

DESCRIPTION

Title of Invention: 3,5-DISUBSTITUTED ALKYNYL BENZENE COMPOUND AND SALT THEREOF

5 Technical Field

[0001]

The present invention relates to a novel 3,5-disubstituted benzene alkynyl compound and a salt thereof that have fibroblast growth factor receptor inhibitory effects; a
10 pharmaceutical composition, an FGFR inhibitor, and an antitumor agent, each comprising the 3,5-disubstituted benzene alkynyl compound or a salt thereof as an active ingredient; a method for treating a tumor; and use of the compound in the treatment of a tumor.

15 Background Art

[0002]

Fibroblast growth factors (FGFs) are involved in the regulation of various physiological processes, such as cell proliferation, chemotaxis, and differentiation. The physiological
20 activity of the FGFs is mediated by fibroblast growth factor receptors (FGFRs), which are specific cell surface receptors. FGFRs belong to a receptor protein tyrosine kinase family, and comprise an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain.
25 Four types of FGFRs (FGFR1, FGFR2, FGFR3, and FGFR4) have been heretofore identified. FGFRs bind to FGFs to form dimers, and are activated by phosphorylation. Activation of the receptors induces mobilization and activation of specific downstream signal transduction molecules, thereby developing physiological
30 functions.

[0003]

Many reports have been made about the relationship between aberrant FGF/FGFR signaling and various human cancers (e.g., NPL 1, NPL 2, and NPL 3). Aberrant activation of FGF/FGFR
35 signaling in human cancer is considered to be attributable to an

autocrine or paracrine mechanism by overexpression of FGFRs and/or gene amplification, gene mutation, chromosomal translocation, or overproduction of FGFs (ligands). Moreover, such aberrant signaling is considered to be partly responsible for therapeutic resistance to existing chemotherapeutic anticancer drugs or other receptor tyrosine kinase inhibitors in human cancer (NPL 4). Furthermore, the aberrant signaling is known to be associated with various diseases caused by abnormal angiogenic processes, such as solid tumor, rheumatoid arthritis, psoriasis, retinopathy, and age-related macular degeneration (NPL 5).

[0004]

Accordingly, therapies targeted for FGF/FGFR signaling not only have a direct antitumor effect on tumor cells that are highly dependent on FGF/FGFR signaling, but also exhibit an inhibitory effect on tumor angiogenesis induced by FGF/FGFR signaling; thus, such therapies are expected to be promising targeted therapies having sufficient antitumor effects. In addition, such therapies are expected to provide drug effect enhancers for existing chemotherapeutic anticancer drugs or other receptor tyrosine kinase inhibitors, or effective therapeutic remedies for cancer types that are resistant or unresponsive to these drugs.

[0005]

PTL 1 discloses a wide range of fused bicyclic compounds having mTOR inhibitory activity; however, the specifically disclosed compounds are all imidazopyrazine compounds, and FGFR inhibitory activity is nowhere mentioned in PTL 1. PTL 2 discloses BTK inhibitor compounds having a characteristic substituent at the 3-position of the pyrazolopyrimidine ring, but is silent about FGFR inhibitory activity. PTL 3 discloses HSP90 inhibitor compounds having a characteristic substituent at the 5-position of the pyrrolopyrimidine ring, but is silent about FGFR inhibitory activity.

Citation List

Patent Literature

[0006]

5 PTL 1: WO 2007/087395

PTL 2: WO 2008/121742

PTL 3: WO 2010/043865

Non-patent Literature

[0007]

10 NPL 1: J. Clin. Oncol. 24, 3664-3671 (2006)

NPL 2: Mol. Cancer Res. 3, 655-667 (2005)

NPL 3: Cancer Res. 70, 2085-2094 (2010)

NPL 4: Clin. Cancer Res. 17, 6130-6139 (2011)

NPL 5: Nat. Med. 1, 27-31 (1995)

15 Summary of Invention

Technical Problem

[0008]

Although FGFR inhibitors are expected to have therapeutic effects on various carcinomas as described above, no
20 potent and highly selective FGFR inhibitor has been found yet.

[0009]

Therefore, an object of the present invention is to provide a novel compound that has FGFR inhibitory activity and that is useful as an anticancer agent.

25 Solution to Problem

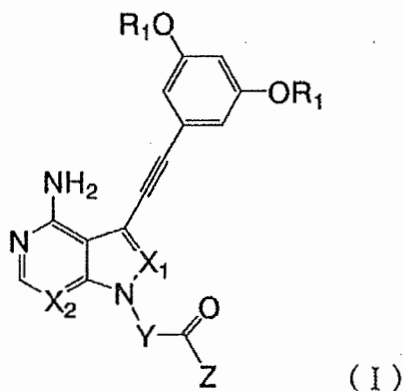
[0010]

The present inventors conducted extensive research to achieve the above object; and found that a benzene alkynyl compound containing a specific substituent has excellent FGFR
30 inhibitory activity and cancer cell growth inhibitory effects, and is useful as a medicament for the treatment of a cancer. The present invention has been accomplished based on this finding.

[0011]

The present invention provides a compound represented
35 by Formula (I)

[0012]



[0013]

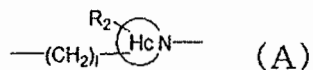
wherein R₁ is the same or different, and each represents C₁-C₆

5 alkyl;

X₁ and X₂ independently represent N or CH;

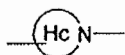
Y is a group represented by Formula (A)

[0014]



10 (wherein the divalent moiety represented by

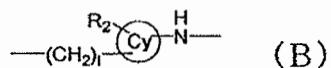
[0015]



is nitrogen-containing C₃-C₁₀ heterocycloalkylene),

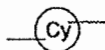
a group represented by Formula (B)

15 [0016]



(wherein the divalent moiety represented by

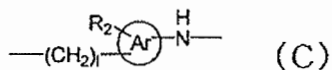
[0017]



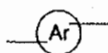
20 is C₃-C₁₀ cycloalkylene), or

a group represented by Formula (C)

[0018]



(wherein the divalent moiety represented by
[0019]



[0020]

5 is C₆-C₁₂ arylene);

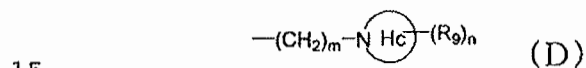
R₂ is hydrogen, C₂-C₆ alkynyl, -C(=O)OR_x, -C(=O)N(R_x)(R_y), hydroxy-C₁-C₆ alkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, or C₂-C₉ heteroaryl optionally having R₃;

R₃ is C₁-C₆ alkyl or di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl;

10 Z is -C(R₄)=C(R₅)(R₆) or -C≡C-R₇;

R₄, R₅, and R₆ are the same or different, and each represents hydrogen, halogen, C₁-C₆ alkyl optionally having R₈, or a group represented by Formula (D)

[0021]



(wherein the monovalent moiety represented by

[0022]



[0023]

20 is nitrogen-containing C₃-C₁₀ heterocycloalkyl),

R₇ is hydrogen, C₁-C₆ alkyl, or hydroxy-C₁-C₆ alkyl;

R₈ is -OR_x or -N(R_x)(R_y);

R₉ is C₁-C₆ alkyl, halogen, or -OR_x;

R_x and R_y are the same or different, and each

25 represents hydrogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, or C₁-C₆ alkoxy-C₁-C₆ alkyl;

l is an integer of 0 to 3;

m is an integer of 1 to 3; and

n is an integer of 0 to 2; or

30 a salt thereof.

[0024]

The present invention provides an FGFR inhibitor.

comprising the compound of Formula (I) or a salt thereof as an active ingredient.

[0025]

5 The present invention further provides a pharmaceutical composition comprising the compound of Formula (I) or a salt thereof and a pharmacologically acceptable carrier.

[0026]

10 The present invention provides an antitumor agent comprising the compound of Formula (I) or a salt thereof as an active ingredient.

[0027]

15 The present invention further provides a method for treating a tumor, comprising administering an effective amount of the compound of Formula (I) or a salt thereof to a patient in need of such a treatment.

[0028]

The present invention further provides a compound of Formula (I) or a salt thereof for use in the treatment of a tumor.

[0029]

20 The present invention provides use of the compound of Formula (I) or a salt thereof in the treatment of a tumor.

[0030]

25 Further, the present invention provides use of the compound of Formula (I) or a salt thereof in the manufacture of an antitumor agent.

Advantageous Effects of Invention

[0031]

30 According to the present invention, there can be provided a novel compound represented by the above Formula (I) or a salt thereof, which is useful as an FGFR inhibitor.

[0032]

35 It has been clarified that the compound or a salt thereof of the present invention has excellent FGFR inhibitory activity, and exhibits cancer cell growth inhibitory effects. Accordingly, the compound or a salt thereof of the present

invention is useful for preventing and/or treating a cancer.

Description of Embodiments

[0033]

5 The compound of the present invention represented by the above Formula (I) is a 3,5-disubstituted benzene alkynyl compound containing a condensed heteroaryl group substituted for an α,β -unsaturated amide via a spacer moiety, and is not disclosed in any of the above prior art documents.

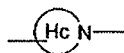
[0034]

10 In the present specification, the term "C₁-C₆ alkyl" refers to a straight or branched alkyl group having 1 to 6 carbon atoms. Specific examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, and the like. The C₁-C₆ alkyl is preferably a straight or
15 branched alkyl group having 1 to 4 carbon atoms (a C₁-C₄ alkyl group), and more preferably methyl, ethyl, isopropyl, and tert-butyl.

[0035]

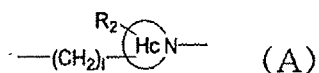
In this specification, the term "C₃-C₁₀ cycloalkyl" refers to a monocyclic or polycyclic cycloalkyl group having 3 to
20 10 carbon atoms, and is preferably a monocyclic cycloalkyl group having 3 to 6 carbon atoms (a C₃-C₆ cycloalkyl group). Specific examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, decalyl, and the like. Cyclopropyl and
25 cyclobutyl are preferable. In this specification, the divalent moiety represented by

[0037]



of the group represented by Formula (A)

30 [0036]

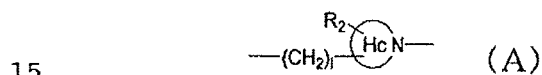


(wherein R₂ and l are as defined above)

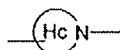
[0038]

is a C₃-C₁₀ divalent heterocycloalkylene group containing at least one nitrogen atom in the ring and further containing 0 to 2 same or different heteroatoms selected from oxygen and sulfur atoms in the ring (a nitrogen-containing C₃-C₁₀ heterocycloalkylene group),
 5 and is preferably a C₃-C₅ heterocycloalkylene group containing 1 to 3 nitrogen atoms in the ring and further containing 0 to 1 oxygen atom in the ring (a nitrogen-containing C₃-C₅ heterocycloalkylene group). Specific examples thereof include
 10 azetidinylene, pyrrolidinylene, piperidinylene, piperazinylene, morpholinylene, octahydroquinolinylene, octahydroindolylene, and the like. Among them, azetidinylene, pyrrolidinylene, piperidinylene, piperazinylene, and morpholinylene are preferable.
 [0039]

The group represented by Formula (A)



refers to a divalent nitrogen-containing C₃-C₁₀ heterocycloalkylene group represented by
 [0040]



20 [0041]

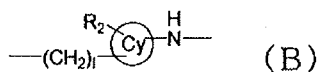
wherein the nitrogen atom has one arm and the other arm is connected to a substituent (-(CH₂)₁-), and a substituent R₂ is present on the ring.

In this specification, the divalent moiety represented by

25 [0043]



of the group represented by Formula (B)
 [0042]



30 (wherein R₂ and l are as defined above)

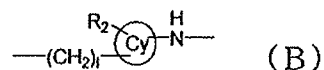
[0044]

refers to a monocyclic or polycyclic divalent cycloalkylene group

having 3 to 10 carbon atoms (a C₃-C₁₀ cycloalkylene group), and preferably a monocyclic divalent cycloalkylene group having 3 to 6 carbon atoms (a C₃-C₆ cycloalkylene group). Specific examples thereof include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, decalylene, and the like. Cyclopropylene and (1,2- or 1,3-)cyclobutylene are preferable.

Formula (B)

[0045]



refers to a divalent C₃-C₁₀ cycloalkylene group represented by

[0046]



[0047]

wherein one arm is connected to an adjacent amino group (NH) and the other arm is connected to a substituent (-(CH₂)₁-), and a substituent R₂ is present on the ring.

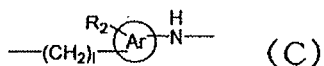
In the present specification, the divalent moiety represented by

[0048]



of the group represented by Formula (C)

[0049]



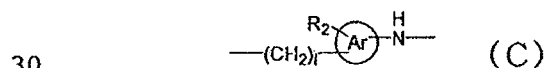
(wherein R₂ and l are as defined above)

[0050]

refers to a divalent arylene group having 6 to 12 carbon atoms (a C₆-C₁₂ arylene group). Specific examples thereof include phenylene, naphthylene, biphenylene, and the like. Phenylene is preferable.

Formula (C)

[0051]



refers to a divalent C₆-C₁₂ arylene group represented by

[0052]

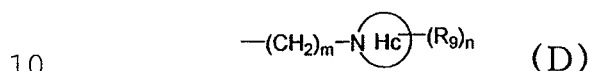


wherein one arm is connected to an adjacent amino group (NH) and the other arm is connected to a substituent $-(\text{CH}_2)_1-$, and a substituent R_2 is present on the ring.

5 In this specification, the monovalent moiety represented by [0054]



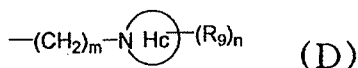
of the group represented by Formula (D) [0053]



(wherein R_9 , m , and n are as defined above) [0055]

refers to a $\text{C}_3\text{--C}_{10}$ heterocycloalkyl group containing at least one nitrogen atom in the ring and further containing 0 to 2 same or
15 different heteroatoms selected from oxygen and sulfur atoms in the ring (a nitrogen-containing $\text{C}_3\text{--C}_{10}$ heterocycloalkyl group), and is preferably a $\text{C}_3\text{--C}_5$ heterocycloalkyl group containing 1 to 3 nitrogen atoms in the ring and further containing 0 to 1 oxygen atom in the ring (a nitrogen-containing $\text{C}_3\text{--C}_5$ heterocycloalkyl
20 group). Specific examples thereof include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, octahydroquinolinyl, octahydroindolyl, and the like. Azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, and morpholinyl are preferable.

25 Formula (D) [0056]



denotes a nitrogen-containing $\text{C}_3\text{--C}_{10}$ heterocycloalkylene group represented by...

30 [0057]



[0058]

wherein the nitrogen atom is bound to a substituent $-(CH_2)_m-$, and n substituents $-(R_9)_n$ are present on the ring.

[0059]

5 In this specification, the "C₂-C₉ heteroaryl" refers to a monocyclic or bicyclic C₂-C₉ heteroaryl group containing 1 to 3 same or different heteroatoms selected from nitrogen, oxygen, and sulfur atoms; and is preferably a monocyclic C₂-C₅ heteroaryl group containing 1 to 3 same or different heteroatoms selected
10 from nitrogen, oxygen, and sulfur atoms (a C₂-C₅ heteroaryl group). Specific examples thereof include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, pyrazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isobenzofuryl, indoliziny, isoindolyl, indolyl, indazolyl,
15 quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, and the like. 1,3,4-Oxadiazolyl is preferable.

[0060]

 In this specification, the term "C₂-C₆ alkynyl" refers to a straight or branched C₂-C₆ alkynyl group having at least one
20 carbon-carbon triple bond. Specific examples thereof include ethynyl, 2-propynyl, 2-hexynyl, and the like. Ethynyl is preferable.

[0061]

 In the present specification, the term "hydroxy-C₁-C₆
25 alkyl" refers to a straight or branched C₁-C₆ alkyl group having one hydroxy group. Specific examples thereof include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, and the like. Among them, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, and 2-
30 hydroxybutyl are preferable.

[0062]

 In this specification, the term "di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl group" refers to a straight or branched C₁-C₆ alkyl group having an amino group having two straight or branched C₁-C₆
35 alkyl groups. A straight or branched C₁-C₄ alkyl group having an

amino group having two straight or branched C₁-C₄ alkyl groups (a di(C₁-C₄ alkyl)amino-C₁-C₄ alkyl group) is preferable. Specific examples thereof include dimethylaminomethyl, dimethylaminoethyl, dimethylaminopropyl, dimethylaminobutyl, dimethylaminopentyl, 5 dimethylaminohexyl, diethylaminomethyl, diethylaminoethyl, diethylaminopropyl, diethylaminobutyl, diethylaminopentyl, diethylaminohexyl, dipropylaminomethyl, dibutylaminomethyl, dipentylaminomethyl, dihexylaminomethyl, ethyl(methyl)aminomethyl, and the like. Dimethylaminomethyl and diethylaminomethyl are 10 preferable.

[0063]

In this specification, the term "C₁-C₆ alkoxy-C₁-C₆ alkyl" refers to a straight or branched C₁-C₆ alkyl group having a straight or branched C₁-C₆ alkoxy group. It is preferably a 15 straight or branched C₁-C₄ alkyl group having a straight or branched C₁-C₄ alkoxy group (a C₁-C₄ alkoxy-C₁-C₄ alkyl group). Specific examples of such groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, methoxypentyl, methoxyhexyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, 20 ethoxybutyl, ethoxypentyl, ethoxyhexyl, propoxymethyl, butoxymethyl, pentyloxymethyl, hexyloxymethyl, and the like. Among them, 2-methoxyethyl is preferable.

[0064]

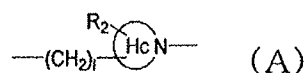
In this specification, examples of the "halogen" 25 include chlorine, bromine, fluorine, and iodine. Fluorine is preferable.

In Formula (I), the following combinations of X₁ and X₂ are preferable. (1) When X₂ is N, X₁ is N or CH. (2) When X₂ is CH, X₁ is CH.

30 In Formula (I), 1 is preferably 0 or 1.

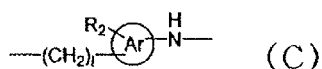
In Formula (I), Y is preferably a group represented by Formula (A)

[0065]



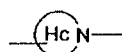
(wherein R_2 and l are as defined above) or a group represented by Formula (C)

[0066]



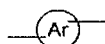
- 5 (wherein R_2 and l are as defined above). More preferably, the divalent moiety represented by

[0067]



- of a group represented by Formula (A) is pyrrolidinylene, azetidinylen, or piperidinylene, or the divalent moiety represented by

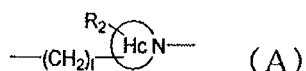
[0068]



of a group represented by Formula (C) is phenylene.

- 15 In Formula (I), the following combinations of Y and Z are preferable. When Y is a group represented by Formula (A)

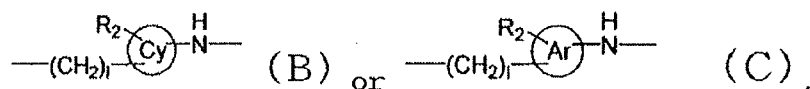
[0069]



(wherein R_2 and l are as defined above),

- 20 Z is $-\text{C}(\text{R}_4)=\text{C}(\text{R}_5)(\text{R}_6)$ or $-\text{C}\equiv\text{C}-\text{R}_7$. When Y is a group represented by the following Formula (B) or (C):

[0070]



(wherein R_2 and l are as defined above), Z is $-\text{C}(\text{R}_4)=\text{C}(\text{R}_5)(\text{R}_6)$.

- 25 [0071]

In Formula (I), R_1 is preferably C_1 - C_4 alkyl, and more preferably methyl or ethyl.

[0072]

In Formula (I), R_2 is preferably C_2 - C_6

- 30 alkynyl, $-\text{C}(=\text{O})\text{OR}_x$, hydroxy- C_1 - C_4 alkyl, or C_2 - C_9 heteroaryl

optionally having R₃, and more preferably ethynyl, methoxycarbonyl, hydroxymethyl, or 1,3,4-oxadiazolyl optionally having R₃.

[0073]

In Formula (I), R₃ is preferably C₁-C₄ alkyl or di-(C₁-C₄ alkyl)amino-C₁-C₄ alkyl, and more preferably methyl or dimethylaminomethyl.

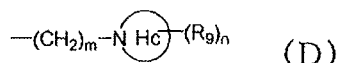
[0074]

In Formula (I), R₄ is preferably hydrogen or halogen, more preferably hydrogen or fluorine, and even more preferably hydrogen.

[0075]

In Formula (I), R₅ and R₆ are preferably hydrogen, C₁-C₄ alkyl group optionally having R₈, or a group represented by Formula (D)

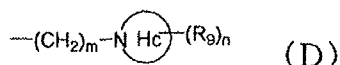
15 [0076]



[0077]

(wherein R₉, m, and n are as defined above), and more preferably hydrogen, methyl having R₈, or a group represented by Formula (D)

20 [0078]



(wherein R₉, m, and n are as defined above).

In Formula (I), m is preferably 1.

In Formula (I), R₉ is preferably C₁-C₄ alkyl, fluorine, or hydroxy, and more preferably methyl, fluorine, or hydroxy.

In Formula (I), n is preferably 0 or 1.

[0079]

In Formula (I), R₇ is preferably hydrogen, C₁-C₄ alkyl, or hydroxy-C₁-C₄ alkyl, and more preferably hydrogen, hydroxymethyl, methyl, or 2-hydroxy-2-methyl-ethyl.

30

[0080]

In Formula (I), R₈ is preferably hydroxy or -N(R_x)(R_y).

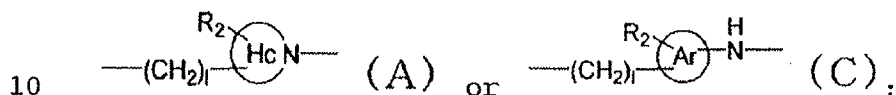
In this formula, R_x and R_y are preferably hydrogen, C₁-C₄ alkyl,

C₃-C₁₀ cycloalkyl, or C₁-C₄ alkoxy-C₁-C₄ alkyl, and more preferably hydrogen, methyl, ethyl, *tert*-butyl, isopropyl, cyclopropyl, cyclobutyl, or 2-methoxyethyl.

[0081]

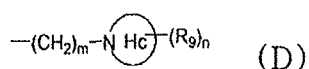
- 5 Preferable compounds of the present invention are compounds represented by Formula (I) wherein R₁ is C₁-C₄ alkyl; X₁ and X₂ are independently N or CH; Y is a group represented by the following Formula (A) or (C):

[0082]



- R₂ is C₂-C₆ alkynyl, -C(=O)OR_x, hydroxy-C₁-C₄ alkyl, or C₂-C₉ heteroaryl optionally having R₃; R₃ is C₁-C₄ alkyl or di(C₁-C₄ alkyl)amino-C₁-C₄ alkyl; Z is -C(R₄)=C(R₅)(R₆) or -C≡C-R₇; R₄ is hydrogen or halogen; R₅ and R₆ are the same or different, and each
15 represents hydrogen, C₁-C₄ alkyl optionally having R₈, or a group represented by Formula (D)

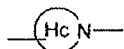
[0083]



- R₇ is hydrogen, C₁-C₄ alkyl, or hydroxy-C₁-C₄ alkyl; R₈ is hydroxy
20 or -N(R_x)(R_y); R₉ is C₁-C₄ alkyl, fluorine, or hydroxy; R_x and R_y are the same or different, and each represents hydrogen, C₁-C₄ alkyl, C₃-C₁₀ cycloalkyl, or C₁-C₄ alkoxy-C₁-C₄ alkyl; and l is 0 or 1, m is 1, and n is 0 or 1.

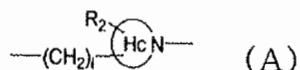
- More preferable compounds of the present invention are compounds
25 represented by Formula (I) wherein R₁ is C₁-C₄ alkyl, X₁ and X₂ are such that (1) when X₂ is N, X₁ is N or CH, and (2) when X₂ is CH, X₁ is CH; in Y, the divalent moiety represented by

[0085]



- 30 of the group represented by Formula (A)

[0084]



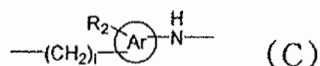
is pyrrolidinylene, azetidinylene, or piperidinylene, or the divalent moiety represented by

[0087]



of the group represented by Formula (C)

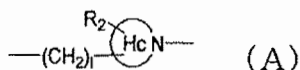
[0086]



is phenylene;

10 (a) when Y is a group represented by Formula (A)

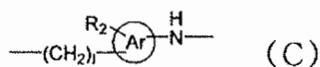
[0088]



(wherein R₂ is ethynyl, methoxycarbonyl, hydroxymethyl, or 1,3,4-oxadiazolyl optionally having R₃; R₃ is C₁-C₄ alkyl; and l is 0 or

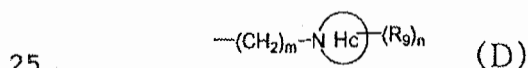
15 1), Z is -C(R₄)=C(R₅)(R₆) or -C≡C-R₇, (b) when Y is a group represented by Formula (C)

[0089]



20 (wherein R₂ is hydrogen; and l is 0 or 1), Z is -C(R₄)=C(R₅)(R₆); R₄ is hydrogen or fluorine; R₅ and R₆ are the same or different, and each represents hydrogen, C₁-C₄ alkyl optionally having R₈, or a group represented by Formula (D)

[0090]

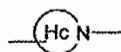


R₇ is hydrogen, hydroxymethyl, methyl, or 2-hydroxy-2-methyl-ethyl; R₈ is -N(R_x)(R_y); R₉ is C₁-C₄ alkyl, fluorine, or hydroxy; R_x and R_y are the same or different, and each represents hydrogen, C₁-C₄ alkyl, C₃-C₁₀ cycloalkyl, or C₁-C₄ alkoxy-C₁-C₄ alkyl, m is 1, 30 and n is 0 or 1.

[0091]

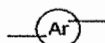
Even more preferable compounds of the present invention are compounds represented by Formula (I) wherein R₁ is methyl or ethyl; X₁ and X₂ are such that (1) when X₂ is N, X₁ is N or CH, and
 5 (2) when X₂ is CH, X₁ is CH; in Y, the divalent moiety represented by

[0092]



is pyrrolidinylene, azetidinylene, piperidinylene, or the
 10 divalent moiety represented by

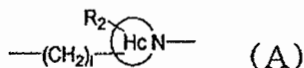
[0093]



is phenylene;

(a) when Y is a group represented by Formula (A)

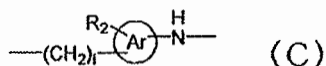
15 [0094]



(wherein R₂ is ethynyl, methoxycarbonyl, hydroxymethyl, or 1,3,4-oxadiazolyl optionally having methyl; and l is 0 or 1), Z

is -C(R₄)=C(R₅)(R₆) or -C≡C-R₇, (b) when Y is a group represented
 20 by Formula (C)

[0095]



(wherein R₂ is hydrogen; and l is 1),

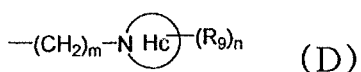
Z is -C(R₄)=C(R₅)(R₆); R₄ is hydrogen; R₅ and R₆ are the same or
 25 different, and each represents hydrogen, methyl having R₈, or the monovalent moiety represented by

[0097]



of the group represented by Formula (D)

30 [0096]



is pyrrolidinyl, piperidinyl, azetidiny, piperazinyl, or morpholinyl; R_7 is hydrogen, hydroxymethyl, methyl, or 2-hydroxy-2-methyl-ethyl; R_8 is $-N(R_x)(R_y)$; R_9 is methyl, fluorine, or hydroxy and; R_x and R_y are the same or different, and each represents hydrogen, methyl, ethyl, *tert*-butyl, isopropyl, cyclopropyl, cyclobutyl, or 2-methoxyethyl; and m is 1, and n is 0 or 1.

[0098]

Specific examples of preferable compounds of the present invention include the following:

(1) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound of Example 2),

(2) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-yn-1-one (Compound of Example 5),

(3) (S)-1-(3-(4-amino-3-((3,5-diethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound of Example 8),

(4) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)prop-2-en-1-one (Compound of Example 9),

(5) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-hydroxybut-2-yn-1-one (Compound of Example 10),

(6) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Compound of Example 12),

(7) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(cyclopropylamino)but-2-en-1-one (Compound of Example 13),

(8) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-

- (isopropylamino)but-2-en-1-one (Compound of Example 14),
(9) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(ethyl(methyl)amino)but-2-en-1-one (Compound of Example 15),
5 (10) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(cyclobutylamino)but-2-en-1-one (Compound of Example 16),
(11) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(diethylamino)but-
10 2-en-1-one (Compound of Example 17),
(12) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(tert-butylamino)but-2-en-1-one (Compound of Example 18),
(13) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-
15 (isopropyl(methyl)amino)but-2-en-1-one (Compound of Example 19),
(14) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(piperidin-1-yl)but-2-en-1-one (Compound of Example 20),
20 (15) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(3-fluoropyrrolidin-1-yl)but-2-en-1-one (Compound of Example 22),
(16) (R)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(3-
25 fluoropyrrolidin-1-yl)but-2-en-1-one (Compound of Example 23),
(17) 1-((2S,4S)-4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-(hydroxymethyl)pyrrolidin-1-yl)prop-2-en-1-one (Compound of Example 28),
(18) 1-(2S,4S)-4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-ethynylpyrrolidin-1-yl)prop-2-
30 en-1-one (Compound of Example 32),
(19) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Compound of Example 38),
35 (20) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-

- pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)prop-2-en-1-one
(Compound of Example 39),
- (21) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(pyrrolidin-1-
5 yl)but-2-en-1-one (Compound of Example 40),
- (22) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(4-
hydroxypiperidin-1-yl)but-2-en-1-one (Compound of Example 42),
- (23) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
10 pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)but-2-yn-1-one
(Compound of Example 46),
- (24) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-hydroxy-4-
methylpent-2-yn-1-one (Compound of Example 47),
- 15 (25) 1-((S)-3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-((S)-3-
fluoropyrrolidin-1-yl)but-2-en-1-one (Compound of Example 49),
- (26) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(piperidin-1-
20 yl)but-2-en-1-one (Compound of Example 50),
- (27) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)prop-2-en-1-one
(Compound of Example 51),
- (28) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
25 pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(dimethylamino)but-
2-en-1-one (Compound of Example 52),
- (29) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(pyrrolidin-1-
yl)but-2-en-1-one (Compound of Example 53),
- 30 (30) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(azetidin-1-yl)but-
2-en-1-one (Compound of Example 55),
- (31) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-
35 (ethyl(methyl)amino)but-2-en-1-one (Compound of Example 56),

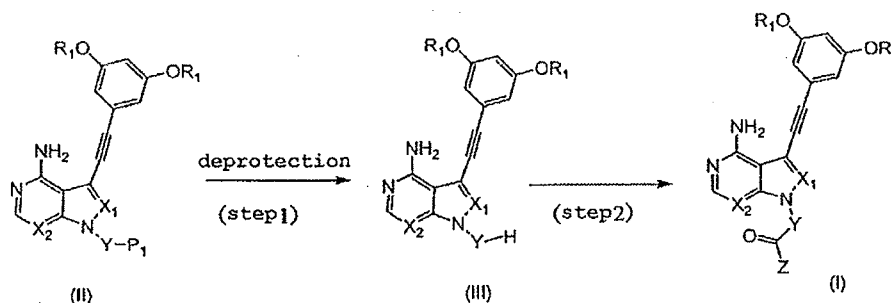
- (32) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(isopropylamino)but-2-en-1-one (Compound of Example 57),
- (33) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(diethylamino)but-2-en-1-one (Compound of Example 59),
- (34) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-((2-methoxyethyl)(methyl)amino)but-2-en-1-one (Compound of Example 60),
- (35) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(4-hydroxypiperidin-1-yl)but-2-en-1-one (Compound of Example 61),
- (36) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(3-hydroxypyrrolidin-1-yl)but-2-en-1-one (Compound of Example 62),
- (37) (R)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(3-hydroxypyrrolidin-1-yl)but-2-en-1-one (Compound of Example 63),
- (38) (2S,4S)-methyl 1-acryloyl-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate (Compound of Example 66),
- (39) 1-((2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound of Example 68), and
- (40) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound of Example 73).

[0099]

Next, the method for producing the compound according to the present invention will be explained. Compound (I) of the present invention can be produced, for example, by the following production methods or by the methods described in Examples. However, the method for producing Compound (I) of the present invention is not limited to these reaction examples.

Production method 1

[0100]



(wherein P₁ is a protecting group of the amino group contained in
 5 Y; and R₁, X₁, X₂, Y, and Z are as defined above.)

[0101]

(Step 1) In this step, the protected amino group of the
 compound of Formula (II) is deprotected to produce the compound
 of Formula (III). The method for the deprotection can be
 10 performed according to a known method, such as the method
 described in Protective Groups in Organic Synthesis, T.W. Greene,
 John Wiley & Sons (1981); or methods similar thereto. An example
 of the protecting group is *tert*-butyloxycarbonyl. If a *tert*-
 butyloxycarbonyl group is used as a protecting group, the
 15 deprotection is preferably performed under acidic conditions.
 Examples of acids that can be used include hydrochloric acid,
 acetic acid, trifluoroacetic acid, sulfuric acid, methanesulfonic
 acid, tosic acid, and the like. Such an acid is preferably used
 in an amount of 1 to 100 moles per mole of Compound (II).

20 [0102]

Any solvent that does not adversely affect the reaction
 can be used. Examples thereof include alcohols (e.g., methanol),
 hydrocarbons (e.g., benzene, toluene, and xylene), halogenated
 hydrocarbons (e.g., methylene chloride, chloroform, and 1,2-
 25 dichloroethane), nitriles (e.g., acetonitrile), ethers (e.g.,
 dimethoxyethane and tetrahydrofuran), aprotic polar solvents
 (e.g., *N,N*-dimethylformamide, dimethyl sulfoxide, and
 hexamethylphosphoramide), or a mixture thereof. The reaction time
 is 0.1 to 100 hours, and preferably 0.5 to 24 hours. The reaction

temperature is 0 to 120°C, and preferably 0 to 90°C.

[0103]

The thus-obtained compound of Formula (III) can be subjected to the subsequent step after or without isolation and purification by known separation and purification means, such as
5 concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0104]

(Step 2) In this step, the compound of Formula (III) is
10 amidated with a carboxylic acid represented by Z-COOH or with an acid halide represented by Z-C(=O)-L (wherein L is chlorine or bromine) to produce the compound of Formula (I).

[0105]

When a carboxylic acid represented by Z-COOH is used as
15 an amidation reagent, the reaction is performed by using the carboxylic acid in an amount of 0.5 to 10 moles, and preferably 1 to 3 moles, per mole of the compound of Formula (III) in the presence of a suitable condensing agent. The carboxylic acid may be a commercially available product, or can be produced according
20 to a known method.

[0106]

Any reaction solvent that does not adversely affect the reaction can be used. Examples of preferable solvents include isopropanol, *tert*-butyl alcohol, toluene, benzene, methylene
25 chloride, chloroform, tetrahydrofuran, 1,4-dioxane, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, and mixed solvents thereof. The reaction temperature is usually -78 to 200°C, and preferably 0 to 50°C. The reaction time is typically 5 minutes to 3 days, and
30 preferably 5 minutes to 10 hours.

[0107]

Examples of the condensing agent include diphenylphosphoryl azide, *N,N'*-dicyclohexylcarbodiimide, benzotriazol-1-yloxy-trisdimethylaminophosphonium salts, 4-(4,6-
35 dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, 1-

ethyl-3-(3-dimethylaminopropyl)carbodiimide, a combination of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1-hydroxybenzotriazole, 2-chloro-1,3-dimethylimidazolinium chloride, O-(7-azabenzotriazo-1-yl)-N,N,N',N'-tetramethylhexauronium
5 hexafluorophosphate, and the like.

[0108]

A base can be optionally added for the reaction. Examples of usable bases include organic bases such as triethylamine, diisopropylethylamine, pyridine, lutidine,
10 collidine, 4-dimethylaminopyridine, potassium *tert*-butyrate, sodium *tert*-butyrate, sodium methoxide, sodium ethoxide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, and butyl lithium; and inorganic bases such as sodium hydrogen carbonate, sodium carbonate, potassium
15 carbonate, cesium carbonate, sodium hydroxide, and sodium hydride. Such a base is added in an amount of 1 to 100 moles, and preferably 1 to 10 moles, per mole of the compound of Formula (III).

[0109]

20 When an acid halide represented by Z-C(=O)-L (wherein L is chlorine or bromine) is used as an amidation reagent, the acid halide is used in an amount of 0.5 to 5 moles, and preferably 0.9 to 1.1 moles, per mole of the compound of Formula (III). The acid halide may be a commercially available product, or can be
25 produced according to a known method.

[0110]

Any reaction solvent that does not adversely affect the reaction can be used. Examples of preferable solvents include toluene, benzene, methylene chloride, chloroform, tetrahydrofuran,
30 1,4-dioxane, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, and mixed solvents thereof. The reaction temperature is typically -78 to 200°C, and preferably -20 to 50°C. The reaction time is typically 5 minutes to 3 days, and preferably 5 minutes to 10 hours.

35 [0111]

A base can be optionally added for the reaction. Examples of usable bases include organic bases such as triethylamine, diisopropylethylamine, pyridine, lutidine, collidine, 4-dimethylaminopyridine, potassium *tert*-butyrate, sodium *tert*-butyrate, sodium methoxide, sodium ethoxide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, and butyl lithium; and inorganic bases such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, and sodium hydride. Such a base is added in an amount of 1 to 100 moles, preferably 1 to 10 moles, per mole of the compound of Formula (III).

[0112]

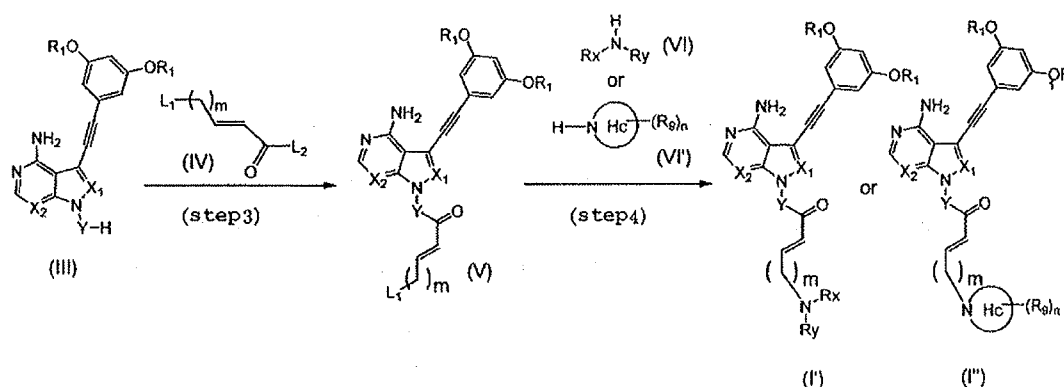
The thus-obtained compound of Formula (I) can be isolated and purified by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0113]

Among the Compounds (I) of the present invention, compound of Formula (I') or (I'') can also be produced by production method 2 using, for example, Compound (III) obtained in step 1 of production method 1 as a starting compound, and using a specific amine.

Production method 2

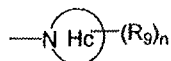
[0114]



25

(wherein L_1 and L_2 are halogen; H of Y-H is hydrogen directly bound to a nitrogen atom; and X_1 , X_2 , Y, R_x , R_y , R_1 ,

[0115]



m, and n are as defined above.)

[0116]

(Step 3) In this step, the compound of Formula (III) is
5 amidated with an acid halide represented by Formula (IV) to
produce the compound of Formula (V).

[0117]

Examples of halogen atoms represented by L₁ or L₂ in
Formula (IV) include bromine and chlorine. The compound
10 represented by Formula (IV) may be a commercially available
product, or can be produced according to a known method.

[0118]

The compound of Formula (IV) is used in an amount of
0.5 to 5 moles, and preferably 0.9 to 1.1 moles, per mole of
15 Compound (III).

[0119]

A base can be optionally added for the reaction.
Examples of usable bases include organic bases such as
triethylamine, diisopropylethylamine, pyridine, lutidine,
20 collidine, 4-dimethylaminopyridine, potassium *tert*-butyrate,
sodium *tert*-butyrate, sodium methoxide, sodium ethoxide, lithium
hexamethyldisilazide, sodium hexamethyldisilazide, potassium
hexamethyldisilazide, and butyl lithium; and inorganic bases such
as sodium hydrogen carbonate, sodium carbonate, potassium
25 carbonate, cesium carbonate, sodium hydroxide, and sodium hydride.
Such a base can be added in an amount of 1 to 100 moles, and
preferably 1 to 10 moles, per mole of compound of Formula (III).

[0120]

Any reaction solvent that does not adversely affect the
30 reaction can be used. Examples of preferable reaction solvents
include toluene, benzene, methylene chloride, chloroform,
tetrahydrofuran, 1,4-dioxane, dimethylformamide,
dimethylacetamide, *N*-methylpyrrolidinone, and mixed solvents
thereof. The reaction temperature is typically -78 to 200°C, and

preferably 0 to 50°C. The reaction time is typically 5 minutes to 3 days, and preferably 5 minutes to 10 hours.

[0121]

The thus-obtained compound of Formula (V) can be
5 subjected to the subsequent step after or without isolation and purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0122]

10 (Step 4) In this step, the compound of Formula (V) is alkylated with an amine represented by Formula (VI) or (VI') to produce the compound (I') or (I'') of the present invention.

[0123]

The compound of Formula (VI) or (VI') can be used in an
15 amount of 1 to 20 moles, and preferably 1 to 10 moles, per mole of the compound of Formula (V).

[0124]

Further, a base can optionally be added for the reaction. Examples of such bases include organic bases such as
20 triethylamine, diisopropylethylamine, pyridine, lutidine, collidine, 4-dimethylaminopyridine, potassium *tert*-butyrate, sodium *tert*-butyrate, sodium methoxide, sodium ethoxide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, and butyl lithium; and inorganic bases such
25 as sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, and sodium hydride. Such a base can be added in an amount of 1 to 100 moles, and preferably 1 to 20 moles, per mole of the compound of Formula (V).

[0125]

30 Any reaction solvent that does not adversely affect the reaction can be used. For example, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, *N*-methylpyrrolidin-2-one, acetonitrile, and the like can be used singly, or as a mixture. The reaction time is 0.1 to 100
35 hours, and preferably 0.5 to 24 hours. The reaction temperature

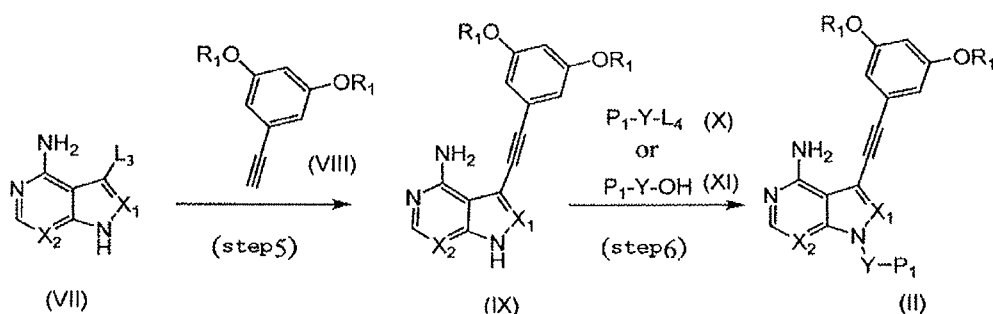
is 0°C to the boiling temperature of the solvent, and preferably 0 to 100°C.

[0126]

The thus-obtained compound of Formula (I') or (I'') can be isolated and purified by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography. The compound of Formula (II) used for producing Compound (I) of the present invention can be produced, for example, by production method 3 or 4.

Production method 3

[0127]



(wherein L₃ and L₄ are leaving groups; and R₁, X₁, X₂, Y, and P₁ are as defined above.)

[0128]

(Step 5) In this step, the compound of Formula (VII) is subjected to a coupling (Sonogashira) reaction with the compound of Formula (VIII) to produce the compound of Formula (IX). This step can be performed according to a generally known method (see, for example, Chemical Reviews, vol. 107, p. 874, 2007), for example, in the presence of a transition metal catalyst and a base in a solvent that does not adversely affect the reaction.

[0129]

In Formula (VII), the leaving group represented by L₃ is bromine or iodine. The compound of Formula (VII) may be a commercially available product, or can be produced by a known method.

[0130]

In this step, the compound of Formula (VIII) can be used in an amount of 1 to 10 moles, and preferably 1 to 3 moles, per mole of the compound of Formula (VII).

5 [0131]

Examples of transition metal catalysts that can be used in this step include palladium catalysts (e.g., palladium acetate, tris(dibenzylideneacetone)dipalladium, and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride
10 dichloromethane complex). If necessary, a ligand (e.g., triphenylphosphine and tri-*tert*-butylphosphine) can be added and a copper reagent (e.g., copper iodide and copper acetate) can be used as a cocatalyst. The amount of the transition metal catalyst used may vary depending on the type of catalyst. The transition
15 metal catalyst is typically used in an amount of 0.0001 to 1 mole, and preferably 0.01 to 0.5 moles, per mole of the compound of Formula (VII). The amount of the ligand used is typically 0.0001 to 4 moles, and preferably 0.01 to 2 moles, per mole of the compound of Formula (VII). The amount of the cocatalyst used is
20 typically 0.0001 to 4 moles, and preferably 0.01 to 2 moles, per mole of the compound of Formula (VII).

[0132]

A base may optionally be added for the reaction. Examples of usable bases include organic bases such as
25 triethylamine, diisopropylethylamine, pyridine, lutidine, collidine, 4-dimethylaminopyridine, potassium *tert*-butyrate, sodium *tert*-butyrate, sodium methoxide, sodium ethoxide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, and butyl lithium; and inorganic bases such
30 as sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, and sodium hydride. Among them, organic bases such as triethylamine and diisopropylethylamine are preferable. The amount of the base used is typically 0.1 to 50 moles, preferably 1 to 20 moles, per mole
35 of the compound of Formula (VII).

[0133]

Any reaction solvent that does not adversely affect the reaction can be used. Examples of usable solvents include hydrocarbons (e.g., benzene, toluene, and xylene), nitriles (e.g.,
5 acetonitrile), ethers (e.g., dimethoxyethane, tetrahydrofuran, and 1,4-dioxane), alcohols (e.g., methanol and ethanol), aprotic polar solvents (e.g., dimethylformamide, dimethyl sulfoxide, and hexamethylphosphoramide), water, and mixtures thereof. The reaction time is 0.1 to 100 hours, and preferably 0.5 to 24 hours.
10 The reaction temperature is 0°C to the boiling temperature of the solvent, and preferably 0 to 150°C.

[0134]

The thus-obtained compound of Formula (IX) can be subjected to the subsequent step after or without isolation and
15 purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0135]

(Step 6) In this step, the compound of Formula (IX) is
20 used with the compound of Formula (X) or (XI) to produce the compound of Formula (II).

[0136]

When the compound of Formula (X) is used as an alkylating reagent, the compound of Formula (II) can be produced
25 in the presence of a base. In Formula (X), L_4 may be a leaving group, such as chlorine, bromine, iodine, a methanesulfonic acid ester, or a *p*-toluenesulfonic acid ester. The alkylating reagents may be a commercially available product, or can be produced according to a known method. The compound of Formula (X) can be
30 used in an amount of 1 to 10 moles, preferably 1 to 5 moles, per mole of the compound of Formula (IX).

[0137]

Examples of usable bases include inorganic bases such as sodium hydrogen carbonate, sodium carbonate, potassium
35 carbonate, cesium carbonate, cesium hydroxide, sodium hydride,

and potassium hydride; and organic amines such as trimethylamine, triethylamine, tripropylamine, diisopropylethylamine, *N*-methylmorpholine, pyridine, 4-(*N,N*-dimethylamino)pyridine, lutidine, and collidine. Such a base can be used in an amount of
5 1 to 100 moles, preferably 2 to 10 moles, per mole of the compound of Formula (IX).

[0138]

As the solvent, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-
10 dioxane, *N*-methylpyrrolidin-2-one, acetonitrile, and the like can be used singly, or as a mixture. The reaction time is 0.1 to 100 hours, and preferably 0.5 to 24 hours. The reaction temperature is 0°C to the boiling temperature of the solvent, and preferably 0 to 100°C.

15 [0139]

When the compound of Formula (XI) is used as an alkylating reagent, the compound of Formula (II) can be produced by using a Mitsunobu reaction. This step can be performed according to a generally known method (see, for example, Chemical
20 Reviews, Vol. 109, p. 2551, 2009), for example, in the presence of Mitsunobu reagents and a phosphine reagent in a solvent that does not adversely affect the reaction. This step is performed using the compound of Formula (XI) in an amount of 1 to 10 moles per mole of the compound of Formula (IX).

25 [0140]

Examples of Mitsunobu reagents include diethyl azodicarboxylate, diisopropyl azodicarboxylate, and the like. Such Mitsunobu reagents are used in an amount of 1 to 10 moles, and preferably 1 to 5 moles, per mole of the compound of Formula
30 (IX).

[0141]

Examples of phosphine reagents include triphenylphosphine, tributylphosphine, and the like. Such a phosphine reagent is used in an amount of 1 to 10 moles, and
35 preferably 1 to 5 moles, per mole of the compound of Formula (IX).

[0142]

Any reaction solvent that does not adversely affect the reaction can be used. Examples of preferable reaction solvents include toluene, benzenetetrahydrofuran, 1,4-dioxane, dimethylformamide, dimethylacetamide, *N*-methylpyrrolidinone, dimethyl sulfoxide, and mixed solvents thereof.

[0143]

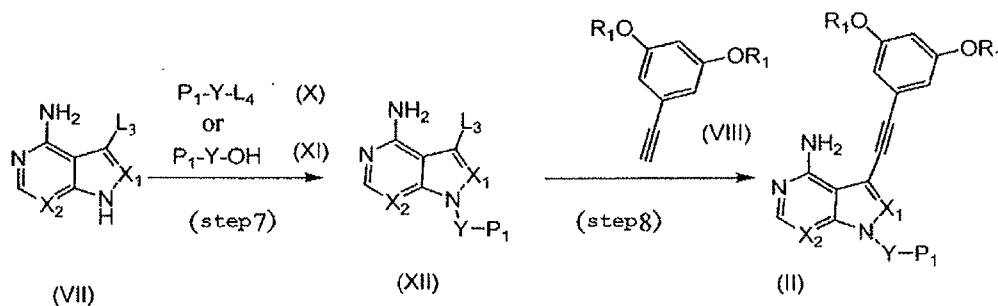
The reaction temperature is typically -78 to 200°C, and preferably 0 to 50°C. The reaction time is typically 5 minutes to 3 days, and preferably 10 minutes to 10 hours.

[0144]

The thus-obtained compound of Formula (II) can be utilized after or without isolation and purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography, to produce the Compound (I) of the present invention.

Production method 4

[0145]



20

(wherein L₃, L₄, R₁, X₁, X₂, Y, and P₁ are as defined above.)

[0146]

(Step 7) This step can be performed in a manner similar to step 6.

25 [0147]

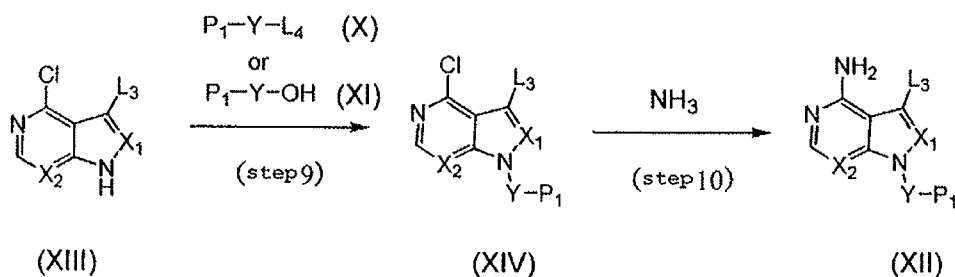
(Step 8) This step can be performed in a manner similar to step 5.

[0148]

The compound of Formula (XII) used in the production of Compound (I) of the present invention can also be produced, for example, by production method 5.

Production method 5

5 [0149]



(wherein L_3 , L_4 , X_1 , X_2 , Y , and P_1 are as defined above.)

[0150]

(Step 9) This step can be performed in a manner similar to step 6.

[0151]

(Step 10) In this step, the compound of Formula (XIV) is reacted with ammonia or a salt thereof to produce the compound of Formula (XII).

15 [0152]

The ammonia or a salt thereof is typically used in an equimolar to excessive molar amount per mole of the compound of Formula (XIII) in this step. Any reaction solvent that does not adversely affect the reaction can be used. Examples of preferable reaction solvents include water, methanol, ethanol, isopropanol, *tert*-butyl alcohol, tetrahydrofuran, 1,4-dioxane, dimethylformamide, *N*-methylpyrrolidone, dimethyl sulfoxide, and mixed solvents thereof.

[0153]

25 The reaction temperature is typically 0 to 200°C, and preferably room temperature to 150°C. The reaction time is typically 5 minutes to 7 days, and preferably 30 minutes to 24 hours.

[0154]

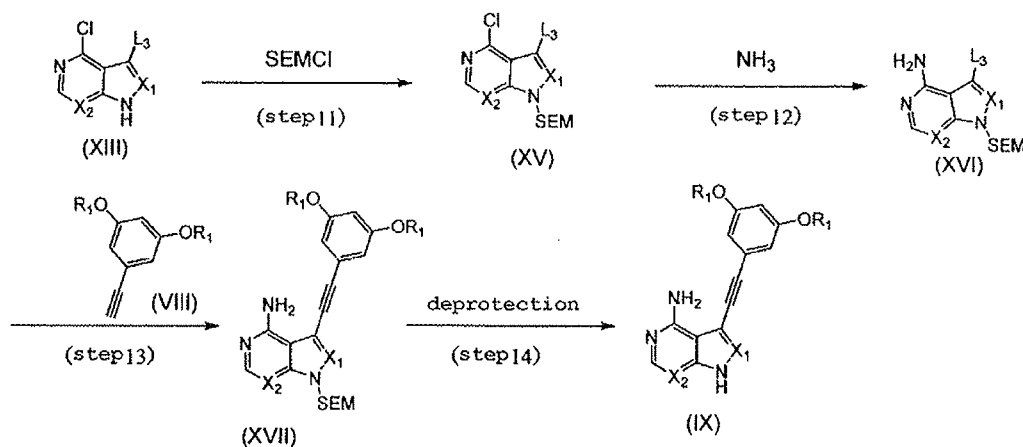
The thus-obtained compound of Formula (XIV) can be subjected to the subsequent step after or without isolation and purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0155]

The compound of Formula (IX) used in the production of Compound (I) of the present invention can also be produced, for example, by production method 6.

Production method 6

[0156]



(wherein L_3 , X_1 , and X_2 are as defined above, and SEM is trimethylsilylethoxymethyl.)

[0157]

(Step 11) In this step, the compound of Formula (XIII) is reacted with SEMCl (trimethylsilylethoxymethylchloride) in the presence of a base to produce the compound of Formula (XV). The compound of Formula (XIII) may be a commercially available product, or can be produced according to a known method.

[0158]

SEMCl is typically used in an equimolar to excessive molar amount per mole of the compound of Formula (XIII) in this step. Any reaction solvent that does not adversely affect the reaction can be used. Examples of preferable reaction solvents

include tetrahydrofuran, 1,4-dioxane, chloroform, methylene chloride, dimethylformamide, N-methylpyrrolidone, and mixed solvents thereof.

[0159]

5 Examples of usable bases include organic bases such as triethylamine, diisopropylethylamine, pyridine, and 4-dimethylaminopyridine; and inorganic bases such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, sodium hydride, and potassium *tert*-
10 butyrate.

[0160]

Such a base is typically used in an equimolar to excessive molar amount, and preferably 1 to 3 moles, per mole of the compound of Formula (III).

15 [0161]

The reaction temperature is typically -78 to 50°C, and preferably 0°C to room temperature. The reaction time is typically 5 minutes to 7 days, and preferably 10 minutes to 24 hours. The thus-obtained compound of Formula (XV) can be
20 subjected to the subsequent step after or without isolation and purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0162]

25 (Step 12) This step can be performed in a manner similar to step 10. The thus-obtained compound of Formula (XVI) can be subjected to the subsequent step after or without isolation and purification by known separation and purification means, such as concentration, vacuum concentration,
30 crystallization, solvent extraction, reprecipitation, and chromatography.

[0163]

(Step 13) This step can be performed in a manner similar to step 5.

35 [0164]

(Step 14) In this step, the compound of Formula (XVII) is deprotected under acidic conditions to produce the compound of Formula (IX). The deprotection can be performed by a known method, such as the method described in Protective Groups in Organic
5 Synthesis, T.W. Greene, John Wiley & Sons (1981); or a method similar thereto. Examples of usable acids include hydrochloric acid, acetic acid, trifluoroacetic acid, sulfuric acid, methanesulfonic acid, tosic acid, and the like. Such an acid is used in an amount of 1 to 100 moles per mole of the compound of
10 Formula (XVII).

[0165]

Any solvent that does not adversely affect the reaction can be used. Examples of usable solvents include alcohols (e.g., methanol), hydrocarbons (e.g., benzene, toluene, and xylene),
15 halogenated hydrocarbons (e.g., methylene chloride, chloroform, and 1,2-dichloroethane), nitriles (e.g., acetonitrile), ethers (e.g., dimethoxyethane, tetrahydrofuran, and 1,4-dioxane), aprotic polar solvents (e.g., *N,N*-dimethylformamide, dimethyl sulfoxide, and hexamethylphosphoramide), and mixtures thereof.
20 The reaction time is 0.1 to 100 hours, and preferably 0.5 to 24 hours. The reaction temperature is 0°C to the boiling temperature of the solvent, and preferably 0 to 100°C.

[0166]

The thus-obtained compound of Formula (IX) can be used
25 in step 6 after or without isolation and purification by known separation and purification means, such as concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, and chromatography.

[0167]

30 In the above production methods 1 to 6, for functional groups having an active proton, such as amino, imino, hydroxy, carboxyl, carbonyl, and amide groups, and indole, protected reagents can be used or a protecting group is introduced into such a functional group according to a usual method, and then the
35 protecting group can be removed in an appropriate step in each

production method.

[0168]

The "protecting group of an amino group or protecting group of an imino group" is not particularly limited insofar as it has a protecting function. Examples of such protecting groups include aralkyl groups such as benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, benzhydryl, trityl, and cumyl; lower alkanoyl groups such as formyl, acetyl, propionyl, butyryl, pivaloyl, trifluoroacetyl, and trichloroacetyl; benzoyl; arylalkanoyl groups such as phenylacetyl and phenoxycetyl; lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, and *tert*-butoxycarbonyl; aralkyloxycarbonyl groups such as *p*-nitrobenzyloxycarbonyl and phenethyloxycarbonyl; lower alkylsilyl groups such as trimethylsilyl and *tert*-butyldimethylsilyl; tetrahydropyranyl; trimethylsilylethoxymethyl; lower alkylsulfonyl groups such as methylsulfonyl, ethylsulfonyl, and *tert*-butylsulfonyl; lower alkylsulfinyl groups such as *tert*-butylsulfinyl; arylsulfonyl groups such as benzenesulfonyl and toluenesulfonyl; and imido groups such as phthalimido. In particular, trifluoroacetyl, acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, trimethylsilylethoxymethyl, cumyl, and the like are preferable.

[0169]

The "protecting group of a hydroxy group" is not particularly limited insofar as it has a protecting function. Examples of such protecting groups include lower alkyl groups such as methyl, ethyl, propyl, isopropyl, and *tert*-butyl; lower alkylsilyl groups such as trimethylsilyl and *tert*-butyldimethylsilyl; lower alkoxymethyl groups such as methoxymethyl and 2-methoxyethoxymethyl; tetrahydropyranyl; trimethylsilylethoxymethyl; aralkyl groups such as benzyl, *p*-methoxybenzyl, 2,3-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, and trityl; and acyl groups such as formyl, acetyl, and trifluoroacetyl. In particular, methyl, methoxymethyl,

tetrahydropyranyl, trimethylsilylethoxymethyl, *tert*-butyldimethylsilyl, acetyl, and the like are preferable.

[0170]

5 The "protecting group of a carboxy group" is not particularly limited insofar as it has a protecting function. Examples of such protecting groups include lower alkyl groups such as methyl, ethyl, propyl, isopropyl, and *tert*-butyl; halo-lower-alkyl groups such as 2,2,2-trichloroethyl; lower alkenyl groups such as allyl; trimethylsilylethoxymethyl; and aralkyl
10 groups such as benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, benzhydryl, and trityl. In particular, methyl, ethyl, *tert*-butyl, allyl, benzyl, *p*-methoxybenzyl, trimethylsilylethoxymethyl, and the like are preferable.

[0171]

15 The "protecting group of a carbonyl group" is not particularly limited insofar as it has a protecting function. Examples of such protecting groups include ketals and acetals, such as ethylene ketal, trimethylene ketal, dimethyl ketal, ethylene acetal, trimethylene acetal, and dimethyl acetal.

20 [0172]

The method for removing such a protecting group may vary depending on the type of protecting group, stability of the desired compound (I), etc. For example, the following methods can be used: solvolysis using an acid or a base according to the
25 method disclosed in a publication (Protective Groups in Organic Synthesis, third edition, T.W. Green, John Wiley & Sons (1999)) or a method similar thereto, i.e., a reaction method using, for example, 0.01 moles or a large excess of an acid, preferably trifluoroacetic acid, formic acid, or hydrochloric acid, or an
30 equimolar amount to a large excess of a base, preferably potassium hydroxide or calcium hydroxide; chemical reduction using a metal hydride complex or the like; or catalytic reduction using a palladium-carbon catalyst, Raney nickel catalyst, or the like.

35 [0173]

The compound of the present invention can be isolated and purified by usual isolation and purification means. Examples of such means include solvent extraction, recrystallization, preparative reversed-phase high-performance liquid chromatography, column chromatography, preparative thin-layer chromatography, and the like.

[0174]

When the compound of the present invention has isomers such as optical isomers, stereoisomers, positional isomers, and rotational isomers, any of the isomers and mixtures thereof are included within the scope of the compound of the present invention. For example, when the compound has optical isomers, optical isomers separated from a racemic mixture are also included within the scope of the compound of the present invention. Each of these isomers can be obtained as a single compound by known synthesis and separation means (e.g., concentration, solvent extraction, column chromatography, and recrystallization).

[0175]

The compound or a salt thereof of the present invention may be crystalline. A single crystal form thereof and a polymorphic mixture thereof are both included within the scope of the compound or a salt thereof of the present invention. These crystals can be produced by crystallization according to a crystallization method known per se in the art. The compound or a salt thereof of the present invention may be a solvate (e.g., a hydrate) or a non-solvate. Any of such forms are included within the scope of the compound or a salt thereof of the present invention. Compounds labeled with an isotope (such as ^3H , ^{14}C , ^{35}S , or ^{125}I) are also included within the scope of the compound or a salt thereof of the present invention.

[0176]

A prodrug of the compound of the present invention or of a salt thereof refers to a compound that can be converted to the compound or a salt thereof of the present invention through a

reaction with an enzyme, gastric acid, or the like under physiological conditions *in vivo*, i.e., a compound that can be converted to the compound or a salt thereof of the present invention by enzymatic oxidation, reduction, hydrolysis, or the like; or a compound that can be converted to the compound or a salt thereof of the present invention by hydrolysis with gastric acid or the like. Further, the prodrug of the compound or a salt thereof of the present invention may be compounds that can be converted to the compound or a salt thereof of the present invention under physiological conditions, such as those described in "Iyakuhin no Kaihatsu [Development of Pharmaceuticals]," Vol. 7, Molecular Design, published in 1990 by Hirokawa Shoten Co., pp. 163-198.

[0177]

The salt of the compound of the present invention refers to a common salt used in the field of organic chemistry. Examples of such salts include base addition salts to carboxyl when the compound has carboxyl, and acid addition salts to an amino or basic heterocyclic group when the compound has an amino or basic heterocyclic group.

[0178]

Examples of base addition salts include alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as calcium salts and magnesium salts; ammonium salts; and organic amine salts such as trimethylamine salts, triethylamine salts, dicyclohexylamine salts, ethanolamine salts, diethanolamine salts, triethanolamine salts, procaine salts, and *N,N'*-dibenzylethylenediamine salts.

[0179]

Examples of acid addition salts include inorganic acid salts such as hydrochlorides, sulfates, nitrates, phosphates, and perchlorates; organic acid salts such as acetates, formates, maleates, fumarates, tartrates, citrates, ascorbates, and trifluoroacetates; and sulfonates such as methanesulfonates, isethionates, benzenesulfonates, and *p*-toluenesulfonates.

[0180]

The compound or a salt thereof of the present invention has excellent FGFR inhibitory activity, and is useful as an antitumor agent. Further, the compound or a salt thereof of the present invention has excellent selectivity toward FGFR, and has advantageously fewer side effects caused by other kinases. Although the target cancer is not particularly limited, examples thereof include head and neck cancer, esophagus cancer, gastric cancer, colon cancer, rectum cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, biliary tract cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, renal cancer, bladder cancer, prostate cancer, testicular tumor, osteosarcoma, soft-tissue sarcoma, blood cancer, multiple myeloma, skin cancer, brain tumor, and mesothelioma. Preferably, the target cancer is blood cancers such as B-cell lymphoma, chronic lymphocytic leukemia, peripheral T-cell lymphoma, myelodysplastic syndrome, acute myeloid leukemia, and acute lymphocytic leukemia.

[0181]

When the compound or a salt thereof of the present invention is used as a pharmaceutical preparation, a pharmaceutical carrier can be added, if required, thereby forming a suitable dosage form according to prevention and treatment purposes. Examples of the dosage form include oral preparations, injections, suppositories, ointments, patches, and the like. Of these, oral preparations are preferable. Such dosage forms can be formed by methods conventionally known to persons skilled in the art.

[0182]

As the pharmaceutical carrier, various conventional organic or inorganic carrier materials used as preparation materials may be blended as an excipient, binder, disintegrant, lubricant, or colorant in solid preparations; or as a solvent, solubilizing agent, suspending agent, isotonizing agent, buffer, or soothing agent in liquid preparations. Moreover,

pharmaceutical preparation additives, such as antiseptics, antioxidants, colorants, sweeteners, and stabilizers, may also be used, if required.

[0183]

5 Oral solid preparations can be prepared as follows. An excipient, optionally together with a binder, disintegrant, lubricant, colorant, taste-masking or flavoring agent, etc., is added to the compound of the present invention to produce tablets, coated tablets, granules, powders, capsules, or the like, using
10 an ordinary method.

[0184]

 When an injection agent is prepared, a pH adjuster, buffer, stabilizer, isotonizing agent, local anesthetic, etc., may be added to the compound of the present invention; and the
15 mixture may be processed into a subcutaneous, intramuscular, or intravenous injection according to an ordinary method.

[0185]

 The amount of the compound of the present invention to be contained in such a dosage unit form varies depending on the
20 condition of the patient, the dosage form, etc. The desirable amount in dosage unit form is 0.05 to 1,000 mg in the case of an oral preparation, 0.01 to 500 mg in the case of an injection, and 1 to 1,000 mg in the case of a suppository.

[0186]

25 Moreover, the daily dose of the medicine having the above-described dosage form may vary depending on the condition, body weight, age, and sex of a patient, etc., and cannot be generalized. Usually, the daily dose is preferably 0.05 to 5000 mg per adult (body weight: 50 kg) per day, and more preferably
30 0.1 to 1000 mg per adult (body weight: 50 kg) per day. Such a dose of the medicine is preferably administered in one dose, or in two to three divided doses, per day.

Examples

[0187]

35 The present invention is explained in detail below with

reference to Examples; however, the scope of the present invention is not limited to these Examples.

[0188]

In the Examples, commercially available reagents were used, unless otherwise specified. Purif-Pack (registered trademark) SI, produced by Moritex Corp.; KP-Sil (registered trademark) Silica prepacked column, produced by Biotage; or HP-Sil (registered trademark) Silica prepacked column, produced by Biotage was used as the silica gel column chromatography. Purif-Pack (registered trademark) NH, produced by Moritex Corp; or KP-NH (registered trademark) prepacked column, produced by Biotage was used as the basic silica gel column chromatography. Kieselgel TM 60F 254, Art. 5744, produced by Merck, or NH₂ Silica Gel 60F254 Plate, produced by Wako, was used as the preparative thin-layer chromatography. NMR spectrum was measured by using AL400 (400 MHz; produced by JEOL), Mercury 400 (400 MHz; produced by Agilent Technologies, Inc.) spectrometer, or Inova 400 (400 MHz; produced by Agilent Technologies, Inc.) model spectrometer equipped with an OMNMR probe (produced by Protasis). When its deuterated solvent contains tetramethylsilane, the tetramethylsilane was used as the internal reference; and when tetramethylsilane is not contained, an NMR solvent was used as the reference. All the delta values are shown by ppm. The microwave reaction was performed using Discover S-class, produced by CEM Corporation.

[0189]

The LCMS spectrum was measured using an Acquity SQD (quadrupole), produced by Waters Corporation, under the following conditions.

Column: YMC-Triart C18, 2.0 x 50 mm, 1.9 μm (produced by YMC)

MS detection: ESI positive

UV detection: 254 and 210 nm

Column flow rate: 0.5 mL/min

Mobile phase: Water/acetonitrile (0.1% formic acid)

Injection volume: 1 μL

Gradient (Table 1)

	Time (min)	Water	Acetonitrile
	0	95	5
	0.1	95	5
	2.1	5	95
5	3.0	STOP	

[0190]

Preparative reversed-phase HPLC purification was performed using a preparative separation system available from Waters Corporation.

- 10 Column: Connected YMC-Actus Triart C18, 20 x 50 mm, 5 μ m
(produced by YMC) and YMC-Actus Triart C18, 20 x 10 mm, 5 μ m
(produced by YMC).
UV detection: 254 nm
MS detection: ESI positive
- 15 Column flow rate: 25 mL/min
Mobile phase: Water/acetonitrile (0.1% formic acid)
Injection volume: 0.1 to 0.5 mL
[0191]

Each symbol stands for the following.

- 20 s: Singlet
d: Doublet
t: Triplet
q: Quartet
dd: Double Doublet
- 25 dt: Double Triplet
td: Triple Doublet
tt: Triple Triplet
ddd: Double Double Doublet
ddt: Double Double Triplet
- 30 dtd: Double Triple Doublet
tdd: Triple Double Doublet
m: Multiplet
br: Broad
brs: Broad Singlet
- 35 DMSO-d₆: Deuterated dimethyl sulfoxide

- CDCl₃: Deuterated chloroform
CD₃OD: Deuterated methanol
THF: Tetrahydrofuran
DMF: N,N-dimethylformamide
5 NMP: 1-Methyl-2-pyrrolidinone
DMSO: Dimethyl sulfoxide
TFA: Trifluoroacetic acid
SEMCl: 2-(Trimethylsilyl)ethoxymethyl chloride
PdCl₂ (dppf) CH₂Cl₂ : 1,1'-bis(diphenylphosphino) ferrocene-
10 palladium (II) dichloride-dichloromethane complex
WSC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt: 1-Hydroxybenzotriazole monohydrate
HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylhexaluronium
hexafluorophosphate
15 HBTU: O-benzotriazol-N,N,N',N'-tetramethyluronium
hexafluorophosphate
DIAD: Diisopropyl azodicarboxylate
TBAF: Tetrabutylammoniumfluoride
DIPEA: Diisopropylethylamine
20 Boc₂O: Di-tert-butyl dicarbonate
DMAP: Dimethylaminopyridine
[0192]
Example 1
Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-
25 pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one
(compound of Example 1)

- (Step 1) Synthesis of 3-((3,5-dimethoxyphenyl)ethynyl)-1H-
pyrazolo[3,4-d]pyrimidin-4-amine
30 [0193]

PdCl₂ (dppf) CH₂Cl₂ (163 mg) was added to a mixture of 3-
iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (520 mg) synthesized by
the method disclosed in WO 2007/126841, 1-ethynyl-3,5-
dimethoxybenzene (504 mg), copper (I) iodide (57.3 mg), and
35 triethylamine (0.56 ml) in DMF (10 ml). After nitrogen purging,

the resulting mixture was stirred at 90°C for 6 hours. Chloroform and water were added to the reaction mixture to separate the organic layer. After being washed with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: chloroform/methanol) to obtain the title compound as a dark-brown solid (120 mg). Physical properties: $m/z[M+H]^+$ 296.0

10 [0194]

(Step 2) Synthesis of *tert*-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate

[0195]

N-Boc-3-pyrrolidinol (1000 mg) was dissolved in chloroform (20 ml). Triethylamine (1.15 ml) and methanesulfonyl chloride (498 μ l) were added thereto at 0°C. After stirring at room temperature for 1.0 hour, ethyl acetate and water were added thereto to separate the organic layer. After being washed with a saturated aqueous sodium bicarbonate solution, a saturated aqueous ammonium chloride solution and water, the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound as a colorless, oily compound (1.2 g). Physical properties: $m/z[M+H]^+$ 266.1

25 [0196]

(Step 3) Synthesis of *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate

A suspension of 3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (62 mg) obtained in Step 1, *tert*-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate (217 mg) obtained in Step 2, and potassium carbonate (221 mg) in DMF (2.0 ml) was stirred at 70°C for 1 hour. Ethyl acetate and water were added thereto to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent

was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a light-yellow, amorphous substance (36.2 mg).

5 Physical properties: $m/z[M+H]^+$ 465.1
[0197]

(Step 4) Synthesis of compound of Example 1

4N-Hydrochloric acid/1,4-dioxane (4 ml) was added to the *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate (32 mg)
10 obtained in Step 3, and the mixture was stirred at room temperature for 1.5 hours. After distilling the solvent of the resulting reaction mixture off under reduced pressure, toluene azeotropic distillation was subsequently performed to obtain a
15 crude product of 3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (32 mg). Chloroform (2.0 ml) and triethylamine (20 μ l) were added to a portion of the resulting crude product (12 mg). After cooling to 0°C, acrylic chloride (2.3 μ l) dissolved in chloroform (100 μ l) was added
20 thereto, and the mixture was stirred at room temperature for 10 minutes. After halting the reaction using a saturated aqueous sodium bicarbonate solution, the resulting product was extracted with ethyl acetate. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure.
25 The resulting residue was purified by silica gel column chromatography (developing solvent: ethyl acetate/methanol) to obtain the title compound as a white solid (6.5 mg). Table 1 shows the physical properties thereof.

[0198]

30 Example 2

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (compound of Example 2)

(Step 1) Synthesis of (R)-*tert*-butyl 3-(methylsulfonyloxy)
35 pyrrolidine-1-carboxylate

[0199]

(R)-N-Boc-3-pyrrolidinol (935 mg) was dissolved in chloroform (15 ml), and triethylamine (1.04 ml) and methanesulfonyl chloride (467 μ l) were added thereto at 0°C.

5 After stirring at room temperature for 1.5 hours, ethyl acetate and water were added thereto to separate the organic layer. After being washed with a saturated aqueous sodium bicarbonate solution, a saturated aqueous ammonium chloride solution and water, the organic layer was dried over anhydrous sodium sulfate, and the
10 solvent was distilled off under reduced pressure to obtain the title compound as a colorless, oily compound (1.1 g). Physical properties: $m/z[M+H]^+$ 266.1

[0200]

(Step 2) Synthesis of (S)-tert-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate
15

[0201]

A suspension of 3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (334 mg) obtained in Example 1
20 (Step 1), (R)-tert-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate (379 mg) obtained in (Step 1) above, and potassium carbonate (391 mg) in DMF (4.0 ml) was stirred at 70°C for 3 hours. Ethyl acetate and water were added thereto to separate the organic layer. The organic layer was dried over anhydrous sodium
25 sulfate, and the solvent was then distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a light-yellow, amorphous substance (149 mg). Physical properties: $m/z[M+H]^+$ 465.1

30 [0202]

(Step 3) Synthesis of compound of Example 2

In accordance with Example 1 (Step 4), except that (S)-tert-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate obtained
35 in (Step 2) above was used in place of tert-butyl 3-(4-amino-3-

((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, a crude product of (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was obtained by removing a Boc group under
5 acidic conditions. Thereafter, amidation was conducted to obtain the title compound as a white solid. Table 1 shows the physical properties thereof.

[0203]

Example 3

10 Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)but-2-en-1-one (compound of Example 3)

In accordance with Example 1 (Step 4), except that crotyl chloride was used in place of acrylic chloride, the title
15 compound was obtained as a white solid. Table 1 shows the physical properties thereof.

[0204]

Example 4

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-
20 1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (compound of Example 4)

The crude product (5.6 mg) of (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine obtained in Example 2 as an intermediate, 4-
25 (dimethylamino)but-2-enoic acid hydrochloride (6.3 mg), and HATU (15 mg) were dissolved in DMF (1.0 ml). DIPEA (50 µl) was added thereto, followed by stirring overnight. Chloroform and water were added to the reaction mixture to separate the organic layer. After being washed with a saturated sodium chloride solution, the
30 organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resulting residue was purified by preparative reversed-phase HPLC purification (water/acetonitrile (0.1% formic acid)) to obtain the title compound as a colorless, amorphous substance (2.3 mg).
35 Table 1 shows the physical properties thereof.

[0205]

Example 5

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-yn-1-one
(compound of Example 5)

The crude product (16 mg) of (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine obtained in Example 2 as an intermediate, 3-(trimethylsilyl)propionic acid (10 mg), HATU (28 mg) were
dissolved in DMF (0.5 ml). DIPEA (31 µl) was added thereto, followed by stirring overnight. Ethyl acetate and a saturated aqueous sodium bicarbonate solution were added to the reaction mixture to separate the organic layer. After drying the organic layer over anhydrous sodium sulfate, the solvent was distilled
off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: ethyl acetate/methanol) to obtain the title compound as a white solid (0.7 mg). Table 1 shows the physical properties thereof.

[0206]

Example 6

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-fluoroprop-2-en-1-one (compound of Example 6)

In accordance with Example 4, except that 2-fluoroacrylic acid was used in place of 4-(dimethylamino)but-2-enoic acid hydrochloride, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0207]

Example 7

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-(pyrrolidin-1-ylmethyl)prop-2-en-1-one (compound of Example 7)

In accordance with Example 4, except that 2-(pyrrolidin-1-ylmethyl)acetic acid (Synth. Commun. 1995, 641) was

used in place of 4-(dimethylamino)but-2-enoic acid hydrochloride, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0208]

5 Example 8

Synthesis of (S)-1-(3-(4-amino-3-((3,5-diethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (compound of Example 8)

[0209]

10 (Step 1) Synthesis of 1,3-diethoxy-5-ethynylbenzene

Carbon tetrabromide (4.78 g) was dissolved in dichloroethane (14 mL), and triphenylphosphine (7.56 g) was added thereto at 0°C. After stirring at 0°C for 5 minutes, a solution of 3,5-diethoxybenzaldehyde (1.40 g) in dichloromethane (7 mL)
15 was added thereto, followed by stirring for 20 minutes. Without performing further treatment, the reaction mixture was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate) to obtain 1-(2,2-dibromovinyl)-3,5-diethoxybenzene. The obtained compound was used for the subsequent reaction without
20 further purification. The compound obtained above was dissolved in THF (30 mL). A 1.63 M n-butyllithium solution in hexane (10.5 mL) was added thereto at -78°C. The resulting mixture was stirred at -78°C for 30 minutes. After adding a saturated aqueous ammonium chloride solution, the reaction mixture was subjected to
25 extraction using ethyl acetate. The resulting organic layer was washed with a saturated sodium chloride solution, and the organic layer was then dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing
30 solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, oily substance (1.31 g). Physical properties:

m/z[M+H]⁺ 191.0

[0210]

(Step 2) In accordance with Example 1, except that 1,3-diethoxy-
35 5-ethynylbenzene obtained in Step 1 was used in place of 1-

ethynyl-3,5-dimethoxybenzene, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0211]

5 Example 9

Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)prop-2-en-1-one (compound of Example 9)

[0212]

10 (Step 1) Synthesis of *tert*-butyl 3-(methylsulfonyloxy)azetidine-1-carboxylate

N-Boc-3-hydroxyazetidine (1.73 g) was dissolved in chloroform (20 ml). Triethylamine (2.09 ml) and methanesulfonyl chloride (856 μ l) were added thereto at 0°C. After stirring at
15 room temperature for 0.5 hours, ethyl acetate and water were added thereto to separate the organic layer. After being washed with a saturated aqueous sodium bicarbonate solution, a saturated aqueous ammonium chloride solution, and water, the organic layer was dried over anhydrous sodium sulfate. The solvent was then
20 distilled off under reduced pressure to obtain the title compound as a colorless, oily compound (2.32 g). Physical properties:
 $m/z[M+H]^+$ 252.0

[0213]

25 (Step 2) Synthesis of *tert*-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidine-1-carboxylate

A suspension of *tert*-butyl 3-(methylsulfonyloxy)azetidine-1-carboxylate (1.32 g) obtained in Step 1 above, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.37 g), and cesium carbonate (3.47 g) in DMF (10 ml) was stirred at 90°C
30 for 10 hours. Ethyl acetate and water were added thereto to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent:
35 hexane/ethyl acetate) to obtain the title compound as a light-

yellow amorphous substance (482 mg). Physical properties:

m/z[M+H]⁺ 417.0

[0214]

(Step 3) Synthesis of *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidine-1-carboxylate

PdCl₂ (dppf) CH₂Cl₂ (39 mg) was added to a mixture of *tert*-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidine-1-carboxylate (200 mg) obtained in Step 2 above, 1-ethynyl-3,5-dimethoxybenzene (117 mg), copper (I) iodide (14 mg), and triethylamine (0.5 ml) in THF (5 ml). After nitrogen purging, the resulting mixture was stirred at 80°C for 1.5 hours. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. After being washed with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (185 mg). Physical properties: m/z[M+H]⁺ 451.1

[0215]

(Step 4) Synthesis of compound of Example 9

In accordance with Example 1 (Step 4), except that *tert*-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidine-1-carboxylate obtained in Step 3 above was used in place of *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, a crude product of 1-(azetidin-3-yl)-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was obtained by removing a Boc group under acidic conditions. Thereafter, amidation was conducted to obtain the title compound as a white solid. Table 1 shows the physical properties thereof.

[0216]

Example 10

35 Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-

pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-hydroxybut-2-yn-1-one (compound of Example 10)

A crude product (6.0 mg) of 1-(azetidin-3-yl)-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine
5 obtained in Example 9 as an intermediate, 4-hydroxybut-2-yn acid (3.7 mg), and HATU (11 mg) were dissolved in DMF (1.0 ml). DIPEA (30 μ l) was added thereto, followed by stirring overnight.

[0217]

Chloroform and water were added to the reaction mixture
10 to separate the organic layer. After being washed with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by preparative reversed-phase HPLC purification (water/acetonitrile
15 (0.1% formic acid)) to obtain the title compound as a colorless, amorphous substance (1.4 mg). Table 1 shows the physical properties thereof.

[0218]

Example 11

20 Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-hydroxy-4-methylpent-2-yn-1-one (compound of Example 11)

In accordance with Example 10, except that 4-hydroxy-4-methylpent-2-ynoic acid was used in place of 4-hydroxybut-2-ynoic
25 acid, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0219]

Example 12

30 Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one (compound of Example 12)

In accordance with Example 10, except that 4-(dimethylamino)but-2-enoic acid hydrochloride was used in place
of 4-hydroxybut-2-yn acid, the title compound was obtained as a
35 colorless, amorphous substance. Table 1 shows the physical

properties thereof.

[0220]

Example 13

Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(cyclopropylamino)but-2-en-1-one (compound of Example 13)

[0221]

(Step 1) Synthesis of 4-bromobut-2-enoyl chloride

Thionyl chloride (3.0 ml) was added to 4-bromocrotonic acid (329 mg), and the mixture was stirred at 80°C for 5 hours. The reaction mixture was concentrated under reduced pressure, and toluene azeotropic distillation was subsequently performed to obtain the title compound as a crude product (394 mg).

[0222]

(Step 2) Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-bromobut-2-en-1-one

A crude product (140 mg) of 1-(azetidin-3-yl)-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine obtained in Example 9 as an intermediate was suspended in THF (4.5 ml), DIPEA (178 µl) was added thereto, and the mixture was cooled to 0°C. A solution of 4-bromobut-2-enoyl chloride (66 mg) obtained in Step 1 above in THF (0.5 ml) was added to the mixture dropwise and stirred at room temperature for 15 minutes. After halting the reaction using a saturated aqueous sodium bicarbonate solution, the resulting product was extracted with ethyl acetate. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound as a crude product (160 mg). Physical properties: m/z[M+H]⁺ 497.0, 499.0

[0223]

(Step 3) Synthesis of compound of Example 13

The crude product (12 mg) of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-bromobut-2-en-1-one obtained in Step 2 above

was dissolved in DMF (0.5 ml). Cyclopropylamine (5 μ l) and DIPEA (10 μ l) were added thereto, and the mixture was stirred at room temperature for 1 hour. After concentrating under reduced pressure, the resulting residue was purified by preparative
5 reversed-phase HPLC purification (water/acetonitrile (0.1% formic acid)) to obtain the title compound as a colorless, amorphous substance (3.4 mg). Table 1 shows the physical properties thereof.
[0224]

Example 14

10 Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(isopropylamino)but-2-en-1-one (compound of Example 14)

In accordance with Example 13 (Step 3), except that isopropylamine was used in place of cyclopropylamine, the title
15 compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.
[0225]

Example 15

Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-
20 pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(ethyl(methyl)amino)but-2-en-1-one (compound of Example 15)

In accordance with Example 13 (Step 3), except that ethylmethylamine was used in place of cyclopropylamine, the title
compound was obtained as a colorless, amorphous substance. Table
25 1 shows the physical properties thereof.
[0226]

Example 16

Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-
pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-
30 (cyclobutylamino)but-2-en-1-one (compound of Example 16)

In accordance with Example 13 (Step 3), except that cyclobutylamine was used in place of cyclopropylamine, the title
compound was obtained as a colorless, amorphous substance. Table
1 shows the physical properties thereof.
35 [0227]

Example 17

Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(diethylamino)but-2-en-1-one (compound of Example 17)

- 5 In accordance with Example 13 (Step 3), except that diethylamine was used in place of cyclopropylamine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0228]

10 Example 18

Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(tert-butylamino)but-2-en-1-one (compound of Example 18)

- In accordance with Example 13 (Step 3), except that
15 tert-butylamine was used in place of cyclopropylamine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0229]

Example 19

- 20 Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(isopropyl(methyl)amino)but-2-en-1-one (compound of Example 19)

- In accordance with Example 13 (Step 3), except that isopropylmethylamine was used in place of cyclopropylamine, the
25 title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0230]

Example 20

- Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-
30 pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(piperidin-1-yl)but-2-en-1-one (compound of Example 20)

- In accordance with Example 13 (Step 3), except that piperidine was used in place of cyclopropylamine, the title
 compound was obtained as a colorless, amorphous substance. Table
35 1 shows the physical properties thereof.

[0231]

Example 21

Synthesis of 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-morpholinobut-2-en-1-one (compound of Example 21)

In accordance with Example 13 (Step 3), except that morpholine was used in place of cyclopropylamine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

10 [0232]

Example 22

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(3-fluoropyrrolidin-1-yl)but-2-en-1-one

15 In accordance with Example 13 (Step 3), except that (S)-3-fluoropyrrolidine was used in place of cyclopropylamine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0233]

20 Example 23

Synthesis of (R)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(3-fluoropyrrolidin-1-yl)but-2-en-1-one

In accordance with Example 13 (Step 3), except that (R)-3-fluoropyrrolidine was used in place of cyclopropylamine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0234]

Example 24

30 Synthesis of 1-(3-(4-amino-3-((3,5-diethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)prop-2-en-1-one (compound of Example 24)

In accordance with Example 9, except that 1,3-diethoxy-5-ethynylbenzene was used in place of 1-ethynyl-3,5-dimethoxybenzene, the title compound was obtained as a colorless,

35

amorphous substance. Table 1 shows the physical properties thereof.

[0235]

Example 25

- 5 Synthesis of 1-(3-(4-amino-3-((3,5-diethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one (compound of Example 25)

In accordance with Example 12, except that 1,3-diethoxy-5-ethynylbenzene was used in place of 1-ethynyl-3,5-dimethoxybenzene, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0236]

Example 26

- 15 Synthesis of 1-(3-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one (compound of Example 26)

[0237]

- (Step 1) Synthesis of *tert*-butyl 3-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carboxylate

[0238]

- DIAD (197 μ l) was added to a suspension of 3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (148 mg) obtained in Example 1 (Step 1), *N*-Boc-3-hydroxymethylpyrrolidine (154 mg), polymer supported triphenylphosphine (upto 3.0 mmol/g, 334 mg) in THF (5.0 ml), followed by stirring at room temperature for 3 hours. The insoluble matter was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (94.5 mg). Physical properties: m/z [M+H]⁺ 479.1

35 [0239]

(Step 2) Synthesis of compound of Example 26

In accordance with Example 1 (Step 4), except that *tert*-butyl 3-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carboxylate
5 obtained in Step 1 above was used in place of *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. Table 1 shows the physical properties thereof.

10 [0240]

Example 27

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one
(compound of Example 27)

15 In accordance with Example 26, except that (R)-1-Boc-3-hydroxypiperidine was used in place of N-Boc-3-hydroxymethylpyrrolidine, the title compound was obtained as a white solid. Table 1 shows the physical properties thereof.

[0241]

20 Example 28

Synthesis of 1-((2S,4S)-4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-(hydroxymethyl)pyrrolidin-1-yl)prop-2-en-1-one (compound of
Example 28)

25 [0242]

(Step 1) Synthesis of (2S,4R)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-4-hydroxypyrrolidine-1-carboxylate
[0243]

1-N-Boc-(2S,4R)-4-hydroxy-2-(hydroxymethyl)-pyrrolidine
30 (500 mg) was dissolved in DMF (4.0 ml), and imidazole (164 mg) was added to the dissolution. After cooling to 0°C, *tert*-butylchlorodiphenylsilane (616 µl) was added to the mixture, and stirred for 1 hour. Ethyl acetate and a saturated aqueous sodium bicarbonate solution were added to the reaction mixture to
35 separate the organic layer. After being washed with a saturated

sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, oily substance (655 mg). Physical properties: $m/z[M+H]^+$ 456.2 [0244]

(Step 2) Synthesis of (2S,4S)-tert-butyl 2-((tert-butylidiphenylsilyloxy)methyl)-4-(methanesulfonyloxy)pyrrolidine-1-carboxylate [0245]

(2S,4R)-tert-Butyl 2-((tert-butylidiphenylsilyloxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (300 mg) obtained in Step 1 above was dissolved in chloroform (3.0 ml). Triethylamine (137 μ l) and methanesulfonyl chloride (56 μ l) were added to the solution at 0°C. After stirring at room temperature for 2.0 hours, chloroform and water were added thereto to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound as a colorless, oily compound (389 mg). Physical properties: $m/z[M+H]^+$ 534.1 [0246]

(Step 3) Synthesis of (2S,4S)-tert-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-((tert-butylidiphenylsilyloxy)methyl)pyrrolidine-1-carboxylate

(2S,4S)-tert-butyl 2-((tert-butylidiphenylsilyloxy)methyl)-4-(methanesulfonyloxy)pyrrolidine-1-carboxylate (389 mg) obtained in Step 2 above, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (188 mg), and potassium carbonate (363 mg) were suspended in DMF (4.0 ml), followed by stirring overnight at 80°C. Ethyl acetate and water were added thereto to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was

purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, oily substance (191 mg). Physical properties:

$m/z[M+H]^+$ 699.1

5 [0247]

(Step 4) Synthesis of (2S,4S)-*tert*-butyl 4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidine-1-carboxylate [0248]

10 $PdCl_2$ (dppf) CH_2Cl_2 (13 mg) was added to a mixture of (2S,4S)-*tert*-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidine-1-carboxylate (113 mg) obtained in Step 3 above, 1-ethynyl-3,5-dimethoxybenzene (52 mg), copper (I) iodide (6 mg), and
15 triethylamine (0.4 ml) in THF (4 ml). After nitrogen purging, the mixture was stirred at 85°C for 3 hours. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. After washing with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the
20 solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (100 mg). Physical properties: $m/z[M+H]^+$ 733.3

25 [0249]

(Step 5) Synthesis of (2S,4S)-*tert*-butyl 4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate

(2S,4S)-*tert*-butyl 4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidine-1-carboxylate (25
30 mg) obtained in Step 4 above was dissolved in THF (1.0 ml). Silica gel-supported tetrabutylammonium fluolide (upto 1.5 mmol/g, 34 mg) was added thereto, followed by stirring overnight. Silica
35 gel-supported tetrabutylammonium fluolide (upto 1.5 mmol/g, 30

mg) was further added thereto, and the mixture was further stirred for 2 days. After filtering the reagent off, the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography

- 5 (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (62 mg). Physical properties: $m/z[M+H]^+$ 495.1

[0250]

(Step 6) Synthesis of compound of Example 28

- 10 In accordance with Example 1 (Step 4), except that 4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate obtained in Step 5 above was used in place of *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-
- 15 d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. Table 1 shows the physical properties thereof.

[0251]

Example 29

- 20 Synthesis of 1-(3-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)azetidin-1-yl)prop-2-en-1-one (compound of Example 29)

- In accordance with Example 26, except that 1-Boc-3-hydroxymethylazetidine was used in place of N-Boc-3-hydroxymethylpyrrolidine, the title compound was obtained as a
- 25 light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0252]

Example 30

- 30 Synthesis of N-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclobutyl)acrylamide (compound of Example 30)

[0253]

- In accordance with Example 1, except that *tert*-butyl 3-hydroxycyclobutylcarbamate was used in place of N-Boc-3-
- 35

hydroxypyrrolidine, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0254]

5 Example 31

Synthesis of 1-(4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (compound of Example 31)

10 In accordance with Example 1, except that *tert*-butyl 4-bromopiperidin-1-carboxylate was used in place of *tert*-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. Table 1 shows the physical properties thereof.

[0255]

15 Example 32

Synthesis of 1-((2S,4S)-4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-ethynylpyrrolidin-1-yl)prop-2-en-1-one (compound of Example 32)

[0256]

20 (Step 1) Synthesis of (2S,4S)-*tert*-butyl 4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-ethynylpyrrolidine-1-carboxylate

3-((3,5-Dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (14 mg) obtained in Example 1 (Step 1),
25 (2S,4R)-*tert*-butyl 2-ethynyl-4-hydroxypyrrolidine-1-carboxylate (15 mg) synthesized by the method disclosed in WO2005/007083, and triphenylphosphine (23 mg) were suspended in THF (1.0 ml). DIAD (18 μ l) was added to the suspension, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was
30 concentrated and dissolved in a solution of DMSO. The resulting solution was purified by preparative reversed-phase HPLC purification (water/acetonitrile (0.1% formic acid)) to obtain the title compound as a colorless, amorphous substance (5.0 mg). Physical properties: $m/z[M+H]^+$ 489.2

35 [0257]

(Step 2) Synthesis of compound of Example 32

In accordance with Example 1 (Step 4), except that (2S,4S)-tert-butyl 4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-ethynylpyrrolidine-1-carboxylate obtained in Step 1 above was used in place of tert-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. Table 1 shows the physical properties thereof.

10 [0258]

Example 33

Synthesis of 1-(4-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)prop-2-en-1-one (compound of Example 33)

15 In accordance with Example 26, except that 1-Boc-4-hydroxymethylpiperidine was used in place of N-Boc-3-hydroxymethylpyrrolidine, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

20 [0259]

Example 34

Synthesis of N-(3-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)phenyl)acrylamide (compound of Example 34)

25 In accordance with Example 26, except that (3-aminophenyl)methanol was used in place of N-Boc-3-hydroxymethylpyrrolidine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

30 [0260]

Example 35

Synthesis of 1-(3-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one (compound of Example 35)

35 In accordance with Example 4, except that 1-(azetidin-

3-ylmethyl)-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (i.e., an intermediate obtained in Example 29) was used in place of (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0261]

Example 36

Synthesis of 1-(4-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one (compound of Example 36)

In accordance with Example 4, except that 3-((3,5-dimethoxyphenyl)ethynyl)-1-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (i.e., the intermediate obtained in Example 31) was used in place of (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0262]

Example 37

Synthesis of 1-(4-((4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one (compound of Example 37)

In accordance with Example 4, except that 3-((3,5-dimethoxyphenyl)ethynyl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (i.e., the intermediate obtained in Example 33) was used in place of (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0263]

Example 38

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-

(dimethylamino)but-2-en-1-one (compound of Example 38)

(Step 1) Synthesis of (S)-tert-butyl 3-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate

5 DIAD (1.41 ml) was added to a solution of 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (1.00 g), (R)-N-Boc-3-pyrrolidinol (1.01 g), and triphenylphosphine (1.88 g) in tetrahydrofuran (40 ml), and the reaction mixture was stirred for 1 hour. The reaction mixture was concentrated and washed with
10 ethyl acetate to obtain the title compound as a white solid (1.04 g). Physical properties: $m/z[M+H]^+$ 448.9 [0264]

(Step 2) Synthesis of (S)-tert-butyl 3-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate

15 Tetrahydrofuran (2.5 ml) and 28% aqueous ammonia (2.5 ml) were added to (S)-tert-butyl 3-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate (400 mg) obtained in Step 1 above. The reaction mixture was stirred at 100°C for 1.5 hours using a microwave reactor. Chloroform and
20 water were added thereto to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound as a white, solid compound (382 mg). Physical properties: $m/z[M+H]^+$ 430.3
25 [0265]

(Step 3) Synthesis of (S)-tert-butyl 3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate

PdCl₂(dppf)₂CH₂Cl₂ (122 mg) was added to a mixture of
30 (S)-tert-butyl 3-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate (660 mg) obtained in Step 2 above, 1-ethynyl-3,5-dimethoxybenzene (374 mg), copper (I) iodide (44 mg), and triethylamine (2.0 ml) in THF (15 ml). After nitrogen purging, the resulting mixture was stirred at 80°C for 3.5 hours.
35 Ethyl acetate and water were added to the reaction mixture to

separate the organic layer. After washing with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (714 mg). Physical properties: $m/z[M+H]^+$ 464.1

[0266]

(Step 4) Synthesis of compound of Example 38

4N-Hydrochloric acid/1,4-dioxane (2 ml) was added to the (S)-*tert*-butyl 3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate (30 mg) obtained in Step 3 above, and the mixture was stirred at room temperature for 1.5 hours. After distilling the solvent of the resulting reaction mixture off under reduced pressure, toluene azeotropic distillation was subsequently performed to obtain a crude product of (S)-5-((3,5-dimethoxyphenyl)ethynyl)-7-(pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (30 mg). A portion of the resulting crude product (10 mg), 4-(dimethylamino)but-2-enoic acid hydrochloride (5.9 mg), and HATU (14 mg) were dissolved in DMF (1.0 ml). DIPEA (50 μ l) was added thereto and stirred at room temperature for 5 minutes. Chloroform and water were added to the reaction mixture to separate the organic layer. After being washed with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by preparative reversed-phase HPLC purification (water/acetonitrile (0.1% formic acid)) to obtain the title compound as a colorless, amorphous substance (3.9 mg). Table 1 shows the physical properties thereof. [0267]

Example 39

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)prop-2-en-1-one (compound of Example 39)

In accordance with Example 1 (Step 4), except that (S)-tert-butyl 3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate obtained in Example 38 (Step 3) was used in place of tert-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, a crude product of (S)-5-((3,5-dimethoxyphenyl)ethynyl)-7-(pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine was obtained by removing a Boc group under acidic conditions. Thereafter, amidation was conducted to obtain the title compound as a white solid. Table 1 shows the physical properties thereof.

[0268]

Example 40

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(pyrrolidin-1-yl)but-2-en-1-one (compound of Example 40)

[0269]

(Step 1) Synthesis of 4-(pyrrolidin-1-yl)but-2-enoic acid hydrochloride

Methyl 4-bromocrotonate (1.79 g) was dissolved in tetrahydrofuran (40 ml), pyrrolidine (1.67 ml) was added thereto at 0°C, and the mixture was stirred at room temperature for 1 hour. Diethyl ether and water were added to the reaction mixture to separate the organic layer. After being washed with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. 3N Hydrochloric acid (40 ml) was added to the resulting product, and the mixture was heated under reflux at 100°C for 1 hour. The reaction mixture was concentrated under reduced pressure, and then the resulting residue was washed with a mixed solvent of 2-isopropanol and ethyl acetate to obtain the title compound as a white solid (939 mg). Physical properties: $m/z[M+H]^+$ 156.0

[0270]

(Step 2) Synthesis of compound of Example 40

In accordance with Example 4 (Step 1), except that (S)-5-((3,5-dimethoxyphenyl)ethynyl)-7-(pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (the intermediate obtained in Example 38 (Step 4)) and 4-(pyrrolidin-1-yl)but-2-enoic acid hydrochloride obtained in Step 1 above were used, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0271]

Example 41

10 Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(4-methylpiperazin-1-yl)but-2-en-1-one (compound of Example 41)

(Step 1) Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-bromobut-2-en-1-one

[0272]

The crude product (100 mg) of (S)-5-((3,5-dimethoxyphenyl)ethynyl)-7-(pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (i.e., the intermediate obtained in Example 38 (Step 4)) was suspended in chloroform (3.0 ml). DIPEA (117 μ l) was added to the suspension, and the mixture was cooled to 0°C. A solution of 4-bromobut-2-enoyl chloride (46 mg) obtained in Example 16 (Step 1) in chloroform (0.3 ml) was added thereto dropwise, and the resulting mixture was stirred at room temperature for 15 minutes. After halting the reaction using a saturated aqueous sodium bicarbonate solution, the resulting product was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound as a crude product (140 mg). Physical properties: m/z [M+H]⁺ 509.9, 511.9

[0273]

(Step 2) Synthesis of compound of Example 41

35 The crude product (12 mg) of (S)-1-(3-(4-amino-5-((3,5-

dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-bromobut-2-en-1-one obtained in Step 1 above was dissolved in DMF (0.5 ml). N-methylpiperazine (4 mg) and DIPEA (10 µl) were added thereto, followed by stirring at room temperature overnight. After concentrating under reduced pressure, the resulting residue was purified by preparative reversed-phase HPLC purification (water/acetonitrile (0.1% formic acid)) to obtain the title compound as a colorless, amorphous substance (3.0 mg). Table 1 shows the physical properties thereof.

10 [0274]

Example 42

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(4-hydroxypiperidin-1-yl)but-2-en-1-one (compound of Example 42)

15 [0275]

In accordance with Example 41 (Step 2), except that 4-hydroxypiperidine was used in place of N-methylpiperazine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

20 [0276]

Example 43

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(4-fluoropiperidin-1-yl)but-2-en-1-one (compound of Example 43)

25 In accordance with Example 41 (Step 2), except that 4-fluoropiperidine was used in place of N-methylpiperazine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0277]

30 Example 44

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(3,3-difluoropyrrolidin-1-yl)but-2-en-1-one (compound of Example 44)

In accordance with Example 41 (Step 2), except that 35 3,3-difluoropyrrolidine was used in place of N-methylpiperazine,

the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0278]

Example 45

- 5 Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(4,4-difluoropiperidin-1-yl)but-2-en-1-one (compound of Example 45)

In accordance with Example 41 (Step 2), except that 4,4-difluoropiperidine was used in place of N-methylpiperazine,
10 the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0279]

Example 46

- 15 Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)but-2-yn-1-one (compound of Example 46)

In accordance with Example 4 (Step 1), except that (S)-5-((3,5-dimethoxyphenyl)ethynyl)-7-(pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (i.e., the intermediate obtained
20 in Example 38 (Step 4)) and 2-butyneic acid were used, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0280]

Example 47

- 25 Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-hydroxy-4-methylpent-2-yn-1-one (compound of Example 47)

In accordance with Example 4 (Step 1), except that (S)-5-((3,5-dimethoxyphenyl)ethynyl)-7-(pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (i.e., the intermediate obtained
30 in Example 38 (Step 4)) and 4-hydroxy-4-methylpent-2-ynoic acid were used, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

35 [0281]

Example 48

Synthesis of 1-((S)-3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-en-1-one (compound of Example 48)

5 [0282]

In accordance with Example 41 (Step 2), except that (R)-3-fluoropyrrolidine was used in place of N-methylpiperazine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

10 [0283]

Example 49

Synthesis of 1-((S)-3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-en-1-one (compound of Example 49)

15 In accordance with Example 41 (Step 2), except that (S)-3-fluoropyrrolidine was used in place of N-methylpiperazine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0284]

20 Example 50

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)-4-(piperidin-1-yl)but-2-en-1-one (compound of Example 50)

In accordance with Example 41 (Step 2), except that
25 piperidine was used in place of N-methylpiperazine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0285]

Example 51

30 Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)prop-2-en-1-one (compound of Example 51)

[0286]

(Step 1) Synthesis of tert-butyl 3-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidine-1-carboxylate
35

DIAD (1.41 ml) was added to a solution of 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (1.00 g), N-Boc-3-hydroxyazetidine (930 mg), and triphenylphosphine (1.85 g) in tetrahydrofuran (40 ml), and the reaction mixture was stirred for 1 hour. After concentrating, the reaction mixture was washed with ethyl acetate to obtain the title compound as a white solid (1.07 g). Physical properties: $m/z[M+H]^+$ 435.0

[0287]

(Step 2) Synthesis of *tert*-butyl 3-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidine-1-carboxylate

Tetrahydrofuran (2.5 ml) and 28% aqueous ammonia (2.5 ml) were added to the *tert*-butyl 3-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidine-1-carboxylate (350 mg) obtained in Step 1 above. The reaction mixture was stirred at 100°C for 1.5 hours using a microwave reactor. Chloroform and water were added thereto to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound as a white solid (340 mg). Physical properties: $m/z[M+H]^+$ 416.0

[0288]

(Step 3) Synthesis of *tert*-butyl 3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidine-1-carboxylate

$PdCl_2(dppf)CH_2Cl_2$ (122 mg) was added to a mixture of *tert*-butyl 3-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidine-1-carboxylate (639 mg) obtained in Step 2 above, 1-ethynyl-3,5-dimethoxybenzene (374 mg), copper (I) iodide (44 mg), and triethylamine (2.0 ml) in THF (15 ml). After nitrogen purging, the resulting mixture was stirred at 80°C for 3.5 hours. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. After being washed with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel

column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (704 mg). Physical properties: $m/z[M+H]^+$ 450.1

[0289]

5 (Step 4) Synthesis of compound of Example 51

In accordance with Example 1 (Step 4), except that *tert*-butyl 3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidine-1-carboxylate obtained in Step 3 was used in place of *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, a crude product of 7-(azetidin-3-yl)-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine was obtained by removing a Boc group under acidic conditions. Thereafter, amidation was conducted to obtain the title compound as a white solid. Table 1 shows the physical properties thereof.

[0290]

Example 52

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Example Compound 52)

In accordance with Example 4 (Step 1), except that the *tert*-butyl 3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidine-1-carboxylate obtained in Example 51 (Step 3) was used in place of *tert*-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

30 [0291]

Example 53

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(pyrrolidin-1-yl)but-2-en-1-one (Example Compound 53)

35 In accordance with Example 4 (Step 1), the 7-(azetidin-

3-yl)-5-((3,5-)dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained in Example 51 (Step 4) as an intermediate, and the 4-(pyrrolidin-1-yl)but-2-enoic acid hydrochloride obtained in Example 40 (Step 1) were used to obtain the title compound as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0292]

Example 54

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)but-2-yn-1-one (Example Compound 54)

In accordance with Example 4 (Step 1), the 7-(azetidin-3-yl)-5-((3,5-)dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained as an intermediate in Example 51 (Step 4) and 2-butyric acid were used to obtain the title compound as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0293]

Example 55

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(azetidin-1-yl)but-2-en-1-one (Example Compound 55)

[0294]

(Step 1) Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-bromobut-2-en-1-one

A crude product of 7-(azetidin-3-yl)-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (160 mg) obtained in Example 52 (Step 4) as an intermediate was suspended in THF (3.0 ml). DIPEA (202 μ l) was added thereto, and the mixture was cooled to 0°C. A solution of 4-bromobut-2-enoyl chloride (75 mg) obtained in Example 16 (Step 1) in THF (0.5 ml) was added to the mixture dropwise, and stirred at room temperature for 15 minutes. After halting the reaction using a saturated sodium bicarbonate solution, the resulting product was

extracted with ethyl acetate. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound as a crude product (204 mg). Physical properties: $m/z[M+H]^+$ 496.0, 498.0

5 [0295]

(Step 2) Synthesis of Example Compound 55

The crude product of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-bromobut-2-en-1-one (10 mg) obtained in Step 10 1 above was suspended in THF (0.5 ml). Azetidine (7 μ l) was added thereto, and the resulting mixture was stirred for 1 hour at room temperature. After concentrating under reduced pressure, the resulting residue was purified by reversed-phase HPLC purification (water/acetonitrile (0.1% formic acid)) to obtain 15 the title compound as a colorless, amorphous substance (1.6 mg). Table 1 shows the physical properties thereof.

[0296]

Example 56

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(ethyl(methyl)amino)but-2-en-1-one (Example 20 Compound 56)

In accordance with Example 55 (Step 2), except that ethylmethylamine was used in place of azetidine, the title 25 compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0297]

Example 57

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(isopropylamino)but-2-en-1-one (Example Compound 57) 30

In accordance with Example 55 (Step 2), except that isopropylamine was used in place of azetidine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows 35 the physical properties thereof.

[0298]

Example 58

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-

5 (isopropyl(methyl)amino)but-2-en-1-one (Example Compound 58)

In accordance with Example 55 (Step 2), except that isopropylmethylamine was used in place of azetidine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

10 [0299]

Example 59

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(diethylamino)but-2-en-1-one (Example Compound 59)

15 In accordance with Example 55 (Step 2), except that diethylamine was used in place of azetidine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0300]

20 Example 60

Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-((2-methoxyethyl)(methyl)amino)but-2-en-1-one (Example Compound 60)

In accordance with Example 55 (Step 2), except that 2-methoxy-N-methylethanamine was used in place of azetidine, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

[0301]

Example 61

30 Synthesis of 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(4-hydroxypiperidin-1-yl)but-2-en-1-one (Example Compound 61)

In accordance with Example 55 (Step 2), except that 4-hydroxypiperidin was used in place of azetidine, the title compound was obtained as a colorless, amorphous substance. Table

35

1 shows the physical properties thereof.

[0302]

Example 62

Synthesis of (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl))-
5 7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(3-
hydroxypyrrolidin-1-yl)but-2-en-1-one (Example Compound 62)

In accordance with Example 55 (Step 2), except that
(S)-3-hydroxypyrrolidine was used in place of azetidine, the
title compound was obtained as a colorless, amorphous substance.
10 Table 1 shows the physical properties thereof.

[0303]

Example 63

Synthesis of (R)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl))-
7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(3-
15 hydroxypyrrolidin-1-yl)but-2-en-1-one (Example Compound 63)

In accordance with Example 55 (Step 2), except that
(R)-3-hydroxypyrrolidine was used in place of azetidine, the
title compound was obtained as a colorless, amorphous substance.
Table 1 shows the physical properties thereof.

20 [0304]

Example 64

Synthesis of 1-(4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl))-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)piperidin-1-yl)prop-2-en-1-one
(Example Compound 64)

25 In accordance with Example 39, except that N-Boc-4-
piperidinol was used in place of (R)-N-Boc-3-pyrrolidinol, the
title compound was obtained as a light-yellow, amorphous
substance. Table 1 shows the physical properties thereof.

[0305]

30 Example 65

Synthesis of 1-(4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl))-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)piperidin-1-yl)-4-
(dimethylamino)but-2-en-1-one (Example Compound 65)

In accordance with Example 38, except that N-Boc-4-
35 piperidinol was used in place of (R)-N-Boc-3-pyrrolidinol, the

title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0306]

Example 66

5 Synthesis of (2S,4S)-methyl 1-acryloyl-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate (Example Compound 66)

[0307]

(Step 1) Synthesis of 4-chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (7.01 g) synthesized by the method disclosed in WO2005/042556 was dissolved in anhydrous THF (125 ml). After cooling to 0°C, 60% sodium hydride (4.02 g) was added to the result, and the resulting mixture was stirred for 20 minutes. Subsequently, SEMCl (13.3 ml) was added thereto, and the mixture was stirred at room temperature overnight. After cooling to 0°C again, water was added to the mixture, and the reaction was halted. The resulting product was extracted with ethyl acetate, and the organic layer was washed with a saturated sodium chloride solution. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a white solid (7.28 g). Physical properties: $m/z[M+H]^+$ 410.0

[0308]

(Step 2) Synthesis of 5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

The 4-chloro-5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (200 mg) obtained in Step 1 above was dissolved in THF (2.0 ml). 28% Aqueous ammonia (2 ml) was added thereto, and the reaction mixture was then stirred at 105°C for 1.5 hours using a microwave reactor. The resulting product was extracted with ethyl acetate, and the organic layer was washed with a saturated sodium chloride

solution. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound as a white solid (192 mg). Physical properties: $m/z[M+H]^+$ 391.0

5 [0309]

(Step 3) Synthesis of 5-((3,5-dimethoxyphenyl)ethynyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

In accordance with Example 1 (Step 1), except that the 5-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained in Step 2 above was used in place of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine, the title compound was obtained as a colorless solid. Physical properties: $m/z[M+H]^+$ 425.4

[0310]

15 (Step 4) Synthesis of 5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

A solution of 5-((3,5-dimethoxyphenyl)ethynyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (4.27 g) obtained in Step 3 in methylene chloride (20 ml) was cooled to 0°C, and TFA 10 ml was added thereto. The reaction mixture was stirred at room temperature for 5 hours, and the solvent was distilled off under reduced pressure. THF (50 ml) was added to the residue, and the mixture was cooled to 0°C. 4N aqueous sodium hydroxide (12.5 ml) was added thereto, and the mixture was stirred at room temperature overnight. The result was extracted with ethyl acetate, and dried over anhydrous magnesium sulfate. Subsequently, the solvent was distilled off under reduced pressure, and chloroform was added to the resulting residue. The mixture was subjected to filtration to obtain the title compound as a white solid (2.60 g). Physical properties: $m/z[M+H]^+$ 295.3

[0311]

(Step 5) Synthesis of (2S,4R)-4-(methylsulfonyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butylester-2-methylester

35 In accordance with Example 1 (Step 2), except that

(2S,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butylester-2-methylester was used in place of N-Boc-3-pyrrolidinol, the title compound was obtained as a colorless, amorphous substance.

5 [0312]

(Step 6) Synthesis of (2S,4S)-1-tert-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate

10 In accordance with Example 1 (Step 3), except that the 5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained in Step 4, the (2S,4R)-4-(methylsulfonyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butylester-2-methylester obtained in Step 5, sodium hydride, and NMP were individually used in place of 3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine, tert-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate, potassium carbonate, and DMF, the title compound was obtained as a colorless, amorphous substance. Physical properties: $m/z[M+H]^+$ 522.4

[0313]

20 (Step 7) Synthesis of (2S,4S)-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate

A solution of (2S,4S)-1-tert-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate (24 mg) obtained in Step 6 above in methylene chloride (2.0 ml) and TFA (2.0 ml) was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure, and the resulting residue was purified by basic silica gel column chromatography (developing solvent: chloroform/methanol). The title compound was thus obtained as a light-yellow, amorphous substance (11.9 mg). Physical properties: $m/z[M+H]^+$ 422.1

[0314]

(Step 8) Synthesis of Example Compound 66

35 Methylene chloride (2.0 ml) and triethylamine (16 μ l)

were added to the (2S,4S)-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate (12 mg) obtained in Step 7 above. After cooling to 0°C, chloroform (100 µl) in which acryloyl chloride (5 µl) was dissolved was added to the resulting mixture, and stirred at room temperature for 10 minutes. After halting the reaction using a saturated sodium bicarbonate solution, the resulting product was extracted with ethyl acetate. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: ethyl acetate/methanol) to obtain the title compound as a colorless, amorphous substance (4.2 mg). Table 1 shows the physical properties thereof.

[0315]

Example 67

Synthesis of 1-((2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((dimethylamino)methyl)pyrrolidin-1-yl)prop-2-en-1-one (Example Compound 67)

[0316]

(Step 1) Synthesis of (2S,4S)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-4-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate

A solution of triphenylphosphine (443 mg) in THF (25 ml) was cooled to 0°C, and DIAD (340 µl) was added thereto dropwise. The reaction mixture was stirred at 0°C for 1 hour. 4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (363 mg) and the (2S,4R)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (651.6 mg) obtained in Example 28 (Step 1) were added thereto, and stirred at room temperature overnight. Ethyl acetate and water were added to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica

gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a light-yellow, amorphous substance (400 mg). $m/z[M+H]^+$ 718.5

[0317]

- 5 (Step 2) Synthesis of (2S,4S)-tert-butyl 4-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((tert-butyl)diphenylsilyloxy)methyl)pyrrolidine-1-carboxylate

THF (10 ml) and an 8N ammonia methanol solution (5 ml) were added to the (2S,4S)-tert-butyl 2-((tert-butyl)diphenylsilyloxy)methyl)-4-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1-carboxylate (400 mg) obtained in Step 1. The mixture was stirred at 120°C for 2 hours under microwave irradiation, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica
10 gel column chromatography (developing solvent: chloroform/ethanol) to obtain the title compound as a light-yellow solid (293 mg). Physical properties: $m/z[M+H]^+$ 698.5

[0318]

- (Step 3) Synthesis of (2S,4S)-tert-butyl 4-(4-(bis(tert-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((tert-butyl)diphenylsilyloxy)methyl)pyrrolidine-1-carboxylate

Boc₂O (188 mg) and DMAP (7 mg) were added to a solution of (2S,4S)-tert-butyl 4-(4-amino-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((tert-butyl)diphenylsilyloxy)methyl)pyrrolidine-1-carboxylate (200 mg) obtained in Step 2 in THF (5 ml), and the resulting mixture was stirred at room temperature overnight. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, and
25 the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a light-yellow, amorphous substance (238 mg). $m/z[M+H]^+$ 898.5

35 [0319]

(Step 4) Synthesis of (2S,4S)-tert-butyl 4-(4-(bis(tert-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate

Silica gel-carrying tetrabutyl ammonium fluoride (700
5 mg) (up to 1.5 mmol/g) was added to a solution of (2S,4S)-tert-butyl 4-(4-(bis(tert-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((tert-butyl)diphenylsilyloxy)methyl)pyrrolidine-1-carboxylate (237.5 mg) obtained in Step 3 in THF (5 ml), and the resulting mixture was
10 stirred at room temperature overnight. Silica gel was separated by filtration, and the solvent of the filtrate was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a light-
15 yellow, amorphous substance (185 mg). Physical properties: m/z[M+H]⁺ 660.2

[0320]

(Step 5) Synthesis of (2S,4S)-tert-butyl 4-(4-(bis(tert-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-
20 formylpyrrolidine-1-carboxylate

Dess-Martin periodinane (51 mg) was added to a solution of (2S,4S)-tert-butyl 4-(4-(bis(tert-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (66 mg) obtained in Step
25 4 in methylene chloride (2 ml), and the resulting mixture was stirred at room temperature for 1 hour. Dess-Martin periodinane (100 mg) was further added to the mixture, and stirred at room temperature for 1 hour. Dess-Martin periodinane (70 mg) was additionally added thereto, and the resulting mixture was stirred
30 at room temperature for 1 hour. Water was added to the reaction mixture to separate the organic layer. The organic layer was washed with a sodium hydrogen carbonate aqueous solution and a 10% sodium thiosulfate aqueous solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced
35 pressure to obtain the title compound as a light-yellow,

amorphous substance (68 mg). Physical properties: $m/z[M+H]^+$ 658.1

[0321]

(Step 6) Synthesis of (2S,4S)-*tert*-butyl 4-(4-(bis(*tert*-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((dimethylamino)methyl)pyrrolidine-1-carboxylate

A 1M dimethylamine THF solution (0.3 ml) and acetic acid (0.2 ml) were added to a solution of (2S,4S)-*tert*-butyl 4-(4-(bis(*tert*-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-formylpyrrolidine-1-carboxylate (68 mg) obtained in Step 5 in methylene chloride (2 ml), and the resulting mixture was cooled to 0°C. Sodium triacetoxyborohydride (127 mg) was added to the reaction mixture, and stirred at 0°C for 2 hours. The reaction mixture was neutralized using a sodium hydrogen carbonate aqueous solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound as a light-yellow, amorphous substance (31.9 mg). Physical properties: $m/z[M+H]^+$ 687.2

20 [0322]

(Step 7) Synthesis of (2S,4S)-*tert*-butyl 4-(4-(bis(*tert*-butoxycarbonyl)amino)-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((dimethylamino)methyl)pyrrolidine-1-carboxylate

25 In accordance with Example 1 (Step 1), except that the (2S,4S)-*tert*-butyl 4-(4-(bis(*tert*-butoxycarbonyl)amino)-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((dimethylamino)methyl)pyrrolidine-1-carboxylate obtained in Step 6 was used in place of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine, 30 the title compound was obtained as a light-yellow, amorphous substance. Physical properties: $m/z[M+H]^+$ 721.5

[0323]

(Step 8) Synthesis of 5-((3,5-dimethoxyphenyl)ethynyl)-7-((3S,5S)-5-((dimethylamino)methyl)pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

35

In accordance with Example 66 (Step 7), except that the (2S,4S)-tert-butyl 4-(4-(bis(tert-butoxycarbonyl)amino)-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((dimethylamino)methyl)pyrrolidine-1-carboxylate obtained in Step 7 was used in place of (2S,4S)-1-tert-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate, the title compound was obtained as a light-yellow, amorphous substance. Physical properties: $m/z[M+H]^+$ 421.1

10 [0324]

(Step 9) Synthesis of Example Compound 67

In accordance with Example 66 (Step 8), except that the 5-((3,5-dimethoxyphenyl)ethynyl)-7-((3S,5S)-5-((dimethylamino)methyl)pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained in Step 8 was used in place of (2S,4S)-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

20 [0325]

Example 68

Synthesis of 1-((2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(1,3,4-oxadiazole-2-yl)pyrrolidin-1-yl)prop-2-en-1-one (Example Compound 68)

[0326]

(Step 1) Synthesis of (2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid

30 The (2S,4S)-1-tert-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate (393.8 mg) obtained in Example 66 (Step 6) was dissolved in methanol (6 ml). After cooling to 0°C, 4N aqueous sodium hydroxide (3 ml) was added thereto. The reaction suspension was stirred at room temperature for 3 hours.

5N hydrochloric acid was added to the reaction mixture to a pH of 5, and ethyl acetate and water were added to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound as a light-yellow solid (280 mg). Physical properties: $m/z[M+H]^+$ 508.3

[0327]

(Step 2) Synthesis of (2S,4S)-*tert*-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-

10 (hydrazine carbonyl)pyrrolidine-1-carboxylate

DIPEA (73 μ l) and hydrazine monohydrate (46 μ l) were added to a solution of (2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (106 mg) obtained in Step 1 above and TBTU (100 mg) in DMF (2 ml), and the resulting mixture was stirred at room temperature for 10 minutes. Ethyl acetate and water were added to the reaction mixture to separate the organic layer, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound as a light-yellow, amorphous substance (93.6 mg). Physical properties: $m/z[M+H]^+$ 522.4

[0328]

(Step 3) Synthesis of (2S,4S)-*tert*-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-

25 (1,3,4-oxadiazole-2-yl)pyrrolidine-1-carboxylate

Toluene (3 ml) and trimethyl orthoformate (79 μ l) were added to the (2S,4S)-*tert*-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydrazine carbonyl)pyrrolidine-1-carboxylate (93.6 mg) obtained in Step 2, and the resulting mixture was stirred at 110°C overnight. Acetic acid (400 μ l) was added to the reaction mixture, and stirred at 110°C for 6 hours. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium

sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: chloroform/methanol) to obtain the title compound as a light-yellow, amorphous substance (50 mg). Physical properties: m/z $[M+H]^+$ 532.2 [0329]

(Step 4) Synthesis of 7-((3S,5S)-5-(1,3,4-oxadiazole-2-yl)pyrrolidin-3-yl)-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

10 In accordance with Example 66 (Step 7), except that the (2S,4S)-*tert*-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(1,3,4-oxadiazole-2-yl)pyrrolidine-1-carboxylate (50 mg) obtained in Step 3 was used in place of (2S,4S)-1-*tert*-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate, the title compound was obtained as a light-yellow, amorphous substance (30.3 mg). m/z $[M+H]^+$ 432.0 [0330]

20 (Step 5) Synthesis of Example Compound 68

In accordance with Example 66 (Step 8), except that 7-((3S,5S)-5-(1,3,4-oxadiazole-2-yl)pyrrolidin-3-yl)-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained in Step 4 was used in place of (2S,4S)-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof. [0331]

30 Example 69

Synthesis of 1-((2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(5-methyl-1,3,4-oxadiazole-2-yl)pyrrolidin-1-yl)prop-2-en-1-one (Example Compound 69)

35 [0332]

(Step 1) Synthesis of (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(5-methyl-1,3,4-oxadiazole-2-yl)pyrrolidine-1-carboxylate

In accordance with Example 68 (Step 3), except that triethyl orthoacetate was used in place of trimethyl orthoformate, the title compound was obtained as a light-yellow, amorphous substance. Physical properties: $m/z[M+H]^+$ 546.5

[0333]

(Step 2) Synthesis of 5-((3,5-dimethoxyphenyl)ethynyl)-7-((3S,5S)-5-(5-methyl-1,3,4-oxadiazole-2-yl)pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

In accordance with Example 66 (Step 7), except that the (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(5-methyl-1,3,4-oxadiazole-2-yl)pyrrolidine-1-carboxylate obtained in Step 1 was used in place of (2S,4S)-1-tert-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate, the title compound was obtained as a light-yellow, amorphous substance. Physical properties: $m/z[M+H]^+$ 466.0

[0334]

(Step 3) Synthesis of Example Compound 69

In accordance with Example 66 (Step 8), except that the 5-((3,5-dimethoxyphenyl)ethynyl)-7-((3S,5S)-5-(5-methyl-1,3,4-oxadiazole-2-yl)pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained in Step 2 was used in place of (2S,4S)-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0335]

Example 70

Synthesis of 1-((2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(5-((dimethylamino)methyl)-1,3,4-oxadiazole-2-yl)pyrrolidin-1-

yl)prop-2-en-1-one (Example Compound 70)

[0336]

(Step 1) Synthesis of (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(2-
5 (2-(dimethylamino)acetyl)hydrazine carbonyl)pyrrolidine-1-carboxylate

In accordance with Example 68 (Step 2), except that 2-(dimethylamino)acetohydrazide was used in place of hydrazine monohydrate, the title compound was obtained as a light-yellow,
10 amorphous substance. Physical properties: $m/z[M+H]^+$ 607.3

[0337]

(Step 2) Synthesis of (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(5-
15 ((dimethylamino)methyl)-1,3,4-oxadiazole-2-yl)pyrrolidine-1-carboxylate

DIPEA (105 μ l) and tosyl chloride (56 mg) were added to a solution of (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(2-
20 (2-(dimethylamino)acetyl)hydrazine carbonyl)pyrrolidine-1-carboxylate (100 mg) obtained in Step 1 in acetonitrile (3 ml), and the mixture was stirred at 40°C for 1 hour. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure.
25 The resulting residue was purified by silica gel column chromatography (developing solvent: chloroform/methanol) to obtain the title compound as a light-yellow, amorphous substance (40.5 mg). Physical properties: $m/z[M+H]^+$ 589.2

[0338]

30 Synthesis of (Step 3) 5-((3,5-dimethoxyphenyl)ethynyl)-7-((3S,5S)-5-(5-((dimethylamino)methyl)-1,3,4-oxadiazole-2-yl)pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

In accordance with Example 66 (Step 7), except that the (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-
35 7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(5-((dimethylamino)methyl)-

1,3,4-oxadiazole-2-yl)pyrrolidine-1-carboxylate obtained in Step (2) was used in place of (2S,4S)-1-tert-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate, the title compound was obtained as a light-yellow, amorphous substance. Physical properties: $m/z[M+H]^+$ 489.2

[0339]

(Step 4) Synthesis of Example Compound 70

In accordance with Example 66 (Step 8), except that the 5-((3,5-dimethoxyphenyl)ethynyl)-7-((3S,5S)-5-(5-((dimethylamino)methyl)-1,3,4-oxadiazole-2-yl)pyrrolidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine obtained in Step 3 was used in place of (2S,4S)-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

[0340]

Example 71

Synthesis of (2S,4S)-1-acryloyl-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-(dimethylamino)ethyl)-N-methylpyrrolidine-2-carboxamide (Example Compound 71)

[0341]

(Step 1) Synthesis of (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((2-(dimethylamino)ethyl)(methyl)carbamoyl)pyrrolidine-1-carboxylate

A solution of (2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (25.4 mg) obtained in Example 68 (Step 1), TBTU (17.7 mg), N,N,N'-trimethylethane-1,2-diamine (13 μ l), and DIPEA (26 μ l) in acetonitrile (3 ml) was stirred at room temperature for 1 hour. Ethyl acetate and water were added to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate, and

the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: chloroform/methanol) to obtain the title compound as a light-yellow, amorphous substance

5 (3 mg). Physical properties: $m/z[M+H]^+$ 592.4
[0342]

(Step 2) Synthesis of (2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-(dimethylamino)ethyl)-N-methylpyrrolidine-2-carboxamide

10 In accordance with Example 66 (Step 7), except that the (2S,4S)-tert-butyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((2-(dimethylamino)ethyl)(methyl)carbamoyl)pyrrolidine-1-carboxylate obtained in Step 1 above was used in place of (2S,4S)-1-tert-butyl
15 butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate, the title compound was obtained as a colorless, amorphous substance. Physical properties: $m/z[M+H]^+$ 492.4
[0343]

20 (Step 3) Synthesis of Example Compound 71

In accordance with Example 66 (Step 8), except that the (2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-(dimethylamino)ethyl)-N-methylpyrrolidine-2-carboxamide obtained in Step 2 was used in
25 place of (2S,4S)-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate, the title compound was obtained as a colorless, amorphous substance. Table 1 shows the physical properties thereof.

30 [0344]

Example 72

Synthesis of 1-(4-((4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Example Compound 72).

35 In accordance with Example 38, except that N-Boc-4-

hydroxymethylpiperidin was used in place of (R)-N-Boc-3-pyrrolidinol, the title compound was obtained as a light-yellow, amorphous substance. Table 1 shows the physical properties thereof.

5 [0345]

Example 73

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Example Compound 73)

10 [0346]

(Step 1) Synthesis of 4-chloro-3-iodo-1H-pyrrolo[3,2-c]pyridine

4-Chloro-1H-pyrrolo[3,2-c]pyridine (247 mg) synthesized by the method disclosed in WO2007/095223 was dissolved in DMF (7.0 ml). After cooling to 0°C, N-iodosuccinimide (382 mg) was added thereto. The resulting mixture was stirred at room temperature for 1 hour, and then chloroform and water were added thereto to separate the organic layer. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a dark-brown solid (455 mg). Physical properties: $m/z[M+H]^+$ 279.1

[0347]

(Step 2) Synthesis of (S)-tert-butyl 3-(4-chloro-3-iodo-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidine-1-carboxylate

The 4-chloro-3-iodo-1H-pyrrolo[3,2-c]pyridine (225 mg) obtained in Step 1 was dissolved in DMF (3.0 ml). After cooling to 0°C, 60% sodium hydride (64.5 mg) was added thereto. The (R)-tert-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate (322 mg) obtained in Example 2 (Step 1) was added to the reaction mixture using DMF (2.0 ml), and the mixture was stirred overnight. 60% Sodium hydride (64.5 mg) was additionally added, and the mixture was stirred at 85°C overnight. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, and

the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a crude product (192 mg). Physical

5 properties: $m/z[M+H]^+$ 448.3

[0348]

(Step 3) Synthesis of (S)-tert-butyl 3-(4-chloro-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidine-1-carboxylate

10 $PdCl_2(dppf)CH_2Cl_2$ (33 mg) was added to a mixture of the crude product of (S)-tert-butyl 3-(4-chloro-3-iodo-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidine-1-carboxylate (180 mg) obtained in Step 2, 1-ethynyl 3,5-dimethoxybenzene (97 mg), copper (I) iodide (15 mg), and triethylamine (1.0 ml) in THF (4.0
15 ml). After nitrogen purging, the resulting mixture was stirred at 50°C for 30 minutes. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. After being washed with a saturated sodium chloride solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent
20 was then distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (133 mg). Physical properties: $m/z[M+H]^+$ 482.4

25 [0349]

(Step 4) Synthesis of (S)-tert-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidine-1-carboxylate

Under a nitrogen atmosphere, the (S)-tert-butyl 3-(4-chloro-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrrolo[3,2-c]pyridin-
30 1-yl)pyrrolidine-1-carboxylate (120 mg) obtained in Step 3, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) (26 mg), sodium tert-butoxide (72 mg), benzophenone imine (92 mg), and tris(dibenzylideneacetone)dipalladium (36 mg) were suspended in
35 toluene (10 ml), and the result was stirred at 115°C for 90

minutes. After dilution with ethyl acetate, celite filtration was performed. The solvent was distilled off under reduced pressure. Hydroxyaminehydrochloride (366 mg), sodium bicarbonate (442 mg), methanol (16 ml), and water (4 ml) were added to the resulting
5 residue, and the resulting mixture was stirred at room temperature for 2 hours. The solvent was distilled off under reduced pressure. Thereafter, ethyl acetate and a saturated sodium chloride solution were added to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate, and
10 the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (35 mg). Physical properties: $m/z[M+H]^+$ 463.4

15 [0350]

(Step 5) Synthesis of Example Compound 73

In accordance with Example 1 (Step 4), except that the (S)-tert-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidine-1-carboxylate obtained in
20 Step (3) was used in place of tert-butyl 3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. Table 1 shows the physical properties thereof.

[0351]

25 Reference Example 1

Synthesis of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one
(Reference Example Compound 1)

The compound was synthesized according to the method
30 disclosed in WO2008/121742. Table 2 shows the physical properties thereof.

[0352]

Reference Example 2

Synthesis of 3-cyclobutyl-1-(phenylethynyl)imidazo [1,5-
35 a]pyrazin-8-amine (Reference Example Compound 2)

The compound was synthesized according to the method disclosed in WO2007/087395. Table 2 shows the physical properties thereof.

[0353]

5 Reference Example 3

Synthesis of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)propan-1-one (Reference Example Compound 3)

10 In accordance with Example 1, (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine and propionyl chloride were used to obtain the title compound as a white solid. Table 2 shows the physical properties thereof.

[0354]

15 Reference Example 4

Synthesis of (S)-1-(3-(4-amino-3-((3,5-diisopropylphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Reference Example Compound 4)

20 (Step 1) Synthesis of 1-ethynyl-3,5-diisopropylbenzene

PdCl₂(dppf)CH₂Cl₂ (163 mg) was added to a mixture of trimethylsilylacetylene (589 mg), 1-bromo-3,5-diisopropylbenzene (480 mg), copper (I) iodide (76 mg), and triethylamine (0.11 ml) in THF (4 ml). After nitrogen purging, the resulting mixture was stirred at 80°C for 4 hours. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. A 2% potassium hydroxide methanol solution (10 ml) was added to the resulting residue, and the result was stirred at room temperature overnight. Chloroform and water were added to the reaction mixture to separate the organic layer. After drying the result over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: hexane) to obtain the title

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compound as a yellow, oily substance (181 mg).

[0355]

(Step 2) Synthesis of (S)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate

5 A suspension of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (446 mg), (R)-tert-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate (450 mg), potassium carbonate (692 mg) in DMF (5.0 ml) was stirred at 85°C for 6 hours. Ethyl acetate and water were added thereto to separate the organic layer. The organic layer
10 was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a light-yellow, amorphous substance (354 mg). Physical properties:
15 $m/z[M+H]^+$ 431.1

[0356]

(Step 3) Synthesis of (S)-tert-butyl 3-(4-amino-3-((3,5-diisopropylphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate

20 $PdCl_2(dppf)CH_2Cl_2$ (8.2 mg) was added to a mixture of 1-ethynyl-3,5-diisopropylbenzene (56 mg) obtained in Step 1, (S)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate (43 mg) obtained in Step 2, copper (I) iodide (3.8 mg), and triethylamine (0.2 ml) in THF (2.0 ml).
25 After nitrogen purging, the resulting mixture was stirred at 80°C for 1.5 hours. Ethyl acetate and water were added to the reaction mixture to separate the organic layer. The organic layer was washed with a saturated sodium chloride solution. After drying the result over anhydrous sodium sulfate, the solvent was
30 distilled off under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (developing solvent: hexane/ethyl acetate) to obtain the title compound as a colorless, amorphous substance (42 mg). Physical properties:
 $m/z[M+H]^+$ 489.2

35 [0357]

(Step 4) Synthesis of (S)-3-((3,5-diisopropylphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

In accordance with Example 66 (Step 7), except that the (S)-tert-butyl 3-(4-amino-3-((3,5-diisopropylphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate obtained in Step (3) was used in place of (2S,4S)-1-tert-butyl 2-methyl 4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-1,2-dicarboxylate, the title compound was obtained as a light-yellow, amorphous substance.

10 [0358]

(Step 5) Synthesis of Reference Example Compound 4

In accordance with Example 4, except that the (S)-3-((3,5-diisopropylphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine obtained in Step (4) was used in place of (S)-3-((3,5-dimethoxyphenyl)ethynyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine, the title compound was obtained as a light-yellow, amorphous substance. Table 2 shows the physical properties thereof.

15

[0359]

20 Reference Example 5

Synthesis of (S)-1-(3-(4-amino-3-((3-methoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Reference Example Compound 5)

[0360]

25 (Step 1) Synthesis of (S)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one

4N-Hydrochloric acid/1,4-dioxane (4 ml) was added to the (S)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate (488 mg) obtained in Reference Example 4 (Step 2), and the resulting mixture was stirred for 1 hour. The solvent was distilled off under reduced pressure. A solution of 4-(dimethylamino)but-2-enoic-acid hydrochloride (281 mg) and HATU (647 mg) in DMF (5.0 ml) was added to the resulting residue. Further, DIPEA (0.78 ml) was added thereto, and the mixture was stirred overnight. The reaction mixture was

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concentrated under reduced pressure, and chloroform (50 ml) and ethanol (50 ml) were added to the resulting residue. The insoluble matter was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was washed with ethyl acetate (5.0 ml) and dried to obtain the crude product of the title compound (458 mg). Physical properties: $m/z[M+H]^+$ 442.0

[0361]

(Step 2) Synthesis of Reference Example Compound 5

- 10 $PdCl_2(dppf)CH_2Cl_2$ (1.3 mg) was added to a mixture of (S)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (8.0 mg) obtained in Step 1, 1-ethynyl-3-methoxybenzene (4.0 mg), copper (I) iodide (0.6 mg), and triethylamine (8.6 μ l) in THF (1.0 ml).
- 15 After nitrogen purging, the resulting mixture was stirred at 80°C overnight. The reaction mixture was diluted with ethyl acetate and methanol. The resulting diluted solution was treated with basic silica gel, and then concentrated. The resulting residue was purified by reversed-phase HPLC purification
- 20 (water/acetonitrile (0.1% formic acid)) to obtain the title compound as a colorless, amorphous substance (1.4 mg). Table 2 shows the physical properties thereof.

[0362]

Reference Example 6

- 25 Synthesis of (S)-N-(3-((4-amino-1-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)ethynyl)phenyl)acetamide (Reference Example Compound 6)

In accordance with Reference Example 5, except that N-(3-ethynylphenyl)acetamide was used in place of 1-ethynyl-3-methoxybenzene, the title compound was obtained as a colorless, amorphous substance. Table 2 shows the physical properties thereof.

[0363]

Reference Example 7

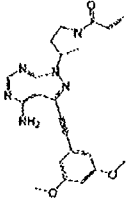
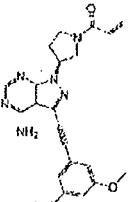
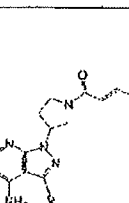
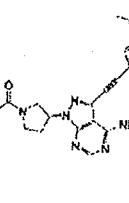
- 35 Synthesis of (S)-1-(3-(4-amino-3-(pyridin-3-ylethynyl)-1H-

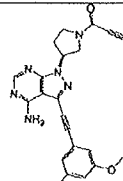
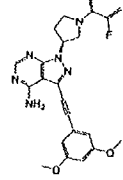
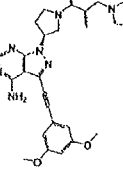
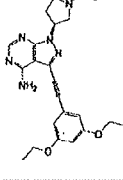
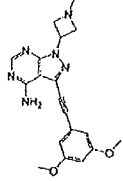
pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Reference Example Compound 7)

In accordance with Reference Example 5, 3-ethynyl pyridine was used in place of 1-ethynyl-3-methoxybenzene, the title compound was obtained as a colorless, amorphous substance. Table 2 shows the physical properties thereof.

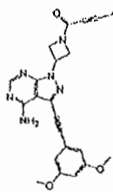
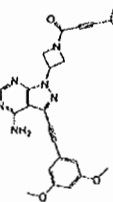
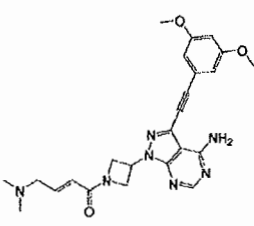
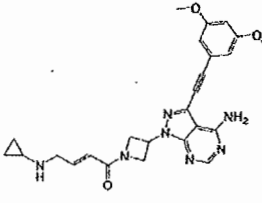
[0364]

Table 1

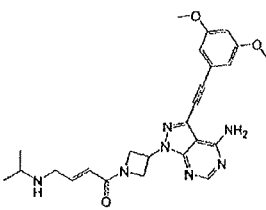
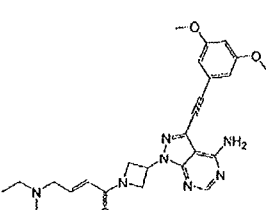
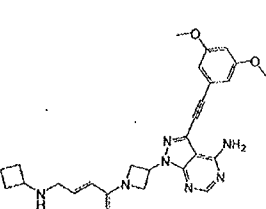
Ex. Comp.	Structural formula	Physical properties
1		¹ H-NMR (DMSO-d ₆) δ: 2.29-2.50 (2H, m), 3.55-4.10 (4H, m), 3.77 (6H, s), 5.40-5.55 (1H, m), 6.62-5.72 (1H, m), 6.10-6.20 (1H, m), 6.50-6.70 (1H, m), 6.64 (1H, d, J = 2.3 Hz), 6.90 (2H, d, J = 2.3 Hz), 8.26 (1H, s). m/z [M+H] ⁺ 419.0
2		¹ H-NMR (DMSO-d ₆) δ: 2.29-2.50 (2H, m), 3.55-4.10 (4H, m), 3.77 (6H, s), 5.40-5.55 (1H, m), 5.62-5.72 (1H, m), 6.10-6.20 (1H, m), 6.50-6.70 (1H, m), 6.64 (1H, d, J = 2.3 Hz), 6.90 (2H, d, J = 2.3 Hz), 8.26 (1H, s). m/z [M+H] ⁺ 419.0
3		¹ H-NMR (DMSO-d ₆) δ: 1.81 (1.5H, dd, J = 6.8, 1.6 Hz), 1.85 (1.5H, dd, J = 6.8, 1.6 Hz), 2.29-2.50 (2H, m), 3.56-3.92 (3.5H, m), 3.77 (6H, s), 4.02-4.10 (0.5H, m), 5.42-5.53 (1H, m), 6.26 (0.5H, dd, J = 15.1, 1.6 Hz), 6.34 (0.5H, dd, J = 15.1, 1.6 Hz), 6.60 (1H, t, J = 2.4 Hz), 6.64-6.74 (1H, m), 6.91 (2H, d, J = 2.4 Hz), 8.26 (0.5H, s), 8.27 (0.5H, s). m/z [M+H] ⁺ 433.1
4		¹ H-NMR (DMSO-d ₆) δ: 2.06 (3H, s), 2.09 (3H, s), 2.20-2.45 (2H, m), 2.95 (1H, d, J = 5.9 Hz), 2.99 (1H, d, J = 5.9 Hz), 3.30-4.10 (4H, m), 5.30-5.50 (1H, m), 6.29 (0.5H, d, J = 15.0 Hz), 6.38 (0.5H, d, J = 15.0 Hz), 6.53-6.65 (3H, m), 6.84 (2H, s), 8.12 (1H, s). m/z [M+H] ⁺ 476.1

5		m/z $[M+H]^+$ 417.0
6		^1H -NMR (CDCl ₃) δ : 2.37-2.68 (2H, m), 3.74-3.82 (2H, m), 3.82 (6H, s), 4.07-4.21 (2H, m), 5.11-5.19 (1H, m), 5.50-5.56 (1H, m), 5.58 (1H, t, J =46.8, 2.0Hz), 5.85 (2H, s), 6.54 (1H, t, J =2.0Hz), 6.74 (2H, d, J =2.4Hz), 8.37 (1H, s) m/z $[M+H]^+$ 437.2
7		^1H -NMR (CDCl ₃) δ : 1.70-1.80 (4H, m), 2.42-2.66 (6H, m), 3.20-3.32 (1H, m), 3.40-3.46 (1H, m), 3.76-3.82 (2H, m), 3.82 (6H, s), 3.91-4.15 (3H, m), 5.32-5.56 (3H, m), 5.91 (2H, s), 6.54 (1H, t, J =2.0Hz), 6.73 (2H, d, J =2.4Hz), 8.36 (1H, s) m/z $[M+H]^+$ 502.2
8		^1H -NMR (CDCl ₃) δ : 1.42 (6H, t, J = 6.8 Hz), 2.39-2.72 (2H, m), 3.71-3.84 (1H, m), 3.96-4.12 (3H, m), 4.03 (4H, q, J = 6.8 Hz), 5.48-5.76 (2H, m), 5.84 (2H, br s), 6.38-6.56 (3H, m), 6.70-6.73 (2H, m), 8.36-8.38 (1H, m). m/z $[M+H]^+$ 447.2
9		^1H -NMR (DMSO- d_6) δ : 3.78 (6H, s), 4.20-4.35 (1H, m), 4.40-4.50 (1H, m), 4.55-4.65 (1H, m), 4.70-4.80 (1H, m), 5.70-5.80 (2H, m), 6.16 (1H, dd, J = 17.1, 2.1 Hz), 6.38 (1H, dd, J = 17.1, 10.2 Hz), 6.61 (1H, t, J = 2.4 Hz), 6.94 (2H, d, J = 2.4 Hz), 8.26 (1H, s). m/z $[M+H]^+$ 405.1

[0366]

10		¹ H-NMR (DMSO-d ₆) δ: 3.73 (6H, s), 4.12-4.28 (3H, m), 4.35-4.50 (2H, m), 4.55-4.65 (1H, m), 5.55 (1H, brs), 5.67 (1H, brs), 6.56 (1H, s), 6.87 (2H, s), 8.40 (1H, s). m/z [M+H] ⁺ 433.3
11		¹ H-NMR (DMSO-d ₆) δ: 1.32 (6H, s), 3.70 (6H, s), 4.14-4.19 (1H, m), 4.33-4.44 (2H, m), 4.57 (1H, t, J = 9.3 Hz), 5.61-5.70 (2H, m), 6.53 (1H, s), 6.87 (2H, d, J = 2.2 Hz), 8.18 (1H, s). m/z [M+H] ⁺ 461.4
12		¹ H-NMR (DMSO-d ₆) δ: 2.08 (6H, s), 2.97 (2H, d, J = 6.2 Hz), 3.72 (6H, d, J = 3.7 Hz), 4.15-4.25 (1H, m), 4.30-4.48 (2H, m), 4.67 (1H, t, J = 9.0 Hz), 5.60-5.70 (1H, m), 6.11 (1H, d, J = 15.0 Hz), 6.55-6.61 (2H, m), 6.88 (2H, d, J = 1.8 Hz), 8.20 (1H, s). m/z [M+H] ⁺ 462.1
13		¹ H-NMR (DMSO-d ₆) δ: 0.00-0.03 (2H, m), 0.12-0.18 (2H, m), 1.84-1.90 (1H, m), 3.59 (6H, s), 4.04-4.09 (1H, m), 4.22 (1H, t, J = 9.3 Hz), 4.32-4.38 (1H, m), 4.52 (1H, t, J = 8.4 Hz), 5.48-5.54 (1H, m), 5.93 (1H, d, J = 15.4 Hz), 6.41 (1H, t, J = 2.3 Hz), 6.54 (1H, dt, J = 15.4, 5.5 Hz), 6.75 (2H, d, J = 2.3 Hz), 8.07 (1H, s). m/z [M+H] ⁺ 474.2

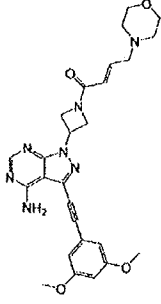
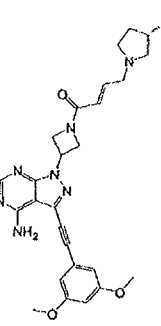
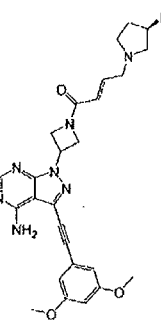
[0367]

14		<p>¹H-NMR (DMSO-d₆) δ: 0.98 (6H, d, J = 6.2 Hz), 2.70-2.76 (1H, m), 3.79 (6H, s), 4.24-4.29 (1H, m), 4.43 (1H, t, J = 9.3 Hz), 4.54-4.58 (1H, m), 4.72 (1H, t, J = 8.6 Hz), 5.70-5.74 (1H, m), 6.17 (1H, d, J = 15.4 Hz), 6.61 (1H, t, J = 2.5 Hz), 6.68-6.80 (1H, m), 6.95 (2H, d, J = 2.5 Hz), 8.33 (1H, s).</p> <p>m/z [M+H]⁺ 476.2</p>
15		<p>¹H-NMR (DMSO-d₆) δ: 0.98 (3H, t, J = 7.1 Hz), 2.13 (3H, s), 2.36 (2H, q, J = 7.1 Hz), 3.11 (2H, d, J = 6.2 Hz), 3.79 (6H, s), 4.23 - 4.30 (1H, m), 4.43 (1H, t, J = 9.2 Hz), 4.50-4.58 (1H, m), 4.73 (1H, t, J = 8.8 Hz), 5.70-5.74 (1H, m), 6.18 (1H, d, J = 15.4 Hz), 6.60-6.70 (2H, m), 6.95 (2H, d, J = 2.6 Hz), 8.28 (1H, s).</p> <p>m/z [M+H]⁺ 476.2</p>
16		<p>¹H-NMR (DMSO-d₆) δ: 1.50-1.70 (4H, m), 2.02-2.10 (2H, m), 3.08-3.15 (1H, m), 3.20-3.25 (2H, m), 3.79 (6H, s), 4.24-4.29 (1H, m), 4.42 (1H, t, J = 9.0 Hz), 4.53-4.58 (1H, m), 4.72 (1H, t, J = 8.6 Hz), 5.70-5.74 (1H, m), 6.13 (1H, d, J = 15.4 Hz), 6.61 (1H, t, J = 2.3 Hz), 6.67-6.74 (1H, m), 6.95 (2H, d, J = 2.3 Hz), 8.27 (1H, s).</p> <p>m/z [M+H]⁺ 488.1</p>

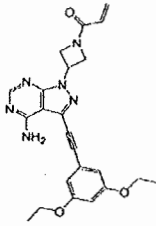
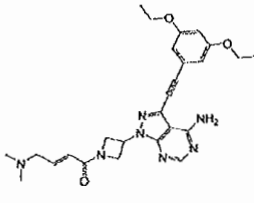
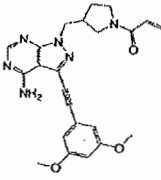
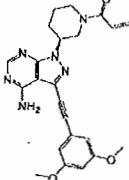
[0368]

17		¹ H-NMR (DMSO-d ₆) δ : 0.96 (6H, t, J = 7.1 Hz), 2.42-2.49 (4H, m), 3.19 (2H, d, J = 4.8 Hz), 3.79 (6H, s), 4.25-4.30 (1H, m), 4.43 (1H, t, J = 9.2 Hz), 4.52-4.57 (1H, m), 4.73 (1H, t, J = 8.6 Hz), 5.69-5.74 (1H, m), 6.19 (1H, d, J = 15.4 Hz), 6.60-6.72 (2H, m), 6.95 (2H, d, J = 2.2 Hz), 8.26 (1H, s). m/z [M+H] ⁺ 490.2
18		¹ H-NMR (DMSO-d ₆) δ : 1.07 (9H, s), 3.78 (6H, s), 4.24-4.29 (1H, m), 4.43 (1H, t, J = 9.5 Hz), 4.50-4.60 (1H, m), 4.72 (1H, t, J = 8.2 Hz), 5.68-5.75 (1H, m), 6.21 (1H, d, J = 15.4 Hz), 6.61 (1H, t, J = 2.3 Hz), 6.70-6.77 (1H, m), 6.94 (2H, d, J = 2.3 Hz), 8.26 (1H, s). m/z [M+H] ⁺ 490.2
19		¹ H-NMR (DMSO-d ₆) δ : 0.94 (6H, d, J = 6.6 Hz), 2.09 (3H, s), 2.73-2.80 (1H, m), 3.13 (2H, d, J = 5.1 Hz), 3.78 (6H, s), 4.24-4.29 (1H, m), 4.40-4.45 (1H, m), 4.53-4.57 (1H, m), 4.70-4.74 (1H, t, J = 8.4 Hz), 5.69-5.73 (1H, m), 6.17 (1H, d, J = 15.4 Hz), 6.60-6.67 (2H, m), 6.95 (2H, d, J = 2.2 Hz), 8.32 (1H, s). m/z [M+H] ⁺ 490.2
20		¹ H-NMR (DMSO-d ₆) δ : 1.36-1.50 (6H, m), 2.32 (4H, brs), 3.05 (2H, d, J = 6.2 Hz), 3.78 (6H, s), 4.24-4.30 (1H, m), 4.42 (1H, t, J = 9.5 Hz), 4.53-4.57 (1H, m), 4.72 (1H, t, J = 8.8 Hz), 5.68-5.74 (1H, m), 6.16 (1H, d, J = 15.4 Hz), 6.60-6.68 (2H, m), 6.94 (2H, d, J = 2.2 Hz), 8.29 (1H, s). m/z [M+H] ⁺ 502.2

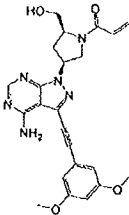
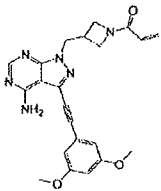
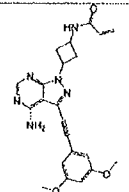
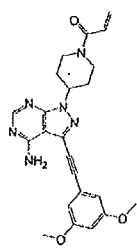
[0369]

21		<p>¹H-NMR (DMSO-d₆) δ: 2.31-2.39 (4H, m), 3.10 (2H, d, J = 5.5 Hz), 3.50-3.60 (4H, m), 3.78 (6H, s), 4.23-4.31 (1H, m), 4.43 (1H, t, J = 9.2 Hz), 4.45-4.58 (1H, m), 4.73 (1H, t, J = 8.8 Hz), 5.67-5.75 (1H, m), 6.20 (1H, d, J = 15.0 Hz), 6.61-6.70 (2H, m), 6.94 (2H, d, J = 1.8 Hz), 8.26 (1H, s).</p> <p>m/z [M+H]⁺ 504.1</p>
22		<p>¹H-NMR (DMSO-d₆) δ: 1.75-1.95 (1H, m), 2.07-2.15 (1H, m), 2.32-2.83 (4H, m), 3.20-3.25 (2H, m), 3.78 (6H, s), 4.25-4.30 (1H, m), 4.43 (1H, t, J = 9.3 Hz), 4.55-4.60 (1H, m), 4.73 (1H, t, J = 8.8 Hz), 5.09-5.13 (0.5H, m), 5.22-5.27 (0.5H, m), 5.69-5.73 (1H, m), 6.19 (1H, d, J = 15.4 Hz), 6.60-6.72 (2H, m), 6.95 (2H, d, J = 2.2 Hz), 8.37 (1H, s).</p> <p>m/z [M+H]⁺ 506.1</p>
23		<p>¹H-NMR (DMSO-d₆) δ: 1.75-1.95 (1H, m), 2.07-2.15 (1H, m), 2.32-2.83 (4H, m), 3.20-3.25 (2H, m), 3.78 (6H, s), 4.25-4.30 (1H, m), 4.43 (1H, t, J = 9.3 Hz), 4.55-4.60 (1H, m), 4.73 (1H, t, J = 8.8 Hz), 5.09-5.13 (0.5H, m), 5.22-5.27 (0.5H, m), 5.69-5.73 (1H, m), 6.19 (1H, d, J = 15.4 Hz), 6.60-6.72 (2H, m), 6.95 (2H, d, J = 2.2 Hz), 8.37 (1H, s).</p> <p>m/z [M+H]⁺ 506.1</p>

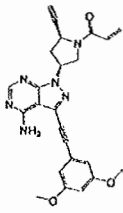
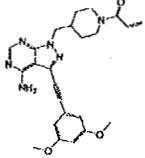
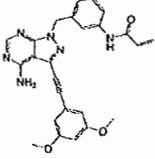
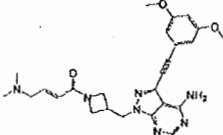
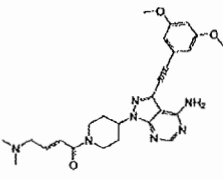
[0370]

24		<p>¹H-NMR (DMSO-d₆) δ: 1.31 (6H, t, J = 7.0 Hz), 4.04 (4H, q, J = 7.0 Hz), 4.30 (1H, dd, J = 10.5, 5.4 Hz), 4.41-4.48 (1H, m), 4.58 (1H, dd, J = 9.3, 5.4 Hz), 4.71-4.78 (1H, m), 5.68-5.76 (2H, m), 6.16 (1H, dd, J = 17.0, 2.1 Hz), 6.38 (1H, dd, J = 17.0, 10.4 Hz), 6.57 (1H, t, J = 2.2 Hz), 6.90 (2H, d, J = 2.2 Hz), 8.26 (1H, s).</p> <p>m/z [M+H]⁺ 433.2</p>
25		<p>¹H-NMR (DMSO-d₆) δ: 1.31 (6H, t, J = 7.1 Hz), 2.14 (6H, s), 3.00-3.05 (2H, m), 4.04 (4H, q, J = 7.1 Hz), 4.27 (1H, dd, J = 10.4, 5.0 Hz), 4.39-4.46 (1H, m), 4.55 (1H, dd, J = 9.3, 5.4 Hz), 4.68-4.76 (1H, m), 5.66-5.75 (1H, m), 6.13-6.20 (1H, m), 6.54-6.69 (2H, m), 6.87-6.91 (2H, m), 8.25 (1H, s).</p> <p>m/z [M+H]⁺ 490.2</p>
26		<p>¹H-NMR (DMSO-d₆) δ: 1.57-1.92 (2H, m), 2.64-2.85 (1H, m), 3.10-3.65 (4H, m), 3.72 (6H, s), 4.28-4.35 (2H, m), 5.53-5.59 (1H, m), 5.95-6.06 (1H, m), 6.38-6.55 (2H, m), 6.83-6.86 (2H, m), 8.16-8.19 (1H, m).</p> <p>m/z [M+H]⁺ 433.1</p>
27		<p>¹H-NMR (DMSO-d₆) δ: 1.55-2.32 (4H, m), 2.87-4.71 (5H, m), 3.78 (6H, m), 5.50-5.75 (1H, m), 6.05-6.20 (1H, m), 6.61 (1H, t, J = 2.2 Hz), 6.65-6.91 (1H, m), 6.91 (2H, d, J = 2.2 Hz), 8.27 (1H, s).</p> <p>m/z [M+H]⁺ 433.1</p>

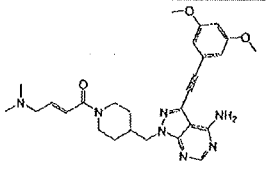
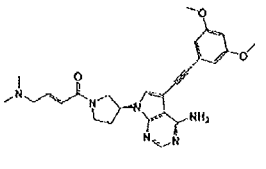
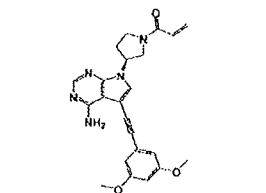
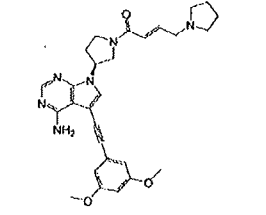
[0371]

28		¹ H-NMR (DMSO-d ₆) δ : 2.48-2.50 (2H, m), 3.27-4.35 (11H, m), 4.89 (0.5H, t, J = 5.7 Hz), 5.02 (0.5H, t, J = 5.7 Hz), 5.28-5.37 (1H, m), 5.66-5.71 (1H, m), 6.13-6.20 (1H, m), 6.60 (1H, t, J = 2.3 Hz), 6.93 (2H, d, J = 2.3 Hz), 8.26 (1H, s). m/z [M+H] ⁺ 449.1
29		¹ H-NMR (CDCl ₃) δ : 3.20-3.35 (1H, m), 3.81 (6H, s), 3.91-4.02 (1H, m), 4.14-4.38 (3H, m), 4.58-4.70 (2H, m), 5.66 (1H, d, J = 10.5 Hz), 5.85-6.05 (2H, m), 6.16 (1H, dd, J = 17.0, 10.4 Hz), 6.33 (1H, d, J = 17.1 Hz), 6.54 (1H, s), 6.74 (2H, dd, J = 3.3, 2.6 Hz), 8.35 (1H, s). m/z [M+H] ⁺ 419.1
30		m/z [M+H] ⁺ 419.2
31		¹ H-NMR (CDCl ₃) δ : 2.08-2.10 (2H, m), 2.20-2.30 (4H, m), 2.81-2.98 (1H, m), 3.22-3.40 (1H, m), 3.82 (6H, s), 4.15-4.25 (1H, m), 4.80-4.88 (1H, m), 4.96-5.04 (1H, m), 5.72 (1H, dd, J=10.8, 2.0Hz), 6.30 (1H, dd, J=16.8, 2.0Hz), 6.54 (1H, t, J=2.0Hz), 6.61 (1H, dd, J=17.2, 10.8Hz), 6.73 (2H, d, J=2.4Hz), 8.42 (1H, s) m/z [M+H] ⁺ 433.2

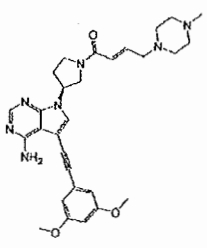
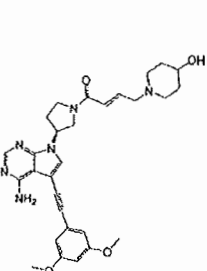
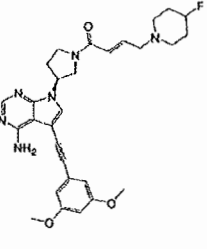
[0372]

32		¹ H-NMR (CDCl ₃) δ: 2.34-2.42 (1H, m), 2.80-3.10 (2H, m), 3.82 (6H, s), 4.05-4.20 (2H, m), 4.20-4.50 (1H, m), 4.70-4.95 (1H, m), 5.30-5.40 (1H, m), 5.75-5.80 (1H, m), 5.98 (2H, brs), 6.40-6.50 (1H, m), 6.54 (1H, s), 6.70-6.73 (2H, m), 8.38 (1H, m). m/z [M+H] ⁺ 443.1
33		m/z [M+H] ⁺ 447.2
34		¹ H-NMR (DMSO-d ₆) δ: 3.77 (6H, s), 5.50 (2H, s), 5.72 (1H, dd, J = 10.2, 2.1 Hz), 6.22 (1H, dd, J = 17.1, 2.1 Hz), 6.38 (1H, dd, J = 17.1, 10.2 Hz), 6.59 (1H, t, J = 2.3 Hz), 6.90 (2H, d, J = 2.3 Hz), 7.00 (1H, d, J = 7.8 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.45 (1H, s), 7.63-7.66 (1H, m), 8.28 (1H, s), 10.12 (1H, s). m/z [M+H] ⁺ 455.2
35		m/z [M+H] ⁺ 476.2
36		¹ H-NMR (CDCl ₃) δ: 2.09 (2H, d, J = 10.7 Hz), 2.29 (8H, m), 2.80-2.98 (1H, m), 3.12 (2H, d, J = 4.9 Hz), 3.19-3.40 (1H, m), 3.81 (6H, s), 4.12-4.32 (1H, m), 4.74-4.90 (1H, m), 4.94-4.96 (1H, m), 5.74-5.85 (2H, m), 6.43-6.55 (2H, m), 6.73 (2H, s), 6.80-6.80 (1H, m), 8.37 (1H, s). m/z [M+H] ⁺ 490.2

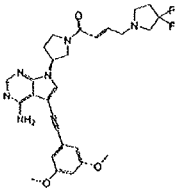
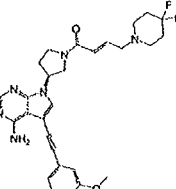
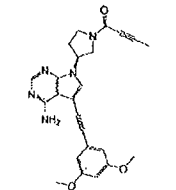
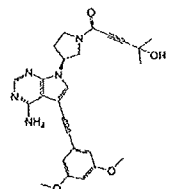
[0373]

37		$m/z [M+H]^+$ 504.2
38		^1H -NMR (DMSO- d_6) δ : 2.13 (3H, s), 2.17 (3H, s), 2.29-2.49 (2H, m), 3.01 (1H, d, J = 6.3 Hz), 3.06 (1H, d, J = 6.3 Hz), 3.40-4.10 (4H, m), 3.76 (6H, m), 5.23-5.37 (1H, m), 6.36 (0.5H, d, J = 15.0 Hz), 6.43 (0.5H, d, J = 15.0 Hz), 6.54 (1H, t, J = 2.2 Hz), 6.60-6.69 (1H, m), 6.74 (2H, d, J = 2.2 Hz), 7.71 (0.5H, s), 7.76 (0.5H, s), 8.16 (1H, t, J = 2.2 Hz). $m/z [M+H]^+$ 475.1
39		^1H -NMR (DMSO- d_6) δ : 2.30-2.50 (2H, m), 3.40-4.15 (4H, m), 3.77 (6H, m), 5.20-5.40 (1H, m), 5.60-5.80 (1H, m), 6.10-6.20 (1H, m), 6.54 (1H, s), 6.54-6.74 (1H, m), 6.74 (2H, s), 7.72 (0.5H, s), 7.76 (0.5H, s), 8.18 (1H, s). $m/z [M+H]^+$ 418.0
40		^1H -NMR (DMSO- d_6) δ : 1.62-1.72 (4H, m), 2.28-2.51 (6H, m), 3.17 (1H, d, J = 5.9 Hz), 3.21 (1H, d, J = 5.9 Hz), 3.52-3.90 (9.5H, m), 4.02-4.12 (0.5H, m), 5.20-5.35 (1H, m), 6.30-6.45 (1H, m), 6.53 (1H, t, J = 2.4 Hz), 6.60-6.80 (3H, m), 7.71 (0.5H, s), 7.75 (0.5H, s), 8.17 (0.5H, s), 8.18 (0.5H, m). $m/z [M+H]^+$ 501.1

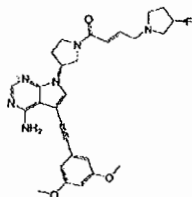
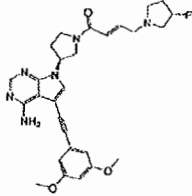
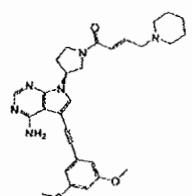
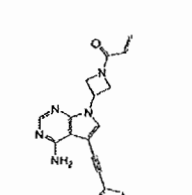
[0374]

41		<p>¹H-NMR (DMSO-d₆) δ: 2.15 (1.5H, s), 2.17 (1.5H, s), 2.18-2.42 (10H, m), 3.05 (1H, d, J = 6.2 Hz), 3.10 (1H, d, J = 6.2 Hz), 3.47-3.94 (9.5H, m), 4.02-4.10 (0.5H, m), 5.22-5.38 (1H, m), 6.32-6.45 (1H, m), 6.54 (1H, d, J = 1.8 Hz), 6.57-6.70 (1H, m), 6.74 (2H, d, J = 1.5 Hz), 7.70 (0.5H, s), 7.75 (0.5H, s), 8.14-8.17 (1H, m).</p> <p>m/z [M+H]⁺ 530.2</p>
42		<p>¹H-NMR (DMSO-d₆) δ: 1.32-1.42 (2H, m), 1.60-1.75 (2H, m), 1.95-2.06 (2H, m), 2.29-2.52 (2H, m), 2.60-2.70 (2H, m), 3.04 (1H, d, J = 6.2 Hz), 3.08 (1H, d, J = 6.2 Hz), 3.35-3.94 (10.5H, m), 4.05-4.10 (0.5H, m), 5.23-5.37 (1H, m), 6.34 (0.5H, d, J = 15.4 Hz), 6.41 (0.5H, d, J = 15.4 Hz), 6.53 (1H, t, J = 2.4 Hz), 6.59-6.68 (1H, m), 6.74 (2H, d, J = 1.5 Hz), 7.71 (0.5H, s), 7.75 (0.5H, s), 8.15-8.17 (1H, m).</p> <p>m/z [M+H]⁺ 531.1</p>
43		<p>¹H-NMR (DMSO-d₆) δ: 1.60-1.90 (4H, m), 2.20-2.50 (6H, m), 3.07 (1H, d, J = 6.1 Hz), 3.12 (1H, d, J = 6.1 Hz), 3.52-3.89 (9.5H, m), 4.03-4.10 (0.5H, m), 4.55-4.80 (1H, m), 5.20-5.40 (1H, m), 6.35-6.46 (1H, m), 6.53 (1H, t, J = 2.2 Hz), 6.55-6.70 (1H, m), 6.74 (2H, d, J = 2.2 Hz), 7.71 (0.5H, s), 7.76 (0.5H, s), 8.17 (0.5H, s), 8.18 (0.5H, m).</p> <p>m/z [M+H]⁺ 533.1</p>

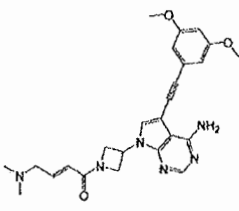
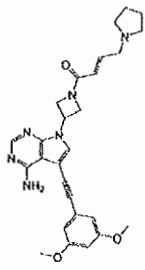
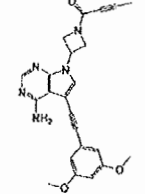
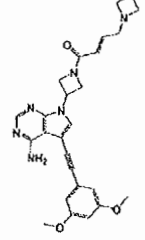
[0375]

44		¹ H-NMR (DMSO-d ₆) δ: 2.18-2.54 (2H, m), 2.66-2.93 (4H, m), 3.18-3.24 (2H, m), 3.65-3.93 (9.5H, m), 4.04-4.10 (0.5H, m), 5.24-5.38 (1H, m), 6.35-6.50 (1H, m), 6.53 (3H, t, J = 2.2 Hz), 6.59-6.69 (1H, m), 6.74 (2H, d, J = 2.2 Hz), 7.71 (0.5H, s), 7.76 (0.5H, s), 8.17 (0.5H, s), 8.18 (0.5H, m). m/z [M+H] ⁺ 537.1
45		¹ H-NMR (DMSO-d ₆) δ: 1.88-2.02 (4H, m), 2.42-2.54 (6H, m), 3.15 (1H, d, J = 6.1 Hz), 3.20 (1H, d, J = 6.1 Hz), 3.49-3.92 (9.5H, m), 4.05-4.10 (0.5H, m), 5.22-5.38 (1H, m), 6.38-6.48 (1H, m), 6.54 (1H, t, J = 2.4 Hz), 6.60-6.70 (1H, m), 6.74 (2H, d, J = 2.4 Hz), 7.71 (0.5H, s), 7.76 (0.5H, s), 8.17 (0.5H, s), 8.18 (0.5H, m). m/z [M+H] ⁺ 551.1
46		¹ H-NMR (DMSO-d ₆) δ: 1.97 (1.5H, s), 2.04 (1.5H, s), 2.37-2.43 (2H, m), 2.97-3.89 (9.5H, m), 4.05-4.12 (0.5H, m), 5.25-5.35 (1H, m), 6.54 (1H, d, J = 2.4 Hz), 6.74 (2H, d, J = 2.4 Hz), 7.74 (0.5H, s), 7.76 (0.5H, s), 8.16 (0.5H, s), 8.17 (0.5H, s). m/z [M+H] ⁺ 430.1
47		¹ H-NMR (DMSO-d ₆) δ: 1.30 (3H, s), 1.37 (3H, s), 2.30-2.50 (2H, s), 3.06-4.10 (4H, m), 3.70 (6H, s), 5.20-5.35 (1H, m), 5.56 (0.5H, s), 5.64 (0.5H, s), 6.47 (1H, s), 6.68 (2H, d, J = 2.2 Hz), 7.70 (0.5H, s), 7.73 (0.5H, s), 8.10 (0.5H, s), 8.11 (0.5H, m). m/z [M+H] ⁺ 474.4

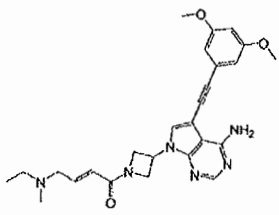
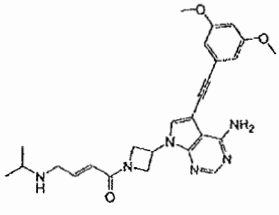
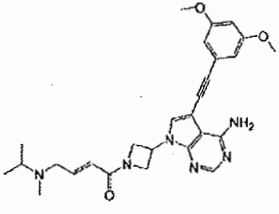
[0376]

48		¹ H-NMR (DMSO-d ₆) δ: 1.76-2.85 (8H, m), 3.16-4.08 (12H, m), 5.05-5.38 (2H, m), 6.35-6.48 (1H, m), 6.53 (1H, t, J = 2.3 Hz), 6.62-6.72 (1H, m), 6.74 (2H, d, J = 2.3 Hz), 7.71 (0.5H, s), 7.76 (0.5H, s), 8.17 (0.5H, s), 8.18 (0.5H, m). m/z [M+H] ⁺ 519.1
49		¹ H-NMR (DMSO-d ₆) δ: 1.76-2.85 (8H, m), 3.16-4.08 (12H, m), 5.05-5.38 (2H, m), 6.35-6.48 (1H, m), 6.53 (1H, t, J = 2.3 Hz), 6.62-6.72 (1H, m), 6.74 (2H, d, J = 2.3 Hz), 7.71 (0.5H, s), 7.76 (0.5H, s), 8.17 (0.5H, s), 8.18 (0.5H, m). m/z [M+H] ⁺ 519.1
50		¹ H-NMR (DMSO-d ₆) δ: 1.20-1.50 (6H, m), 2.19-2.43 (6H, m), 2.96 (1H, d, J = 6.2 Hz), 3.00 (1H, d, J = 5.5 Hz), 3.31-4.02 (4H, m), 3.73 (6H, s), 5.15-5.30 (1H, m), 6.31 (1H, dd, J = 28.7, 15.0 Hz), 6.47 (1H, d, J = 2.1 Hz), 6.50-6.65 (1H, m), 6.66 (2H, d, J = 2.1 Hz), 7.63 (0.5H, s), 7.68 (0.5H, s), 8.10 (1H, s). m/z [M+H] ⁺ 515.1
51		¹ H-NMR (DMSO-d ₆) δ: 3.76 (6H, s), 4.20-4.27 (1H, m), 4.30-4.39 (1H, m), 4.50-4.60 (1H, m), 4.62-4.68 (1H, m), 5.50-5.60 (1H, m), 5.64 (1H, dd, J = 10.3, 2.3 Hz), 6.08 (1H, dd, J = 16.9, 2.3 Hz), 6.29 (1H, dd, J = 16.9, 10.3 Hz), 6.47 (1H, t, J = 2.1 Hz), 6.67 (2H, d, J = 2.1 Hz), 7.98 (1H, s), 8.09 (1, s). m/z [M+H] ⁺ 404.0

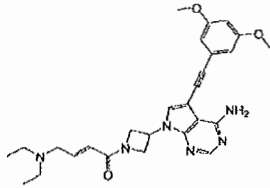
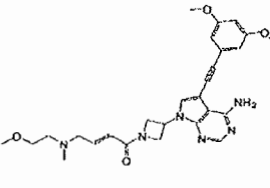
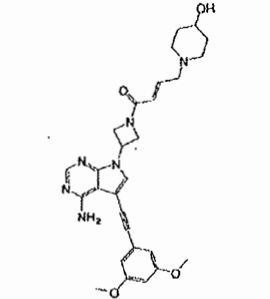
[0377]

52		<p>¹H-NMR (DMSO-d₆) δ: 2.72 (6H, s), 3.76 (6H, s), 3.84 (2H, d, J = 6.8 Hz), 4.30-4.35 (1H, m), 4.44 (1H, t, J = 9.5 Hz), 4.60-4.75 (2H, m), 5.50-5.60 (1H, m), 6.42 (1H, d, J = 15.4 Hz), 6.54 (1H, t, J = 2.4 Hz), 6.59-6.67 (1H, m), 6.73 (2H, d, J = 2.4 Hz), 8.03 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 461.1</p>
53		<p>¹H-NMR (DMSO-d₆) δ: 1.69 (4H, brs), 2.35-2.55 (4H, m), 3.22 (2H, brs), 3.76 (6H, s), 4.25-4.45 (2H, m), 4.55-4.75 (2H, m), 5.49-5.59 (1H, t, m), 6.15 (1H, d, J = 15.5 Hz), 6.54 (1H, t, J = 2.3 Hz), 6.66 (1H, dt, J = 15.5, 6.0 Hz), 6.74 (2H, d, J = 2.3 Hz), 8.05 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 487.1</p>
54		<p>¹H-NMR (DMSO-d₆) δ: 2.01 (3H, s), 3.77 (6H, s), 4.25-4.41 (1H, m), 4.38 (1H, t, J = 9.3 Hz), 4.52-4.63 (2H, m), 5.52-5.57 (1H, m), 6.54 (1H, t, J = 2.2 Hz), 6.74 (2H, d, J = 2.2 Hz), 8.03 (1H, s), 8.16 (1H, s).</p> <p>m/z [M+H]⁺ 416.4</p>
55		<p>¹H-NMR (DMSO-d₆) δ: 1.94-2.00 (2H, m), 3.11-3.15 (6H, t, J = 7.0 Hz), 3.77 (6H, s), 4.25-4.28 (1H, m), 4.39 (1H, t, J = 9.3 Hz), 4.58-4.75 (2H, m), 5.50-5.58 (1H, m), 6.07 (1H, d, J = 15.4 Hz), 6.50-6.58 (2H, m), 6.74 (2H, d, J = 2.6 Hz), 8.05 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 473.1</p>

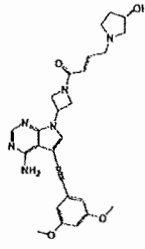
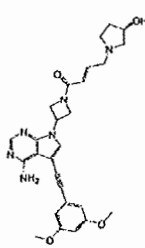
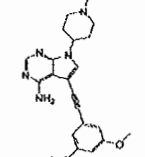
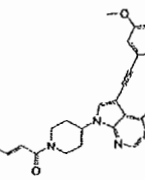
[0378]

56		<p>¹H-NMR (DMSO-d₆) δ: 0.98 (3H, t, J = 7.1 Hz), 2.13 (3H, s), 2.35 (2H, q, J = 7.2 Hz), 3.10 (2H, d, J = 6.2 Hz), 3.77 (6H, s), 4.24-4.29 (1H, m), 4.40 (1H, t, J = 9.5 Hz), 4.65-4.75 (2H, m), 5.53-5.57 (1H, m), 6.15 (1H, d, J = 15.4 Hz), 6.54 (1H, t, J = 2.5 Hz), 6.64 (1H, dt, J = 15.4, 6.1 Hz), 6.74 (2H, d, J = 2.5 Hz), 8.05 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 475.1</p>
57		<p>¹H-NMR (DMSO-d₆) δ: 0.95 (3H, d, J = 6.6 Hz), 1.14 (3H, d, J = 6.6 Hz), 3.05-3.15 (1H, m), 3.64 (2H, d, J = 5.9 Hz), 3.77 (6H, s), 4.22-4.70 (4H, m), 5.50-5.60 (1H, m), 6.25-6.36 (1H, m), 6.52-6.57 (1H, m), 6.63-6.70 (1H, m), 6.73-6.79 (2H, m), 8.02 (0.5H, s), 8.04 (0.5H, s), 8.16 (1H, s).</p> <p>m/z [M+H]⁺ 475.1</p>
58		<p>¹H-NMR (DMSO-d₆) δ: 0.94 (6H, d, J = 6.6 Hz), 2.09 (3H, s), 2.74-2.80 (1H, m), 3.13 (2H, d, J = 5.1 Hz), 3.77 (6H, s), 4.24-4.29 (1H, m), 4.40 (1H, t, J = 9.2 Hz), 4.63-4.72 (1H, m), 5.53-5.57 (1H, m), 6.15 (1H, d, J = 15.3 Hz), 6.54 (1H, t, J = 2.2 Hz), 6.62 (2H, dt, J = 15.3, 6.0 Hz), 6.74 (2H, d, J = 2.2 Hz), 8.05 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 489.2</p>

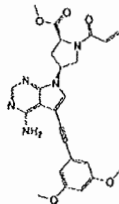
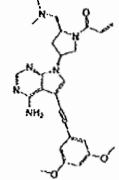
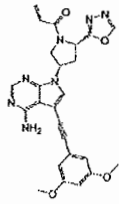
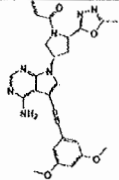
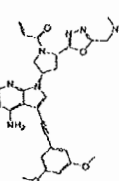
[0379]

59		<p>¹H-NMR (DMSO-d₆) δ: 0.95 (6H, t, J = 7.1 Hz), 2.45 (4H, q, J = 7.1 Hz), 3.18 (2H, d, J = 5.9 Hz), 3.76 (6H, s), 4.25-4.29 (1H, m), 4.40 (1H, t, J = 9.5 Hz), 4.57-4.59 (1H, m), 4.68 (1H, t, J = 8.8 Hz), 5.52-5.70 (1H, m), 6.17 (1H, d, J = 15.0 Hz), 6.53-6.56 (1H, m), 6.66 (1H, dt, J = 15.0, 6.1 Hz), 6.74-6.75 (2H, m), 8.06 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 489.2</p>
60		<p>¹H-NMR (DMSO-d₆) δ: 2.18 (3H, s), 3.15 (2H, d, J = 5.5 Hz), 3.22 (3H, s), 3.77 (6H, s), 4.25-4.30 (1H, m), 4.40 (1H, t, J = 9.7 Hz), 4.55-4.75 (2H, m), 5.51-5.59 (1H, m), 6.17 (1H, d, J = 15.4 Hz), 6.54 (1H, t, J = 2.4 Hz), 6.63 (1H, dt, J = 15.4, 6.0 Hz), 6.74 (2H, d, J = 2.4 Hz), 8.05 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 505.1</p>
61		<p>¹H-NMR (DMSO-d₆) δ: 1.30-1.42 (2H, m), 1.65-1.75 (2H, m), 2.03 (2H, t, J = 10.3 Hz), 2.62-2.70 (2H, m), 3.06 (2H, d, J = 5.1 Hz), 3.77 (6H, s), 4.22-4.30 (1H, m), 4.40 (1H, t, J = 9.2 Hz), 4.55-4.72 (2H, m), 5.52-5.58 (1H, m), 6.13 (1H, d, J = 15.0 Hz), 6.54 (1H, t, J = 2.3 Hz), 6.58-6.65 (1H, m), 6.74 (2H, d, J = 2.3 Hz), 8.06 (1H, s), 8.15 (1H, s).</p> <p>m/z [M+H]⁺ 517.1</p>

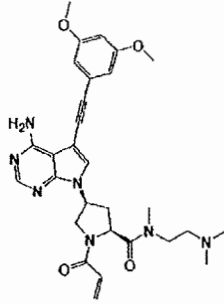
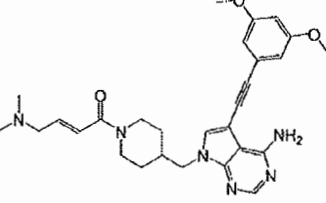
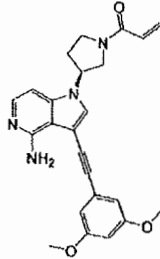
[0380]

62		<p>¹H-NMR (DMSO-d₆) δ: 1.48-1.58 (1H, m), 1.92-2.00 (1H, m), 2.31-2.71 (4H, m), 3.19 (2H, brs), 3.77 (6H, s), 4.15-4.30 (2H, m), 4.35-4.44 (1H, m), 4.55-4.72 (2H, m), 5.50-5.60 (1H, m), 6.15 (1H, d, J = 15.4 Hz), 6.54 (1H, t, J = 2.2 Hz), 6.60-6.70 (1H, m), 6.75 (2H, d, J = 2.2 Hz), 8.05 (1H, s), 8.15 (1H, d, J = 1.8 Hz).</p> <p>m/z [M+H]⁺ 503.1</p>
63		<p>¹H-NMR (DMSO-d₆) δ: 1.48-1.58 (1H, m), 1.92-2.00 (1H, m), 2.31-2.71 (4H, m), 3.19 (2H, brs), 3.77 (6H, s), 4.15-4.30 (2H, m), 4.35-4.44 (1H, m), 4.55-4.72 (2H, m), 5.50-5.60 (1H, m), 6.15 (1H, d, J = 15.4 Hz), 6.54 (1H, t, J = 2.2 Hz), 6.60-6.70 (1H, m), 6.75 (2H, d, J = 2.2 Hz), 8.05 (1H, s), 8.15 (1H, d, J = 1.8 Hz).</p> <p>m/z [M+H]⁺ 503.1</p>
64		<p>¹H-NMR (CDCl₃) δ: 1.67-2.22 (4H, m), 2.71-2.95 (1H, m), 3.19-3.35 (1H, m), 3.81 (6H, s), 4.09-4.25 (1H, m), 4.83-4.95 (2H, m), 5.61-5.78 (3H, m), 6.28-6.68 (6H, m), 7.24 (1H, s), 8.31 (1H, s).</p> <p>m/z [M+H]⁺ 432.2</p>
65		<p>¹H-NMR (CDCl₃) δ: 1.65-2.00 (4H, m), 2.29 (6H, s), 2.77-2.92 (1H, m), 3.12 (2H, d, J = 5.9 Hz), 3.22-3.38 (1H, m), 3.81 (6H, s), 4.14-4.30 (1H, m), 4.85-4.97 (2H, m), 5.66 (2H, br s), 6.44-6.55 (2H, m), 6.65 (2H, d, J = 2.2 Hz), 6.84-6.95 (1H, m), 7.24 (1H, s), 8.31 (1H, s).</p> <p>m/z [M+H]⁺ 489.2</p>

[0381]

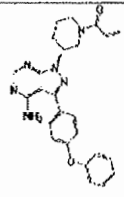
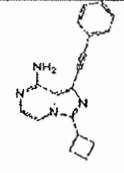
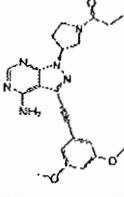
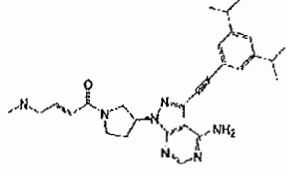
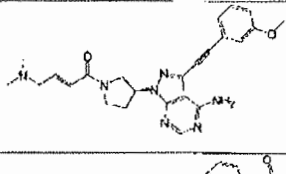
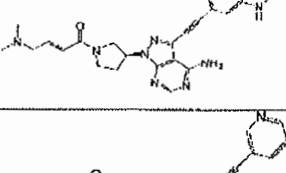
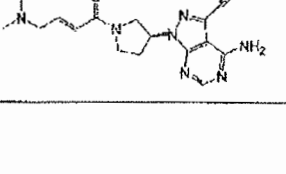
66		¹ H-NMR (CDCl ₃) δ: 2.37-2.48 (1H, m), 2.82-2.93 (1H, m), 3.41-3.52 (1H, m), 3.82 (9H, s), 3.86-3.95 (1H, m), 4.25-4.38 (1H, m), 4.69 (1H, t, J = 8.3 Hz), 5.43-5.56 (1H, m), 5.65-5.83 (2H, m), 6.36-6.50 (3H, m), 6.65 (2H, d, J = 2.0 Hz), 7.37 (1H, s), 8.30 (1H, s). m/z [M+H] ⁺ 476.2
67		m/z [M+H] ⁺ 475.2
68		¹ H-NMR (CDCl ₃) δ: 2.75-2.95 (1H, m), 2.99-3.15 (1H, m), 3.82 (6H, s), 4.00 (1H, t, J = 9.8 Hz), 4.32-4.50 (1H, m), 5.44-5.85 (5H, m), 6.44 (2H, d, J = 5.9 Hz), 6.49 (1H, t, J = 2.2 Hz), 6.66 (2H, d, J = 2.2 Hz), 7.44 (1H, br s), 8.30 (1H, s), 8.40 (1H, s). m/z [M+H] ⁺ 486.1
69		m/z [M+H] ⁺ 500.2
70		¹ H-NMR (CDCl ₃) δ: 2.36 (6H, br s), 2.69-2.90 (1H, m), 2.94-3.10 (1H, m), 3.69-3.80 (2H, m), 3.82 (6H, s), 3.92-4.05 (1H, m), 4.32-4.47 (1H, m), 5.39-5.83 (5H, m), 6.35-6.47 (2H, m), 6.49 (1H, t, J = 2.1 Hz), 6.65 (2H, d, J = 2.2 Hz), 7.44 (1H, br s), 8.30 (1H, s). m/z [M+H] ⁺ 543.2

[0382]

71		<p>¹H-NMR (CDCl₃) δ: 2.30 (6H, d, J = 7.6 Hz), 2.35-2.68 (3H, m), 2.77-2.92 (1H, m), 3.14 (3H, d, J = 79.5 Hz), 3.31-3.47 (1H, m), 3.69-3.81 (1H, m), 3.82 (6H, s), 3.95 (2H, q, J = 9.9 Hz), 4.35 (1H, t, J = 8.9 Hz), 5.08 (1H, t, J = 7.3 Hz), 5.50-5.79 (4H, m), 6.37-6.52 (3H, m), 6.65 (2H, t, J = 2.2 Hz), 7.59 (1H, d, J = 28.0 Hz), 8.30 (1H, s).</p> <p>m/z [M+H]⁺ 546.3</p>
72		<p>m/z [M+H]⁺ 503.3</p>
73		<p>¹H-NMR (DMSO-d₆) δ: 2.21-2.44 (2H, m), 3.34-3.87 (9.5H, m), 4.00-4.10 (0.5H, m), 5.02-5.18 (1H, m), 5.58-5.68 (1H, m), 5.88 (2H, brs), 6.05-6.18 (1H, m), 6.45-6.65 (4H, m), 6.82-6.88 (1H, m), 7.60-7.63 (2H, m).</p> <p>m/z [M+H]⁺ 417.5</p>

[0383]

Table 2

Ref. Ex. Comp.	Structural formula	Physical properties
1		$m/z [M+H]^+$ 441.2
2		$m/z [M+H]^+$ 289.1
3		$m/z [M+H]^+$ 421.2
4		$m/z [M+H]^+$ 500.3
5		$m/z [M+H]^+$ 446.2
6		$m/z [M+H]^+$ 473.2
7		$m/z [M+H]^+$ 417.2

[0384]

Test Example 1

5 Measurement of Inhibitory Effect on FGFR2 Kinase Activity

When setting conditions for the measurement of the inhibitory effect of the compounds on FGFR2 kinase activity, FL-Peptide 22 (Caliper Life Sciences, Inc.) was used as a substrate.

The purified recombinant human FGFR2 protein used in the test was purchased from Carpa Biosciences, Inc. In the measurement of the inhibitory effect of the compounds, first, a test compound was gradually diluted with dimethylsulfoxide (DMSO) to a concentration that was 20 times higher than the final concentration. Next, the purified human FGFR2 protein, FL-Peptide 22 (final concentration: 1.5 μ M), magnesium chloride (final concentration: 5 mM), ATP (final concentration: 75 μ M), and the test compound DMSO solution (final concentration of DMSO: 5%) were added to a reaction buffer (15 mM Tris-HCl pH 7.5, 0.01% Tween-20, 2 mM DTT), and the mixture was incubated at 25°C for 120 minutes to perform a kinase reaction. EDTA (final concentration: 30 mM) diluted with a separation buffer (Caliper Life Sciences, Inc.) was added thereto to terminate the kinase reaction. Finally, using a LabChip (registered trademark) 3000 system (Caliper Life Sciences, Inc.; excitation wavelength: 488 nm, detection wavelength: 530 nm), phosphorylated peptides and non-phosphorylated peptides were separated, and the amount of each peptide was measured. The level of phosphorylation was determined from the quantitative ratio. The compound concentration at which phosphorylation was inhibited by 50% was defined as the IC₅₀ value (nM). Table 3 shows the results.

[0385]

The results demonstrated that all of the compounds of the present invention, represented by the test compounds, which had a dialkoxy benzene ethynyl group and a partial structure of α,β -unsaturated amide, exhibited a high FGFR2 inhibitory effect. Conversely, the compounds of the Reference Examples, which did not have a dialkoxy benzene ethynyl group or a partial structure of α,β unsaturated amide, showed a remarkably lower FGFR2 inhibitory effect.

[0386]

[Table 3]

Test compound	IC ₅₀ value (nM)
Ex. Compound 1	2.4
Ex. Compound 2	1.1
Ex. Compound 5	1.1
Ex. Compound 8	6.9
Ex. Compound 9	1.1
Ex. Compound 10	1.2
Ex. Compound 12	2.2
Ex. Compound 14	3.8
Ex. Compound 15	3.0
Ex. Compound 16	3.8
Ex. Compound 17	4.1
Ex. Compound 18	4.3
Ex. Compound 19	2.7
Ex. Compound 20	3.3
Ex. Compound 22	5.6
Ex. Compound 23	6.8
Ex. Compound 24	7.2
Ex. Compound 28	3.7
Ex. Compound 29	9.3
Ex. Compound 32	0.4
Ex. Compound 38	4.7
Ex. Compound 39	0.4
Ex. Compound 40	3.2
Ex. Compound 42	6.6
Ex. Compound 46	4.3
Ex. Compound 47	2.0

Test compound	IC ₅₀ value (nM)
Ex. Compound 48	6.8
Ex. Compound 49	7.0
Ex. Compound 50	5.8
Ex. Compound 51	<0.3
Ex. Compound 52	1.0
Ex. Compound 53	0.6
Ex. Compound 55	2.5
Ex. Compound 56	1.5
Ex. Compound 57	1.5
Ex. Compound 59	1.2
Ex. Compound 60	1.5
Ex. Compound 61	2.3
Ex. Compound 63	1.0
Ex. Compound 64	7.9
Ex. Compound 65	7.0
Ex. Compound 66	<0.3
Ex. Compound 68	1.2
Ex. Compound 69	8.8
Ex. Compound 73	4.9
Ref. Ex. Compound 1	280
Ref. Ex. Compound 2	270
Ref. Ex. Compound 3	190
Ref. Ex. Compound 4	>10000
Ref. Ex. Compound 5	190
Ref. Ex. Compound 6	110
Ref. Ex. Compound 7	1600

[0387]

Test Example 2

Cell Growth-Inhibitory Effect on Human-Derived Gastric Cancer

5 Cell Lin with High Expression of FGFR

Human-derived gastric cancer OCUM-2MD3 cells, which overexpressed FGFR2 were subcultured daily in a Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) at a cell density of not more than 80%. In order to
10 initiate a test of the cell growth-inhibitory effect of the compounds, the OCUM-2MD3 cells were suspended in the above DMEM medium and seeded in a 96-well flat-bottom plate so that each well contained 3,000 cells. Then, the cells were cultured in an incubator containing 5% carbon dioxide gas at 37°C for one day.
15 On the following day, the test compound was gradually diluted

with DMSO to a concentration 100 times higher than the final concentration. The DMSO solution of the test compound was diluted with the medium used for cultivation, and the diluted solution was added to each well of the cell culture plate so that the
5 final concentration of DMSO became 0.5%. Then, the cells were cultured in an incubator containing 5% carbon dioxide gas at 37°C for 72 hours. The number of cells was measured at the time of the addition of the test compound and 72 hours later after culture by using a Cell Counting Kit-8 (produced by Dojindo Laboratories)
10 according to a protocol recommended by Dojindo Laboratories. The reagent of the kit was added to each plate, and a color reaction was performed in an incubator containing 5% carbon dioxide gas at 37°C for a predetermined time. After completion of the reaction, the absorbance at a wavelength of 450 nm was measured by a
15 microplate reader. The cell-growth inhibition rate was calculated by the following formula, and the concentration of the test compound at which the cell growth was inhibited by 50% (GI₅₀ (nM)) was determined. Table 4 shows the results.

[0388]

20 The results demonstrated that all of the compounds of the present invention, represented by the test compounds, showed a high growth inhibitory effect on the human-derived gastric cancer OCUM-2MD3 cell line.

[0389]

25
$$\text{Growth inhibition rate (\%)} = (C - T) / (C - C_0) \times 100$$

T: absorbance of well to which test compound was added

C: absorbance of well to which test compound was not added

C₀: absorbance of well measured before addition of compound

[0390]

30 [Table 4]

Test compound	GI ₅₀ (nM)
Ex. Compound 2	<4.6
Ex. Compound 4	17
Ex. Compound 8	5
Ex. Compound 12	<4.6
Ex. Compound 15	<4.6
Ex. Compound 17	4.6
Ex. Compound 19	<4.6
Ex. Compound 24	13
Ex. Compound 25	13
Ex. Compound 28	5
Ex. Compound 29	20
Ex. Compound 32	<4.6
Ex. Compound 39	<4.6
Ex. Compound 40	7
Ex. Compound 64	12
Ex. Compound 65	13
Ex. Compound 66	<4.6
Ex. Compound 68	8
Ex. Compound 73	7

[0391]

Test Example 3

Measurement of Inhibitory Effect on FGFR1 Kinase Activity

5 When setting conditions for the measurement of the inhibitory effect of the compounds on FGFR1 kinase activity, a biotinylated peptide (biotin-EEPLYWSFPAKKK) was synthesized for use as a substrate by utilizing the amino acid sequence of FL-Peptide 22 (Caliper Life Sciences, Inc.) with biotin. The

10 purified recombinant human FGFR1 protein used in the test was purchased from Carna Biosciences, Inc. In the measurement of the inhibitory effect of the compounds, first, a test compound was gradually diluted with dimethylsulfoxide (DMSO) to a concentration 20 times higher than the final concentration. Next,

15 the purified human FGFR1 protein, substrate peptide (final concentration: 250 nM), magnesium chloride (final concentration: 5 mM), ATP (final concentration: 190 μ M), and the test compound DMSO solution (final concentration of DMSO: 5%) were added to a reaction buffer (15 mM Tris-HCl pH 7.5, 0.01% Tween-20, 2 mM DTT),

20 and the mixture was incubated at 25°C for 120 minutes to perform a

kinase reaction. EDTA was added thereto to a final concentration of 40 mM to thereby terminate the reaction. Then, a detection solution containing Eu-labeled anti-phosphorylated tyrosine antibody PT66 (PerkinElmer) and SureLight APC-SA (PerkinElmer) was added, and the resulting mixture was allowed to stand at room temperature for 2 hours or more. Finally, the intensity of fluorescence when excitation light with a wavelength of 337 nm was irradiated was measured by a PHERAstar FS (BMG LABTECH) at two wavelengths of 620 nm and 665 nm. The amount of phosphorylation was determined from the fluorescence intensity ratio of the two wavelengths. The compound concentration at which phosphorylation was inhibited by 50% was defined as the IC₅₀ value (nM). Table 5 below shows the results.

[0392]

15 Test Example 4

Measurement of Inhibitory Effect on FGFR3 Kinase Activity

The inhibitory effect of the compounds on FGFR3 kinase activity was measured according to the method of Test Example 3. Purified recombinant human FGFR3 protein was purchased from Carina Biosciences, Inc. The final concentration of ATP was 50 μ M. Table 5 shows the results.

[0393]

Test Example 5

Measurement of Inhibitory Effect on FGFR4 Kinase Activity

25 The inhibitory effect of the compounds on FGFR4 kinase activity was measured according to the method of Test Example 3. Purified recombinant human FGFR4 protein was purchased from Carina Biosciences, Inc. The final concentration of ATP was 200 μ M. Table 5 shows the results.

30 [0394]

The results of Test Examples 3 to 5 demonstrated that all of the compounds of the present invention, represented by the test compound, showed a high inhibitory effect on FGFR1, FGFR3, and FGFR4, and served as pan-FGFR inhibitors.

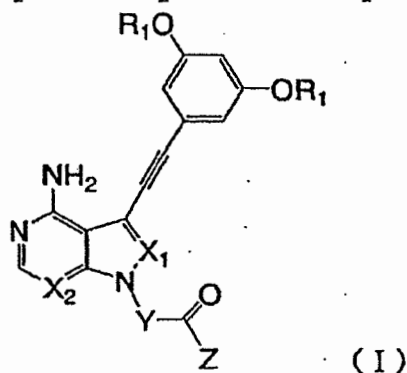
35 [0395]

[Table 5]

Test compound	IC ₅₀ value (nM)		
	Test Example 3	Test Example 4	Test Example 5
Ex. Compound 2	3.6	0.5	3.4
Ex. Compound 5	1.4	0.2	0.5
Ex. Compound 9	3.2	0.3	4.9
Ex. Compound 47	20	0.5	11
Ex. Compound 51	1.2	0.1	1.7
Ex. Compound 52	2.8	0.7	21
Ex. Compound 62	3.1	0.7	19

CLAIMS

[Claim 1] A compound represented by Formula (I)

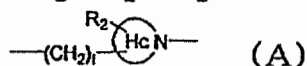


or a salt thereof,

wherein R_1 is the same or different, and each represents C_1 - C_6 alkyl;

X_1 and X_2 independently represent N or CH;

Y is a group represented by Formula (A)

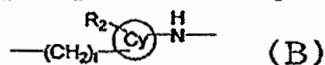


wherein the divalent moiety represented by



is a nitrogen-containing C_3 - C_{10} heterocycloalkylene group,

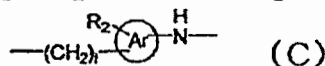
a group represented by Formula (B)



wherein the divalent moiety represented by



is a C_3 - C_{10} cycloalkylene group, or
a group represented by Formula (C)



wherein the divalent moiety represented by



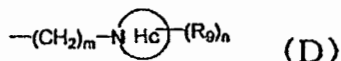
is a C_6 - C_{12} arylene group;

R_2 is hydrogen, C_2 - C_6 alkynyl, $-C(=O)OR_x$, $-C(=O)N(R_x)(R_y)$, hydroxy- C_1 - C_6 alkyl, di(C_1 - C_6 alkyl)amino- C_1 - C_6 alkyl, or C_2 - C_9 heteroaryl optionally having R_3 ; and

R_3 is C_1 - C_6 alkyl or di(C_1 - C_6 alkyl)amino- C_1 - C_6 alkyl;

Z is $-C(R_4)=C(R_5)(R_6)$ or $-C\equiv C-R_7$;

R_4 , R_5 , and R_6 are the same or different, and each represents hydrogen, halogen, C_1 - C_6 alkyl optionally having R_8 , or a group represented by Formula (D)



wherein the monovalent moiety represented by

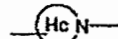


is a nitrogen-containing C₃-C₁₀ heterocycloalkyl group, R₇ is hydrogen, C₁-C₆ alkyl, or hydroxy-C₁-C₆ alkyl; R₈ is -OR_x or -N(R_x)(R_y); R₉ is C₁-C₆ alkyl, halogen, or -OR_x; R_x and R_y are the same or different, and each represents hydrogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, di(C₁-C₆ alkyl)amino-C₁-C₆ alkyl, or C₁-C₆ alkoxy-C₁-C₆ alkyl; l is an integer of 0 to 3; m is an integer of 1 to 3; and n is an integer of 0 to 2.

[Claim 2] The compound or a salt thereof according to claim 1 wherein in Formula (I), (1) when X₂ is N, X₁ is N or CH, and (2) when X₂ is CH, X₁ is CH.

[Claim 3] The compound or a salt thereof according to claim 1 or 2 wherein in Formula (I), l is 0 or 1.

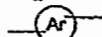
[Claim 4] The compound or a salt thereof according to any one of claims 1 to 3 wherein in Formula (I), (1) when Y is a group represented by Formula (A), the group represented by



is azetidinylene, pyrrolidinylene, piperidinylene, piperazinylene, or morpholinylene, and (2) when Y is a group represented by Formula (B), the group represented by



is cyclopropylene or cyclobutylene, and (3) when Y is a group represented by Formula (C), the group represented by



is phenylene.

[Claim 5] The compound or a salt thereof according to any one of claims 1 to 4 wherein in Formula (I), (1) when Y is a group represented by Formula (A), Z is -C(R₄)=C(R₅)(R₆) or C≡C-R₇, and (2) when Y is a group represented by Formula (B) or (C), Z is C(R₄)=C(R₅)(R₆).

[Claim 6] The compound or a salt thereof according to any one of claims 1 to 5 wherein in Formula (I), R₁ is methyl or ethyl.

[Claim 7] The compound or a salt thereof according to any one of claims 1 to 6 wherein in Formula (I), R₂ is C₂-C₆ alkynyl, -C(=O)OR_x, hydroxy-C₁-C₄ alkyl, or C₂-C₉ heteroaryl optionally having R₃.

[Claim 8] The compound or a salt thereof according to any one of claims 1 to 7 wherein the compound is selected from the following group of compounds:

- (1) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one,
- (2) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-yn-1-one,
- (3) (S)-1-(3-(4-amino-3-((3,5-diethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one,
- (4) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)prop-2-en-1-one,
- (5) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-hydroxybut-2-yn-1-one,
- (6) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(dimethylamino)but-2-en-1-one,
- (7) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(cyclopropylamino)but-2-en-1-one,
- (8) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(isopropylamino)but-2-en-1-one,
- (9) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(ethyl(methyl)amino)but-2-en-1-one,
- (10) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(cyclobutylamino)but-2-en-1-one,
- (11) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(diethylamino)but-2-en-1-one,
- (12) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(tert-butylamino)but-2-en-1-one,
- (13) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(isopropyl(methyl)amino)but-2-en-1-one,
- (14) 1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(piperidin-1-yl)but-2-en-1-one,
- (15) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(3-fluoropyrrolidin-1-yl)but-2-en-1-one,
- (16) (R)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)azetidin-1-yl)-4-(3-fluoropyrrolidin-1-yl)but-2-en-1-one,
- (17) 1-((2S,4S)-4-(4-amino-3-((3,5-

- dimethoxyphenyl) ethynyl) -1H-pyrazolo[3,4-d]pyrimidin-1-yl) -2-(hydroxymethyl)pyrrolidin-1-yl)prop-2-en-1-one,
 (18) 1-(2S,4S)-4-(4-amino-3-((3,5-dimethoxyphenyl) ethynyl) -1H-pyrazolo[3,4-d]pyrimidin-1-yl) -2-ethynylpyrrolidin-1-yl)prop-2-en-1-one,
 (19) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl) -4-(dimethylamino)but-2-en-1-one,
 (20) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)prop-2-en-1-one,
 (21) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl) -4-(pyrrolidin-1-yl)but-2-en-1-one,
 (22) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl) -4-(4-hydroxypiperidin-1-yl)but-2-en-1-one,
 (23) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl)but-2-yn-1-one,
 (24) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl) -4-hydroxy-4-methylpent-2-yn-1-one,
 (25) 1-((S)-3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl) -4-((S)-3-fluoropyrrolidin-1-yl)but-2-en-1-one,
 (26) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidin-1-yl) -4-(piperidin-1-yl)but-2-en-1-one,
 (27) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)prop-2-en-1-one,
 (28) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl) -4-(dimethylamino)but-2-en-1-one,
 (29) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl) -4-(pyrrolidin-1-yl)but-2-en-1-one,
 (30) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl) -4-(azetidin-1-yl)but-2-en-1-one,
 (31) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl) -4-(ethyl(methyl)amino)but-2-en-1-one,
 (32) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl) -4-(isopropylamino)but-2-en-1-one,
 (33) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl) -4-(diethylamino)but-2-en-1-one,
 (34) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl) ethynyl) -7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl) -4-((2-

methoxyethyl) (methyl amino) but-2-en-1-one,

(35) 1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(4-hydroxypiperidin-1-yl)but-2-en-1-one,

(36) (S)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(3-hydroxypyrrolidin-1-yl)but-2-en-1-one,

(37) (R)-1-(3-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)azetidin-1-yl)-4-(3-hydroxypyrrolidin-1-yl)but-2-en-1-one,

(38) (2S,4S)-methyl 1-acryloyl-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)pyrrolidine-2-carboxylate,

(39) 1-((2S,4S)-4-(4-amino-5-((3,5-dimethoxyphenyl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)prop-2-en-1-one, and

(40) (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one.

[Claim 9] An FGFR inhibitor comprising the compound or a salt thereof according to any one of claims 1 to 8 as an active ingredient.

[Claim 10] A pharmaceutical composition comprising the compound or a salt thereof according to any one of claims 1 to 8, and a pharmacologically acceptable carrier.

[Claim 11] An antitumor agent comprising the compound or a salt thereof according to any one of claims 1 to 8 as an active ingredient.

[Claim 12] The compound or a salt thereof according to any one of claims 1 to 8 for use in the treatment of a tumor.

[Claim 13] Use of the compound or a salt thereof according to any one of claims 1 to 8 in the manufacture of an antitumor agent.