Water was added, and the precipitated solid was filtered to obtain Compound 19 (19 g, yield 96%).

¹H-NMR (DMSO-d₆) δ: 1.52-1.61 (m, 4H), 1.97-2.05 (m, 4H), 3.46-3.57 (m, 4H), 3.90 (m, 2H), 4.24 (m, 2H), 4.26 (s, 2H), 4.69 (m, 1H), 6.61 (t, J = 4.4Hz, 1H), 6.96 (dd, J = 8.8, 2.8Hz, 1H), 7.10 (d, J = 2.8Hz, 1H), 8.22 (d, J = 8.8Hz, 1H), 8.36 (d, J = 4.4Hz, 2H), 9.11 (s, 1H), 13.54 (s, 1H).

LC/MS (ESI): m/z = 557 [M+H]⁺, RT = 2.44 min, LC/MS Method 1

[0133]

Step 7 Synthesis of Compound (I-082)

To Compound 19 (795 mg, 1.43 mmol) were added dimethylformamide (8 mL), Compound 20 (431 mg, 1.71 mmol), HATU (706 mg, 1.86 mmol) and triethylamine (0.495 mL, 3.57 mmol) at room temperature. The mixture was stirred for 2 hours. Water was added to the reaction solution, and the precipitated solid was filtered. To the solid were added dichloromethane (5 mL) and trifluoroacetic acid (5 mL, 65 mmol), and the mixture was stirred at room temperature for 2 hours. Aqueous sodium bicarbonate was added to neutralize the mixture, and then 10% aqueous citric acid solution was added to acidify again, and the mixture was extracted with chloroform. The organic layer was washed with water and dried over anhydrous

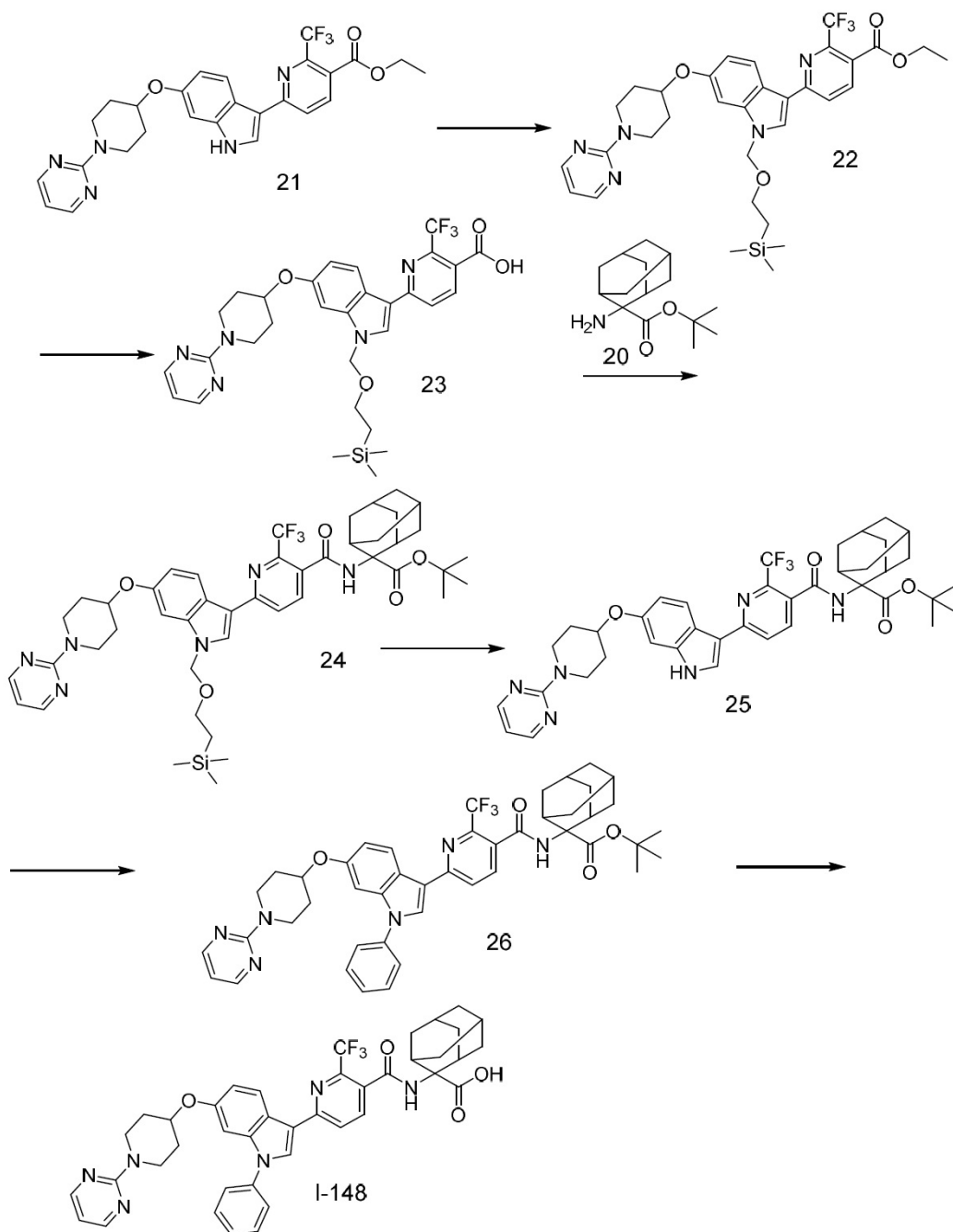
magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform-methanol) to afford Compound (I-082) (820 mg, yield 78%).

^1H -NMR (DMSO- d_6) δ : 1.52-1.60 (m, 6H), 1.65-1.69 (m, 4H), 1.80 (m, 2H), 1.94-2.17 (m, 8H), 2.54 (brs, 2H), 3.46-3.58 (m, 4H), 3.90 (m, 2H), 4.22 (s, 2H), 4.26 (m, 2H), 4.67 (m, 1H), 6.61 (t, J = 4.4Hz, 1H), 6.93 (dd, J = 8.8, 2.0Hz, 1H), 7.08 (d, J = 2.0Hz, 1H), 8.17 (d, J = 8.8Hz, 1H), 8.36 (d, J = 4.4Hz, 2H), 8.46 (s, 1H), 8.68 (s, 1H), 12.34 (s, 1H).

[0134]

Example 4

Synthesis of Compound (I-148)



Step 1: Synthesis of Compound 22

To a solution of Compound 21 (100 mg, 0.20 mmol) (see Example 6 for the synthetic method) in dimethylformamide (1 mL) were added 60 wt% sodium hydride (11 mg, 0.29 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (49 mg, 0.29 mmol) under ice-cooling, and the mixture was stirred at room temperature for

1.5 hours. Saturated aqueous ammonium chloride solution was added, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 22 (74 mg, yield 59%).

LC/MS (ESI): m/z = 642 [M+H]⁺, RT=1.182 min, LC/MS Method 7

[0135]

Step 2 Synthesis of Compound 23

To a solution of Compound 22 (74 mg, 0.12 mmol) in ethanol (0.7 mL) was added 4 mol/L lithium hydroxide solution (0.28 mL, 1.16 mmol), and the mixture was stirred at 50°C for 1 h 40 min. 10% aqueous citric acid solution was added, and the mixture was extracted with chloroform. After drying the organic layer with anhydrous sodium sulfate, the solvent was removed under reduced pressure to afford Compound 23 (73 mg) as a crude product.

LC/MS (ESI): m/z = 614 [M+H]⁺, RT= 3.04 min, LC/MS Method 1

[0136]

Step 3 Synthesis of Compound 24

Compound 23 (71 mg, 0.12 mmol) was dissolved in dimethylformamide (1.0 mL), and Compound 20 (30 mg, 0.12 mmol), HATU (52 mg, 0.14 mmol) and triethylamine (17 mg, 0.17 mmol) were added. After stirring at room temperature for 17 hours, water was added, and the precipitated solid was filtered to obtain Compound 24 (93 mg, yield 96%).

LC/MS (ESI): m/z = 847 [M+H]⁺, RT=2.80 min, LC/MS Method 7

[0137]

Step 4: Synthesis of Compound 25

To a solution of Compound 24 (84 mg, 0.10 mmol) in tetrahydrofuran (0.3 mL) were added 1 mol/L tetrabutylammonium fluoride-tetrahydrofuran solution (0.50 mL, 0.50 mmol) and ethylenediamine (89 mg, 1.50 mmol), and the mixture was stirred with heating under reflux for 8 hours. 10% aqueous ammonium

chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 25 (70 mg, yield 99%).

LC/MS (ESI): m/z = 717 [M+H]⁺, RT=1.42 min, LC/MS Method 1

[0138]

Step 5: Synthesis of Compound 26

To Compound 25 (460 mg, 0.64 mmol) were added 1,4-dioxane (6.9 mL), (1R,2R)-cyclohexane-1,2-diamine (22 mg, 0.19 mmol), tripotassium phosphate (272 mg, 1.28 mmol), iodobenzene (236 mg, 1.16 mmol) and copper(I) iodide (12 mg, 0.06 mmol), and the mixture was stirred with heating under reflux for 8 hours. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 26 (500 mg, yield 98%).

LC/MS (ESI): m/z = 793 [M+H]⁺, RT=3.71 min, LC/MS Method 1

[0139]

Step 6: Synthesis of Compound (I-148)

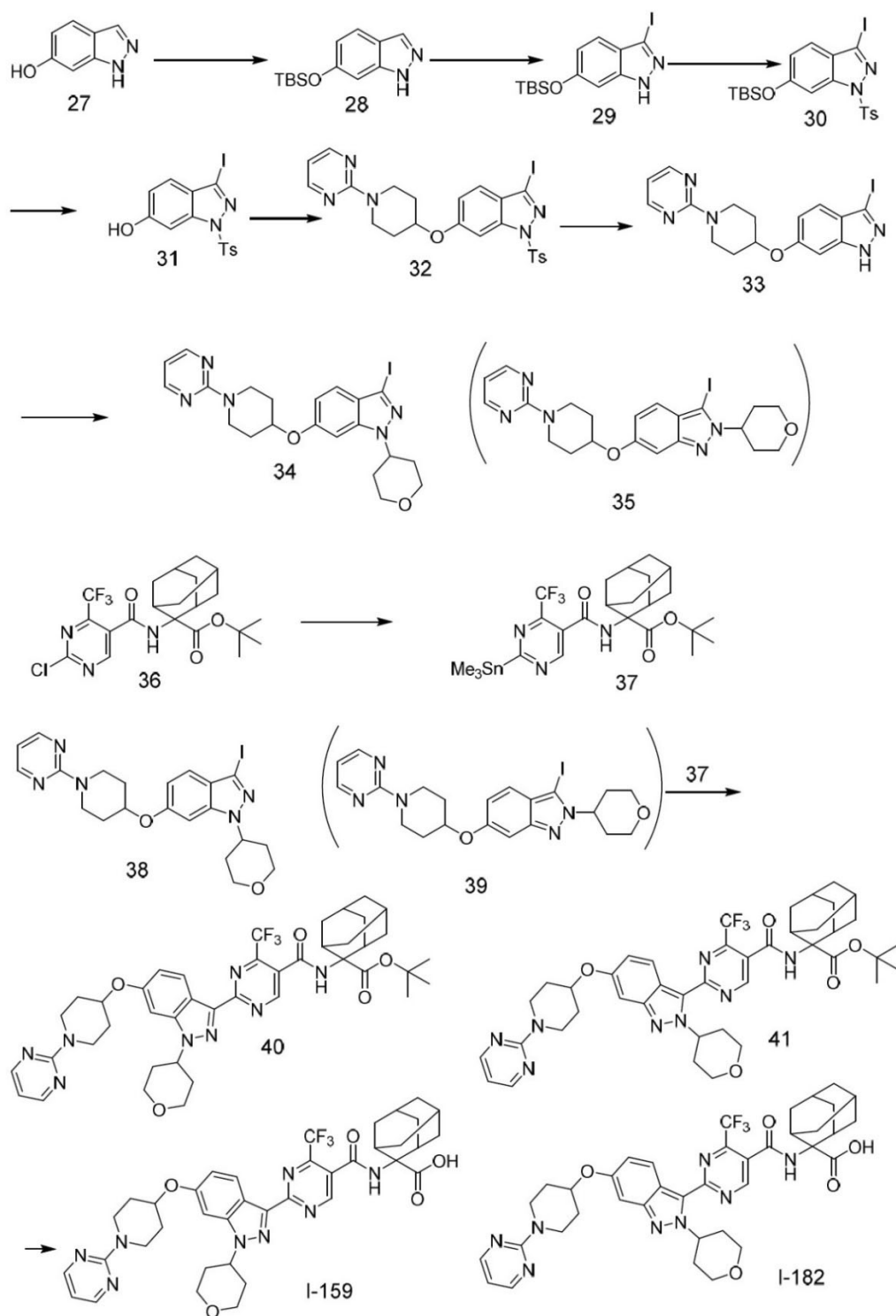
The compound was synthesized in the same manner as in Step 8 of Example 10.

¹H-NMR (DMSO-d₆) δ : 1.66-1.71 (m, 10H), 2.00-2.13 (m, 6H), 2.59 (s, 2H), 3.53-3.57 (m, 2H), 4.16 (dd, J = 13.0, 6.4, 3.9 Hz, 2H), 4.66-4.72 (m, 1H), 6.60 (t J = 4.8 Hz, 1H), 7.07-7.10 (m, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.64-7.66 (m, 2H), 7.70-7.72 (m, 2H), 7.80 (d, J = 8.3 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 4.8 Hz, 2H), 8.53-8.54 (m, 3H), 12.32 (s, 1H).

[0140]

Example 5

Synthesis of Compound (I-159) and Compound (I-182)



Step 1: Synthesis of Compound 28

To a solution of Compound 27 (2.01 g, 15.00 mmol) in dimethylformamide (20.1 mL) were added imidazole (1.53 g, 22.50

mmol) and tert-butyldimethylsilyl chloride (2.71 g, 18.00 mmol), and the mixture was stirred at room temperature for 40 minutes. Water was added, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 28 (3.79 g, yield 100%).

LC/MS (ESI): m/z = 249 [M+H]⁺, RT = 2.66 min, LC/MS Method 1

[0141]

Step 2: Synthesis of Compound 29

To a solution of Compound 28 (3.73 g, 15.00 mmol) in tetrahydrofuran (74.5 mL) were added potassium tert-butoxide (3.87 g, 34.50 mmol) and iodine (8.76 g, 34.50 mmol) under ice-cooling, and the mixture was stirred for 1 hour under ice-cooling. 20% aqueous sodium thiosulfate solution was added, the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford Compound 29 (5.42 g) as a crude product.

LC/MS (ESI): m/z = 375 [M+H]⁺, RT = 3.09 min, LC/MS Method 1

[0142]

Step 3: Synthesis of Compound 30

To a solution of Compound 29 (5.42 g, 14.48 mmol) in dichloromethane (54.2 mL) were added triethylamine (2.49 g, 24.61 mmol) and p-toluenesulfonyl chloride (2.49 g, 17.37 mmol) under ice-cooling. The mixture was stirred at room temperature for 18 hours and filtered off the insoluble material. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 30 (6.48 g, yield 82%).

LC/MS (ESI): m/z = 529 [M+H]⁺, RT = 3.67 min, LC/MS Method 1

[0143]

Step 4: Synthesis of Compound 31

To a solution of Compound 30 (6.39 g, 12.09 mmol) in tetrahydrofuran (31.9 mL) was added 1 mol/L tetrabutylammonium fluoride-tetrahydrofuran solution (13.3 mL, 13.3 mmol) under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. 0.4 mol/L hydrochloric acid was added, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate), and solidified with hexane-ethyl acetate to afford Compound 31 (2.87 g, yield 57%).

LC/MS (ESI): m/z = 415 $[M+H]^+$, RT=2.30 min, LC/MS Method 1

[0144]

Step 5: Synthesis of Compound 32

The compound was synthesized in the same manner as in Step 3 of Example 6.

LC/MS (ESI): m/z = 576 $[M+H]^+$, RT=3.03 min, LC/MS Method 1

[0145]

Step 6: Synthesis of Compound 33

To Compound 32 (6.09 g, 10.58 mmol) were added ethanol (122 mL), water (146 mL) and 8 mol/L aqueous sodium hydroxide solution (6.61 mL, 52.90 mL), and the mixture was stirred at 80°C for 80 minutes. The organic solvent was removed under reduced pressure, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was suspended to chloroform, and solid was filtered to afford Compound 33 (2.93 g, yield 66%).

LC/MS (ESI): m/z = 422 $[M+H]^+$, RT=2.21 min, LC/MS Method 1

[0146]

Step 7: Synthesis of Compound 34 and Compound 35

Compound 33 (3.45 g, 8.19 mmol) was dissolved in dimethylformamide (34.5 mL), and cesium carbonate (5.33 g, 16.36

mmol) and tetrahydro-2H-pyran-4-yl methanesulfonate (681 mg, 16.36 mmol) was added, and the mixture was stirred at 80°C for 6 hours. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 34 and Compound 35 as about 4:1 mixture (4.20 g, yield 100%).

Compound 34

LC/MS (ESI): m/z = 506 [M+H]⁺, RT = 2.65 min, LC/MS Method 1

Compound 35

LC/MS (ESI): m/z = 506 [M+H]⁺, RT = 2.39 min, LC/MS Method 1

[0147]

Step 8: Synthesis of Compound 37

Compound 36 (2.00 g, 4.35 mmol), which was synthesized in the same manner as Compound 3, was suspended in toluene (40 mL), and 1,1,1,2,2,2-hexamethyldistannane (2.00 g, 4.35 mmol) and Pd(PPh₃)₄ (0.75 g, 0.65 mmol), and the mixture was stirred with heating under reflux for 1 hour. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 37 (1.74 g, yield 68%).

LC/MS (ESI): m/z = 590 [M+H]⁺, RT = 3.34 min, LC/MS Method 1

[0148]

Step 9: Synthesis of Compound 40 and Compound 41

The 4:1 mixture of Compound 38 and Compound 39 (1.01 g, 2.00 mmol) were dissolved in dimethylformamide (20 mL), and Compound 37 (1.74 g, 2.96 mmol) and Pd(PPh₃)₄ (0.35 g, 0.30 mmol), lithium chloride (0.17 g, 4.00 mmol) and copper(I) iodide (38 mg, 0.20 mmol) were added, and the mixture was stirred at 95°C for 8.5 hours. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over

anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 40 (505 mg, yield 31%) and Compound 41 (120 mg, yield 8%).

Compound 40.

LC/MS (ESI): m/z = 803 [M+H]⁺, RT = 3.43 min, LC/MS Method 1

Compound 41

LC/MS (ESI): m/z = 803 [M+H]⁺, RT = 3.50 min, LC/MS Method 1

[0149]

Step 10: Synthesis of Compound (I-159) and compound (I-182)

The compound was synthesized in the same manner as in Step 8 of Example 10.

Compound (I-159)

¹H-NMR (CDCl₃) δ: 1.78-1.83 (m, 6H), 1.92-1.95 (m, 4H), 2.03-2.12 (m, 6H), 2.23 (d, J = 12.4 Hz, 2H), 2.56 (ddd, J = 24.8, 12.4, 4.3 Hz, 2H), 2.67 (s, 2H), 3.64 (t, J = 12.4 Hz, 2H), 3.79-3.85 (m, 2H), 4.14-4.21 (m, 4H), 4.70-4.76 (m, 2H), 6.38 (s, 1H), 6.51 (t, J = 4.8 Hz, 1H), 6.97 (d, J = 1.8 Hz, 1H), 7.06 (dd, J = 9.0, 1.8 Hz, 1H), 8.34 (d, J = 4.8 Hz, 2H), 8.49 (d, J = 9.0 Hz, 1H), 9.16 (s, 1H), 12.12 (s, 1H).

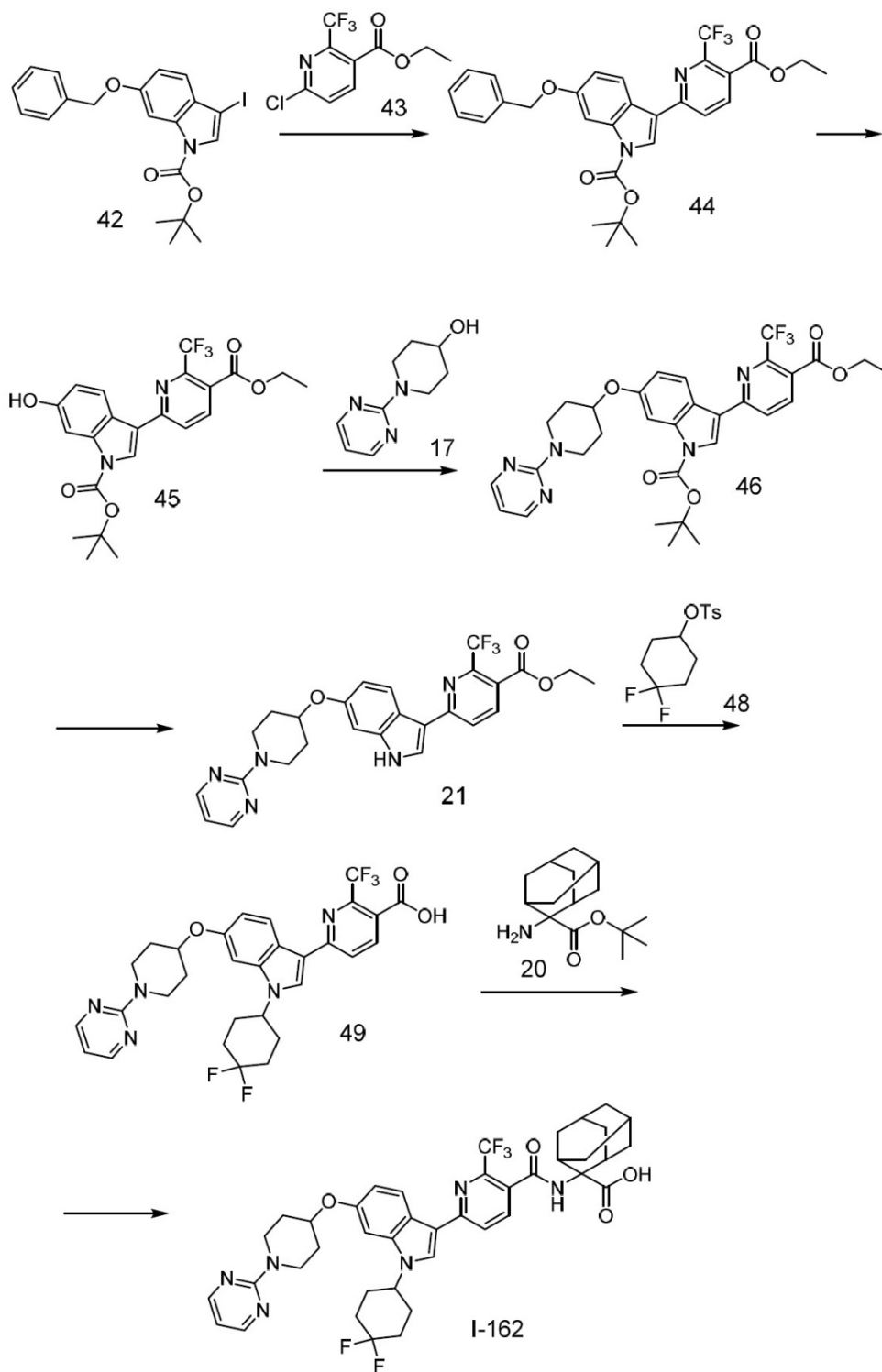
Compound (I-182)

¹H-NMR (CDCl₃) δ: 1.79-2.26 (m, 18H), 2.50 (ddd, J = 24.2, 11.5, 4.2 Hz, 2H), 2.68 (s, 2H), 3.60 (t, J = 11.5 Hz, 2H), 3.68-3.74 (m, 2H), 4.15-4.26 (m, 4H), 4.64-4.69 (m, 1H), 5.95 (tt, J = 11.5, 4.0 Hz, 1H), 6.30 (s, 1H), 6.49 (t, J = 4.8 Hz, 1H), 7.01 (dd, J = 9.2, 1.9 Hz, 1H), 7.17 (d, J = 1.9 Hz, 1H), 8.32-8.33 (m, 3H), 9.15 (s, 1H), 12.12 (s, 1H).

[0150]

Example 6

Synthesis of Compound (I-162)



Step 1: Synthesis of Compound 44

To Compound 42 (10 g, 22.3 mmol) were added tetrahydrofuran (100 mL) and triisopropylborate (4.19 g, 22.3 mmol), and the

mixture was cooled to -78°C with dry ice-acetone. To the solution was added dropwise 1.59 mol/L n-butyl lithium-hexane solution (19.6 mL, 31.2 mmol). The solution was stirred at -78°C for 20 minutes. The reaction was quenched by adding saturated aqueous ammonium chloride solution, warmed to room temperature, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. To the residue obtained were added 1,4-dioxane (102 mL), Compound 43 (6.2 g, 24.5 mmol), $\text{PdCl}_2(\text{dppf})$ (1.82 g, 2.23 mmol) and 2.2 mol/L aqueous potassium carbonate solution (20.4 mL, 44.5 mmol), and the mixture was stirred at 100°C for 2 hours. After cooling, water was added, followed by extraction with ethyl acetate. The layers were separated, and the organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 44 (7.1 g, yield 59%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (t, $J = 7.2\text{Hz}$, 3H), 1.70 (s, 9H), 4.44 (q, $J = 7.2\text{Hz}$, 2H), 5.17 (s, 2H), 7.10 (dd, $J = 8.8, 2.8\text{Hz}$, 1H), 7.34 (m, 1H), 7.40 (m, 2H), 7.48 (m 2H), 7.77-7.90 (m, 2H), 8.11-8.16 (m, 2H), 8.47 (d, $J = 8.8\text{Hz}$, 1H).

LC/MS(ESI): $m/z = 541[\text{M}+\text{H}]^+$, $\text{RT} = 3.21$ min, LC/MS Method 1

[0151]

Step 2: Synthesis of Compound 45

To Compound 44 (30.7 g, 56.8 mmol) were added tetrahydrofuran (307 mL) and 20 wt% palladium on activated carbon (6.34 g, 11.7 mmol). The mixture was stirred at room temperature under hydrogen atmosphere for 2 hours. The mixture was filtered with Celite (registered trademark), and the filtrate was concentrated under reduced pressure. Ethyl acetate-hexane was added to the residue, and the solid was filtered to obtain Compound 45 (22.0 g, yield 86%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (t, $J = 7.2\text{Hz}$, 3H), 1.71 (s, 9H), 4.44 (q, $J = 7.2\text{Hz}$, 2H), 4.94 (s, 1H), 6.93 (dd, $J = 8.8, 2.4\text{Hz}$, 1H), 7.71

(brs, 1H), 7.88 (d, J = 8.4Hz, 1H), 8.11 (s, 1H), 8.14 (d, J = 8.4Hz, 1H), 8.46 (d, J = 8.8Hz, 1H).

LC/MS (ESI): m/z = 451 [M+H]⁺, RT = 2.84 min, LC/MS Method 1

[0152]

Step 3: Synthesis of Compound 46

To Compound 45 (3.27 g, 7.26 mmol) were added tetrahydrofuran (39.2 mL), Compound 17 (1.69 g, 9.44 mmol), triphenylphosphine (2.48 g, 9.44 mmol) and DMEAD (2.21 g, 9.44 mmol). The mixture was stirred at 50°C for 1 hour, the reaction was quenched with water. The organic layer was extracted with ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 46 (4.07 g, yield 92%).

¹H-NMR (CDCl₃) δ: 1.42 (t, J = 7.2Hz, 3H), 1.72 (s, 9H), 1.90 (m, 2H), 2.06 (m, 2H), 3.76 (m, 2H), 4.19 (m, 2H), 4.44 (q, J = 7.2Hz, 2H), 4.67 (m, 1H), 6.48 (t, J = 4.4Hz, 1H), 7.06 (dd, J = 8.8, 2.0Hz, 1H), 7.83 (brs, 1H), 7.89 (d, J = 8.0Hz, 1H), 8.13-8.16 (m, 2H), 8.32 (d, J = 4.8Hz, 2H), 8.49 (d, J = 8.8Hz, 1H).

LC/MS (ESI): m/z = 612 [M+H]⁺, RT = 3.59 min, LC/MS Method 1

[0153]

Step 4: Synthesis of Compound 21

To Compound 46 (4.17 g, 6.82 mmol) were added dichloromethane (41.7 mL) and trifluoroacetic acid (41.7 mL, 541 mmol), and the mixture was stirred at room temperature for 1 hour 30 minutes. The reaction solution was concentrated under reduced pressure and neutralized with saturated aqueous sodium bicarbonate solution. The mixture was extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and chloroform was added to the residue. The solid was filtered to obtain Compound 47 (800 mg, yield 22%). The filtrate was again concentrated under reduced pressure. Toluene was added to solidify the residue, and the solid was filtered to obtain Compound 47 (1.73 g, yield 48%). The filtrate was further concentrated under

reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 21 (520 mg, yield 15%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (t, $J = 7.2\text{Hz}$, 3H), 1.88 (m, 2H), 2.06 (m, 2H), 3.71 (m, 2H), 4.21 (m, 2H), 4.43 (q, $J = 7.2\text{Hz}$, 2H), 4.61 (m, 1H), 6.48 (t, $J = 4.8\text{Hz}$, 1H), 6.98 (d, $J = 2.0\text{Hz}$, 1H), 7.02 (dd, $J = 8.8, 2.0\text{Hz}$, 1H), 7.78-7.84 (m, 2H), 8.11 (d, $J = 8.4\text{Hz}$, 1H), 8.32 (d, $J = 4.8\text{Hz}$, 2H), 8.42-8.48 (m, 2H).

LC/MS (ESI): $m/z = 512$ $[\text{M}+\text{H}]^+$, $\text{RT} = 2.80$ min, LC/MS Method 1

[0154]

Step 5: Synthesis of Compound 49

Compound 21 (800 mg, 1.56 mmol) was dissolved in dimethylformamide (12 mL), and 60 wt% sodium hydride (94 mg, 2.35 mmol) and Compound 48 (681 mg, 2.35 mmol) were added under ice-cooling. After stirring at 90°C for 30 minutes, the mixture was again cooled under ice bath and 60 wt% sodium hydride (94 mg, 2.35 mmol) and Compound 48 (681 mg, 2.35 mmol) were added. After stirring at 90°C for 30 minutes, the mixture was again cooled under ice bath and 60 wt% sodium hydride (94 mg, 2.35 mmol) and Compound 48 (681 mg, 2.35 mmol) were added. After stirring at 90°C for 30 minutes, the mixture was again cooled under ice bath and 60 wt% sodium hydride (94 mg, 2.35 mmol) and Compound 48 (681 mg, 2.35 mmol) were added, and the mixture was stirred at 90°C for 30 minutes. The reaction solution was poured into 10% aqueous citric acid solution to quench the reaction, followed by extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform-methanol) to afford Compound 49 (900 mg, yield 96%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.71-2.24 (m, 10H), 2.35 (m, 2H), 3.77 (m, 2H), 4.20 (m, 2H), 4.32 (m, 1H), 4.67 (m, 1H), 6.54 (t, $J = 4.8\text{Hz}$, 1H),

6.96 (d, J = 2.0Hz, 1H), 7.05 (dd, J = 8.8, 2.0Hz, 1H), 7.80 (d, J = 8.4Hz, 1H), 7.82 (s, 1H), 8.23 (d, J = 8.0Hz, 1H), 8.39 (t, J = 4.8Hz, 2H), 8.50 (d, J = 8.8Hz, 1H).

LC/MS (ESI): m/z = 602 [M+H]⁺, RT = 2.71 min, LC/MS Method 1

[0155]

Step 6: Synthesis of Compound (I-162)

The compound was synthesized in the same manner as in Step 7 of Example 3.

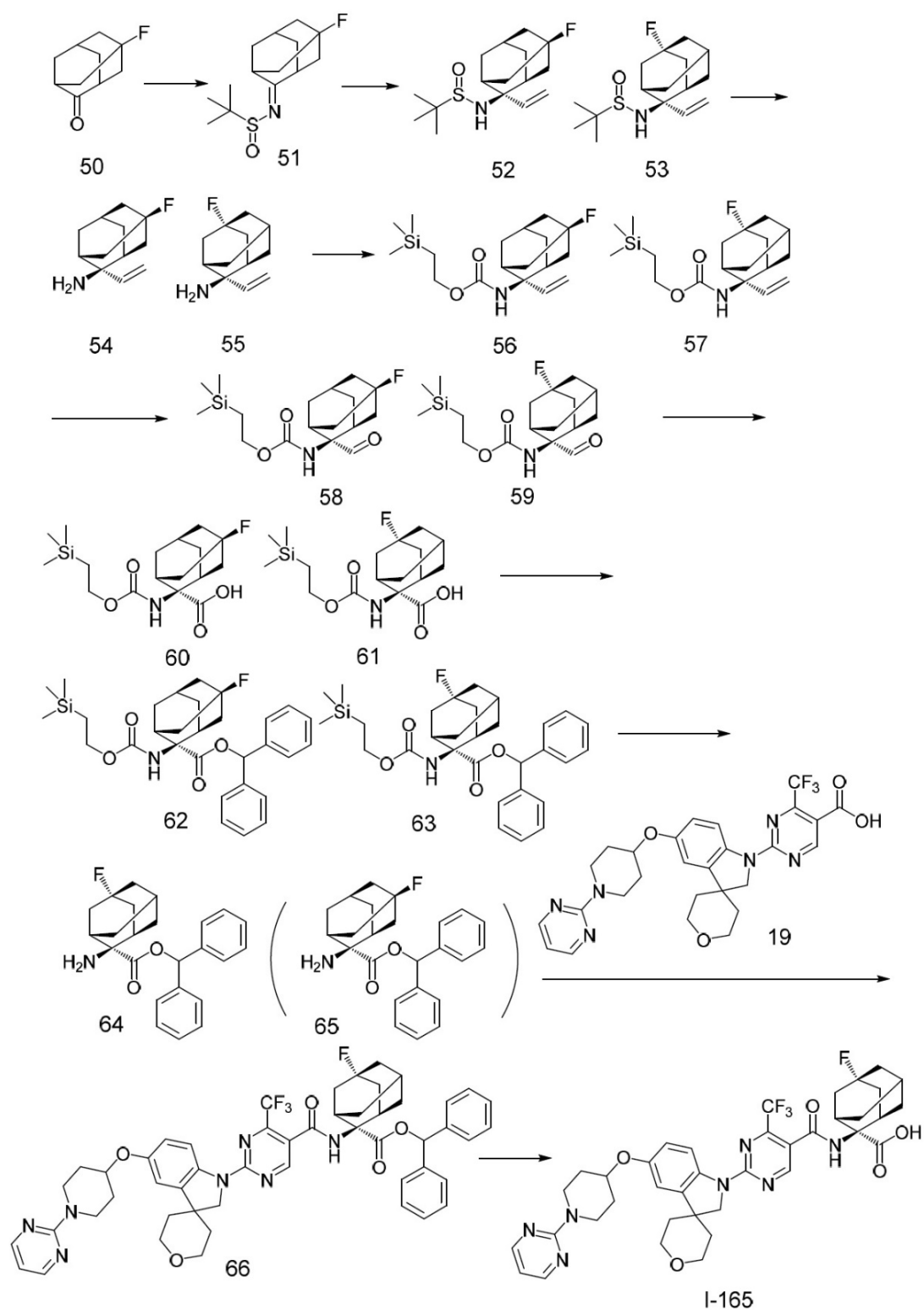
¹H-NMR (DMSO-d₆) δ: 1.55-1.71 (m, 8H), 1.81 (brs, 2H), 1.98-2.25 (m, 14H), 2.58 (s, 2H), 3.62 (m, 2H), 4.19 (m, 2H), 4.68-4.78 (m, 2H), 6.62 (t, J = 4.8Hz, 1H), 6.98 (dd, J = 8.8, 2.0Hz, 1H), 7.31 (d, J = 2.0Hz, 1H), 7.73 (d, J = 8.4Hz, 1H), 8.17 (d, J = 8.4Hz, 1H), 8.37 (d, J = 4.4Hz, 2H), 8.41-8.44 (m, 2H), 8.49 (s, 1H), 12.32 (s, 1H).

LC/MS (ESI): m/z = 779 [M+H]⁺, RT = 3.06 min, LC/MS Method 1

[0156]

Example 7

Synthesis of Compound (I-165)



Step 1: Synthesis of Compound 51

Compound 50 (49.9 g, 297 mmol) and 2-methyl-2

propanesulfinamide (53.9 g, 445 mmol) were added to tetrahydrofuran (250 mL), and tetraethyl orthotitanate (137mL, 653 mmol) was added at room temperature. The mixture was stirred at 80°C for 1 hour and then poured into acetonitrile (1 L). Water (53.5 g) was added to quench the reaction. After stirring for 10 minutes, anhydrous magnesium sulfate was added, and the solid was filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 51 (58.9 g, yield 70%). LC/MS (ESI): m/z = 272 [M+H]⁺, RT=1.81 min, LC/MS Method 2

[0157]

Step 2: Synthesis of mixture of Compound 52 and Compound 53

Compound 51 (70.3 g, 241 mmol) was dissolved in tetrahydrofuran (211 mL), and 1 mol/L vinylmagnesium bromide (361 mL, 361 mmol) was added dropwise under ice-cooling. The reaction was quenched with aqueous ammonium chloride solution, followed by extraction with ethyl acetate and washed with water, and the organic layer was concentrated under reduced pressure. The resulting solid was suspended with hexane, and the solid was filtered to obtain a mixture of Compound 52 and Compound 53 (46.1 g, yield 64%). LC/MS (ESI): m/z = 300 [M+H]⁺, RT=2.01 min, LC/MS Method 2

[0158]

Step 3: Synthesis of mixture of Compound 54 and Compound 55

To the mixture of Compound 52 and Compound 53 (70.7 g, 236 mmol) was added 2 mol/L hydrogen chloride methanol solution (354 mL, 708 mmol) and stirred at room temperature for 1 hour. Water and ethyl acetate were added for extraction. The aqueous layer was neutralized by adding aqueous sodium bicarbonate solution, followed by extraction with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to afford a mixture of Compound 54 and Compound 55 as crude product (55.2 g). LC/MS (ESI): m/z = 196 [M+H]⁺, RT=1.01 min, LC/MS Method 2

[0159]

Step 4: Synthesis of mixture of Compound 56 and Compound 57

The mixture of Compound 54 and Compound 55 (55.2 g, 223 mmol) was dissolved in tetrahydrofuran (497 mL), and 1-[2-(trimethylsilyl)ethoxycarbonyl]pyrrolidine-2,5-dione (100 g, 387 mmol) was added. After stirring at room temperature for 1 hour, 1-[2-(trimethylsilyl)ethoxycarbonyl]pyrrolidine-2,5-dione (12.5 g, 48.2 mmol) was added additionally. After stirring for 1 hour 40 minutes, aqueous citric acid solution was added. The mixture was extracted with ethyl acetate. The organic layer was washed with water and concentrated under reduced pressure. Hexane was added to the resulting solid, and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford a mixture of Compound 56 and Compound 57 (65.0 g, yield 86%).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.03 (s, 9H), 0.92-0.98 (m, 2H), 1.49-1.56 (m, 2H), 1.73-1.80 (m, 2H), 1.87-2.01 (m, 4H), 2.13-2.28 (m, 3H), 2.56 (brs, 2H), 4.09 (m, 2H), 4.62 (s, 1H), 5.20-5.31 (m, 2H), 6.10 (dd, $J = 17.6, 2.8\text{Hz}$, 1H).

[0160]

Step 5: Synthesis of mixture of Compound 58 and Compound 59

The mixture of Compound 56 and Compound 57 (67.0 g, 197 mmol) was dissolved in acetonitrile (1179 mL), and water (395 mL), sodium periodate (127 g, 592 mmol), 2,6-lutidine (63.4 g, 592 mmol), potassium osmate dihydrate (7.27 g, 19.7 mmol) were added. The mixture was stirred at 60°C for 1 hour, then sodium periodate (42.2 g, 197 mmol) was added. After 2 hours, the reaction was cooled under ice bath and quenched with aqueous sodium thiosulfate. The mixture was extracted with ethyl acetate, and the organic layer was washed with 10% aqueous citric acid solution, and washed with 3% aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford a

mixture of Compound 58 and Compound 59 (32.5 g, yield 48%).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.03 (s, 9H), 0.92–1.00 (m, 2H), 1.56–1.98 (m, 8H), 2.09–2.28 (m, 3H), 2.63–2.69 (m, 2H), 4.12 (m, 2H), 4.81–4.89 (m, 1H), 9.60–9.74 (m, 2H).

[0161]

Step 6: Synthesis of mixture of Compound 60 and Compound 61

The mixture of Compound 58 and Compound 59 (36.1 g, 106 mmol) were dissolved in tert-butyl alcohol (361 mL) and water (65 mL), and 2-methyl-2-butene (63.8 mL, 603 mmol) was added. Potassium dihydrogen phosphate (57.5 g, 423 mmol) and sodium chlorite (76 g, 846 mmol) were dissolved in water (300 mL) and added dropwise under ice-cooling. After stirring under ice-cooling for 1 hour, the reaction was quenched with aqueous sodium thiosulfate. The mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to afford a mixture of Compound 60 and Compound 61 as a crude product (45 g).

LC/MS (ESI): m/z = 356 $[\text{M-H}]^-$, RT = 2.32 min and 2.41 min, LC/MS Method 2

[0162]

Step 7: Synthesis of mixture of Compound 62 and Compound 63

The crude product of mixture of Compound 60 and Compound 61 (45 g) was dissolved in tetrahydrofuran (227 mL) and methanol (227 mL), and diphenyldiazomethane (61.8 g, 318 mmol) was added. After stirring at room temperature for 2 hours, acetic acid (18.2 mL) was added. After stirring at room temperature for 1 hour, water was added, followed by extraction with ethyl acetate. The organic layer was washed with aqueous sodium carbonate solution and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate). The fraction was concentrated, and the residue was solidified by adding hexane, and the solid was filtered to obtain a mixture of Compound 62 and Compound 63 (21.5 g, yield 39%).

¹H-NMR (CDCl₃) δ: 0.03 (s, 9H), 0.73-0.94 (m, 2H), 1.50-1.56 (m, 2H), 1.75-1.96 (m, 6H), 2.10-2.20 (m, 3H), 2.84 (brs, 2H), 3.95 (m, 2H), 4.83 (brs, 1H), 6.90-6.93 (m, 1H), 7.25-7.31 (m, 10H).

[0163]

Step 8: Synthesis of Compound 64

To the mixture of Compound 62 and Compound 63 (43.2 g, 82 mmol) were added 1 mol/L tetrabutylammonium fluoride-tetrahydrofuran solution (866 mL) and acetic acid (42.4 mL), and the mixture was stirred with heating under reflux for 15 hours. Aqueous sodium bicarbonate solution was added to neutralize, followed by extraction with ethyl acetate. The organic layer was washed three times with aqueous ammonium chloride solution, followed by sodium bicarbonate solution and brine. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to separate the less polar Compound 65 from the high polar Compound 64 to afford Compound 64 (19.5 g, yield 56%).

¹H-NMR (DMSO-d₆) δ: 1.30-1.35 (m, 2H), 1.65-1.77 (m, 6H), 1.99-2.11 (m, 3H), 2.19-2.27 (m, 2H), 2.35 (brs, 2H), 6.82 (s, 1H), 7.27 (m, 2H), 7.35 (m, 4H), 7.45 (m, 4H).

[0164]

Step 9: Synthesis of Compound 66

Compound 66 was synthesized in the same manner as in Step 3 of Example 4.

LC/MS (ESI): m/z = 918 [M+H]⁺, RT=3.06 min, LCMS method 1

[0165]

Step 10: Synthesis of Compound (I-165)

Compound 66 (66 mg, 0.072 mmol) was dissolved in dichloromethane (4 mL), and anisole (40 mg, 0.37 mmol) and trifluoroacetic acid (2 mL) were added under ice-cooling. After stirring for 30 minutes under ice-cooling, the reaction mixture was concentrated under reduced pressure. The residue was dissolved

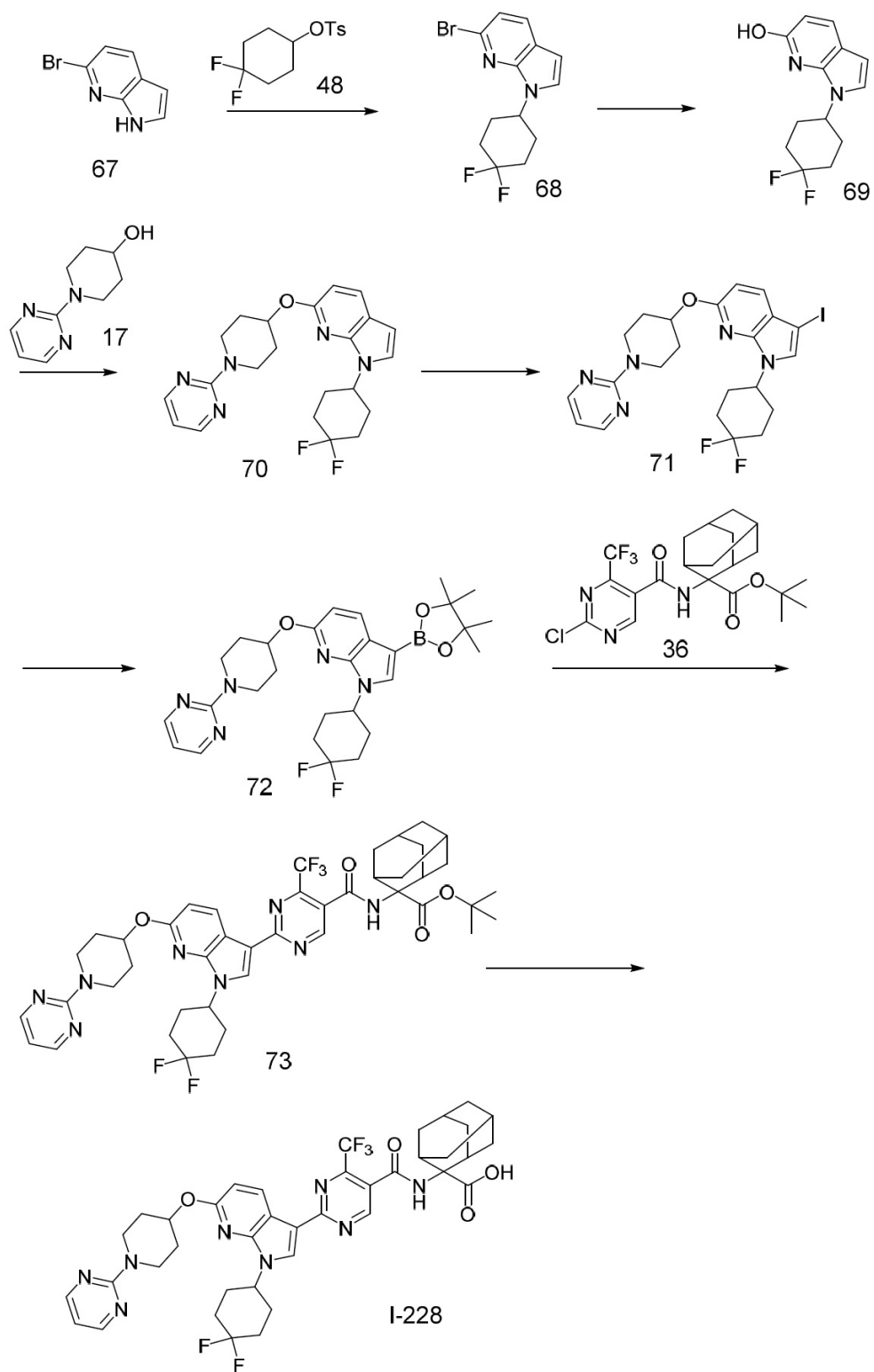
in dichloromethane and neutralized with aqueous sodium carbonate. Citric acid solution was added to the aqueous layer, followed by extraction with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol) to afford Compound (I-165) (33 mg, yield 61%).

^1H -NMR (DMSO- d_6) δ : 1.45-1.48 (m, 2H), 1.53-1.60 (m, 4H), 1.78-1.84 (m, 4H), 1.97-2.05 (m, 6H), 2.16-2.24 (m, 3H), 2.82 (s, 2H), 3.48-3.56 (m, 4H), 3.88-3.92 (m, 2H), 4.22-4.26 (m, 4H), 4.64-4.70 (m, 1H). 6.61 (t, J = 4.8Hz, 1H), 6.94 (d, J = 8.0Hz, 1H), 7.09 (d, J = 2.4Hz, 1H), 8.17 (d, J = 4.4Hz, 1H), 8.36 (d, J = 4.8Hz, 2H), 8.63 (brs, 1H), 8.71 (s, 1H), 12.67 (brs, 1H).

[0166]

Example 8

Synthesis of Compound (I-228)



Step 1: Synthesis of Compound 68

To a solution of Compound 67 (300 mg, 1.52 mmol) in N-

methyldipyrrolidone (4.42 mL) was added 60 wt% sodium hydride (61 mg, 1.53 mmol) with stirring under argon flow at room temperature, and the mixture was stirred for 10 min at room temperature. Compound 48 (442 mg, 1.52 mmol) was then added at room temperature. After stirring at 100°C for 3 hours, Compound 48 (442 mg, 1.52 mmol) and 60 wt% sodium hydride (61 mg, 1.53 mmol) were added, and the mixture was stirred at 80°C for 5 hours. After completion of the reaction, saturated aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 68 (252 mg, yield 53%).

LC/MS(DUIS):m/z= 315 [M+H]⁺, RT=1.59min, LC/MS Method 9

[0167]

Step 2: Synthesis of Compound 69

Compound 68 (50 mg, 0.16 mmol) was dissolved in 1,4-dioxane (0.5 mL) and water (0.5 mL), and 8 mol/L potassium hydroxide solution (0.06 mL, 0.48 mmol), Pd₂(dba)₃ (15 mg, 0.02 mmol), 5-(Di-*t*-butylphosphino)-1',3',5'-triphenyl-1,4'-bi-1H-pyrazole (16 mg, 0.03 mmol) were added with stirring under argon flow at room temperature, and mixture was stirred at 75°C. After 2 hours, water was added, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 69 as crude product (51 mg).

LC/MS(DUIS):m/z= 253 [M+H]⁺, RT=1.04min, LC/MS Method 9

[0168]

Step 3: Synthesis of Compound 70

To the crude product of Compound 69 (49 mg, 0.19 mmol) in tetrahydrofuran (0.98 mL) were added Compound 17 (70 mg, 0.39

mmol), 1.9 mol/L DIAD-toluene solution (145 μ L, 0.28 mmol), triphenylphosphine (74 mg, 0.28 mmol) under argon flow at room temperature, and the mixture was stirred for 2 hours at room temperature. After completion of the reaction, aqueous sodium bicarbonate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 70 (47 mg, 58%).

LC/MS (DUI): m/z = 414 [M+H]⁺, RT= 1.77min, LC/MS Method 9

[0169]

Step 4: Synthesis of Compound 71

The compound was synthesized in the same manner as in Step 5 of Example 9.

LC/MS (DUI): m/z = 540 [M+H]⁺, RT=1.98min, LC/MS Method 9

[0170]

Step 5: Synthesis of Compound 72

The compound was synthesized in the same manner as in Step 6 of Example 9.

LC/MS (DUI): m/z = 540 [M+H]⁺, RT=2.00min, LC/MS Method 9

[0171]

Step 6: Synthesis of Compound 73

The compound was synthesized in the same manner as in Step 1 of Example 6.

LC/MS (DUI): m/z = 837 [M+H]⁺, RT=2.29min, LC/MS Method 9

[0172]

Step 7: Synthesis of Compound (I-228)

The compound was synthesized in the same manner as in Step 8 of Example 10.

¹H-NMR (DMSO- d_6) δ : 1.55-1.84 (m, 10H), 2.02-2.28 (m, 14H), 2.55-2.58 (m, 2H), 3.45-3.55 (m, 2H), 4.30-4.42 (m, 2H), 4.70-4.83 (m,

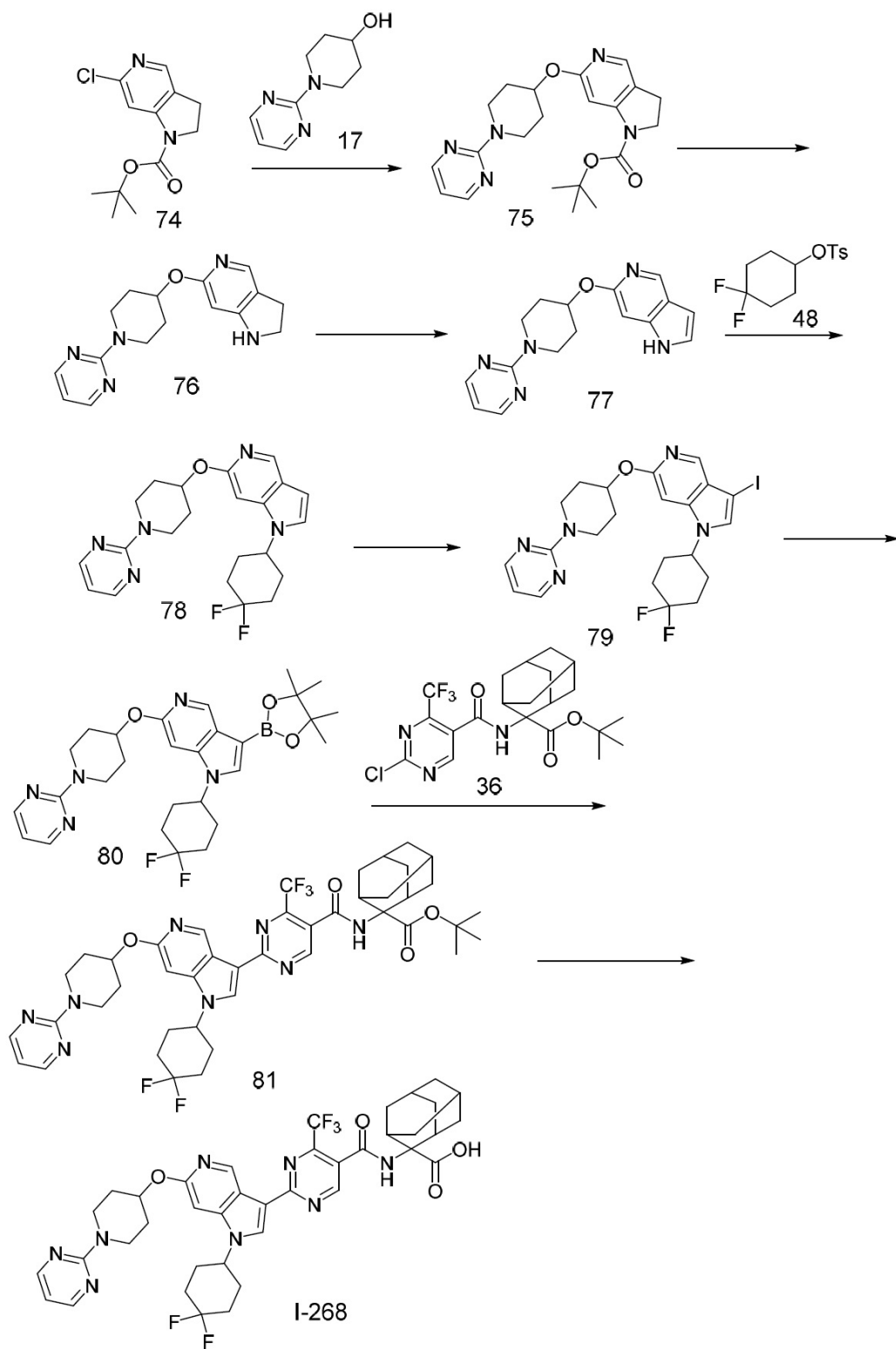
1H), 5.23-5.33 (m, 1H), 6.63 (t, J = 4.8Hz, 1H), 6.79 (d, J = 8.5Hz, 1H), 8.31 (s, 1H), 8.37 (d, J = 4.6Hz, 2H), 8.61 (d, J = 8.5Hz, 1H), 8.65 (brs, 1H), 8.87 (s, 1H), 12.51 (brs, 1H).

LC/MS (ESI): m/z = 781 [M+H]⁺, RT=1.86min, LC/MS Method 10

[0173]

Example 9

Synthesis of Compound (I-268)



Step 1: Synthesis of Compound 75

To a solution of Compound 17 (760 mg, 4.24 mmol) in toluene

(10 mL) was added 60 wt% sodium hydride (283 mg, 7.08 mmol) with stirring under argon flow at room temperature, and the mixture was stirred at 70°C for 15 min. Compound 74 (910 mg, 3.57 mmol), Pd₂(dba)₃ (324 mg, 0.354 mmol), (R)-(+)-TolBINAP (240 mg, 0.354 mmol) were added at room temperature, and the mixture was stirred at 100°C. After 30 min, water was added, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 75 (899 mg, yield 63%).

LC/MS(DUIS):m/z= 398 [M+H]⁺, RT= 1.17 min, LC/MS Method 9

[0174]

Step 2: Synthesis of Compound 76

To a solution of Compound 75 (899 mg, 2.26 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (2 mL, 26.1 mmol) with stirring under argon flow at room temperature, and the mixture was stirred for 6 hours. After completion of the reaction, aqueous sodium bicarbonate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to obtain Compound 76 (695 mg, yield 100%).

LC/MS(DUIS):m/z= 298 [M+H]⁺, RT=0.35 min, LC/MS Method 9

[0175]

Step 3: Synthesis of Compound 77

To a solution of Compound 76 (530 mg, 1.78 mmol) in toluene (15.9 mL) was added manganese dioxide (775 mg, 8.91 mmol) at room temperature with stirring under argon flow, and the mixture was stirred at 120°C for 6 hours. Then, after stirring at room temperature for 18 hours, manganese dioxide (775 mg, 8.91 mmol) was added at room temperature with stirring under argon flow, followed by stirring at 120°C for 2 hours. After completion of the reaction, the solution was filtered through Celite (registered

trademark), washed with ethyl acetate, and the filtrate was concentrated under reduced pressure to afford Compound 77 (342 mg, yield 65%).

LC/MS (DUIS): m/z = 296 [M+H]⁺, RT=0.36 min, LC/MS Method 9

[0176]

Step 4: Synthesis of Compound 78

To a solution of Compound 77 (370 mg, 1.25 mmol) in N-methylpyrrolidone (7.4 mL) were added cesium carbonate (1.22 g, 3.74 mmol) and Compound 48 (1.09 g, 3.75 mmol) at room temperature with stirring under argon flow, and the mixture was stirred at 120°C for 3 hours. Then, cesium carbonate (1.22 g, 3.74 mmol) and Compound 48 (1.09 g, 3.75 mmol) were added at room temperature, and the mixture was stirred at 120°C for 2 hours. Additionally, cesium carbonate (1.22 g, 3.74 mmol) and Compound 48 (1.09 g, 3.75 mmol) were added at room temperature, and the mixture was stirred at 120°C for 2 hours. After completion of the reaction, water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 78 (520 mg, yield 100%).

LC/MS (DUIS): m/z = 414 [M+H]⁺, RT=0.91 min, LC/MS Method 9

[0177]

Step 5: Synthesis of Compound 79

To a solution of Compound 78 (470 mg, 1.14 mmol) in dimethylformamide (4.7 mL) was added N-iodosuccinimide (280 mg, 1.25 mmol) at room temperature with stirring under argon flow, and the mixture was stirred at room temperature for 30 minutes. After completion of the reaction, aqueous sodium bicarbonate solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by

silica gel column chromatography (hexane-ethyl acetate) to afford Compound 79 (180 mg, yield 29%).

LC/MS (ESI): m/z = 540 [M+H]⁺, RT=1.43 min, LC/MS Method 10

[0178]

Step 6: Synthesis of Compound 80

To a solution of Compound 79 (180 mg, 0.33 mmol) in 1,4-dioxane (3.6 mL) were added triethylamine (185 μ L, 1.33 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (195 μ L, 1.34 mmol), X-Phos (32 mg, 0.07 mmol), Pd₂(dba)₃ (31 mg, 0.03 mmol) at room temperature with stirring under argon flow, and the mixture was stirred at 95°C for 1 hour. After completion of the reaction, water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 80 (111 mg, yield 62%).

LC/MS (ESI): m/z = 540 [M+H]⁺, RT=1.29 min, LC/MS Method 10

[0179]

Step 7: Synthesis of Compound 81

The compound was synthesized in the same manner as in Step 1 of Example 6.

LC/MS (ESI): m/z = 837 [M+H]⁺, RT=1.99 min, LC/MS Method 10

[0180]

Step 8: Synthesis of Compound (I-268)

The compound was synthesized in the same manner as in Step 8 of Example 10.

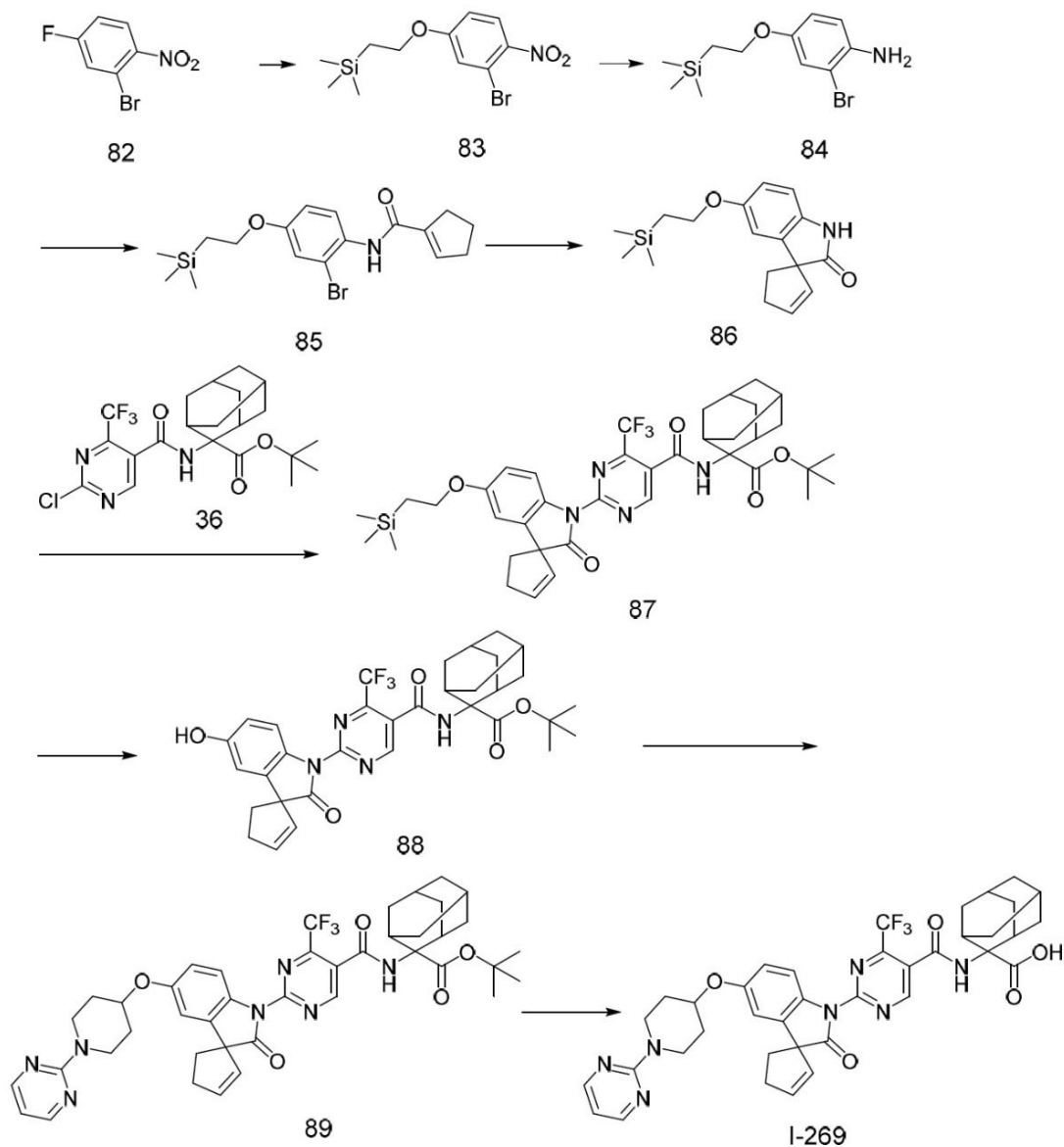
¹H-NMR (DMSO-d₆) δ : 1.49-1.84 (m, 10H), 2.01-2.22 (m, 14H), 2.56-2.60 (m, 2H), 3.54-3.63 (m, 2H), 4.21-4.31 (m, 2H), 4.60-4.73 (m, 1H), 5.33-5.43 (m, 1H), 6.62 (t, J = 4.8 Hz, 1H), 7.15 (s, 1H), 8.37 (d, J = 4.8 Hz, 2H), 8.41 (brs, 1H), 8.51 (brs, 1H), 8.89 (s, 1H), 9.23 (s, 1H), 12.51 (brs, 1H).

LC/MS (DUIS): m/z = 781 [M+H]⁺, RT=1.56 min, LC/MS Method 9

[0181]

Example 10

Synthesis of Compound (I-269)



Step 1: Synthesis of Compound 83

2-(Trimethylsilyl)ethan-1-ol (1.08 g, 9.10 mmol) was dissolved in tetrahydrofuran (10 mL), and 60 wt% sodium hydride (218 mg, 5.46 mmol) was added under ice-cooling. After 5 minutes, Compound 82 (1.00 g, 4.55 mmol) was added, and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with water,

followed by extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 83 (1.45 g, yield 100%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.10 (s, 9H), 1.16 (t, $J = 8.0\text{Hz}$, 2H), 4.14 (t, $J = 8.0\text{Hz}$, 2H), 6.88 (dd, $J = 9.2, 2.8\text{Hz}$, 1H), 7.18 (d, $J = 2.8\text{Hz}$, 1H), 7.98 (d, $J = 9.2\text{Hz}$, 1H).

[0182]

Step 2: Synthesis of Compound 84

Compound 83 (500 mg, 1.57 mmol) was dissolved in ethanol (5 mL), and water (1 mL), ammonium chloride (336 mg, 6.28 mmol) and iron (438 mmol, 7.85 mmol) were added, and the mixture was stirred at 90°C for 3 hours. The reaction solution was cooled and then diluted with ethyl acetate (30 mL), and the insoluble material was filtered off using Celite (registered trademark). Water was added to the filtrate, followed by extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 84 (303 mg, yield 67%). LC/MS(ESI): $m/z = 288$ $[\text{M}+\text{H}]^+$, $\text{RT}=2.83$ min, LC/MS Method 1

[0183]

Step 3: Synthesis of Compound 85

Compound 84 (1.93 g, 6.70 mmol) was dissolved in dimethylformamide (10 mL), and cyclopent-1-ene-1-carboxylic acid (1.08 g, 1.44 mmol), triethylamine (3.39 g, 33.5 mmol) and HATU (3.80 g, 10.1 mmol) were added, and the mixture was stirred at room temperature for 6 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and washed with water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column

chromatography (hexane-ethyl acetate) to afford Compound 85 (816 mg, yield 32%).

LC/MS (ESI): m/z = 382 [M+H]⁺, RT = 3.08 min, LC/MS Method 1

[0184]

Step 4: Synthesis of Compound 86

Compound 85 (816 mg, 2.13 mmol) was dissolved in dimethylformamide (6 mL), and triethylamine (1.08 g, 10.6 mmol) and PdCl₂(dppf) (156 mg, 0.213 mmol) were added, and the mixture was stirred at 80°C for 2 hours. After the reaction solution was allowed to cool, water was added, followed by extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 86 (467 mg, yield 73%).

LC/MS (ESI): m/z = 302 [M+H]⁺, RT = 2.50 min, LC/MS Method 1

[0185]

Step 5: Synthesis of Compound 87

Compound 86 (218 mg, 0.723 mmol) was dissolved in 1,4-dioxane (2 mL), and Compound 36 (399 mg, 0.868 mmol), cesium carbonate (707 mg, 2.17 mmol) and Xantphos Pd G2 (129 mg, 0.145 mmol) were added, and the mixture was stirred at 100°C for 1 hour under nitrogen atmosphere. After cooling, the mixture was diluted with ethyl acetate (10 mL), and the insoluble material was filtered off. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 87 (404 mg, yield 77%).

LC/MS (ESI): m/z = 725 [M+H]⁺, RT = 3.54 min, LC/MS Method 1

[0186]

Step 6: Synthesis of Compound 88

To Compound 87 (404 mg, 0.557 mmol) was added 1 mol/L tetrabutylammonium fluoride-tetrahydrofuran solution (10 mL, 10 mmol), and the mixture was stirred at 80°C for 1 hour. After cooling, water was added, followed by extraction with ethyl

acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in dimethylformamide (8 mL), and triethylamine (169 mg, 1.67 mmol) and HATU (318 mg, 0.835 mmol) were added, and the mixture was stirred at room temperature for 30 minutes. Methanol (20 mL) and potassium carbonate (231 mg, 1.67 mmol) were added, and the mixture was stirred at room temperature for 30 minutes, water was added to the reaction solution, followed by extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 88 (203 mg, yield 58%). LC/MS (ESI): m/z = 625 [M+H]⁺, RT=2.77 min, LC/MS Method 1

[0187]

Step 7: Synthesis of Compound 89

The compound was synthesized in the same manner as in Step 5 of Example 3.

LC/MS (ESI): m/z = 786 [M+H]⁺, RT=3.11 min, LC/MS Method 1

[0188]

Step 8: Synthesis of Compound (I-269)

Compound 89 (50 mg, 0.064 mmol) was dissolved in trifluoroacetic acid (4 mL), and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated, dissolved in dichloromethane, and neutralized with saturated aqueous sodium bicarbonate solution. Aqueous citric acid solution was added to the reaction solution to acidify again, followed by extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (chloroform-methanol) to afford Compound (I-269) (30 mg, yield 65%).

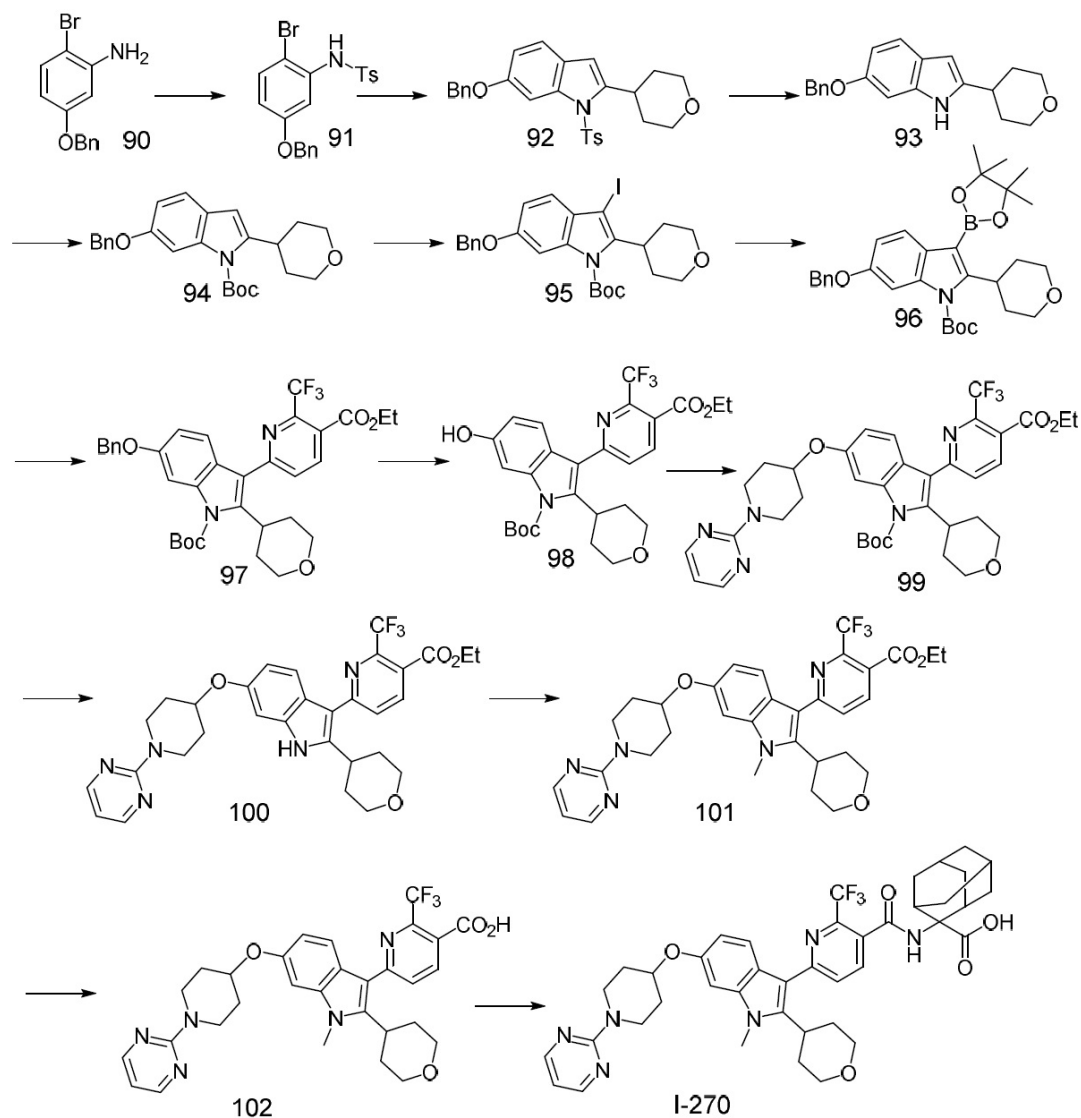
¹H-NMR (CDCl₃) δ: 1.77-2.05 (m, 15H), 2.19-2.27 (m, 3H), 2.61-2.67 (m, 3H), 2.70-2.76 (m, 1H), 2.78-2.87 (m, 1H), 3.69-3.75 (m, 2H),

4.11-4.19 (m, 2H), 4.51-4.57 (m, 1H), 5.53-5.56 (m, 1H), 6.24-6.27 (m, 1H), 6.49 (t, $J = 5.2\text{Hz}$, 1H), 6.55 (brs, 1H), 6.81 (d, $J = 2.8\text{Hz}$, 1H), 6.90 (dd, $J = 8.8, 2.4\text{Hz}$, 1H), 7.88 (d, $J = 9.2\text{Hz}$, 1H), 8.32 (d, $J = 4.8\text{Hz}$, 2H), 9.12 (s, 1H).

[0189]

Example 11

Synthesis of Compound (I-270)



Step 1: Synthesis of Compound 91

Compound 90 (1.64 g, 5.60 mmol) was dissolved in dichloromethane (16.4 mL), and pyridine (1.33 g, 16.80 mmol) and

paratoluenesulfonyl chloride (2.14 g, 11.20 mmol) were added under ice-cooling. After stirring at room temperature for 1.5 hours, triethylamine (1.70 g, 16.80 mmol) and 1-methylpiperazine (1.12 g, 11.20 mmol) were added, and the mixture was stirred for 30 minutes. Concentrated hydrochloric acid was added under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 91 (2.08 g, yield 86%).

LC/MS (ESI): m/z = 432 $[M+H]^+$, RT = 2.76 min, LC/MS Method 1

[0190]

Step 2: Synthesis of Compound 92

Compound 91 (0.45 g, 1.04 mmol) was dissolved in dimethylformamide (2.89 mL), and 4-ethynyltetrahydro-2H-pyran (0.17 g, 1.56 mmol), copper(I) iodide (39 mg, 0.21 mmol), triethylamine (2.11 g, 20.82 mmol) and $PdCl_2(dppf)$ (76 mg, 0.10 mmol) were added, and the mixture was stirred at 100°C for 8 hours. After adding water, the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 92 (0.35 g, yield 73%).

LC/MS (ESI): m/z = 462 $[M+H]^+$, RT = 2.99 min, LC/MS Method 1

[0191]

Step 3: Synthesis of Compound 93

To a solution of Compound 92 (200 mg, 0.43 mmol) in tetrahydrofuran (0.4 mL) was added 1 mol/L tetrabutylammonium fluoride-tetrahydrofuran solution (8.67 mL, 8.67 mmol), and the mixture was stirred with heating under reflux for 17 hours. After addition of 1 mol/L hydrochloric acid, the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column

chromatography (chloroform-methanol) to afford Compound 93 (130 mg, yield 98%).

LC/MS (ESI): m/z = 308 [M+H]⁺, RT=2.35 min, LC/MS Method 1

[0192]

Step 4: Synthesis of Compound 94

To a solution of Compound 93 (130 mg, 0.42 mmol) in tetrahydrofuran (1.3 mL) were added Boc₂O (220 mg, 1.01 mmol) and DMAP (5.2 mg, 0.04 mmol), and the mixture was stirred at room temperature for 21 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 94 (160 mg, yield 93%).

LC/MS (ESI): m/z = 408 [M+H]⁺, RT=3.18 min, LC/MS Method 1

[0193]

Step 5: Synthesis of Compound 95

Iodine (62 mg, 0.25 mmol) was dissolved in dichloromethane (0.5 mL), and pyridine (39 mg, 0.49 mmol) and iodobenzene bis(trifluoroacetate (106 mg, 0.25 mmol) were added, and the mixture was stirred at room temperature for 15 min. To this solution was added the solution of Compound 94 (100 mg, 0.25 mmol) in dichloromethane (2 mL) under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. After addition of 10% aqueous sodium thiosulfate solution, the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 95 (115 mg, yield 88%).

¹H-NMR (CDCl₃) δ : 1.63-1.65 (m, 2H), 1.67 (s, 9H), 2.70 (ddd, J = 25.3, 11.8, 4.1 Hz, 2H), 3.53 (td, J = 11.8, 1.7 Hz, 2H), 3.76-3.82 (m, 1H), 4.11 (dd, J = 11.8, 4.1 Hz, 2H), 5.13 (s, 2H), 6.99 (dd, J = 8.6, 2.2 Hz, 1H), 7.29-7.33 (m, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.45 (d, J = 7.3 Hz, 2H), 7.60 (d, J = 2.2 Hz, 1H).

[0194]

Step 6: Synthesis of Compound 96

Compound 95 (113 mg, 0.21 mmol) was dissolved in 1,4-dioxane (2.3 mL), and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (163 mg, 1.27 mmol), X-Phos (30 mg, 0.06 mmol), Pd₂(dba)₃ (39 mg, 0.04 mmol) and triethylamine (129 mg, 1.27 mmol) were added, and the mixture was stirred at 95°C for 2.5 hours. Water was added, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 96 (110 mg, yield 97%).

¹H-NMR (CDCl₃) δ: 1.40 (s, 12H), 1.67 (s, 9H), 1.73 (d, J = 12.0 Hz, 2H), 2.42 (ddd, J = 24.8, 12.0, 4.1 Hz, 2H), 3.50 (t, J = 10.9 Hz, 2H), 3.72-3.77 (m, 1H), 4.07 (dd, J = 10.9, 4.1 Hz, 2H), 5.11 (s, 2H), 6.92 (dd, J = 8.5, 2.3 Hz, 1H), 7.29-7.39 (m, 3H), 7.45 (d, J = 7.2 Hz, 2H), 7.59 (d, J = 2.3 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H).

[0195]

Step 7: Synthesis of Compound 97

Compound 96 (108 mg, 0.20 mmol) was dissolved in 1,4-dioxane (1.4 mL), and Compound 43 (57 mg, 0.22 mmol), PdCl₂(dppf) (17 mg, 0.02 mmol), water (0.3 mL) and cesium carbonate (132 mg, 0.41 mmol) were added, and the mixture was stirred with heating under reflux for 1 hour. After cooling, water was added, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 97 (92 mg, yield 73%).

LC/MS(ESI):m/z= 625[M+H]⁺, RT= 3.45 min, LC/MS Method 1

[0196]

Step 8: Synthesis of Compound 98

To Compound 97 (90 mg, 0.14 mmol) were added tetrahydrofuran (0.63 mL), ethanol (0.63 mL) and 20 wt% palladium carbon (18 mg,

0.17 mmol). The mixture was stirred for 2.5 hours at room temperature under hydrogen atmosphere. The reaction mixture was filtered through Celite (registered trademark), the filtrate was concentrated under reduced pressure to afford Compound 98 (100 mg) as a crude product.

LC/MS (ESI): m/z = 535 [M+H]⁺, RT = 2.72 min, LC/MS Method 1

[0197]

Step 9: Synthesis of Compound 99

The compound was synthesized in the same manner as in Step 3 of Example 6.

LC/MS (ESI): m/z = 696 [M+H]⁺, RT = 3.08 min, LC/MS Method 1

[0198]

Step 10: Synthesis of Compound 100

The compound was synthesized in the same manner as in Step 4 of Example 6.

LC/MS (ESI): m/z = 596 [M+H]⁺, RT = 2.61 min, LC/MS Method 1

[0199]

Step 11: Synthesis of Compound 101

To a solution of Compound 100 (34 mg, 0.06 mmol) in dimethylformamide (0.5 mL) were added 60 wt% sodium hydride (3.4 mg, 0.09 mmol) and methyl iodide (16 mg, 0.11 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. After adding ice water, the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 101 (26 mg, yield 75%).

LC/MS (ESI): m/z = 610 [M+H]⁺, RT = 3.04 min, LC/MS Method 1

[0200]

Step 12: Synthesis of Compound 102

The compound was synthesized in the same manner as in Step 2

of Example 4.

LC/MS (ESI): m/z = 582 [M+H]⁺, RT = 2.25 min, LC/MS Method 1

[0201]

Step 13: Synthesis of Compound (I-270)

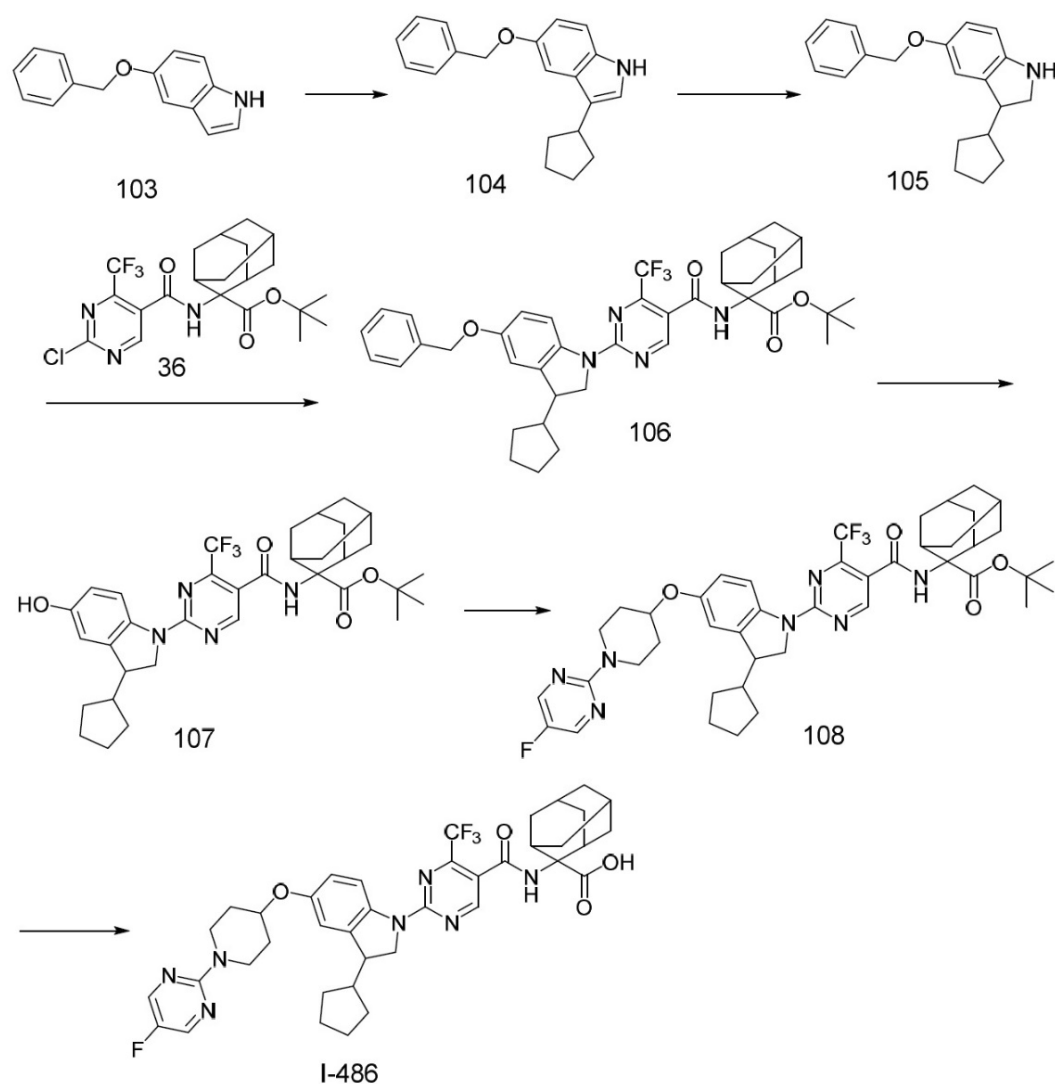
The compound was synthesized in the same manner as in Step 6 of Example 6.

¹H-NMR (CDCl₃) δ: 1.78-2.32 (m, 20H), 2.70 (s, 2H), 3.48 (t, J = 11.0 Hz, 2H), 3.73 (ddd, J = 13.2, 8.3, 4.1 Hz, 2H), 3.91-3.94 (m, 4H), 4.08-4.15 (m, 2H), 4.19 (dq, J = 13.2, 4.1 Hz, 2H), 4.59-4.65 (m, 1H), 6.14 (s, 1H), 6.49 (t, J = 4.7 Hz, 1H), 6.90-6.91 (m, 2H), 7.60 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.33 (d, J = 4.7 Hz, 2H), 12.12 (s, 1H).

[0202]

Example 12

Synthesis of Compound (I-486)



Step 1: Synthesis of Compound 104

A solution of triethylsilane (1.7 mL, 10.75 mmol) and trichloroacetic acid (1.1 g, 6.72 mmol) in toluene (5 mL) was stirred at 70°C, and a solution of Compound 103 (1 g, 4.48 mmol) and cyclopentanone (414 mg, 4.93 mmol) in toluene (10 mL) was added dropwise. The mixture was stirred at 70°C for 40 min. The mixture was cooled to room temperature, and 10% aqueous sodium carbonate solution was added. The mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 104 (600

mg, yield 46%).

LC/MS (ESI): m/z = 292 [M+H]⁺, RT = 2.98 min, LC/MS Method 1

[0203]

Step 2: Synthesis of Compound 105

Compound 104 (570 mg, 1.96 mmol) was dissolved in acetic acid (2 mL), and sodium cyanoborohydride (246 mg, 3.91 mmol) was added under ice-cooling. After stirring at room temperature for 50 minutes, aqueous potassium carbonate solution was added to neutralize the mixture. The mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 105 (340 mg, yield 59%).

LC/MS (ESI): m/z = 294 [M+H]⁺, RT = 1.74 min, LC/MS Method 1

[0204]

Step 3: Synthesis of Compound 106

Compound 36 (266 mg, 0.58 mmol), diisopropylamine (0.2 mL, 1.16 mmol) and Compound 105 (170 mg, 0.58 mmol) were dissolved in 1,4-dioxane (2.55 mL) and stirred at 90°C for 1 hour. Water was added, followed by extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by amino column chromatography (hexane-ethyl acetate) to afford Compound 106 (330 mg, yield 80%).

LC/MS (ESI): m/z = 717 [M+H]⁺, RT = 2.96 min, LC/MS Method 7

[0205]

Step 4: Synthesis of Compound 107

The compound was synthesized in the same manner as in Step 4 of Example 3.

LC/MS (ESI): m/z = 627 [M+H]⁺, RT = 3.42 min, LC/MS Method 1

[0206]

Step 5: Synthesis of Compound 108

The compound was synthesized in the same manner as in Step 5 of Example 3.

LC/MS (ESI): m/z = 806 [M+H]⁺, RT = 3.12 min, LC/MS Method 7

[0207]

Step 6: Synthesis of Compound (I-486)

The compound was synthesized in the same manner as in Step 8 of Example 10.

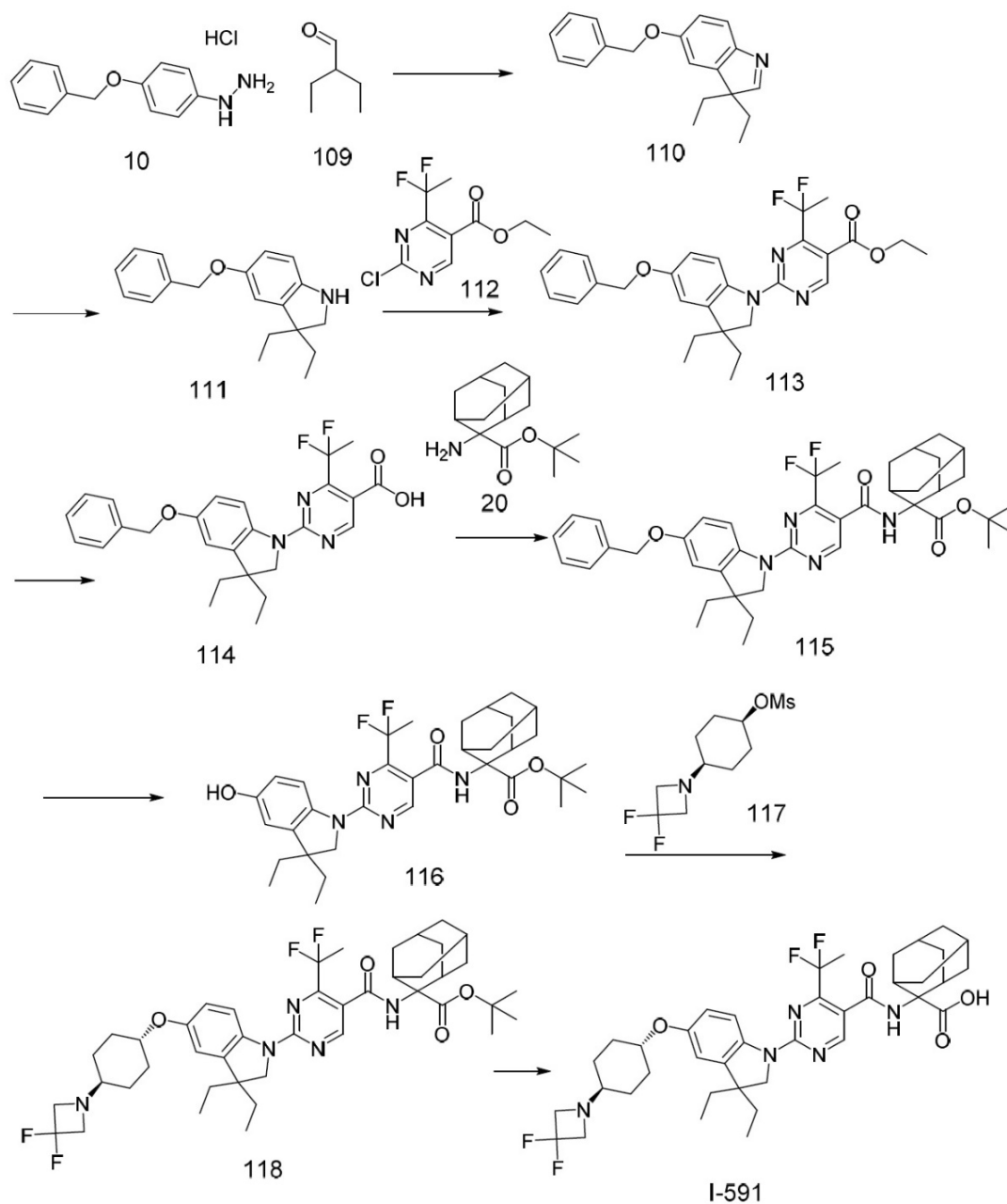
¹H-NMR (CDCl₃) δ: 1.23-1.72 (m, 5H), 1.81 (dd, J = 14.9, 7.5 Hz, 9H), 1.95-1.99 (m, 8H), 2.15-2.21 (m, 3H), 2.68 (s, 2H), 3.38-3.41 (m, 1H), 3.66-3.68 (m, 2H), 4.09-4.14 (m, 3H), 4.28 (t, J = 10.5 Hz, 1H), 4.50-4.53 (m, 1H), 6.02 (s, 1H), 6.86-6.92 (m, 2H), 8.20 (s, 2H), 8.28 (d, J = 8.3 Hz, 1H), 8.78 (s, 1H), 12.34 (s, 1H).

LC/MS (ESI): m/z = 750 [M+H]⁺, RT = 3.56 min, LC/MS Method 1

[0208]

Example 13

Synthesis of Compound (I-591)



Step 1: Synthesis of Compound 110

Compound 10 (42g, 166 mmol) and Compound 109 (16.6 g, 166 mmol) were suspended in dichloromethane (250 mL) and cooled under ice bath. Trifluoroacetic acid (25.6 mL, 332 mmol) was added, and the mixture was warmed to 45°C, and stirred for 5 hours. The mixture was cooled under ice bath, and neutralized by the addition of aqueous sodium carbonate solution, followed by extraction with chloroform. The organic layer was washed with water and dried over

anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 110 (8.9 g, yield 19%).

LC/MS (ESI): m/z = 280 $[M+H]^+$, RT=2.59 min, LC/MS Method 1

[0209]

Step 2: Synthesis of Compound 111

The Compound was synthesized in the same manner as in Step 2 of Example 3.

LC/MS (ESI): m/z = 282 $[M+H]^+$, RT=1.57 min, LC/MS Method 1

[0210]

Step 3: Synthesis of Compound 113

The Compound was synthesized in the same manner as in Step 3 of Example 3.

LC/MS (ESI): m/z = 496 $[M+H]^+$, RT=3.60 min, LC/MS Method 1

[0211]

Step 4: Synthesis of Compound 114

The compound was synthesized in the same manner as in Step 6 of Example 3.

LC/MS (ESI): m/z = 468 $[M+H]^+$, RT=3.14 min, LC/MS Method 1

[0212]

Step 5: Synthesis of Compound 115

Compound 114 (570 mg, 1.22 mmol) and Compound 20 (429 mg, 1.71 mmol) were dissolved in dimethylformamide (8.6 mL), and HATU (788 mg, 2.07 mmol) and triethylamine (0.39 mL, 2.8 mmol) were added. After stirring at room temperature for 15 hours, water was added. The precipitated solid was filtered and purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 115 (740 mg, yield 87%).

LC/MS (ESI): m/z = 701 $[M+H]^+$, RT= 3.88 min, LC/MS Method 1

[0213]

Step 6: Synthesis of Compound 116

The compound was synthesized in the same manner as in Step 4 of Example 3.

LC/MS (ESI): m/z = 611 [M+H]⁺, RT = 1.42 min, LC/MS Method 7

[0214]

Step 7: Synthesis of Compound 118

Compound 116 (70 mg, 0.115 mmol) was dissolved in dimethylformamide (1.05 mL). Cesium carbonate (45 mg, 0.14 mmol) and Compound 117 (31 mg, 0.11 mmol) were added, and the mixture was stirred at 90°C for 1 hour. The same amount of cesium carbonate and Compound 117 were added four times every 30 minutes. After confirming the consumption of starting material, water was added to quench the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by amino column chromatography (hexane-ethyl acetate) to afford Compound 118 (63 mg, yield 70%).

LC/MS (ESI): m/z = 784 [M+H]⁺, RT = 3.17 min, LC/MS Method 1

[0215]

Step 8: Synthesis of Compound (I-591)

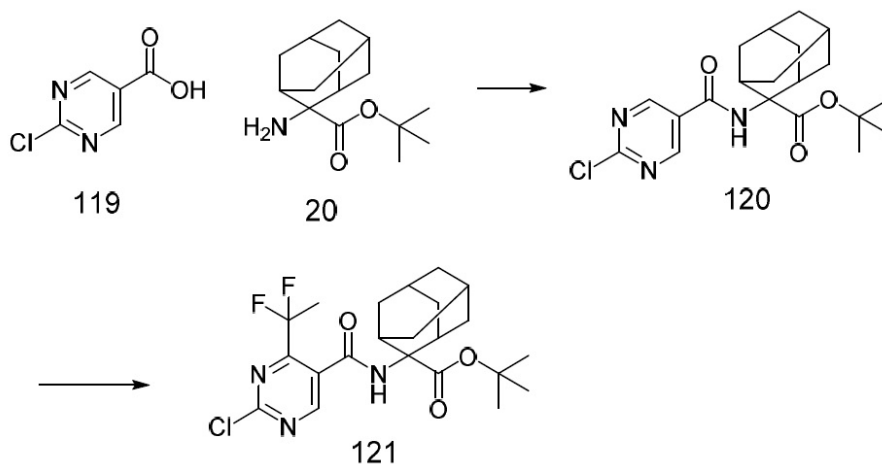
The compound was synthesized in the same manner as in Step 8 of Example 10.

¹H-NMR (DMSO-d₆) δ: 0.70 (t, J = 7.3 Hz, 6H), 1.12-1.24 (m, 2H), 1.29-1.39 (m, 2H), 1.53-1.78 (m, 14H), 1.98-2.24 (m, 10H), 2.50-2.55 (m, 2H), 3.54 (t, J = 12.4 Hz, 4H), 3.95 (s, 2H), 4.26-4.29 (m, 1H), 6.81-6.83 (m, 2H), 8.16 (d, J = 8.8 Hz, 1H), 8.29 (s, 1H), 8.47 (s, 1H), 12.27 (br s, 1H).

[0216]

Example 14

Synthesis of Compound (I-594)



Step 1: Synthesis of Compound 120

Compound 119 (3 g, 18.9 mmol) was dissolved in dichloromethane (30 mL), and oxalyl chloride (1.8 mL, 20.8 mmol) and dimethylformamide (0.15 mL, 1.9 mmol) were added under ice-cooling. After stirring at room temperature for 1 hour, the reaction solution was concentrated under reduced pressure.

The residue was dissolved in dichloromethane (5 mL), and added dropwise to a solution of Compound 20 (4.76 g, 18.9 mmol) and triethylamine (5.3 mL, 37.8 mmol) in dichloromethane (30 mL) under ice-cooling. After 1 hour, the reaction was quenched by adding water, followed by extraction with chloroform. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was suspended in ethyl acetate and diisopropyl ether. The solid was filtered to obtain Compound 120 (7.0 g, yield 94%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (s, 9H), 1.73–1.82 (m, 6H), 1.86–1.99 (m, 4H), 2.17 (m, 2H), 2.59 (s, 2H), 6.14 (s, 1H), 8.95 (s, 2H).

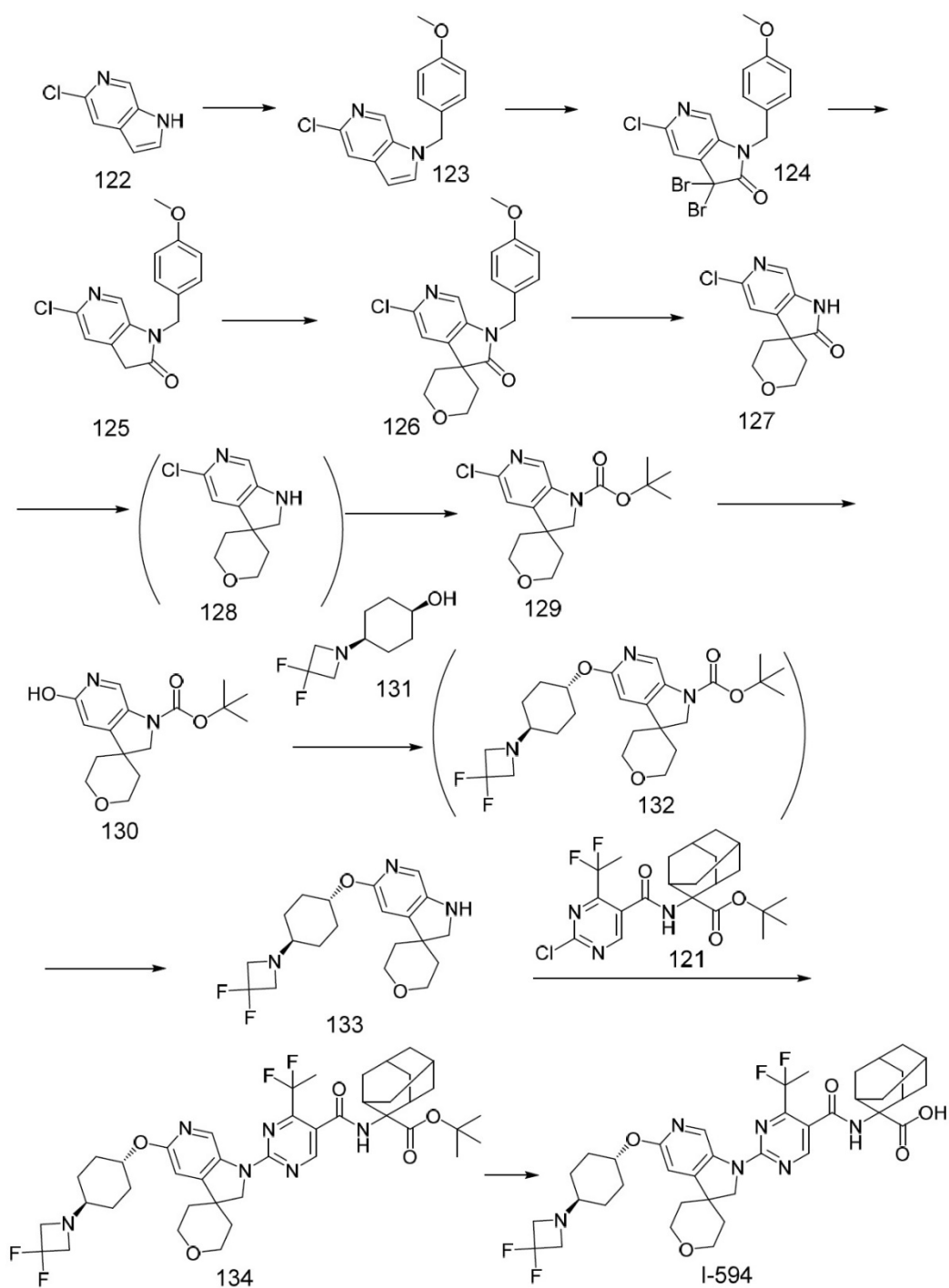
[0217]

Step 2: Synthesis of Compound 121

Compound 120 (3.8 g, 9.7 mmol) was suspended in acetonitrile (30 mL) and water (15 mL), and 2,2-difluoropropionic acid (2.1 g, 19.4 mmol), silver nitrate (4.9 g, 29.1 mmol) and ammonium persulfate (8.8 g, 38.8 mmol) were added. The mixture was warmed to 80°C, and stirred for 1 hour. The reaction was cooled under

ice bath, quenched with aqueous sodium thiosulfate solution, followed by filtration through Celite (registered trademark). The filtrate was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 121 (670 mg, yield 15%).

^1H -NMR (DMSO- d_6) δ : 1.42 (s, 9H), 1.56 (m, 2H), 1.65-1.79 (m, 4H), 1.99 (t, $J = 19.2\text{Hz}$, 3H), 2.05 (m, 4H), 2.53 (s, 2H), 8.54 (s, 1H), 8.74 (s, 1H).



Step 1: Synthesis of Compound 123

Compound 122 (51.5 g, 337 mmol) was dissolved in dimethylformamide (386 mL), and cesium carbonate (165 g, 506 mmol), 4-methoxybenzyl chloride (53.4 g, 341 mmol) were added. After stirring at room temperature for 45 minutes, water was added. The

mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was solidified by adding hexane and ethyl acetate, and filtered to obtain Compound 123 (90.9 g, yield 99%).

LC/MS (ESI): m/z = 273 [M+H]⁺, RT = 2.21 min, LC/MS Method 1

[0218]

Step 2: Synthesis of Compound 124

Compound 123 (81.2 g, 298 mmol) was dissolved in 1,4-dioxane (812 mL), and pyridinium tribromide (349 g, 1.09 mol) was added. After stirring at room temperature for 45 minutes, water was added. The mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford Compound 124 (154.6 g) as a crude product.

LC/MS (ESI): m/z = 445 [M+H]⁺, RT = 2.58 min, LC/MS Method 1

[0219]

Step 3: Synthesis of Compound 125

The crude product of Compound 124 (154.6 g) was dissolved in tetrahydrofuran (1065 mL) and methanol (266 mL) and acetic acid (42.6 mL), and zinc (97 g, 1490 mmol) was added under ice-cooling. After stirring for 1 hour, the reaction solution was filtered through Celite (registered trademark) to remove insoluble material. The filtrate was concentrated under reduced pressure, and water was added to the resulting solid. The suspension was stirred at room temperature, and the solid was filtered to obtain Compound 125 (87 g, yield 100%).

LC/MS (ESI): m/z = 289 [M+H]⁺, RT = 2.58 min, LC/MS Method 1

[0220]

Step 4: Synthesis of Compound 126

Compound 125 (220 mg, 0.76 mmol) was dissolved in dimethylformamide (3.3 mL), and cesium carbonate (745 mg, 2.29 mmol) and 2-iodoethyl ether (497 mg, 1.52 mmol) were added. After

stirring at room temperature for 3 hours, water was added. The mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 126 (245 mg, yield 90%).

LC/MS (ESI): m/z = 359 [M+H]⁺, RT=2.05 min, LC/MS Method 1

[0221]

Step 5: Synthesis of Compound 127

To Compound 126 (130 mg, 0.36 mmol) were added trifluoroacetic acid (0.52 mL) and trifluoromethanesulfonic acid (0.33 mL), and the mixture was stirred at 50°C for 1 hour. The reaction solution was poured into aqueous sodium carbonate solution and neutralized, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was solidified by adding ethyl acetate and diisopropyl ether, and the solid was filtered to obtain Compound 127 (56 mg, yield 65%).

LC/MS (ESI): m/z = 239 [M+H]⁺, RT=1.22 min, LC/MS Method 1

[0222]

Step 6: Synthesis of Compound 129

To Compound 127 (640 mg, 2.68 mmol) was added 0.91 mol/L borane-tetrahydrofuran complex-tetrahydrofuran solution (20 mL, 18.2 mmol), and the mixture was stirred at 70°C for 30 minutes. After ice cooling, methanol (10 mL) was added, and the mixture was stirred at 80°C for 30 minutes. After cooling, the reaction solution was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (10 mL). Triethylamine (1.36 g, 13.4 mmol), Boc₂O (2.92 g, 13.4 mmol), dimethylaminopyridine (327 mg, 2.68 mmol) were added, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 129 (550 mg, yield 63%).

LC/MS (ESI): m/z = 325 [M+H]⁺, RT=2.27 min, LC/MS Method 1

[0223]

Step 8: Synthesis of Compound 130

Compound 129 (200 mg, 0.616 mmol) was dissolved in 1,4-dioxane (3 mL), and Me4tBuXphos (30 mg, 0.062 mmol), Pd₂(dba)₃ (28 mg, 0.031 mmol), 6 mol/L aqueous potassium hydroxide solution (0.36 mL, 2.16 mmol) were added, and the mixture was stirred at 100°C for 1 hour. After cooling, the mixture was neutralized with 2 mol/L hydrochloric acid solution and extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. Ethyl acetate-diisopropyl ether was added to the residue obtained, and the precipitated solid was filtered to obtain Compound 130 (171 mg, yield 91%).

LC/MS(ESI):m/z= 307 [M+H]⁺, RT=1.42 min, LC/MS Method 1

[0224]

Step 9: Synthesis of Compound 133

Compound 130 (171 mg, 0.558 mmol) was dissolved in tetrahydrofuran (2 mL), and triphenylphosphine (293 mg, 1.12 mmol), Compound 131 (213 mg, 1.12 mmol) and DIAD (226 mg, 1.12 mmol) were added, and the mixture was stirred at room temperature. After 30 minutes, triphenylphosphine (293 mg, 1.12 mmol), Compound 131 (213 mg, 1.12 mmol) and DIAD (226 mg, 1.12 mmol) were added. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure.

Trifluoroacetic acid (4 mL) was added to the residue and stirred at room temperature for 1 hour. The reaction solution was concentrated. Dichloromethane was added to the residue to dissolve. Aqueous sodium bicarbonate solution was added to neutralize, and the layers were separated. The aqueous layer was extracted with dichloromethane, and the organic layers were combined and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 133 (212 mg, yield 100%).

LC/MS(ESI):m/z= 380 [M+H]⁺, RT=0.80 min, LC/MS Method 1

[0225]

Step 10: Synthesis of Compound 134

Compound 133 (70 mg, 0.184 mmol) was dissolved in 1,4-dioxane (2 mL), and Compound 121 (101 mg, 0.221 mmol), potassium carbonate (76 mg, 0.552 mmol), Xanthos Pd G3 (26 mg, 0.028 mmol) were added. The mixture was stirred at 80°C for 90 minutes under a nitrogen atmosphere. Water was added and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 134 (66 mg, yield 45%). LC/MS (ESI): m/z = 799 [M+H]⁺, RT = 2.49 min, LC/MS Method 8

[0226]

Step 11: Synthesis of Compound (I-594)

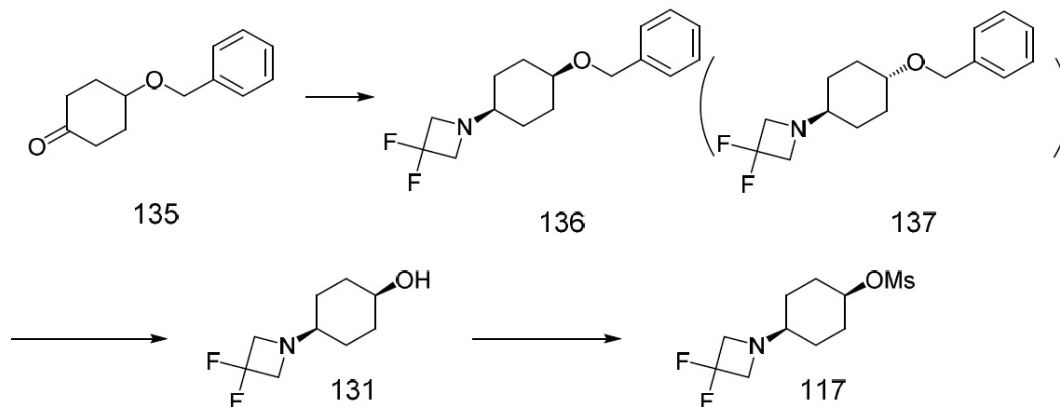
Compound 134 (66 mg, 0.083 mmol) was dissolved in trifluoroacetic acid (4 mL) and stirred at room temperature for 1 hour. The reaction solution was concentrated, dissolved in dichloromethane, and neutralized with aqueous sodium bicarbonate solution. The reaction solution was made acidic again by adding aqueous citric acid solution, and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed, and the residue was purified by silica gel column chromatography (chloroform-methanol) to afford compound (I-594) (37 mg, yield 60%).

¹H-NMR (DMSO-d₆) δ: 1.12-1.24 (m, 2H), 1.35-1.43 (m, 2H), 1.53-1.79 (m, 12H), 1.90-2.14 (m, 11H), 2.20-2.26 (m, 1H), 2.56 (s, 2H), 3.50-3.58 (m, 6H), 3.87-3.90 (m, 2H), 4.21 (s, 2H), 4.88-4.95 (m, 1H), 6.85 (s, 1H), 8.37 (brs, 1H), 8.54 (s, 1H), 8.91 (s, 1H), 12.33 (brs, 1H).

[0227]

(Reference Example)

Synthesis of Compound 117 and Compound 131



Step 1: Synthesis of Compound 131 and Compound 117

Compound 135 (1.0 g, 4.90 mmol) was dissolved in dichloromethane (10 mL), and 3,3-Difluoroazetidine hydrochloride (1.27 g, 9.79 mmol), triethylamine (1.26 mL, 9.79 mmol), acetic acid (0.28 mL, 4.90 mmol) and sodium triacetoxyborohydride (2.08 g, 9.79 mmol) were added and stirred for 3 hours. Water was added, followed by extraction with chloroform. The organic layer was washed with water and dried over anhydrous sodium sulfate. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford Compound 136 (846 mg, 61% yield) and Compound 137 (454 mg, yield 33%).

Compound 136

$^1\text{H-NMR}$ (CDCl_3) δ : 1.44–1.60 (m, 6H), 1.90–1.96 (m, 2H), 2.14–2.19 (m, 1H), 3.53 (t, $J = 12.4\text{Hz}$, 4H), 3.55 (m, 1H), 4.50 (s, 2H), 7.23–7.28 (m, 1H), 7.30–7.36 (m, 4H).

LC/MS (ESI): $m/z = 282$ $[\text{M}+\text{H}]^+$, $\text{RT} = 1.24$ min, LC/MS Method 1

Compound 137

$^1\text{H-NMR}$ (CDCl_3) δ : 1.08–1.18 (m, 2H), 1.26–1.39 (m, 2H), 1.77–1.81 (m, 2H), 2.05–2.15 (m, 3H), 3.33–3.40 (m, 1H), 3.54 (t, $J = 11.6\text{Hz}$, 4H), 4.54 (s, 2H), 7.25–7.30 (m, 1H), 7.31–7.34 (m, 4H).

LC/MS (ESI): $m/z = 282$ $[\text{M}+\text{H}]^+$, $\text{RT} = 1.20$ min, LC/MS Method 1

[0228]

Step 2: Synthesis of Compound 131

Compound 136 (0.72 g, 2.55 mmol) was dissolved in ethanol (10.7 mL), and 10 wt% palladium carbon (1.09 g, 0.51 mmol) was added. The mixture was stirred at 50°C for 3 hours under hydrogen atmosphere. The reaction solution was filtered through Celite (registered trademark), and the filtrate was concentrated under reduced pressure to afford Compound 131 (0.42 g, yield 86%).

Compound 131

¹H-NMR (CDCl₃) δ: 1.30 (brs, 1H), 1.44-1.61 (m, 6H), 1.69-1.79 (m, 2H), 2.20 (m, 1H), 3.53 (t, J = 12.0Hz, 4H), 3.81 (m, 1H).

[0229]

Step 3: Synthesis of Compound 117

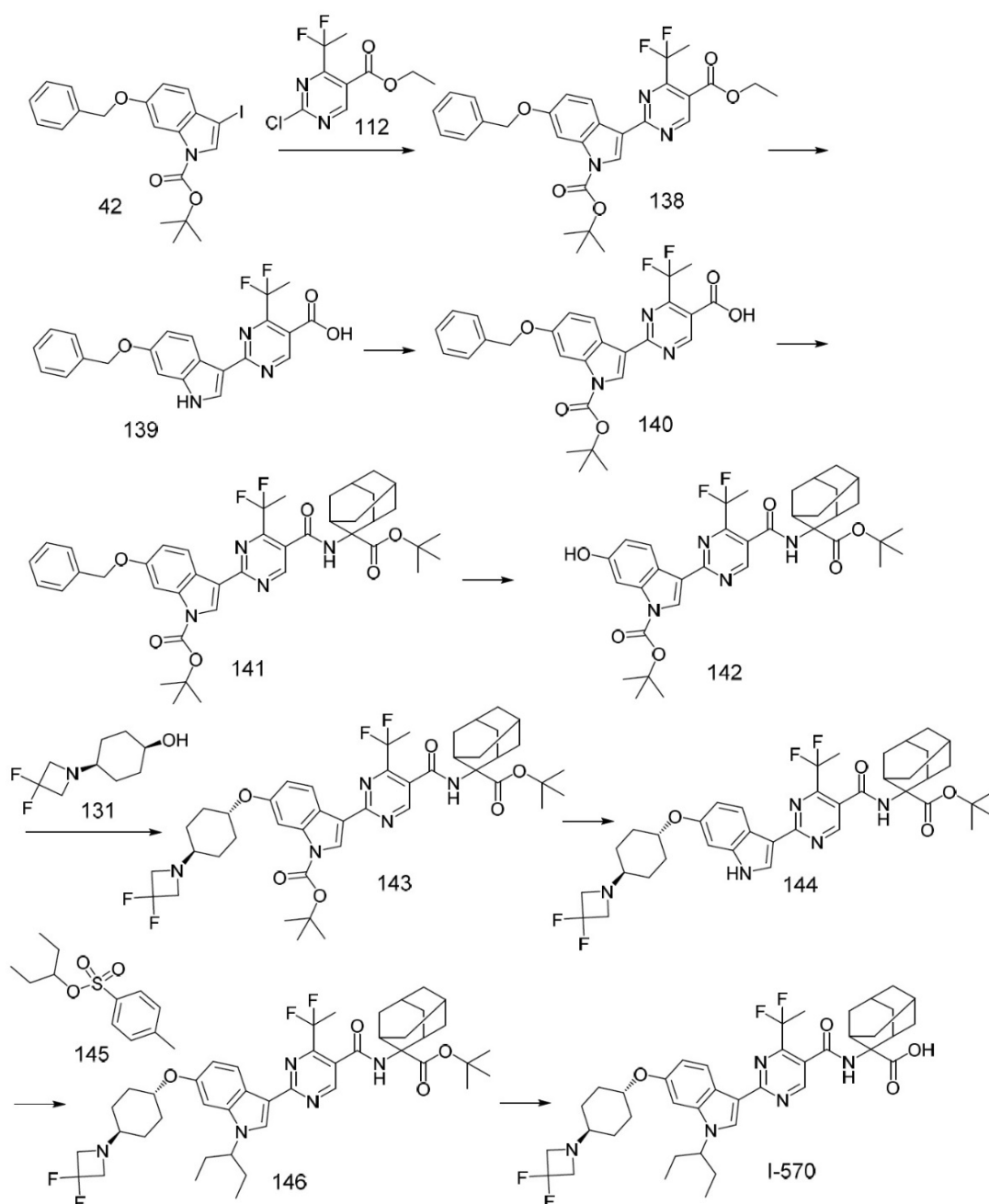
Compound 131 (300 mg, 1.57 mmol) was dissolved in dichloromethane (3 mL), and triethylamine (0.44 mL, 3.14 mmol) and methanesulfonyl chloride (0.18 mL, 2.35 mmol) were added under ice-cooling. After 1 hour 30 minutes, aqueous ammonium chloride solution was added, followed by extraction with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to afford Compound 117 (419 mg, yield 99%).

¹H-NMR (CDCl₃) δ: 1.53-1.59 (m, 4H), 1.62-1.72 (m, 2H), 2.03-2.13 (m, 2H), 2.23 (m, 1H), 3.00 (s, 3H), 3.54 (t, J = 12.0Hz, 4H), 4.86 (m, 1H).

[0230]

Example 15

Synthesis of Compound (I-570)



Step 1: Synthesis of Compound 138

The compound was synthesized in the same manner as in Step 1 of Example 6.

$^1\text{H-NMR}$ (DMSO-d_6) δ : ppm 1.33 (t, $J=7.15$ Hz, 3 H), 1.67 (s, 9 H),

2.17 (t, J=19.32 Hz, 3 H), 4.38 (q, J=7.15 Hz, 2 H), 5.21 (s, 2 H), 7.16 (dd, J=8.9, 2.3 Hz, 1 H), 7.32-7.38 (m, 1 H), 7.39-7.44 (m, 2 H), 7.48-7.52 (m, 2 H), 7.82 (d, J=2.1 Hz, 1 H), 8.43 (s, 1 H), 8.45 (d, J=8.9 Hz, 1 H), 9.19 (s, 1 H).

LC/MS(DUIS):m/z= 538 [M+H]⁺, RT=2.08 min, LC/MS Method 9

[0231]

Step 2: Synthesis of Compound 139

To a solution of Compound 138 (7.48 g, 13.9 mmol) in tetrahydrofuran (59.8 mL), methanol (29.9 mL) and water (15.0 mL) was added lithium hydroxide monohydrate (2.92 g, 69.6 mmol) at room temperature, and the mixture was stirred for 5 hours at room temperature. After completion of the reaction, the mixture was concentrated under reduced pressure, and the residue was diluted with water and neutralized with 2 mol/L hydrochloric acid (35 mL, 70.0 mmol), and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford Compound 139 (4.81 g, yield 84%).

¹H-NMR (DMSO-d₆) δ: ppm 2.14 (t, J=19.1 Hz, 3 H), 5.16 (s, 2 H), 6.96 (dd, J=8.8, 2.3 Hz, 1 H), 7.07 (d, J=2.3 Hz, 1 H), 7.29-7.37 (m, 1 H), 7.38-7.45 (m, 2 H), 7.47-7.52 (m, 2 H), 8.23 (d, J=2.9 Hz, 1 H), 8.34 (d, J=8.7 Hz, 1 H), 9.00 (s, 1 H), 11.76 (d, J=2.4 Hz, 1 H), 13.45 (br s, 1 H).

LC/MS(DUIS):m/z= 410 [M+H]⁺, RT=1.32 min, LC/MS Method 9

[0232]

Step 3: Synthesis of Compound 140

To a solution of Compound 139 (4.8 g, 11.72 mmol) in dichloromethane (48.0 mL) and dimethylformamide (2.0 mL) were added triethylamine (2.45 mL, 17.58 mmol), Boc₂O (3.23 mL, 14.06 mmol) and DMAP (72 mg, 0.59 mmol) at room temperature with stirring under argon flow, and the mixture was stirred at room temperature for 4 hours. After completion of the reaction, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with 0.5 mol/L hydrochloric acid and brine, dried

over anhydrous magnesium sulfate, and concentrated under reduced pressure. Then hexane-ethyl acetate mixture was added, and the mixture was sonicated and filtered. Washing with additional hexane-ethyl acetate mixture and drying to afford Compound 140 (2.46 g, yield 41%).

¹H-NMR (DMSO-d₆) δ: ppm 1.67 (s, 9 H), 2.16 (t, J=19.3 Hz, 3 H), 5.21 (s, 2 H), 7.16 (dd, J=8.8, 2.4 Hz, 1 H), 7.32-7.37 (m, 1 H), 7.39-7.44 (m, 2 H), 7.48-7.52 (m, 2 H), 7.83 (d, J=2.3 Hz, 1 H), 8.42 (s, 1 H), 8.46 (d, J=8.8 Hz, 1 H), 9.17 (s, 1 H), 13.81 (br s, 1 H).

LC/MS(DUIS):m/z= 510 [M+H]⁺, RT=1.79 min, LC/MS Method 9

[0233]

Step 4: Synthesis of Compound 141

The compound was synthesized in the same manner as in Step 3 of Example 4.

¹H-NMR (DMSO-d₆) δ: ppm 1.45 (s, 9 H), 1.54-1.60 (m, 2 H), 1.67 (s, 9 H), 1.68-1.73 (m, 4 H), 1.77-1.86 (m, 2 H), 2.10 (t, J=19.2 Hz, 3 H), 2.00-2.18 (m, 4 H), 2.52-2.57 (m, 2 H), 5.21 (s, 2 H), 7.16 (dd, J=8.9, 2.3 Hz, 1 H), 7.32-7.37 (m, 1 H), 7.39-7.44 (m, 2 H), 7.48-7.52 (m, 2 H), 7.82 (d, J=2.4 Hz, 1 H), 8.40 (s, 1 H), 8.48 (d, J=8.8 Hz, 1 H), 8.56 (br s, 1 H), 8.79 (s, 1 H).

LC/MS(DUIS):m/z= 743 [M+H]⁺, RT=2.37 min, LC/MS Method 9

[0234]

Step 5: Synthesis of Compound 142

The compound was synthesized in the same manner as in Step 2 of Example 6.

¹H-NMR (DMSO-d₆) δ: ppm 1.45 (s, 9 H), 1.57 (m, 2 H), 1.62-1.73 (m, 4 H), 1.67 (s, 9 H), 1.78-1.84 (m, 2 H), 2.10 (t, J=19.1 Hz, 3 H), 2.00-2.18 (m, 4 H), 2.51-2.55 (m, 2 H), 6.89 (dd, J=8.7, 2.3 Hz, 1 H), 7.63 (d, J=2.1 Hz, 1 H), 8.32 (s, 1 H), 8.36 (d, J=8.7 Hz, 1 H), 8.55 (br s, 1 H), 8.77 (s, 1 H), 9.68 (s, 1 H).

LC/MS(DUIS):m/z= 653 [M+H]⁺, RT=1.92 min, LC/MS Method 9

[0235]

Step 6: Synthesis of Compound 143

The compound was synthesized in the same manner as in Step 5 of Example 3.

¹H-NMR (DMSO-d₆) δ: ppm 1.12-1.25 (m, 2 H), 1.39-1.51 (m, 2 H), 1.45 (s, 9 H), 1.54-1.62 (m, 2 H), 1.68 (s, 9 H), 1.69-1.73 (m, 4 H), 1.75-1.85 (m, 4 H), 2.10 (t J=19.1 Hz, 3 H), 2.01-2.18 (m, 6 H), 2.21-2.30 (m, 1 H), 2.52-2.55 (m, 2 H), 3.55 (t, J=12.3 Hz, 4 H), 4.32-4.42 (m, 1 H), 7.06 (dd, J=8.8, 2.3 Hz, 1 H), 7.69 (d J=2.1 Hz, 1 H), 8.40 (s, 1 H), 8.45 (d, J=8.8 Hz, 1 H), 8.55 (br s, 1 H), 8.78 (s, 1 H).

LC/MS(DUIS):m/z= 826 [M+H]⁺, RT=1.88 min, LC/MS Method 9

[0236]

Step 7: Synthesis of Compound 144

The compound was synthesized in the same manner as in Step 2.

¹H-NMR (DMSO-d₆) δ ppm 1.12-1.24 (m, 2 H), 1.37-1.42 (m, 2 H), 1.45 (s, 9 H), 1.53-1.61 (m, 2 H), 1.65-1.74 (m, 4 H), 1.75-1.85 (m, 4 H), 2.08 (t, J=19.0 Hz, 3 H), 2.00-2.19 (m, 6 H), 2.20-2.28 (m, 1 H), 2.52-2.55 (m, 2 H), 3.55 (t, J=12.4 Hz, 4 H), 4.25-4.37 (m, 1 H), 6.86 (dd, J=8.8, 2.3 Hz, 1 H), 7.00 (d, J=2.3Hz, 1 H) 8.19 (d, J=2.8 Hz, 1 H), 8.32 (d, J=8.8 Hz, 1 H), 8.46 (s, 1 H), 8.64 (s, 1 H), 11.62 (d, J=2.6 Hz, 1 H).

LC/MS(DUIS):m/z= 726 [M+H]⁺, RT=1.47 min, LC/MS Method 9

[0237]

Step 8: Synthesis of Compound 146

To a solution of Compound 144 (50 mg, 0.07 mmol) in N-methylpyrrolidone (1.0 mL) were added cesium carbonate (67 mg, 0.21 mmol) and Compound 145 (50 mg, 0.21 mmol) at room temperature with stirring under argon flow, and the mixture was stirred at 100°C for 2 hours. Then, cesium carbonate (67 mg, 0.21 mmol) and Compound 145 (50 mg, 0.21 mmol) were added, and the mixture was stirred at 100°C for 3 hours. Further, cesium carbonate (67 mg, 0.21 mmol) and Compound 145 (50 mg, 0.21 mmol) were added, and the mixture was stirred at 100°C for 4 hours. After completion of

the reaction, water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate). Further purification by amino column chromatography (hexane-ethyl acetate) afforded Compound 146 (42 mg, 77%).

$^1\text{H-NMR}$ (DMSO-d_6) δ : ppm 0.72 (t, $J=7.3$ Hz, 6 H), 1.19-1.28 (m, 2 H), 1.35-1.43 (m, 2 H), 1.45 (s, 9 H), 1.53-1.62 (m, 2 H), 1.65-1.72 (m, 4H), 1.74-1.83 (m, 4 H), 1.91 (qd, $J=7.2$ Hz, 4 H), 2.09 (t, $J=19.0$ Hz, 3 H), 2.01-2.18 (m, 6 H), 2.20-2.30 (m, 1 H), 2.52-2.56 (m, 2 H), 3.55 (t, $J=12.4$ Hz, 4 H), 4.32-4.47 (m, 2H), 6.89 (dd, $J=8.9, 2.1$ Hz, 1 H), 7.21 (d, $J=1.9$ Hz, 1 H), 8.24 (s, 1 H), 8.35 (d, $J=8.8$ Hz, 1 H), 8.45 (br s, 1 H), 8.63 (s, 1 H).

LC/MS(ESI): m/z = 796 $[\text{M}+\text{H}]^+$, RT=1.82 min, LC/MS Method 10

[0238]

Step 9: Synthesis of Compound (I-570)

The compound was synthesized in the same manner as in Step 8 of Example 10.

$^1\text{H-NMR}$ (DMSO-d_6) δ : ppm 0.71 (t, $J=7.3$ Hz, 6 H), 1.18-1.29 (m, 2 H), 1.34-1.47 (m, 2 H), 1.48-1.59 (m, 2 H), 1.59-1.73 (m, 4 H), 1.75-1.83 (m, 4 H), 1.86-1.94 (m, 4 H), 2.08 (t, $J=19.0$ Hz, 3H), 2.00-2.18 (m, 6 H), 2.19-2.28 (m, 1 H), 2.55-2.61 (m, 2 H), 3.55 (t, $J=12.4$ Hz, 4 H), 4.34-4.47 (m, 2 H), 6.88 (dd, $J=8.9, 2.1$ Hz, 1 H), 7.20 (d, $J=1.9$ Hz, 1 H), 8.21 (s, 1 H), 8.35 (d, $J=8.8$ Hz, 1 H), 8.46 (br s, 1 H), 8.64 (s, 1 H), 12.45 (br s, 1 H).

LC/MS(DUIS): m/z = 740 $[\text{M}+\text{H}]^+$, RT=1.36 min, LC/MS Method 9

[0239]

The following compounds were synthesized according to the above general synthesis methods and the Examples as described above.

In the structural formula, "wedge-shaped" and "dashed line" indicate stereo configuration. In particular, for compounds where the stereo configuration is indicated, the column of "stereochemistry" is defined as follows.

blank: as indicated

a: racemate

b: single isomer, but its stereochemistry is unknown

c: diastereomeric mixture, provided that I-273, I-371, I-376, I-403, I-414, I 451, I-11, I-12 and I-13 include their racemates.

d: the configuration of the substituent group of $Z^c(R^7)$ is as indicated, and the configuration of the substituent group of R^4 is unknown

e: the configuration of the substituent group of $Z^c(R^7)$ is unknown, and the configuration of the substituent group of R^4 is as indicated

f: racemate, and the relative configuration of cis/trans is single but unknown.

[0240]

[Table 1]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-1		551	2.76	1	
I-2		537	2.57	2	
I-3		571	2.72	3	
I-4		555	2.87	3	
I-5		532	2.35	3	
I-6		565	2.49	3	
I-7		523	2.42	3	
I-8		563	2.54	3	

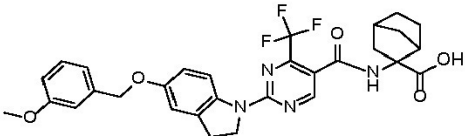
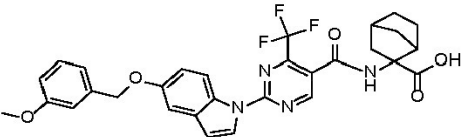
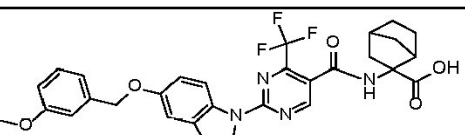
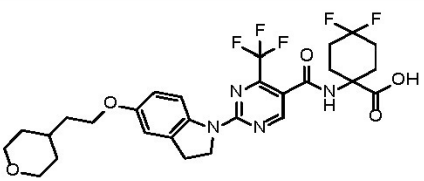
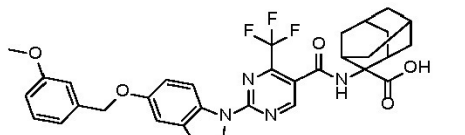
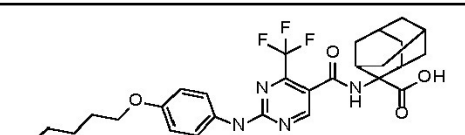
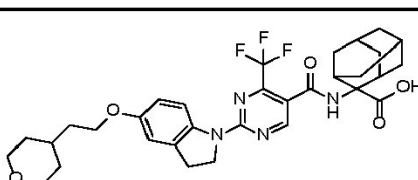
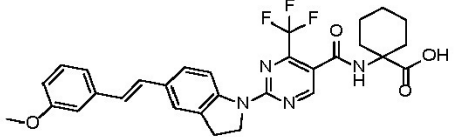
[0241]

[Table 2]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-9		555	2.75	3	
I-10		539	2.88	3	
I-11		549	2.59	3	c
I-12		575	2.55	4	c
I-13		583	2.80	4	c
I-14		573	2.43	1	
I-15		573	2.41	1	
I-16		583	2.79	1	b

[0242]

[Table 3]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-17		583	2.81	1	b
I-18		581	2.87	1	b
I-19		583	2.77	1	b
I-20		599	2.55	1	
I-21		623	3.04	1	
I-22		589	2.87	1	
I-23		615	2.90	1	
I-24		567	2.92	1	

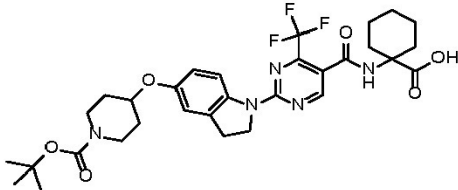
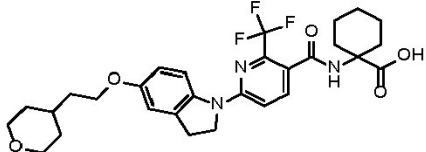
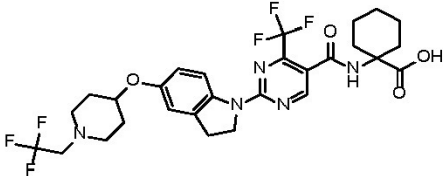
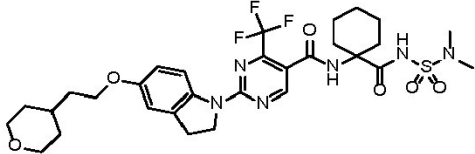
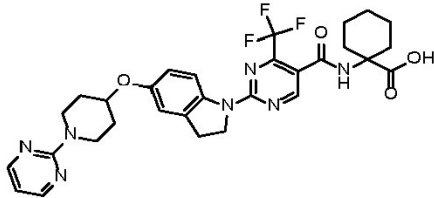
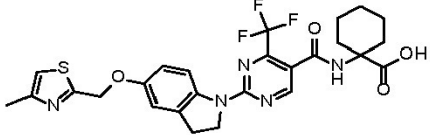
[0243]

[Table 4]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-25		569	2.97	1	
I-26		569	2.95	1	
I-27		572	2.51	1	
I-28		562	2.41	1	
I-29		601	2.74	1	
I-30		572	2.12	1	
I-31		616	2.01	1	

[0244]

[Table 5]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-32		634	2.84	1	
I-33		562	2.56	1	
I-34		616	2.54	1	
I-35		669	2.78	1	
I-36		612	2.61	1	
I-37		562	2.48	1	
I-38		711	2.71	1	

[Table 6]

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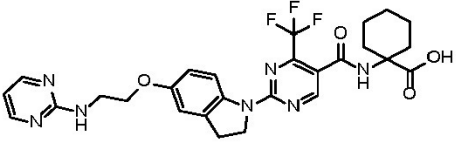
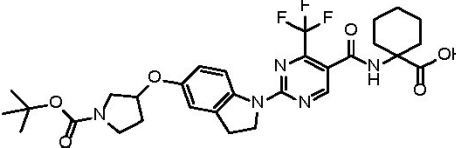
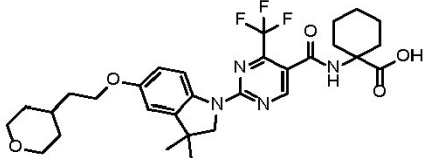
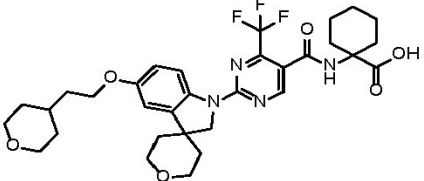
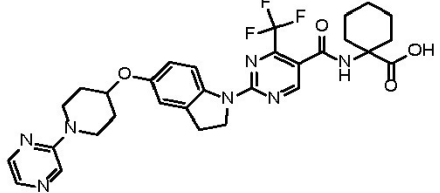
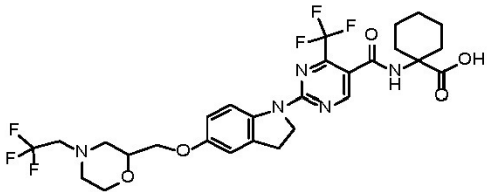
[0246]

[Table 7]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-46		584	2.33	1	
I-47		614	2.16	1	
I-48		598	2.43	1	
I-49		648	2.51	1	
I-50		626	2.70	1	a
I-51		611	2.01	1	

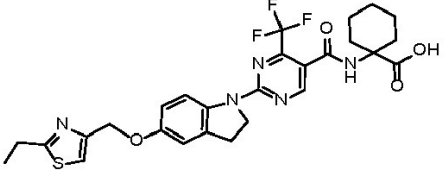
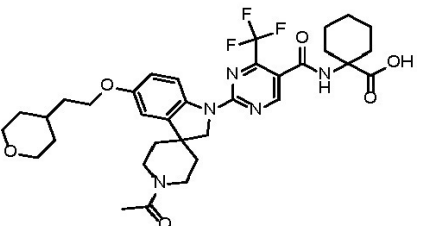
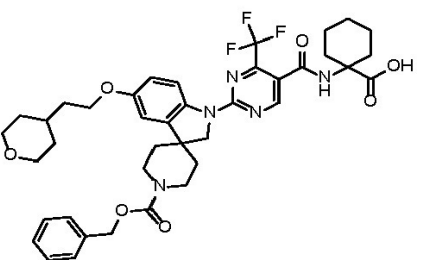
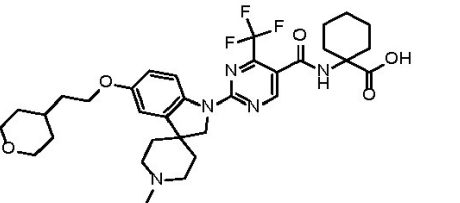
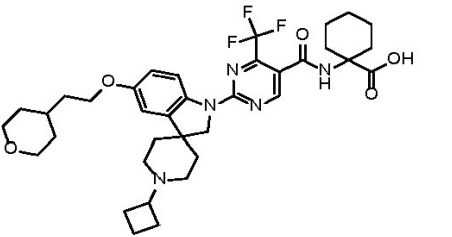
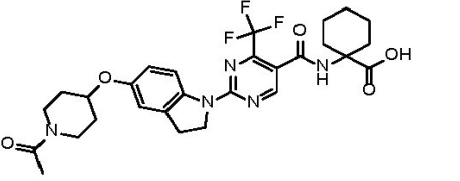
[0247]

[Table 8]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-52		572	2.07	1	
I-53		618	2.69	1	a
I-54		591	2.80	1	
I-55		631	3.09	1	
I-56		633	2.54	1	
I-57		612	2.48	1	
I-58		632	2.61	1	a

[0248]

[Table 9]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-59		576	2.59	1	
I-60		674	2.32	1	
I-61		766	2.92	1	
I-62		646	2.06	1	
I-63		686	2.32	1	
I-64		576	2.11	1	

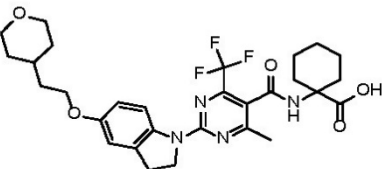
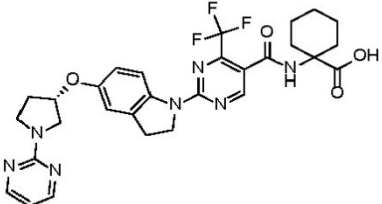
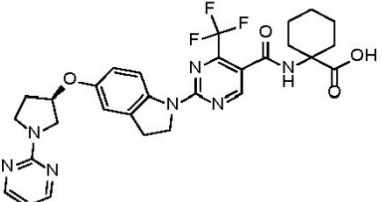
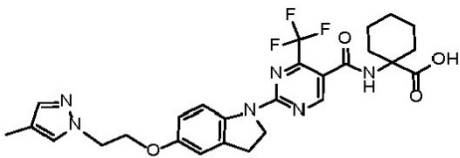
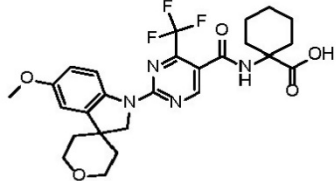
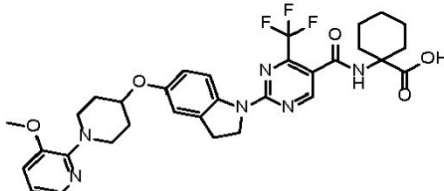
[0249]

[Table 10]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-65		604	2.38	1	
I-66		628	2.48	1	a
I-67		611	2.01	1	
I-68		517	2.69	1	
I-69		628	1.94	1	
I-70		606	2.16	1	
I-71		594	2.76	1	

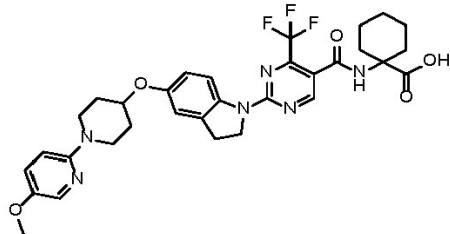
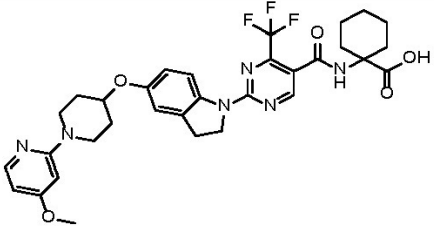
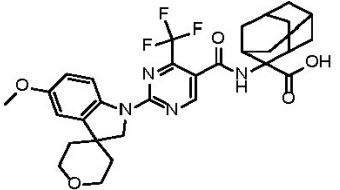
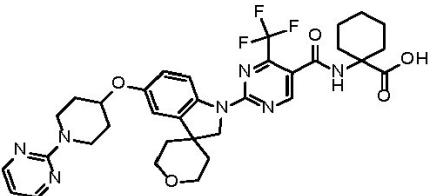
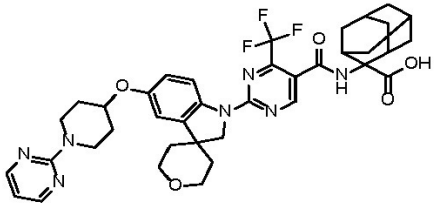
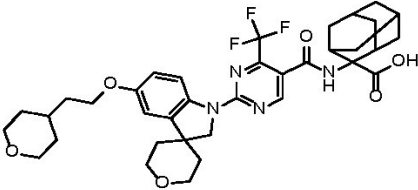
[0250]

[Table 11]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-72		577	2.66	3	
I-73		598	2.24	1	
I-74		598	2.24	1	
I-75		559	2.33	1	
I-76		535	2.35	1	
I-77		641	1.97	1	

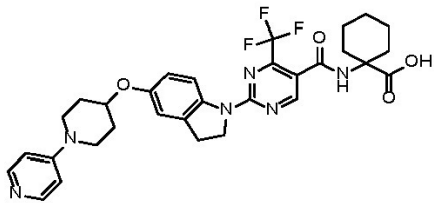
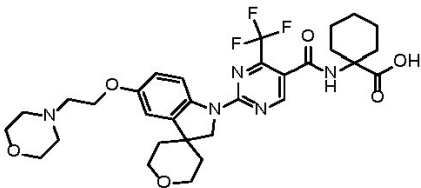
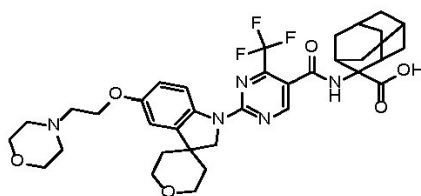
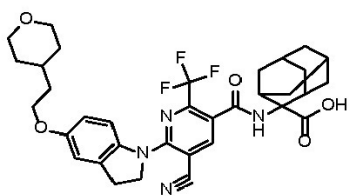
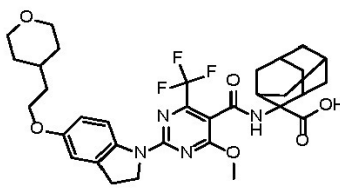
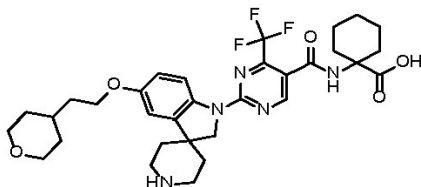
[0251]

[Table 12]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-78		641	1.94	1	
I-79		641	1.84	1	
I-80		587	2.63	1	
I-81		682	2.55	1	
I-82		734	2.85	1	
I-83		685	2.80	1	

[0252]

[Table 13]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-84		611	2.02	1	
I-85		634	1.85	3	
I-86		686	2.16	1	
I-87		639	2.85	3	
I-88		645	2.93	3	
I-89		632	2.13	1	

[0253]

[Table 14]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-90		536	2.39	3	
I-91		588	2.70	3	
I-92		696	2.39	1	
I-93		684	2.63	1	
I-94		663	2.76	1	
I-95		644	3.05	3	

[Table 15]

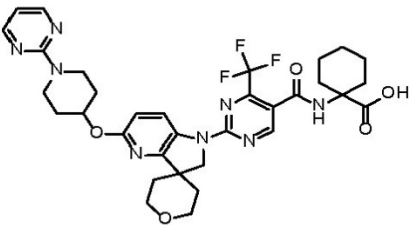
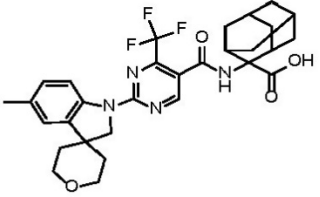
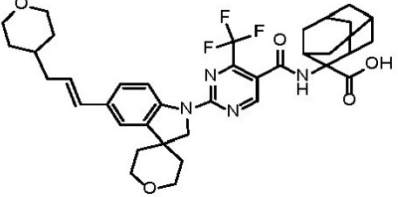
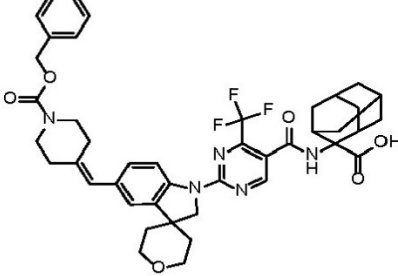
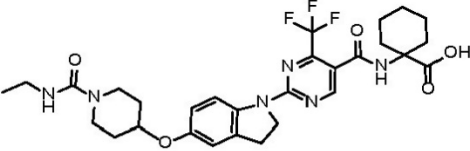
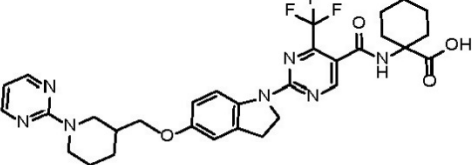
163

[Table 16]

164

[0256]

[Table 17]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-108		683	2.63	3	
I-109		571	2.82	3	
I-110		681	2.99	3	
I-111		786	3.18	3	
I-112		605	1.59	3	
I-113		626	2.02	3	a

[Table 18]

166

[0258]

[Table 19]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-120		587	2.66	3	
I-121		586	2.54	3	
I-122		570	2.81	3	
I-123		613	2.90	2	
I-124		515	2.71	2	
I-125		614	2.81	3	
I-126		615	2.52	3	

[0259]

[Table 20]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-127		627	2.89	2	
I-128		623	3.22	1	
I-129		625	3.26	1	
I-130		671	2.81	1	
I-131		697	2.82	1	
I-132		704	3.19	1	

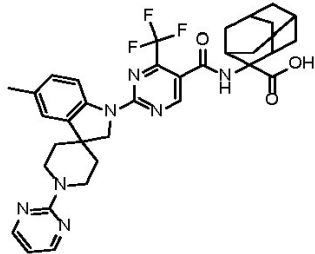
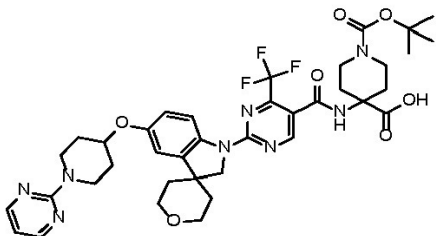
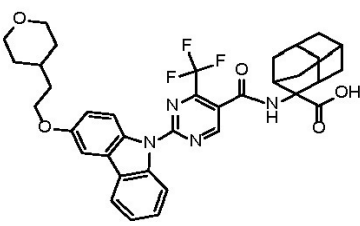
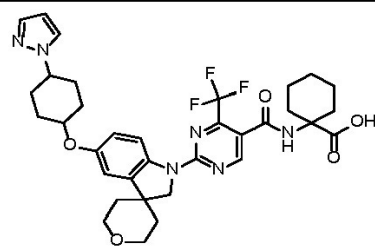
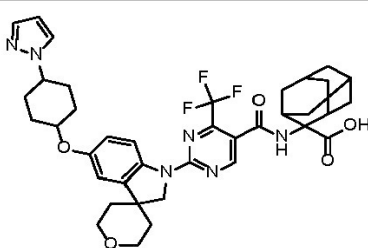
[0260]

[Table 21]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-133		585	2.94	1	
I-134		570	2.15	5	
I-135		733	2.77	1	
I-136		652	3.17	1	
I-137		628	2.86	1	
I-138		641	2.60	1	

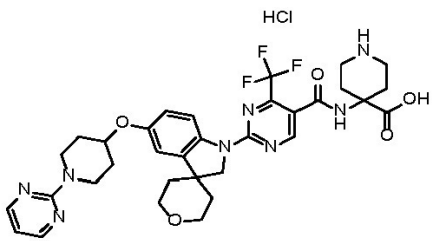
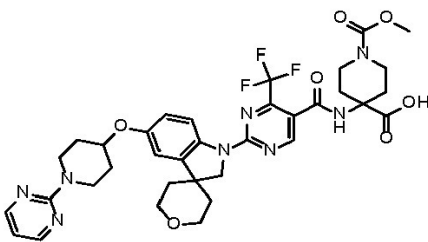
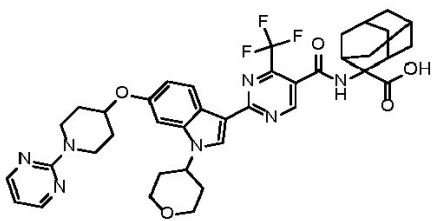
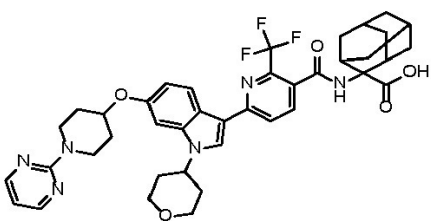
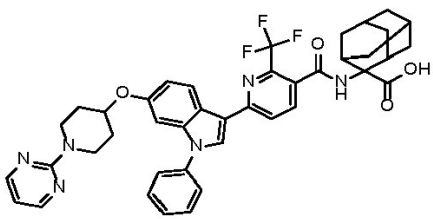
[0261]

[Table 22]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-139		648	3.09	1	
I-140		783	2.62	1	
I-141		663	3.18	1	
I-142		669	2.47	1	c
I-143		721	2.75	1	c

[0262]

[Table 23]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-144		683	1.51	3	
I-145		741	2.11	3	
I-146		746	2.57	3	
I-147		745	2.61	3	
I-148		737	2.86	3	

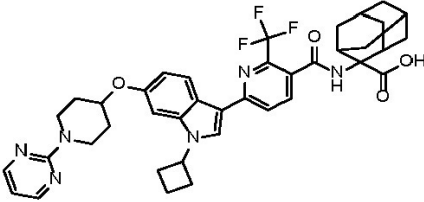
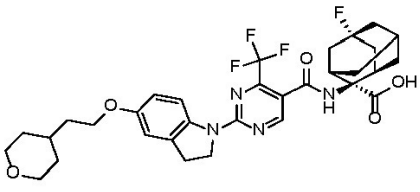
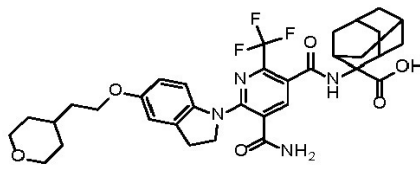
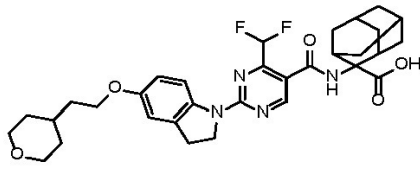
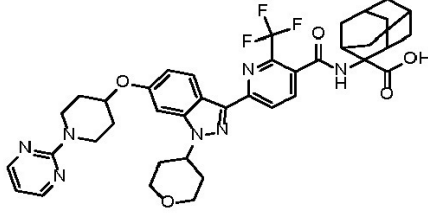
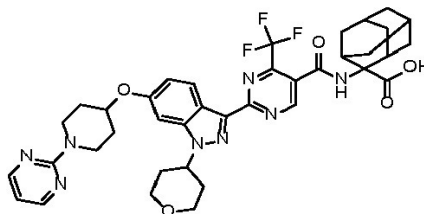
[0263]

[Table 24]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-149		788	2.60	1	
I-150		787	3.43	1	
I-151		717	2.76	1	
I-152		789	2.98	1	
I-153		715	3.03	1	

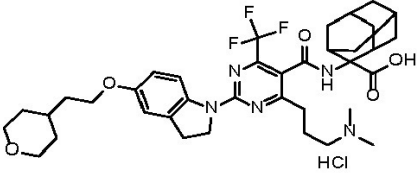
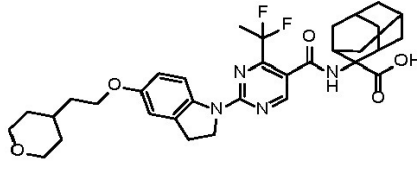
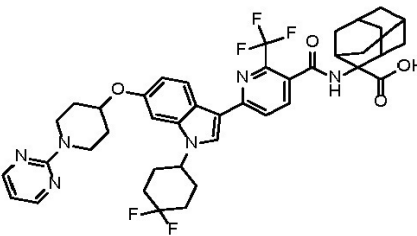
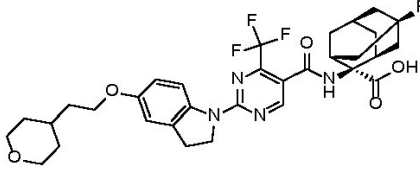
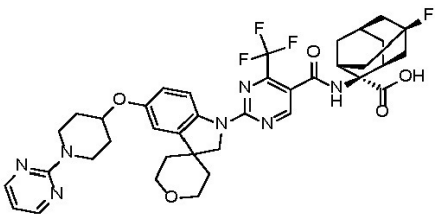
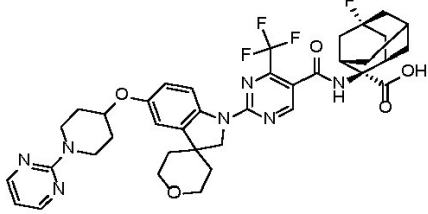
[0264]

[Table 25]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-154		715	3.10	1	
I-155		633	2.25	3	
I-156		657	2.23	3	
I-157		597	2.58	3	
I-158		746	2.95	1	
I-159		747	2.77	1	

[0265]

[Table 26]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-160		700	1.98	3	
I-161		611	2.64	3	
I-162		779	3.06	1	
I-163		633	2.53	3	
I-164		752	2.56	3	
I-165		752	2.43	3	

[0266]

[Table 27]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-166		751	2.41	3	
I-167		658	1.98	3	
I-168		805	2.05	3	
I-169		732	2.52	3	
I-170		685	1.57	3	
I-171		683	1.56	3	

[0267]

[Table 28]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-172		569	1.50	3	
I-173		747	2.70	3	
I-174		761	2.66	3	
I-175		738	3.02	1	
I-176		738	2.67	1	
I-177		738	2.79	1	

[0268]

[Table 29]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-178		625	2.70	3	
I-179		607	2.66	3	
I-180		665	2.81	3	
I-181		625	1.82	3	
I-182		747	2.83	1	
I-183		819	2.43	5	

[0269]

[Table 30]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-184		712	1.76	3	
I-185		768	2.92	1	
I-186		768	2.94	1	
I-187		645	2.56	3	
I-188		849	3.34	2	
I-189		707	2.48	2	a

[Table 31]

179

[0271]

[Table 32]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-196		739	2.53	2	
I-197		739	2.60	2	
I-198		739	2.61	2	
I-199		831	2.04	3	
I-200		705	2.44	1	
I-201		573	2.21	3	

[0272]

[Table 33]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-202		647	2.05	3	
I-203		705	2.33	3	
I-204		699	1.95	3	
I-205		746	2.47	2	
I-206		670	1.98	6	
I-207		614	1.74	1	

[0273]

[Table 34]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-208		760	2.86	3	
I-209		698	1.88	6	
I-210		764	2.23	2	b
I-211		764	2.31	2	b
I-212		682	2.06	6	
I-213		663	1.84	1	

[0274]

[Table 35]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-214		732	3.05	1	
I-215		570	2.25	1	a
I-216		584	2.33	1	a
I-217		598	2.45	1	a
I-218		759	2.37	1	
I-219		759	2.38	1	
I-220		642	1.78	1	

[0275]

[Table 36]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-221		797	2.89	1	
I-222		763	2.66	1	
I-223		698	1.89	5	
I-224		762	2.75	5	
I-225		758	1.27	9	
I-226		684	1.99	5	

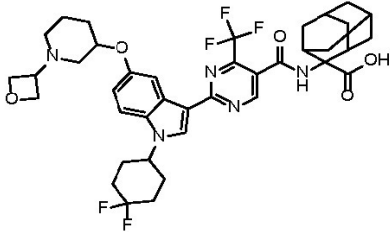
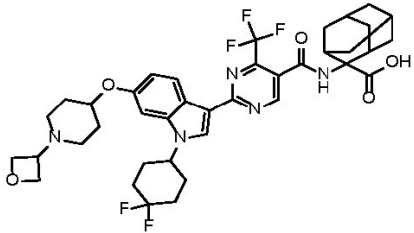
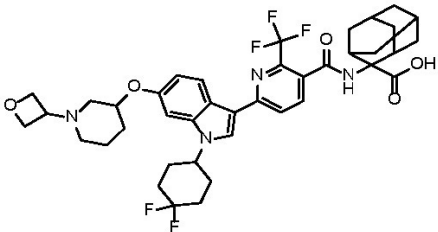
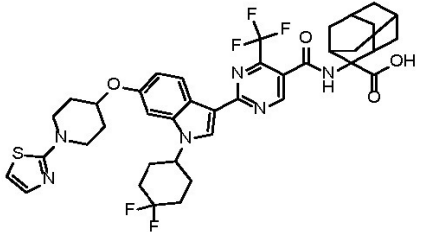
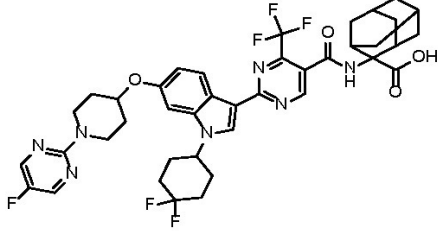
[0276]

[Table 37]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-227		797	3.07	2	
I-228		781	1.86	10	
I-229		748	2.82	2	
I-230		712	2.14	2	
I-231		722	2.04	2	
I-232		767	1.69	9	

[0277]

[Table 38]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-233		758	1.18	9	a
I-234		758	1.19	9	
I-235		757	1.24	10	a
I-236		785	1.61	9	
I-237		798	1.87	9	

[0278]

[Table 39]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-238		768	2.88	2	
I-239		780	1.78	9	
I-240		757	1.15	9	
I-241		797	1.87	9	
I-242		786	1.22	9	

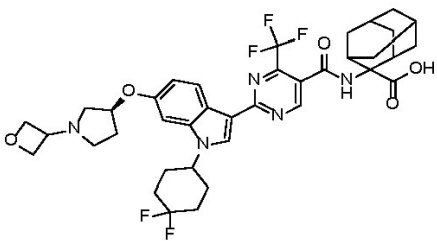
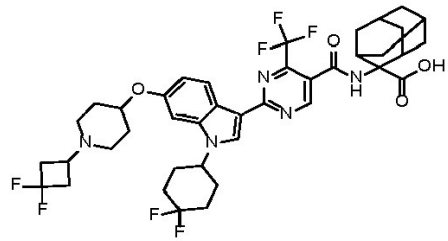
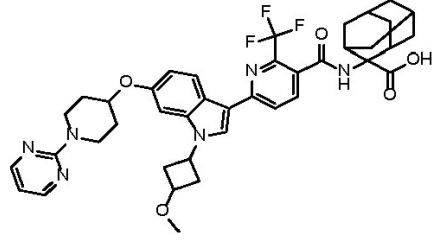
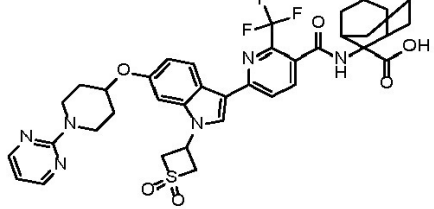
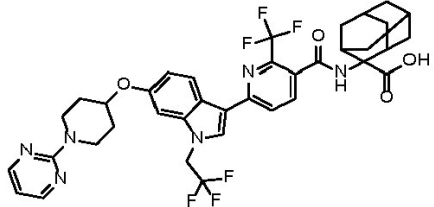
[0279]

[Table 40]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-243		716	2.95	1	a
I-244		718	3.00	1	
I-245		760	2.68	1	
I-246		744	1.24	9	
I-247		744	1.49	10	

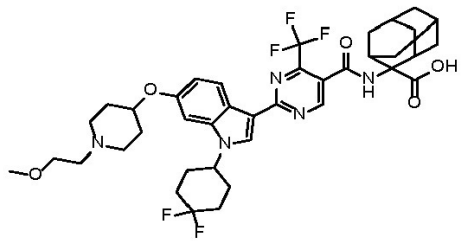
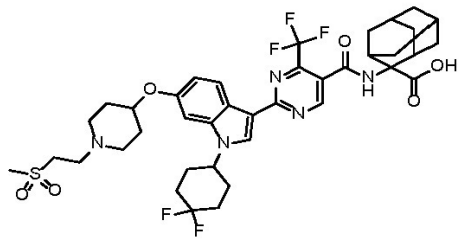
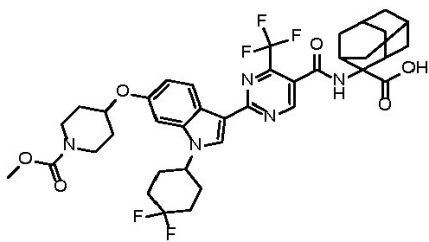
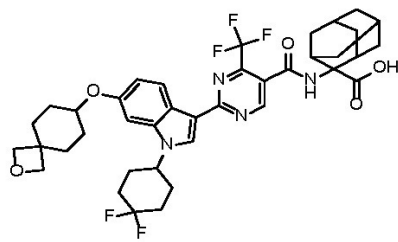
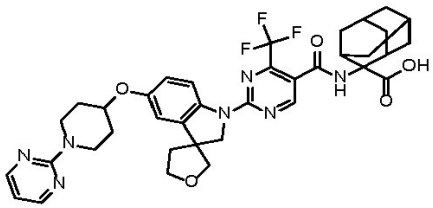
[0280]

[Table 41]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-248		744	1.25	9	
I-249		792	1.38	9	
I-250		745	1.71	9	c
I-251		765	1.58	9	
I-252		743	1.70	9	

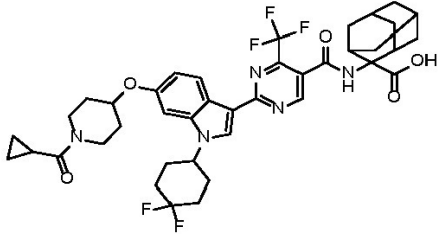
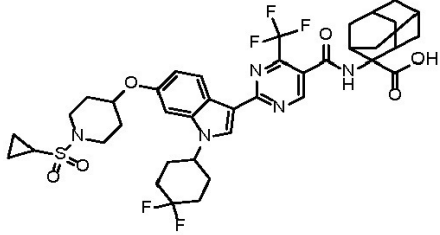
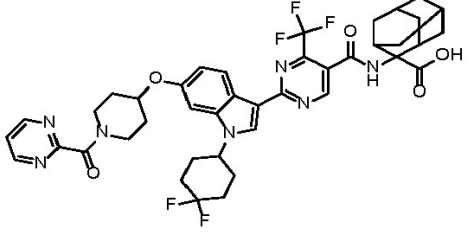
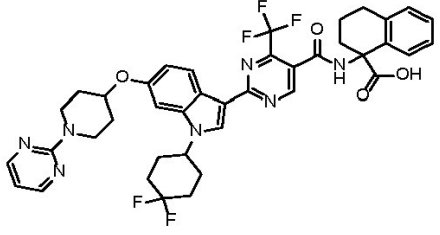
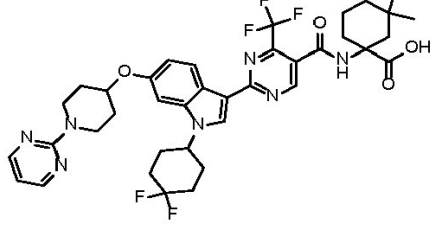
[0281]

[Table 42]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-253		760	1.19	10	
I-254		808	1.18	10	
I-255		760	1.64	10	
I-256		743	1.67	10	
I-257		720	2.63	1	a

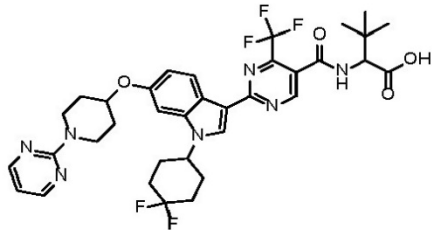
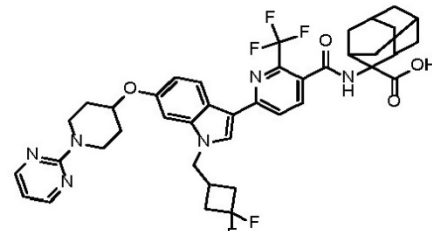
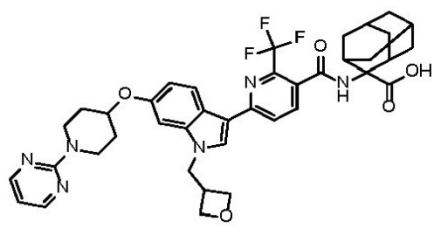
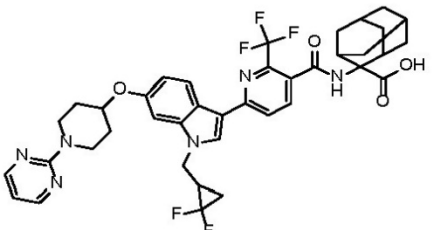
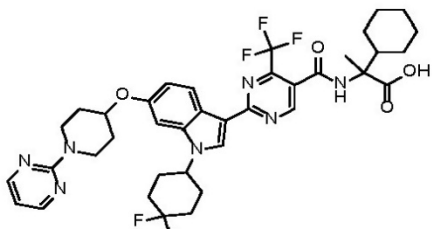
[0282]

[Table 43]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-258		770	1.67	11	
I-259		806	1.63	10	
I-260		808	1.47	10	
I-261		776	1.68	9	a
I-262		756	1.73	9	a

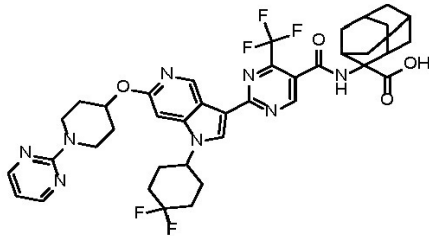
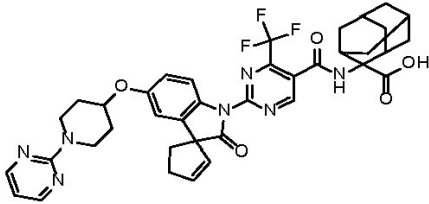
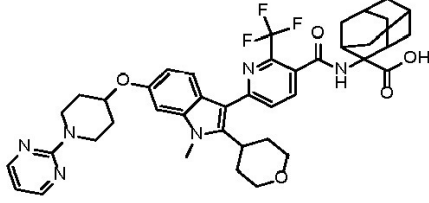
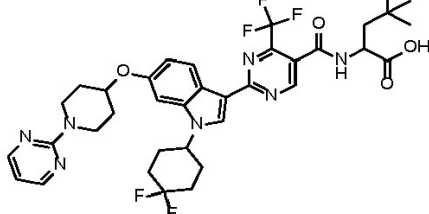
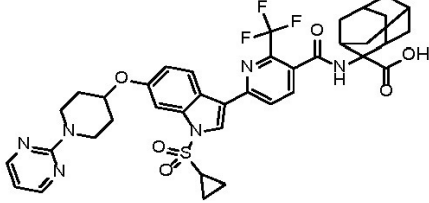
[0283]

[Table 44]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-263		716	1.62	9	a
I-264		765	1.72	10	
I-265		731	1.55	10	
I-266		751	1.68	10	a
I-267		756	1.71	10	a

[0284]

[Table 45]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-268		781	1.56	9	
I-269		730	2.68	1	a
I-270		759	2.62	1	
I-271		730	1.67	9	a
I-272		765	1.70	9	

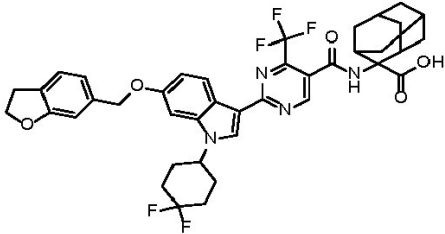
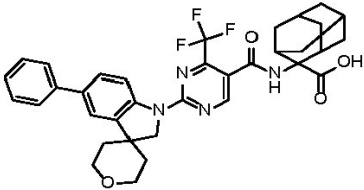
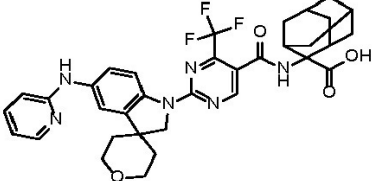
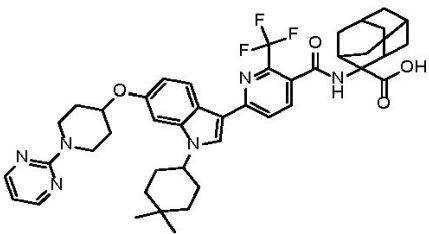
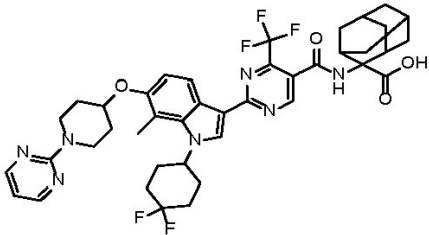
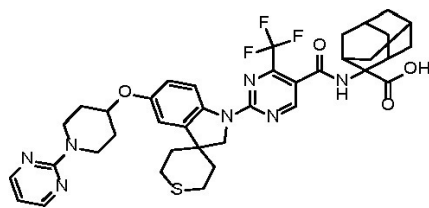
[0285]

[Table 46]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-273		794	1.82	10	c
I-274		802	3.31	1	
I-275		752	2.84	1	
I-276		758	2.80	1	
I-277		772	1.35	9	a

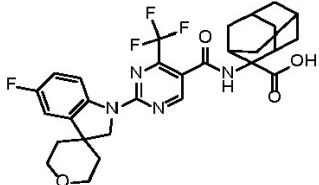
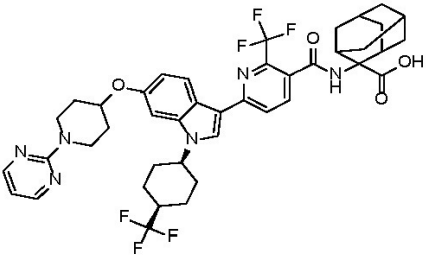
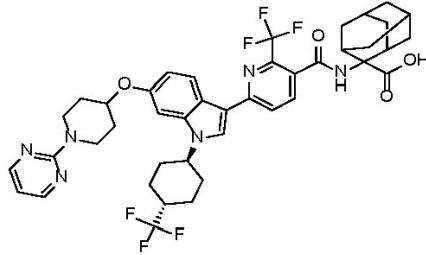
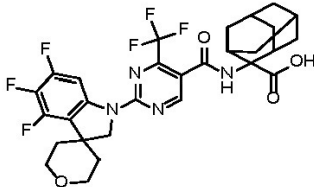
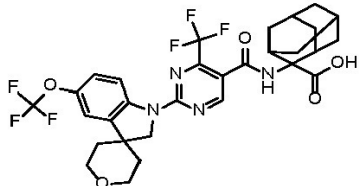
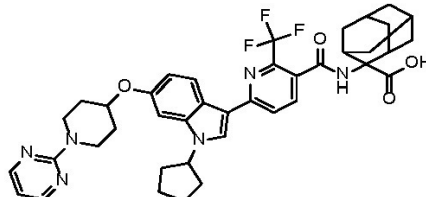
[0286]

[Table 47]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-278		751	1.80	9	
I-279		633	1.78	9	
I-280		649	1.03	10	
I-281		771	3.12	1	
I-282		794	2.89	1	
I-283		750	2.85	1	

[0287]

[Table 48]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-284		575	2.66	1	
I-285		811	3.19	1	
I-286		811	2.99	1	
I-287		611	2.74	1	
I-288		641	2.80	1	
I-289		729	1.82	10	

[Table 49]

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[Table 50]

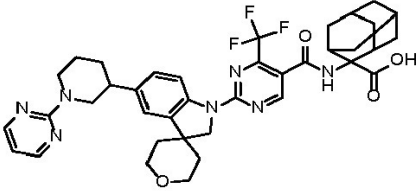
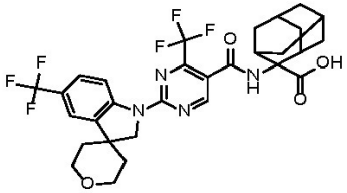
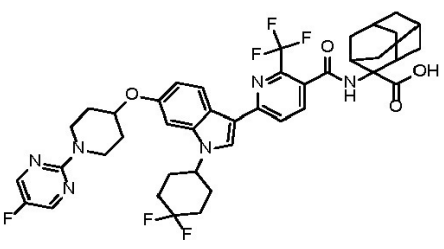
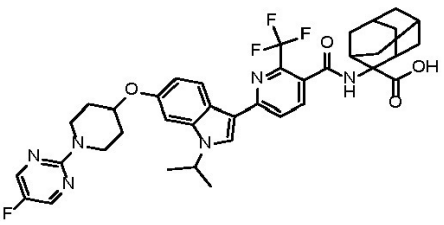
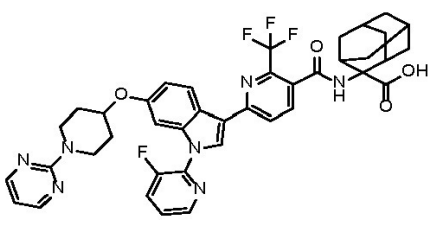
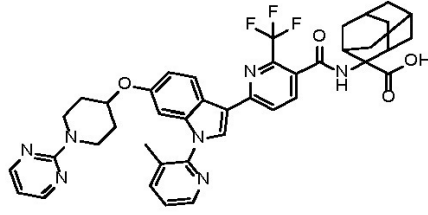
198

[Table 51]

199

[0291]

[Table 52]

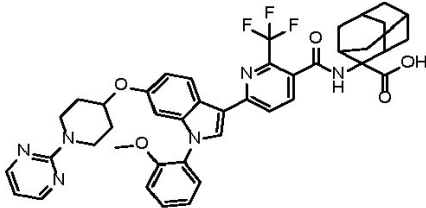
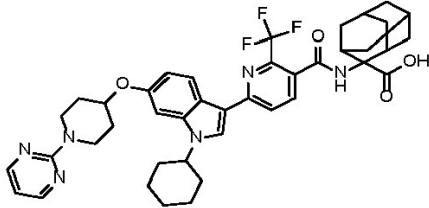
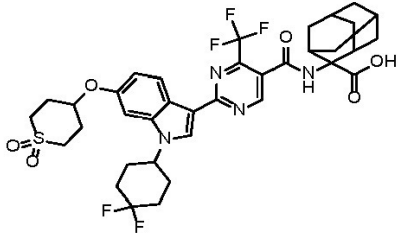
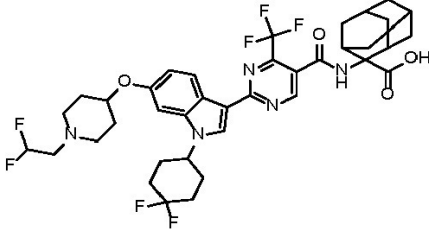
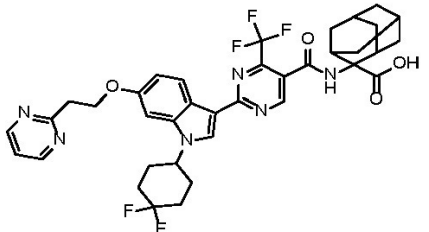
Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-306		717	2.69	1	a
I-307		625	2.82	1	
I-308		797	3.01	1	
I-309		721	2.96	1	
I-310		756	2.92	4	
I-311		752	2.88	4	

[Table 53]

201

[0293]

[Table 54]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-318		767	3.06	4	
I-319		743	1.87	9	
I-320		751	1.53	9	
I-321		766	1.25	10	
I-322		725	1.57	10	

[0294]

[Table 55]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-323		676	1.48	10	
I-324		731	1.77	9	c
I-325		768	2.82	4	
I-326		768	2.41	4	
I-327		805	3.08	4	
I-328		741	2.72	4	

[0295]

[Table 56]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-329		806	2.88	4	
I-330		758	2.89	1	b
I-331		758	3.06	1	b
I-332		752	2.62	1	
I-333		775	2.08	1	a

[Table 57]

205

[Table 58]

206

[0298]

[Table 59]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-344		726	1.57	10	
I-345		797	1.81	9	
I-346		731	1.62	9	a
I-347		637	1.69	9	
I-348		649	1.76	9	
I-349		716	2.68	1	

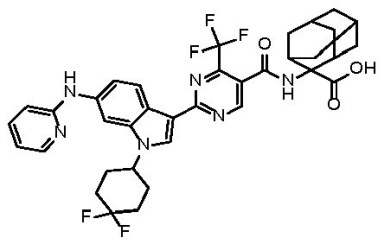
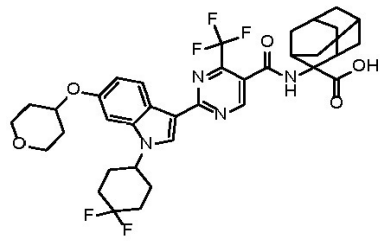
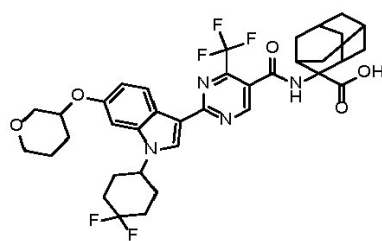
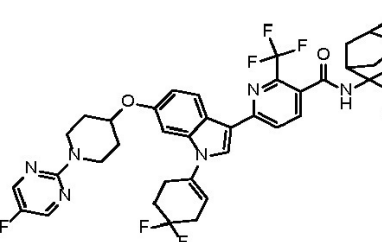
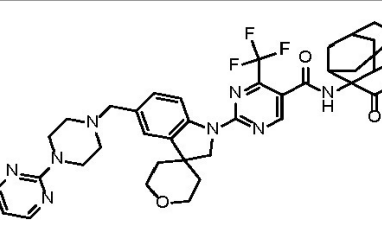
[0299]

[Table 60]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-350		719	3.17	1	
I-351		706	1.87	1	
I-352		696	1.89	1	
I-353		747	1.38	9	
I-354		792	1.39	9	
I-355		679	1.85	10	

[0300]

[Table 61]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-356		695	1.19	10	
I-357		703	1.65	9	
I-358		703	1.69	9	a
I-359		795	3.24	1	
I-360		733	1.97	1	

[0301]

[Table 62]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-361		815	2.98	1	a
I-362		761	2.40	1	a
I-363		786	1.26	9	
I-364		790	2.53	1	a
I-365		800	2.86	1	

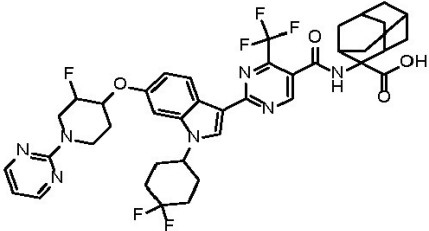
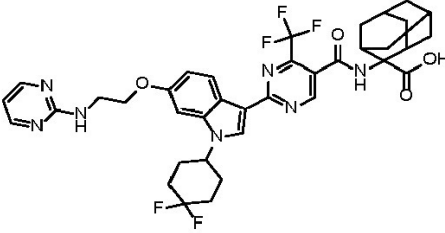
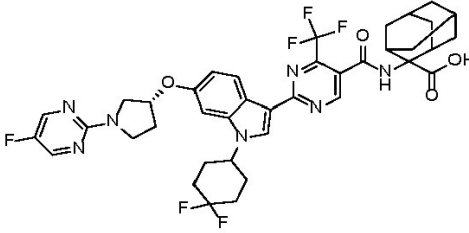
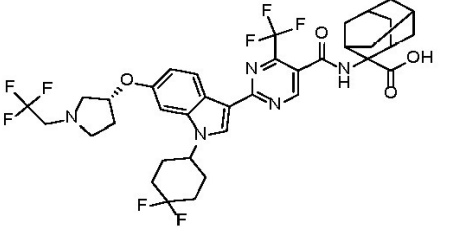
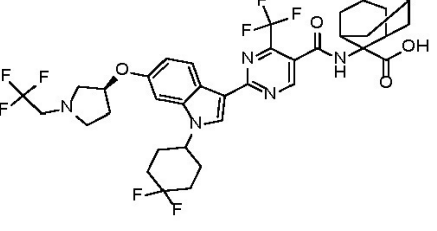
[0302]

[Table 63]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-366		727	1.60	10	
I-367		745	1.67	9	a
I-368		751	1.72	9	
I-369		820	1.67	10	
I-370		824	1.57	10	

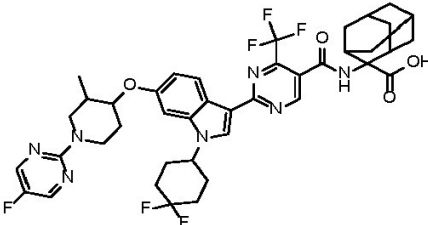
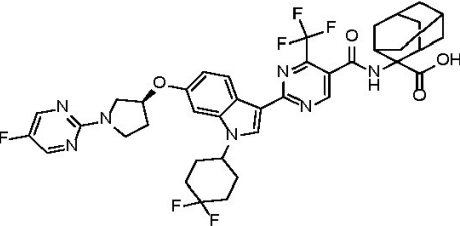
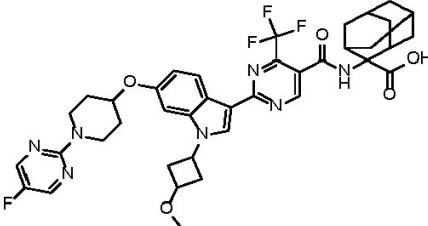
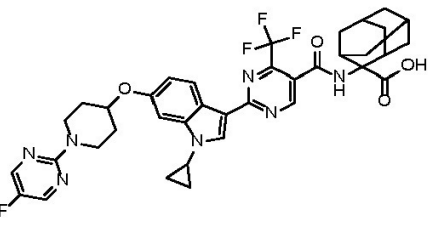
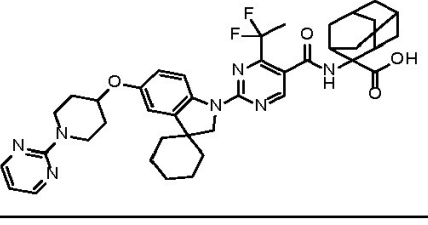
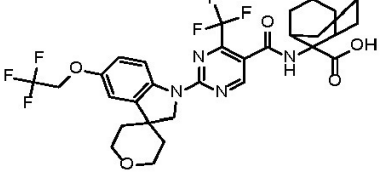
[0303]

[Table 64]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-371		798	1.76	10	c
I-372		740	1.58	10	
I-373		784	1.74	9	
I-374		770	1.75	9	
I-375		770	1.75	9	

[0304]

[Table 65]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-376		812	1.95	10	c
I-377		784	1.74	9	
I-378		764	1.82	9	c
I-379		720	1.85	9	
I-380		728	3.34	1	
I-381		655	2.81	1	

[0305]

[Table 66]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-382		736	3.32	1	
I-383		750	3.53	1	
I-384		738	2.80	1	
I-385		812	1.91	10	f
I-386		812	1.92	10	f
I-387		770	1.71	10	

[Table 67]

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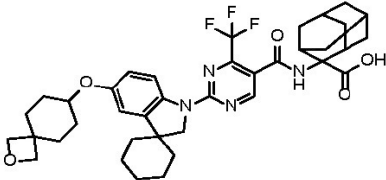
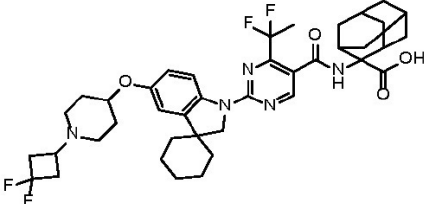
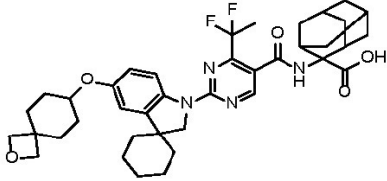
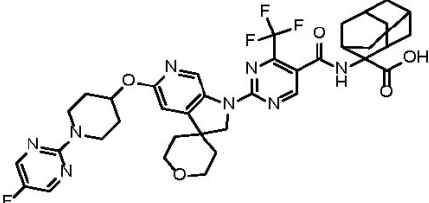
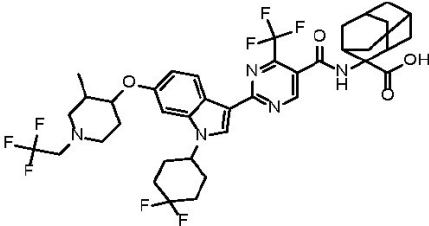
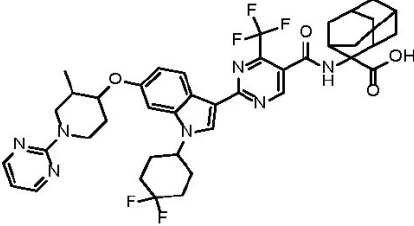
[0307]

[Table 68]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-393		744	2.33	1	
I-394		750	3.35	1	
I-395		750	3.42	1	f
I-396		746	3.55	1	
I-397		779	3.20	1	b
I-398		779	2.98	1	b

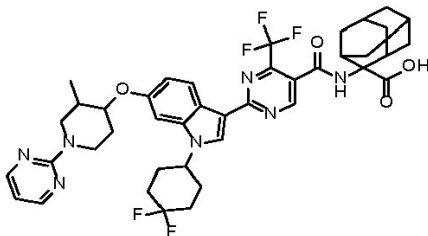
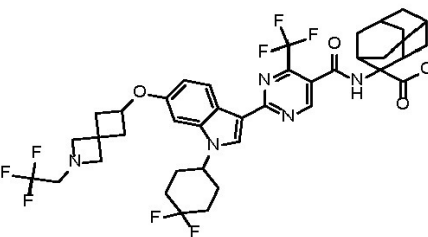
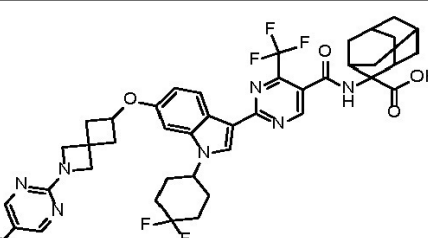
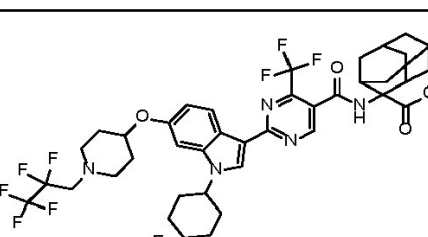
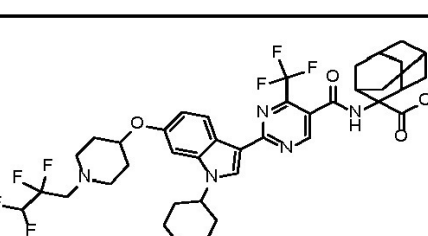
[0308]

[Table 69]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-399		695	3.24	1	
I-400		740	2.19	1	
I-401		691	3.19	1	
I-402		753	3.60	1	
I-403		798	1.85	9	c
I-404		794	1.84	9	b

[0309]

[Table 70]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-405		794	1.83	9	b
I-406		796	1.55	9	
I-407		810	1.75	9	
I-408		834	1.90	9	
I-409		816	1.76	9	

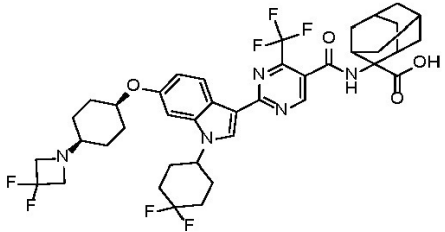
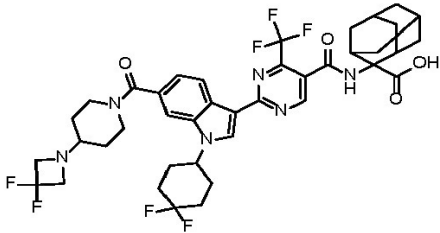
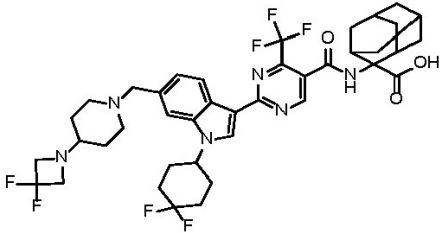
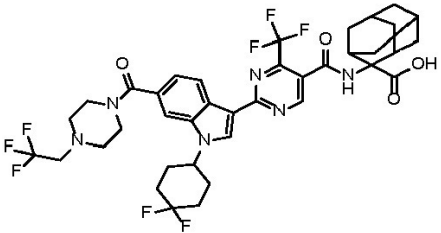
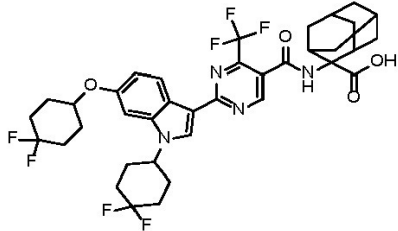
[0310]

[Table 71]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-410		750	1.76	9	a
I-411		797	1.69	9	
I-412		764	1.45	10	b
I-413		764	1.56	10	b
I-414		798	1.83, 1.84	10	c

[0311]

[Table 72]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-415		792	1.36	9	
I-416		805	1.31	10	
I-417		791	1.18	10	
I-418		797	1.62	10	
I-419		737	1.82	10	

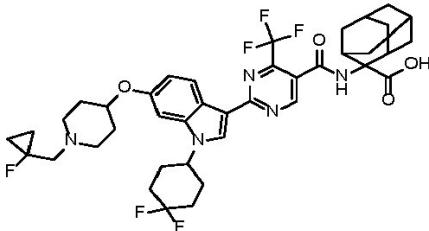
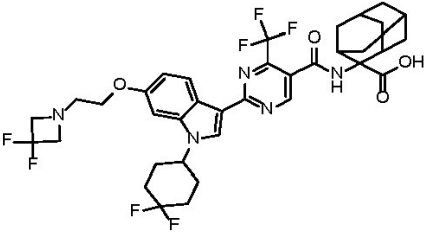
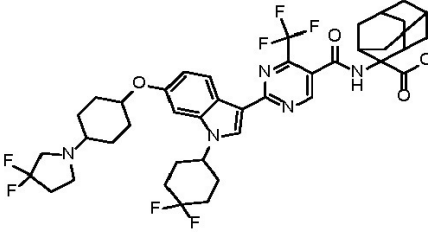
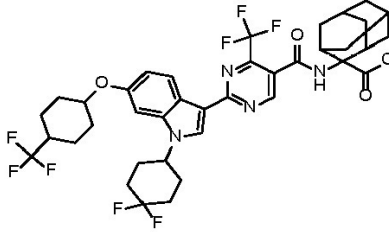
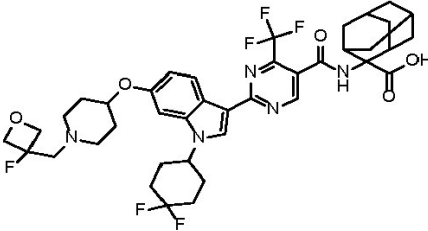
[0312]

[Table 73]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-420		803	1.85	9	
I-421		750	1.94	9	
I-422		780	1.31	9	
I-423		792	1.89	9	b
I-424		792	1.85	9	b

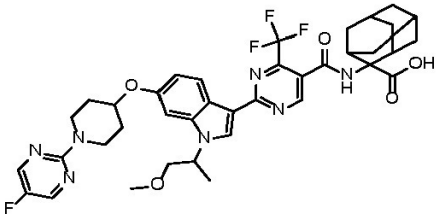
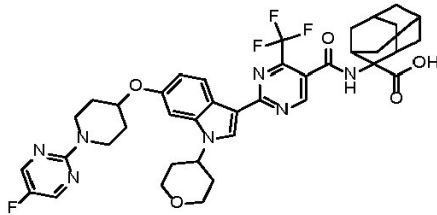
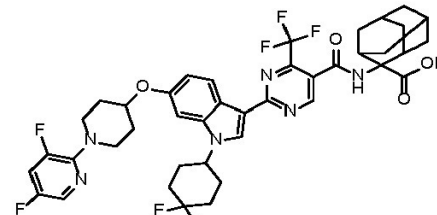
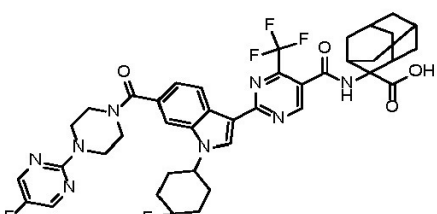
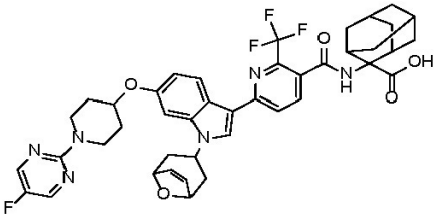
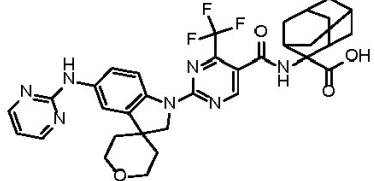
[0313]

[Table 74]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-425		774	1.20	9	
I-426		738	1.35	9	
I-427		806	1.29	10	b
I-428		769	1.90	10	c
I-429		790	1.24	9	

[0314]

[Table 75]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-430		752	1.81	10	a
I-431		764	1.76	9	
I-432		815	1.90	9	
I-433		811	1.63	10	
I-434		787	3.07	1	b
I-435		650	1.41	9	

[0315]

[Table 76]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-436		717	1.67	9	
I-437		804	1.80	9	
I-438		744	2.40	2	
I-439		750	3.44	1	
I-440		732	3.29	2	
I-441		796	3.34	2	

[Table 77]

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[0317]

[Table 78]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-448		812	1.83	9	
I-449		798	1.85	9	a
I-450		812	1.85	9	
I-451		778	1.41	9	c
I-452		791	1.35	9	

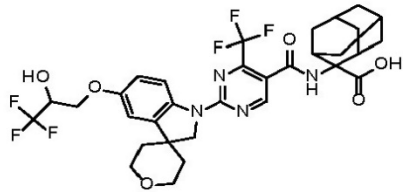
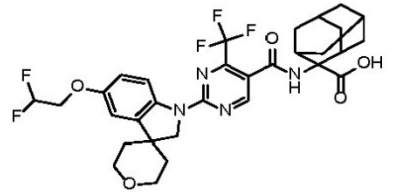
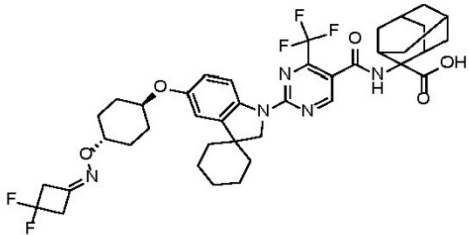
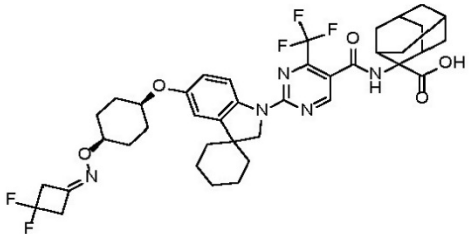
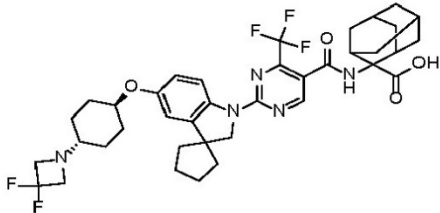
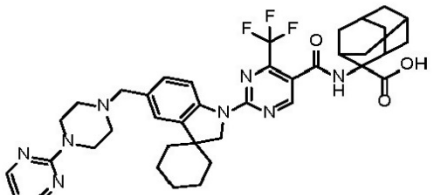
[0318]

[Table 79]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-453		741	2.85	2	
I-454		633	2.89	1	
I-455		633	2.90	1	
I-456		800	3.61	1	
I-457		800	3.57	1	

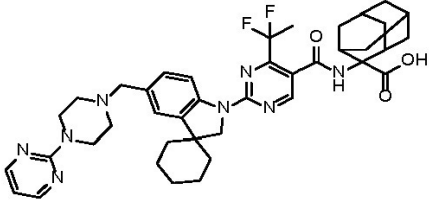
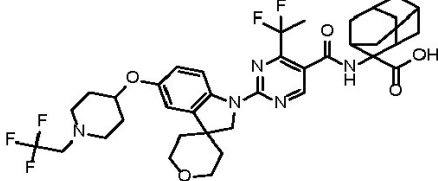
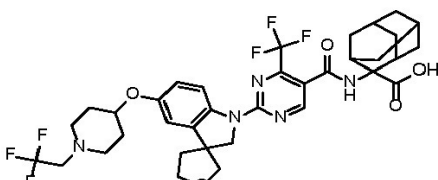
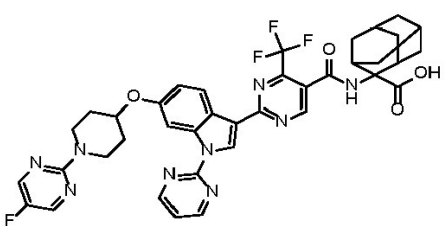
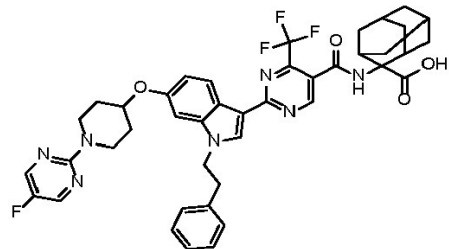
[0319]

[Table 80]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-458		685	2.59	1	a
I-459		637	2.71	1	
I-460		772	3.57	1	
I-461		772	3.54	1	
I-462		730	2.36	1	
I-463		731	2.14	2	

[0320]

[Table 81]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-464		727	2.21	2	
I-465		734	2.74	2	
I-466		641	2.80	1	a
I-467		724	2.77	1	a
I-468		758	1.90	10	
I-469		784	1.92	10	

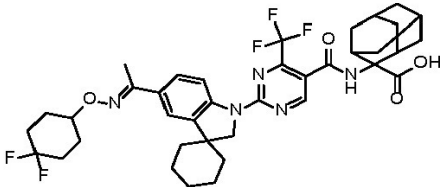
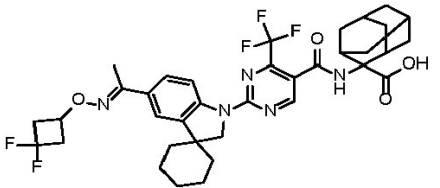
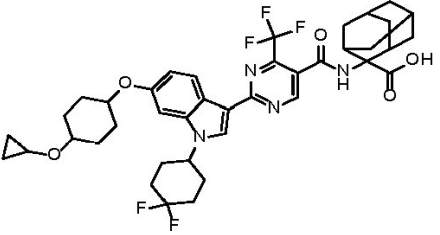
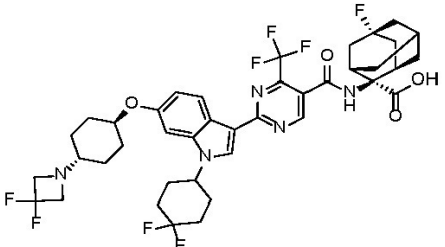
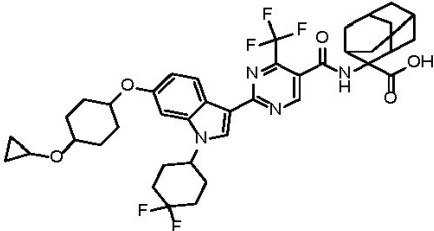
[0321]

[Table 82]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-470		784	1.85	9	a
I-471		674	1.62	10	
I-472		760	1.63	10	
I-473		776	3.38	2	
I-474		722	3.22	1	
I-475		772	3.49	1	a

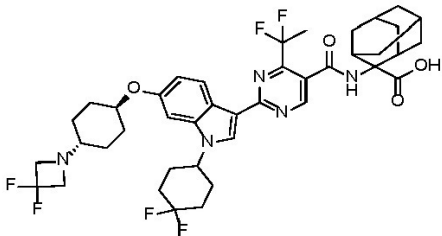
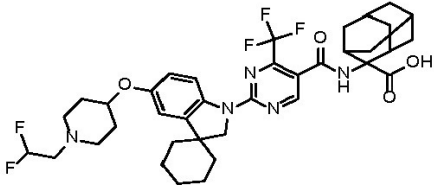
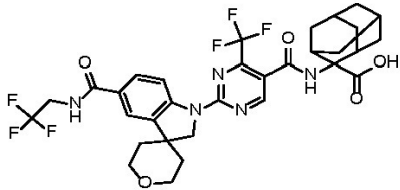
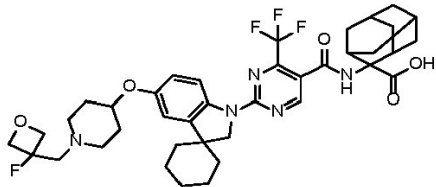
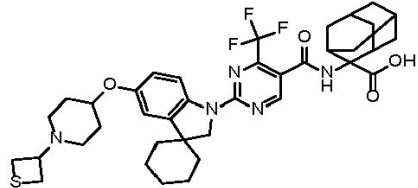
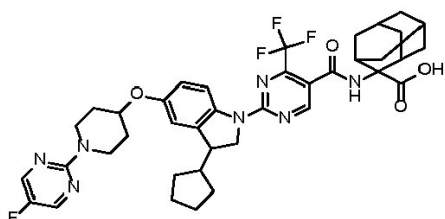
[0322]

[Table 83]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-476		730	3.59	1	b
I-477		702	3.46	1	b
I-478		757	1.88	9	b
I-479		810	1.27	9	
I-480		757	1.88	9	b

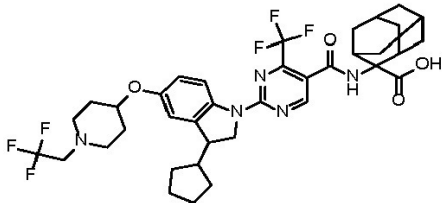
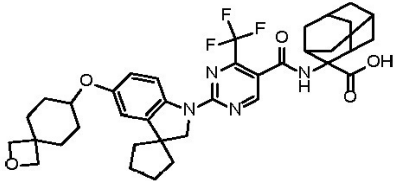
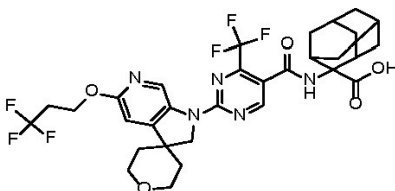
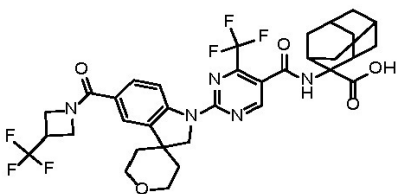
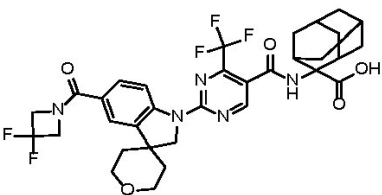
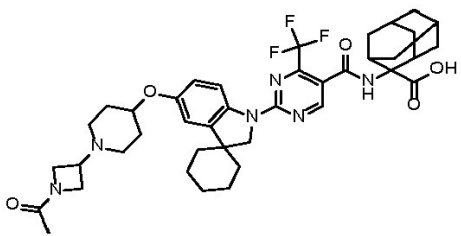
[0323]

[Table 84]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-481		788	1.34	10	
I-482		718	2.28	1	
I-483		682	2.48	1	
I-484		742	2.23	1	
I-485		726	2.37	1	
I-486		750	3.56	1	a

[0324]

[Table 85]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-487		736	3.36	1	a
I-488		681	3.17	1	
I-489		670	2.80	1	
I-490		708	2.52	1	
I-491		676	2.47	1	
I-492		751	2.52	1	

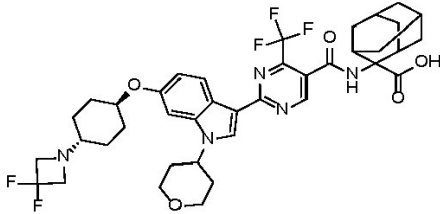
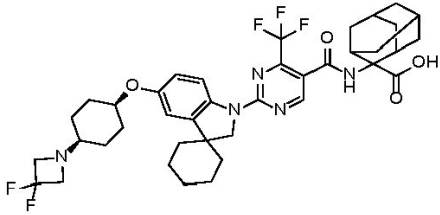
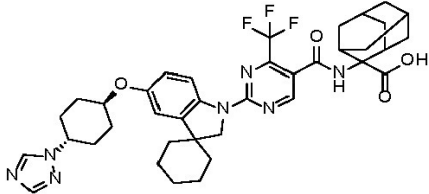
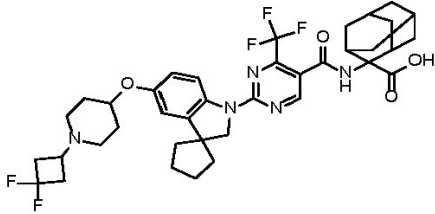
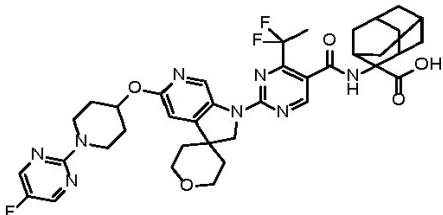
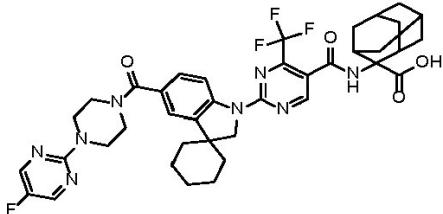
[0325]

[Table 86]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-493		772	3.09	1	
I-494		722	3.23	1	
I-495		708	3.22	1	
I-496		744	1.40	9	
I-497		714	1.28	9	
I-498		798	1.24	9	

[0326]

[Table 87]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-499		758	1.22	9	
I-500		744	2.49	1	
I-501		720	2.98	1	
I-502		730	2.29	1	
I-503		749	2.94	1	
I-504		763	3.07	1	

[0327]

[Table 88]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-505		749	3.00	1	
I-506		742	2.13	1	
I-507		746	1.25	10	
I-508		746	1.25	10	
I-509		774	1.34	10	e
I-510		774	1.33	9	e

[Table 89]

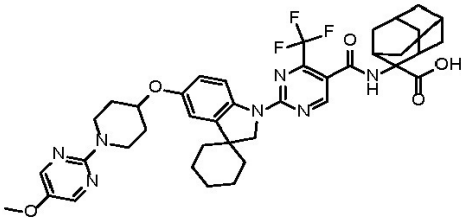
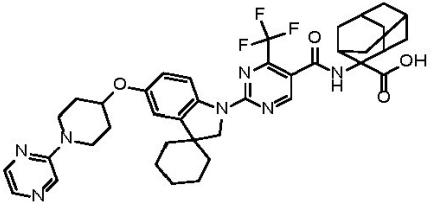
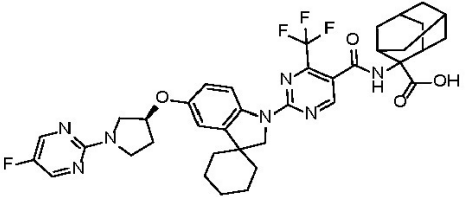
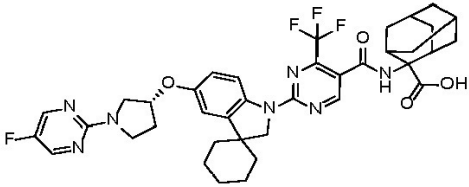
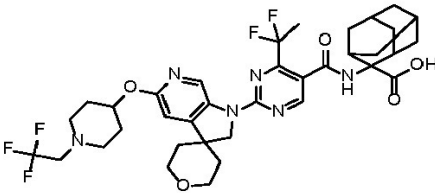
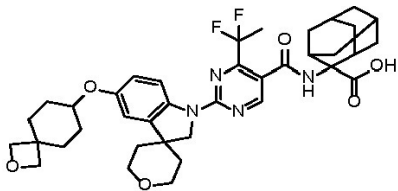
237

[Table 90]

238

[0330]

[Table 91]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-522		762	3.45	1	
I-523		732	3.26	1	
I-524		736	2.42	1	
I-525		736	2.42	1	
I-526		735	2.62	1	
I-527		693	2.70	1	

[0331]

[Table 92]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-528		691	2.44	1	
I-529		748	2.22	1	
I-530		710	1.26	10	
I-531		754	1.46	10	
I-532		722	1.95	1	
I-533		756	2.14	1	

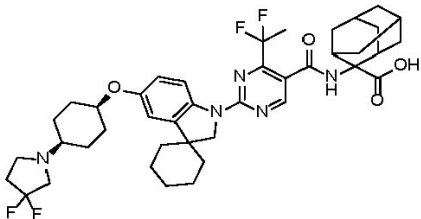
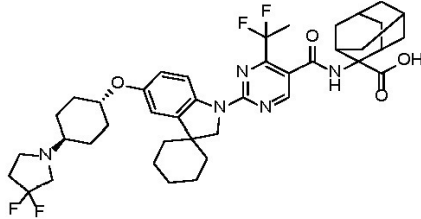
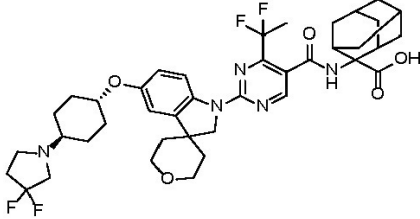
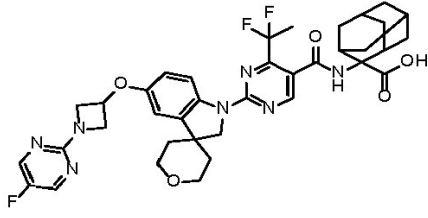
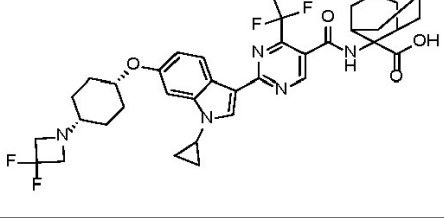
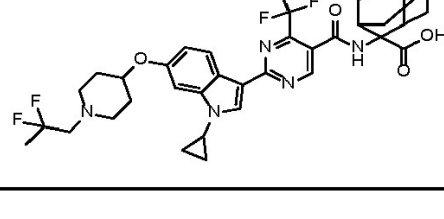
[0332]

[Table 93]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-534		736	3.15	1	
I-535		802	3.43	1	
I-536		802	3.53	1	
I-537		762	3.50	1	
I-538		756	2.24	1	

[0333]

[Table 94]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-539		754	2.81	1	
I-540		754	2.77	1	
I-541		756	2.24	1	
I-542		720	2.71	1	
I-543		714	1.25	9	
I-544		702	1.21	9	

[0334]

[Table 95]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-545		793	1.34	9	
I-546		788	1.28	9	
I-547		754	1.14	9	
I-548		730	2.15	1	
I-549		774	2.39	1	
I-550		772	2.96	1	

[0335]

[Table 96]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-551		742	2.24	1	
I-552		748	2.21	1	
I-553		762	2.88	1	
I-554		760	2.00	1	
I-555		741	2.46	1	
I-556		759	2.29	1	

[0336]

[Table 97]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-557		747	3.51	1	
I-558		751	3.54	1	
I-559		716	2.08	1	
I-560		734	2.81	1	
I-561		720	2.74	1	
I-562		747	2.94	1	

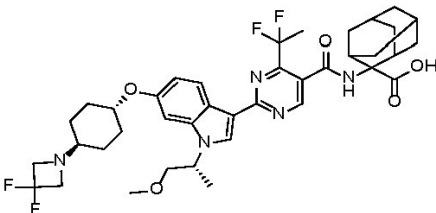
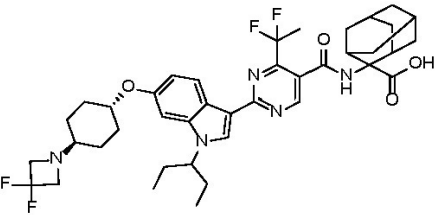
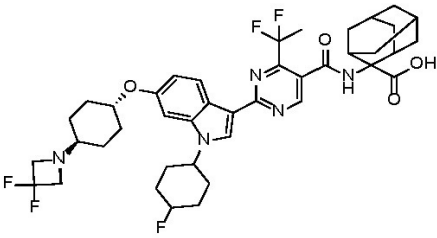
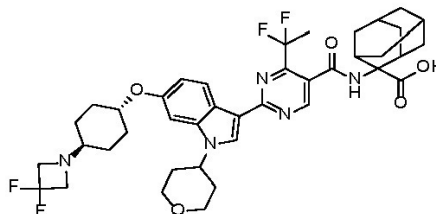
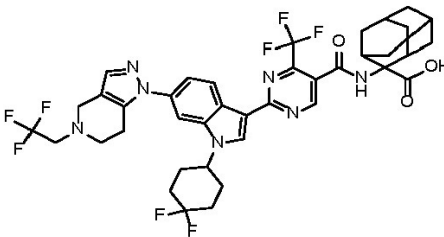
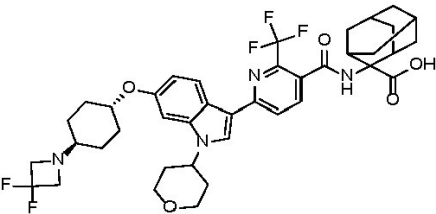
[0337]

[Table 98]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-563		716	2.99	1	
I-564		724	2.14	1	
I-565		718	3.25	1	
I-566		708	3.22	1	
I-567		742	1.23	10	
I-568		770	1.32	10	e

[0338]

[Table 99]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-569		742	1.22	9	
I-570		740	1.36	9	
I-571		770	1.30	9	e
I-572		754	1.18	9	
I-573		806	1.75	10	
I-574		757	1.23	10	

[0339]

[Table 100]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-575		743	1.39	10	
I-576		734	1.16	10	
I-577		745	1.25	10	
I-578		746	1.15	10	
I-579		773	1.33	10	e
I-580		794	1.24	10	

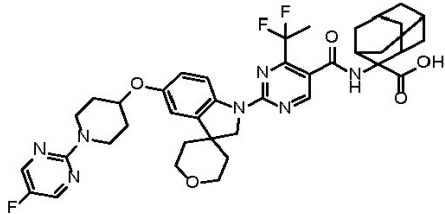
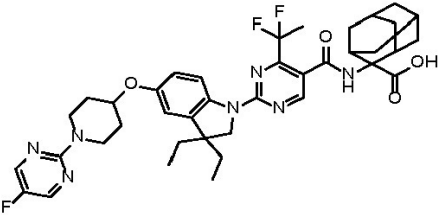
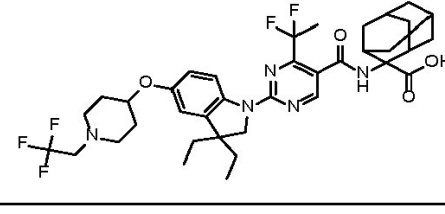
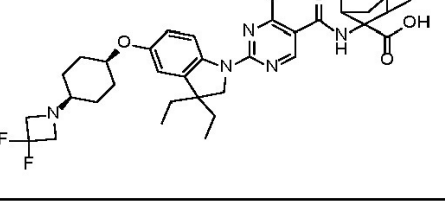
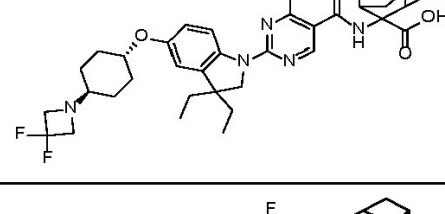
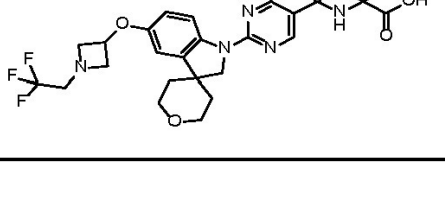
[0340]

[Table 101]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-581		745	1.24	10	
I-582		797	1.25	10	
I-583		776	1.26	9	
I-584		773	1.33	9	e
I-585		746	1.21	9	
I-586		742	2.07	1	

[0341]

[Table 102]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-587		748	3.06	1	
I-588		734	3.50	1	
I-589		720	3.28	1	
I-590		728	2.53	1	
I-591		728	2.54	1	
I-592		706	2.72	1	

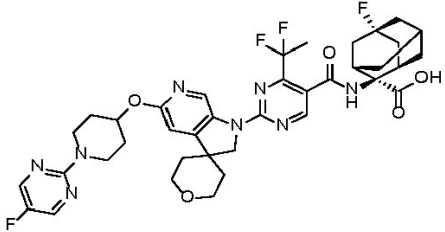
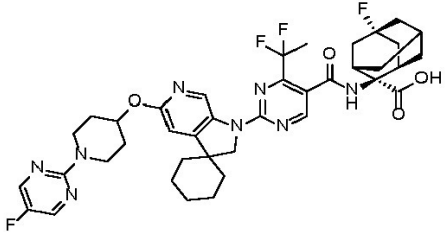
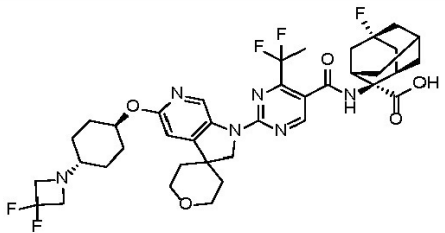
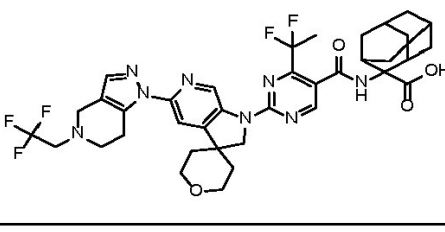
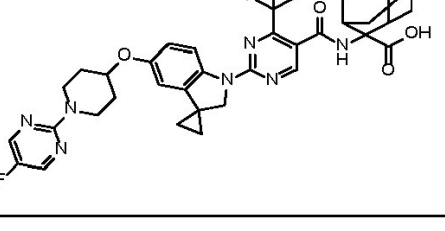
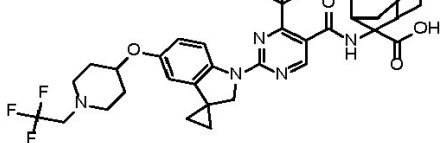
[0342]

[Table 103]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-593		756	2.12	1	
I-594		743	2.00	1	
I-595		745	2.10	1	
I-596		756	2.79	1	
I-597		698	2.42	1	
I-598		704	3.18	1	

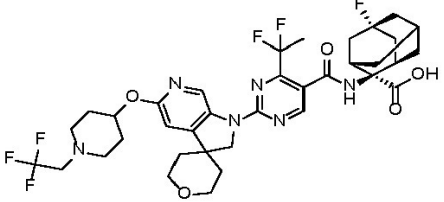
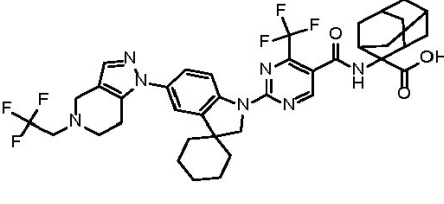
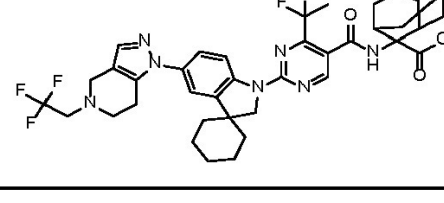
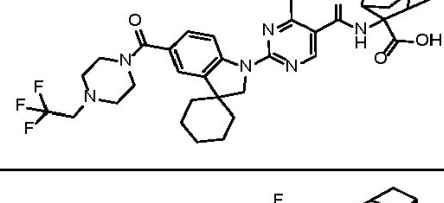
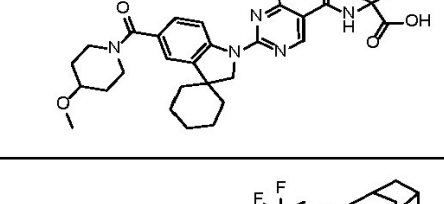
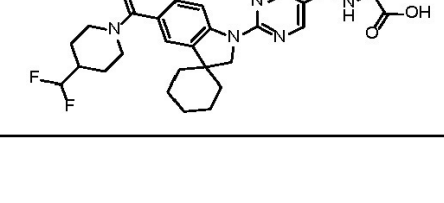
[0343]

[Table 104]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-599		767	2.77	1	
I-600		765	3.33	1	
I-601		761	1.88	1	
I-602		757	2.79	1	
I-603		704	3.25	1	
I-604		690	3.01	1	

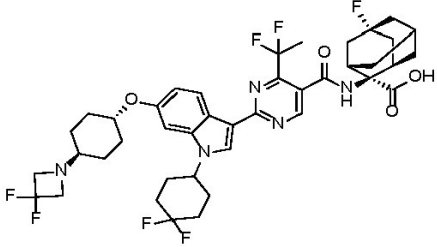
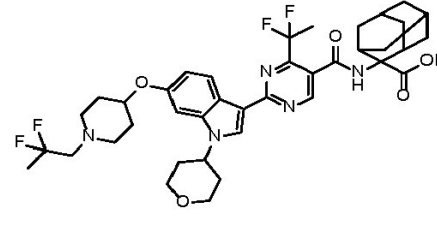
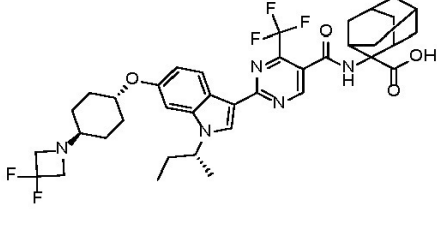
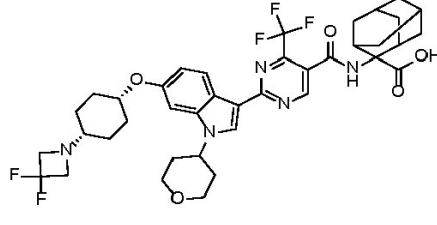
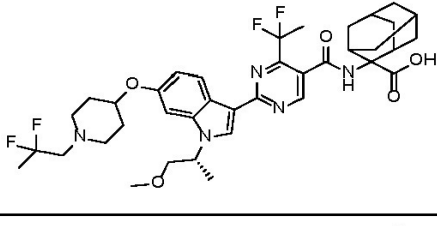
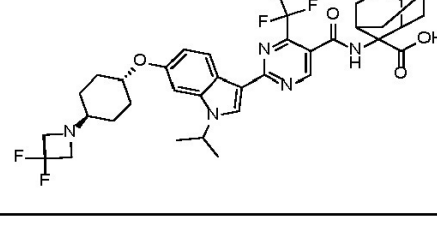
[0344]

[Table 105]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-605		753	2.43	1	
I-606		758	3.30	1	
I-607		754	3.28	1	
I-608		745	2.98	1	
I-609		692	2.82	1	
I-610		712	2.95	1	

[0345]

[Table 106]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-611		806	1.26	10	
I-612		742	1.14	10	
I-613		730	1.36	10	
I-614		758	1.20	10	
I-615		730	1.17	10	
I-616		716	1.28	9	

[0346]

[Table 107]

Compound No.	Chemical Structure	[M+H]	Retention Time (min)	LC/MS Condition	Stereo-Chemistry
I-617		730	1.33	9	
I-618		712	1.24	9	
I-619		760	1.40	9	b
I-620		714	1.29	10	d
I-621		726	1.22	9	b
I-622		746	1.24	10	

[0347]

Biological Test Examples for the compounds of the invention are described below.

A compound of the formula (I) of the present invention has an inhibitory effect on cytopathic effect caused by RS virus and inhibits cytopathic effect in humans.

Specifically, in the evaluation method described below, the IC₅₀ value is preferably 5000 nM or less, more preferably 1000 nM or less, and even more preferably 100 nM or less.

[0348]

Test Example 1: In vitro CPE (CytoPathic Effect) Inhibition Effect Evaluation Test

The test sample is diluted in advance to an appropriate concentration with DMSO, and 3-fold series of serial dilutions were prepared on a 384-well plate (0.32 μ L/well). HEp-2 cells (CCL-23; ATCC) adjusted at appropriate number (2.4×10^5 cells/mL) in 2% FBS E-MEM (prepared by adding kanamycin and FBS to Eagle's Minimum Essential Medium; Invitrogen) were added at 12.5 μ L/well to the 384-well plate previously aliquoted with the test samples. The RSV A2 strain was diluted to an appropriate concentration in a culture medium and added to the 384-well plate containing the test sample at 12.5 μ L/well. The culture medium was added additionally to the 384-well plate, and the test was started with 50 μ L/well. Control wells were prepared with only virus-free culture medium. The plate was incubated in a 5% CO₂ incubator at 37°C for 4 days, and the plate was then placed at room temperature for 30 minutes. CellTiter-Glo (registered trademark) 2.0 assay (Promega) was added at 15 μ L/well, mixed for 30 seconds, and the plate was placed for approximately 1 hour. The luminescent signal was then measured by EnVision (PerkinElmer). The inhibitory effect of the test agents on RSV-induced CPE was calculated as 0% and 100% inhibition rate for each sample concentration based on the level of remaining viable cells by CellTiter-Glo (registered trademark) 2.0, with the EC₅₀ value for each compound calculated by nonlinear regression as the concentration that inhibits RSV-

induced CPE by 50%. In the case of evaluation against RSV type B, RSV B (Wash/18537 strain) was infected in the same manner as the type A, cultured for 5 days, and quantitated in the same manner as for the A2 strain.

(Result)

The compounds of the invention were tested essentially as described above. The inhibitory effect of the compounds against RSV type A is shown below. EC50 values less than 10 nM, 10 nM or more and less than 100 nM, and 100 nM or more and 5000 nM or less are indicated as "A", "B" and "C", respectively.

Compound No. I-23: 0.96 nM
Compound No. I-33: 7.5 nM
Compound No. I-82: 0.27 nM
Compound No. I-148: 1.5 nM
Compound No. I-159: 0.88 nM
Compound No. I-162: 0.88 nM
Compound No. I-165: 0.37 nM
Compound No. I-182: 0.39 nM
Compound No. I-228: 1.3 nM
Compound No. I-268: 1.4 nM
Compound No. I-269: 1.3 nM
Compound No. I-270: 37 nM
Compound No. I-486: 3 nM
Compound No. I-570: 0.70 nM
Compound No. I-591: 0.61 nM
Compound No. I-594: 0.38 nM

[0349]

[Table 108]

Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)
I-1	B	I-54	A	I-106	A	I-158	A
I-2	B	I-55	A	I-107	A	I-160	B
I-3	B	I-56	A	I-108	A	I-161	A
I-4	B	I-57	A	I-109	A	I-163	A
I-5	B	I-58	B	I-110	A	I-164	A
I-6	B	I-59	B	I-111	A	I-166	A
I-7	B	I-60	B	I-112	B	I-167	C
I-8	B	I-61	A	I-113	A	I-168	A
I-9	B	I-62	A	I-114	A	I-169	A
I-10	C	I-63	A	I-115	A	I-170	A
I-11	A	I-64	C	I-116	A	I-171	B
I-12	A	I-65	B	I-117	B	I-172	C
I-13	A	I-66	B	I-118	A	I-173	B
I-14	C	I-67	B	I-119	A	I-174	A
I-15	B	I-68	B	I-120	A	I-175	A
I-16	A	I-69	C	I-121	A	I-176	A
I-17	A	I-70	B	I-122	A	I-177	A
I-18	A	I-71	A	I-123	A	I-178	B
I-19	A	I-72	A	I-124	B	I-179	A
I-20	B	I-73	B	I-125	B	I-180	A
I-21	A	I-74	A	I-126	A	I-181	B
I-22	A	I-75	B	I-127	A	I-183	A
I-24	B	I-76	B	I-128	A	I-184	A
I-25	B	I-77	A	I-129	A	I-185	A
I-26	B	I-78	A	I-130	A	I-186	A
I-27	B	I-79	B	I-131	A	I-187	B
I-28	B	I-80	A	I-132	B	I-188	A
I-29	A	I-81	A	I-133	A	I-189	A
I-30	B	I-83	A	I-134	A	I-190	A
I-31	A	I-84	B	I-135	A	I-191	A
I-32	B	I-85	B	I-136	A	I-192	A
I-34	A	I-86	A	I-137	A	I-193	A
I-35	B	I-87	A	I-138	A	I-194	A
I-36	A	I-88	A	I-139	A	I-195	A
I-37	A	I-89	C	I-140	B	I-196	A
I-38	B	I-90	C	I-141	A	I-197	A
I-39	B	I-91	A	I-142	A	I-198	A
I-40	A	I-92	A	I-143	A	I-199	A
I-41	A	I-93	A	I-144	C	I-200	A
I-42	A	I-94	A	I-145	B	I-201	B
I-43	B	I-95	A	I-146	A	I-202	B
I-44	B	I-96	A	I-147	A	I-203	A
I-45	A	I-97	B	I-149	A	I-204	A
I-46	B	I-98	A	I-150	A	I-205	A
I-47	B	I-99	A	I-151	A	I-206	A
I-48	A	I-100	A	I-152	A	I-207	B
I-49	B	I-101	A	I-153	A	I-208	A
I-50	B	I-102	A	I-154	A	I-209	A
I-51	B	I-103	A	I-155	A	I-210	A
I-52	B	I-104	A	I-156	C	I-211	A
I-53	B	I-105	A	I-157	A	I-212	C

[0350]

[Table 109]

Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)
I-213	A	I-265	A	I-319	A	I-370	A
I-214	A	I-266	A	I-320	A	I-371	A
I-215	B	I-267	A	I-321	A	I-372	A
I-216	B	I-271	A	I-322	A	I-373	A
I-217	A	I-272	A	I-323	A	I-374	A
I-218	A	I-273	A	I-324	A	I-375	A
I-219	A	I-274	A	I-325	A	I-376	A
I-220	A	I-275	A	I-326	A	I-377	A
I-221	A	I-276	A	I-327	A	I-378	A
I-222	A	I-277	A	I-328	A	I-379	A
I-223	A	I-278	A	I-329	A	I-380	A
I-224	A	I-279	A	I-330	A	I-381	A
I-225	B	I-280	A	I-331	A	I-382	A
I-226	A	I-281	A	I-332	A	I-383	A
I-227	A	I-282	A	I-333	A	I-384	A
I-229	A	I-283	A	I-334	A	I-385	A
I-230	A	I-284	A	I-335	A	I-386	A
I-231	A	I-285	A	I-336	A	I-387	A
I-232	A	I-286	B	I-337	A	I-388	A
I-233	B	I-287	A	I-338	A	I-389	A
I-234	A	I-288	B	I-339	A	I-390	A
I-235	A	I-289	A	I-340	A	I-391	A
I-236	A	I-290	A	I-341	A	I-392	A
I-237	A	I-291	A	I-342	C	I-393	A
I-238	A	I-292	A	I-343	B	I-394	A
I-239	A	I-293	B	I-344	B	I-395	A
I-240	A	I-294	A	I-345	A	I-396	A
I-241	A	I-295	B	I-346	A	I-397	A
I-242	A	I-296	A	I-347	A	I-398	A
I-243	A	I-297	A	I-348	A	I-399	A
I-244	A	I-298	A	I-349	A	I-400	A
I-245	A	I-299	B	I-350	A	I-401	A
I-246	A	I-300	A	I-351	B	I-402	A
I-247	A	I-301	A	I-352	B	I-403	A
I-248	A	I-302	A	I-353	A	I-404	A
I-249	A	I-303	A	I-354	A	I-405	A
I-250	A	I-304	A	I-355	A	I-406	A
I-251	A	I-305	A	I-356	A	I-407	A
I-252	A	I-306	A	I-357	A	I-408	A
I-253	A	I-307	A	I-358	A	I-409	A
I-254	B	I-308	A	I-359	A	I-410	A
I-255	A	I-309	A	I-360	A	I-411	A
I-256	A	I-310	A	I-361	A	I-412	A
I-257	A	I-311	A	I-362	A	I-413	A
I-258	A	I-312	A	I-363	A	I-414	A
I-259	A	I-313	A	I-364	A	I-415	A
I-260	B	I-314	A	I-365	A	I-416	A
I-261	B	I-315	A	I-366	A	I-417	A
I-262	A	I-316	A	I-367	A	I-418	A
I-263	A	I-317	A	I-368	A	I-419	A
I-264	A	I-318	A	I-369	A	I-420	A

[0351]

[Table 110]

Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)
I-421	A	I-472	A	I-524	A	I-576	A
I-422	A	I-473	A	I-525	A	I-577	A
I-423	A	I-474	A	I-526	A	I-578	A
I-424	A	I-475	A	I-527	A	I-579	A
I-425	A	I-476	B	I-528	A	I-580	A
I-426	A	I-477	B	I-529	A	I-581	A
I-427	A	I-478	A	I-530	A	I-582	A
I-428	A	I-479	A	I-531	A	I-583	A
I-429	A	I-480	A	I-532	A	I-584	A
I-430	A	I-481	A	I-533	A	I-585	A
I-431	A	I-482	A	I-534	A	I-586	A
I-432	A	I-483	A	I-535	A	I-587	A
I-433	A	I-484	A	I-536	A	I-588	A
I-434	A	I-485	A	I-537	A	I-589	A
I-435	A	I-487	A	I-538	A	I-590	A
I-436	A	I-488	A	I-539	A	I-592	A
I-437	A	I-489	A	I-540	A	I-593	A
I-438	A	I-490	A	I-541	A	I-595	A
I-439	A	I-491	A	I-542	A	I-596	A
I-440	A	I-492	A	I-543	A	I-597	A
I-441	B	I-493	A	I-544	A	I-598	A
I-442	A	I-494	A	I-545	A	I-599	A
I-443	A	I-495	A	I-546	A	I-600	A
I-444	A	I-496	A	I-547	A	I-601	A
I-445	A	I-497	A	I-548	A	I-602	A
I-446	A	I-498	A	I-549	A	I-603	A
I-447	A	I-499	A	I-550	A	I-604	A
I-448	A	I-500	A	I-551	A	I-605	A
I-449	A	I-501	A	I-552	A	I-606	A
I-450	A	I-502	A	I-553	A	I-607	A
I-451	A	I-503	A	I-554	A	I-608	A
I-452	A	I-504	A	I-555	A	I-609	A
I-453	A	I-505	A	I-556	A	I-610	A
I-454	B	I-506	A	I-557	A	I-611	A
I-455	B	I-507	A	I-558	A	I-612	A
I-456	B	I-508	A	I-559	A	I-613	A
I-457	B	I-509	A	I-560	A	I-614	A
I-458	A	I-510	A	I-561	A	I-615	A
I-459	A	I-511	A	I-562	A	I-616	A
I-460	A	I-512	A	I-563	A	I-617	A
I-461	B	I-513	A	I-564	A	I-618	A
I-462	A	I-514	A	I-565	A	I-619	A
I-463	A	I-515	A	I-566	A	I-620	A
I-464	A	I-516	A	I-567	A	I-621	A
I-465	A	I-517	A	I-568	A	I-622	A
I-466	A	I-518	A	I-569	A		
I-467	A	I-519	A	I-571	A		
I-468	A	I-520	A	I-572	A		
I-469	A	I-521	A	I-573	A		
I-470	A	I-522	A	I-574	A		
I-471	A	I-523	A	I-575	A		

[0352]

The compounds of the invention were tested essentially as described above. The inhibitory effect of the compounds against RSV type B is shown below. EC50 values less than 10 nM, 10 nM or more and less than 100 nM, and 100 nM or more and 5000 nM or less are indicated as "A", "B" and "C", respectively.

Compound No. I-23: 16 nM
Compound No. I-33: 110 nM
Compound No. I-82: 0.34 nM
Compound No. I-148: 2.8 nM
Compound No. I-159: 3 nM
Compound No. I-162: 3.3 nM
Compound No. I-165: 0.62 nM
Compound No. I-182: 2.1 nM
Compound No. I-228: 36 nM
Compound No. I-268: 4.3 nM
Compound No. I-486: 28 nM
Compound No. I-570: 2.1 nM
Compound No. I-591: 2.2 nM
Compound No. I-594: 4.2 nM

[0353]

[Table 111]

Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)	Compound No.	EC50 (nM)
I-1	C	I-237	A	I-465	A	I-520	A	I-571	A
I-2	C	I-239	A	I-466	B	I-521	B	I-572	A
I-3	B	I-245	A	I-467	A	I-522	A	I-573	A
I-4	C	I-249	B	I-472	A	I-523	A	I-574	A
I-5	C	I-250	A	I-473	C	I-524	C	I-575	A
I-7	C	I-256	A	I-474	B	I-525	A	I-576	A
I-8	B	I-257	A	I-475	B	I-526	A	I-577	A
I-9	C	I-272	B	I-476	C	I-527	A	I-578	A
I-16	B	I-275	A	I-477	C	I-528	C	I-579	A
I-21	B	I-276	A	I-478	A	I-529	A	I-580	A
I-31	B	I-301	A	I-479	A	I-530	A	I-581	A
I-36	B	I-353	A	I-480	B	I-531	A	I-582	A
I-45	A	I-354	A	I-481	A	I-532	B	I-583	A
I-56	B	I-370	B	I-482	B	I-533	A	I-584	A
I-72	C	I-379	A	I-483	C	I-534	A	I-585	A
I-80	A	I-380	A	I-484	B	I-535	B	I-586	A
I-81	A	I-382	B	I-485	B	I-536	B	I-587	A
I-83	A	I-384	A	I-487	B	I-537	B	I-588	A
I-86	A	I-393	B	I-488	A	I-538	A	I-589	A
I-87	B	I-396	A	I-489	A	I-539	B	I-590	A
I-88	B	I-397	A	I-490	A	I-540	B	I-592	A
I-91	B	I-399	B	I-491	B	I-541	A	I-593	A
I-92	A	I-400	B	I-492	B	I-542	A	I-595	A
I-93	B	I-401	B	I-493	A	I-543	A	I-596	A
I-109	B	I-402	A	I-494	A	I-544	B	I-597	A
I-135	B	I-406	B	I-495	A	I-545	A	I-598	A
I-146	A	I-407	C	I-496	A	I-546	A	I-599	A
I-147	A	I-412	B	I-497	A	I-547	A	I-600	A
I-151	A	I-413	B	I-498	A	I-548	A	I-601	A
I-152	A	I-415	A	I-499	A	I-549	A	I-602	A
I-155	B	I-418	A	I-500	A	I-550	B	I-603	A
I-158	A	I-421	A	I-501	A	I-551	A	I-604	A
I-160	C	I-422	A	I-502	B	I-552	A	I-605	A
I-175	A	I-423	A	I-503	A	I-553	B	I-606	A
I-176	A	I-429	B	I-504	A	I-554	A	I-607	A
I-177	A	I-430	A	I-505	A	I-555	B	I-608	A
I-183	B	I-431	A	I-506	A	I-556	B	I-609	A
I-184	A	I-434	A	I-507	A	I-557	A	I-610	A
I-189	A	I-437	A	I-508	A	I-558	A	I-611	A
I-190	A	I-438	A	I-509	A	I-559	A	I-612	A
I-191	A	I-440	B	I-510	A	I-560	A	I-613	A
I-193	A	I-443	A	I-511	B	I-561	A	I-614	A
I-199	B	I-444	A	I-512	B	I-562	A	I-615	A
I-203	A	I-445	A	I-513	A	I-563	A	I-616	A
I-204	B	I-447	A	I-514	B	I-564	A	I-617	A
I-214	A	I-451	B	I-515	B	I-565	A	I-618	A
I-218	A	I-452	A	I-516	B	I-566	A	I-619	A
I-221	C	I-453	A	I-517	B	I-567	A	I-620	A
I-227	A	I-463	C	I-518	A	I-568	A	I-621	A
I-234	B	I-464	C	I-519	A	I-569	A	I-622	A

[0354]

Test Example 2: In Vivo Mouse Drug Efficacy Test

Although mice are semipermissive for human RSV replication, they are frequently used as a model in preclinical screening tests for RSV therapeutics. In vivo drug efficacy is evaluated using Balb/c mice, which is good for RSV A2 strain propagation. BALB/c mice (female, 6 week old) are inoculated intranasally with RSV A2 strain at 5×10^6 PFU/mouse. After infection, test sample is administered at a fixed dose twice daily (8h/16h interval), and a lung is removed on day 4 or 5. The lung is homogenized in PBS, rapidly frozen and stored at -80°C . Viral titers in supernatants of lung homogenates are quantified by tissue culture infectious dose 50 (TCID₅₀) method using immunoblotting.

[0355]

Test Example 3: CYP inhibition test

Using commercially available pooled human liver microsomes, and as marker reactions of human main five CYP enzyme isoforms (CYP1A2, 2C9, 2C19, 2D6, 3A4), 7-ethoxyresorufin O-deethylation (CYP1A2), tolbutamide methyl-hydroxylation (CYP2C9), mephenytoin 4'-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), and terfenadine hydroxylation (CYP3A4), an inhibitory degree of each metabolite production amount by the compound of the present invention is assessed.

[0356]

The reaction conditions are as follows: substrate, 0.5 $\mu\text{mol/L}$ ethoxyresorufin (CYP1A2), 100 $\mu\text{mol/L}$ tolbutamide (CYP2C9), 50 $\mu\text{mol/L}$ S-mephenytoin (CYP2C19), 5 $\mu\text{mol/L}$ dextromethorphan (CYP2D6), 1 $\mu\text{mol/L}$ terfenadine (CYP3A4); reaction time, 15 minutes; reaction temperature, 37°C ; enzyme, pooled human liver microsomes 0.2 mg protein/mL; concentrations of the compound of the present invention, 1, 5, 10, 20 $\mu\text{mol/L}$ (four points).

[0357]

Each five kinds of substrates, human liver microsomes, or the compound of the present invention in 50 mmol/L Hepes buffer are added to a 96-well plate at the composition as described above as a reaction solution, NADPH, as a cofactor is added to initiate metabolism reactions. After the incubation at 37°C for 15 minutes, methanol/acetonitrile = 1/1 (V/V) solution is added to stop the reaction. After the centrifugation at 3000 rpm for 15 minutes, resorufin (CYP1A2 metabolite) in the supernatant is quantified by a fluorescent multilabel counter or LC/MS/MS, and hydroxy tolbutamide (CYP2C9 metabolite), 4'-hydroxy mephenytoin (CYP2C19 metabolite), dextrorphan (CYP2D6 metabolite), and terfenadine alcohol metabolite (CYP3A4 metabolite) are quantified by LC/MS/MS.

The dilution concentration and dilution solvent are changed as necessary.

[0358]

Addition of only DMSO being a solvent dissolving a compound of the present invention to a reaction system is adopted as a control (100%), remaining activity (%) is calculated at each concentration of a compound of the present invention added as the solution and IC₅₀ is calculated by reverse presumption by a logistic model using a concentration and an inhibition rate..

[0359]

Test Example 4: CYP3A4 (MDZ) MBI Test

CYP3A4 (MDZ) MBI test is a test of investigating mechanism based inhibition (MBI) potential on CYP3A4 inhibition of a compound. CYP3A4 inhibition is evaluated using 1-hydroxylation reaction of midazolam (MDZ) by pooled human liver microsomes as a marker reaction.

[0360]

The reaction conditions are as follows: substrate, 10 µmol/L MDZ; pre-reaction time, 0 or 30 minutes; substrate reaction time, 2 minutes; reaction temperature, 37°C; protein content of pooled human liver microsomes, at pre-reaction time 0.5 mg/mL, at

reaction time 0.05 mg/mL (at 10-fold dilution); concentrations of the compound of the present invention, at pre-reaction time 1, 5, 10, 20 $\mu\text{mol/L}$ or 0.83, 5, 10, 20 $\mu\text{mol/L}$ (four points).

[0361]

Pooled human liver microsomes and a compound of the present invention solution in a K-Pi buffer (pH 7.4) as a pre-reaction solution are added to a 96-well plate at the composition of the pre-reaction. A part of pre-reaction solution is transferred to another 96-well plate, and diluted 10-fold by K-Pi buffer containing a substrate. NADPH as a co-factor is added to initiate the marker reaction (preincubation 0 min). After a predetermined time of the reaction, methanol/acetonitrile=1/1 (v/v) solution is added to stop the reaction. On the other hand, NADPH is also added to a remaining pre-reaction solution to initiate a pre-reaction (preincubation 30 min). After a predetermined time of the pre-reaction, a part is transferred to another 96-well plate, and diluted 10-fold by a substrate in a K-Pi buffer containing a substrate to initiate the marker reaction. After a predetermined time of the reaction, methanol/acetonitrile = 1/1 (v/v) solution is added to stop the reaction. After centrifuged at 3000 rpm for 15 minutes, 1-hydroxymidazolam in the supernatant is quantified by LC/MS/MS.

The concentration and solvent for dilution is changed as necessary.

[0362]

The sample adding DMSO to a reaction system instead of compound of the present invention solution is adopted as a control (100 %), because DMSO is used as a solvent to dissolve a compound of the present invention. Remaining activity (%) is calculated at each concentration of the compound of the present invention compared to a control, and IC value is calculated by reverse-presumption by a logistic model using a concentration and an inhibition rate. IC at Preincubation 0 min/IC at Preincubation 30 min is defined as a value of Shifted IC, and a case that Shifted IC is 1.5 or

more is regarded as Positive, and a case that Shifted IC is 1.0 or less is regarded as Negative.

[0363]

Test Example 5: BA test

Materials and methods for experiments to evaluate oral absorption

(1) Animal: mice or rats are used.

(2) Breeding conditions: mice or rats are allowed to freely take solid food and sterilized tap water.

(3) Dose and grouping setting: oral administration and intravenous administration are performed with a predetermined dosage. Grouping is set as follows (dosage changed per compound):

Oral administration: 2 to 60 $\mu\text{mol/kg}$ or 1 to 30 mg/kg ($n = 2$ to 3)

Intravenous administration: 1 to 30 $\mu\text{mol/kg}$ or 0.5 to 10 mg/kg ($n = 2$ or 3)

(4) Preparation of dosing formulation: oral administration is performed in the form of a suspension or a solution. Intravenous administration is performed after solubilization.

(5) Routes of administration: oral administration into the stomach is performed using feeding tube. Intravenous administration into tail vein is performed using a syringe equipped with injection needle.

(6) Evaluation items: blood is collected over time, and the concentration of the compound of the invention in plasma is measured by LC/MS/MS.

(7) Statistical analysis: regarding the plasma concentration profile of the compound of the invention, the area under the concentration time curve (AUC) is calculated by the moment analysis method, and the bioavailability (BA) of the compound of the invention is calculated from the dose ratio and the AUC ratio of the oral administration group and the intravenous administration group.

The dilution concentration and dilution solvent should be changed as necessary.

[0364]

Test Example 6: Clearance Evaluation Test

Material and method

- (1) Animal: SD rats are used.
- (2) Breeding conditions: rats are allowed to freely take solid food and sterilized tap water.
- (3) Dose and grouping setting: intravenous administration is performed with a predetermined dosage. Grouping is set as follows: Intravenous administration: 1 $\mu\text{mol/kg}$ ($n = 2$)
- (4) Preparation of dosing formulation: The test sample is solubilized using a solvent of dimethyl sulfoxide/propylene glycol = 1/1, and administered.
- (5) Route of administration: Administration into tail vein is performed using a syringe equipped with injection needle.
- (6) Evaluation Items: Blood is collected over time, and the concentration of the compound of the invention in plasma is measured by LC/MS/MS.
- (7) Statistical analysis: regarding plasma concentration profile of the compound, total body clearance (CL_{tot}) is calculated by the moment analysis method. The dilution concentration and dilution solvent should be changed as necessary.

[0365]

Test Example 7: Metabolic Stability Test

Using pooled human liver microsomes and pooled rat liver microsomes, a compound of the invention is reacted for a constant time, and the remaining rate is calculated by comparing the reacted sample and the unreacted sample, thereby, a degree of metabolism in liver is assessed.

[0366]

A reaction is performed (oxidative reaction) at 37°C for 0 or 30 minutes in the presence of 1 mmol/L NADPH in 0.2 mL of a buffer (50 mmol/L Tris-HCl pH 7.4, 150 mmol/L potassium chloride, 10 mmol/L magnesium chloride) containing 0.5 mg protein/mL of human or rat liver microsomes. After the reaction, 50 μL of the reaction solution is added to 100 μL of a methanol/acetonitrile = 1/1 (v/v)

solution, mixed and centrifuged at 3000 rpm for 15 minutes. The compound of the invention in the centrifuged supernatant is quantified by LC/MS/MS or solid-phase extraction (SPE)/MS. The amount of the compound of the invention remaining after the reaction is calculated with the amount of the compound at 0 minutes of the reaction defined as 100%. Hydrolysis reaction is performed in the absence of NADPH, and glucuronidation reaction is performed in the presence of 5 mmol/L UDP-glucuronic acid in place of NADPH, followed by similar procedures. Dilution concentrations and dilution solvents are changed if necessary.

[0367]

Test Example 8: Metabolic stability Test (hepatocytes)

Using human, rat, dog or monkey hepatocytes, a compound of the invention is reacted for a constant time, and the remaining rate is calculated by comparing the reacted sample and the unreacted sample, thereby, a degree of metabolism in liver is assessed. In order to take into account the effect of serum protein binding on metabolism, up to 10% of serum of the species corresponding to each hepatocyte may be added to the medium.

[0368]

Human, rat, dog or monkey hepatocytes are suspended in William's medium E at 1×10^6 cells/mL and reacted with the compound of the invention at 37°C for 0, 1 or 2 hours. If the serum is added, up to 10% of the serum is added to William's medium E in advance, and then the hepatocytes are suspended. After the reaction, 120 μ L of methanol/acetonitrile = 1/1 (v/v) solution to 30 μ L of the reaction solution, mixed and centrifuged at 3000 rpm for 15 minutes. The compound of the invention in the centrifuged supernatant is quantified by LC/MS/MS or solid-phase extraction (SPE)/MS. The amount of the compound of the invention remaining after the reaction is calculated with the amount of the compound at 0 minutes of the reaction defined as 100%. Dilution concentrations and dilution solvents are changed if necessary.

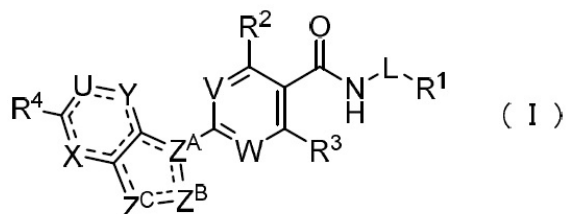
Industrial Applicability

[0369]

The compound of the invention has an inhibitory effect on RSV and is useful for the treatment and/or prevention of RSV infection and related diseases caused by the infection.

Claims

1. A compound of the formula (I):



wherein:

the dashed line indicates the presence or absence of a bond;

R^1 is carboxy, cyano, substituted or unsubstituted aromatic heterocyclyl, $-C(=O)-NR^{1B}R^{1C}$ or $-CH=CHC(=O)-OH$;

R^{1B} and R^{1C} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted aminosulfonyl or substituted or unsubstituted non-aromatic heterocyclylsulfonyl;

L is substituted or unsubstituted non-aromatic carbocyclyldiyl, substituted or unsubstituted non-aromatic heterocyclyldiyl or substituted or unsubstituted alkylene;

R^2 is substituted or unsubstituted alkyl;

R^3 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted amino or substituted or unsubstituted carbamoyl;

X is $=CR^X-$ or $=N-$;

Y is $=CR^Y-$ or $=N-$;

U is $-CR^U=$ or $-N=$;

V is $-CR^V=$ or $-N=$;

W is $=CR^W-$ or $=N-$;

Z^A is $-C=$ or $-N-$;

Z^B is $-CR^5R^6-$, $-CR^5=$, $-NR^5-$ or $-N=$;

Z^C is $-CR^7R^8-$, $-CR^7=$, $-NR^7-$ or $=N-$;

R^X , R^Y , R^V and R^W are each independently a hydrogen atom, cyano, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted carbamoyl;

R^U is a hydrogen atom, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy,

substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl or substituted or unsubstituted non-aromatic carbocyclyl;

R⁵ and R⁶ are each independently a hydrogen atom, substituted or unsubstituted non-aromatic heterocyclyl, hydroxy or substituted or unsubstituted alkyl, or R⁵ and R⁶ are taken together to form oxo;

R⁷ and R⁸ are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted non-aromatic carbocyclylsulfonyl, substituted or unsubstituted alkylsulfonyl, or R⁷ and R⁸ are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring; or

R⁵ and R⁷ are taken together with the carbon atoms to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted aromatic carbon ring; or

R⁴ is a hydrogen atom, substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted aromatic heterocyclyloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic

heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocyclyl or substituted or unsubstituted non-aromatic heterocyclylcarbonyl, or R^4 and R^U are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic heterocyclic ring, or a pharmaceutically acceptable salt thereof.

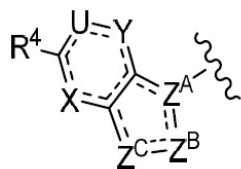
2. The compound according to claim 1, wherein R^1 is carboxy, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein L is substituted or unsubstituted non-aromatic carbocyclldiyl, or a pharmaceutically acceptable salt thereof.

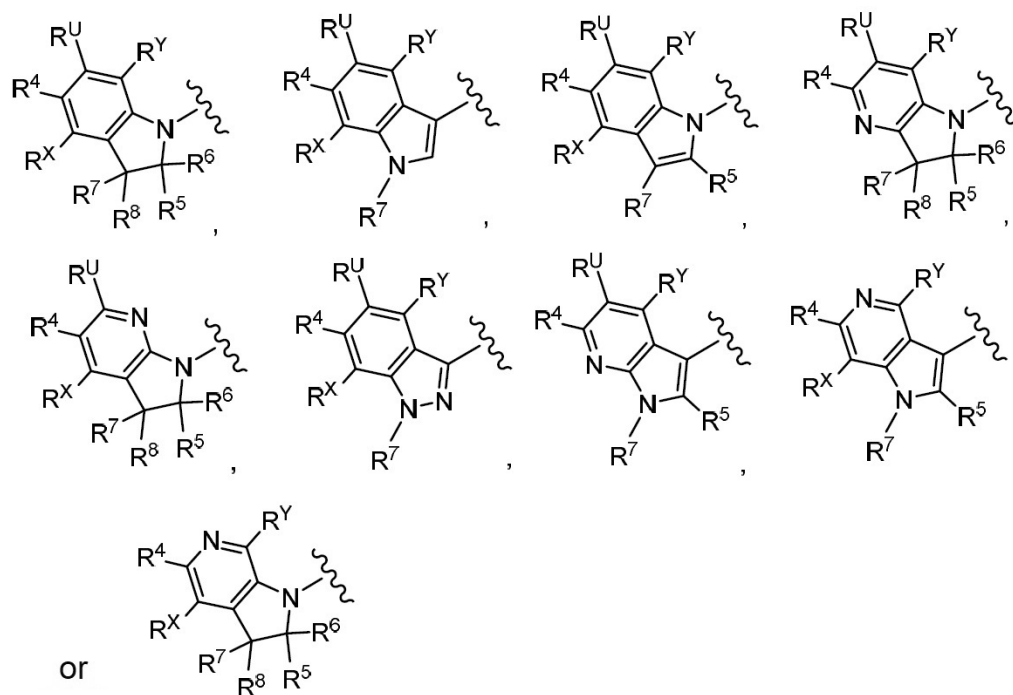
4. The compound according to any one of claims 1 to 3, wherein R^3 is a hydrogen atom, or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 to 4, wherein V is $-N=$ and W is $=N-$, or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1 to 5, wherein the group of the formula:

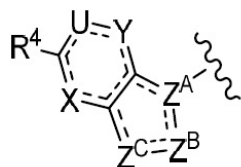


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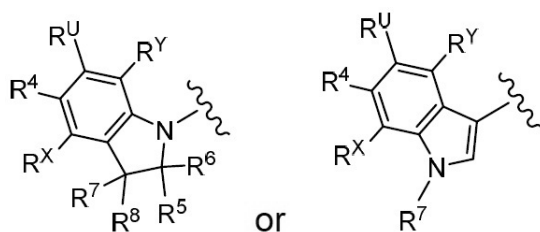


wherein each symbol is as defined in claim 1,
or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1 to 6, wherein
the group of the formula:

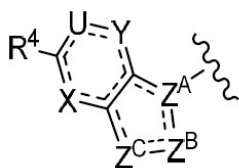


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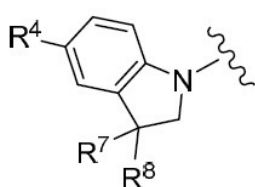


wherein each symbol is as defined in claim 1,
or a pharmaceutically acceptable salt thereof.

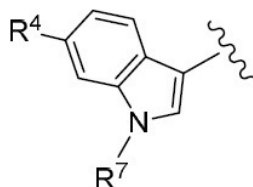
8. The compound according to any one of claims 1 to 7, wherein
the group of the formula:



is

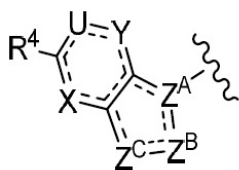


or

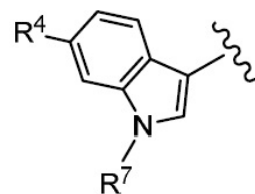


wherein each symbol is as defined in claim 1,
or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 1 to 8, wherein
the group of the formula:



is

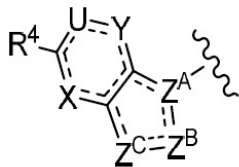


wherein

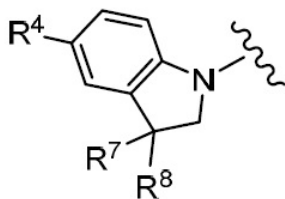
R^4 is as defined in claim 1; and

R^7 is substituted or unsubstituted alkyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic carbocycloxy carbonyl, substituted or unsubstituted non-aromatic heterocycloxy carbonyl or substituted or unsubstituted non-aromatic carbocyclylsulfonyl,
or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1 to 8, wherein the group of the formula:



is



wherein

R^4 is as defined in claim 1; and

R^7 and R^8 are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted non-aromatic carbon ring or a substituted or unsubstituted non-aromatic heterocyclic ring, or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of claims 1 to 10, wherein R^4 is substituted or unsubstituted alkyloxy, substituted or unsubstituted non-aromatic heterocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted amino, hydroxy, halogen, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic heterocyclyl or substituted or unsubstituted non-aromatic carbocyclyl, or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1 to 11, wherein R^4 is substituted or unsubstituted non-aromatic heterocycloxy

or substituted or unsubstituted non-aromatic carbocyclyloxy,
or a pharmaceutically acceptable salt thereof.

13.The compound according to claim 1 selected from the group consisting of compounds I-082, I-162, I-481, I-496, I-503, I-506, I-549, I-552, I-568, I-569, I-570, I-571, I-591, I-613, I-617 and I-618, or a pharmaceutically acceptable salt thereof.

14.A pharmaceutical composition comprising the compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof.

15.The pharmaceutical composition according to claim 14 having an anti-RS virus activity.

16.A method for the treatment and/or prevention of RSV infection, characterized in that the compound of any of the claims 1 to 13 or a pharmaceutically acceptable salt thereof is administered.

17.The compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof, for the treatment and/or prevention of RSV infection.

18.Use of the compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prevention of RSV infection.