DESCRIPTION

Title of Invention: QUINAZOLINE COMPOUND

Technical Field

[0001]

The present invention relates to a quinazoline compound which is useful as a pharmaceutical composition and a G12C mutation KRAS inhibitor, and is expected to be useful as an active ingredient of a pharmaceutical composition, for example, a pharmaceutical composition for treating lung cancer.

Background Art

[0002]

It has been reported that the number of deaths due to lung cancer is the largest as 19% of all cancer deaths, and 1.8 million new cases per year worldwide are newly affected (GLOBOCAN, 2012). In non-small cell lung cancer (NSCLC) which is set to occupy nearly 80% of lung cancer, (American Cancer Society. Cancer Facts and Figures, 2016), although surgical therapy has been considered until a certain stage, and after that stage, chemotherapy or radiotherapy is used as a main treatment without having surgical adaptation. Based on cell morphology, adenocarcinoma and squamous cell carcinoma are classified as the most common type of NSCLC. The clinical course of these tumors is similar, but adenocarcinoma is characterized by the peripheral localization of the lungs.

[0003]

RAS protein is a small molecule guanosine triphosphate (GTP) binding protein of approximately 21 kDa consisting of 188 to 189 amino acids, and there are four main proteins (KRAS (KRAS4A and KRAS4B), NRAS, HRAS) generated from three genes such as KRAS gene, NRAS gene, and HRAS gene. RAS protein has two types of a GTP binding type which is an active form and a guanosine diphosphate (GDP) binding type which is an inactive form. The RAS protein is activated by exchanging GDP for GTP by ligand stimulation to cell membrane receptor such as EGFR. The active form RAS binds to about 20 kinds of effector proteins such as RAF, PI3K, and RALGDS, and activates a signal cascade on the downstream. On the other hand, active form RAS becomes inactive by converting GTP to GDP by endogenous GTP hydrolysis (GTPase) activity. This GTPase activity is enhanced by GAP (GTPase activating protein). From this, RAS plays an important "molecular switch" function in intracellular signaling pathway such as EGFR and plays an important role in progress of cell growth, proliferation, and blood vessel formation (Nature rev. cancer, 11, 761, 2011, Nature rev. drug discov., 13, 828, 2014, Nature rev. drug discov., 15, 771, 2016).

[0004]

When amino acid substitution occurs due to mutation of RAS gene, it is considered that the proportion of the active form increases due to a decrease in endogenous GTPase activity or a decrease in affinity for GAP. It is considered that excessive signal transmission resulting from this causes carcinogenesis and cancer growth proliferation. In the lung cancer, the mutation of the RAS gene was observed in 32% of pulmonary adenocarcinoma. It has been reported that the breakdown of the mutation frequency is 96% of the KRAS gene, 3% of the NRAS gene, and 1% of the HRAS gene, and there are many point mutations of KRAS exon 2 (codon 12, codon 13). In particular, the G12C mutation in which glycine at codon 12 is substituted with cysteine is a frequent mutation in the KRAS gene and occupies the highest proportion as 44% of the KRAS gene mutation observed in pulmonary adenocarcinoma (Nature rev. drug discov., 13, 828, 2014).

[0005]

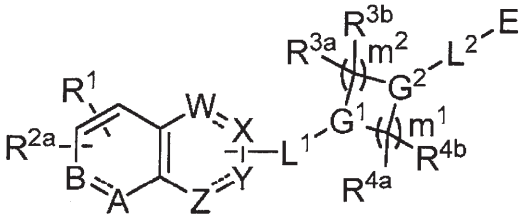
In the creation of a KRAS inhibitor, it is ideal to selectively inhibit a function of KRAS mutant protein. On the other hand, since a resulting mutation site is a distal from an effector binding site, obtaining a compound having selectivity in an inhibitory activity of a mutant type and a wild type is generally considered to be difficult (Bioorg. Med. Chem. Lett., 22, 5766, 2012). In recent years, a compound which is irreversibly bonded to G12C mutation KRAS (Nature, 503, 548, 2013, Angew. Chem., Int. Ed. Engl., 53, 199, 2014, Cancer Discov., 6, 316, 2016) by forming a covalent bond with respect to a mutation cysteine has been reported along with the existence of an allosteric pocket in the vicinity of a region called switch II being shown (Nature, 503, 548, 2013) against the G12C mutation KRAS. A G12C mutation KRAS selective inhibitor inhibits conversion from the inactive form to the active form by covalently binding to the G12C mutation KRAS and induces cancer cell death by blocking the downstream signal. Accordingly, a compound with this mechanism of action has been reported to be useful for a treatment of KRAS G12C mutation positive lung cancer.

[0006]

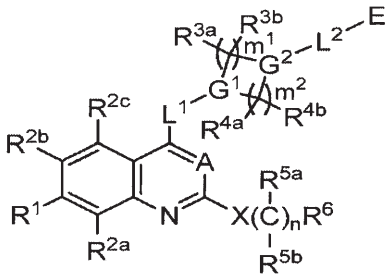
It has been reported that compounds represented by Formula (A) and Formula (B) have binding capacity for the G12C mutation KRAS (Patent Documents 1, 2, and 3), and Patent Document 2 discloses a compound of Example I-59 (hereinafter, also referred to as Compound C).

[0007]

[Chem. 1]

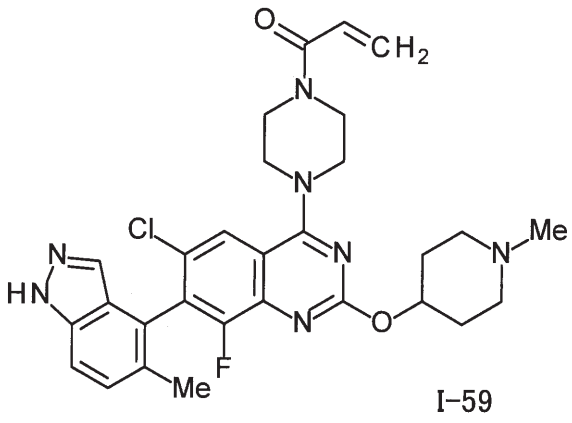


(A)



(B)

(The meanings of the symbols in the formulae refer to Patent Documents)



I-59

Related Art Document

Patent Document

[0008]

[Patent Document 1] Pamphlet of International Publication No. WO 2015/054572

[Patent Document 2] Pamphlet of International Publication No. WO 2016/164675

[Patent Document 3] Pamphlet of International Publication No. WO 2017/087528

Disclosure of Invention

Problems to be Solved by the Invention

[0009]

There is provided a compound which is useful as a pharmaceutical composition such as a G12C mutation KRAS inhibitor, and is expected to be useful as an active ingredient of a pharmaceutical composition for treating lung cancer and KRAS G12C mutation positive lung cancer.

Means for Solving the Problems

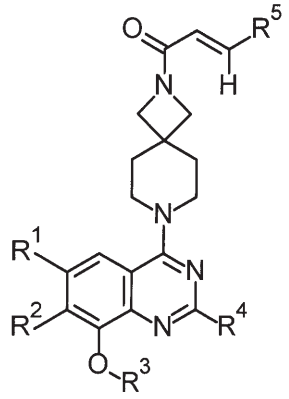
[0010]

The present inventors have earnestly studied compounds useful as an active ingredient of a pharmaceutical composition for treating lung cancer, and as a result, it was

found that a quinazoline compound of Formula (I) has an excellent G12C mutation KRAS inhibitory activity, and thereby the present invention has been completed.

That is, the present invention relates to a compound of Formula (I) or a salt thereof, and a pharmaceutical composition containing the compound of Formula (I) or the salt thereof, and an excipient.

[Chem. 2]



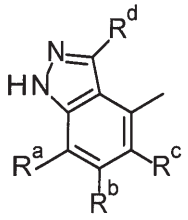
(I)

(in the formula,

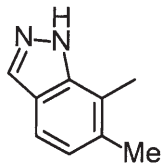
R^1 is vinyl, (E)-1-propenyl or cyclopropyl,

R^2 is Formula (II) or (III),

[Chem. 3]



(II)

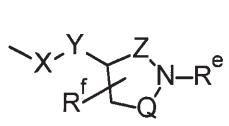


(III)

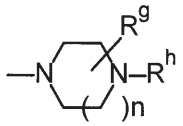
R^3 is C_{3-4} alkyl, methyl or n-propyl each of which may be substituted with two or more F's, ethyl or C_{3-4} cycloalkyl each of which may be substituted with F, benzyl which may be substituted with C_{1-3} alkyl, benzyl which may be substituted with -O-C_{1-3} alkyl, or benzyl which may be substituted with -O-(C_{1-3} alkyl which is substituted with F),

R^4 is -O-C_{3-5} alkyl which may be substituted, -O-cycloalkyl which may be substituted, or Formula (IV), (V), (VI), or (VII),

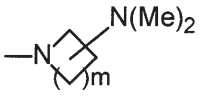
[Chem. 4]



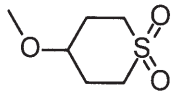
(IV)



(V)



(VI)



(VII)

R^5 is H or CF_3,

R^a is H or F,

R^b is H or F,

R^c is H, methyl, vinyl, or Cl,
R^d is H or Cl,
R^e is CO_2Me, COMe, $CON(Me)_2$, SO_2Me, C_{3-4} cycloalkyl, a nonaromatic heterocyclic group having 4 to 6 ring members which may be substituted, or C_{1-3} alkyl which may be substituted with a group selected from the Group G,
the Group G is -O-C_{1-3} alkyl, -O-(C_{1-3} alkyl which is substituted with F or C_{3-4} cycloalkyl), C_{3-4} cycloalkyl, -F, -CN, -SO_2Me, and aromatic heterocyclic group, a nonaromatic heterocyclic group having 4 to 6 ring members, -N(C_{1-3} alkyl)$_2$, and -$C(Me)_2OH$,
R^f is H, methyl, or F,
R^g is H, methyl, or ethyl,
R^h is C_{1-3} alkyl which may be substituted with -OMe,
X is O, NH, S, or methylene,
Y is a bond or methylene,
Z is a bond, methylene, or ethylene,
Q is methylene or ethylene,
n is an integer of 1 or 2, and
m is an integer in a range of 1 to 3.)

[0011]

Unless otherwise specified, in a case where symbols in certain chemical formulae in this specification are also used in other chemical formulae, the same symbols have the same meaning.

[0012]

In addition, the present invention relates to a pharmaceutical composition for treating lung cancer, which contains a compound of Formula (I) or a salt thereof, and particularly, relates to a pharmaceutical composition for treating KRAS G12C mutation positive lung cancer. Note that, the pharmaceutical composition includes a therapeutic agent for lung cancer, particularly, KRAS G12C mutation positive lung cancer, which contains the compound of Formula (I) or the salt thereof.

In addition, the present invention relates to a compound of Formula (I) or a salt thereof which is a G12C mutation KRAS inhibitor; the compound of Formula (I) or the salt thereof for use as the G12C mutation KRAS inhibitor; the G12C mutation KRAS inhibitor containing the compound of Formula (I) or the salt thereof; use of the compound of Formula (I) or the salt thereof for the manufacture of a pharmaceutical composition for treating lung cancer, particularly, KRAS G12C mutation positive lung cancer; use of the compound of Formula (I) or the salt thereof for treating lung cancer, particularly, KRAS G12C mutation positive lung cancer; the compound of Formula (I) or the salt thereof for use in the treatment of lung cancer, particularly, KRAS G12C mutation positive lung cancer; and a method of treating lung cancer, particularly, KRAS G12C mutation positive

lung cancer including administering an effective dose of the compound of Formula (I) or the salt thereof to a target. Note that, "target" is a human or other animals in need of treatment thereof, and as an embodiment, the target is a human in need of prevention or treatment thereof.

Effects of the Invention

[0013]

The compound of Formula (I) or the salt thereof has G12C mutation KRAS inhibitory activity, and can be used as a therapeutic agent for lung cancer.

Embodiments for Carrying Out the Invention

[0014]

Hereinafter, the present invention will be described in detail.

In the present specification, a phrase "may be substituted with" means having no substituted group or 1 to 3 substituents.

[0015]

"Substituted" means having 1 to 5 substituents, and "substituted with two or more F's" means having 2 to 5 F atoms.

[0016]

"C_{1-3} alkyl" is a linear or branched alkyl having 1 to 3 carbon atoms, and examples thereof include methyl, ethyl, n-propyl, and isopropyl. As an embodiment, C_{1-3} alkyl is methyl, ethyl, or n-propyl, as an embodiment, it is methyl or ethyl, as an embodiment, it is methyl or n-propyl, as an embodiment, it is ethyl or n-propyl, as an embodiment, it is methyl, as an embodiment, it is ethyl, and as an embodiment, it is n-propyl.

[0017]

"C_{3-4} alkyl" means a linear or branched alkyl having 3 to 4 carbon atoms, and examples thereof include n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl. As an embodiment, C_{3-4} alkyl is n-propyl or isobutyl, and as an embodiment, it is isobutyl.

[0018]

"C_{3-5} alkyl" means a linear or branched alkyl having 3 to 5 carbon atoms, and examples thereof include n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl. As an embodiment, C_{3-5} alkyl is n-propyl, n-butyl, or n-pentyl, as an embodiment, it is n-propyl or n-butyl, and as an embodiment, it is n-propyl.

[0019]

"Cycloalkyl" means a saturated hydrocarbon ring group having 3 to 10 ring members which may have a crosslink, and examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl. As an

embodiment, Cycloalkyl is cyclopentyl, cyclohexyl, or cycloheptyl, and as an embodiment, it is cyclohexyl.

[0020]

"C_{3-4} cycloalkyl" means cycloalkyl having 3 to 4 ring members. As an embodiment, C_{3-4} cycloalkyl is cyclopropyl or cyclobutyl, as an embodiment, it is cyclopropyl, and as an embodiment, it is cyclobutyl.

[0021]

A "nonaromatic heterocyclic group having 4 to 6 ring members" means a monovalent group of a nonaromatic heterocyclic group having 4 to 6 ring members, which has 1 to 2 identical or different heteroatoms selected from the group consisting of N, O, and S, and examples thereof include azetidinyl, oxetanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrofuryl, tetrahydrothienyl, and tetrahydrothiopyranyl. As an embodiment, the nonaromatic heterocyclic group having 4 to 6 ring members is oxetanyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, or morpholinyl, as an embodiment, it is oxetanyl or tetrahydropyranyl, as an embodiment, it is pyrrolidinyl, morpholinyl, or tetrahydropyranyl, as an embodiment, it is oxetanyl, and as an embodiment, it is tetrahydropyranyl.

[0022]

An "aromatic heterocyclic group" means a monovalent group of an aromatic heterocycle having 5 to 10 ring members having 1 to 4 identical or different heteroatoms selected from the group consisting of N, O and S, and examples thereof include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, thienyl, furyl, and 1,2,4-oxadiazolyl, as an embodiment, it is an aromatic heterocyclic group having 5 to 6 ring members having 1 to 2 N atoms, and as an embodiment, it is pyridyl.

[0023]

"G12C mutation" indicates a mutation in the wild-type gene in which the residue corresponding to position 12 is converted from glycine into cysteine.

[0024]

"G12C mutation KRAS" means KRAS having the above-described "G12C mutation" in the gene encoding wild-type KRAS.

[0025]

"Lung cancer" is, for example, small cell lung cancer and non-small cell lung cancer, and as an embodiment, it is non-small cell lung cancer, as an embodiment, it is pulmonary adenocarcinoma, as an embodiment, it is KRAS G12C mutation positive lung cancer, as an embodiment, it is KRAS G12C mutation positive non-small cell lung cancer, and as an embodiment, it is KRAS G12C mutation positive pulmonary adenocarcinoma.

[0026]

An embodiment of the compound of Formula (I) of the present invention or the salt thereof will be described below.

(1) A compound or a salt thereof in which R^1 is vinyl, (E)-1-propenyl, or cyclopropyl. As an embodiment, a compound or a salt thereof in which R^1 is vinyl or cyclopropyl. As an embodiment, a compound or a salt thereof in which R^1 is vinyl. As an embodiment, a compound or a salt thereof in which R^1 is cyclopropyl.

(2) A compound or a salt thereof in which R^2 is Formula (II) or Formula (III). As an embodiment, a compound or a salt thereof in which R^2 is Formula (II). As an embodiment, a compound or a salt thereof in which R^2 is Formula (III).

(3) A compound or a salt thereof in which R^a is H or F in Formula (II). As an embodiment, a compound or a salt thereof in which R^a is H in Formula (II). As an embodiment, a compound or a salt thereof in which R^a is F in Formula (II).

(4) A compound or a salt thereof in which R^b is H or F in Formula (II). As an embodiment, a compound or a salt thereof in which R^b is H in Formula (II). As an embodiment, a compound or a salt thereof in which R^b is F in Formula (II).

(5) A compound or a salt thereof in which R^c is methyl, vinyl, or Cl in Formula (II). As an embodiment, a compound or a salt thereof in which R^c is methyl or Cl in Formula (II). As an embodiment, a compound or a salt thereof in which R^c is methyl or vinyl in Formula (II). As an embodiment, a compound or a salt thereof in which R^c is methyl in Formula (II). As an embodiment, a compound or a salt thereof in which R^c is vinyl in Formula (II). As an embodiment, a compound or a salt thereof in which R^c is Cl in Formula (II).

(6) A compound or a salt thereof in which R^d is H or Cl in Formula (II). As an embodiment, a compound or a salt thereof in which R^d is H in Formula (II). As an embodiment, a compound or a salt thereof in which R^d is Cl in Formula (II).

(7) A compound or a salt thereof in which R^3 is C_{3-4} alkyl, methyl or n-propyl each of which is substituted with two or more F's, ethyl or C_{3-4} cycloalkyl each of which may be substituted with F, benzyl which may be substituted with C_{1-3} alkyl, benzyl which may be substituted with -O-C_{1-3} alkyl, or benzyl which may be substituted with -O-(C_{1-3} alkyl which is substituted with F). As an embodiment, a compound or a salt thereof in which R^3 is C_{3-4} alkyl, methyl or n-propyl each of which is substituted with two or more F's, or ethyl or C_{3-4} cycloalkyl each of which may be substituted with F. As an embodiment, a compound or a salt thereof in which R^3 is C_{3-4} alkyl, methyl or n-propyl each of which is substituted with two or more F's. As an embodiment, a compound or a salt thereof in which R^3 is ethyl, cyclopropyl, or cyclobutyl each of which may be substituted with F. As an embodiment, a compound or a salt thereof in which R^3 is ethyl which may be substituted with F. As an embodiment, a compound or a salt thereof in which R^3 is ethyl, difluoroethyl, or trifluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is ethyl or difluoroethyl. As an embodiment, a compound or a salt thereof in which R^3

is ethyl or trifluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is ethyl or 2,2,2-trifluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is difluoroethyl, or trifluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is ethyl. As an embodiment, a compound or a salt thereof in which R^3 is difluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is 2,2-difluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is trifluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is 2,2,2-trifluoroethyl. As an embodiment, a compound or a salt thereof in which R^3 is C_{3-4} alkyl. As an embodiment, a compound or a salt thereof in which R^3 is isobutyl. As an embodiment, a compound or a salt thereof in which R^3 is methyl or n-propyl each of which is substituted with two or more F's. As an embodiment, a compound or a salt thereof in which R^3 is C_{3-4} cycloalkyl which may be substituted with F. As an embodiment, a compound or a salt thereof in which R^3 is cyclobutyl which may be substituted with F. As an embodiment, a compound or a salt thereof in which R^3 is cyclobutyl. As an embodiment, a compound or a salt thereof in which R^3 is ethyl or cyclobutyl each of which may be substituted with F.

(8) A compound or a salt thereof in which R^4 is -O-C_{3-5} alkyl which may be substituted, -O-cycloalkyl which may be substituted, or Formula (IV), (V), (VI), or (VII). As an embodiment, a compound or a salt thereof in which R^4 is -O-C_{3-5} alkyl which may be substituted or is -O-cycloalkyl which may be substituted. As an embodiment, a compound or a salt thereof in which R^4 is Formula (IV). As an embodiment, a compound or a salt thereof in which R^4 is Formula (V). As an embodiment, a compound or a salt thereof in which R^4 is Formula (VI). As an embodiment, a compound or a salt thereof in which R^4 is Formula (VII).

(9) A compound or a salt thereof in which R^e in Formula (IV) is a nonaromatic heterocyclic group having 4 to 6 ring members which may be substituted, or C_{1-3} alkyl which may be substituted with a substituent selected from the Group G. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is oxetanyl, tetrahydropyranyl, or C_{1-3} alkyl which may be substituted with a substituent selected from the group consisting of -O-C_{1-3} alkyl and -$C(Me)_2OH$. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is oxetanyl, tetrahydropyranyl, or C_{1-3} alkyl which may be substituted with a substituent selected from the group consisting of -OMe, -OEt, and -$C(Me)_2OH$. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is C_{1-3} alkyl which may be substituted with -OMe. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is C_{1-3} alkyl which may be substituted with -OEt. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is C_{1-3} alkyl which may be substituted with -$C(Me)_2OH$. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is C_{1-3} alkyl. As an embodiment, a compound or

a salt thereof in which R^e in Formula (IV) is methyl or ethyl. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is methyl. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is ethyl. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is methoxyethyl. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is ethoxyethyl. As an embodiment, a compound or a salt thereof in which R^e in Formula (IV) is methoxypropyl.

(10) A compound or a salt thereof in which R^f in Formula (IV) is H, methyl, or F. As an embodiment, a compound or a salt thereof in which R^f in Formula (IV) is H. As an embodiment, a compound or a salt thereof in which R^f in Formula (IV) is methyl. As an embodiment, a compound or a salt thereof in which R^f in Formula (IV) is F.

(11) A compound or a salt thereof in which X in Formula (IV) is O, NH, S, or methylene. As an embodiment, a compound or a salt thereof in which X in Formula (IV) is O. As an embodiment, a compound or a salt thereof in which X in Formula (IV) is NH. As an embodiment, a compound or a salt thereof in which X in Formula (IV) is S. As an embodiment, a compound or a salt thereof in which X in Formula (IV) is methylene.

(12) A compound or a salt thereof in which Y in Formula (IV) is a bond or methylene. As an embodiment, a compound or a salt thereof in which Y in Formula (IV) is a bond. As an embodiment, a compound or a salt thereof in which Y in Formula (IV) is methylene.

(13) A compound or a salt thereof in which Z in Formula (IV) is a bond, methylene, or ethylene. As an embodiment, a compound or a salt thereof in which Z in Formula (IV) is a bond. As an embodiment, a compound or a salt thereof in which Z in Formula (IV) is methylene. As an embodiment, a compound or a salt thereof in which Z in Formula (IV) is ethylene.

(14) A compound or a salt thereof in which Q in Formula (IV) is methylene or ethylene. As an embodiment, a compound or a salt thereof in which Q in Formula (IV) is methylene. As an embodiment, a compound or a salt thereof in which Q in Formula (IV) is ethylene.

(15) A compound or a salt thereof in which R^5 is H or CF_3. As an embodiment, a compound or a salt thereof in which R^5 is H. As an embodiment, a compound or a salt thereof in which R^5 is CF_3.

(16) A compound or a salt thereof which is a combination of arbitrary two or more which are not contradictory, among the embodiments described in the above (1) to (15).

[0027]

Examples of the embodiments described in the above (16) include the following compounds or salts thereof.

(17) A compound or a salt thereof in which R^1 is vinyl, (E)-1-propenyl, or cyclopropyl, R^2 is Formula (II) or (III), R^3 is C_{2-4} alkyl, methyl or n-propyl each of which is substituted with two or more F's, ethyl or C_{3-4} cycloalkyl each of which may be substituted with F,

benzyl which may be substituted with C_{1-3} alkyl, benzyl which may be substituted with -O-C_{1-3} alkyl, or benzyl which may be substituted with -O-(C_{1-3} alkyl substituted with F), R^4 is -O-C_{3-5} alkyl which may be substituted, -O-cycloalkyl which may be substituted, or Formula (IV), (V), (VI), or (VII), R^5 is H or CF_3, R^a is H or F, R^b is H or F, R^c is H, methyl, vinyl, or Cl, R^d is H or Cl, R^e is CO_2Me, COMe, $CON(Me)_2$, SO_2Me, or C_{3-4} cycloalkyl, a nonaromatic heterocyclic group having 4 to 6 ring members which may be substituted, C_{1-3} alkyl which may be substituted with a group selected from the Group G in which the Group G is -O-C_{1-3} alkyl, -O-(C_{1-3} alkyl substituted with F or C_{3-4} cycloalkyl), C_{3-4} cycloalkyl, -F, -CN, -SO_2Me, an aromatic heterocyclic group, a nonaromatic heterocyclic group having 4 to 6 ring members, -$N(C_{1-3}$ alkyl$)_2$, and -$C(Me)_2OH$, R^f is H, methyl, or F, R^g is H, methyl, or ethyl, R^h is C_{1-3} alkyl which may be substituted with -OMe, X is O, NH, S, or methylene, Y is a bond or methylene, Z is a bond, methylene, or ethylene, Q is methylene or ethylene, n is an integer of 1 or 2, and m is an integer in a range of 1 to 3.

(18) The compound or the salt thereof described in (17) in which R^2 is Formula (II).

(19) The compound or the salt thereof described in (18) in which R^4 is Formula (IV).

(20) The compound or the salt thereof described in (19) in which X is O.

(21) The compound or the salt thereof described in (20) in which R^5 is H.

(22) The compound or the salt thereof described in (21) in which R^1 is vinyl or cyclopropyl.

(23) The compound or the salt thereof described in (22) in which R^a is H, R^b is H or F, R^c is methyl or Cl, and R^d is H.

(24) The compound or the salt thereof described in (23) in which R^3 is C_{3-4} alkyl, methyl or n-propyl each of which is substituted with two or more F's, or ethyl or C_{3-4} cycloalkyl each of which may be substituted with F.

(25) The compound or the salt thereof described in (24) in which R^e is a nonaromatic heterocyclic group having 4 to 6 ring members which may be substituted, or C_{1-3} alkyl which may be substituted with a substituent selected from the Group G.

(26) The compound or the salt thereof described in (25) in which R^e is oxetanyl, tetrahydropyranyl, or C_{1-3} alkyl which may be substituted with a substituent selected from the group consisting of -OMe, -OEt, and -$C(Me)_2OH$.

(27) The compound or the salt thereof described in (25) or (26) in which R^f is H.

(28) The compound or the salt thereof described in (27) in which Y is a bond.

(29) The compound or the salt thereof described in (28) in which Z is ethylene.

(30) The compound or the salt thereof described in (29) in which Q is methylene.

[0028]

As the combination of the embodiments described in the above (16), specific examples are as follows.

(31) A compound of Formula (I) or a salt thereof in which R^1 is vinyl or cyclopropyl, R^2 is Formula (II), R^3 is ethyl, cyclopropyl, or cyclobutyl each of which is substituted with F, R^4 is Formula (IV), R^5 is H, R^a is H, R^b is H or F, R^c is methyl or Cl, R^d is H, R^e is oxetanyl, tetrahydropyranyl, or C_{1-3} alkyl which may be substituted with a substituent selected from the group consisting of -OMe, -OEt, and $-C(Me)_2OH$, R^f is H, X is O, Y is a bond or methylene, Z is a bond, methylene, or ethylene, Q is methylene or ethylene.

(32) A compound of Formula (I) or a salt thereof in which R^1 is vinyl or cyclopropyl, R^2 is Formula (II), R^3 is ethyl, cyclopropyl, or cyclobutyl each of which may be substituted with F, R^4 is Formula (IV), R^5 is H, R^a is H, R^b is H or F, R^c is methyl or Cl, R^d is H, R^e is C_{1-3} alkyl which may be substituted with -OMe, R^f is H, X is O, Y is a bond or methylene, Z is a bond, methylene, or ethylene, Q is methylene or ethylene.

(33) A compound of Formula (I) or a salt thereof in which R^1 is vinyl or cyclopropyl, R^2 is Formula (II), R^3 is ethyl or 2,2,2-trifluoroethyl, R^4 is Formula (IV), R^5 is H, R^a is H, R^b is H, R^c is methyl, R^d is H, R^e is C_{1-3} alkyl which may be substituted with -OMe, R^f is H, X is O, Y is a bond, Z is ethylene, Q is methylene.

[0029]

As an example of specific compounds included in the present invention, the following compounds can be exemplified as an embodiment.

1-(7-{8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,

1-(7-{6-cyclopropyl-8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,

1-(7-{6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,

1-{7-[6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one, and

1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one, and a salt thereof.

[0030]

As an example of specific compounds included in the present invention, the following compounds can be exemplified as another embodiment.

1-(7-{8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,

1-(7-{6-cyclopropyl-8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,

1-(7-{6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,

1-{7-[6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,
(+)-1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,
1-{7-[6-cyclopropyl-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
1-{7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one, and a salt thereof.

[0031]

Further, as an example of specific compounds included in the present invention, the following compounds can be exemplified as another embodiment.
(+)-1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,
(+)-1-{7-[6-cyclopropyl-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[2-{[1-(2-ethoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one, and
(+)-1-{7-[2-{[1-(2-hydroxy-2-methylpropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one, and a salt thereof.

[0032]

A tautomer or a geometric isomer may be present in the compound of Formula (I) depending on the type of the substituent. In the present specification, the compound of Formula (I) is described in only one embodiment of the isomer; however, the present invention includes other isomers, separated isomers, or a mixture thereof.

In addition, the compound of Formula (I) may have asymmetric carbon atom and axis chirality, and based thereon, an optical isomer may exist. The present invention also includes separated forms of optical isomers of the compound of Formula (I), or a mixture thereof.

[0033]

The present invention further includes a pharmaceutically acceptable prodrug of the compounds of Formula (I). A pharmacologically acceptable prodrug is a compound having a group that can be converted into an amino group, a hydroxyl group, a carboxyl group or the like by solvolysis or under physiological conditions. Examples of a group forming a prodrug include groups disclosed in Prog. Med., 5, 2157-2161 (1985) and "Development of pharmaceuticals" (Hirokawa Shoten, 1990) Volume 7, Molecular Design 163-198.

[0034]

In addition, the salt of the compound of Formula (I) is a pharmaceutically acceptable salt of the compound of Formula (I), and depending on the kind of the substituent, it may form an acid addition salt or a salt with a base. Specifically, examples thereof include an acid addition salt of an inorganic acid such as a hydrochloric acid, a hydrobromic acid, a hydroiodic acid, a sulfuric acid, a nitric acid, and a phosphoric acid, and an organic acid such as a formic acid, an acetic acid, a propionic acid, an oxalic acid, a malonic acid, a succinic acid, a fumaric acid, a maleic acid, a lactic acid, a malic acid, a mandelic acid, a tartaric acid, a dibenzoyltartaric acid, a ditoluoyltartaric acid, a citric acid, a methanesulfonic acid, an ethanesulfonic acid, a benzenesulfonic acid, a p-toluenesulfonic acid, an aspartic acid, and a glutamic acid, a salt with inorganic metal such as sodium, potassium, magnesium, calcium, and aluminum, a salt with an organic base such as methylamine, ethylamine, and ethanolamine, various amino acids such as acetyl leucine, lysine, and ornithine, a salt with amino acid derivative, and an ammonium salt.

[0035]

Furthermore, the present invention also includes various hydrates and solvates of the compound of Formula (I) and salts thereof, and substances of crystalline polymorphism. In addition, the invention also includes compounds labeled with various radioactive or nonradioactive isotopes.

[0036]

(Preparing method)

The compound of Formula (I) and a salt thereof can be prepared by applying various known synthetic methods by using features based on the basic structure thereof or the type of substituent. Depending on the type of the functional group, it may be effective to substitute a functional group with an appropriate protecting group (a group which can be easily converted into the functional group) at a stage from a starting material to the intermediate. As such a protecting group, for example, a protecting group disclosed in "Greene's Protective Groups in Organic Synthesis (5 Edition, 2014)" written by Wuts (P. G. M. Wuts) and Greene (T. W. Greene) can be exemplified, and it may be appropriately selected and used according to these reaction conditions. In such a method, a desired compound can be obtained by introducing the protecting group and performing the reaction, and then removing the protecting group as necessary.

In addition, similar to the above-described protecting group, the prodrug of the compound of Formula (I) can be prepared by introducing a specific group at the stage from the starting material to the intermediate or further performing the reaction by using the obtained compound of Formula (I). The reaction can be performed by applying methods known to those skilled in the art such as ordinary esterification, amidation, dehydration, and the like.

Hereinafter, a typical preparing method of the compound of Formula (I) will be described. Each preparing method can also be performed with reference to the references attached to the explanation. The preparing method of the present invention is not limited to the examples described below.

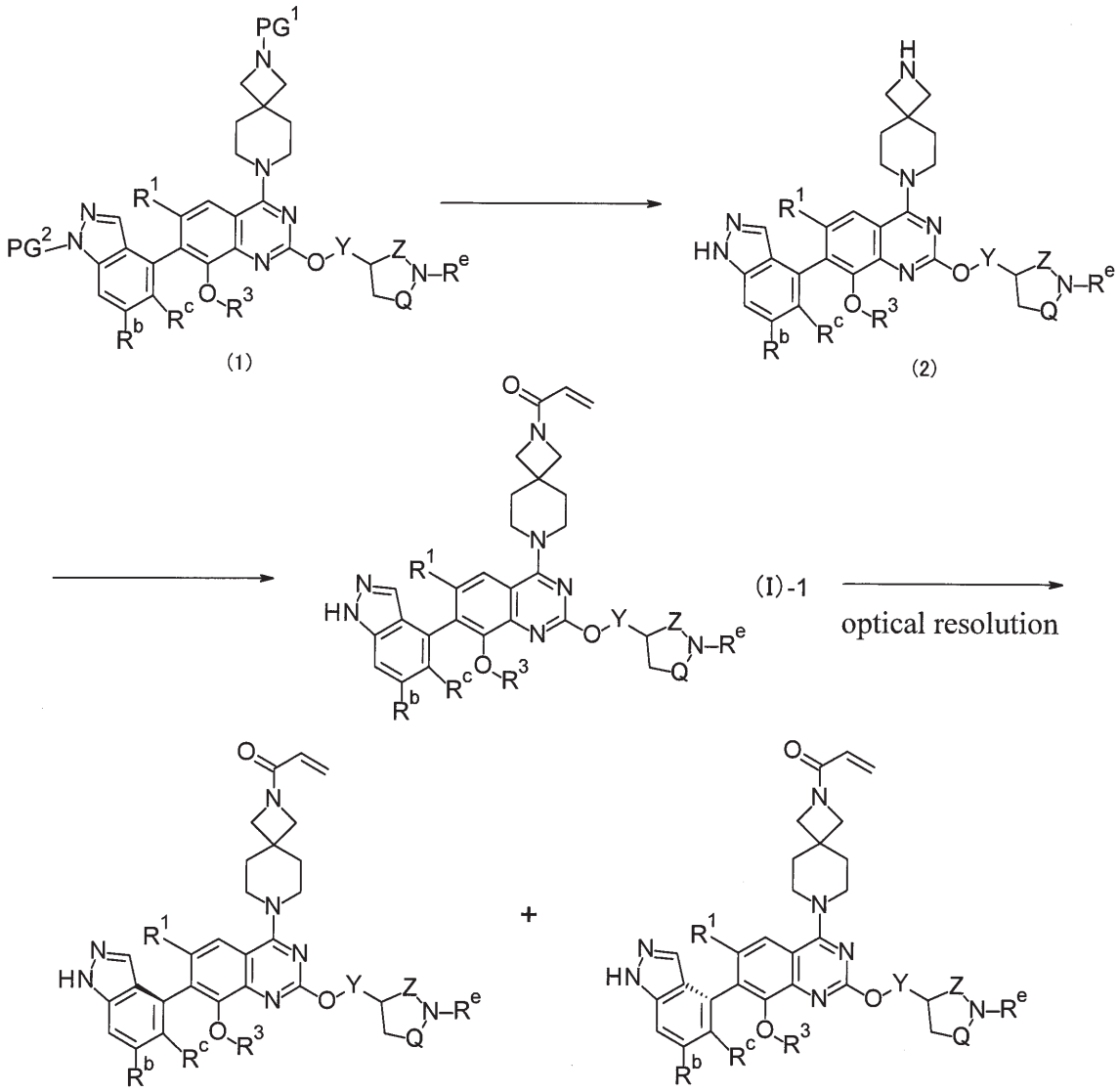
[0037]

In the present specification, the following abbreviations may be used.

TEA: triethylamine, DIPEA: N,N-diisopropylethylamine, NMO: N-methylmorpholine, DABCO: 1,4-diazabicyclo[2.2.2]octane, THF: tetrahydrofuran, DMF: N,N-dimethylformamide, DMSO: dimethyl sulfoxide

[0038]

[Chem. 5]



(in the formula, PG^1 represents a protecting group, and PG^2 represents a protecting group or a hydrogen atom.)

[0039]

A compound of Formula (I)-1 representing the compound of Formula (I) can be obtained by subjecting the compound (1) to a deprotection reaction so as to obtain a compound (2), and then subjecting to an acylation reaction. Here, examples of the protecting group include a tert-butoxycarbonyl group, a benzyl group, a benzyloxycarbonyl group, a (trimethylsilyl)ethoxymethyl group, a trifluoroacetyl group, an allyl group, and a tetrahydro-2H-pyran-2-yl group.

The deprotection reaction performed with reference to "Protective Groups in Organic Synthesis" written by Greene and Wuts, 5th Edition, published by John Wiley & Sons Inc, 2014.

In the acylation reaction, an equivalent amount of the compound (2) obtained in the preceding step and an acylation reagent, or an excess amount of one thereof is used, the mixture is reacted in a solvent inert to the reaction, under the presence of a base, and stirred the mixture under cooling to heating, at a preferably temperature of -20°C to 80°C, usually for 0.1 hours to 1 day. The solvent to be used here is not particularly limited, and examples thereof include halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, aromatic hydrocarbons such as benzene, toluene, and xylene, ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, DMF, DMSO, ethyl acetate, acetonitrile, water, and a mixture thereof. In addition, examples of the base used here include an inorganic base such as sodium carbonate, potassium carbonate, and sodium hydrogen carbonate, or an organic base such as TEA, DIPEA, and NMO. Further, examples of the acylation reagent include an acyl halide and an acid anhydride. Examples of the acyl halide include such as acryloyl chloride and 3-chloropropanoyl chloride. In addition, a method of reacting the mixture obtained by using an equivalent amount of the compound (2) and a carboxylic acid, or an excess amount of one thereof under the presence of a condensing agent can be used. The condensing agent is not particularly limited, and examples thereof include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole, diphenylphosphate azide, and phosphorus oxychloride.

Note that, the present reaction may be performed after once isolating the compound (2) which is an amine compound obtained by deprotection reaction.

It may also be necessary to remove excessively reacted acylation reagent under the presence of the inorganic base such as an aqueous sodium carbonate solution.

In addition, in order to obtain the compound of Formula (I)-1, it may be necessary to subject a compound obtained by acylation reaction with 3-chloropropanoyl chloride or the like to elimination reaction under the presence of a base in a solvent inert to the reaction. The solvent used here is not particularly limited, and examples thereof include alcohols such as isopropyl alcohol, water, and a mixture thereof. In addition, examples of the base include an inorganic base such as sodium hydroxide.

Further, the compound of Formula (I)-1 may have axial chirality, and can be obtained as a mixture of atropisomers, but the respective atropisomers can be isolated by performing ordinary resolution operation, for example, optical resolution using supercritical fluid chiral column chromatography.

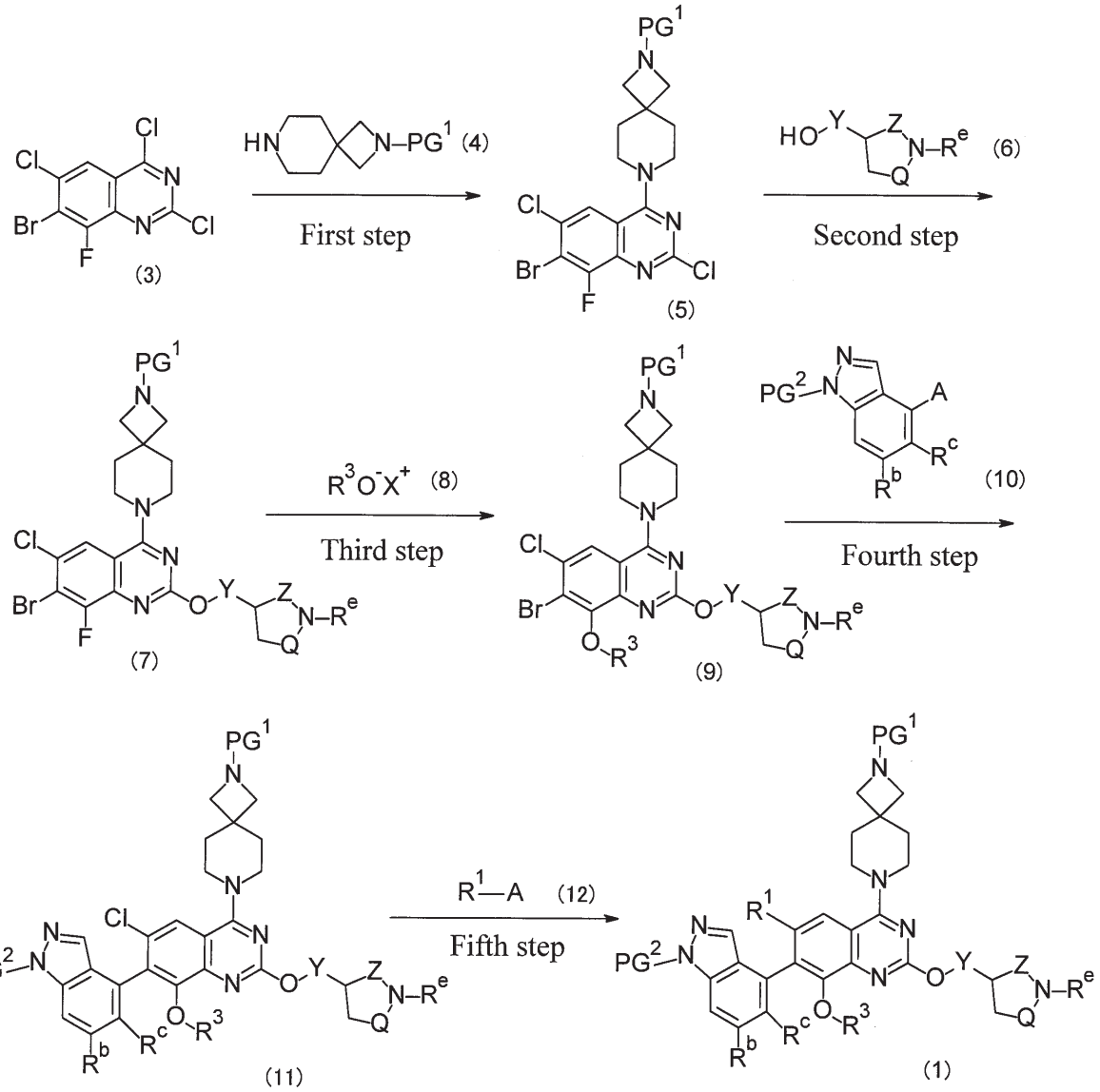
[Reference]

J. Med. Chem. 43, 2591-2600, 2000

[0040]

(Starting material synthesis 1)

[Chem. 6]



(In the formula, A represents a boronic acid, boronate ester, or a trifluoroborate salt. In addition, X^+ represents a metal cation, such as Na^+, K^+, and Cs^+.)

[0041]

The present preparing method is a first method of preparing a starting compound (1).

[0042]

(First step)

This step is a method of preparing the compound (5) by an ipso-substitution reaction between the compound (3) and the compound (4).

In the present reaction, an equivalent amount of the compound (3) and compound (4), or an excess amount of one thereof is used, and the mixture thereof is stirred in a solvent inert to the reaction, or under the absence of solvent, under cooling to heating reflux, preferably temperature of 0°C to 80°C, usually for 0.1 hours to 5 days. The solvent to be used here is not particularly limited, and examples thereof include

halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, aromatic hydrocarbons such as benzene, toluene, and xylene, ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, DMF, DMSO, ethyl acetate, acetonitrile, and a mixture thereof. It may be advantageous to perform the reaction in the presence of an organic base such as TEA, DIPEA, NMO, and DABCO, and an inorganic base such as potassium carbonate, sodium carbonate, and cesium carbonate in order to smoothly progress the reaction.

[0043]

(Second step)

This step is a method of preparing the compound (7) by an ipso-substitution reaction between the compound (5) and the compound (6).

The reaction conditions are similar to the first step of Starting material synthesis 1.

[0044]

(Third step)

This step is a method of preparing the compound (9) by an ipso-substitution reaction between the compound (7) and the compound (8).

The reaction conditions are similar to the first step of Starting material synthesis 1.

The compound (8) used in the present reaction may be prepared by stirring the corresponding alcohol with base in a solvent inert to the reaction under cooling to room temperature usually for 0.1 hours to 1 hour. The solvent to be used herein is not particularly limited, and examples thereof include ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, DMF, DMSO, and a mixture thereof. Further, examples of the base used here include an inorganic base such as sodium hydride and cesium carbonate, or an organic base such as potassium tert-butoxide.

[0045]

(Fourth step)

This step is a method of preparing the compound (11) by Suzuki coupling reaction between the compound (9) and the compound (10).

In the present reaction, an equivalent amount of the compound (9) and compound (10), or an excess amount of one thereof is used, and the mixture thereof is stirred in a solvent inert to the reaction under the presence of a base and a palladium catalyst under room temperature to heating reflux, usually for 0.1 hours to 5 days. The solvent to be used here is not particularly limited, and examples thereof include halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, aromatic hydrocarbons such as benzene, toluene, and xylene, ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, alcohols such as methanol, ethanol, isopropyl alcohol, and butanol, DMF, DMSO, acetonitrile, 1,3-dimethylimidazolidin-2-one, water, and a mixture thereof. Examples of the base include an inorganic base such as tripotassium

phosphate, sodium carbonate, potassium carbonate, and sodium hydroxide. Examples of a palladium catalyst include tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium(II) dichloride, [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane adduct, and (1E, 4E)-1,5-diphenylpenta-1,4-dien-3-one/palladium (3:2). It may be advantageous to perform the reaction in the presence of a ligand such as dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine in order to smoothly progress the reaction. It may be advantageous to heat the mixture by microwave irradiation in order to smoothly progress the reaction.

[Reference]

J. Am. Chem. Soc. 127, 4685-4696, 2005

[0046]

(Fifth step)

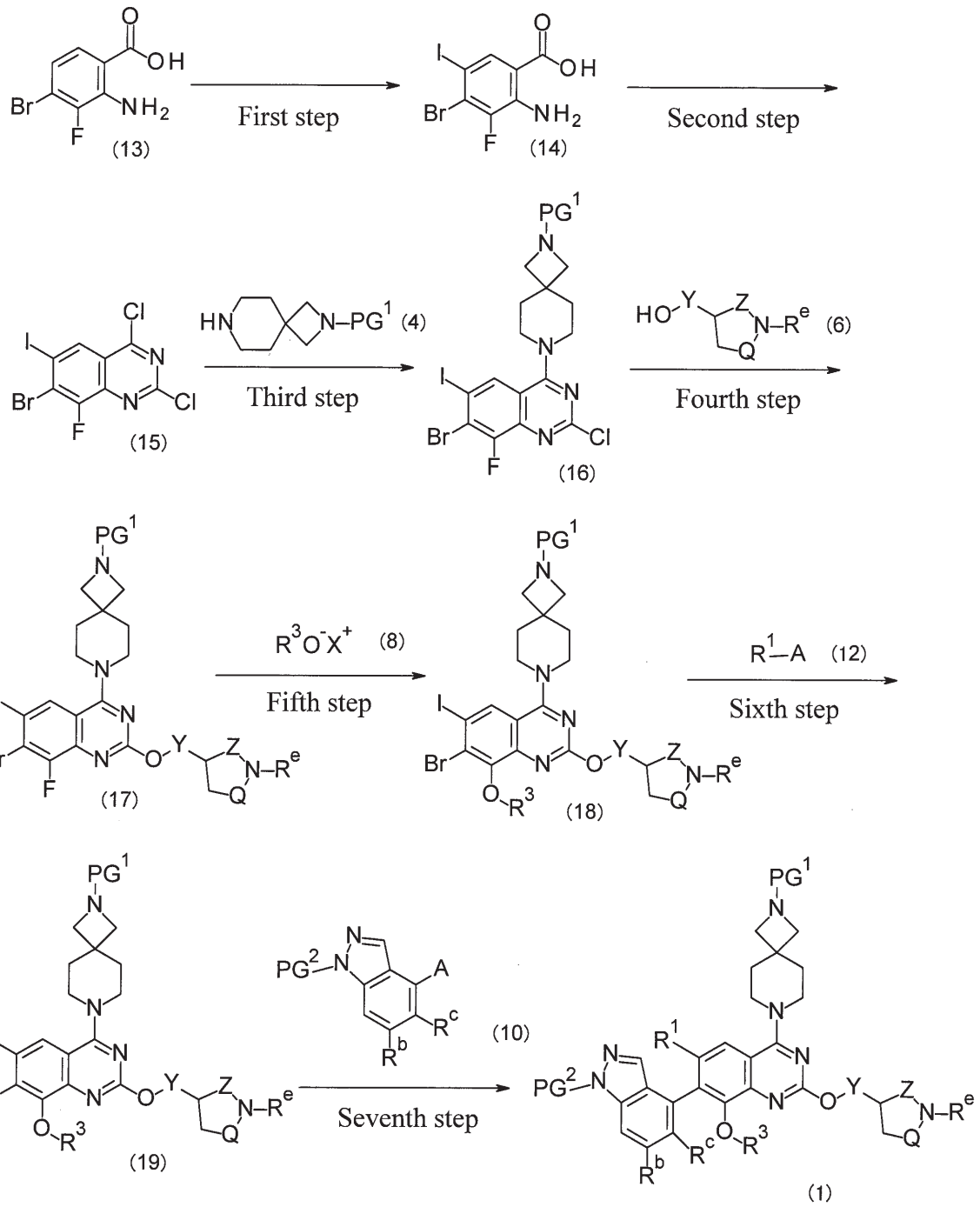
This step is a method of preparing the compound (1) by Suzuki coupling reaction between the compound (11) and the compound (12).

The reaction conditions are similar to the fourth step of Starting material synthesis 1.

[0047]

(Starting material synthesis 2)

[Chem. 7]



[0048]

The present preparing method is a second method of preparing a starting compound (1).

[0049]

(First step)

This step is a method of preparing a compound (14) by subjecting the compound (13) to an iodination reaction.

In the present reaction, an equivalent amount of the compound (13) and an iodination reagent, or an excess amount of one thereof is used, and the mixture thereof is stirred in a solvent inert to the reaction under room temperature to heating reflux, usually

for 0.1 hours to 5 days. The solvent to be used here is not particularly limited, and examples thereof include halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, alcohols such as methanol, ethanol, isopropyl alcohol, and butanol, DMF, DMSO, and a mixture thereof. As the iodination reagent, N-iodosuccinimide or the like is preferable.

[Reference]

J. Med. Chem. 58, 3548-3571, 2015

[0050]

(Second step)

In this step, cyclization reaction of the compound (14) with urea is performed and then the resultant cyclized compound is subjected to chlorination reaction to prepare the compound (15).

In the present reaction, an equivalent amount of the compound (14) and urea, or an excess amount of one thereof is used, and the mixture thereof is stirred in a solvent inert to the reaction, or under the absence of solvent, under room temperature to heating reflux, usually for 0.1 hours to 1 day, and an equivalent amount of the obtained cyclized product and chlorination reagent, or an excess amount of one thereof is used, and the mixture thereof is stirred in a solvent inert to the reaction, or under the absence of solvent, under room temperature to heating reflux, usually for 0.1 hours to 1 day. The solvent to be used here are not particularly limited, and examples thereof include halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, aromatic hydrocarbons such as benzene, toluene, and xylene, ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, DMF, DMSO, and a mixture thereof. As the chlorination reagent, phosphorus oxychloride, thionyl chloride and the like are preferable. It may be advantageous to perform the reaction in the presence of the organic base such as DIPEA in order to smoothly progress the reaction.

The cyclized product as an intermediate in this step can be obtained by subjecting the compound (14) to a condensation reaction with aqueous ammonia in a solvent inert to the reaction under the presence of condensing agent, and then by reacting the obtained amide product with 1,1'-carbonyldiimidazole in a solvent inert to the reaction under the presence of base. The solvent to be used here is not particularly limited, and examples thereof include halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, aromatic hydrocarbons such as benzene, toluene, and xylene, ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, DMF, DMSO, and a mixture thereof. In addition, as the condensing agent, 1H-benzotriazol-1-ol, 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide, and the like are preferable. Further, examples of the

base include an inorganic base such as potassium carbonate, sodium carbonate, and cesium carbonate, and an organic base such as TEA, DIPEA, and NMO.

Note that, it may be advantageous to perform the following reaction after isolating the intermediate amide and cyclized products respectively in order to smoothly progress the reaction.

[Reference]

J. Med. Chem. 58, 3548-3571, 2015

[0051]

(Third step)

This step is a method of preparing the compound (16) by an ipso-substitution reaction between the compound (15) and the compound (4).

The reaction conditions are similar to the first step of Starting material synthesis 1.

[0052]

(Fourth step)

This step is a method of preparing the compound (17) by an ipso-substitution reaction between the compound (16) and the compound (6).

The reaction conditions are similar to the second step of Starting material synthesis 1.

[0053]

(Fifth step)

This step is a method of preparing the compound (18) by an ipso-substitution reaction between the compound (17) and the compound (8).

The reaction conditions are similar to the third step of Starting material synthesis 1.

[0054]

(Sixth step)

This step is a method of preparing the compound (19) by Suzuki coupling reaction between the compound (18) and the compound (12).

The reaction conditions are similar to the fifth step of Starting material synthesis 1.

[0055]

(Seventh step)

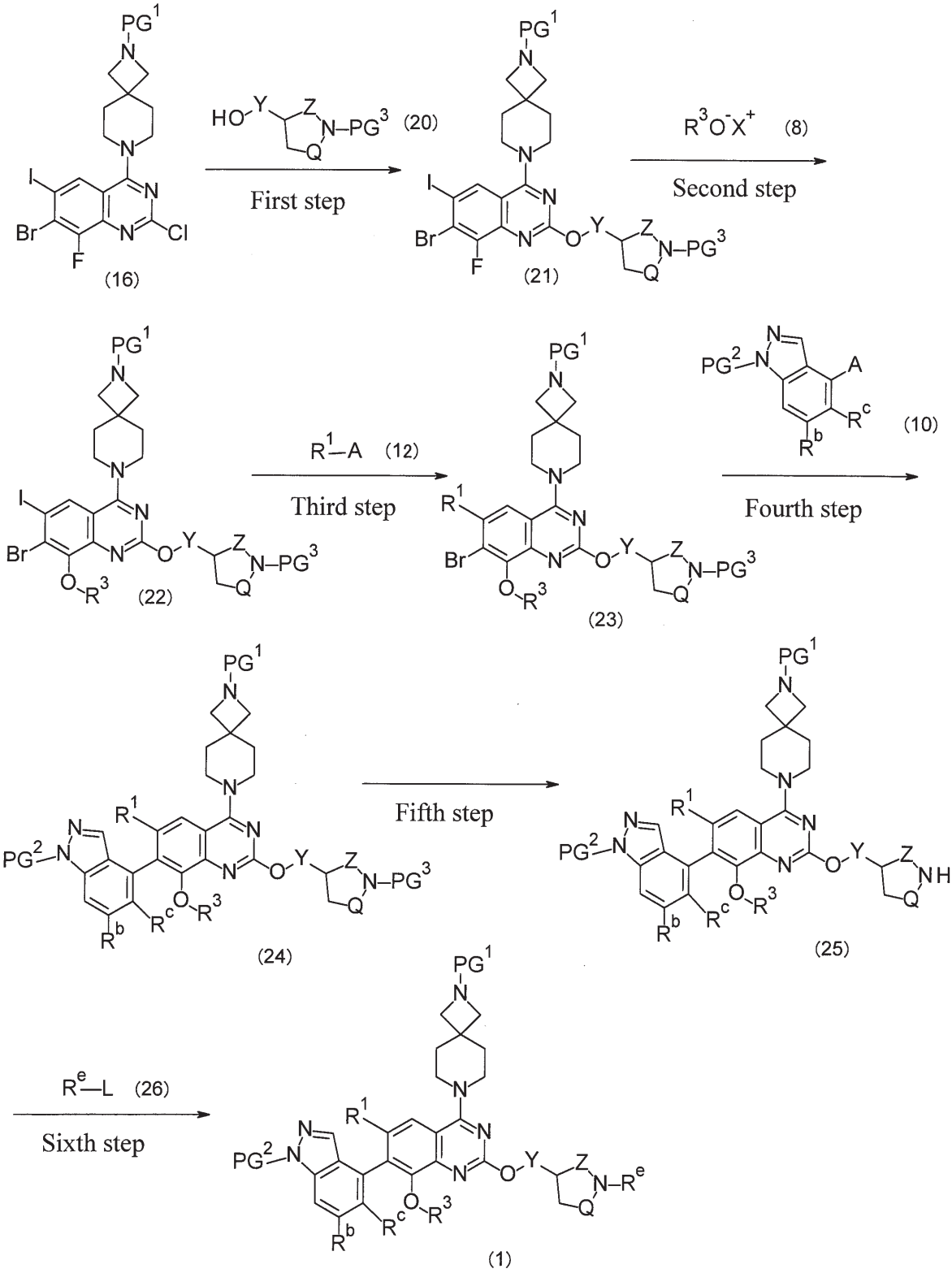
This step is a method of preparing the compound (1) by Suzuki coupling reaction between the compound (19) and the compound (10).

The reaction conditions are similar to the fourth step of Starting material synthesis 1.

[0056]

(Starting material synthesis 3)

[Chem. 8]



(in the formula, PG^3 represents a protecting group, and L represents a leaving group.)

[0057]

The present preparing method is a third method of preparing a starting compound (1).

[0058]

(First step)

This step is a method of preparing the compound (21) by an ipso-substitution reaction between the compound (16) and the compound (20).

The reaction conditions are similar to the second step of Starting material synthesis 1.

[0059]

(Second step)

This step is a method of preparing the compound (22) by an ipso-substitution reaction between the compound (21) and the compound (8).

The reaction conditions are similar to the third step of Starting material synthesis 1.

[0060]

(Third step)

This step is a method of preparing the compound (23) by Suzuki coupling reaction between the compound (22) and the compound (12).

The reaction conditions are similar to the fifth step of Starting material synthesis 1.

[0061]

(Fourth step)

This step is a method of preparing the compound (24) by Suzuki coupling reaction between the compound (23) and the compound (10).

The reaction conditions are similar to the fourth step of Starting material synthesis 1.

[0062]

(Fifth step)

This step is a method of preparing a compound (25) by subjecting the protecting group represented by PG^3 of the compound (24) to a selective deprotection reaction. Here, examples of PG^3 include a 2-(trimethylsilyl)ethoxycarbonyl group, a tert-butoxycarbonyl group, a benzyl group, a benzyloxycarbonyl group, a (trimethylsilyl)ethoxymethyl group, a trifluoroacetyl group, and an allyl group. The deprotection reaction performed with reference to "Protective Groups in Organic Synthesis" written by Greene and Wuts, 5th Edition, published by John Wiley & Sons Inc, 2014.

[0063]

(Sixth step)

This step is a method of preparing the compound (1) by a reaction between the compound (25) and the compound (26). Here, examples of the leaving group include halogen, methanesulfonyloxy, and a p-toluenesulfonyloxy group. It is possible to obtain a

desired compound (1) by reacting an epoxide compound such as 2,2-dimethyloxirane instead of the compound (26).

In the present reaction, an equivalent amount of the compound (25) and compound (26), or an excess amount of one thereof is used, and the mixture thereof is stirred in a solvent inert to the reaction, or under the absence of solvent, under cooling to heating reflux, preferably temperature of 0°C to 120°C, usually for 0.1 hours to 5 days. The solvent to be used here is not particularly limited, and examples thereof include halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, aromatic hydrocarbons such as benzene, toluene, and xylene, ethers such as diethyl ether, THF, 1,4-dioxane, and 1,2-dimethoxyethane, alcohols such as methanol, ethanol, isopropyl alcohol, and butanol, DMF, DMSO, ethyl acetate, acetonitrile, water, and a mixture thereof. It may be advantageous to perform the reaction in the presence of the organic base such as TEA, DIPEA, or NMO, or the inorganic base such as potassium carbonate, sodium carbonate, cesium carbonate, or potassium hydroxide in order to smoothly progress the reaction. It may be advantageous to heat the mixture by microwave irradiation in order to smoothly progress the reaction.

[0064]

The compound of Formula (I) is isolated and purified as a free compound, a salt thereof, a hydrate, a solvate or a substance of crystalline polymorphism. The salt of the compound of Formula (I) can also be prepared by subjecting it to a conventional salt formation reaction.

The isolation and purification are carried out by applying ordinary chemical operations such as extraction, fractional crystallization, various fractionation chromatography and the like.

Various kinds of isomers can be prepared by selecting an appropriate starting compound or can be separated utilizing a difference in physicochemical properties between isomers. For example, the optical isomer can be obtained by a general optical resolution method of the racemic compound (for example, fractional crystallization leading to a diastereomeric salt with an optically active base or an acid, chromatography using a chiral column or the like), and can also be prepared from a suitably optical active starting compound.

[0065]

The pharmacological activity of the compound of Formula (I) was confirmed by the following test.

[0066]

Test example 1

Evaluation of KRAS G12C/SOS/c-Raf complex formation inhibitory action

Human Recombinant KRAS G12C, SOS, and c-Raf protein were used, and with respect to the complex formation of these proteins, an inhibitory action of the test compound was examined through a time-resolved fluorescence resonance energy transfer (TR-FRET) method.

Biotinylated AviTag-KRAS G12C (amino acid region 1-185, GDP) (2.5 μL; 400 nM) dissolved in assay buffer (50mM HEPES, 150 mM NaCl, 5 mM $MgCl_2$, 0.05% Tween 20, pH 7.4) and test compound were added in a volume of 2.5 μL from 4,000 nM to 4 nM were added to 384 well plate (Corning Inc). Son of Sevenless (SOS) (amino acid region 564-1049, 2.5 μL; 1.3 μM) and c-Raf (amino acid region 51-131) GST containing GTP (Sigma-Aldrich Co. LLC) (2.5 μL; 130 nM and 4 μM of each) were added to the above mixture, and the resultant was left to stand for one hour at room temperature. Thereafter, a mixed solution (10 μL) of LANCE Ulight-anti-GST (120 nM, PerkinElmer. Co., Ltd) and LANCE Eu-W1024 labeled Streptoavidin (100 ng/mL, PerkinElmer. Co., Ltd) was added, and a fluorescence intensity on the condition of wavelength of 620 nm and 665 nm was measured by using EnVision 2103 Multilabel Reader (PerkinElmer Co., Ltd.) under the condition of excitation wavelength of 337 nm. After a value at the fluorescence intensity in reference wavelength of 620 nm was standardized, when a signal value in a solvent treatment was set as 0% inhibition, and a signal value without addition of GTP was set as 100% inhibition, 50% inhibitory concentration (IC_{50}) was calculated through Sigmoid-Emax model nonlinear regression analysis. The results of several test compounds of Formula (I) are indicated in Table 1. In Tables, Ex represents Example numbers described later. In addition, in Tables, Compound C represents a test compound of Example I-59 disclosed in Pamphlet of International Publication No. WO 2016/164675, and the structures of Reference Example 1 and Reference Example 2 are indicated in Table 168 described below (the same shall apply hereinafter).

[0067]

[Table 1]

Ex	IC_{50} (nM)	Ex	IC_{50} (nM)	Ex	IC_{50} (nM)
1	34	33	44	65	46
2	37	34	36	66	47
3	29	35	17	67	43
4	35	36	21	68	45
5	31	37	17	69	50
6	37	38	15	70	79
7	33	39	14	71	40
8	32	40	15	72	41
9	55	41	42	73	44
10	34	42	44	74	50
11	38	43	50	75	51
12	23	44	41	76	43
13	37	45	38	77	56
14	50	46	48	78	47
15	52	47	43	79	57
16	45	48	54	80	166
17	34	49	41	81	41
18	46	50	50	82	43
19	48	51	59	83	108
20	32	52	56	84	43
21	65	53	37	85	56
22	39	54	60	86	72
23	39	55	83	87	39
24	21	56	63	88	148
25	48	57	52	89	53
26	41	58	57	90	55
27	40	59	63	91	42
28	38	60	98	Reference example 1	37
29	49	61	56	Reference example 2	35
30	45	62	37	Compound C	68
31	45	63	53		
32	39	64	32		

[0068]

Test example 2

Evaluation of ERK phosphorylation inhibitory action with respect to human KRAS G12C mutation positive non-small cell lung cancer strain NCI-H1373

The ERK phosphorylation inhibitory action by the test compound was evaluated by measuring phosphorylation of 202th threonine (Thr 202) and 204th tyrosine (Tyr 204) of ERK on the downstream of the KRAS signal by Cell ELISA.

NCI-H1373 cells (ATCC, CRL-5866) were seeded in 384 well plates (Greiner bio-one) at 36 μL/ well each so as to be 2 x 10^4 cell per well. Cell culture was performed under the conditions of temperature of 37°C in the presence of 5% CO_2 by using RPMI 1640 medium (Sigma-Aldrich Co. LLC) containing 10% fetal bovine serum (GE Life Sciences).

The next day, the test compounds (six points in a range of final concentration 1,000 nM to 0.3 nM), final concentration 1 μM of Trametinib (GlaxoSmithKline Inc.; MEK inhibitor) as a positive control, and DMSO which is a solvent of the test compound as a negative control were diluted 100-fold with fresh medium, 4 μL each was added to each well, and then cultured for 2 hours. Immediately after culturing, 30 μL of 30% glyoxal solution (Wako; 40% glyoxal diluted with Phosphate Buffered Saline (PBS; Wako)) was added to each well, and the cells were left to stand at room temperature for one hour to be fixed. Thereafter, the supernatant was removed by centrifuging the plate (110 × g for 7 seconds, unless otherwise stated below under the same conditions), and 20 μL of PBS containing 0.1% Triton X-100 (Amersham Biosciences Corp.) was added to each well. After being left to stand at room temperature for 10 minutes, the supernatant was removed by centrifugation, and the same operation was repeated. Next, 20 μL of PBS containing 0.5% SDS (Invitrogen) was added to each well, and the mixture was left to stand at room temperature for 30 minutes, and then centrifuged to remove the supernatant. Subsequently, 20 μL of a blocking solution (ODYSSEY Blocking Buffer; LI-COR Biosciences) was added to each well, and left to stand at room temperature for one hour. The supernatant was removed by centrifugation, and 10 μL of a blocking solution prepared by diluting ERK (Thr 202/Tyr 204) of a phosphorylation antibody (Cell Signaling Technology, Inc.) as a primary antibody to be 1/2, 500 amount with respect to a stock solution was added to each well and was left to stand at 4°C for overnight.

The next day, a reaction liquid is removed by centrifuging the plate, 20 μL of 0.05% Tween-20-containing PBS (Thermo Scientific; 20 x PBS Tween-20 diluted 20-fold with ion exchanged water) was added to each well, and each well was washed by removing the supernatant by centrifugation. Washing was performed three times in total. After washing, 10 μL of a blocking solution prepared by diluting IRDye 800CW Goat anti-Rabbit IgG (LI-COR Biosciences) as a secondary antibody to be 1/1,000 amount with respect to a stock solution was added to each well and was left to stand at room temperature for one hour. The reaction liquid was removed by centrifuging the plate, and each well was washed three times with 0.05% Tween-20-containing PBS in the same manner as after primary antibody reaction. The centrifugation after the third wash was

171 × g for 17 seconds. After removal of the cleaning solution, the plate was left to air dry at room temperature for three hours or more and the fluorescent signal at 800 nm was measured by Aerius (LI-COR Biosciences).

When a signal value at the time of adding DMSO was set as 0% inhibition, and a signal value at the time of adding 1 μM of Trametinib was set as 100% inhibition, a value of 50% inhibition (IC_{50}) was calculated through Sigmoid-Emax model nonlinear regression analysis. The results of several test compounds of Formula (I) are indicated in Table 2.

[0069]

[Table 2]

Ex	IC_{50} (nM)	Ex	IC_{50} (nM)	Ex	IC_{50} (nM)
1	6.4	33	4.6	65	9.3
2	4.4	34	5.8	66	9.7
3	3.3	35	2.5	67	11
4	2.9	36	3.0	68	12
5	4.7	37	2.5	69	12
6	3.5	38	3.4	70	18
7	8.8	39	3.0	71	14
8	2.6	40	3.1	72	14
9	3.8	41	6.2	73	15
10	5.7	42	4.4	74	15
11	10	43	5.0	75	15
12	6.7	44	5.1	76	15
13	11	45	5.2	77	16
14	6.1	46	5.5	78	16
15	11	47	5.6	79	16
16	9.1	48	5.9	80	16
17	4.9	49	2.9	81	16
18	5.9	50	6.4	82	16
19	4.5	51	8.9	83	16
20	6.5	52	6.7	84	17
21	14	53	6.8	85	17
22	4.6	54	7.2	86	12
23	4.9	55	7.4	87	18
24	3.7	56	7.7	88	19
25	2.5	57	8.2	89	19
26	3.3	58	8.4	90	22
27	3.3	59	8.4	91	22
28	3.5	60	8.8	Reference example 1	22
29	4.2	61	8.8	Reference example 2	17
30	3.1	62	8.8	Compound C	210
31	6.3	63	6.6		
32	5.7	64	9.1		

[0070]

Test example 3

Evaluation of anchorage-independent cell proliferation inhibitory action with respect to human KRAS G12C mutation positive non-small cell lung cancer strain NCI-H1373

An anchorage-independent cell proliferation inhibitory action by the test compound was evaluated by a spheroid three-dimensional culture.

NCI-H1373 cells were seeded in cell low adsorption U bottom 384 well plates (Prime Surface: Sumitomo Bakelite Co., Ltd.) at 36 μL/ well each so as to be 5 x 10^2 cell per well. The cell culture was performed under the same conditions as Test example 2.

The next day, the test compounds (six points in a range of final concentration 1,000 nM to 0.3 nM) and DMSO which is a solvent of the test compound as a negative control were diluted 100-fold with fresh medium, 4 μL each was added to each well. After culturing at 37°C in the presence of 5% CO_2 for six days, 20 μL of CellTiter Glo or CellTiter Glo 2.0 (Promega Corporation) was added to each well. After stirring for one hour at room temperature using a plate mixer (FINEPCR), an emission signal was measured with ARVO X3 (PerkinElmer Co., Ltd.).

When a signal value in a DMSO treatment was set as 0% inhibition, and a signal value in cell-free medium only was set as 100% inhibition, a value of 50% inhibition (IC_{50}) was calculated through Sigmoid-Emax model nonlinear regression analysis. The results of several test compounds of Formula (I) are indicated in Table 3.

[0071]

[Table 3]

Ex	IC_{50} (nM)	Ex	IC_{50} (nM)	Ex	IC_{50} (nM)
1	12	33	8.7	65	27
2	6.2	34	7.5	66	39
3	4.7	35	2.5	67	18
4	3.4	36	3.2	68	16
5	8.1	37	8.8	69	17
6	12	38	2.5	70	71
7	11	39	4.3	71	10
8	3.5	40	5.1	72	24
9	5.5	41	14	73	28
10	10	42	13	74	21
11	12	43	6.0	75	43
12	11	44	7.6	76	25
13	13	45	7.3	77	32
14	8.8	46	8.1	78	24
15	14	47	17	79	43
16	10	48	15	80	75
17	12	49	4.6	81	26
18	7.3	50	16	82	62
19	15	51	24	83	51
20	11	52	16	84	33
21	27	53	9.8	85	27
22	15	54	6.8	86	37
23	5.9	55	43	87	35
24	6.1	56	21	88	90
25	5.2	57	39	89	40
26	8.6	58	17	90	53
27	6.5	59	26	91	39
28	5.8	60	35	Reference example 1	32
29	10	61	17	Reference example 2	22
30	5.4	62	14	Compound C	320
31	8.3	63	14		
32	7.1	64	15		

[0072]

Test example 4

Evaluation of intratumoral pERK inhibitory action

The phosphorylation amount of ERK in tumor sample after administration of test compound was examined by using pERK measurement kit (Advanced ERK phospho-T202/Y204 kit, Cisbio co.,Ltd) through a TR-FRET method.

2.0 to 5.0 × 10^6 NCI-H1373 cells were prepared by using a solution in which an equivalent amount of Matrigel (Becton, Dickinson and Company) was added to PBS, were

injected subcutaneously in a volume of 100 μL and planted to male nude mice of 4-5 weeks old (CAnN.Cg-Foxn 1 nu/CrlCrlj (nu/nu), Charles River Laboratories Japan, Inc.), and then the male nude mice were used for the test 15 to 26 days later. The test was conducted with three mice in a solvent group and three mice in a test compound administration group, and the test compounds were prepared by using a solvent such that the dosage thereof is as indicated in Table 4. The test compound was administered subcutaneously or orally. For subcutaneous administration, physiological saline supplemented with equimolar hydrochloric acid was used as a solvent. For oral administration, 6% 2-hydroxypropyl-β-cyclodextrin (Sigma-Aldrich Co. LLC) was used as a solvent. Six hours after the administration, a tumor was excised from a cervical dislocated mouse under isoflurane anesthesia, and a part thereof was put into a 2 mL Eppendorf tube and frozen using liquid nitrogen. The tumor sample was stored in a deep freezer at -80°C until it was subjected to the pERK measurement test.

500 μL of lysis buffer 1 (Phospholysis buffer [Cisbio Co.,Ltd], Complete EDTA free [Roche Diagnostics K.K.], Phosphatase inhibitor cocktail 2 [Sigma-Aldrich Co. LLC]) and one bead (5 mm YTZ ball [Nikkato Corp.]) was added to the tumor sample, and crushed (frequency 25/s for 3 minutes) by using Tissue Lyser II (QIAGEN GmbH). The whole amount was transferred to a new tube and centrifuged (20,400 × g for 10 minutes, 4°C) by using a micro amount high speed cooling centrifuge so as to obtain a tumor lysate which is a supernatant. Protein quantification of tumor lysate was performed by using a protein quantification kit (Pierce 660 nm Protein Assay Kit [Thermo Fisher Scientific Inc.]), and each sample was diluted by using lysis buffer 2 (Phosphorysis buffer [Cisbio Co.,Ltd], Blocking Agent [attached to pERK measurement kit]) such that the amount thereof is to be a final concentration of 0.5 μg/μL.

Each of p-ERK1/2 Cryptate antibody and p-ERK1/2 d2 antibody (attached to pERK measurement kit) was diluted 20-fold with each detection buffer (attached to pERK measurement kit), and thereby a mixed solution of these two types of antibodies was prepared. A mixed solution of antibody was added to a 384 well plate at a volume of 4 μL/well. Further, tumor lysate diluted to 0.5 μg/μL was added at a volume of 16 μL/well. After standing at room temperature in a wet box for about 17 hours, the fluorescence intensity at 620 nm and 665 nm was measured under the condition of excitation wavelength of 337 nm by using EnVision 2103 Multilabel Reader (PerkinElmer Co., Ltd.). After normalizing the value with the fluorescence intensity at the reference wavelength of 620 nm, the count of the vehicle administration group was set as 0% inhibition, the count without addition of lysate was set as 100% inhibition, and an inhibition value of the test compound administration sample was calculated % by inhibition rate. The results of several test compounds of Formula (I) are indicated in Table 4.

[0073]

[Table 4]

Ex	Route of administration	Dosage (mg/kg)	pERK inhibition (%)
2	Subcutaneous administration	1	54
3	Subcutaneous administration	1	57
4	Subcutaneous administration	1	58
5	Subcutaneous administration	3	72
7	Subcutaneous administration	3	59
15	Subcutaneous administration	3	53
16	Subcutaneous administration	3	51
24	Oral administration	40	72
25	Oral administration	10	66
26	Oral administration	10	50
28	Oral administration	10	46
29	Oral administration	10	62
30	Oral administration	10	56
31	Oral administration	10	51
32	Oral administration	10	55
33	Oral administration	10	71
34	Oral administration	10	54
35	Oral administration	10	68
36	Oral administration	10	46
37	Oral administration	10	63
38	Oral administration	10	66
39	Oral administration	10	43
40	Oral administration	10	58
50	Oral administration	10	63
52	Oral administration	10	68
56	Oral administration	10	53
65	Oral administration	10	68
Compound C	Subcutaneous administration	30	54

[0074]

Test example 5

Evaluation of antitumor effect in human KRAS G12C mutation positive non-small cell lung cancer strain NCI-H1373 tumor-bearing mouse

A cell suspension prepared per 3.0 x 10^7/mL by suspending NCI-H1373 cells in PBS, an equivalent amount of Matrigel (Becton, Dickinson and Company) was added

thereto, and the cell suspension was subcutaneously planted in a volume of 100 μL to male nude mice of 4-5 weeks old (CAnN.Cg-Foxn1nu/CrlCrlj (nu/nu), Charles River Laboratories Japan, Inc.). Approximately 2 weeks after planting, groups were divided so that tumor volume and body weight between the groups were almost equivalent to each other, and administration of the test compound was started from the next day. The test was conducted with five mice in a solvent group and five mice in a test compound administration group, and an aqueous solution of 6% 2-hydroxypropyl-β-cyclodextrin (Sigma-Aldrich Co. LLC) was orally administered to the solvent group and an aqueous solution of 6% 2-hydroxypropyl- β-cyclodextrin which the test compound (10 or 40 mg/kg) was mixed was orally administered to the test compound administration group. The administration was performed once a day for 13 or 14 days, and tumor diameter and volume were measured twice a week. For calculation of tumor volume, the following formula was used.

[tumor volume (mm^3)] = [major diameter (mm) of tumor] x [minor diameter (mm) of tumor]^2 x 0.5

The tumor growth inhibition rate (%) by the test compound was calculated by setting the tumor volume of the test compound administration group on the day before the administration started as 100% inhibition, and the tumor volume of the solvent group on the last day of administration as 0% inhibition. In addition, in a case where the tumor volume of the test compound administration group was lower than the tumor volume on the day before the administration started, the tumor regression rate (%) of the test compound was calculated by setting the tumor volume on the day before the administration started as 0% regression, and the tumor volume 0 as 100% regression. The results of several test compounds of Formula (I) are indicated in Table 5.

[0075]

[Table 5]

Ex	Dosage (mg/kg)	Antitumor effect
24	40	48% regression
35	10	72% regression
36	10	43% regression
37	10	58% regression
38	10	58% regression
39	10	96% inhibition
40	10	15% regression

[0076]

As a result of the above tests, G12C mutation KRAS inhibitory action was confirmed in several compounds of Formula (I). Accordingly, the compound of Formula

(I) can be used for treatment of lung cancer, KRAS G12C mutation positive lung cancer, and the like.

[0077]

A pharmaceutical composition containing the compound of Formula (I) or one or more kinds of salts as active ingredients can be prepared by using an excipient commonly used in this field, that is, an excipient for pharmaceuticals and a carrier for pharmaceuticals through the commonly used methods.

The administration may be any of oral administration with tablets, pills, capsules, granules, powders, solutions, and the like, and parenteral administration with injections such as intra-articular, intravenous, intramuscular, and the like, suppositories, eye drops, ophthalmic ointments, transdermal solutions, ointments, transdermal patches, transmucosal solutions, transmucosal patches, and inhalant.

[0078]

As a solid composition for the oral administration, tablets, powders, granules and the like are used. In such a solid composition, one or more active ingredients are mixed with at least one kind of inert excipient. The composition may contain an inert additive such as a lubricant, a disintegrant, a stabilizer, and a solubilizing agent according to the conventional method. The tablets or pills may be coated with a sugar coating or a film of gastric or enteric substance, if necessary.

A liquid composition for the oral administration includes a pharmaceutically acceptable emulsion, a solution, a suspension, a syrup, an elixir, and the like, and further includes commonly used inert diluent such as purified water or ethanol. The liquid composition may include a solubilizing agent, a wetting agent, an adjuvant such as a suspending agent, a sweetening agent, a flavoring agent, an aromatic, and a preservative, in addition to the inert diluent.

[0079]

An injection for parenteral administration includes a sterile aqueous or nonaqueous solution, a suspension, or an emulsion. Examples of an aqueous solvent include distilled water for injection or physiological saline. Examples of a nonaqueous solvent include alcohols such as ethanol. Such a composition may further include an isotonizing agent, a preservative, a wetting agent, an emulsifying agent, a dispersing agent, a stabilizing agent, or a solubilizing agent. These compositions are sterilized, for example, by filtration through a bacteria-retaining filter, blending of a sterilizing agent, or irradiation. In addition, these compositions are used to prepare a sterile solid composition, and can be used by being dissolved or suspended in sterile water or a sterile injectable solvent before use.

[0080]

A transmucosal agent such as an inhalation agent and a transnasal agent are in a state of solid, liquid, or semisolid, and can be prepared according to conventionally known methods. For example, in addition to the well-known excipient, a pH adjuster, a preservative, a surfactant, a lubricant, a stabilizer, and a thickener may be appropriately added. For administration, a device for suitable inhalation or insufflation can be used. For example, using a known device such as a metered administration inhalation device or a nebulizer, the compound may be administered alone or as a powder of the formulated mixture, or as a solution or a suspension in combination with a pharmaceutically acceptable carrier. A dry powder inhaler or the like may be used for single or multiple administrations, and dry powder or powder containing capsules can be used. Alternatively, a suitable ejection agent, for example, a form of pressurized aerosol spray using suitable gases such as chlorofluoroalkane or carbon dioxide may be employed.

[0081]

In a case of the common oral administration, a suitable dosage per day is approximately in a range of 0.001 to 100 mg/kg per body weight, is preferably in a range of 0.1 to 30 mg/kg, and further preferably in a range of 0.1 to 10 mg/kg, and the administration is performed once or two to four divided dosages. In a case of intravenous administration, a suitable dosage per day is approximately in a range of 0.0001 to 10 mg/kg per body weight, and the administration is performed once a day to several times a day. Further, as the transmucosal agent, approximately 0.001 to 100 mg/kg per body weight is administered once to several times a day. The dosage is appropriately decided according to individual cases in consideration of symptoms, age, sex, and the like.

[0082]

Depending on an administration route, a dosage form, an administration site, the types of excipients and additives, the pharmaceutical composition of the present invention contains one or more kinds of the compounds of Formula (I) or salts thereof having active ingredients in a range of 0.01% to 100% by weight, and as an embodiment, active ingredients in a range of 0.01% to 50% by weight.

[0083]

The compound of Formula (I) can be used in combination with various therapeutic or prophylactic agents for diseases in which the compound of Formula (I) is considered to exhibit efficacy. The combination may be administered simultaneously, or separately in succession, or at a desired time interval. Co-administered preparation may be a compounding agent or separately formulated.

[Examples]

[0084]

Hereinafter, the preparation method of the compound of Formula (I) will be described in more detail based on the Example. It is to be noted that the present invention is not limited to the compounds described in the following Examples. In addition, the preparing method of the starting compound is described in Preparation Examples respectively. Further, the preparing method of the compound of Formula (I) is not limited to only the preparing methods of the specific examples described below, and the compound of Formula (I) may be prepared by combining these preparing methods, or may be prepared by methods obvious to those skilled in the art.

[0085]

In the present specification, there are cases where naming software such as ACD/Name (registered trademark, Advanced Chemistry Development, Inc.) is used for naming compounds.

[0086]

Also, for convenience, the concentration mol/L is represented as M. For example, 1 M sodium hydroxide aqueous solution means 1 mol/L sodium hydroxide aqueous solution.

[0087]

Preparation Example 1

A mixture of 2-amino-4-bromo-3-fluorobenzoic acid (4.0 g), N-iodosuccinimide (4.0 g), and N,N-dimethylformamide (hereinafter, abbreviated as DMF) (40 mL) was stirred at 50°C for 2 hours under an argon flow. N-iodosuccinimide (1.5 g) was added to the reaction mixture at 50°C, and the mixture was stirred at the same temperature for 1.5 hours. N-iodosuccinimide (1.5 g) was added to the reaction mixture at 50°C, and the mixture was stirred at the same temperature overnight. The reaction mixture was cooled to room temperature, then water was added and the mixture was stirred at room temperature for 5 hours. The precipitated solid was collected by filtration and air-dried at room temperature. The obtained solid was suspended in water and stirred at room temperature for 1 hour. The solid was collected by filtration, washed with water and dried at 50°C under reduced pressure to obtain 2-amino-4-bromo-3-fluoro-5-iodobenzoic acid (5.6 g) as a solid.

[0088]

Preparation Example 2

A mixture of 2-amino-4-bromo-3-fluoro-5-iodobenzoic acid (5.6 g) and urea (4.7 g) was stirred at 200°C for 3 hours. The reaction mixture was cooled to room temperature, then water was added and the mixture was stirred at room temperature for 15 minutes. The solid was collected by filtration, washed with water, and dried at 50°C under reduced pressure. The obtained solid was ground into powder, then was mixed with phosphorus oxychloride (80 mL), cooled in ice bath, and N,N-diisopropylethylamine

(hereinafter, abbreviated as DIPEA) (8.0 mL) was added dropwise to the mixture in a nitrogen flow. The reaction mixture was stirred at 150°C for 2.5 hours. The reaction mixture was cooled to room temperature, then concentrated under reduced pressure, and ethyl acetate was added to the obtained residue. The reaction mixture was poured into ice water, then an insoluble material was separated by filtration, and the filtrate was extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate so as to concentrate a solution under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain 7-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline (3.6 g) as a solid.

[0089]

Preparation Example 3

A mixture of 7-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline (3.6 g) and 1,4-dioxane (35 mL) was cooled in ice bath, then DIPEA (8.0 mL) and tert-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (2.0 g) were added to the mixture in a nitrogen flow, and the mixture was stirred at room temperature for 1.5 hours. Water was added to the reaction mixture and extracted with chloroform. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/ethyl acetate) so as to obtain tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (4.6 g) as a solid.

[0090]

Preparation Example 4

1-methylpiperidin-4-ol (3.5 mL), cesium carbonate (9.6 g), and 1,4-diazabicyclo[2.2.2]octane (hereinafter, abbreviated as DABCO) (220 mg) were added to a mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (6.0 g), DMF (60 mL) and tetrahydrofuran (hereinafter, abbreviated as THF) (60 mL) under the argon atmosphere, and then stirred at room temperature for 14 hours. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water) so as to obtain tert-butyl 7-{7-bromo-8-fluoro-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (6.3 g).

[0091]

Preparation Example 5

A mixture of 2,2-difluoroethanol (0.37 mL) and DMF (20 mL) were cooled in ice bath, sodium hydride (55%, liquid paraffin dispersion, 250 mg) was added to the mixture, stirred at the same temperature for 5 minutes under the argon atmosphere, and then stirred at room temperature for 20 minutes (mixture A). A mixture of tert-butyl 7-{7-bromo-8-fluoro-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.0 g) and THF (40 mL) were cooled in ice bath, the mixture A was added dropwise to the mixture, stirred at the same temperature for 1 hour under the argon atmosphere, and then stirred at room temperature for 2 hours. Under the argon atmosphere, a mixture of 2,2-difluoroethanol (92 μL) and DMF (5 mL) were cooled in ice bath, sodium hydride (55%, liquid paraffin dispersion, 63 mg) was added to the mixture, stirred at the same temperature for 5 minutes, and then stirred at room temperature for 20 minutes (mixture B). The reaction mixture was cooled in ice bath, then the mixture B was added, and the mixture was stirred at room temperature for 3 hours. Water and a saturated aqueous sodium chloride solution were added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-8-(2,2-difluoroethoxy)-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.0 g).

[0092]

Preparation Example 6

Potassium carbonate (1.1 g) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane adduct (hereinafter, abbreviated as $PdCl_2(dppf)\cdot CH_2Cl_2$) (210 mg) were added to a mixture of tert-butyl 7-{7-bromo-8-(2,2-difluoroethoxy)-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.0 g), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.88 mL), 1,4-dioxane (40 mL), and water (4.0 mL), and the mixture was stirred at 80°C for 1 hour. After the reaction mixture was cooled to room temperature, and ethyl acetate and a saturated aqueous sodium chloride solution were added to the reaction mixture. An insoluble material was separated by filtration, then a filtrate was extracted with ethyl acetate, and an organic layer was dried with anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). The obtained purified product was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Ethyl acetate and hexane were added to the obtained purified product, the solvent was evaporated under reduced pressure so as to obtain tert-butyl 7-{7-bromo-8-(2,2-difluoroethoxy)-2-[(1-

methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.4 g).

[0093]

Preparation Example 7

A mixture of tert-butyl 7-{7-bromo-8-(2,2-difluoroethoxy)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.4 g), (5-methyl-1H-indazol-4-yl)boronic acid (760 mg), 1,4-dioxane (17 mL), and water (1.7 mL) was bubbled under argon, then tripotassium phosphate (2.3 g), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (hereinafter, abbreviated as SPhos) (270 mg), and (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one/palladium (3:2) (hereinafter, abbreviated as $Pd_2(dba)_3$) (400 mg) were added to the mixture, and the mixture was stirred at 120°C for 1 hour under microwave irradiation. Ethyl acetate was added to the reaction mixture, and the mixture was washed with a saturated aqueous sodium chloride solution. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). The obtained purified product was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water) so as to obtain tert-butyl 7-{8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (290 mg).

[0094]

Preparation Example 8

Sodium ethoxide (390 mg) was added to a mixture of tert-butyl 7-{7-bromo-8-fluoro-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.3 g) and THF (65 mL), and the mixture was stirred at 40°C overnight. Sodium ethoxide (390 mg) was added to the reaction mixture, and the mixture was stirred at 40°C overnight. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-8-ethoxy-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.3 g) as a solid.

[0095]

Preparation Example 9

A mixture of tert-butyl 7-{7-bromo-8-ethoxy-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.3 g), 1,4-dioxane (25 mL), water (5.0 mL), cyclopropylboronic acid (160 mg), tripotassium phosphate (1.4 g),

$PdCl_2(dppf)\cdot CH_2Cl_2$ (150 mg) was stirred at 100°C overnight under the argon atmosphere. The reaction mixture was cooled to room temperature, then water was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-6-cyclopropyl-8-ethoxy-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (800 mg).

[0096]

Preparation Example 10

Under the argon atmosphere, tert-butyl 7-{7-bromo-6-cyclopropyl-8-ethoxy-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (420 mg), (5-methyl-1H-indazol-4-yl)boronic acid (230 mg), $Pd_2(dba)_3$ (61 mg), SPhos (55 mg), tripotassium phosphate (500 mg), 1,4-dioxane (10 mL), and water (1.0 mL) were mixed, and the mixture was stirred at 120°C for 2 hours under microwave irradiation. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{6-cyclopropyl-8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (180 mg).

[0097]

Preparation Example 11

A mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (5.0 g), benzyl 4-hydroxypiperidine-1-carboxylate (3.7 mL), DMF (75 mL), cesium carbonate (8.0 g), and DABCO (140 mg) was stirred at room temperature for 16 hours under the argon atmosphere. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain tert-butyl 7-[2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-7-bromo-8-fluoro-6-iodoquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (4.1 g).

[0098]

Preparation Example 12

A mixture of 2,2-difluoroethanol (0.42 mL) and DMF (30 mL) was cooled in ice bath, sodium hydride (55%, liquid paraffin dispersion, 290 mg) was added to the mixture,

and stirred at room temperature for 5 minutes under the argon atmosphere. The reaction mixture was cooled in ice bath, and then a mixture of tert-butyl 7-[2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-7-bromo-8-fluoro-6-iodoquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.7 g) and DMF (15 mL) was added thereto. The reaction mixture was stirred at the same temperature for 10 minutes, and then stirred at room temperature for 4 hours. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-7-bromo-8-(2,2-difluoroethoxy)-6-iodoquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.7 g) as a solid.

[0099]

Preparation Example 13

Cyclopropylboronic acid (290 mg), tripotassium phosphate (2.3 g), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (250 mg) were added to a mixture of tert-butyl 7-[2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-7-bromo-8-(2,2-difluoroethoxy)-6-iodoquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.6 g), 1,4-dioxane (52 mL), and water (10 mL), and the mixture was stirred at 90°C for 14 hours under the argon atmosphere. A cyclopropylboronic acid (100 mg) was added to the reaction mixture, and the mixture was stirred at 90°C for 8 hours. After the reaction mixture was cooled to room temperature, a saturated aqueous sodium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain tert-butyl 7-[2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-7-bromo-6-cyclopropyl-8-(2,2-difluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.4 g) as a solid.

[0100]

Preparation Example 14

A mixture of tert-butyl 7-[2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-7-bromo-6-cyclopropyl-8-(2,2-difluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.4 g), 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (700 mg), tripotassium phosphate (1.2 g), SPhos (140 mg), $Pd_2(dba)_3$ (160 mg), 1,4-dioxane (30 mL), and water (3.0 mL) was divided into equal amounts, and under the argon atmosphere, the mixture was stirred at 120°C for 1 hour under microwave irradiation. The reaction mixture was mixed, and the mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel

column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-6-cyclopropyl-8-(2,2-difluoroethoxy)-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (820 mg) as a solid.

[0101]

Preparation Example 15

Formaldehyde (37% aqueous solution, 0.40 mL) and 10% palladium carbon (wetted with ca. 50% water, 180 mg) were added to a mixture of tert-butyl 7-{2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)-6-cyclopropyl-8-(2,2-difluoroethoxy)-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (820 mg) and methanol (16 mL), and the mixture was stirred at room temperature under hydrogen atmosphere for 8 hours. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{6-cyclopropyl-8-(2,2-difluoroethoxy)-2-[(1-methylpiperidin-4-yl)oxy]-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (530 mg) as a solid.

[0102]

Preparation Example 16

A mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.0 g), [(2S)-1-methylpyrrolidin-2-yl]methanol (2.4 mL), acetonitrile (30 mL), and potassium carbonate (2.1 g) was stirred at 80°C for 18 hours under the argon atmosphere. [(2S)-1-methylpyrrolidin-2-yl]methanol (0.60 mL) was added to the reaction mixture, and the mixture was stirred at 80°C for 5 hours. The reaction mixture was cooled to room temperature, then water was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.8 g).

[0103]

Preparation Example 17

A mixture of 2,2-difluoroethanol (600 mg) and DMF (30 mL) were cooled in ice bath, sodium hydride (55%, liquid paraffin dispersion, 310 mg) was added to the mixture, and stirred at room temperature for 5 minutes under the argon atmosphere (mixture C). After the mixture of tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.8 g), and THF

(30 mL) was cooled in ice bath, the mixture C was added to the mixture, the mixture was stirred at the same temperature for 10 minutes, and then stirred at room temperature for 3 hours. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[7-bromo-8-(2,2-difluoroethoxy)-6-iodo-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.3 g).

[0104]

Preparation Example 18

A mixture of tert-butyl 7-[7-bromo-8-(2,2-difluoroethoxy)-6-iodo-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.2 g), 1,4-dioxane (45 mL), water (4.5 mL), cyclopropylboronic acid (280 mg), tripotassium phosphate (2.3 g), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (240 mg) was stirred at 95°C for 8 hours under the argon atmosphere, and then stirred at 100°C for 16 hours. The reaction mixture was cooled to room temperature, then water was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[7-bromo-6-cyclopropyl-8-(2,2-difluoroethoxy)-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (980 mg).

[0105]

Preparation Example 19

Under the argon atmosphere, tert-butyl 7-[7-bromo-6-cyclopropyl-8-(2,2-difluoroethoxy)-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (980 mg), (5-methyl-1H-indazol-4-yl)boronic acid (520 mg), $Pd_2(dba)_3$ (140 mg), SPhos (120 mg), tripotassium phosphate (1.1 g), 1,4-dioxane (15 mL), and water (1.2 mL) were mixed, and the mixture was stirred at 120°C for 2 hours under microwave irradiation. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (470 mg).

[0106]

Preparation Example 20

A mixture of 7-bromo-2,4,6-trichloro-8-fluoroquinazoline (30 g) and 1,4-dioxane (300 mL) was cooled in ice bath, then DIPEA (85 mL) and tert-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (21 g) were added to the mixture in a nitrogen flow, and the mixture was stirred at room temperature for overnight. Water was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The precipitated solid was collected by filtration, washed with water, and then washed with hexane/ethyl acetate (4:1). The obtained solid was dried at 50°C under reduced pressure so as to obtain tert-butyl 7-(7-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (47 g) as a solid.

[0107]

Preparation Example 21

A mixture of tert-butyl 7-(7-bromo-2,6-dichloro-8-fluoroquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (5.0 g), 1-methylpiperidin-4-ol (2.8 mL), DMF (50 mL), and cesium carbonate (11 g), and DABCO (160 mg) was stirred at room temperature for 3 days. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-6-chloro-8-fluoro-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (4.9 g) as a solid.

[0108]

Preparation Example 22

Sodium ethoxide (830 mg) was added to a mixture of tert-butyl 7-{7-bromo-6-chloro-8-fluoro-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (4.9 g) and THF (100 mL), and the mixture was stirred at room temperature for 1 day. Sodium ethoxide (830 mg) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 day. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-6-chloro-8-ethoxy-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.8 g) as a solid.

[0109]

Preparation Example 23

A mixture of tert-butyl 7-{7-bromo-6-chloro-8-ethoxy-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.8 g), (5-methyl-1H-indazol-4-yl)boronic acid (1.6 g), $Pd_2(dba)_3$ (1.1 g), SPhos (1.0 g), 1,4-dioxane (60 mL), tripotassium phosphate (6.5 g), and water (15 mL) was stirred at 115°C for 3 hours under the argon atmosphere. The reaction mixture was cooled to room temperature, then water was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol). The obtained purified product was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). The obtained purified product was purified by silica gel column chromatography (chloroform/methanol) so as to obtain tert-butyl 7-{6-chloro-8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.0 g) as a solid.

[0110]

Preparation Example 24

A mixture of tert-butyl 7-{6-chloro-8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.0 g), 1,4-dioxane (12 mL), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.3 mL), $Pd_2(dba)_3$ (140 mg), SPhos (180 mg), tripotassium phosphate (1.6 g), and water (3.0 mL) was stirred at 150°C for 1.5 hours under microwave irradiation. 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.25 mL), $Pd_2(dba)_3$ (140 mg), and SPhos (180 mg) were added to the reaction mixture, and the mixture was stirred at 150°C for 30 minutes under microwave irradiation, and further stirred at the same temperature for 30 minutes. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol). The obtained purified product was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (360 mg).

[0111]

Preparation Example 24-2

A mixture of tert-butyl 7-{7-bromo-8-ethoxy-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (5.7 g), (5-methyl-1H-indazol-4-yl)boronic acid (2.4 g), $Pd_2(dba)_3$ (850 mg), SPhos (760 mg), 1,4-dioxane (60

mL), tripotassium phosphate (10 g), and water (12 mL) was stirred at 120°C for 4 hours under the argon atmosphere. After the reaction mixture was cooled to room temperature, ethyl acetate and a saturated aqueous sodium chloride solution were added to the reaction mixture, and an insoluble material was separated by filtration. The filtrate was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Acetonitrile was added to the obtained purified product, and then the mixture was stirred at room temperature for 6 hours. The precipitated solid was collected by filtration so as to obtain tert-butyl 7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.2 g) as a solid.

[0112]

Preparation Example 28

A trifluoroacetic acid (hereinafter, abbreviated as TFA) (5.0 mL) was added to a mixture of tert-butyl 7-{8-(cyclobutyloxy)-6-cyclopropyl-2-[(1-methylpiperidin-4-yl)oxy]-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (540 mg) and dichloromethane (10 mL), and the mixture was stirred at room temperature for 4 hours. Toluene was added to the reaction mixture, and the mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water) so as to obtain 8-(cyclobutyloxy)-6-cyclopropyl-4-(2,7-diazaspiro[3.5]non-7-yl)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazoline (310 mg) as a solid.

[0113]

Preparation Example 33

TFA (1.0 mL) was added to a mixture of tert-butyl 7-{8-ethoxy-2-[(1-ethylpiperidine-4-yl)oxy]-7-(5-methyl-1H-indazol-4-yl)-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (560 mg) and dichloromethane (1.0 mL), and the mixture was stirred at room temperature for 1 hour. After concentrating the reaction mixture under reduced pressure, the obtained residue was purified by silica gel column chromatography (octadecylsilyl (hereinafter, abbreviated as ODS) silica gel, water/acetonitrile/TFA). A saturated aqueous sodium hydrogen carbonate solution and water were added to the obtained purified product, a mixture was extracted with chloroform/methanol (4:1), and an organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure so as to obtain 4-(2,7-diazaspiro[3.5]non-7-yl)-8-ethoxy-2-[(1-ethylpiperidin-4-yl)oxy]-7-(5-methyl-1H-indazol-4-yl)-6-vinylquinazoline (370 mg).

[0114]

Preparation Example 34

After a mixture of 3-bromo-5-fluoro-2,4-dimethylaniline (1.1 g), 12M hydrochloric acid (6.0 mL), and water (4.0 mL) was cooled in ice bath, a mixture of sodium nitrite (380 mg) and water (4.0 mL) was added dropwise to the mixture, and the mixture was stirred at the same temperature for 30 minutes. 12M hydrochloric acid (2.0 mL) was added to the reaction mixture, and the mixture was stirred at the same temperature for 1 hour. Sodium tetrafluoroborate (720 mg) was added to the reaction mixture, and the mixture was stirred at the same temperature for 1 hour. The precipitated solid was collected by filtration, washed with cold water, and then air-dried so as to obtain a solid (solid A). A mixture of potassium acetate (670 mg), 1,4,7,10,13,16-hexaoxacyclooctadecane (47 mg), and chloroform (44 mL) were added to a solid A, and the mixture was stirred at room temperature for 5 hours. After an insoluble material was separated by filtration, a filtrate was washed with a saturated aqueous sodium chloride solution, and dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain 4-bromo-6-fluoro-5-methyl-1H-indazole (240 mg) as a solid.

[0115]

Preparation Example 35

3,4-dihydro-2H-pyran (0.24 mL) and p-toluenesulfonic acid monohydrate (40 mg) were added to a mixture of 4-bromo-6-fluoro-5-methyl-1H-indazole (240 mg) and dichloromethane (10 mL), and the mixture was stirred at room temperature for 2 hours. After the reaction mixture was cooled in ice bath, a saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the reaction mixture was extracted with chloroform. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so obtain 4-bromo-6-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (350 mg) as an oil.

[0116]

Preparation Example 36

Potassium acetate (310 mg) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (68 mg) were added to a mixture of 4-bromo-6-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (330 mg), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (320 mg), and 1,4-dioxane (7.0 mL), and the mixture was stirred at 100°C for 3 hours under the argon atmosphere. The reaction mixture was cooled to room temperature, then ethyl acetate was added, and an insoluble material was separated by filtration. After concentrating the filtrate under reduced pressure, the obtained residue was purified by silica gel column chromatography

(hexane/ethyl acetate) so as to obtain 6-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (220 mg) as an oil.

[0117]

Preparation Example 39

A mixture of tert-butyl 7-{7-bromo-6-chloro-2-[(1-ethylpiperidin-4-yl)oxy]-8-fluoroquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.5 g), 2,2,2-trifluoroethanol (0.59 mL), cesium carbonate (2.7 g), and DMF (25 mL) was stirred at room temperature under the argon atmosphere for 3 days. Water was added to the reaction mixture, the mixture was stirred at room temperature for 10 minutes, and then the precipitated solid was collected by filtration. The obtained solid was dissolved in dichloromethane, dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-6-chloro-2-[(1-ethylpiperidin-4-yl)oxy]-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.4 g).

[0118]

Preparation Example 94

Potassium carbonate (5.5 g) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (1.1 g) were added to a mixture of tert-butyl 7-{7-bromo-8-ethoxy-6-iodo-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (9.5 g), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (4.5 mL), 1,4-dioxane (100 mL), and water (10 mL), and the mixture was stirred at 80°C for 1 hour under the argon atmosphere. After the reaction mixture was cooled to room temperature, ethyl acetate, a saturated aqueous sodium chloride solution, and celite were added to the reaction mixture, and the reaction mixture was stirred at room temperature for 10 minutes. An insoluble material was separated by filtration, then a filtrate was extracted with ethyl acetate, and an organic layer was dried with anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-8-ethoxy-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (6.8 g) as a solid.

[0119]

Preparation Example 95

A mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (8.1 g), 1-(2-methoxyethyl)piperidin-4-ol (5.3 g), cesium carbonate (13 g), DABCO (220 mg), DMF (65 mL), and THF (65 mL) was stirred at room temperature for 3 days under the argon atmosphere. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a

saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (7.9 g).

[0120]

Preparation Example 96

A mixture of tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.8 g), 2,2,2-trifluoroethanol (0.75 mL), cesium carbonate (3.4 g), and DMF (40 mL) was stirred at room temperature for 20 hours under the argon atmosphere. 2,2,2-trifluoroethanol (0.40 mL) and cesium carbonate (1.7 g) were added to the reaction mixture, and the mixture was stirred at room temperature for 24 hours under the argon atmosphere. Water was added to the reaction mixture, and the mixture was stirred at room temperature for 10 minutes. The precipitated solid was collected by filtration, then chloroform/methanol (9:1) was added thereto, and the obtained solution was dried with anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[7-bromo-6-iodo-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.1 g) as a solid.

[0121]

Preparation Example 99

Potassium carbonate (1.5 g) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (30 mg) were added to a mixture of tert-butyl 7-[7-bromo-6-iodo-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.0 g), potassium vinyltrifluoroborate (640 mg), 1,4-dioxane (30 mL), and water (3.0 mL), and the mixture was stirred at 50°C for 2 hours under a nitrogen atmosphere. $PdCl_2(dppf)\cdot CH_2Cl_2$ (150 mg) was added to the reaction mixture, and the mixture was stirred at 60°C for 4 hours under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, then ethyl acetate and water were added thereto. An insoluble material was separated by filtration, and a filtrate was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[7-bromo-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.2 g).

[0122]

Preparation Example 100

(5-methyl-1H-indazol-4-yl)boronic acid (490 mg), $Pd_2(dba)_3$ (130 mg), and SPhos (120 mg) were added to a mixture of tert-butyl 7-[7-bromo-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.0 g), tripotassium phosphate (900 mg), 1,4-dioxane (10 mL), and water (2.0 mL), and the mixture was stirred at 130°C for 4 hours under the argon atmosphere. The reaction mixture was cooled to room temperature, then ethyl acetate and water were added thereto. An insoluble material was separated by filtration, and a filtrate was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). The obtained purified product was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). Acetonitrile was added to the obtained solid, and then the mixture was stirred at room temperature. The precipitated solid was collected by filtration so as to obtain tert-butyl 7-[2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (630 mg) as a solid.

[0123]

Preparation Example 101

A mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (9.5 g), 1-(3-methoxypropyl)piperidin-4-ol (6.8 g), cesium carbonate (15 g), DABCO (260 mg), DMF (76 mL), and THF (76 mL) was stirred at room temperature for overnight under the argon atmosphere. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, diisopropyl ether was added to the obtained solid, and the mixture was stirred at room temperature. The solid was collected by filtration, and dried at 50°C under reduced pressure so as to obtain tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (9.1 g) as a solid.

[0124]

Preparation Example 102

A mixture of tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (5.0 g), 2,2,2-trifluoroethanol (1.4 mL), cesium carbonate (6.5 g), and DMF (50 mL) was stirred at room temperature for 5 hours. The reaction mixture was stirred at 50°C for 1.5 hours. The reaction mixture was cooled to room temperature, then water

was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[7-bromo-6-iodo-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (5.5 g).

[0125]

Preparation Example 105

A mixture of tert-butyl 7-[7-bromo-6-iodo-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.7 g), cyclopropylboronic acid (560 mg), tripotassium phosphate (2.5 g), $PdCl_2(dppf)\cdot CH_2Cl_2$ (270 mg), 1,4-dioxane (20 mL), acetonitrile (20 mL), and water (8.6 mL) was stirred at 100°C for 4 hours under the argon atmosphere. After the reaction mixture was cooled to room temperature, a saturated aqueous sodium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[7-bromo-6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.9 g).

[0126]

Preparation Example 106

Under the argon atmosphere, tert-butyl 7-[7-bromo-6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.9 g), (5-methyl-1H-indazol-4-yl)boronic acid (710 mg), $Pd_2(dba)_3$ (230 mg), SPhos (210 mg), tripotassium phosphate (2.2 g), 1,4-dioxane (15 mL), and water (2.8 mL) were mixed, and the mixture was stirred at 120°C for 70 minutes under microwave irradiation. After concentrating the reaction mixture under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). Acetonitrile was added to the obtained purified product, and then the mixture was stirred at room temperature for 30 minutes. The precipitated solid was collected by filtration so as to obtain tert-butyl 7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (630 mg) as a solid.

[0127]

Preparation Example 111

A mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (4.5 g), 1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ol (4.1 g), cesium carbonate (7.2 g), DABCO (120 mg), DMF (45 mL), and THF (45 mL) was stirred at room temperature for 16 hours. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate, and then chloroform/methanol/28% ammonia water). The obtained purified product was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (5.2 g) as a solid.

[0128]

Preparation Example 112

A mixture of tert-butyl 7-(7-bromo-8-fluoro-6-iodo-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}quinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (5.2 g), 2,2,2-trifluoroethanol (1.5 mL), cesium carbonate (6.7 g), and DMF (50 mL) was stirred at 50°C for overnight. The reaction mixture was cooled to room temperature, then water was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). Diisopropyl ether was added to the obtained solid, and the mixture was stirred at room temperature for 1 hour. The solid was collected by filtration so as to obtain tert-butyl 7-[7-bromo-6-iodo-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (4.1 g) as a solid.

[0129]

Preparation Example 113

Potassium carbonate (740 mg) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (15 mg) were added to a mixture of tert-butyl 7-[7-bromo-6-iodo-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.5 g), potassium vinyltrifluoroborate (290 mg), 1,4-dioxane (15 mL), and water (1.5 mL), and the mixture was stirred at 40°C for 18 hours under the argon atmosphere. After the reaction mixture was cooled to room temperature, ethyl acetate, water and a saturated aqueous sodium chloride solution were added to the reaction mixture. An insoluble material was separated by filtration, and a filtrate was extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution,

and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). Diisopropyl ether was added to the obtained solid, and the mixture was stirred at room temperature for 1 hour. The solid was collected by filtration so as to obtain tert-butyl 7-[7-bromo-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (940 mg) as a solid.

[0130]

Preparation Example 114

$Pd_2(dba)_3$ (120 mg), and SPhos (110 mg) were added to a mixture of tert-butyl 7-[7-bromo-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (940 mg), (5-methyl-1H-indazol-4-yl)boronic acid (330 mg), tripotassium phosphate (1.3 g), 1,4-dioxane (10 mL), and water (2.0 mL), and the mixture was stirred at 120°C for 4 hours under the argon atmosphere. After the reaction mixture was cooled to room temperature, ethyl acetate, water, and a saturated aqueous sodium chloride solution were added to the reaction mixture. An insoluble material was separated by filtration, and a filtrate was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). Acetonitrile was added to the obtained solid, and then the mixture was stirred at room temperature for 5 hours. The precipitated solid was collected by filtration so as to obtain tert-butyl 7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (610 mg) as a solid.

[0131]

Preparation Example 115

2-(trimethylsilyl)ethyl 4-hydroxypiperidine-1-carboxylate (1.0 g), cesium carbonate (2.7 g), and DABCO (31 mg) were added to a mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.7 g), DMF (5.0 mL), and THF (5.0 mL), and the mixture was stirred at room temperature for 16 hours under the argon atmosphere. 2,2,2-trifluoroethanol (0.60 mL) and cesium carbonate (1.8 g) were added to the reaction mixture, and the mixture was stirred at room temperature for 3 days. Water was added to the reaction mixture, and the mixture was stirred at room temperature for 2 hours. The precipitated solid was collected by filtration so as to obtain tert-butyl 7-{7-bromo-6-iodo-8-(2,2,2-trifluoroethoxy)-2-[(1-{[2-(trimethylsilyl)ethoxy]carbonyl}piperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.7 g) as a solid.

[0132]

Preparation Example 118

Tetrabutylammonium fluoride (1M THF solution, 3.6 mL) was added dropwise to a mixture of tert-butyl 7-{7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]-8-(2,2,2-trifluoroethoxy)-2-[(1-{[2-(trimethylsilyl)ethoxy]carbonyl}piperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.7 g) and THF (25 mL), and the mixture was stirred at 50°C for 5 hours. The reaction mixture was cooled to room temperature, and then was concentrated under reduced pressure. Ethyl acetate was added to the obtained residue, and the mixture was washed with water and a saturated aqueous sodium chloride solution. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure so as to obtain tert-butyl 7-{7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]-2-(piperidin-4-yloxy)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.3 g).

[0133]

Preparation Example 119

tert-butyl 7-{7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]-2-(piperidin-4-yloxy)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (500 mg), 2,2-dimethyloxirane (68 μL), triethylamine (0.18 mL), and ethanol (4.0 mL) were mixed, and the mixture was stirred at 80°C for 30 minutes under microwave irradiation. The reaction mixture was stirred at 100°C for 30 minutes under microwave irradiation. 2,2-dimethyloxirane (28 μL) was added to the reaction mixture, and the mixture was stirred at 100°C for 1 hour under microwave irradiation. The reaction mixture was stirred at 120°C for 1 hour under microwave irradiation. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol). The obtained purified product was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[2-{[1-(2-hydroxy-2-methylpropyl)piperidin-4-yl]oxy}-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (450 mg).

[0134]

Preparation Example 132

A mixture of 2,2,6,6-tetramethylpiperidine (4.3 mL) and THF (50 mL) was cooled to -70°C, then n-butyllithium (1.6M hexane solution, 16 mL) was added dropwise to the mixture under the argon atmosphere, and the mixture was stirred at the same temperature

for 10 minutes. A mixture of 1-bromo-4,5-difluoro-2-methylbenzene (5.0 g) and THF (25 mL) was added dropwise to the reaction mixture, and the mixture was stirred at the same temperature for 2 hours. After DMF (2.0 mL) was added to the reaction mixture, the temperature of the reaction mixture was raised to -20°C. 1M hydrochloric acid was added dropwise to the reaction mixture, and the reaction mixture was extracted with diethyl ether. An organic layer was washed with 1M hydrochloric acid and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. A solvent was evaporated under reduced pressure so as to obtain 2-bromo-5,6-difluoro-3-methylbenzaldehyde (5.2 g) as a solid.

[0135]

Preparation Example 133

O-methylhydroxylamine hydrochloride (2.2 g) was added to a mixture of 2-bromo-5,6-difluoro-3-methylbenzaldehyde (5.2 g), potassium carbonate (3.9 g), and 1,2-dimethoxyethane (25 mL), and the mixture was stirred at room temperature for 3 days. An insoluble material was separated by filtration and a filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate). Hydrazine monohydrate (20 mL) was added to a mixture of the obtained oil (4.2 g) and 1,2-dimethoxyethane (20 mL), and the mixture was stirred at 100°C for 20 hours. After the reaction mixture was cooled to room temperature, ethyl acetate was added to the reaction mixture, and the mixture was washed with a saturated aqueous sodium chloride solution. An organic layer was dried by anhydrous magnesium sulfate, and then a solvent was evaporated under reduced pressure so as to obtain 4-bromo-7-fluoro-5-methyl-1H-indazole (3.6 g) as a solid.

[0136]

Preparation Example 136

Potassium carbonate (3.0 g) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (580 mg) were added to a mixture of 5-bromo-4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (2.3 g), trivinylboroxine/pyridine (1:1) (1.4 g), 1,4-dioxane (22 mL), and water (4.5 mL), and the mixture was stirred at 70°C for 15 hours under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, then ethyl acetate and water were added, and an insoluble material was separated by filtration. After extracting the filtrate with ethyl acetate, an organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain 4-chloro-1-(tetrahydro-2H-pyran-2-yl)-5-vinyl-1H-indazole (1.6 g) as a solid.

[0137]

Preparation Example 137

Potassium acetate (720 mg), palladium acetate (26 mg), and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (120 mg) were added to a mixture of 4-chloro-1-(tetrahydro-2H-pyran-2-yl)-5-vinyl-1H-indazole (630 mg), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.0 g), and 1,4-dioxane (6.0 mL), and the mixture was stirred at 100°C for 15 hours under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, then ethyl acetate was added, and an insoluble material was separated by filtration. After concentrating the filtrate under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-vinyl-1H-indazole (390 mg) as an oil.

[0138]

Preparation Example 138

4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (720 mg), potassium acetate (700 mg), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (190 mg) were added to a mixture of 7-bromo-6-methyl-1H-indazole (500 mg) and 1,4-dioxane (8.0 mL), and the mixture was stirred at 100°C for 18 hours under the argon atmosphere. The reaction mixture was cooled to room temperature, then ethyl acetate and water were added, and an insoluble material was separated by filtration. After extracting the filtrate with ethyl acetate, an organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain 6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (350 mg) as a solid.

[0139]

Preparation Example 139

1-({[2-(trimethylsilyl)ethoxy]carbonyl}oxy)pyrrolidine-2,5-dione (4.0 g) was added to a mixture of methyl piperidin-4-ylacetate hydrochloride (3.0 g), triethylamine (5.4 mL), and DMF (15 mL), and the mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture and extracted with ethyl acetate/hexane (10:1). An organic layer was washed with 1M aqueous sodium hydroxide solution, 1M hydrochloric acid, and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure so as to obtain 2-(trimethylsilyl)ethyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (4.7 g) as an oil.

[0140]

Preparation Example 140

1M aqueous sodium hydroxide solution (31 mL) was added to 2-(trimethylsilyl)ethyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (4.7 g) and

methanol (23 mL), and the mixture was stirred at room temperature for 3 hours. After the reaction mixture was concentrated under reduced pressure, 1M hydrochloric acid (31 mL) was added to the reaction mixture, and then extracted with chloroform. An organic layer was dried by anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure so as to obtain (1-{[2-(trimethylsilyl)ethoxy]carbonyl}piperidin-4-yl)acetic acid (4.2 g) as a solid.

[0141]

Preparation Example 141

1,3-difluoropropan-2-yl p-toluenesulfonate (13 g) was added to a mixture of piperidin-4-ol (5.0 g), potassium iodide (1.6 g), potassium carbonate (13 g), and DMF (40 mL), and the mixture was stirred at 70°C for 16 hours. The reaction mixture was cooled to room temperature, and an insoluble material was separated by filtration. After concentrating the filtrate under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain 1-(1,3-difluoropropan-2-yl)piperidin-4-ol (5.0 g) as an oil.

[0142]

Preparation Example 142

A mixture of 2-amino-4-bromo-3-fluoro-5-iodobenzoic acid (1.0 g), 1H-benzotriazole-1-ol (450 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (640 mg), and DMF (5.0 mL) was stirred at room temperature for 30 minutes. 28% ammonia water (0.28 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 1.5 hours. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was stirred at room temperature. The precipitated solid was collected by filtration, and washed with water, and the obtained solid was dried at 50°C under reduced pressure so as to obtain 2-amino-4-bromo-3-fluoro-5-iodobenzamide (1.0 g) as a solid.

[0143]

Preparation Example 143

1,1'-carbonyldiimidazole (920 mg) was added to a mixture of 2-amino-4-bromo-3-fluoro-5-iodobenzamide (1.0 g), potassium carbonate (1.0 g), and DMF (5.0 mL), and the mixture was stirred at room temperature for 30 minutes. 1,1'-carbonyldiimidazole (1.4 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 30 minutes. Water and 1M hydrochloric acid were added to the reaction mixture, and the mixture was stirred at room temperature for 2 hours. The precipitated solid was collected by filtration, washed with water, and dried at 50°C under reduced pressure so as to obtain 7-bromo-8-fluoro-6-iodoquinazoline-2,4(1H,3H)-dione (1.0 g) as a solid.

[0144]

Preparation Example 144

2-bromoethyl cyclopropylmethyl ether (170 mg) was added to a mixture of tert-butyl 7-{7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]-2-(piperidin-4-yloxy)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (500 mg), DIPEA (0.33 mL), and DMF (5.0 mL), and the mixture was stirred at 70°C for 16 hours. The reaction mixture was cooled to room temperature, then water was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[2-({1-[2-(cyclopropylmethoxy)ethyl]piperidin-4-yl}oxy)-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (470 mg).

[0145]

Preparation Example 155

Sodium triacetoxyborohydride (180 mg) was added to a mixture of tert-butyl 7-[7-(5-methyl-1H-indazol-4-yl)-2-(piperidin-4-yloxy)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (310 mg), tetrahydro-2H-pyran-4-carbaldehyde (100 mg), acetic acid (0.12 mL), and dichloromethane (3.0 mL), and the mixture was stirred at room temperature for 18 hours. A saturated aqueous sodium hydrogen carbonate solution and water were added to the reaction mixture, and the mixture was extracted with chloroform. An organic layer was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water) so as to obtain tert-butyl 7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-ylmethyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (300 mg) as an oil.

[0146]

Preparation Example 175

A mixture of tert-butyl 7-{7-bromo-8-fluoro-6-iodo-2-[(1-methylpiperidin-4-yl)sulfanyl]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (180 mg), 2,2,2-trifluoroethanol (92 μL), cesium carbonate (420 mg), and DMF (5.0 mL) was stirred at room temperature for overnight. Water was added to the reaction mixture, and extracted with chloroform, and an organic layer was dried with anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). Potassium carbonate (60 mg) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mg) were added to a mixture of the obtained purified product (100 mg), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (50 μL), 1,4-dioxane (5.0 mL), and water (0.50 mL), and the mixture was stirred at 60°C for 2

hours. After the reaction mixture was cooled to room temperature, a saturated aqueous sodium chloride solution was added to the reaction mixture, and the mixture was extracted with chloroform. An organic layer was dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-2-[(1-methylpiperidin-4-yl)sulfanyl]-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (73 mg).

[0147]

Preparation Example 181

Cesium carbonate (1.0 g) and sodium chloro(difluoro)acetate (490 mg) were added to a mixture of tert-butyl 7-{7-bromo-8-hydroxy-6-iodo-2-[(1-{[2-(trimethylsilyl)ethoxy]carbonyl}piperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.1 g), DMF (10 mL), and water (1.0 mL), and the mixture was stirred at 100°C for 2 hours. After the reaction mixture was cooled to room temperature, ethyl acetate was added to the reaction mixture, and the mixture was washed with water and a saturated aqueous sodium chloride solution. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-8-(difluoromethoxy)-6-iodo-2-[(1-{[2-(trimethylsilyl)ethoxy]carbonyl}piperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.0 g).

[0148]

Preparation Example 227

A mixture of tert-butyl 7-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (2.0 g), 1-methylpiperidine-4-amine (750 mg), DIPEA (1.7 mL), and 1-methylpyrrolidin-2-one (20 mL) was stirred at 100°C for overnight. The reaction mixture was cooled to room temperature, then water was added, and the mixture was extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution, and then dried by anhydrous sodium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-8-fluoro-6-iodo-2-[(1-methylpiperidin-4-yl)amino]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (730 mg).

[0149]

Preparation Example 235

A mixture of tert-butyl 7-[7-(5-methyl-1H-indazol-4-yl)-2-(piperidin-4-yloxy)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (300 mg), triethylamine (0.18 mL), and dichloromethane (6.0 mL) was cooled in ice bath,

and then dimethylcarbamoyl chloride (39 μL) was added dropwise to the mixture, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was purified by silica gel column chromatography (chloroform/methanol) so as to obtain tert-butyl 7-[2-{[1-(dimethylcarbamoyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (290 mg).

[0150]

Preparation Example 253

N-chlorosuccinimide (32 mg) was added to a mixture of tert-butyl 7-[2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (150 mg), 1M aqueous sodium hydroxide solution (1.6 mL), and ethanol (3.0 mL), and the mixture was stirred at room temperature for 30 minutes. N-chlorosuccinimide (16 mg) was added to the reaction mixture, and the mixture was stirred at room temperature for 15 minutes. A sodium sulfite aqueous solution was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution, and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate) so as to obtain tert-butyl 7-[7-(3-chloro-5-methyl-1H-indazol-4-yl)-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (130 mg) as a solid.

[0151]

Preparation Example 283

Thionyl chloride (2.0 mL) was added to a mixture of (1-{[2-(trimethylsilyl)ethoxy]carbonyl}piperidin-4-yl)acetic acid (1.9 g) and toluene (20 mL), and the mixture was stirred at 60°C for 1 hour. The reaction mixture was cooled to room temperature, and then was concentrated under reduced pressure. The obtained residue was azeotroped with toluene. 2-amino-4-bromo-3-fluoro-5-iodobenzamide (2.0 g) and pyridine (2.0 mL) were added to a mixture of the obtained residue and dichloromethane (20 mL), and then the mixture was stirred at room temperature for overnight. After concentrating the reaction mixture under reduced pressure, 1,4-dioxane (30 mL) and 1M aqueous sodium hydroxide solution (30 mL) were added to the obtained residue, and the mixture was stirred at room temperature for 2 hours. 1 M hydrochloric acid (30 mL) was added to the reaction mixture, and then the precipitated solid was collected by filtration. The obtained solid was purified by silica gel column chromatography (chloroform/methanol) so as to obtain 2-(trimethylsilyl)ethyl 4-[(7-bromo-8-fluoro-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methyl]piperidine-1-carboxylate (3.5 g) as a solid.

[0152]

Preparation Example 284

(1H-benzotriazol-1-yloxy)[tri(pyrrolidin-1-yl)]phosphonium hexafluorophosphate (4.4 g) was added to a mixture of 2-(trimethylsilyl)ethyl 4-[(7-bromo-8-fluoro-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methyl]piperidine-1-carboxylate (3.5 g), tert-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (1.9 g), 1,8-diazabicyclo[5.4.0]-7-undecene (1.7 mL), and acetonitrile (50 mL), and the mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with 1M hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution, and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) so as to obtain tert-butyl 7-{7-bromo-8-fluoro-6-iodo-2-[(1-{[2-(trimethylsilyl)ethoxy]carbonyl}piperidin-4-yl)methyl]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (3.7 g).

[0153]

The compounds indicated in Tables 6 to 118 below were prepared in the same manner as the preparation methods in the Preparation Examples described above. The preparing method, structure, and physicochemical data of the compounds in the respective Preparation Examples are indicated in Tables 6 to 118

[0154]

Example 1

A mixture of tert-butyl 7-{8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (290 mg), and dichloromethane (6.0 mL) was cooled in ice bath, then TFA (3.0 mL) was added to the mixture, and the mixture was stirred at room temperature for 1 hour. After concentrating the reaction mixture under reduced pressure, the reaction mixture was azeotroped with toluene, and then was azeotroped with THF. After a mixture of the obtained residue and THF (6.0 mL) was cooled in ice bath, a saturated aqueous sodium hydrogen carbonate solution (3.0 mL) and acryloyl chloride (35 μL) were added to the mixture, and the mixture was stirred at the same temperature for 30 minutes. A saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution were added to the reaction mixture, and was extracted with chloroform/isopropyl alcohol (hereinafter, abbreviated as IPA) (4:1). An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Acetonitrile was added to the obtained purified product, and then the mixture was stirred at room temperature. The precipitated

solid was collected by filtration so as to obtain 1-(7-{8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (77 mg).

[0155]

Example 2

A mixture of tert-butyl 7-{6-cyclopropyl-8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (180 mg) and dichloromethane (3.0 mL) was cooled in ice bath, then TFA (3.0 mL) was added to the mixture, and the mixture was stirred at the same temperature for 1 hour. After concentrating the reaction mixture under reduced pressure, the reaction mixture was azeotroped with toluene. After a mixture of the obtained residue and THF (5.0 mL) was cooled in ice bath, 1M sodium hydrogen carbonate solution (5.0 mL) and acryloyl chloride (24 μL) were added to the mixture, and the mixture was stirred at the same temperature for 3 hours. After concentrating the reaction mixture, the obtained residue was purified by silica gel column chromatography (ODS silica gel, water/acetonitrile). Hexane and ethyl acetate were added to the obtained purified product and sonicated. The precipitated solid was collected by filtration so as to obtain 1-(7-{6-cyclopropyl-8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (62 mg) as a solid.

[0156]

Example 3

TFA (5.0 mL) was added to a mixture of tert-butyl 7-{6-cyclopropyl-8-(2,2-difluoroethoxy)-2-[(1-methylpiperidin-4-yl)oxy]-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (530 mg), and dichloromethane (10 mL), and the mixture was stirred at room temperature for 4 hours. After concentrating the reaction mixture under reduced pressure, the reaction mixture was azeotroped with toluene. After a mixture of the obtained residue and THF (10 mL) was cooled in ice bath, a saturated aqueous sodium hydrogen carbonate solution (4.0 mL) and acryloyl chloride (55 μL) were added to the mixture, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was extracted with chloroform/IPA (4:1). An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ODS silica gel, water/methanol). The obtained purified product was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Hexane was added to the obtained purified product and sonicated. The precipitated solid was collected by filtration so as to obtain 1-(7-{6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-

methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (120 mg) as a solid.

[0157]

Example 4

TFA (2.5 mL) was added to a mixture of tert-butyl 7-[6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (470 mg), and dichloromethane (9.0 mL), and the mixture was stirred at room temperature for 1 hour. After concentrating the reaction mixture under reduced pressure, the reaction mixture was azeotroped with THF. After a mixture of the obtained residue and THF (9.0 mL) was cooled in ice bath, a saturated aqueous sodium hydrogen carbonate solution (4.0 mL) and THF (2.0 mL) solution of acryloyl chloride (63 μL) were added to the mixture, and the mixture was stirred at the same temperature for 1 hour. Water was added to the reaction mixture, and the reaction mixture was extracted with chloroform/IPA (4:1). An organic layer was dried by anhydrous sodium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ODS silica gel, water/acetonitrile) so as to obtain 1-{7-[6-cyclopropyl-8-(2,2-difluoroethoxy)-7-(5-methyl-1H-indazol-4-yl)-2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (88 mg) as a solid.

[0158]

Example 5

TFA (1.0 mL) was added to a mixture of tert-butyl 7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (360 mg), and dichloromethane (6.0 mL), and the mixture was stirred at room temperature for 1 hour. After concentrating the reaction mixture under reduced pressure, the reaction mixture was azeotroped with chloroform. After THF (3.0 mL), water (3.0 mL), and sodium hydrogen carbonate (740 mg) were added to the obtained residue, and cooled in ice bath, THF (1.0 mL) solution of acryloyl chloride (54 μL) was added to the mixture. The reaction mixture was stirred at room temperature for 1 hour. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was stirred for 10 minutes. Water was added to the reaction mixture and extracted with chloroform. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol). Hexane was added to the obtained purified product and sonicated. The precipitated solid was collected by filtration so as to obtain 1-(7-{8-

ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (85 mg) as a solid.

[0159]

Example 5-2

A mixture of tert-butyl 7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (1.3 g), and 1M hydrochloric acid (13 mL) was stirred at room temperature for 18 hours. After the reaction mixture was cooled in ice bath, dichloromethane (6.5 mL), 3-chloropropanoyl chloride (0.41 mL), sodium hydrogen carbonate (1.6 g) were added to the reaction mixture, and the mixture was stirred at the same temperature for 30 minutes. IPA (13 mL) and 4M aqueous sodium hydroxide solution (4.9 mL) were added to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 4 hours. After the reaction mixture was cooled in ice bath, 1M hydrochloric acid (6.4 mL), 5% aqueous sodium hydrogen carbonate solution (26 mL), and chloroform (39 mL) were added to the reaction mixture, and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was filtered through celite and the filtrate was extracted with chloroform. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Acetonitrile was added to the obtained purified product, and then the precipitated solid was collected by filtration. The obtained solid was dried at 50°C under reduced pressure so as to obtain 1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (980 mg) as a solid.

[0160]

Example 6

After a mixture of DIPEA (0.22 mL) and THF (3.0 mL) was cooled in ice bath, acryloyl chloride (0.10 mL) was added to the mixture. THF (6.0 mL) solution of 8-(cyclobutyloxy)-6-cyclopropyl-4-(2,7-diazaspiro[3.5]non-7-yl)-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazoline (310 mg) was added dropwise to the mixture, and the mixture was stirred at the same temperature for 30 minutes. 1M aqueous sodium hydroxide solution (3.0 mL) was added dropwise to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 1 hour. Water and a saturated aqueous sodium chloride solution were added to the reaction mixture, and the mixture was extracted with chloroform/IPA (4:1). An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (ODS silica gel, water/methanol). Hexane and ethyl acetate were added to the obtained purified product and triturated. The

precipitated solid was collected by filtration so as to obtain 1-(7-{8-(cyclobutyloxy)-6-cyclopropyl-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]quinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (120 mg) as a solid.

[0161]

Example 7

A mixture of 4-(2,7-diazaspiro[3.5]non-7-yl)-8-ethoxy-2-[(1-ethylpiperidin-4-yl)oxy]-7-(5-methyl-1H-indazol-4-yl)-6-vinylquinazoline (150 mg), sodium hydrogen carbonate (320 mg), THF (1.5 mL), and water (1.5 mL) were cooled in ice bath, and a THF (0.50 mL) solution of acryloyl chloride (21 μL) was added to the mixture, and the mixture was stirred at the same temperature for 30 minutes. After concentrating the reaction mixture, the obtained residue was purified by silica gel column chromatography (ODS silica gel, water/acetonitrile). Acetonitrile was added to the obtained purified product, and a solvent was evaporated under reduced pressure. The precipitated solid was collected by filtration so as to obtain 1-(7-{8-ethoxy-2-[(1-ethylpiperidin-4-yl)oxy]-7-(5-methyl-1H-indazol-4-yl)-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (90 mg) as a solid.

[0162]

Example 24

1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (1.5 g) was fractionated by supercritical fluid chromatography (chiral column, carbon dioxide/ethanol/triethylamine). Hexane and ethyl acetate were added to the obtained fractionated product and triturated. The precipitated solid was collected by filtration so as to obtain (+)-1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (670 mg) as a solid.

A solid (3.0 g) obtained by performing the above-described method a plurality of times was purified by silica gel column chromatography (ODS silica gel, water/methanol). Acetonitrile was added to the obtained purified product, and then the mixture was stirred at room temperature. The precipitated solid was collected by filtration, and the obtained solid was dried at 40°C under reduced pressure so as to obtain (+)-1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one (2.0 g) as a crystal.

[0163]

Example 25

A mixture of tert-butyl 7-[6-cyclopropyl-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (800 mg) and dichloromethane (4.0 mL) was cooled

in ice bath, TFA (1.2 mL) was added to the mixture, and the mixture was stirred at room temperature for 6 hours. Chloroform/IPA (4:1) and 2M potassium carbonate aqueous solution (11 mL) were added to the reaction mixture. A water layer was extracted with chloroform/IPA (4:1), and an organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure (residue A). After a mixture of DIPEA (0.45 mL) and THF (16 mL) was cooled in an ice-methanol bath, acryloyl chloride (0.20 mL) was added to the mixture. To this mixture, a THF (12 mL) solution of residue A was added dropwise, and the mixture was stirred at the same temperature for 20 minutes. 1M aqueous sodium hydroxide solution (5.0 mL) was added dropwise to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 4 hours. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Acetonitrile was added to the obtained purified product and sonicated. The precipitated solid was collected by filtration so as to obtain 1-{7-[6-cyclopropyl-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (410 mg) as a solid.

[0164]

Example 26

A mixture of tert-butyl 7-[2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (470 mg), and 1M hydrochloric acid (4.1 mL) was stirred at 50°C for 1 hour. After the reaction mixture was cooled in ice bath, dichloromethane (2.3 mL), 3-chloropropanoyl chloride (0.13 mL), sodium hydrogen carbonate (520 mg) were added to the reaction mixture, and the mixture was stirred at the same temperature for 1 hour. IPA (4.7 mL) and 4M aqueous sodium hydroxide solution (2.3 mL) were added to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Acetonitrile was added to the obtained purified product, and then the mixture was stirred at room temperature for 5 minutes. The precipitated solid was collected by filtration, and dried at 30°C under reduced pressure so as to obtain 1-{7-[2-{[1-(2-

methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (320 mg) as a solid.

[0165]

Example 28

A mixture of tert-butyl 7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (630 mg) and 1M hydrochloric acid (5.5 mL) was stirred at 50°C for 1 hour under the argon atmosphere. After the reaction mixture was cooled in ice bath, dichloromethane (3.2 mL), 3-chloropropanoyl chloride (0.17 mL), sodium hydrogen carbonate (670 mg) were added to the reaction mixture, and the mixture was stirred at the same temperature for 30 minutes. IPA (9.3 mL) and 4M aqueous sodium hydroxide solution (3.0 mL) were added to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 3 hours. After the reaction mixture was cooled in ice bath, then 1M hydrochloric acid (10 mL), a saturated aqueous sodium hydrogen carbonate solution, and ethyl acetate were added to the reaction mixture, and the reaction mixture was stirred at room temperature for 5 minutes. The reaction mixture was extracted with ethyl acetate, and then an organic layer was washed with a saturated aqueous sodium chloride solution. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol). Acetonitrile was added to the obtained purified product, and then the mixture was stirred at room temperature for 1 hour. The precipitated solid was collected by filtration so as to obtain 1-{7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (230 mg) as a solid.

[0166]

Example 30

A mixture of tert-butyl 7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (610 mg), and 1M hydrochloric acid (5.2 mL) was stirred at 50°C for 30 minutes. After the reaction mixture was cooled in ice bath, dichloromethane (3.0 mL), 3-chloropropanoyl chloride (0.17 mL), sodium hydrogen carbonate (650 mg) were added to the reaction mixture, and the mixture was stirred at the same temperature for 1 hour. IPA (6.0 mL) and 4M aqueous sodium hydroxide solution (3.0 mL) were added to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 4 hours. After the reaction mixture was cooled in ice bath, then 1M hydrochloric acid (7.0 mL), a saturated aqueous sodium hydrogen carbonate

solution, and ethyl acetate were added to the reaction mixture, and the reaction mixture was stirred at room temperature for 5 minutes. The reaction mixture was extracted with ethyl acetate, and an organic layer was dried with anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Acetonitrile was added to the obtained purified product, and the precipitated solid was collected by filtration so as to obtain 1-{7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (420 mg) as a solid.

[0167]

Example 31

A mixture of 1-(4-{[4-(2,7-diazaspiro[3.5]non-7-yl)-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-2-yl]oxy}piperidin-1-yl)-2-methylpropan-2-ol (290 mg), 1M hydrochloric acid (3.0 mL), and dichloromethane (1.5 mL) was cooled in ice bath, and then 3-chloropropanoyl chloride (90 μL) was added thereto. Sodium hydrogen carbonate (430 mg) was added to the reaction mixture, and the mixture was stirred at the same temperature for 15 minutes. IPA (3.0 mL) and 4M aqueous sodium hydroxide solution (1.6 mL) were added to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Hexane and ethyl acetate were added to the obtained purified product and triturated. The precipitated solid was collected by filtration so as to obtain 1-{7-[2-{[1-(2-hydroxy-2-methylpropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (110 mg) as a solid.

[0168]

Example 36

1-{7-[2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (2.0 g) was fractionated by supercritical fluid chromatography (chiral column, carbon dioxide/methanol/triethylamine, carbon dioxide/ethanol/triethylamine). The obtained fractionated material was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water) so as to obtain (+)-1-{7-[2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (810 mg).

[0169]

Example 38

1-{7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (2.2 g) was fractionated by supercritical fluid chromatography (chiral column, carbon dioxide/ethanol/triethylamine). The obtained fractionated material was purified by silica gel column chromatography (chloroform/methanol) so as to obtain (+)-1-{7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (1.1 g).

[0170]

Example 39

1-{7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (2.0 g) was fractionated by high performance liquid chromatography (chiral column, hexane/ethanol/triethylamine). The obtained fractionated material was purified by silica gel column chromatography (chloroform/methanol) so as to obtain (+)-1-{7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (930 mg).

[0171]

Example 41

A mixture of tert-butyl 7-[2-({1-[2-(cyclopropylmethoxy)ethyl]piperidin-4-yl}oxy)-7-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (470 mg), 1M hydrochloric acid (4.0 mL), and THF (2.0 mL) was stirred at room temperature for 6 days. After the reaction mixture was cooled in ice bath, dichloromethane (3.0 mL), 3-chloropropanoyl chloride (0.12 mL), sodium hydrogen carbonate (450 mg) were added to the reaction mixture, and the mixture was stirred at the same temperature for 30 minutes. IPA (5.0 mL) and 4M aqueous sodium hydroxide solution (2.0 mL) were added to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture and extracted with ethyl acetate. An organic layer was washed with a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water). Acetonitrile was added to the obtained purified product, and then the precipitated solid was collected by filtration. The obtained solid was dried at 50°C under reduced pressure so as to obtain 1-{7-[2-({1-[2-(cyclopropylmethoxy)ethyl]piperidin-4-yl}oxy)-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-

trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (82 mg) as a solid.

[0172]

Example 51

Tripotassium phosphate (120 mg), $Pd_2(dba)_3$ (30 mg), and SPhos (30 mg) were added to a mixture of tert-butyl 7-{7-bromo-2-[(1-methylpiperidin-4-yl)sulfanyl]-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]nonane-2-carboxylate (73 mg), (5-methyl-1H-indazol-4-yl)boronic acid (28 mg), 1,4-dioxane (5.0 mL), water (1.0 mL), and the mixture was stirred at 120°C for 4 hours. The reaction mixture was cooled to room temperature, and an insoluble material was separated by filtration. After concentrating the filtrate under reduced pressure, the obtained residue was purified by silica gel column chromatography (amino silica gel, hexane/ethyl acetate). A mixture of the obtained purified product (40 mg) and 1M hydrochloric acid (2.0 mL) was stirred at 60°C for 1 hour. After the reaction mixture was cooled in ice bath, dichloromethane (0.80 mL), 3-chloropropanoyl chloride (12 μL), sodium hydrogen carbonate (180 mg) were added to the reaction mixture, and the mixture was stirred at the same temperature for 30 minutes. IPA (2.4 mL) and 4M aqueous sodium hydroxide solution (0.80 mL) were added to the reaction mixture at the same temperature, and the mixture was stirred at room temperature for 4 hours. After the reaction mixture was cooled in ice bath, then 1M hydrochloric acid (1.7 mL) and saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture, and the reaction mixture was extracted with ethyl acetate. An organic layer was dried by anhydrous magnesium sulfate, and then a solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol/28% ammonia water) so as to obtain 1-{7-[7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)sulfanyl]-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one (10 mg).

[0173]

Example 82

A mixture of 6-cyclopropyl-4-(2,7-diazaspiro[3.5]non-7-yl)-8-(2,2-difluoroethoxy)-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)quinazoline (100 mg), (2E)-4,4,4-trifluorobut-2-enoic acid (33 mg), O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (89 mg), DIPEA (80 μL), and DMF (2.0 mL) was stirred at room temperature for overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. An organic layer was washed with water and a saturated aqueous sodium chloride solution, and then dried by anhydrous magnesium sulfate. After concentrating the solution under reduced pressure, the obtained

residue was purified by silica gel column chromatography (amino silica gel, chloroform/methanol) so as to obtain (2E)-1-{7-[6-cyclopropyl-8-(2,2-difluoroethoxy)-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}-4,4,4-trifluorobut-2-en-1-one (25 mg) as a solid.

[0174]

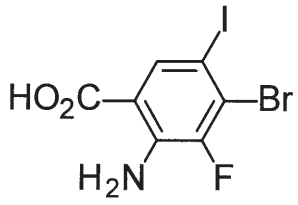
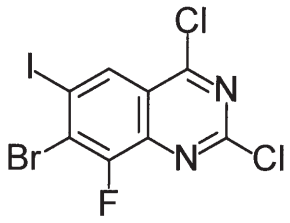
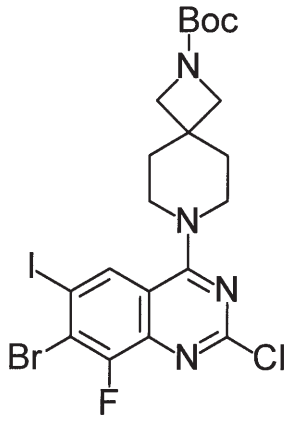
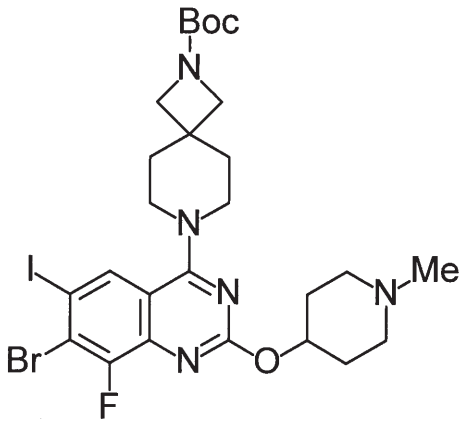
The compounds indicated in Tables 119 to 160 below were prepared in the same manner as the preparation methods of Examples described above. In addition, structures of compounds in the respective Examples are indicated in Tables 119 to 160 described below, and preparing methods and physicochemical data of compounds in the respective Examples are indicated in Tables 161 to 167.

[0175]

In Tables described below, the following abbreviations may be used.
PEx: the number of Preparation Examples, Ex: the number of Examples, PSyn: the number of Preparation Examples prepared using the similar method, Syn: the number of Examples prepared using the similar method (for example, E1 represents Example 1), Str: chemical structural formula (Me: methyl, Et: ethyl, Boc: tert-butoxycarbonyl, THP: tetrahydro-2H-pyran-2-yl, Cbz: benzyloxycarbonyl, and Teoc: 2-(trimethylsilyl)ethoxycarbonyl. Note that, a compound denoted by "*" in a chemical structural formula indicates that the compound is an isomer having a stereochemistry of the notation structure. In addition, a compound denoted by "#" represents a single optical isomer based on axial chirality.), Dat: physicochemical data, ESI+: m/z value in mass spectrometry (ionization method ESI, unless otherwise $[M+H]^+$), ESI-: m/z value in mass spectrometry (ionization method ESI, unless otherwise $[M-H]^-$), CI+: m/z value in mass spectrometry (ionization method CI, unless otherwise $[M+H]^+$), NMR: a δ value (ppm) of a signal in ^{1}H-NMR in DMSO-d6, s: singlet (spectrum), d: doublet (spectrum), t: triplet (spectrum), m: multiplet (spectrum), $[\alpha]_D^{20}$: specific rotation at 20°C, c: concentration at the measurement of specific rotation (g/100 mL).

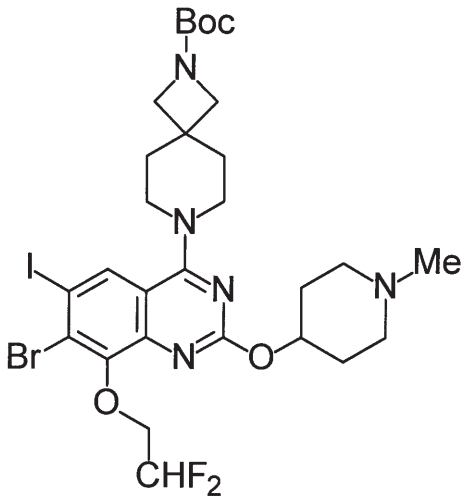
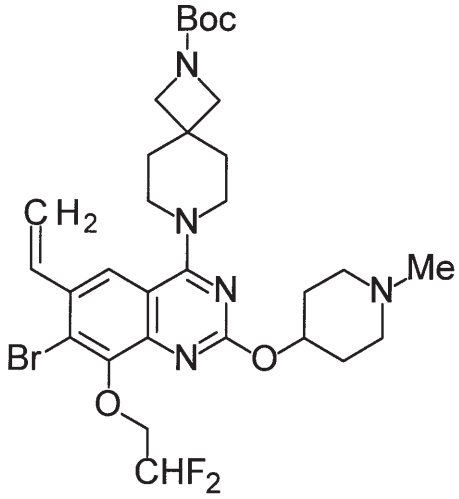
[0176]

[Table 6]

PEx	PSyn	Str	Dat
1	1		ESI-; 359.8
2	2		CI+; 422.9
3	3		ESI+; 611.2, 613.2
4	4		ESI+; 692.3

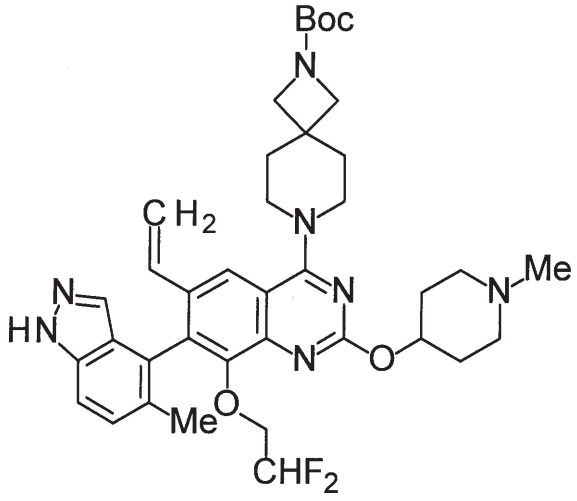
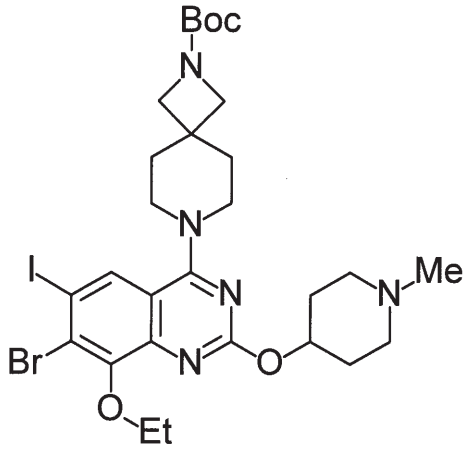
[0177]

[Table 7]

PEx	PSyn	Str	Dat
5	5		ESI+; 754.3
6	6		ESI+; 654.4

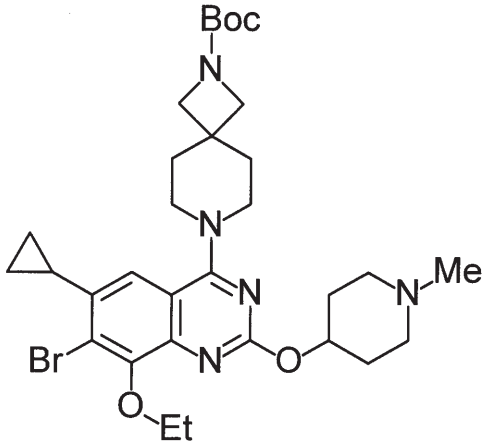
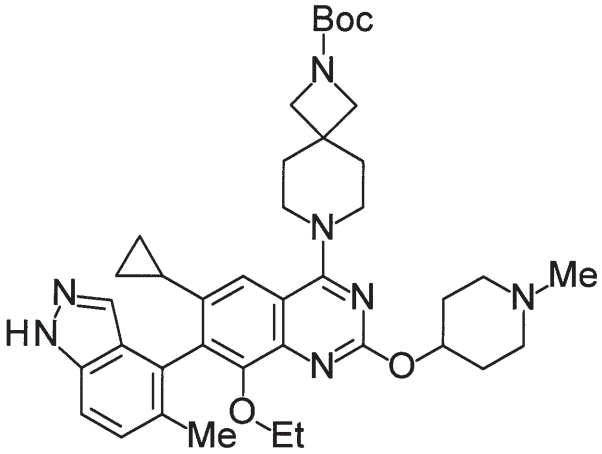
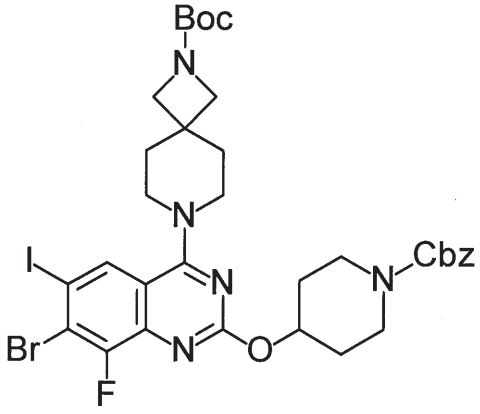
[0178]

[Table 8]

PEx	PSyn	Str	Dat
7	7		ESI+; 704.6
8	8		ESI+; 718.3

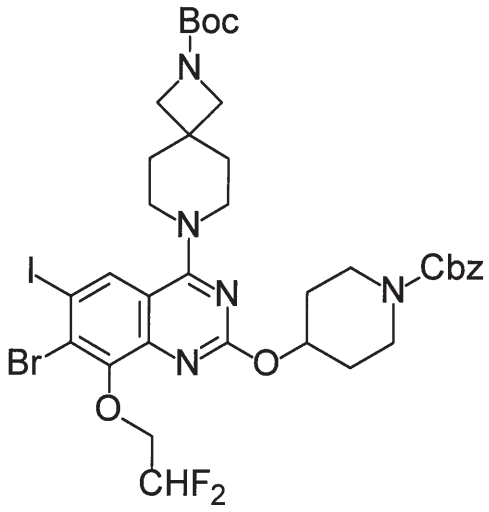
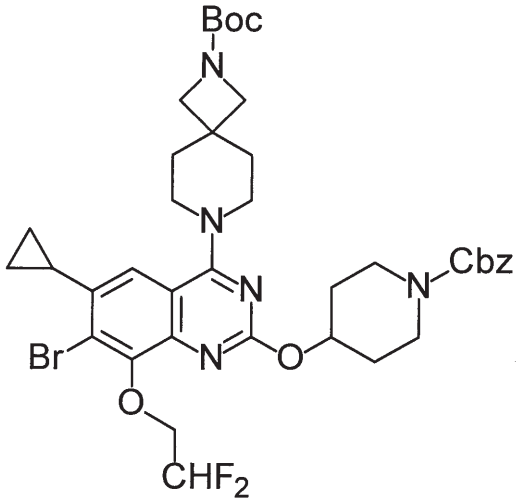
[0179]

[Table 9]

PEx	PSyn	Str	Dat
9	9		ESI+; 632.5
10	10		ESI+; 682.7
11	11		ESI+; 810.3

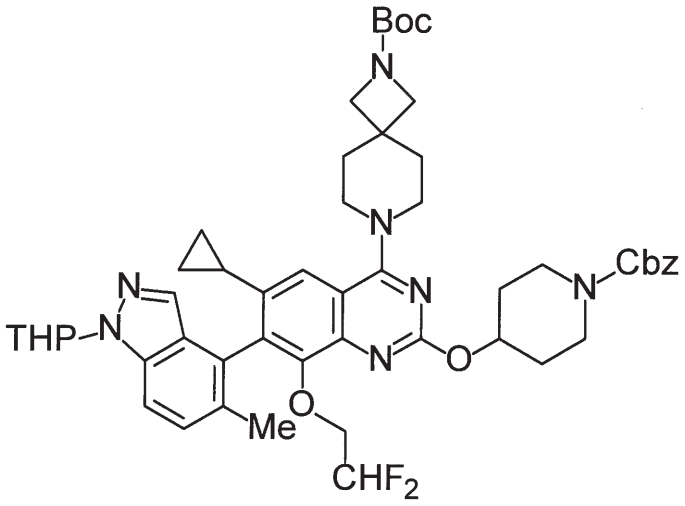
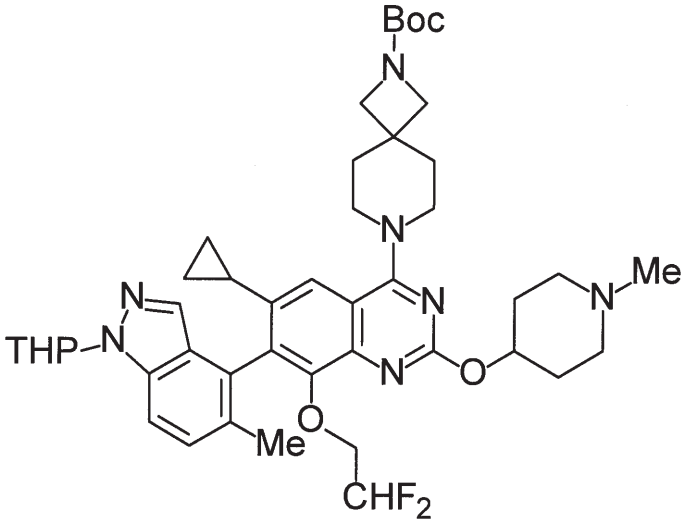
[0180]

[Table 10]

PEx	PSyn	Str	Dat
12	12		ESI+; 874.4
13	13		ESI+; 788.5

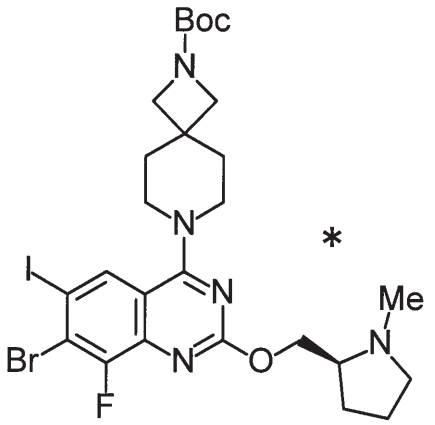
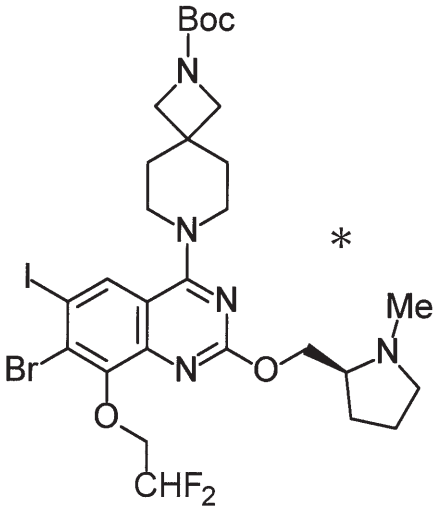
[0181]

[Table 11]

PEx	PSyn	Str	Dat
14	14		ESI+; 922.8
15	15		ESI+; 802.7

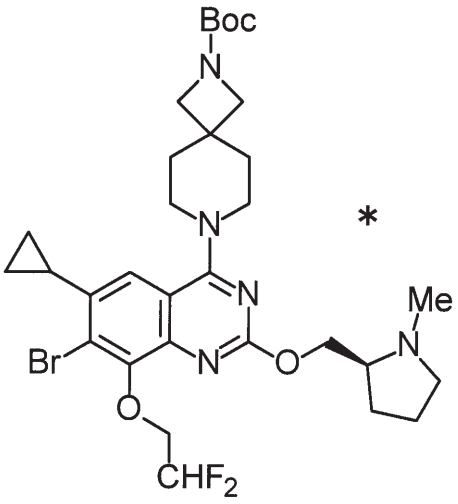
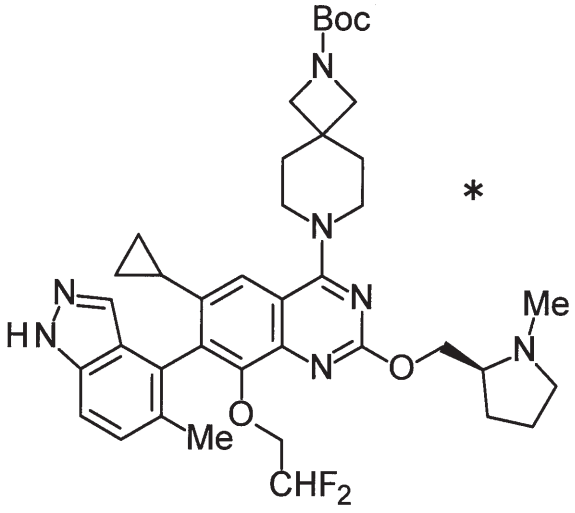
[0182]

[Table 12]

PEx	PSyn	Str	Dat
16	16		ESI+; 690.3
17	17		ESI+; 754.4

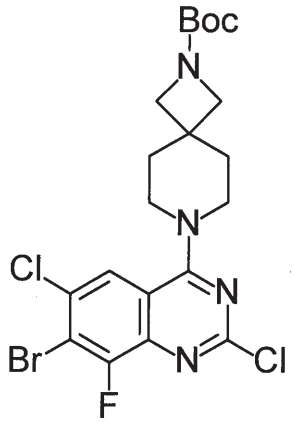
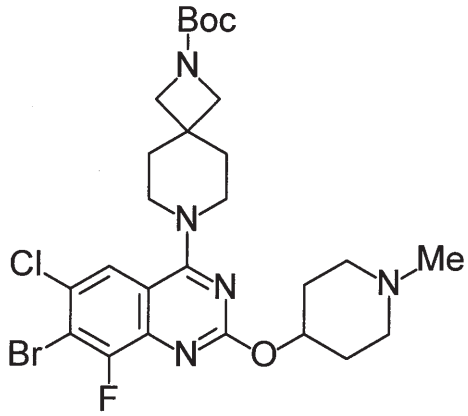
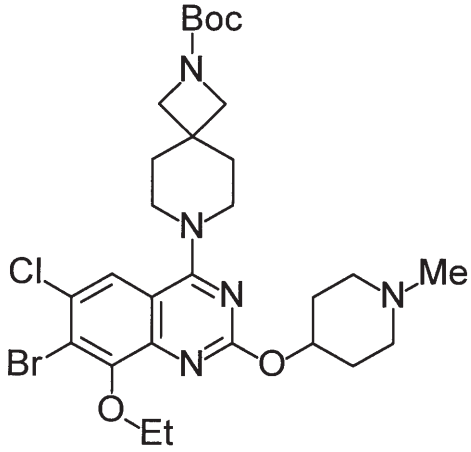
[0183]

[Table 13]

PEx	PSyn	Str	Dat
18	18		ESI+; 668.5
19	19		ESI+; 718.6

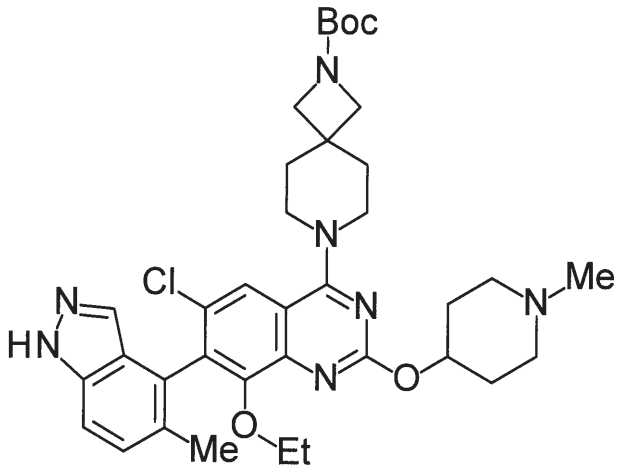
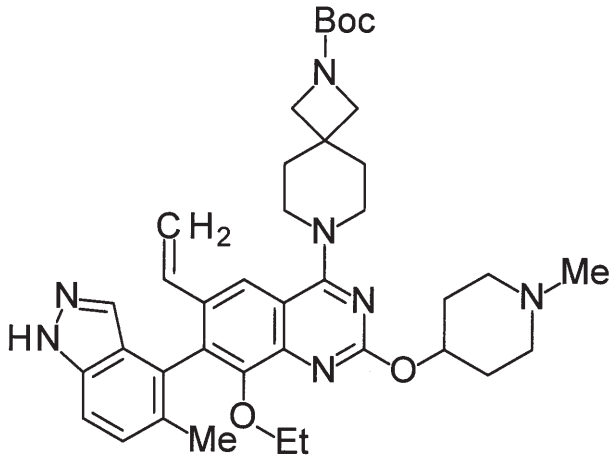
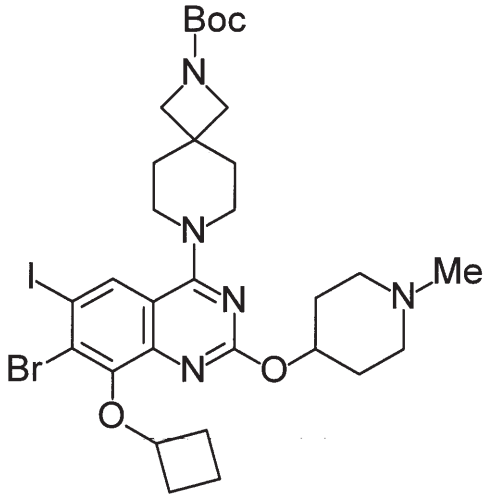
[0184]

[Table 14]

PEx	PSyn	Str	Dat
20	20		ESI+; 521.2
21	21		ESI+; 598.2, 600.2
22	22		ESI+; 624.1, 626.1

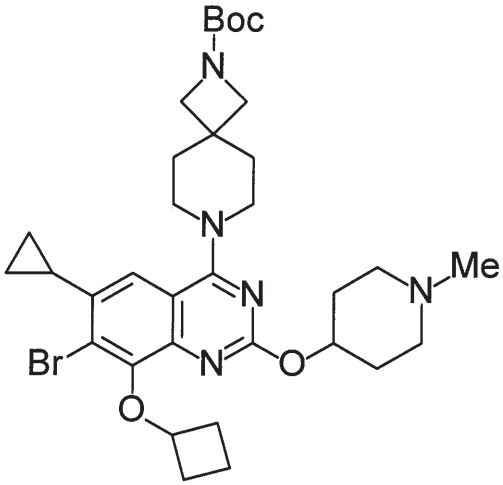
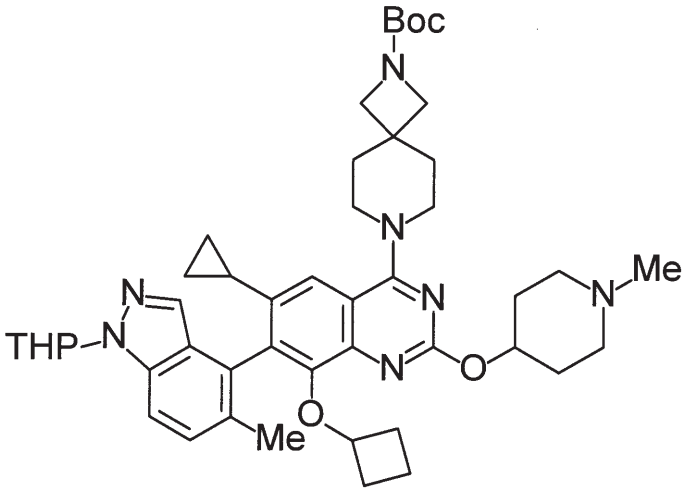
[0185]

[Table 15]

PEx	PSyn	Str	Dat
23	23		ESI+; 676.3
24	24 24-2		ESI+; 668.3
25	5		ESI+; 744.3

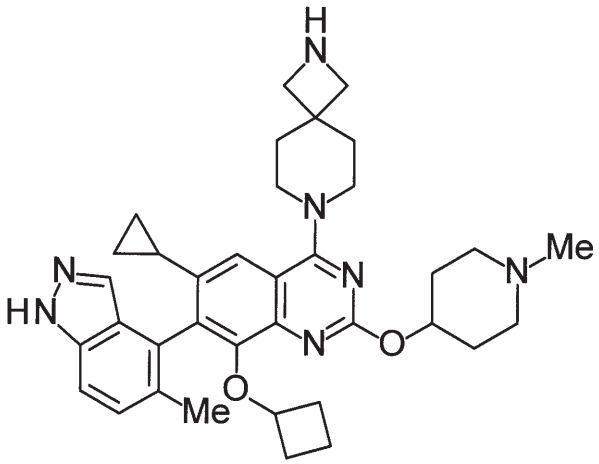
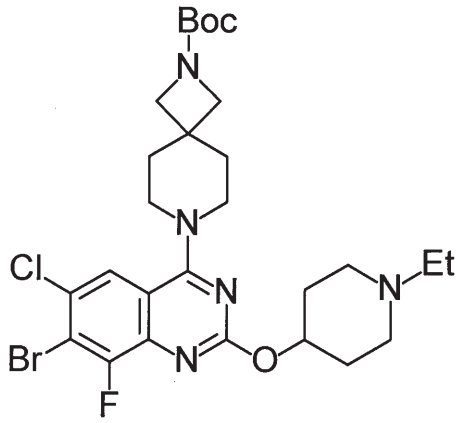
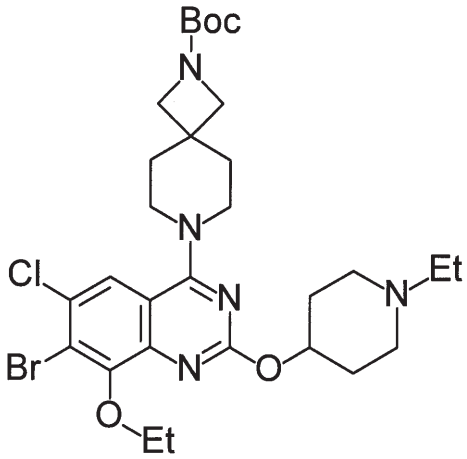
[0186]

[Table 16]

PEx	PSyn	Str	Dat
26	9		ESI+; 658.5
27	7		ESI+; 792.7

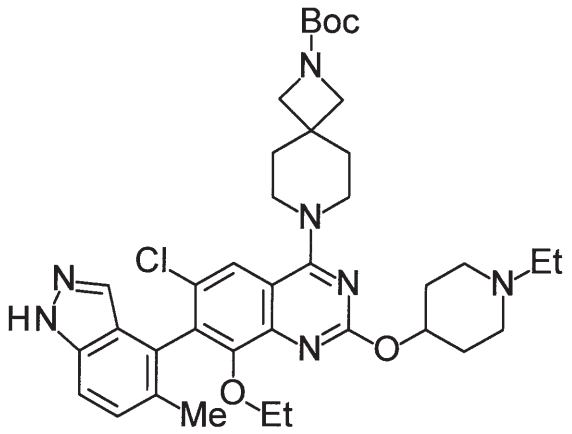
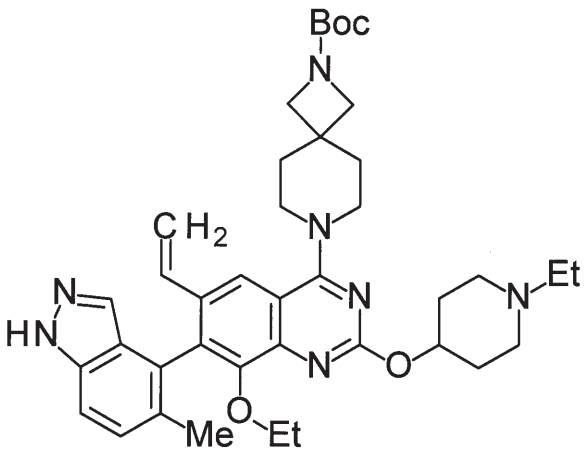
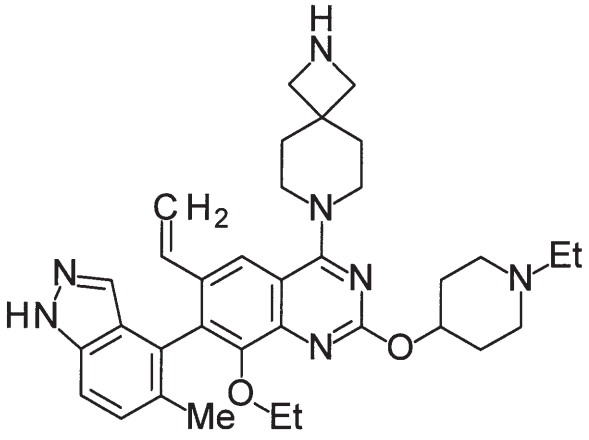
[0187]

[Table 17]

PEx	PSyn	Str	Dat
28	28		ESI+; 608.6
29	4		ESI+; 612.4, 614.4
30	8		ESI+; 638.4, 640.4

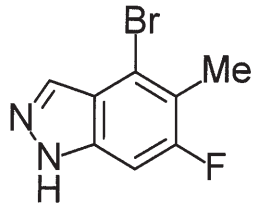
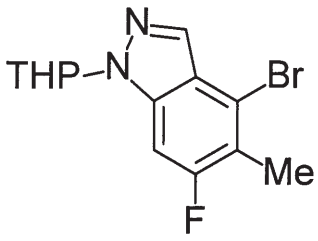
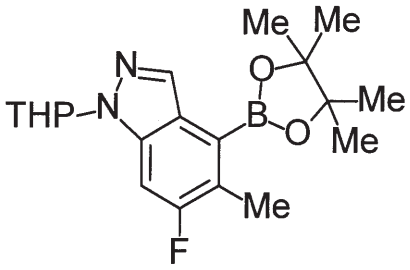
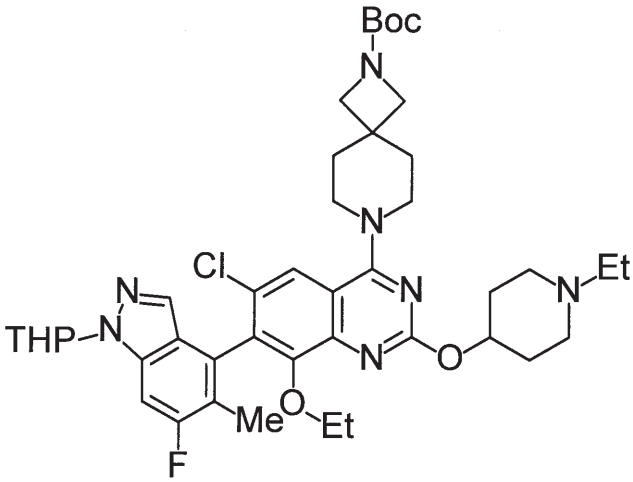
[0188]

[Table 18]

PEx	PSyn	Str	Dat
31	23		ESI+; 690.7
32	24		ESI+; 682.6
33	33		ESI+; 582.6

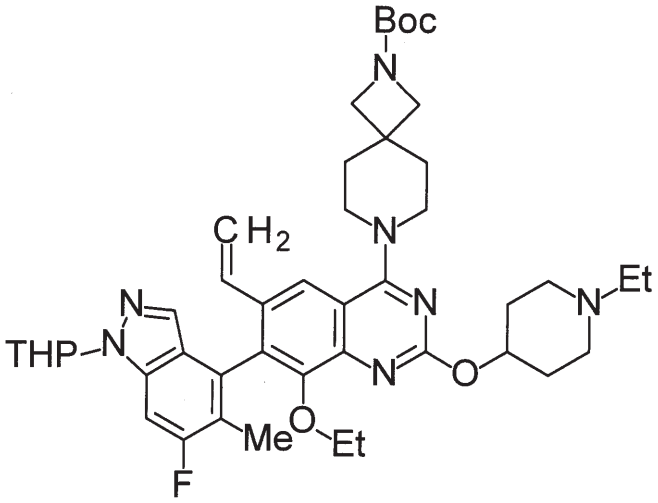
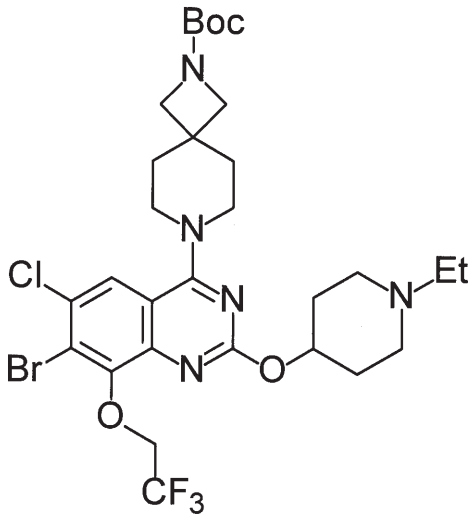
[0189]

[Table 19]

PEx	PSyn	Str	Dat
34	34		ESI+; 231.0
35	35		ESI+; 313.1
36	36		ESI+; 361.3
37	7		ESI+; 792.7

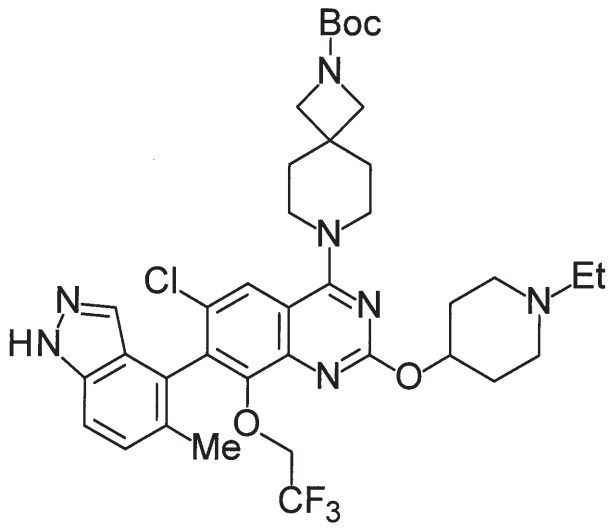
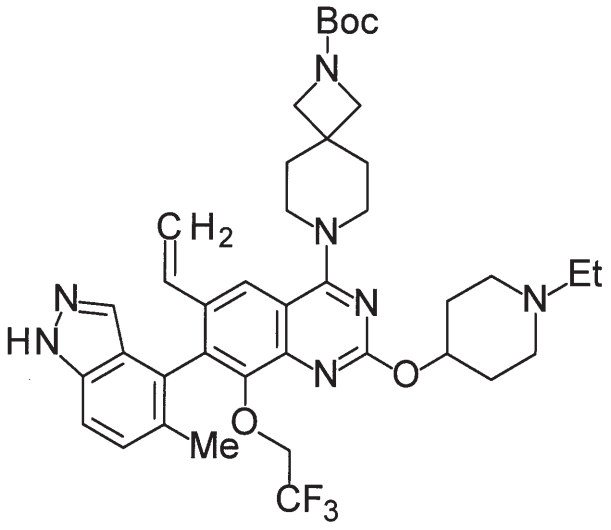
[0190]

[Table 20]

PEx	PSyn	Str	Dat
38	24		ESI+; 784.7
39	39		ESI+; 692.5, 694.4

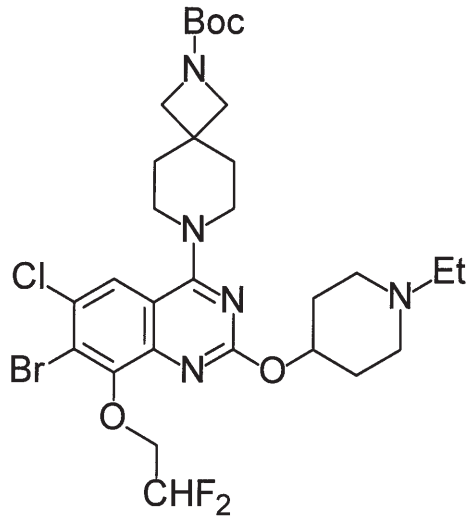
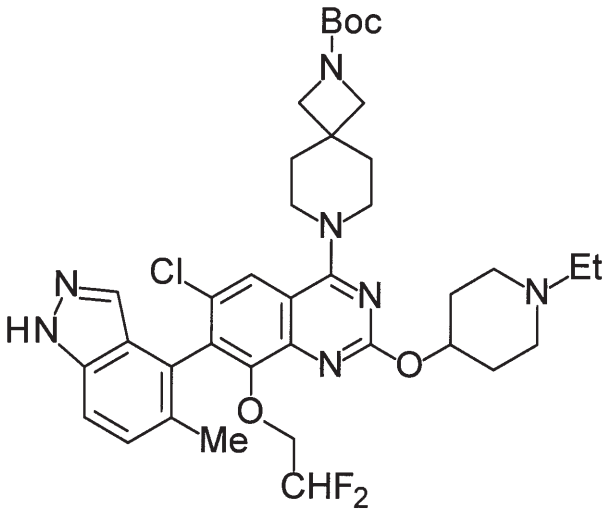
[0191]

[Table 21]

PEx	PSyn	Str	Dat
40	7		ESI+; 744.6, 746.5
41	24		ESI+; 736.6

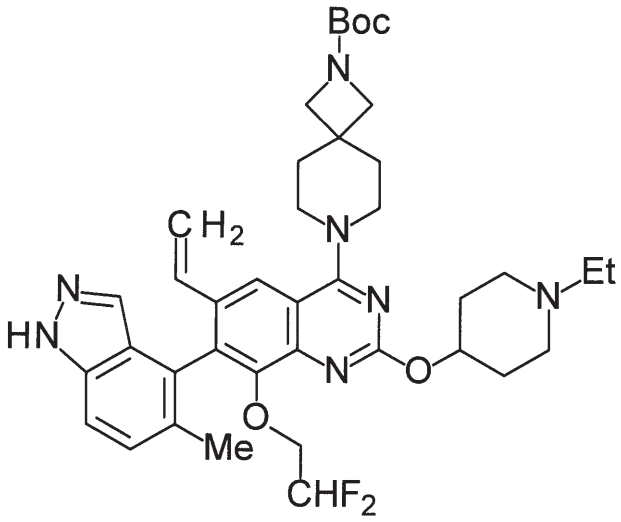
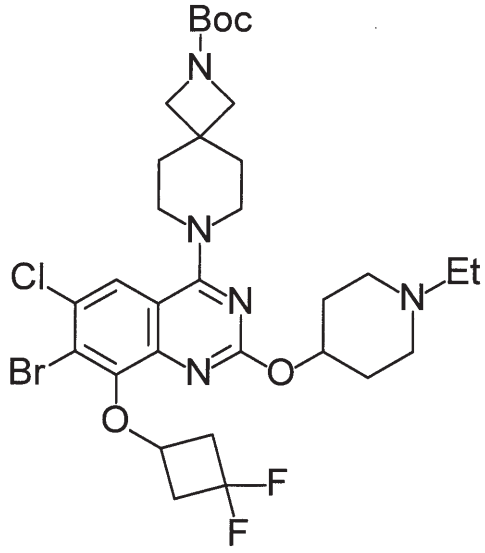
[0192]

[Table 22]

PEx	PSyn	Str	Dat
42	5		ESI+; 676.4
43	23		ESI+; 726.6

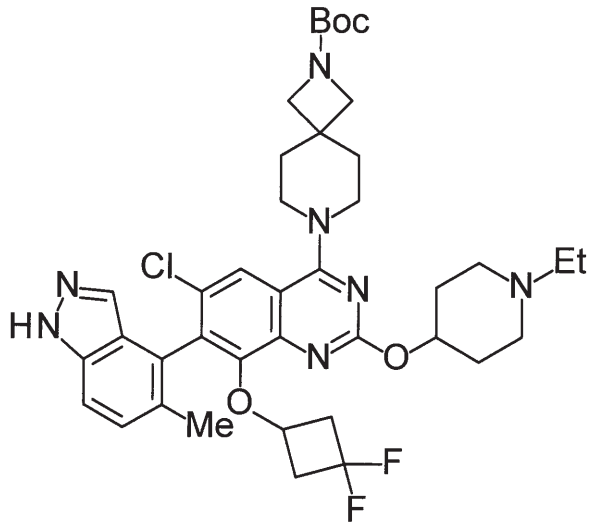
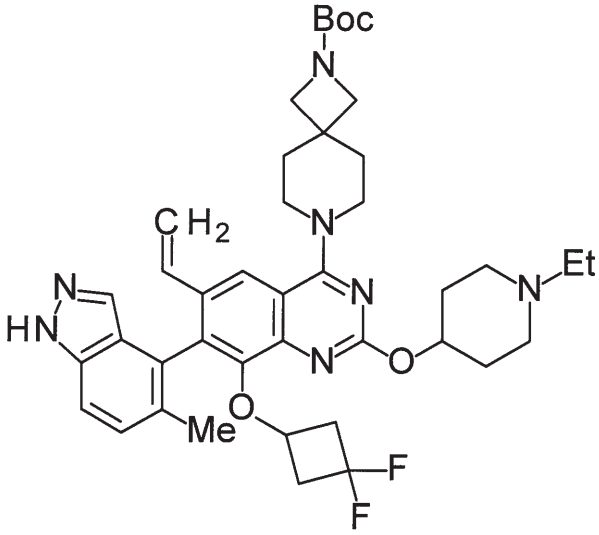
[0193]

[Table 23]

PEx	PSyn	Str	Dat
44	24		ESI+; 718.7
45	5		ESI+; 700.2, 702.2

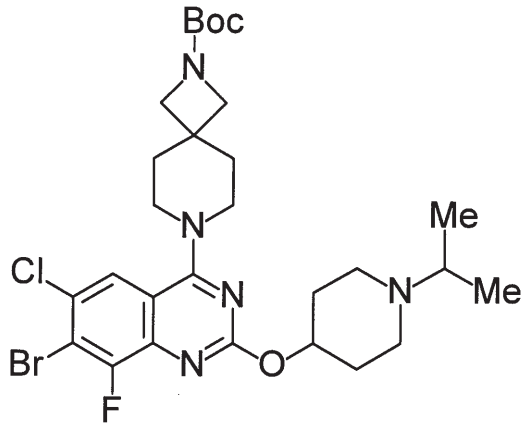
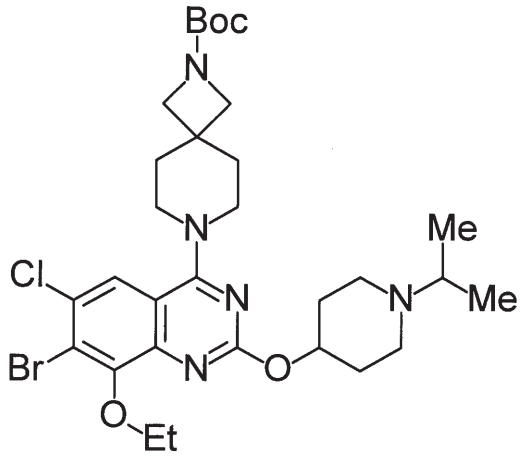
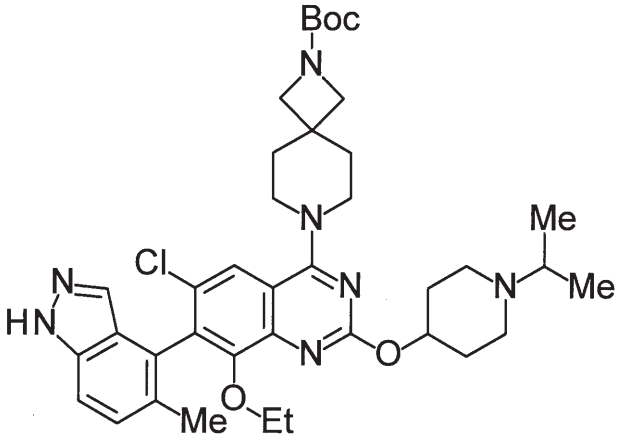
[0194]

[Table 24]

PEx	PSyn	Str	Dat
46	7		ESI+; 752.6, 754.5
47	24		ESI+; 744.6

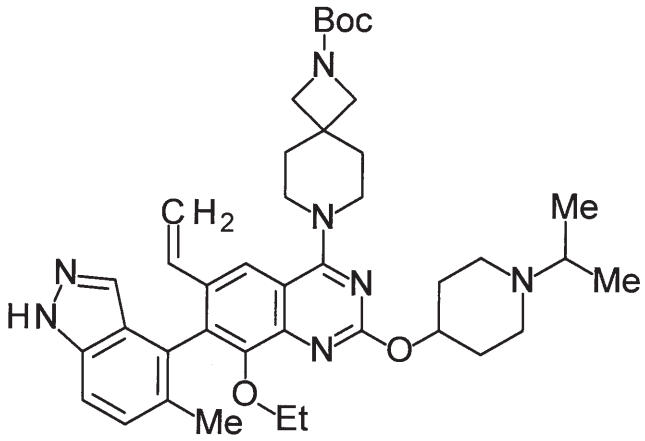
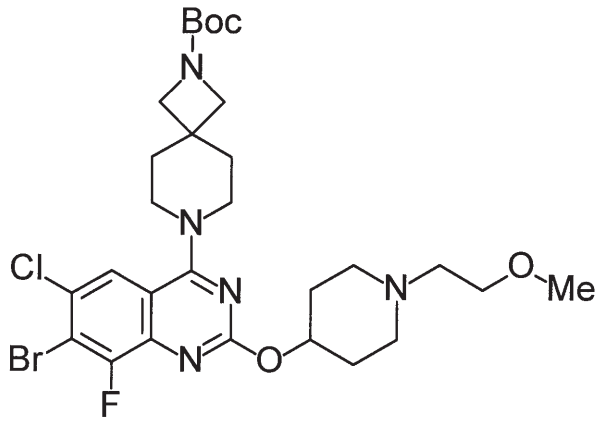
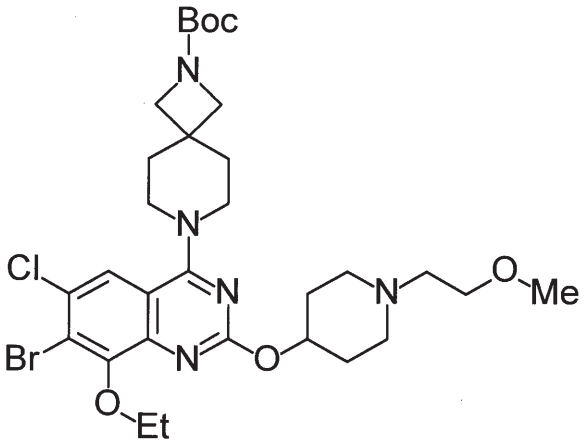
[0195]

[Table 25]

PEx	PSyn	Str	Dat
48	4		ESI+; 628.2
49	8		ESI+; 652.2, 654.2
50	7		ESI+; 704.4

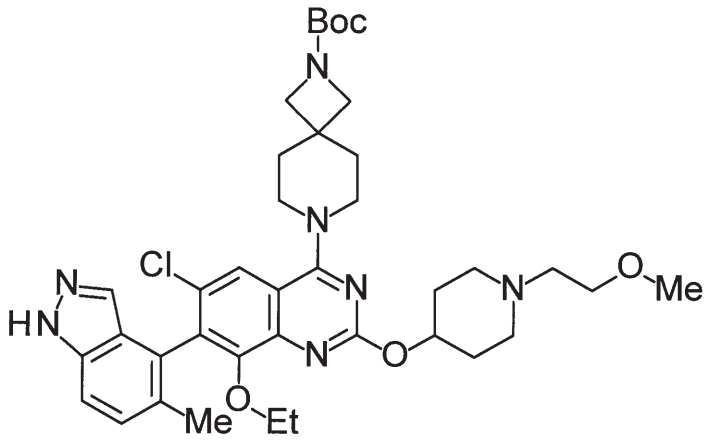
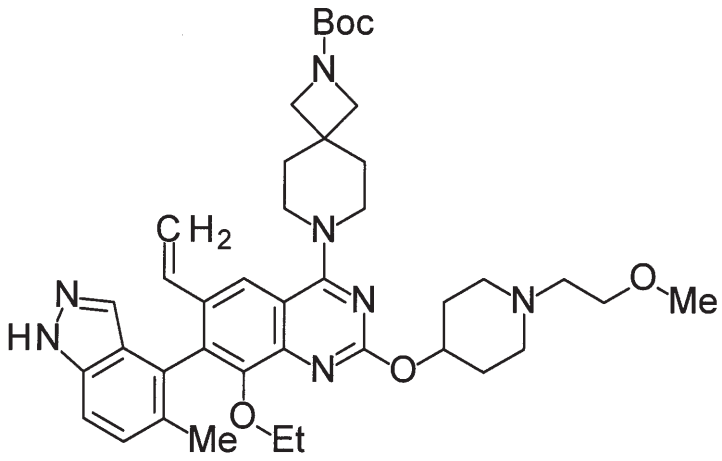
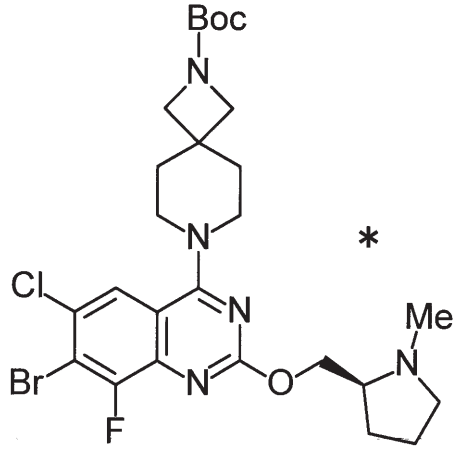
[0196]

[Table 26]

PEx	PSyn	Str	Dat
51	24		ESI+; 696.3
52	4		ESI+; 644.1
53	8		ESI+; 668.2, 670.2

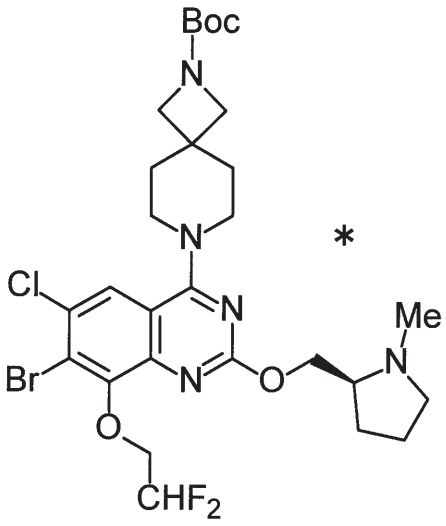
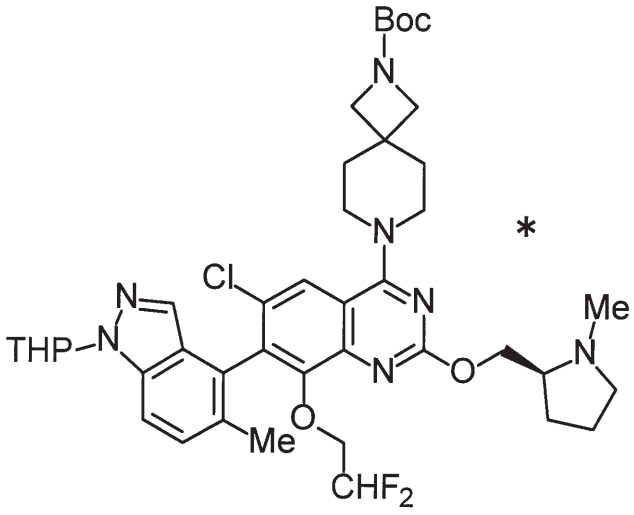
[0197]

[Table 27]

PEx	PSyn	Str	Dat
54	7		ESI+; 720.5
55	24		ESI+; 712.6
56	16		ESI+; 598.3, 600.3

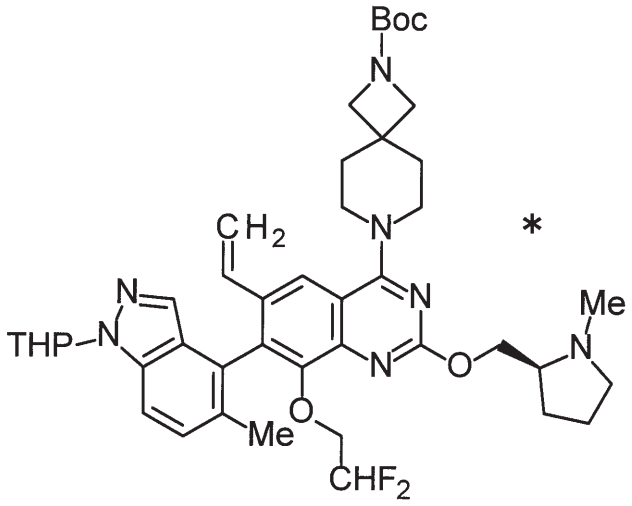
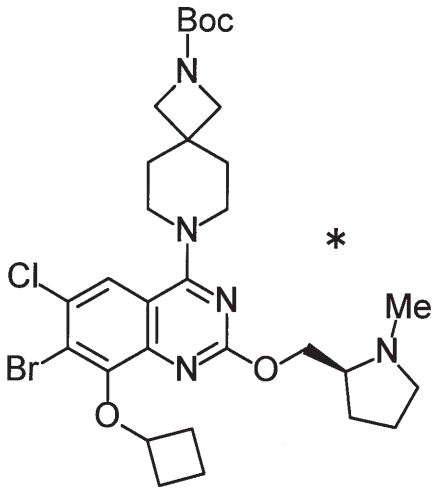
[0198]

[Table 28]

PEx	PSyn	Str	Dat
57	5		ESI+; 660.4, 662.4
58	7		ESI+; 796.6

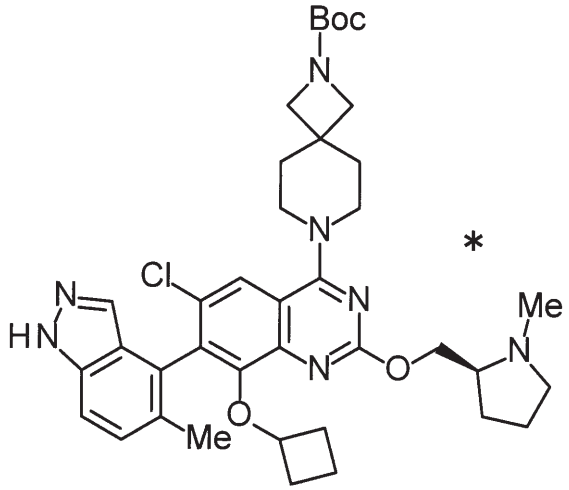
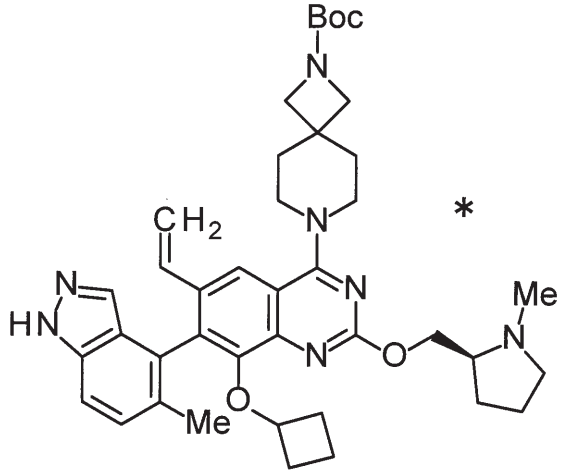
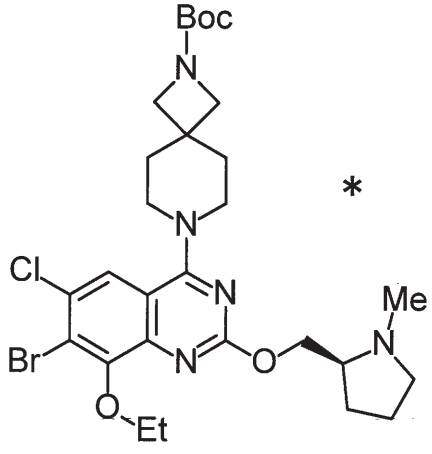
[0199]

[Table 29]

PEx	PSyn	Str	Dat
59	24		ESI+; 788.8
60	5		ESI+; 650.5, 652.5

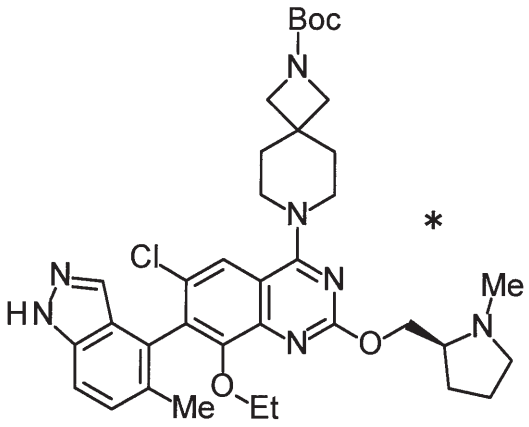
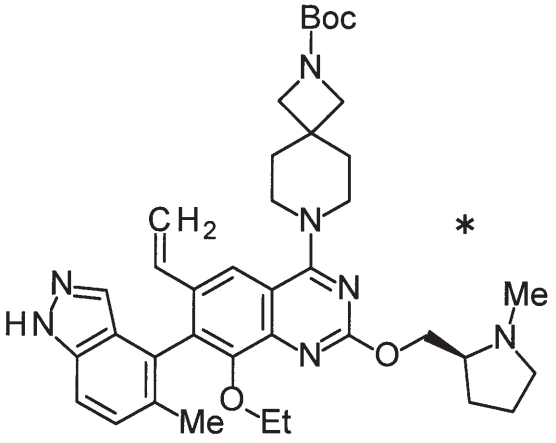
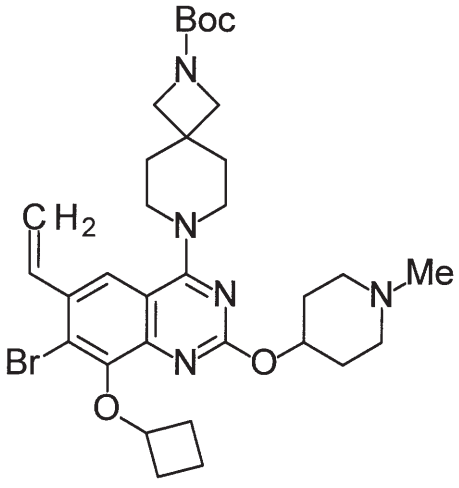
[0200]

[Table 30]

PEx	PSyn	Str	Dat
61	7		ESI+; 702.4
62	24		ESI+; 694.6
63	8		ESI+; 624.4, 626.4

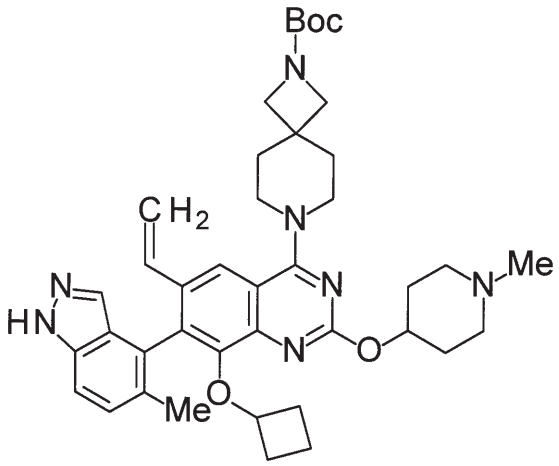
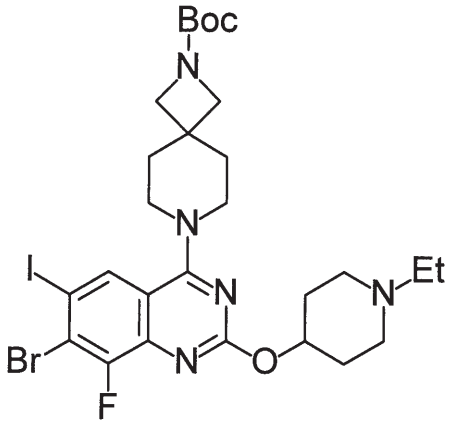
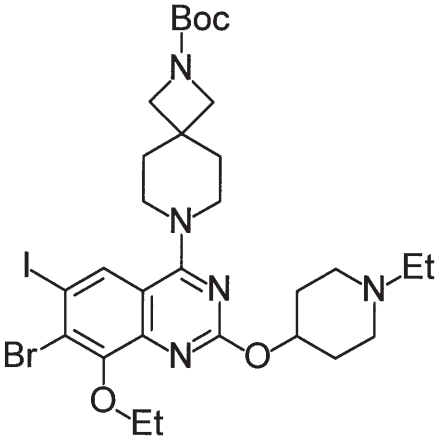
[0201]

[Table 31]

PEx	PSyn	Str	Dat
64	23		ESI+; 676.6, 678.6
65	24		ESI+; 668.5
66	6		ESI+; 644.4

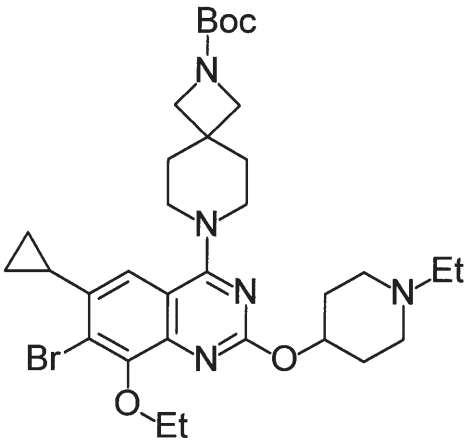
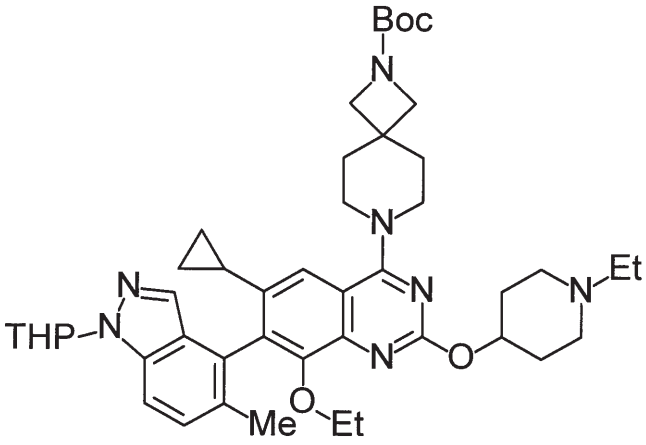
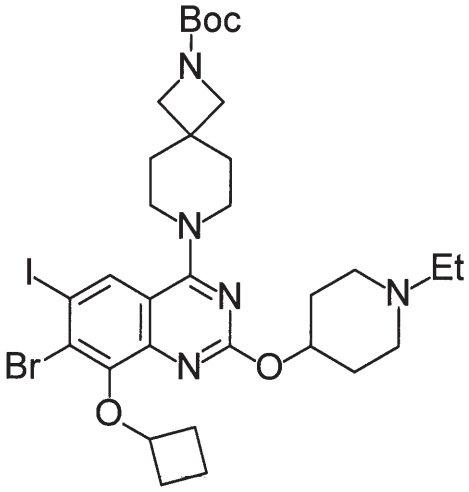
[0202]

[Table 32]

PEx	PSyn	Str	Dat
67	7		ESI+; 694.6
68	4		ESI+; 706.3
69	8		ESI+; 732.3

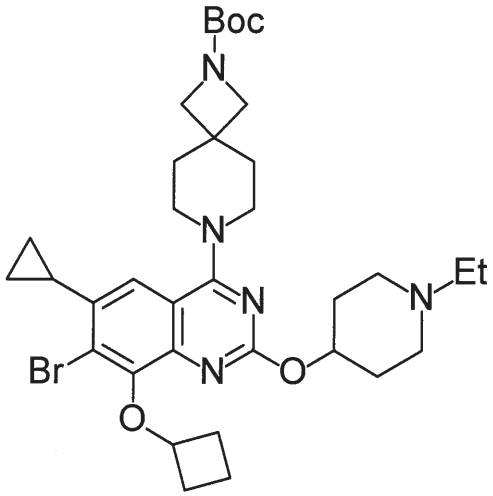
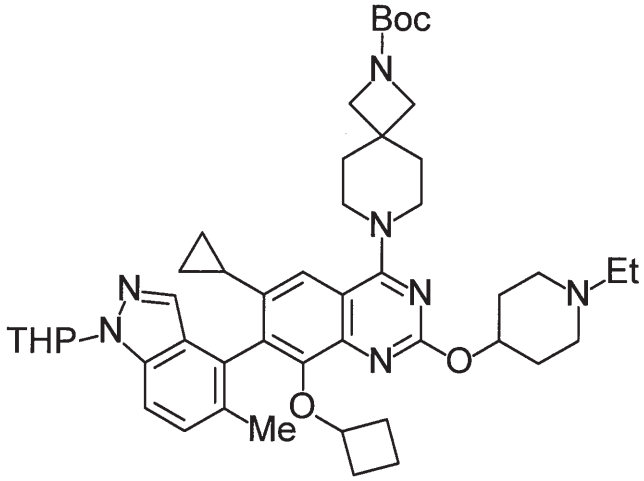
[0203]

[Table 33]

PEx	PSyn	Str	Dat
70	9		ESI+; 646.5
71	7		ESI+; 780.6
72	5		ESI+; 758.4

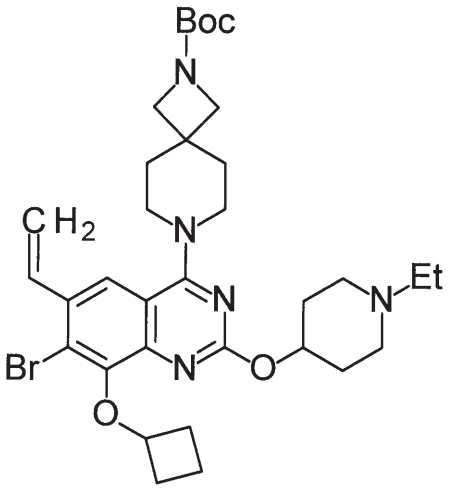
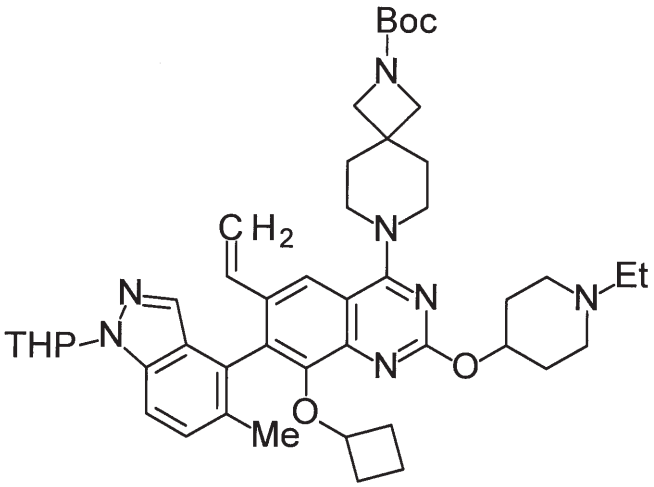
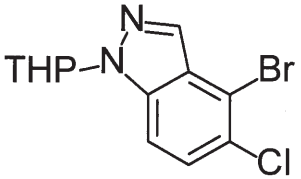
[0204]

[Table 34]

PEx	PSyn	Str	Dat
73	9		ESI+; 670.5
74	7		ESI+; 806.8

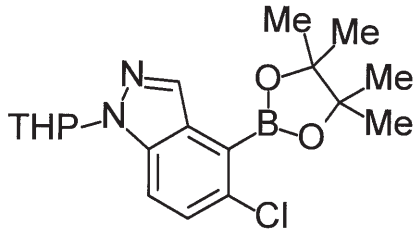
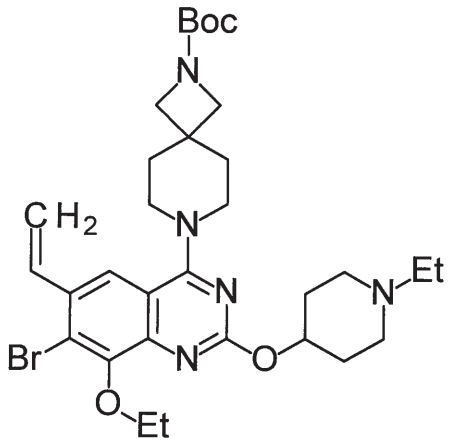
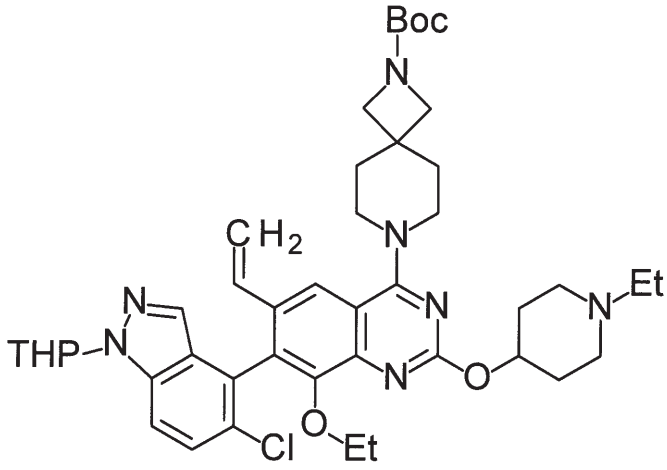
[0205]

[Table 35]

PEx	PSyn	Str	Dat
75	6		ESI+; 658.4
76	7		ESI+; 792.7
77	35		ESI+; 317.1

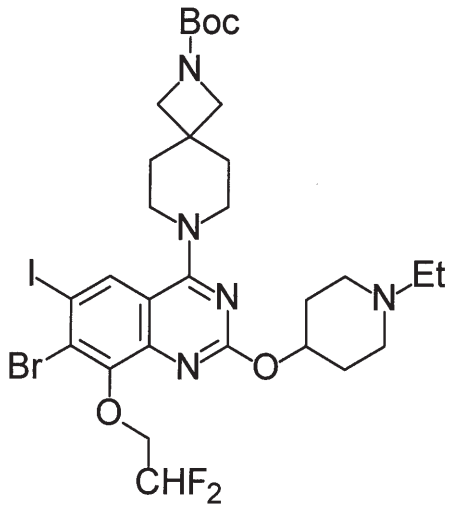
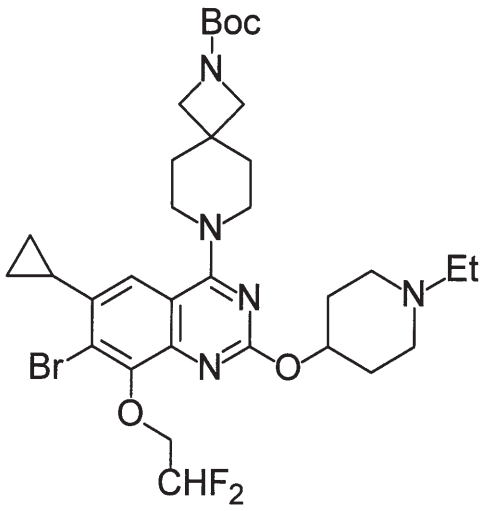
[0206]

[Table 36]

PEx	PSyn	Str	Dat
78	36		ESI+; 363.3
79	6		ESI+; 632.5
80	7		ESI+; 786.6

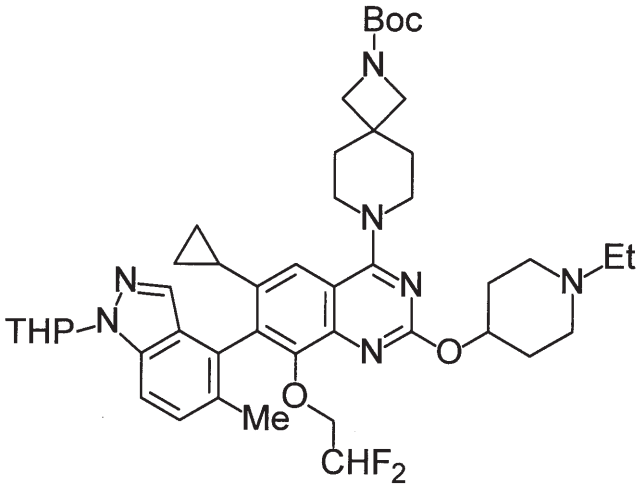
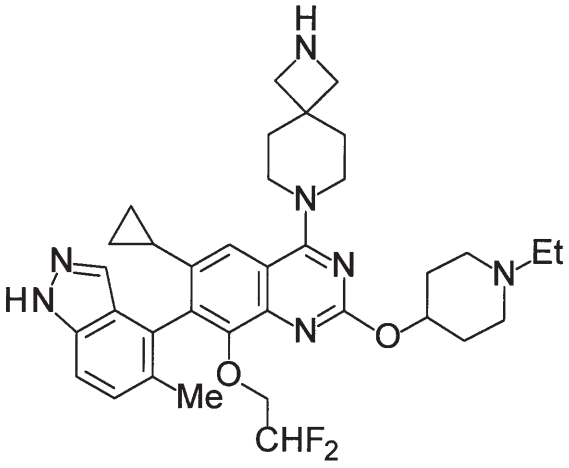
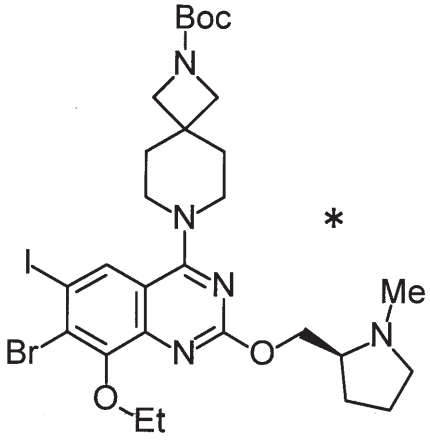
[0207]

[Table 37]

PEx	PSyn	Str	Dat
81	5		ESI+; 768.3
82	9		ESI+; 680.5

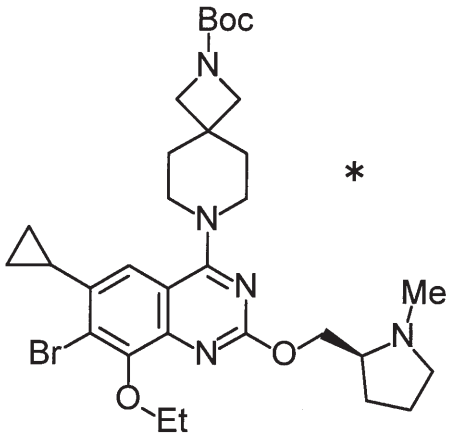
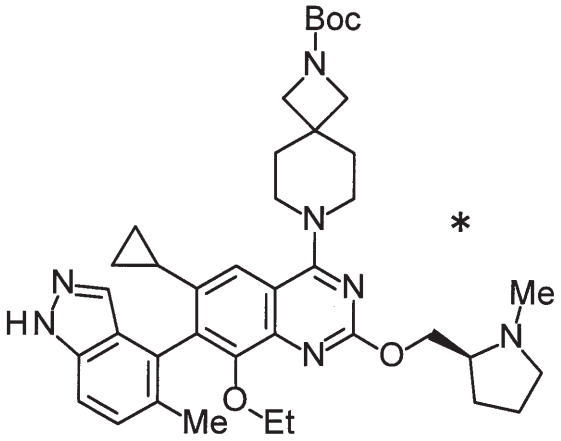
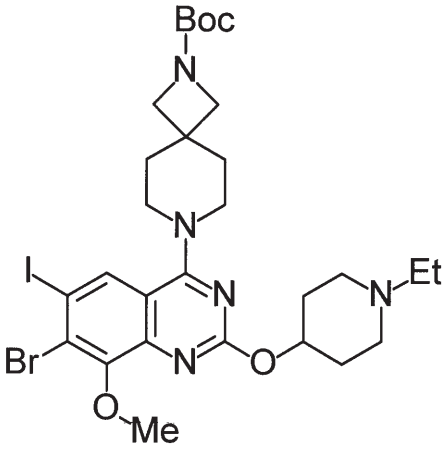
[0208]

[Table 38]

PEx	PSyn	Str	Dat
83	7		ESI+; 816.6
84	28		ESI+; 632.5
85	8		ESI+; 718.3

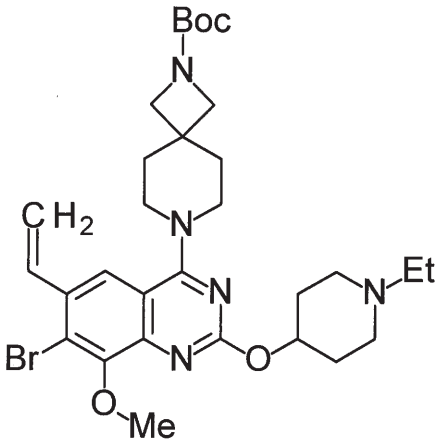
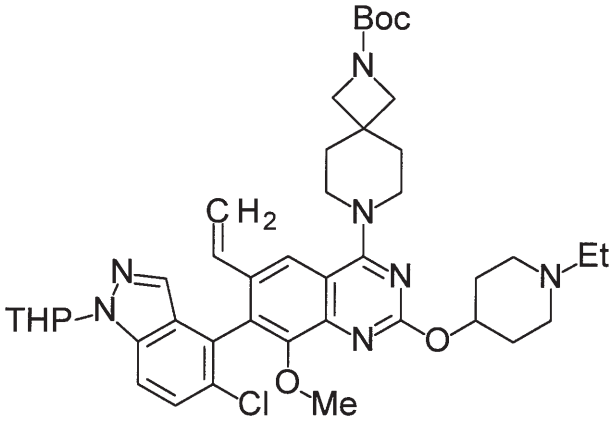
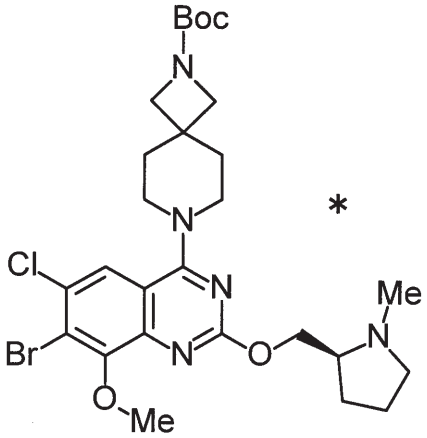
[0209]

[Table 39]

PEx	PSyn	Str	Dat
86	9		ESI+; 632.5
87	7		ESI+; 682.6
88	8		ESI+; 716.3

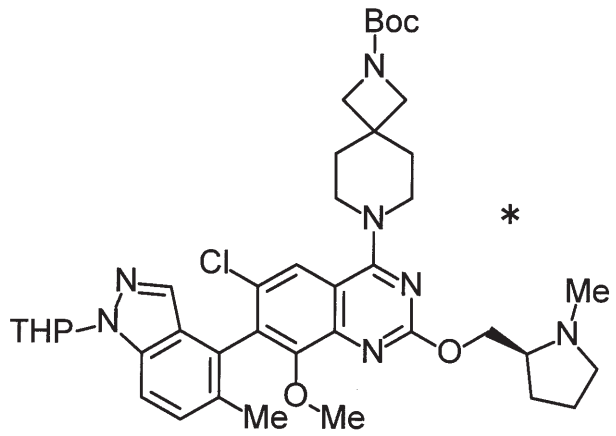
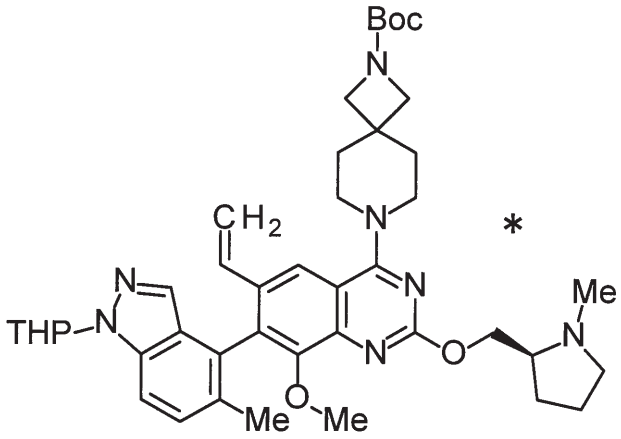
[0210]

[Table 40]

PEx	PSyn	Str	Dat
89	6		ESI+; 618.4
90	7		ESI+; 772.6
91	8		ESI+; 612.2

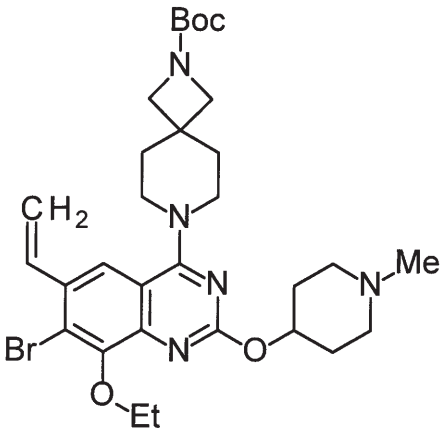
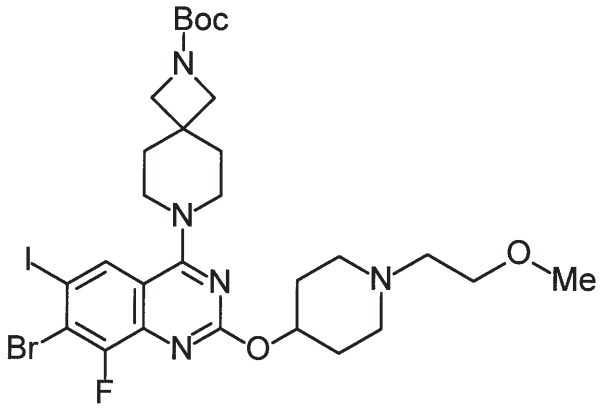
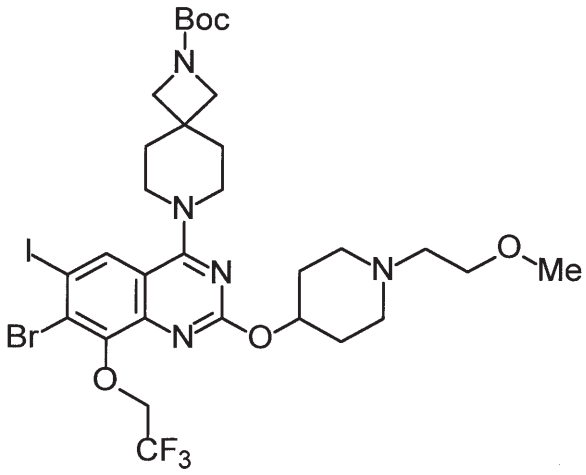
[0211]

[Table 41]

PEx	PSyn	Str	Dat
92	7		ESI+; 746.4
93	24		ESI+; 738.4

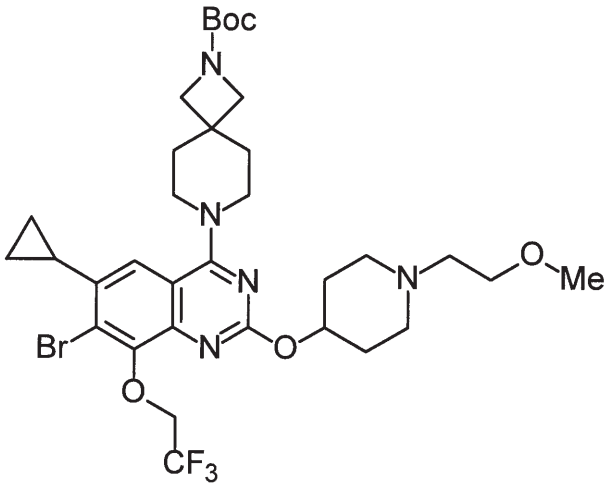
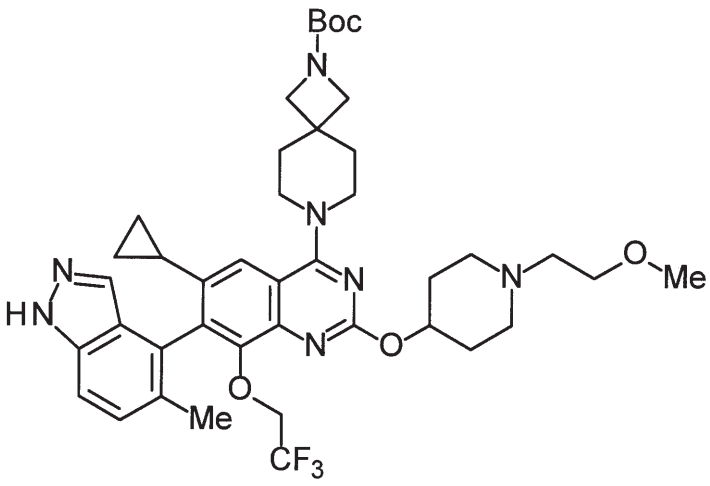
[0212]

[Table 42]

PEx	PSyn	Str	Dat
94	94		ESI+; 618.3
95	95		ESI+; 734.3
96	96		ESI+; 814.2

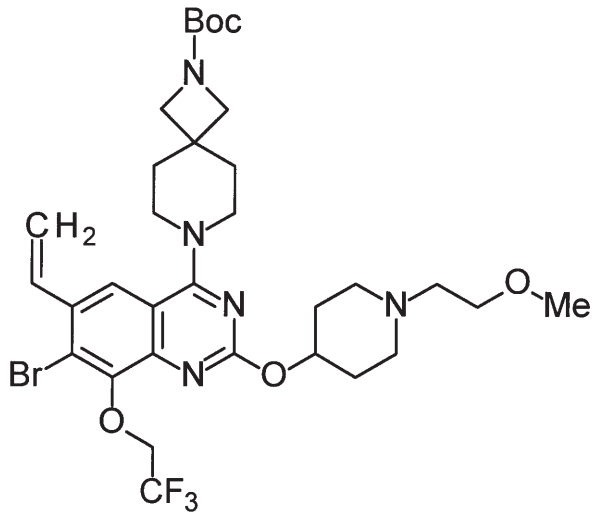
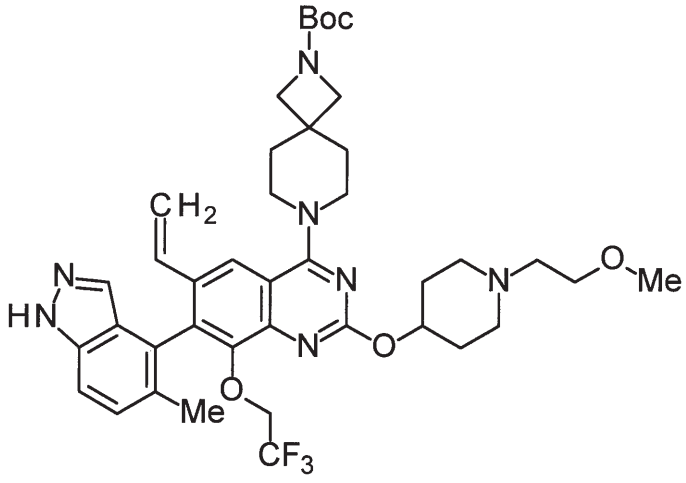
[0213]

[Table 43]

PEx	PSyn	Str	Dat
97	9		ESI+; 730.4
98	7		ESI+; 780.6

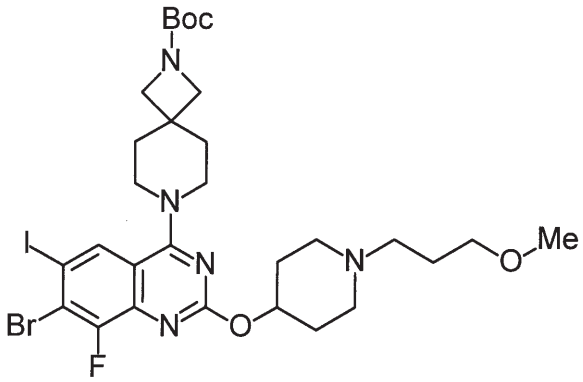
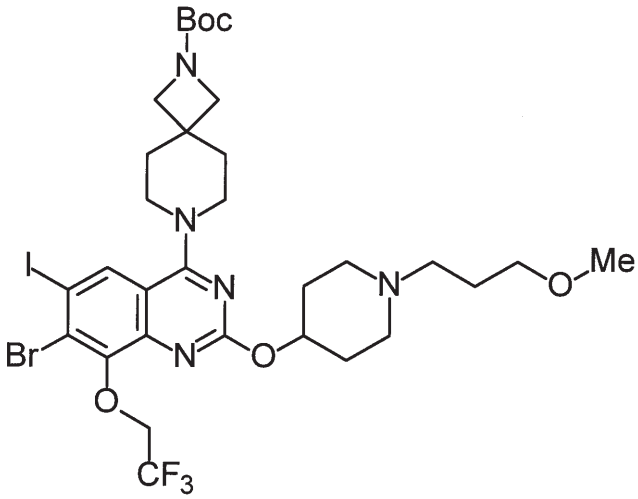
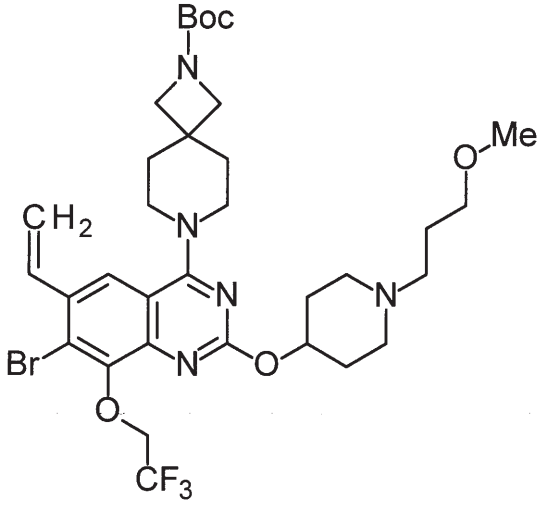
[0214]

[Table 44]

PEx	PSyn	Str	Dat
99	99		ESI+; 716.4
100	100		ESI+; 766.5

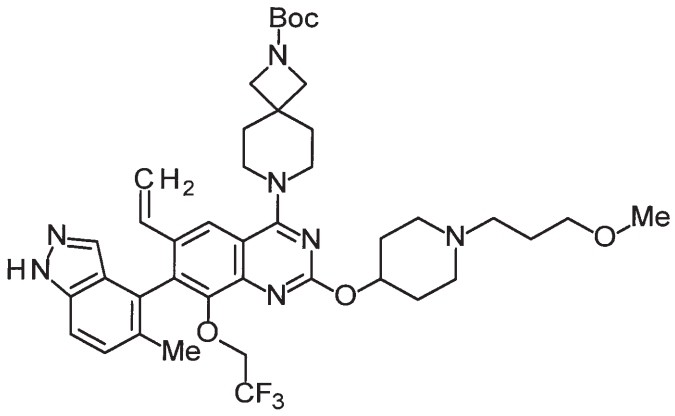
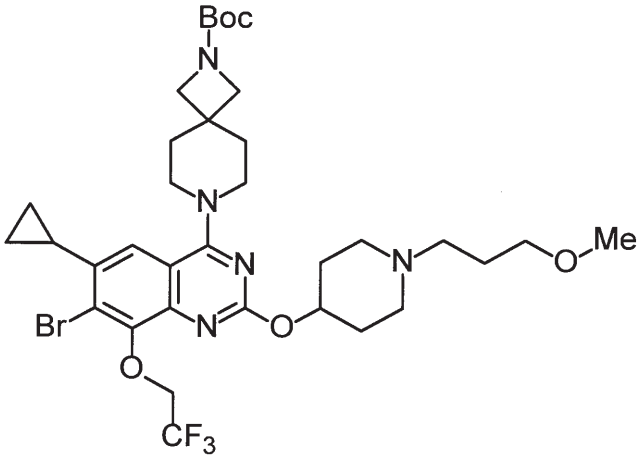
[0215]

[Table 45]

PEx	PSyn	Str	Dat
101	101		ESI+; 748.3
102	102		ESI+; 830.2
103	6		ESI+; 730.4

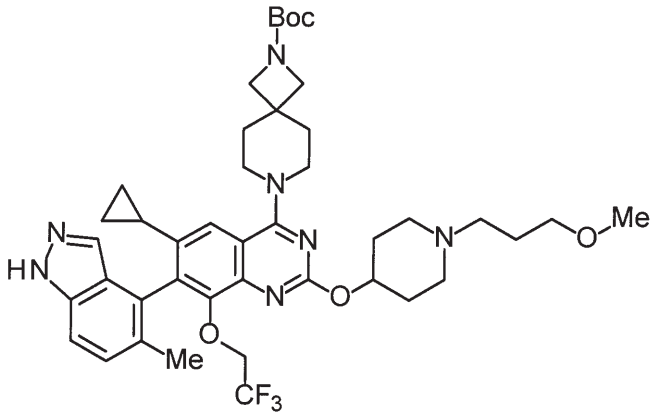
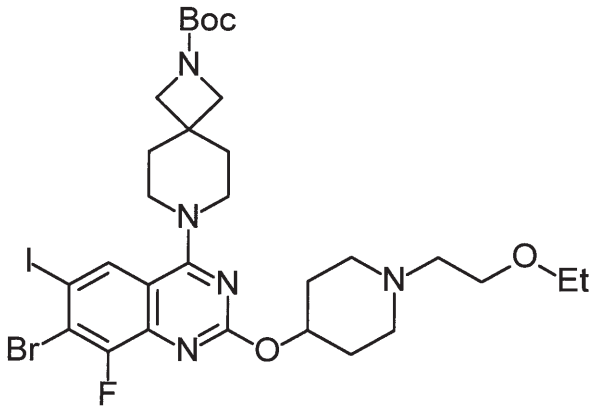
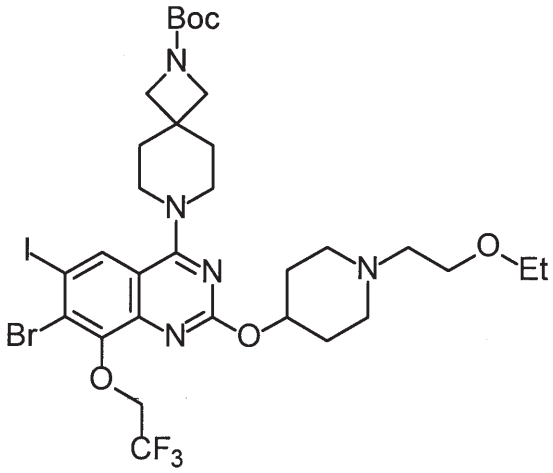
[0216]

[Table 46]

PEx	PSyn	Str	Dat
104	23		ESI+; 780.6
105	105		ESI+; 744.3

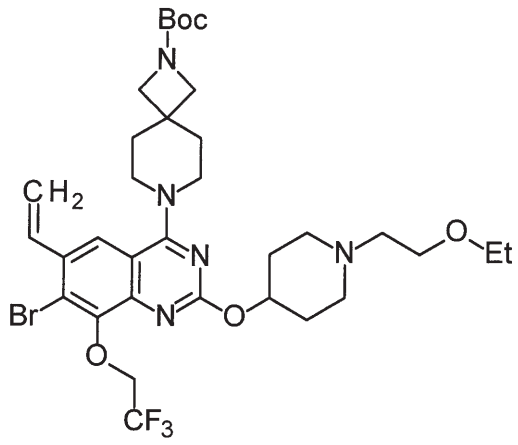
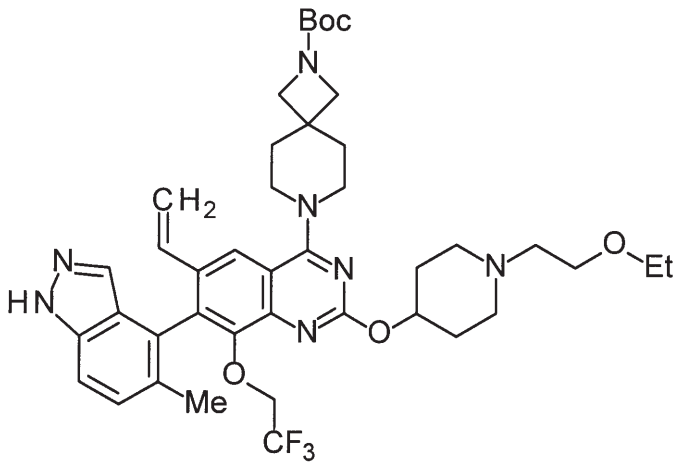
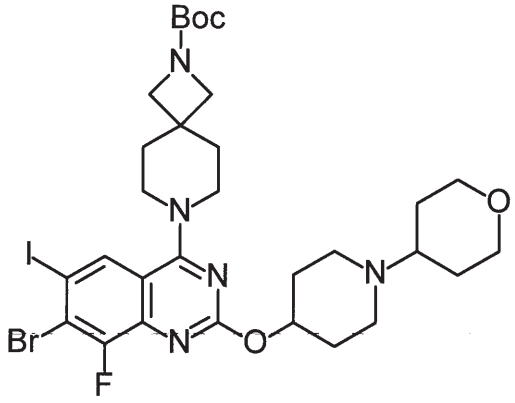
[0217]

[Table 47]

PEx	PSyn	Str	Dat
106	106		ESI+; 794.5
107	4		ESI+; 750.3
108	39		ESI+; 830.3

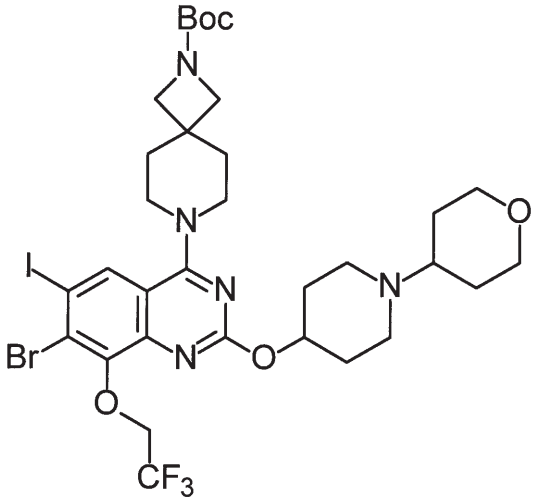
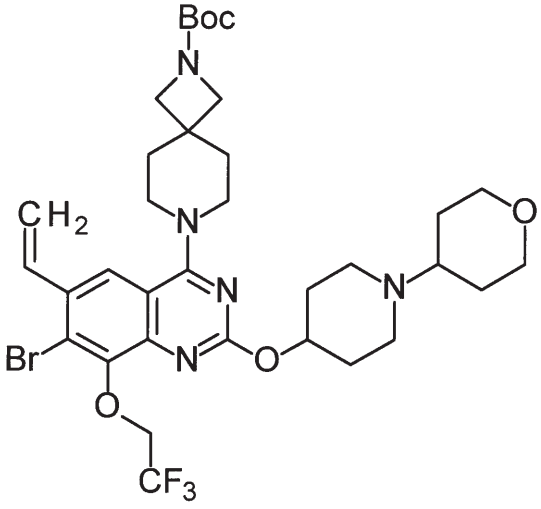
[0218]

[Table 48]

PEx	PSyn	Str	Dat
109	6		ESI+; 728.4, 730.3
110	23		ESI+; 780.6
111	111		ESI+; 760.3, 762.4

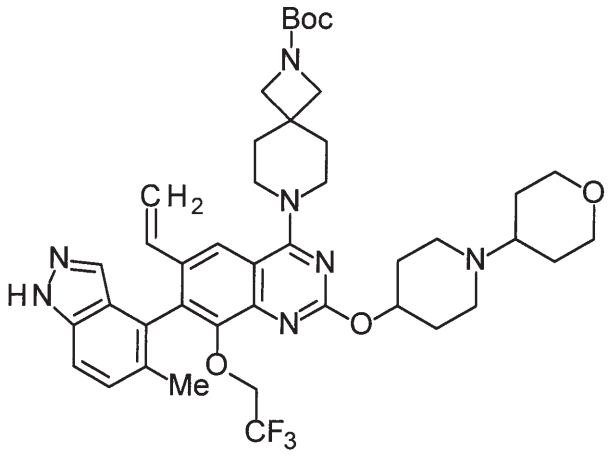
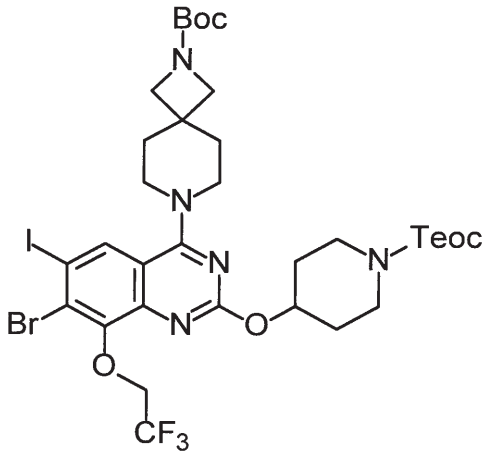
[0219]

[Table 49]

PEx	PSyn	Str	Dat
112	112		ESI+; 840.3
113	113		ESI+; 740.6

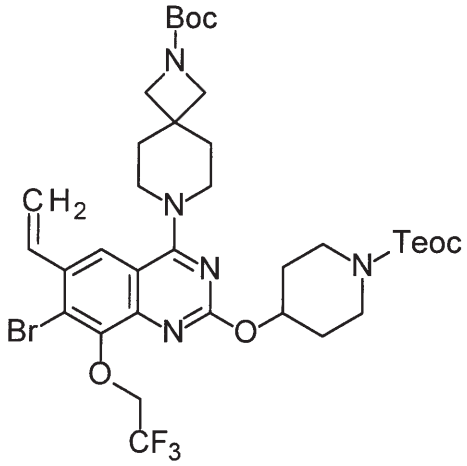
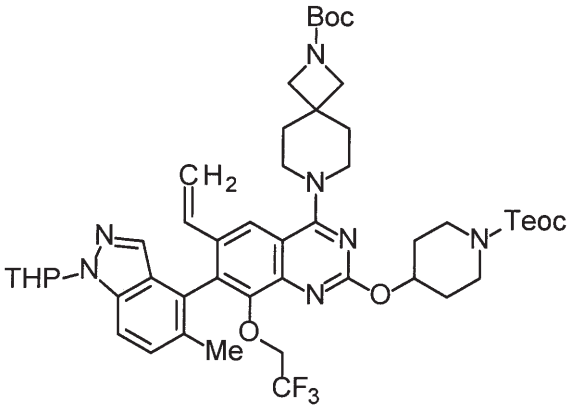
[0220]

[Table 50]

PEx	PSyn	Str	Dat
114	114		ESI+; 792.6
115	115		ESI+; 900.4, 902.4

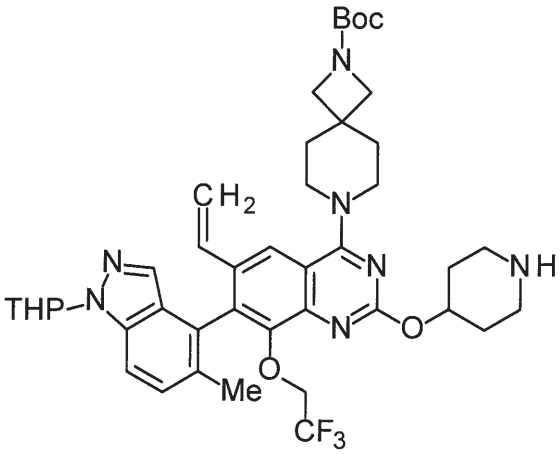
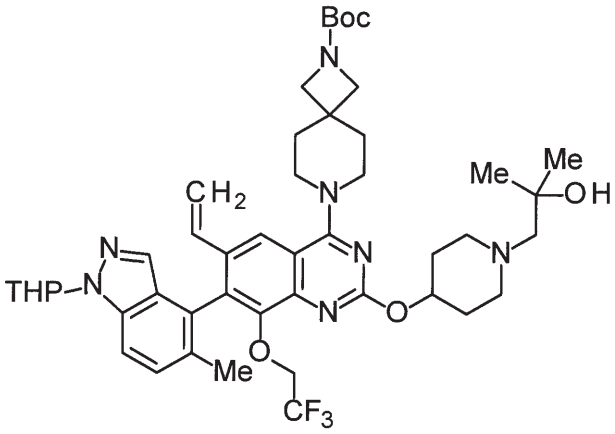
[0221]

[Table 51]

PEx	PSyn	Str	Dat
116	6		ESI+; 800.5, 802.5
117	23		ESI+; 936.6

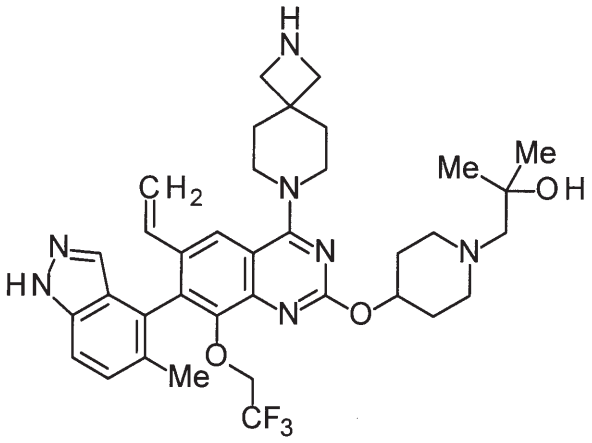
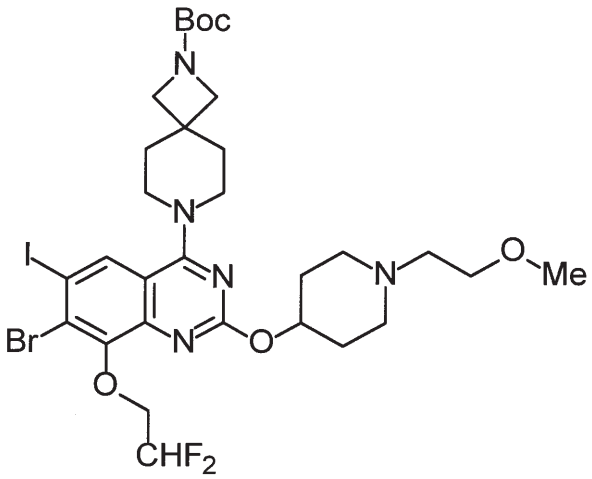
[0222]

[Table 52]

PEx	PSyn	Str	Dat
118	118		ESI+; 792.5
119	119		ESI+; 864.6

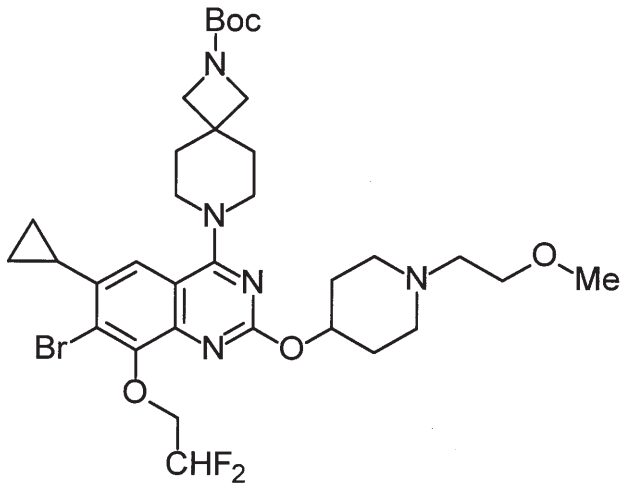
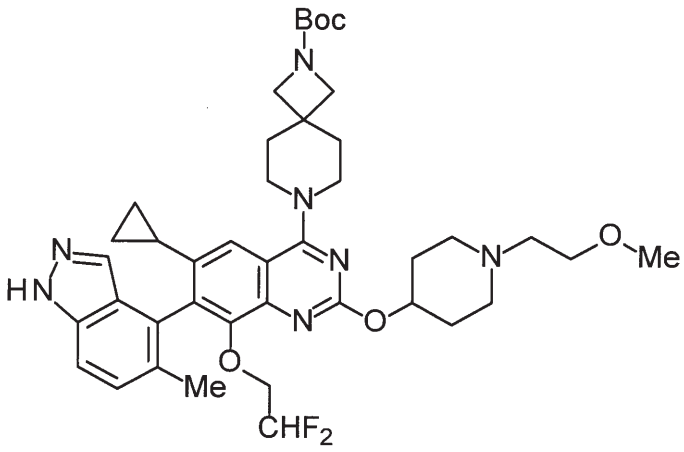
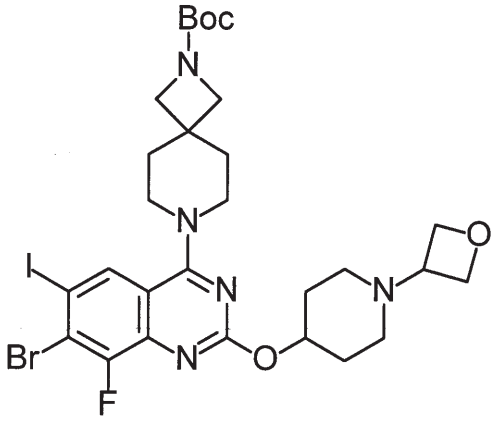
[0223]

[Table 53]

PEx	PSyn	Str	Dat
120	28		ESI+; 680.5
121	39		ESI+; 798.3

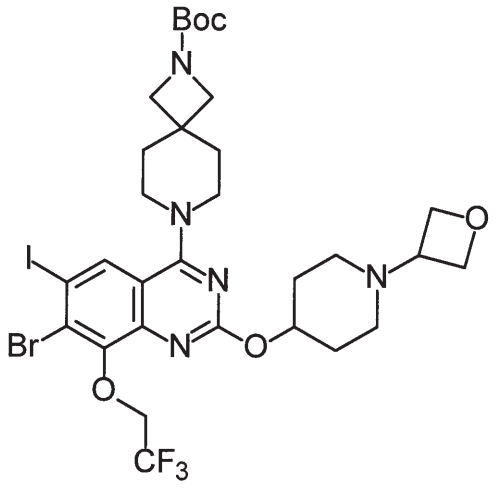
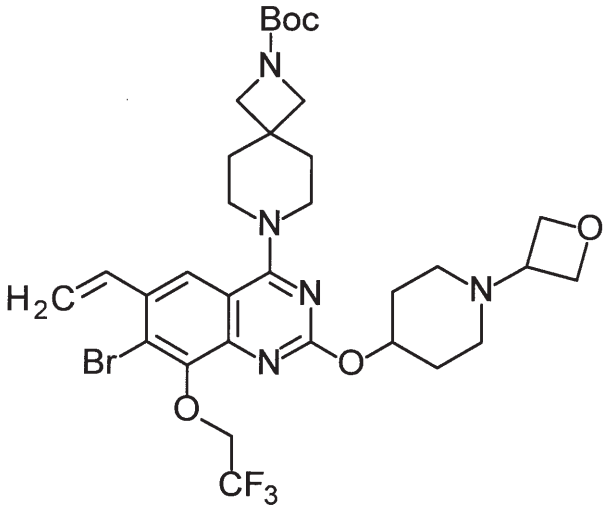
[0224]

[Table 54]

PEx	PSyn	Str	Dat
122	9		ESI+; 712.5
123	23		ESI+; 762.6
124	4		ESI+; 732.2

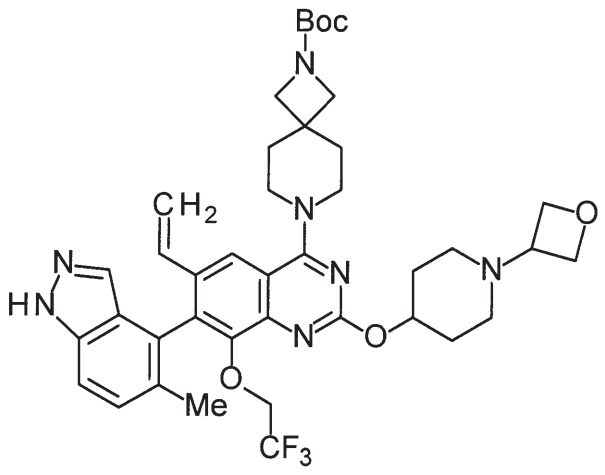
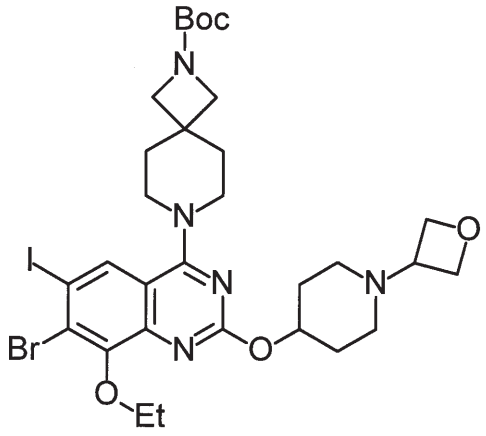
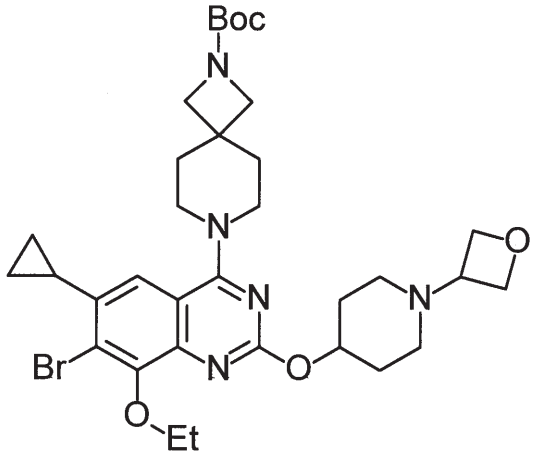
[0225]

[Table 55]

PEx	PSyn	Str	Dat
125	39		ESI+; 812.3, 814.3
126	6		ESI+; 712.4, 714.4

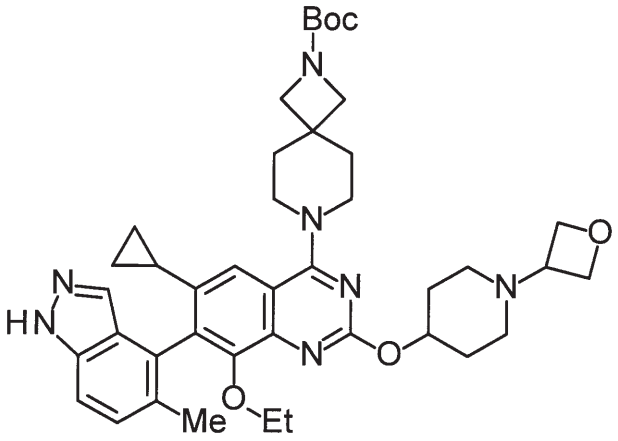
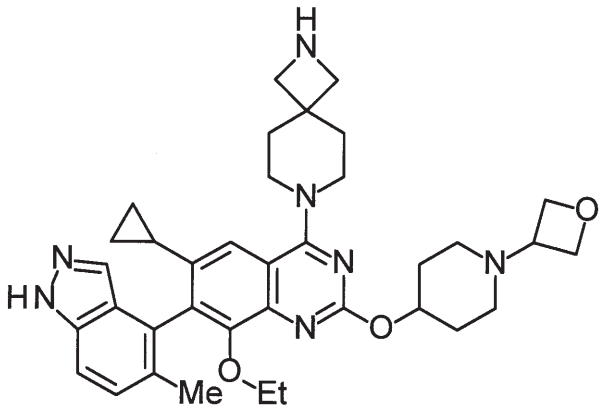
[0226]

[Table 56]

PEx	PSyn	Str	Dat
127	23		ESI+; 764.5
128	8		ESI+; 760.2
129	9		ESI+; 672.5, 674.4

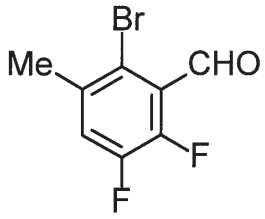
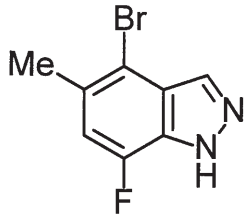
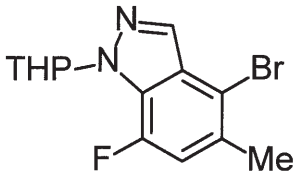
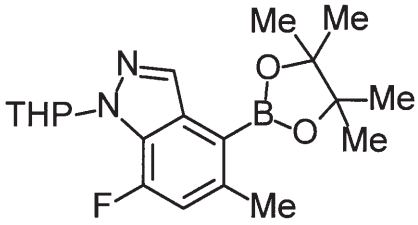
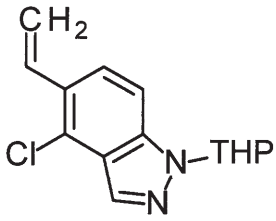
[0227]

[Table 57]

PEx	PSyn	Str	Dat
130	7		ESI+; 724.7
131	33		ESI+; 624.5

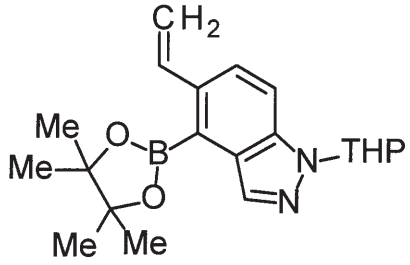
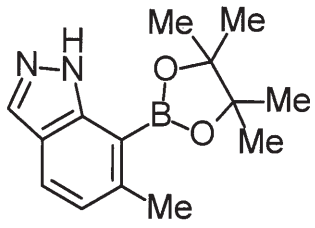
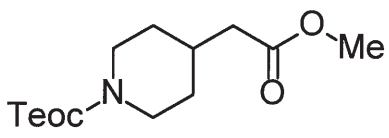
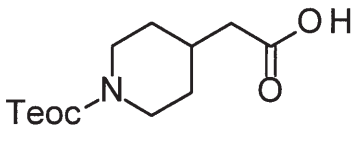
[0228]

[Table 58]

PEx	PSyn	Str	Dat
132	132		CI+; 235.0
133	133		ESI+; 228.9
134	35		ESI+; 313.0
135	36		ESI+; $[M+Na]^+$ 383.3
136	136		ESI+; 263.2

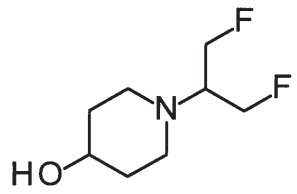
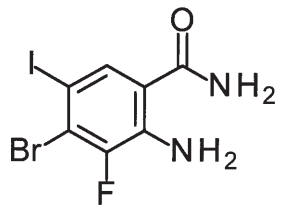
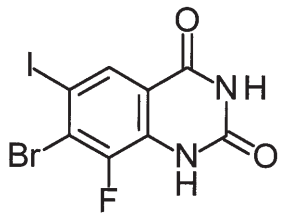
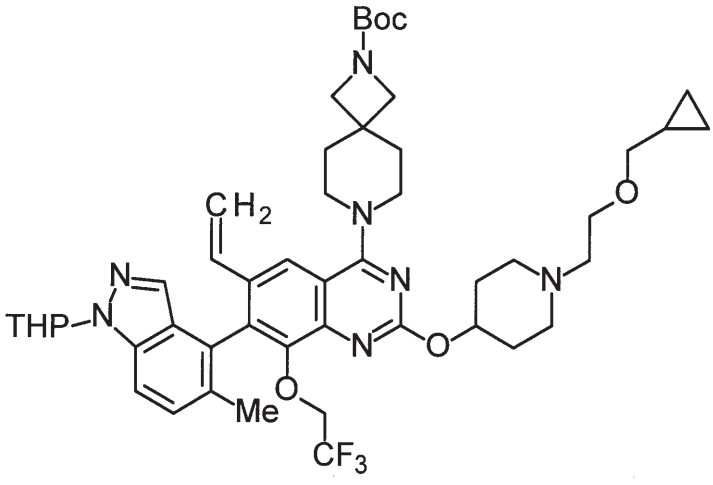
[0229]

[Table 59]

PEx	PSyn	Str	Dat
137	137		ESI+; 355.3
138	138		ESI+; 259.2
139	139		ESI+; $[M+Na]^+$ 324.2
140	140		ESI+; $[M+Na]^+$ 310.1

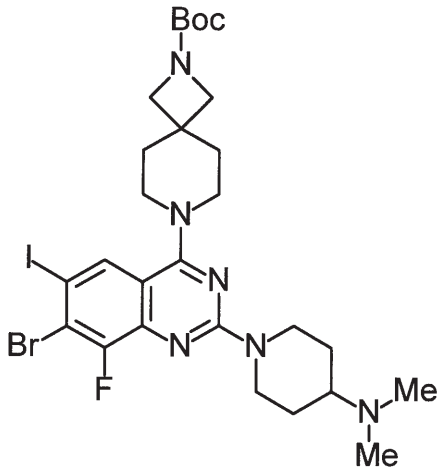
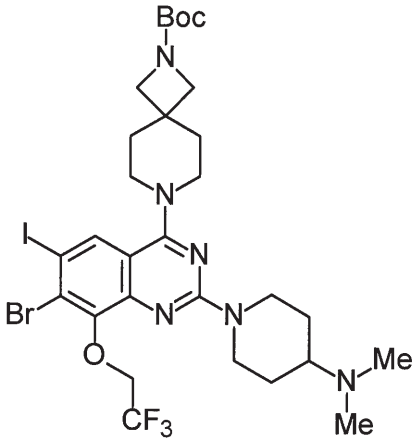
[0230]

[Table 60]

PEx	PSyn	Str	Dat
141	141		ESI+; 180.1
142	142		ESI+; 359.0
143	143		ESI+; 385.0, 386.9
144	144		ESI+; 890.7

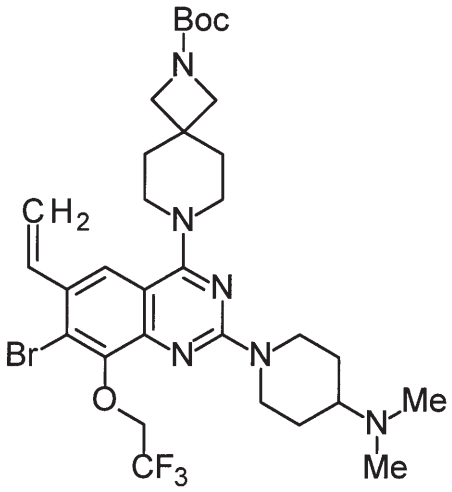
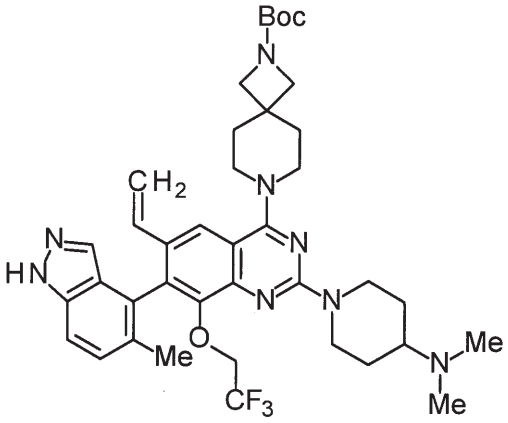
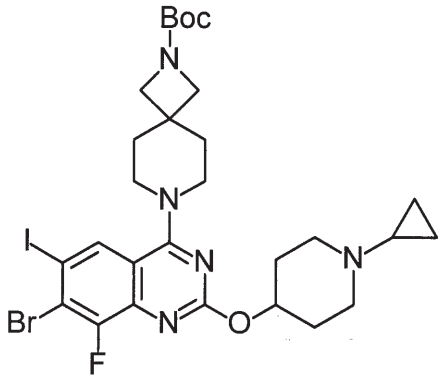
[0231]

[Table 61]

PEx	PSyn	Str	Dat
145	4		ESI+; 705.3
146	39		ESI+; 785.2

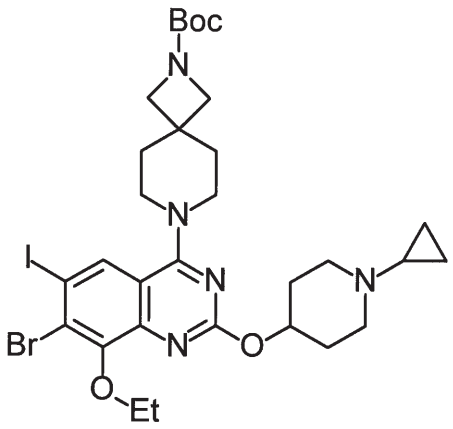
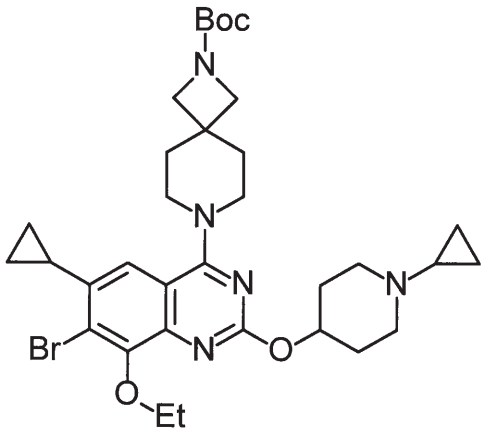
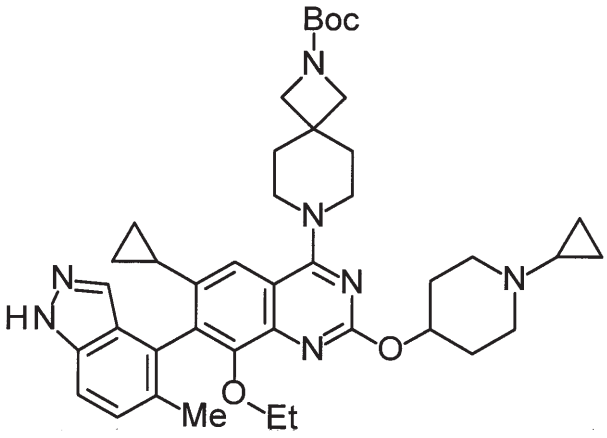
[0232]

[Table 62]

PEx	PSyn	Str	Dat
147	6		ESI+; 683.4
148	7		ESI+; 735.5
149	4		ESI+; 718.1

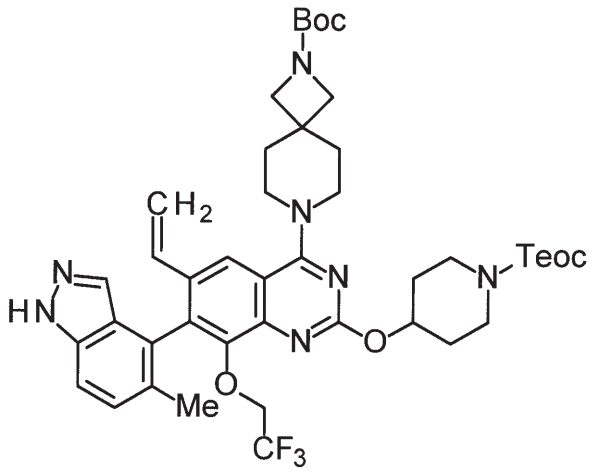
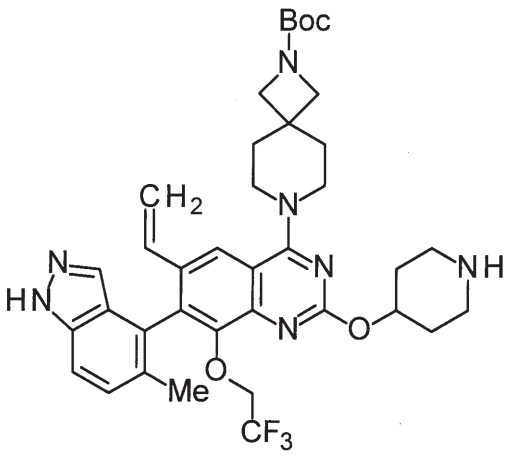
[0233]

[Table 63]

PEx	PSyn	Str	Dat
150	8		ESI+; 744.1
151	9		ESI+; 658.3
152	7		ESI+; 708.4

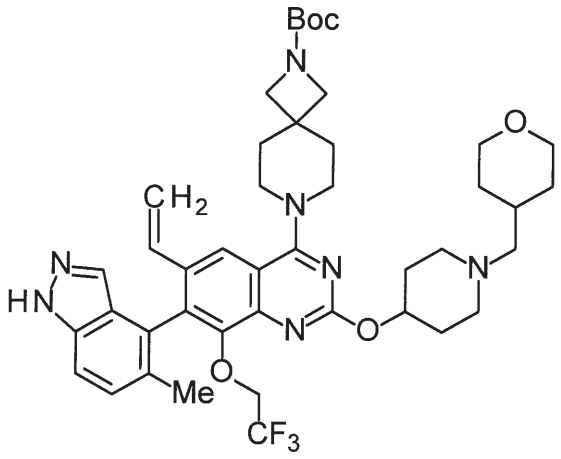
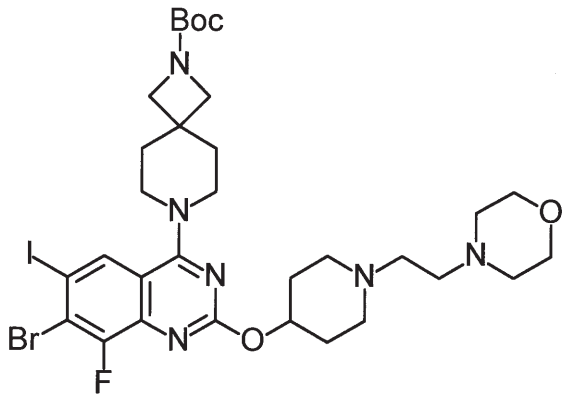
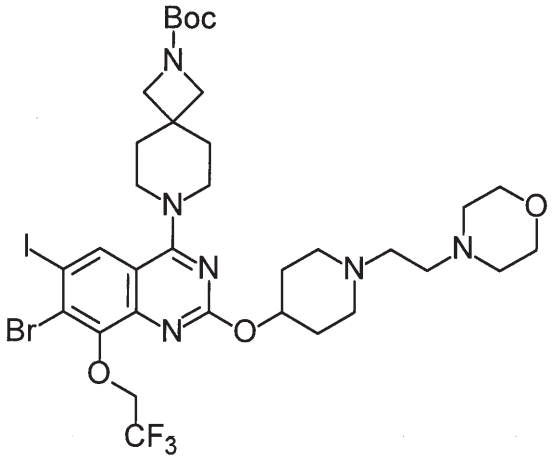
[0234]

[Table 64]

PEx	PSyn	Str	Dat
153	23		ESI+; 852.6
154	118		ESI+; 708.5

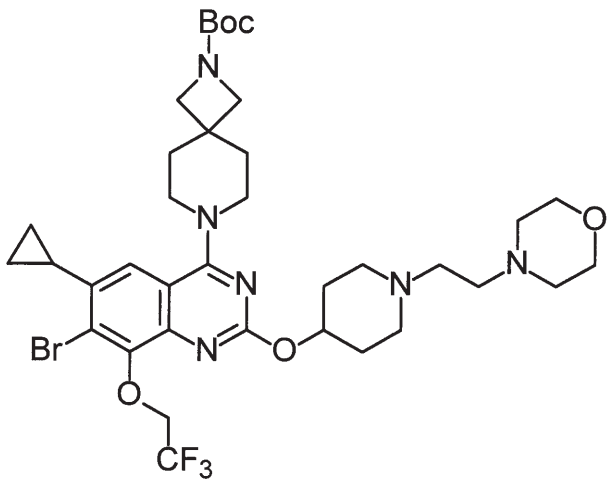
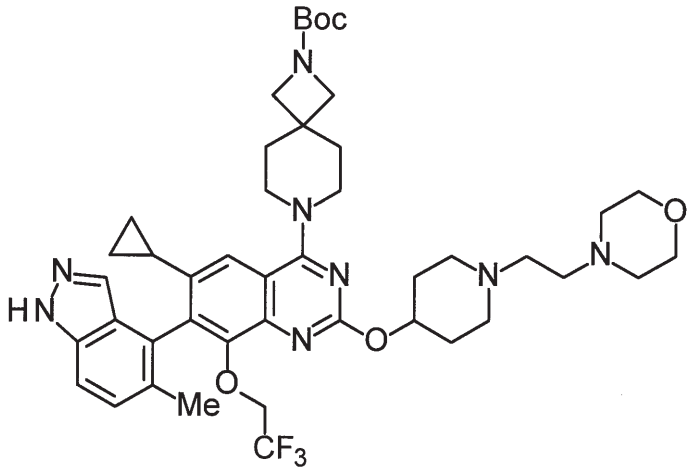
[0235]

[Table 65]

PEx	PSyn	Str	Dat
155	155		ESI+; 806.6
156	4		ESI+; 791.3
157	39		ESI+; 871.2

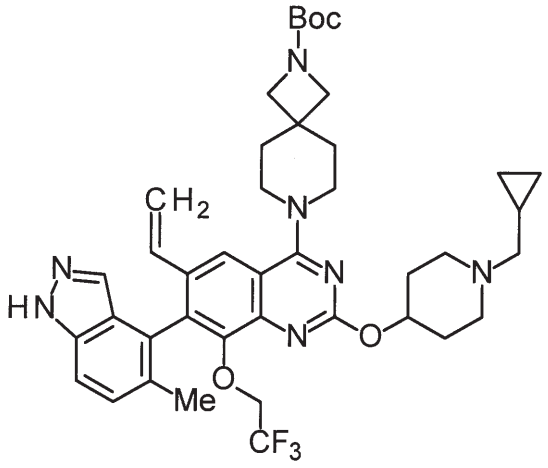
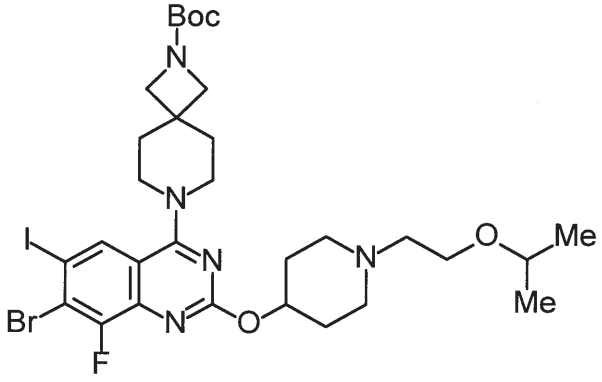
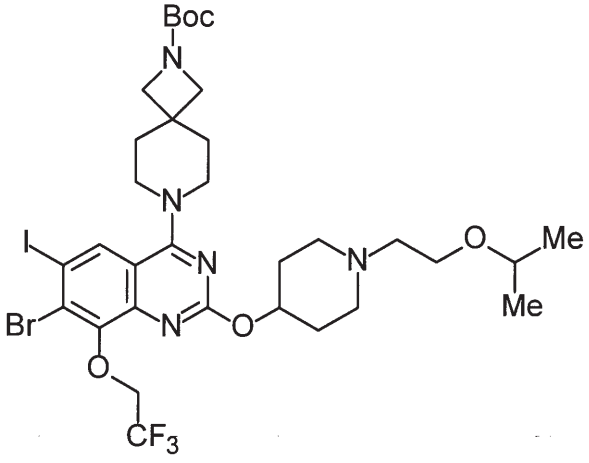
[0236]

[Table 66]

PEx	PSyn	Str	Dat
158	9		ESI+; 785.5
159	23		ESI+; 835.6

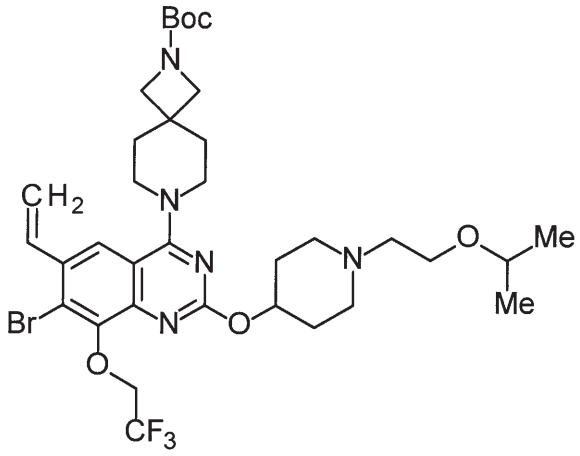
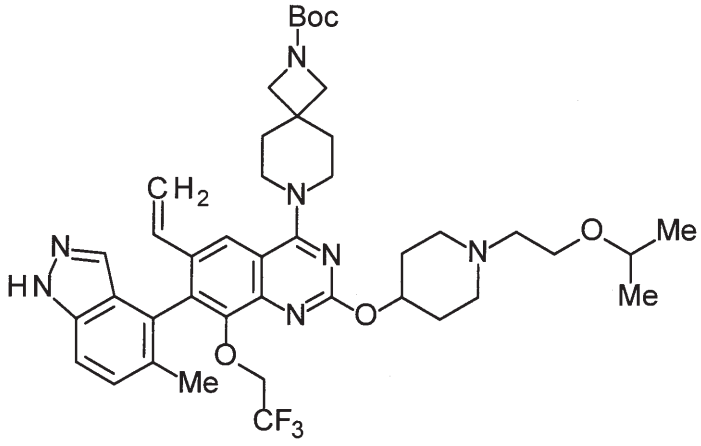
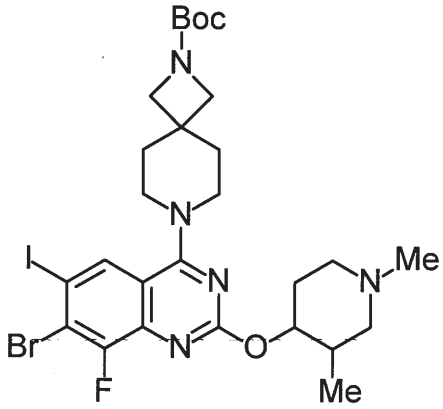
[0237]

[Table 67]

PEx	PSyn	Str	Dat
160	155		ESI+; 762.4
161	4		ESI+; 762.4
162	39		ESI+; 844.3

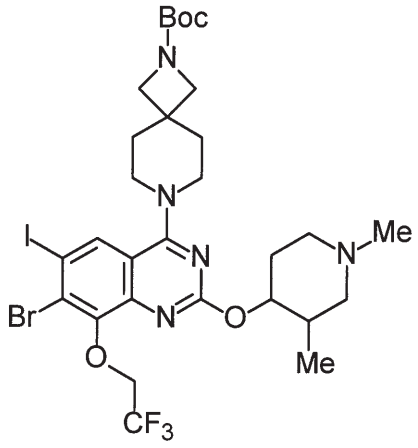
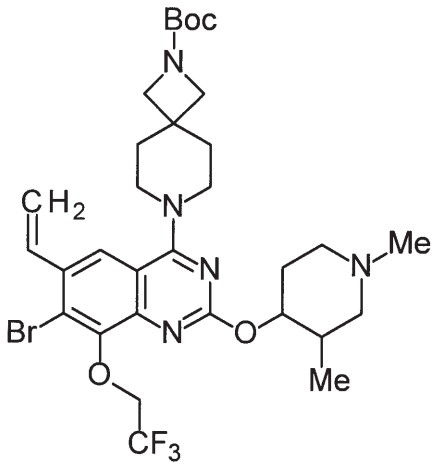
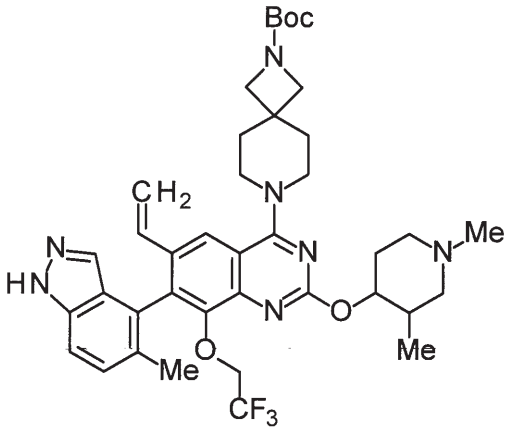
[0238]

[Table 68]

PEx	PSyn	Str	Dat
163	6		ESI+; 744.4
164	23		ESI+; 794.6
165	4		ESI+; 706.2

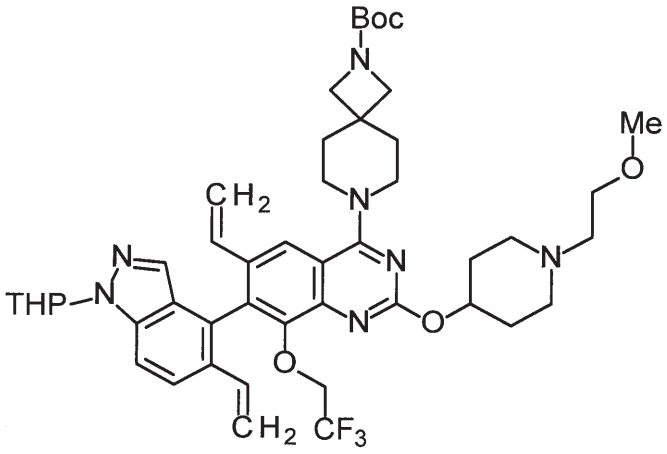
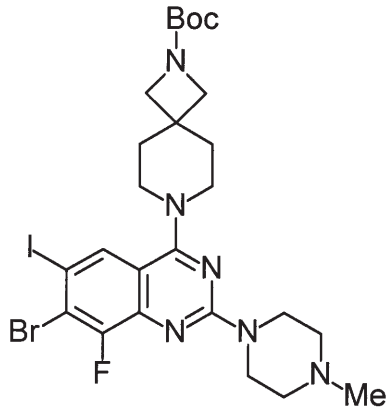
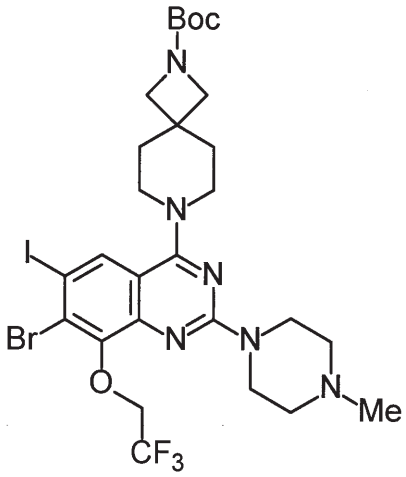
[0239]

[Table 69]

PEx	PSyn	Str	Dat
166	39		ESI+; 786.2
167	6		ESI+; 686.4
168	23		ESI+; 736.5

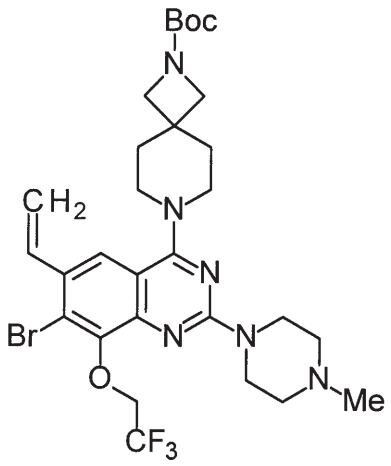
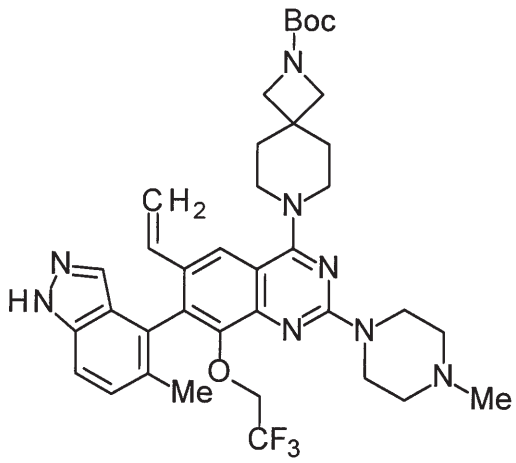
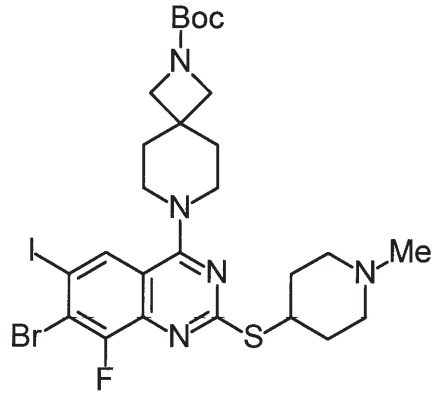
[0240]

[Table 70]

PEx	PSyn	Str	Dat
169	23		ESI+; $[M+Na]^+$ 884.8
170	4		ESI+; 677.2
171	39		ESI+; 757.2

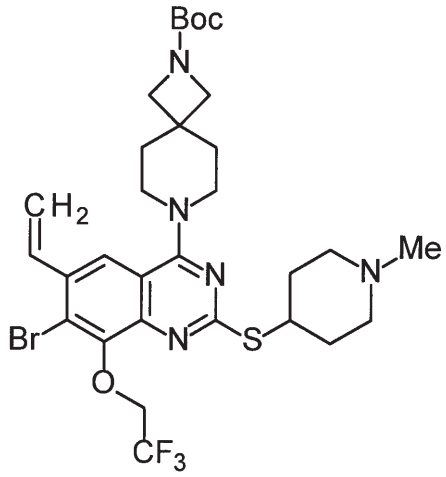
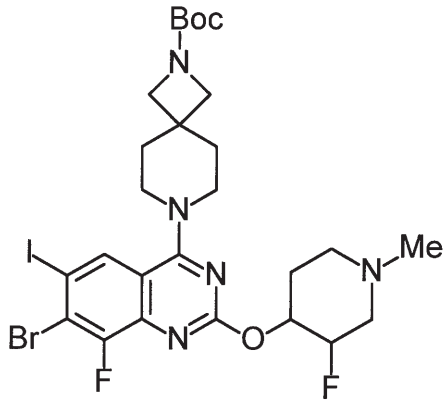
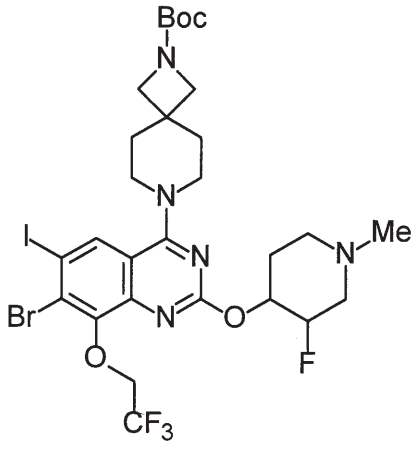
[0241]

[Table 71]

PEx	PSyn	Str	Dat
172	6		ESI+; 657.3
173	7		ESI+; 707.5
174	4		ESI+; 706.2

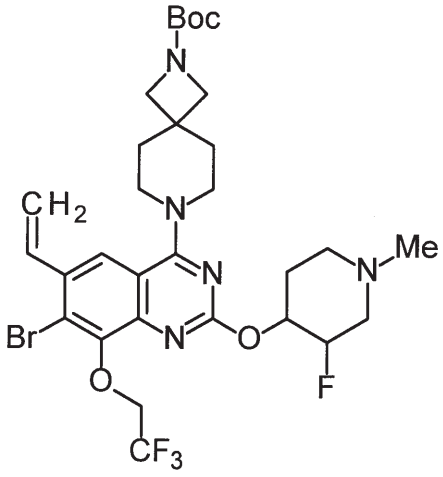
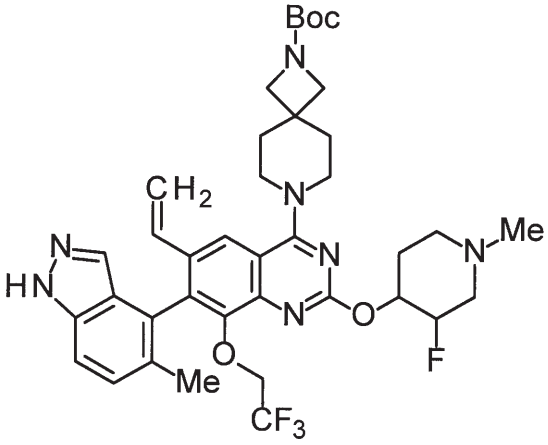
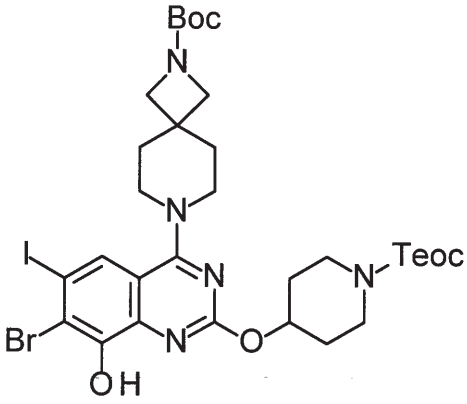
[0242]

[Table 72]

PEx	PSyn	Str	Dat
175	175		ESI+; 688.3
176	4		ESI+; 708.2, 710.2
177	39		ESI+; 790.2

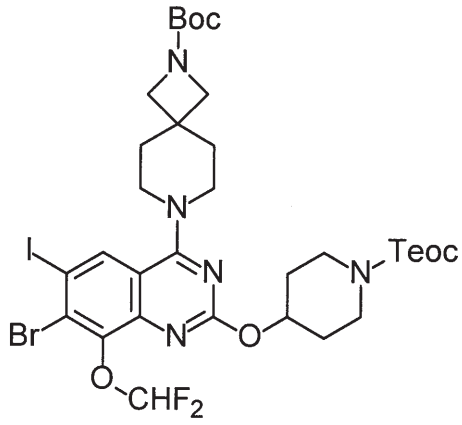
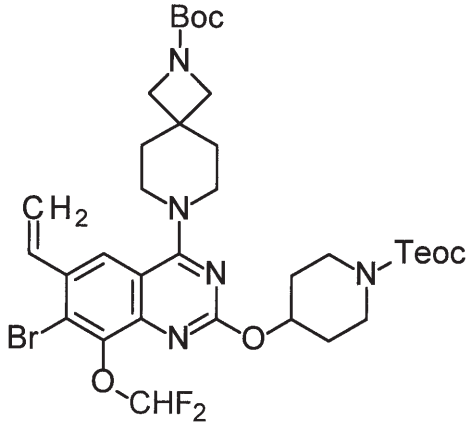
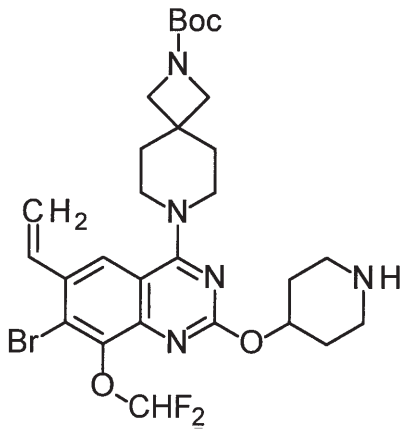
[0243]

[Table 73]

PEx	PSyn	Str	Dat
178	6		ESI+; 690.3
179	23		ESI+; 740.5
180	115		ESI+; 818.3, 820.2

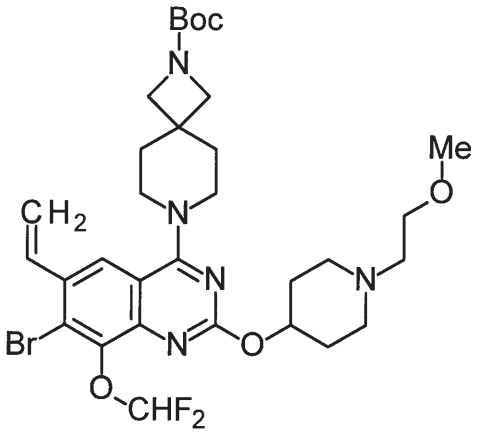
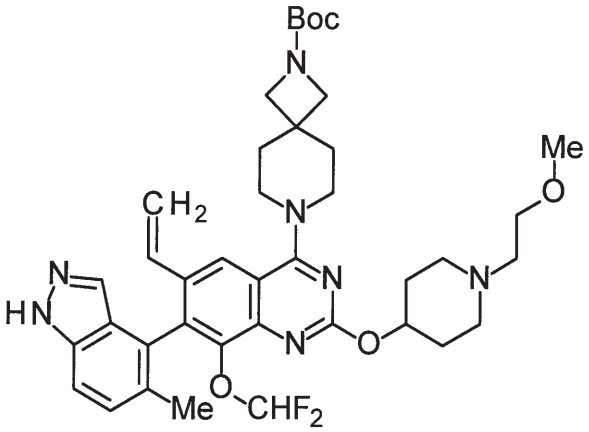
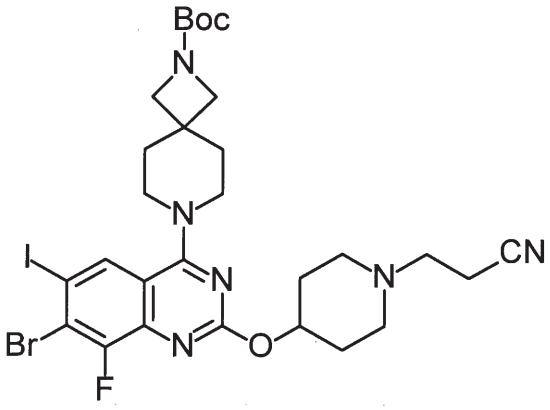
[0244]

[Table 74]

PEx	PSyn	Str	Dat
181	181		ESI+; 868.3, 870.3
182	6		ESI+; 768.5, 770.4
183	118		ESI+; 624.4

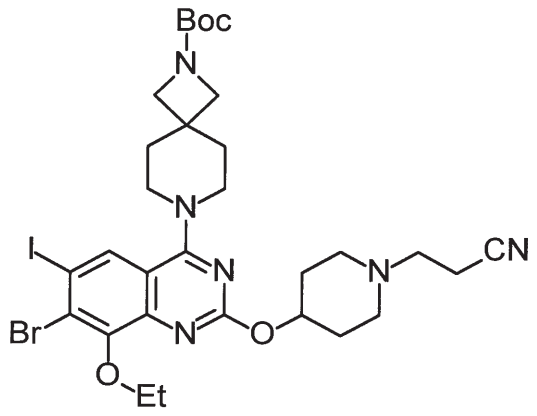
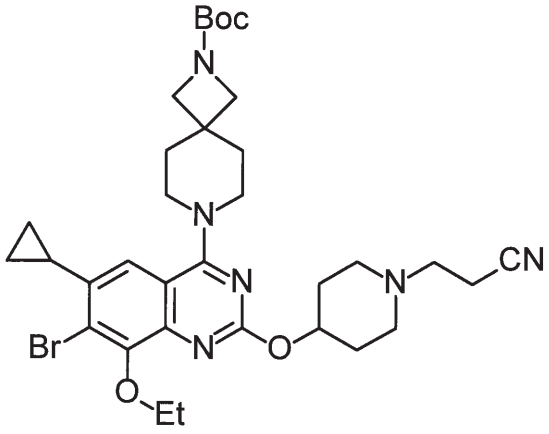
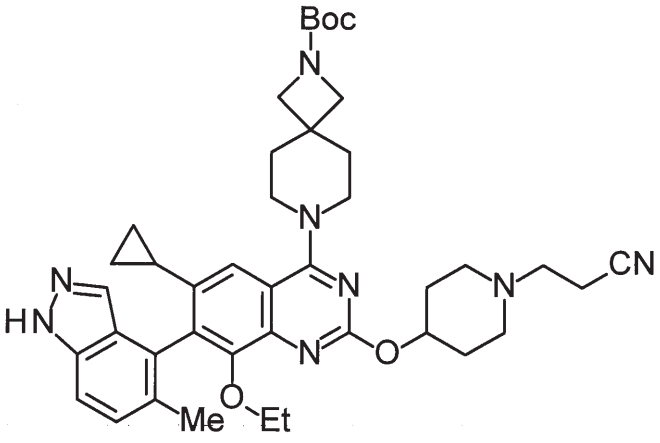
[0245]

[Table 75]

PEx	PSyn	Str	Dat
184	144		ESI+; 684.4
185	23		ESI+; 734.6
186	4		ESI+; 731.0

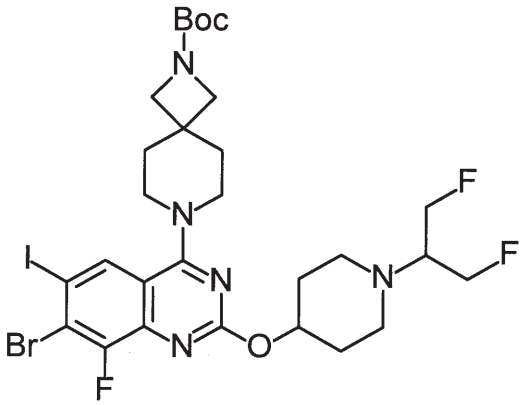
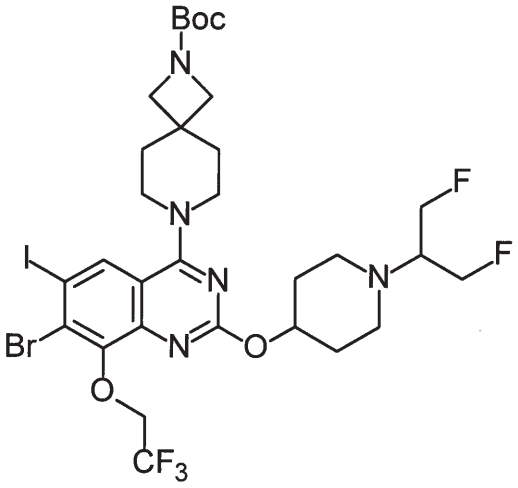
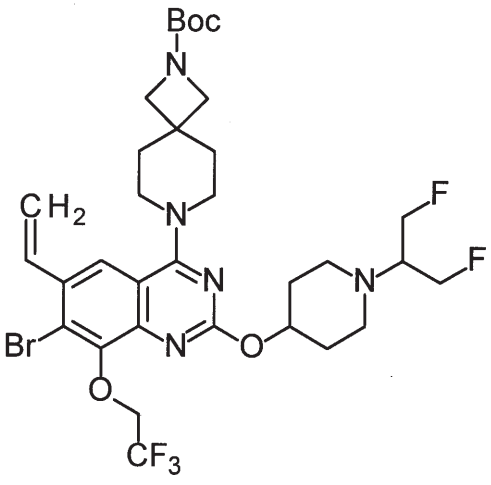
[0246]

[Table 76]

PEx	PSyn	Str	Dat
187	8		ESI+; 755.1
188	9		ESI+; 671.2
189	7		ESI+; 721.4

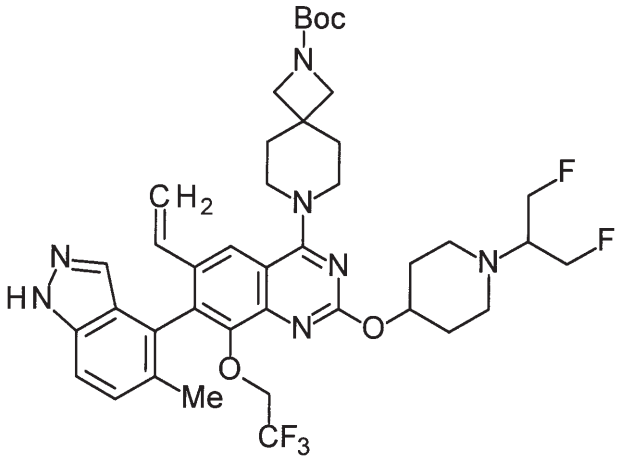
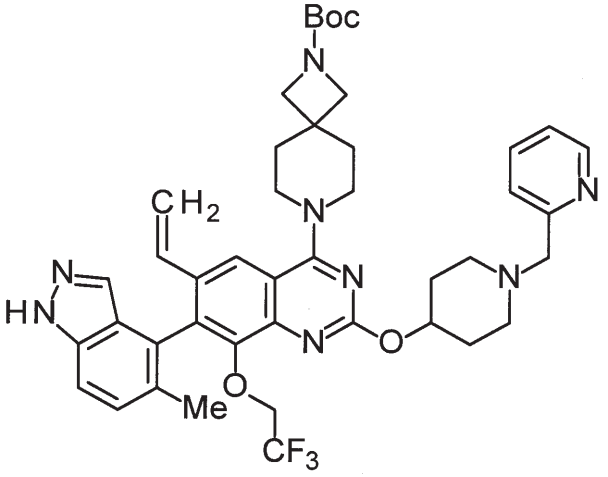
[0247]

[Table 77]

PEx	PSyn	Str	Dat
190	4		ESI+; 756.2
191	39		ESI+; 836.3
192	6		ESI+; 736.3

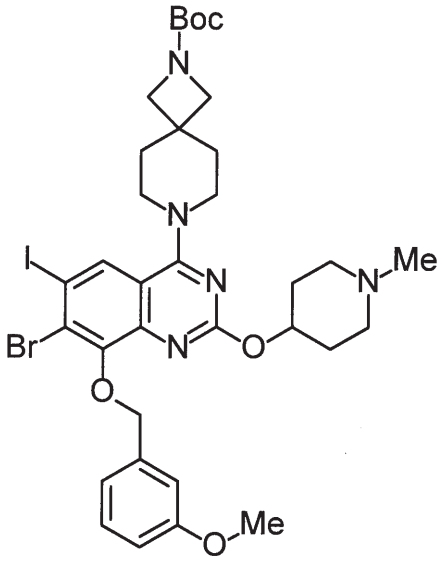
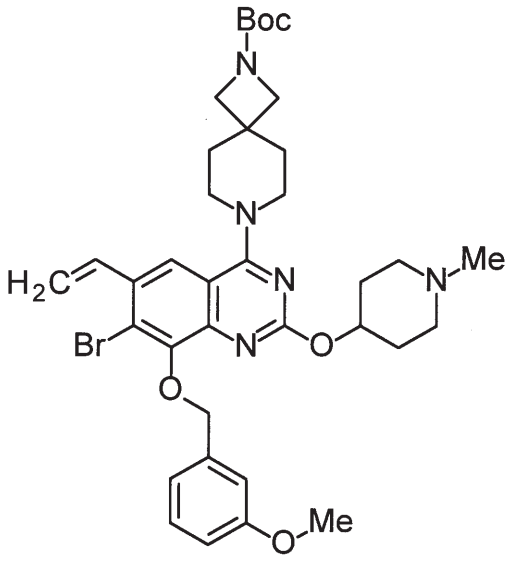
[0248]

[Table 78]

PEx	PSyn	Str	Dat
193	23		ESI+; 786.5
194	155		ESI+; 799.5

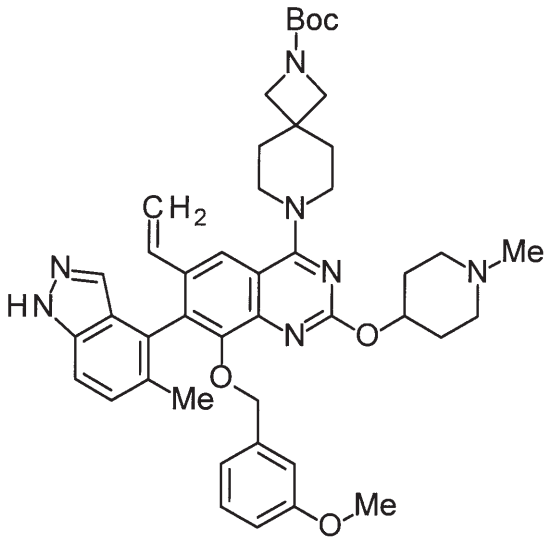
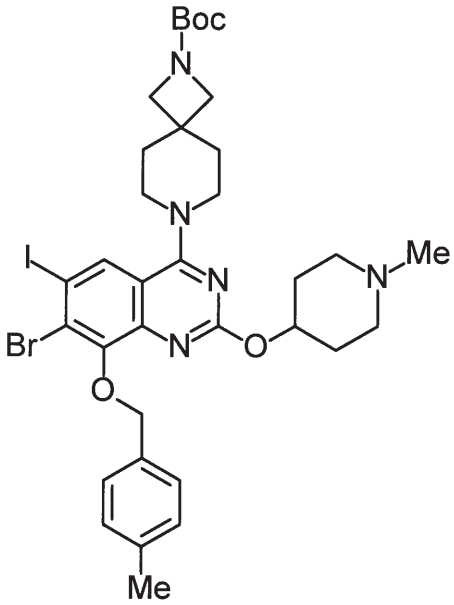
[0249]

[Table 79]

PEx	PSyn	Str	Dat
195	5		ESI+; 810.3
196	6		ESI+; 710.5

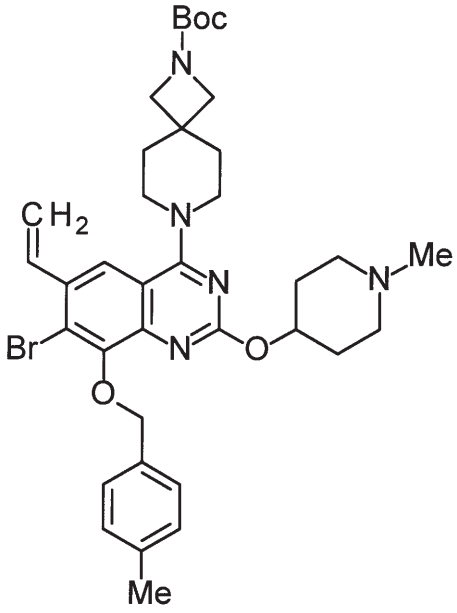
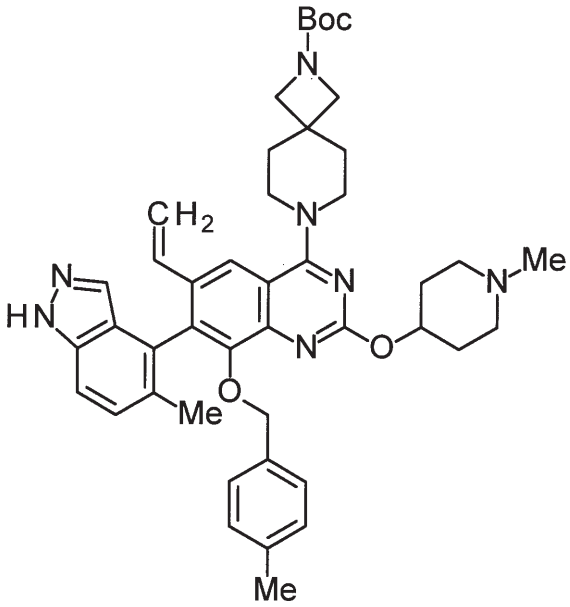
[0250]

[Table 80]

PEx	PSyn	Str	Dat
197	23		ESI+; 760.7
198	5		ESI+; 794.3

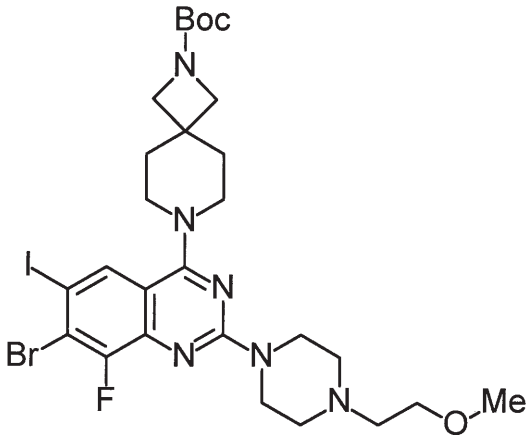
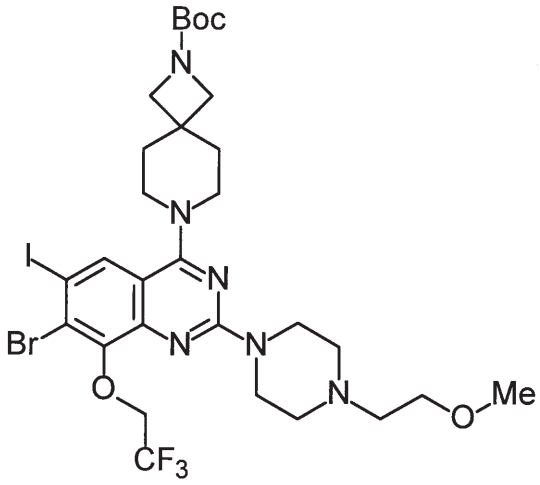
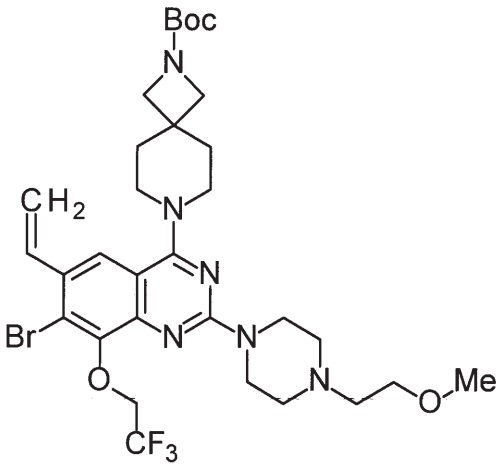
[0251]

[Table 81]

PEx	PSyn	Str	Dat
199	6		ESI+; 694.4
200	23		ESI+; 744.7

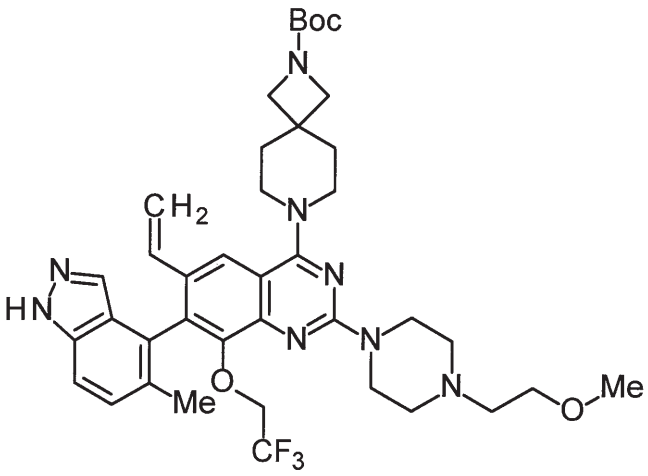
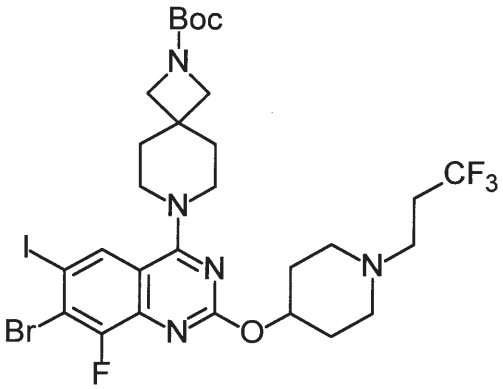
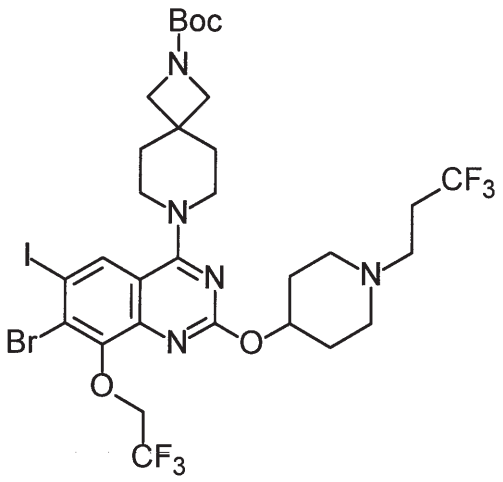
[0252]

[Table 82]

PEx	PSyn	Str	Dat
201	4		ESI+; 721.3
202	39		ESI+; 801.3
203	6		ESI+; 699.4

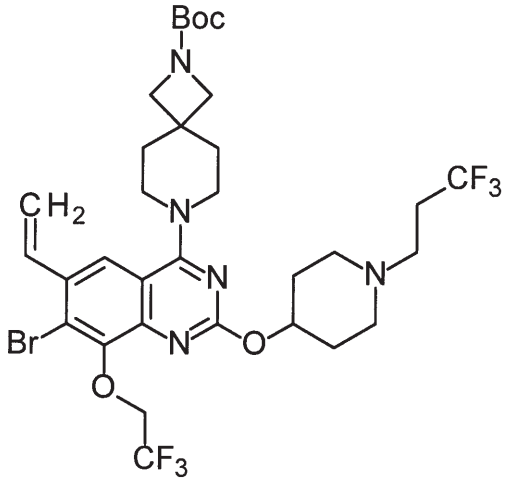
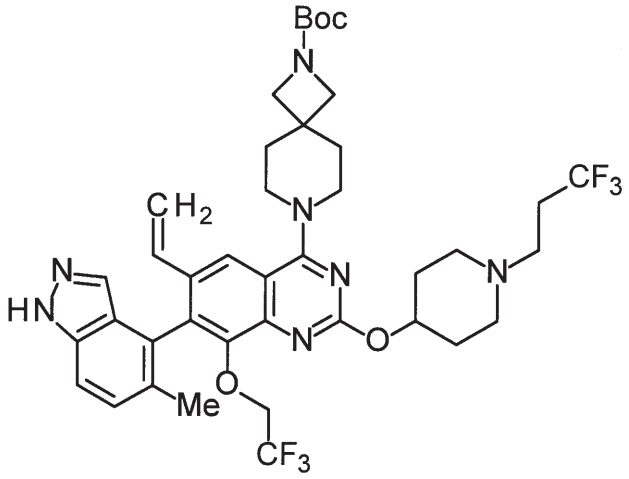
[0253]

[Table 83]

PEx	PSyn	Str	Dat
204	7		ESI+; 751.5
205	4		ESI+; 772.2, 774.2
206	39		ESI+; 854.4

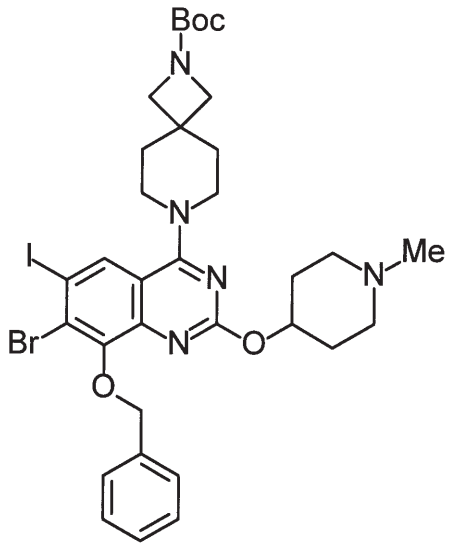
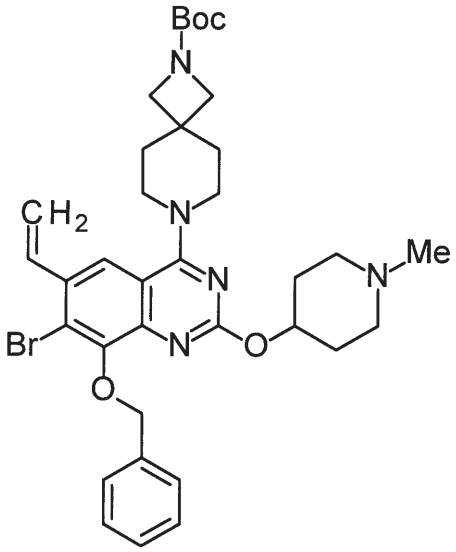
[0254]

[Table 84]

PEx	PSyn	Str	Dat
207	6		ESI+; 752.3, 754.3
208	23		ESI+; 804.5

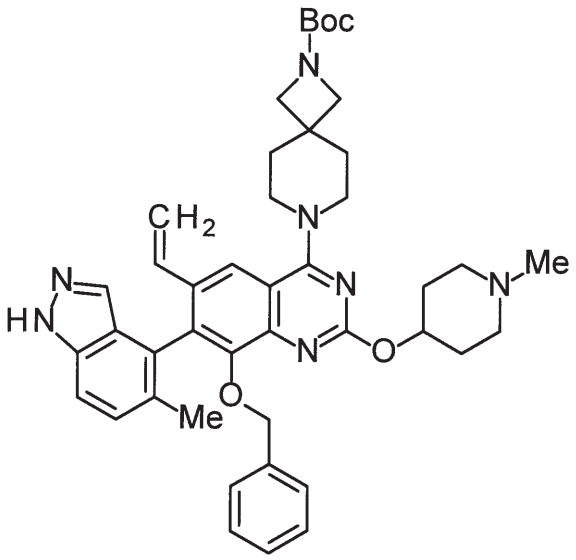
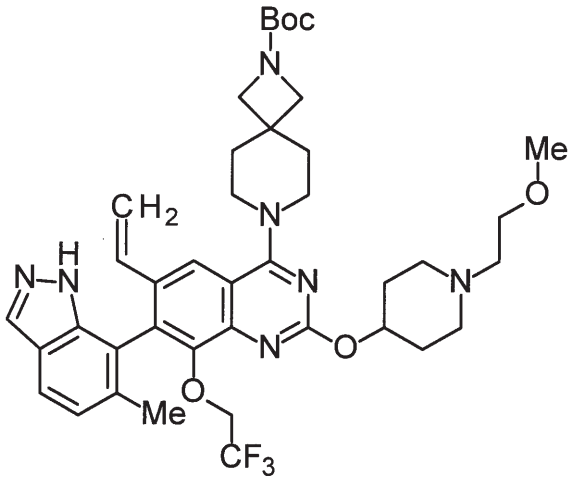
[0255

[Table 85]

PEx	PSyn	Str	Dat
209	5		ESI+; 778.3
210	6		ESI+; 678.4, 680.3

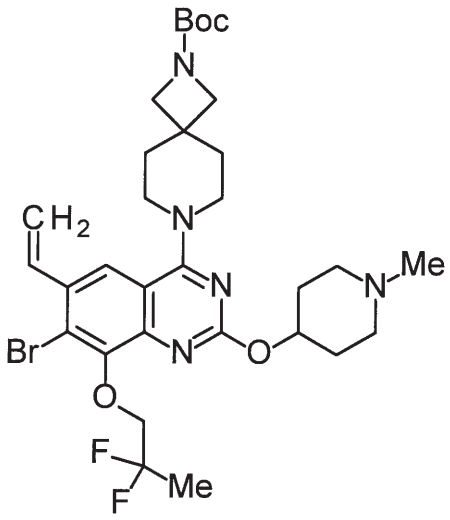
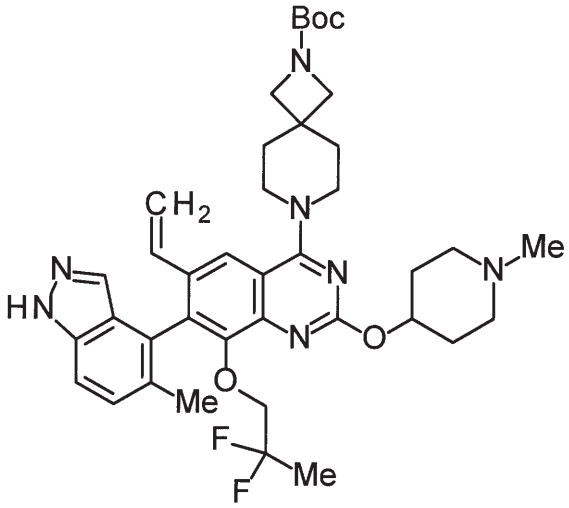
[0256]

[Table 86]

PEx	PSyn	Str	Dat
211	23		ESI+; 730.7
212	23		ESI+; 766.6

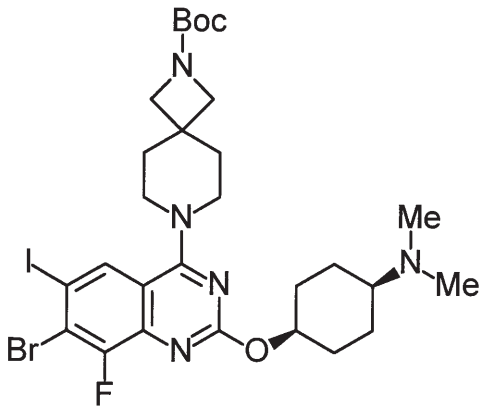
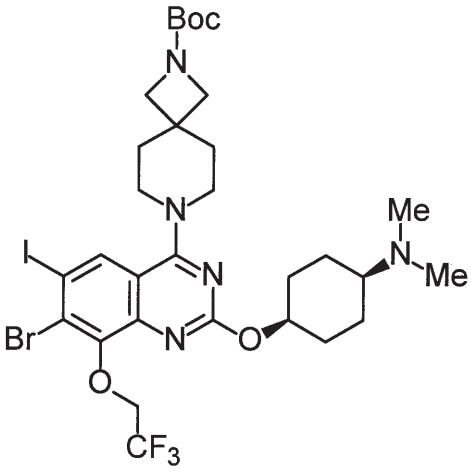
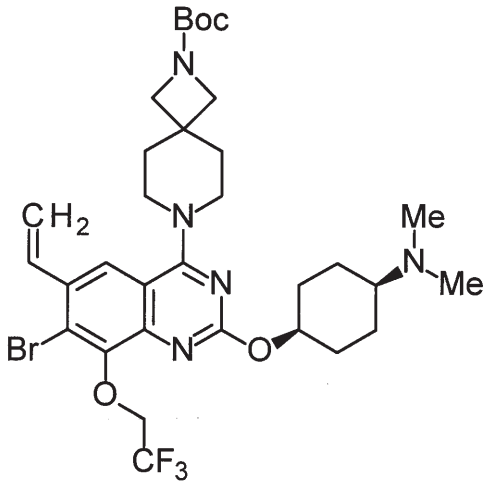
[0257]

[Table 87]

PEx	PSyn	Str	Dat
213	175		ESI+; 668.3
214	7		ESI+; $[M+Na]^+$ 740.5

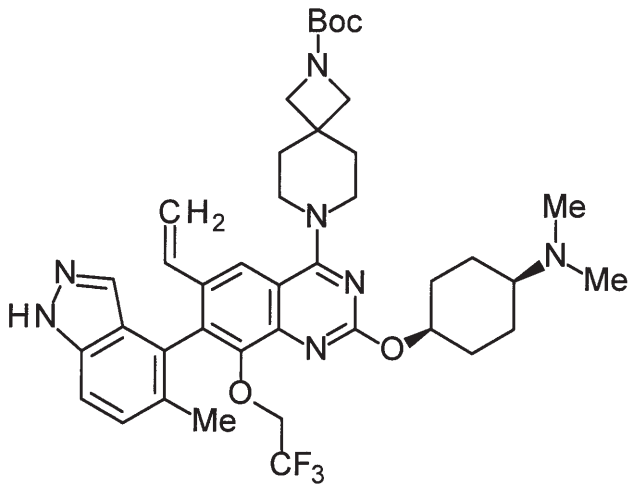
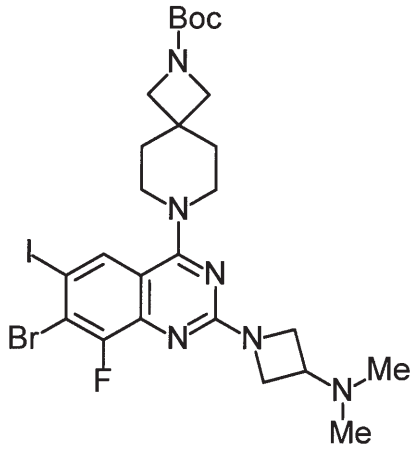
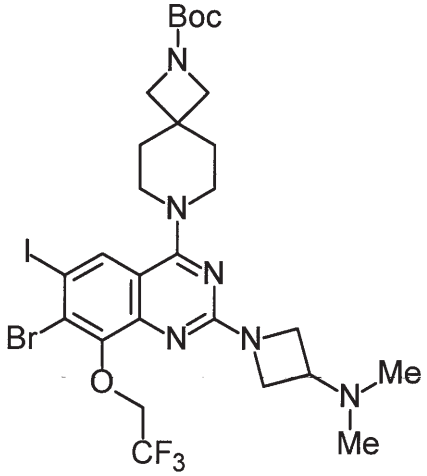
[0258]

[Table 88]

PEx	PSyn	Str	Dat
215	4		ESI+; 718.2, 720.2
216	39		ESI+; 800.2
217	6		ESI+; 700.5

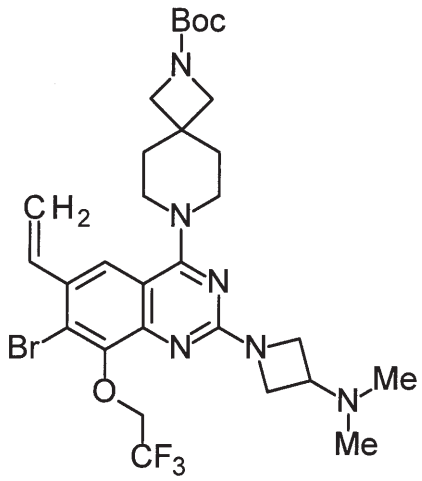
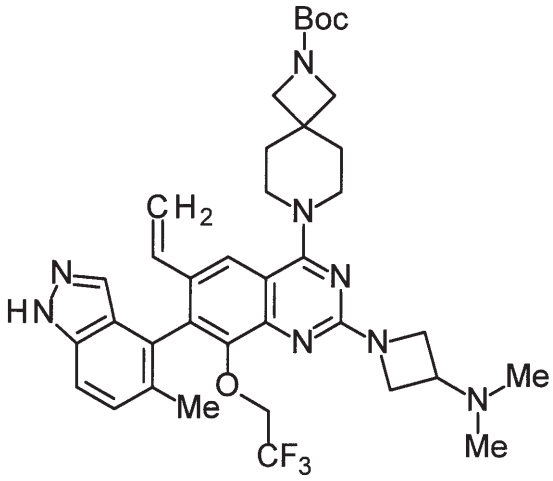
[0259]

[Table 89]

PEx	PSyn	Str	Dat
218	23		ESI+; 750.6
219	4		ESI+; 677.2
220	39		ESI+; 757.3

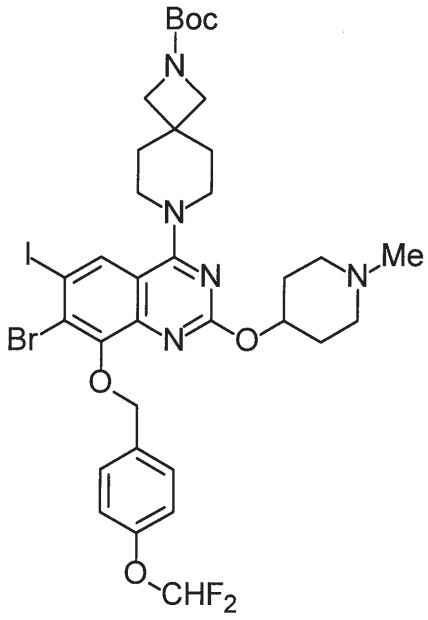
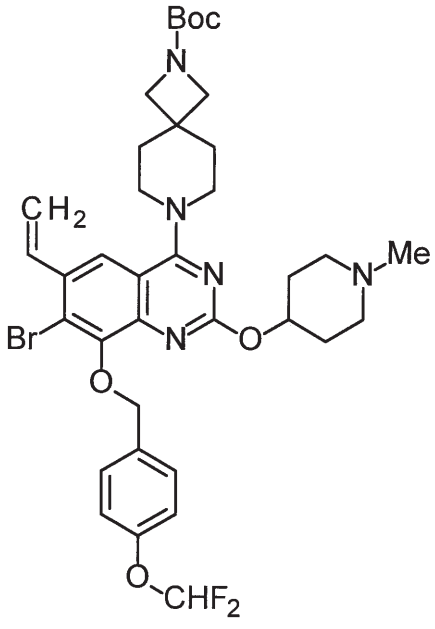
[0260]

[Table 90]

PEx	PSyn	Str	Dat
221	6		ESI+; 657.3
222	7		ESI+; 707.6

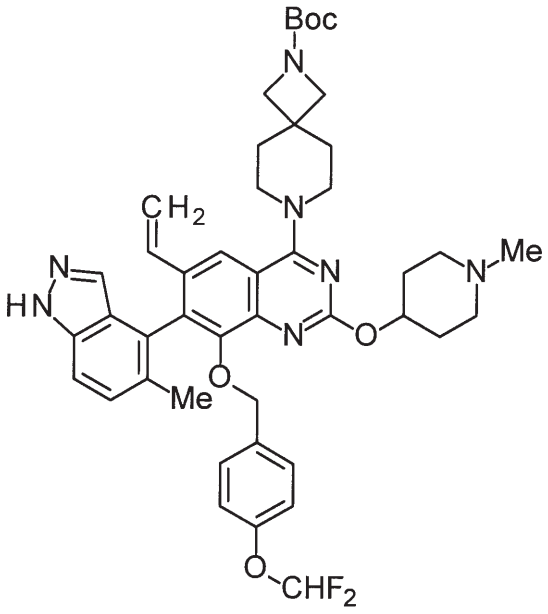
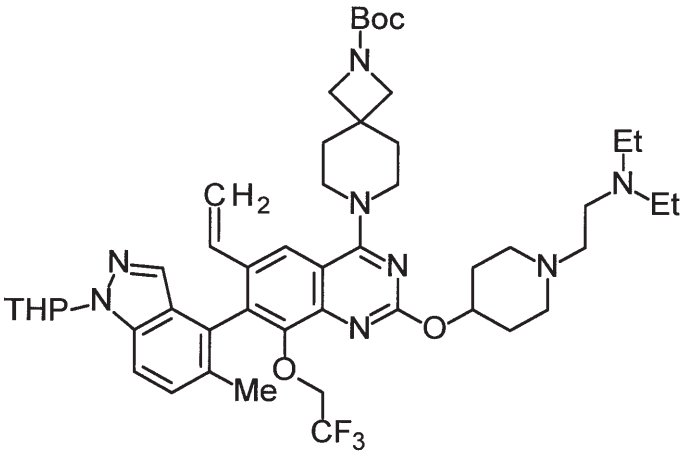
[0261]

[Table 91]

PEx	PSyn	Str	Dat
223	5		ESI+; 846.2
224	6		ESI+; 746.5

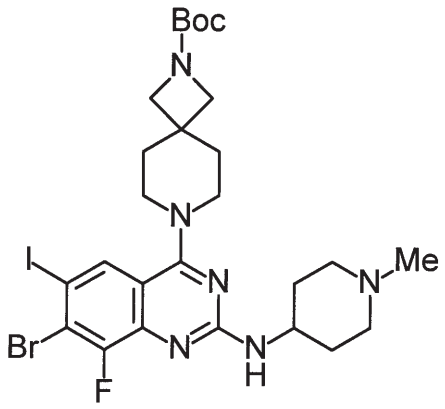
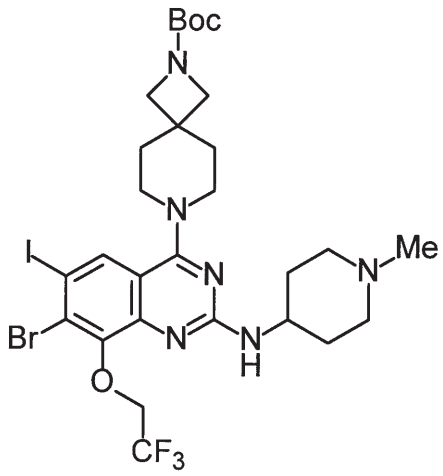
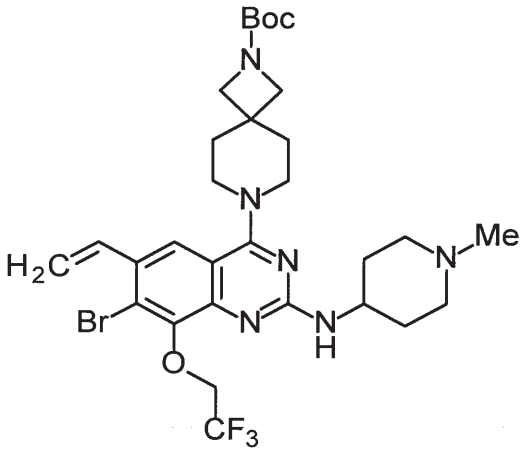
[0262]

[Table 92]

PEx	PSyn	Str	Dat
225	23		ESI+; 796.6
226	144		ESI+; 891.7

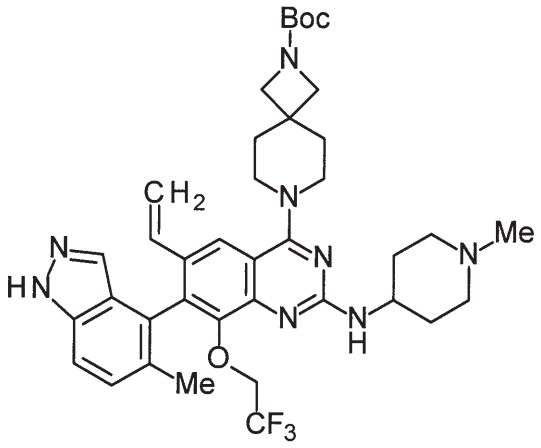
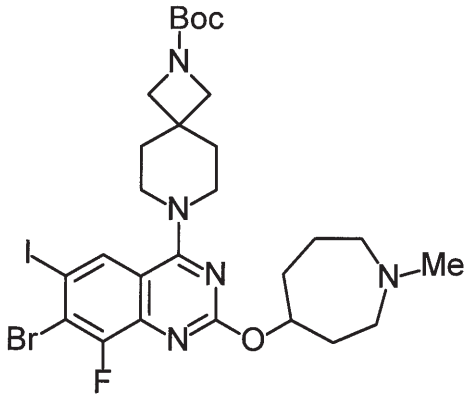
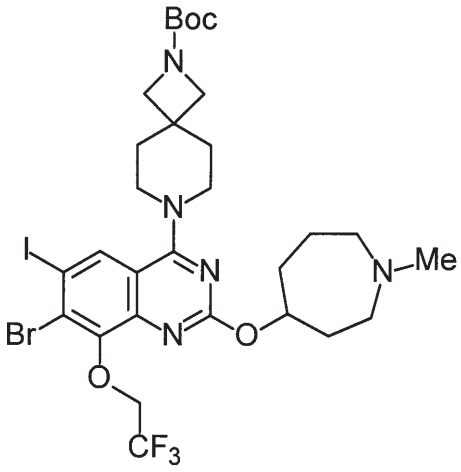
[0263]

[Table 93]

PEx	PSyn	Str	Dat
227	227		ESI+; 689.2, 691.2
228	39		ESI+; 769.3, 771.3
229	6		ESI+; 671.3

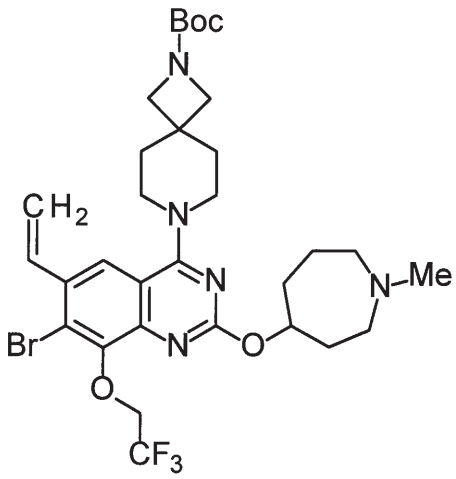
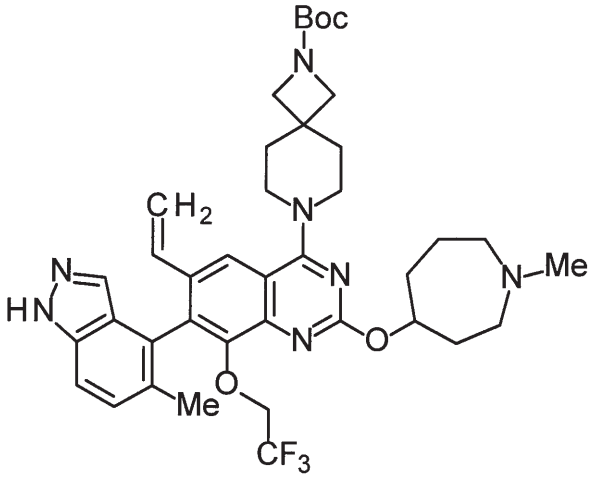
[0264]

[Table 94]

PEx	PSyn	Str	Dat
230	23		ESI+; 721.5
231	4		ESI+; 704.2, 706.2
232	39		ESI+; 784.3

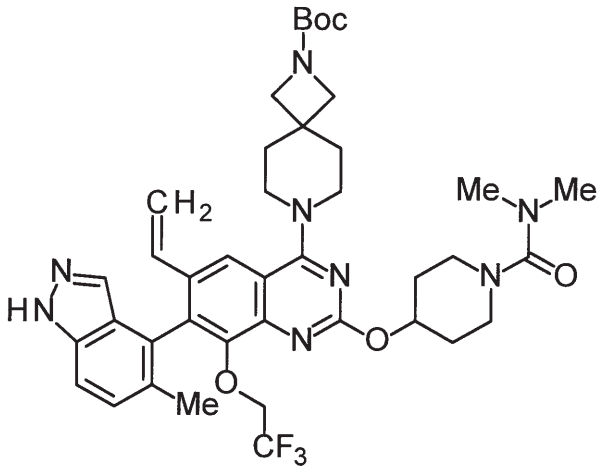
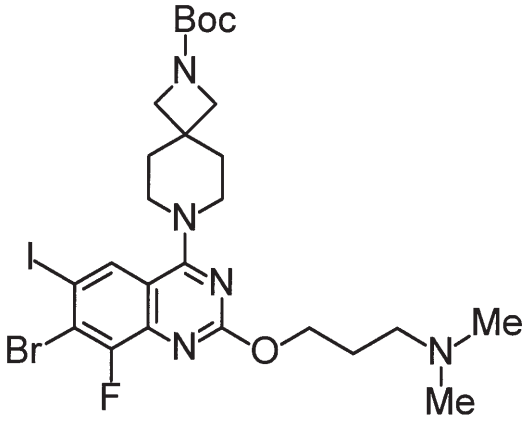
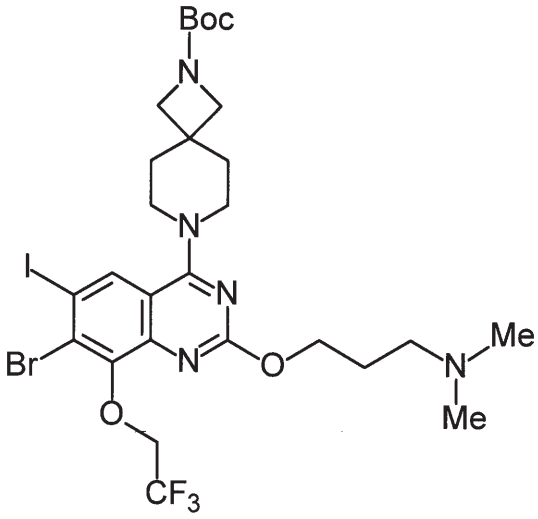
[0265]

[Table 95]

PEx	PSyn	Str	Dat
233	6		ESI+; 684.5
234	23		ESI+; $[M+Na]^+$ 758.5

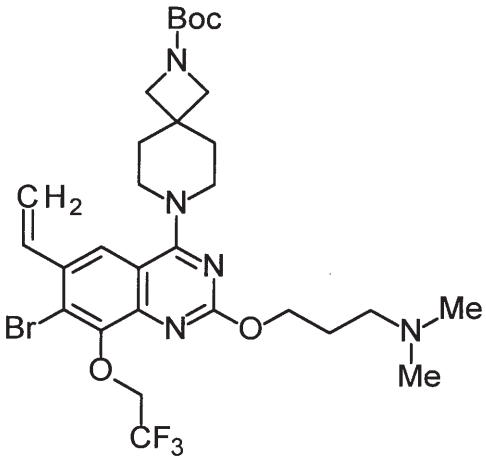
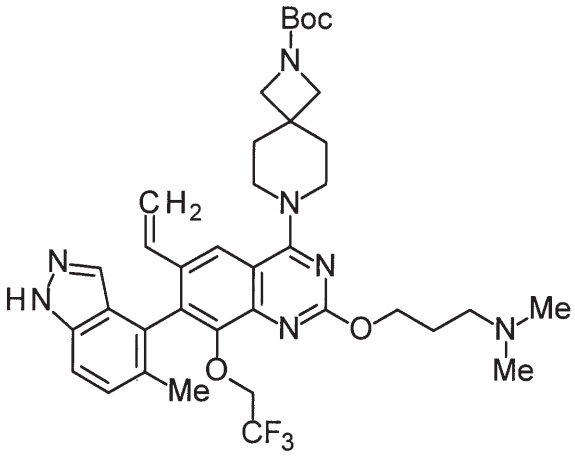
[0266]

[Table 96]

PEx	PSyn	Str	Dat
235	235		ESI+; 779.6
236	4		ESI+; 680.2
237	39		ESI+; 760.2

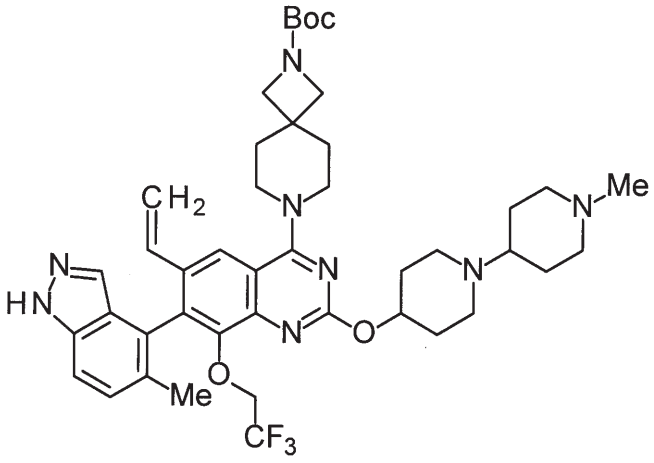
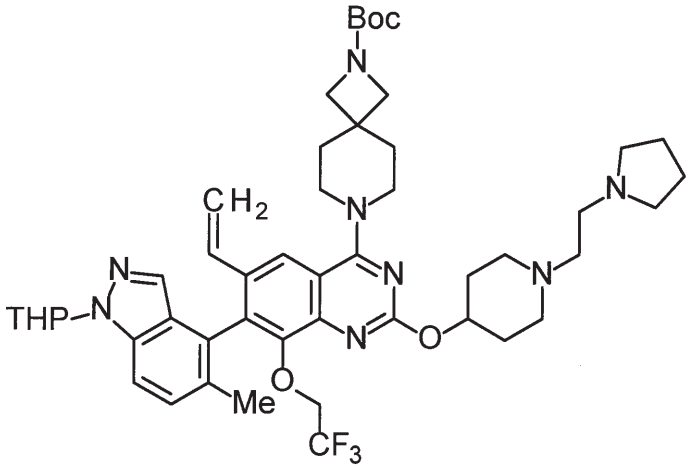
[0267]

[Table 97]

PEx	PSyn	Str	Dat
238	6		ESI+; 660.3
239	23		ESI+; 710.5

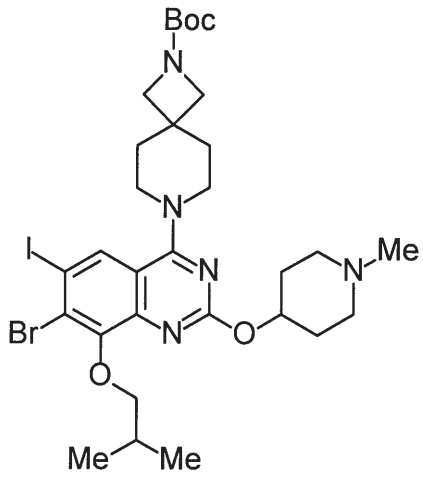
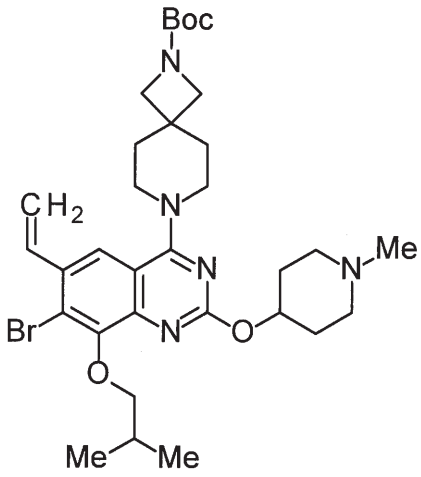
[0268]

[Table 98]

PEx	PSyn	Str	Dat
240	155		ESI+; 805.5
241	141		ESI+; 889.5

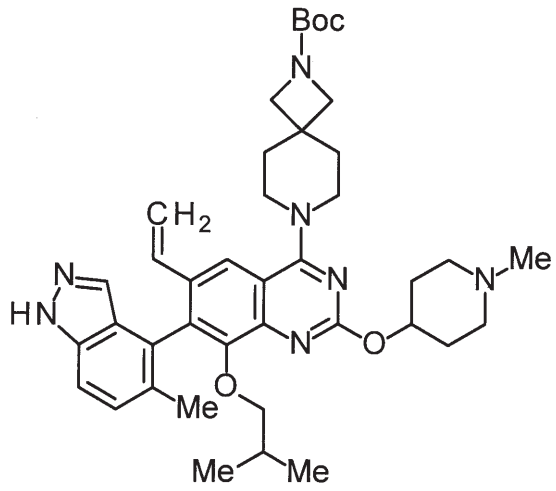
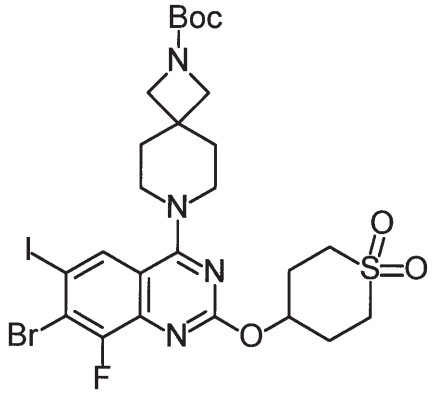
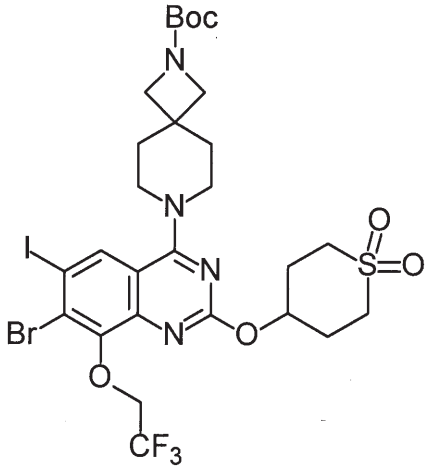
[0269]

[Table 99]

PEx	PSyn	Str	Dat
242	5		ESI+; 746.3
243	6		ESI+; 646.4

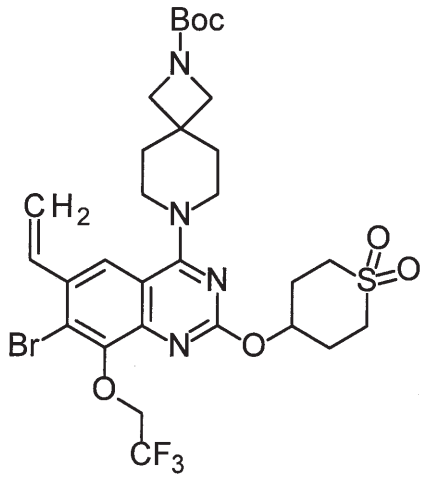
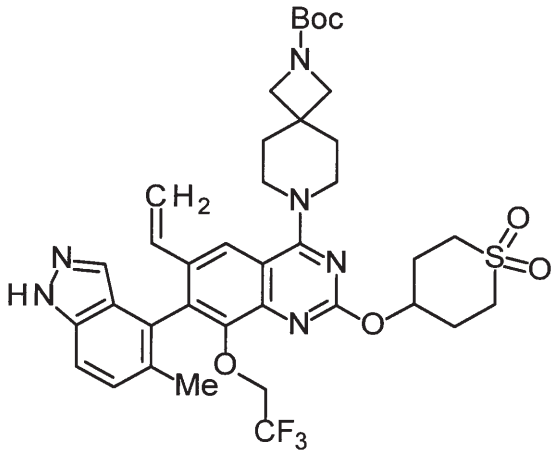
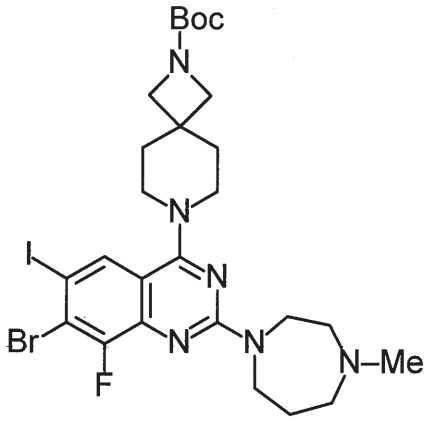
[0270]

[Table 100]

PEx	PSyn	Str	Dat
244	23		ESI+; 696.6
245	4		ESI+; 727.2
246	39		ESI+; 805.2, 807.2

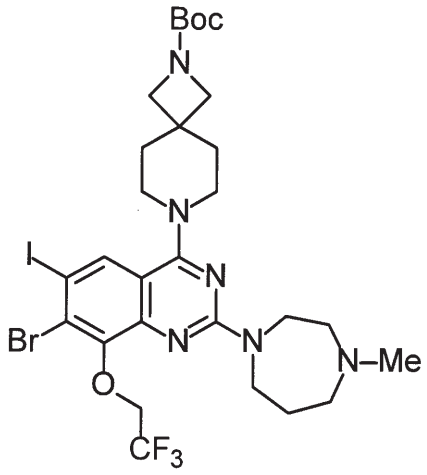
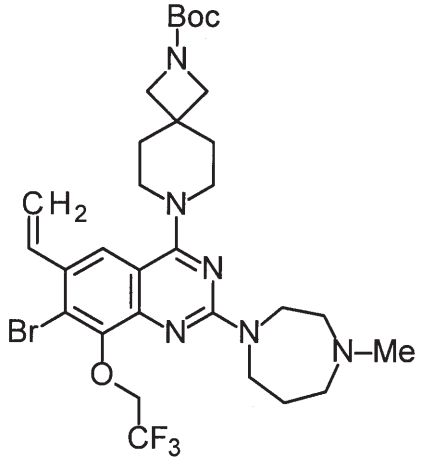
[0271]

[Table 101]

PEx	PSyn	Str	Dat
247	6		ESI+; 705.3, 707.3
248	23		ESI+; 757.5
249	4		ESI+; 691.2

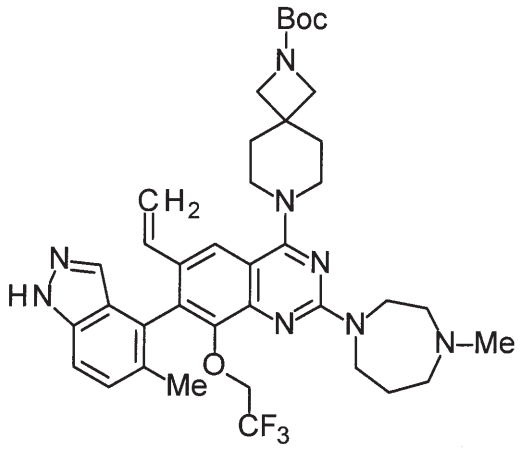
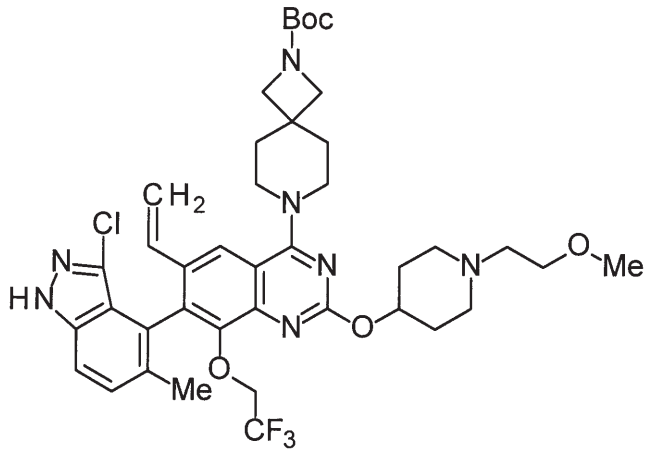
[0272]

[Table 102]

PEx	PSyn	Str	Dat
250	39		ESI+; 771.3
251	6		ESI+; 671.4

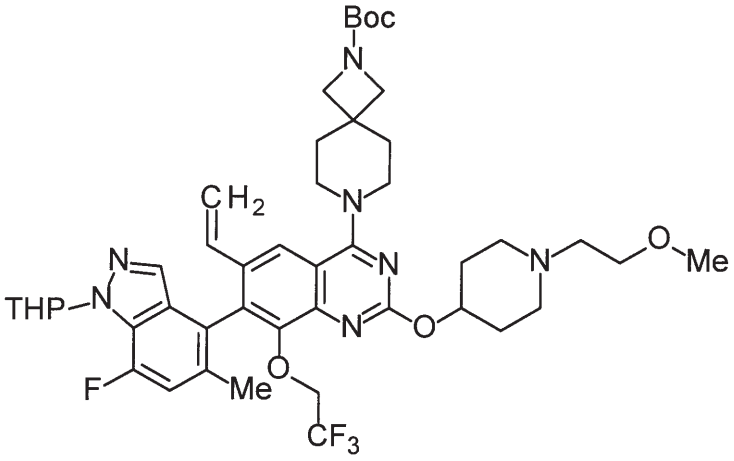
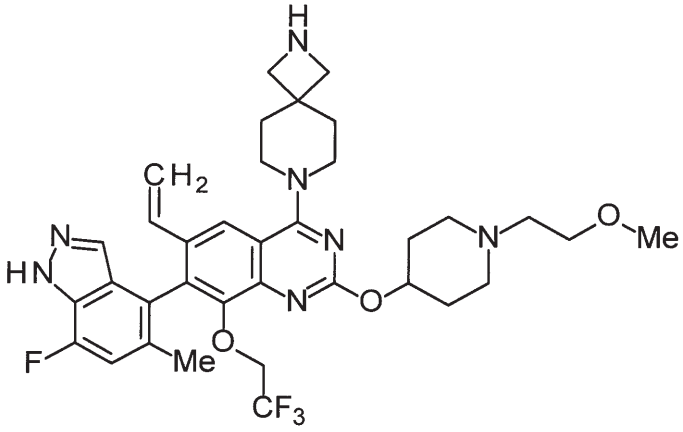
[0273]

[Table 103]

PEx	PSyn	Str	Dat
252	23		ESI+; 721.5
253	253		ESI+; 800.4, 802.5

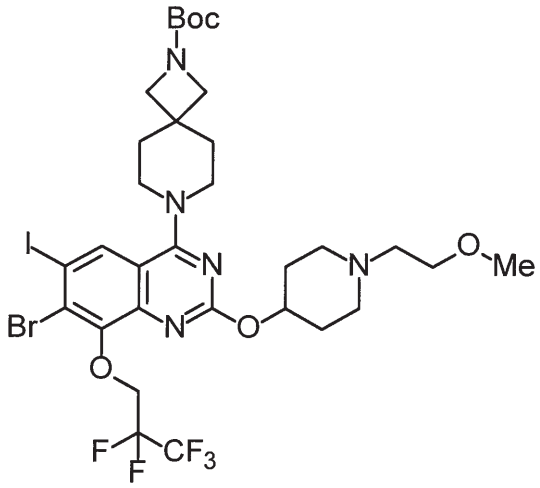
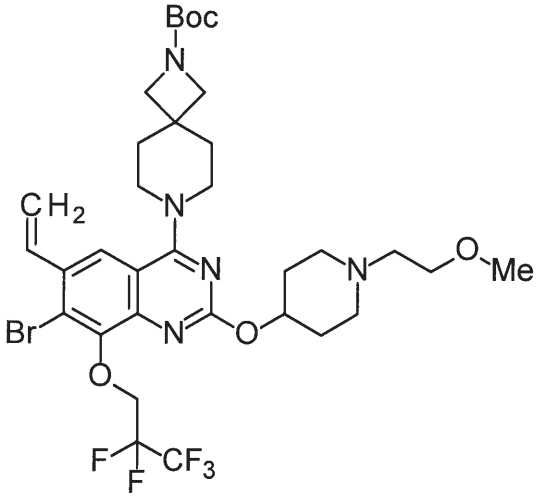
[0274]

[Table 104]

PEx	PSyn	Str	Dat
254	7		ESI+; 868.5
255	28		ESI+; 684.5

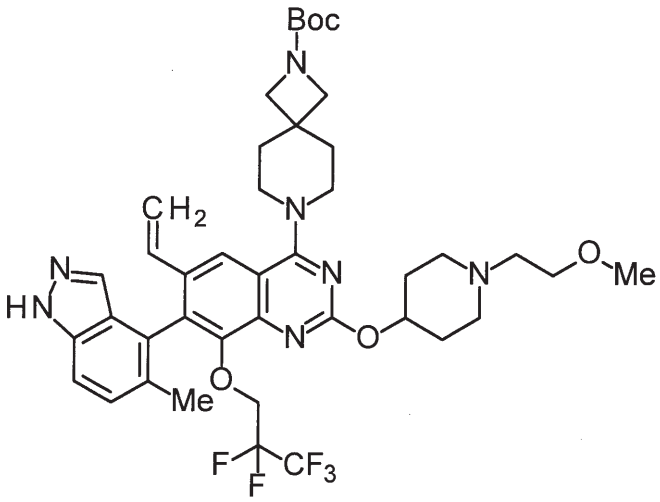
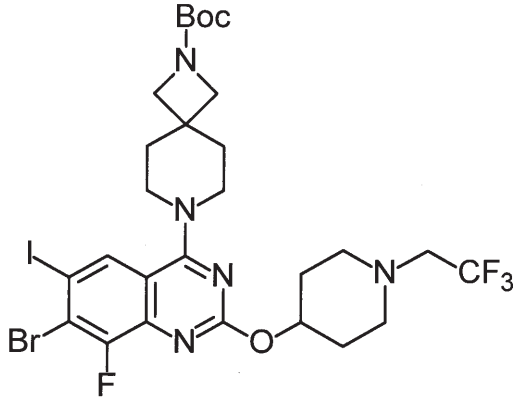
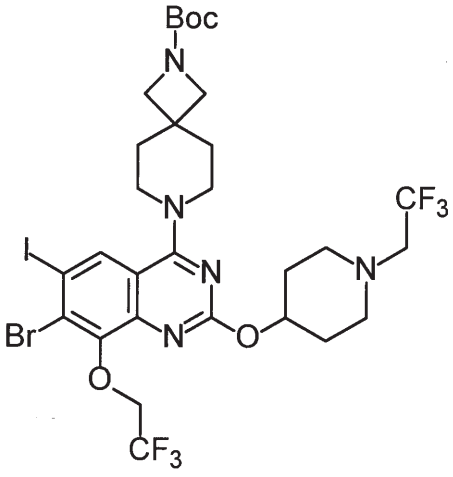
[0275]

[Table 105]

PEx	PSyn	Str	Dat
256	39		ESI+; 864.4, 866.4
257	6		ESI+; 764.4, 766.3

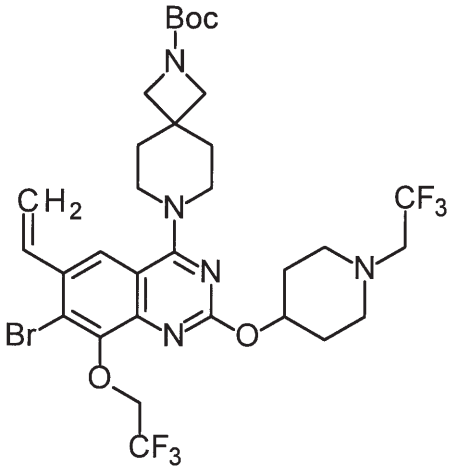
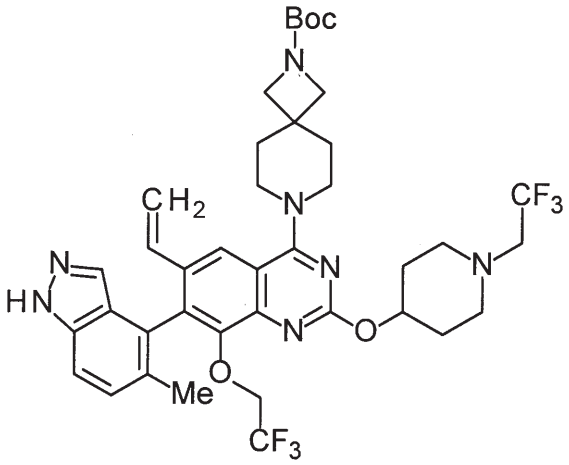
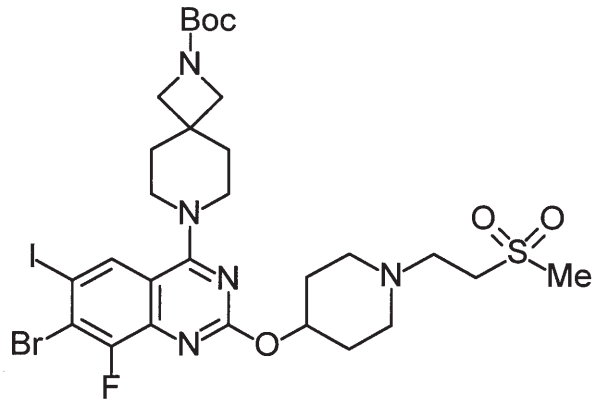
[0276]

[Table 106]

PEx	PSyn	Str	Dat
258	23		ESI+; 816.5
259	4		ESI+; 758.3, 760.3
260	39		ESI+; 838.2, 840.2

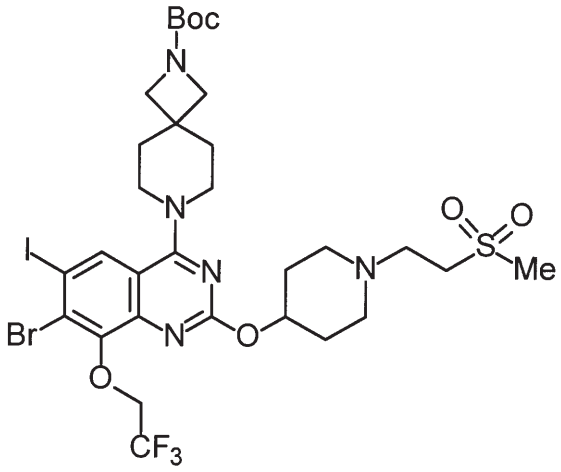
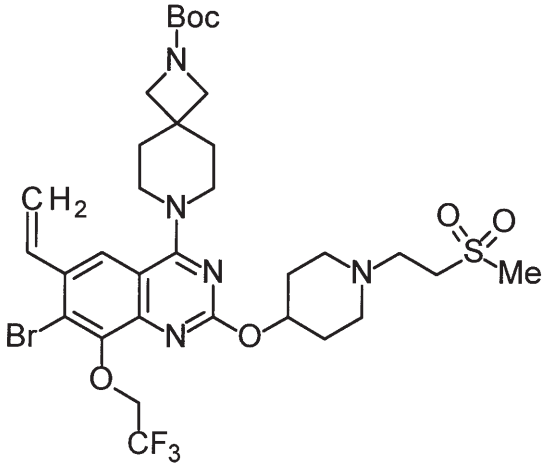
[0277]

[Table 107]

PEx	PSyn	Str	Dat
261	6		ESI+; 740.3
262	23		ESI+; 790.6
263	4		ESI+; 784.0

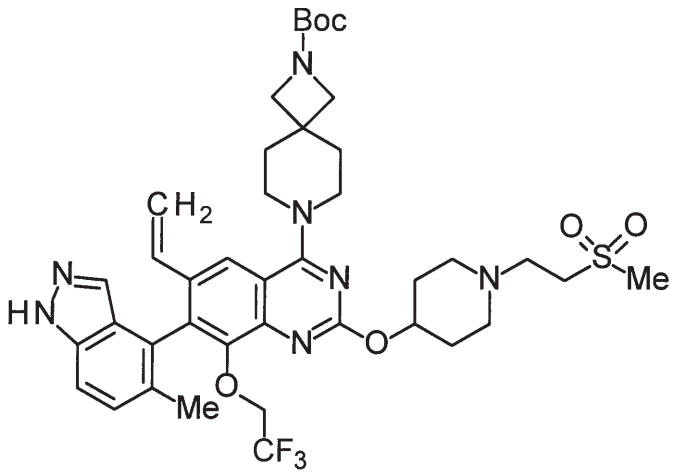
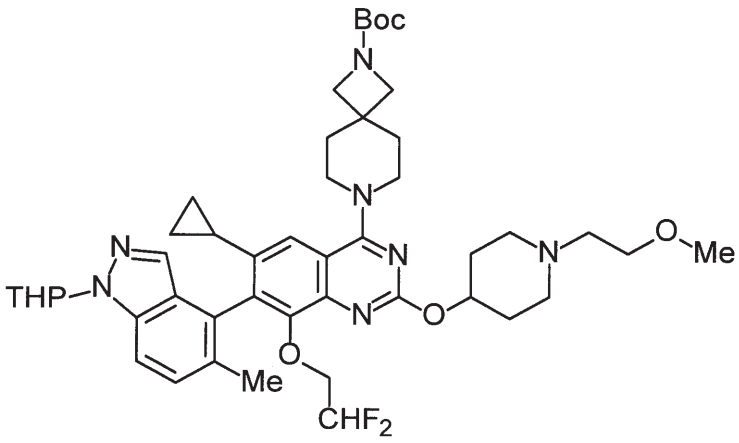
[0278]

[Table 108]

PEx	PSyn	Str	Dat
264	39		ESI+; 864.0
265	6		ESI+; 764.2

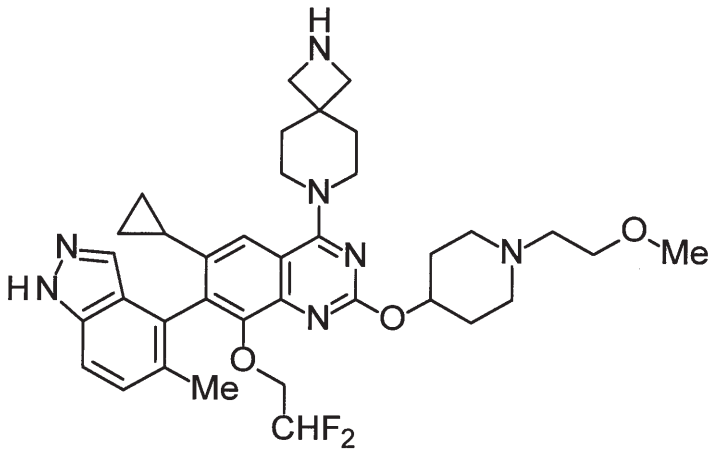
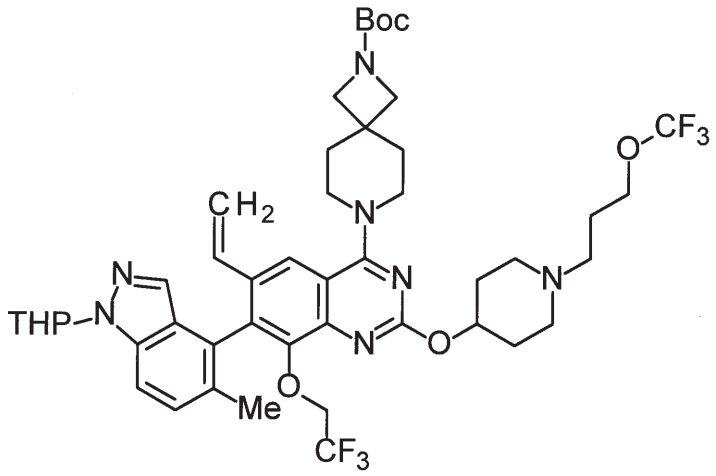
[0279]

[Table 109]

PEx	PSyn	Str	Dat
266	23		ESI+; 814.3
267	23		ESI+; 846.6

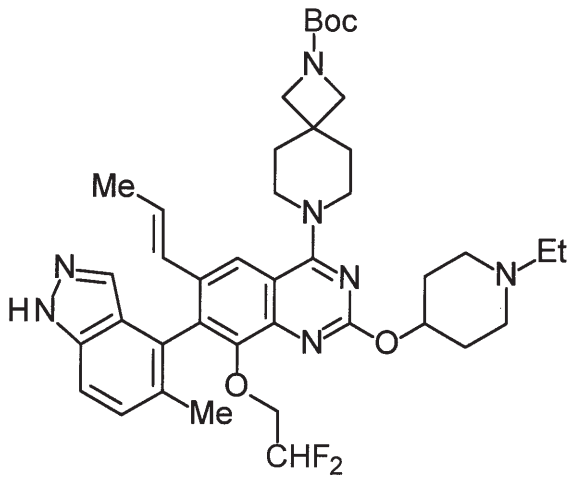
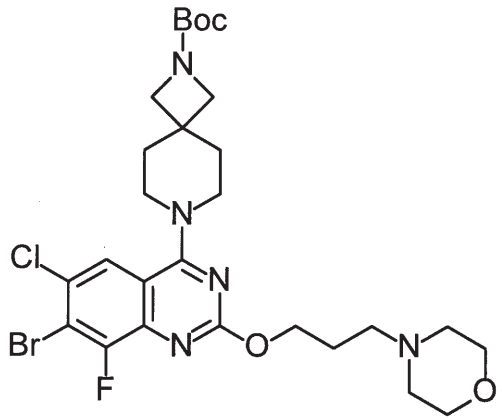
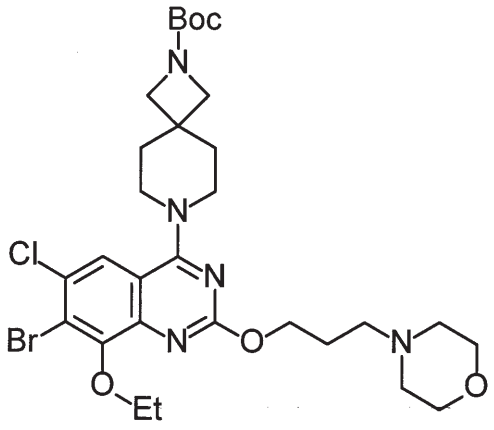
[0280]

[Table 110]

PEx	PSyn	Str	Dat
268	28		ESI+; 662.5
269	144		ESI+; 918.5

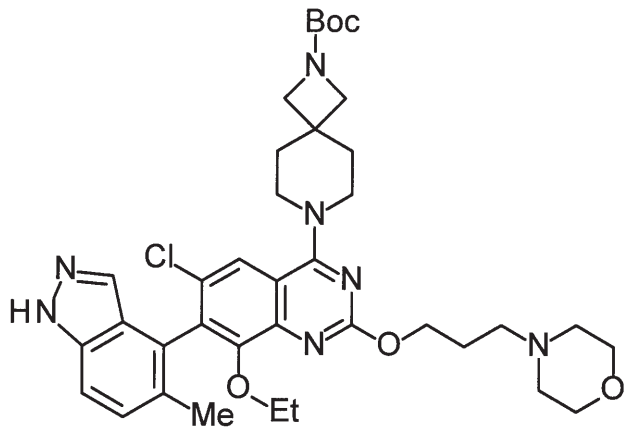
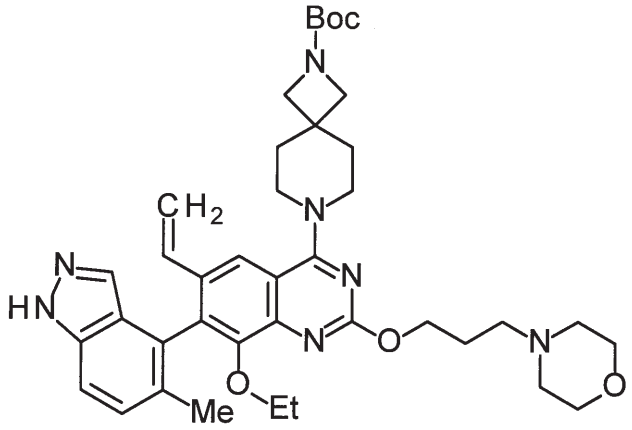
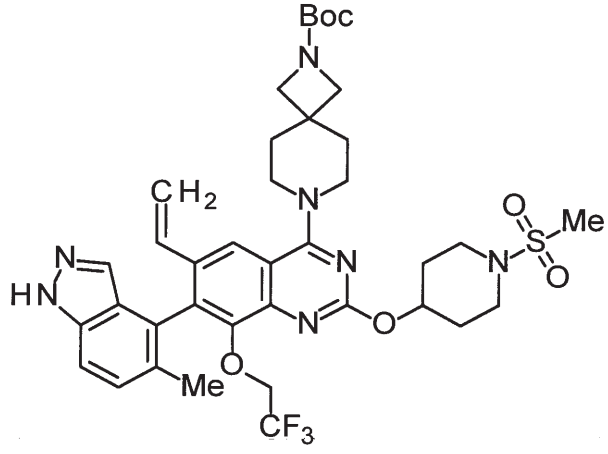
[0281]

[Table 111]

PEx	PSyn	Str	Dat
270	24		ESI+; 732.7
271	4		ESI+; 628.4, 630.4
272	8		ESI+; 654.4, 656.4

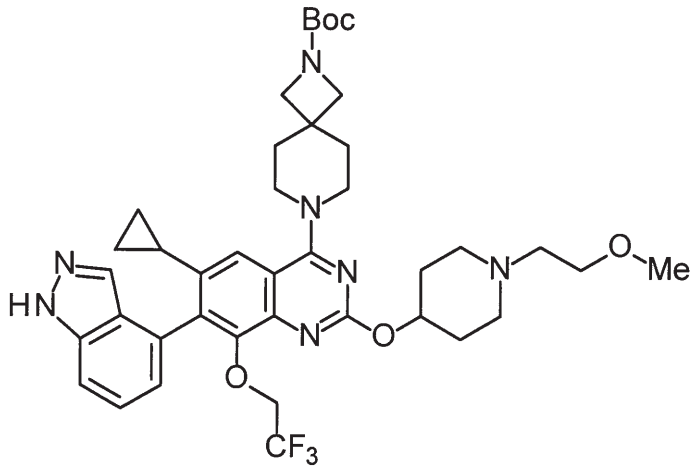
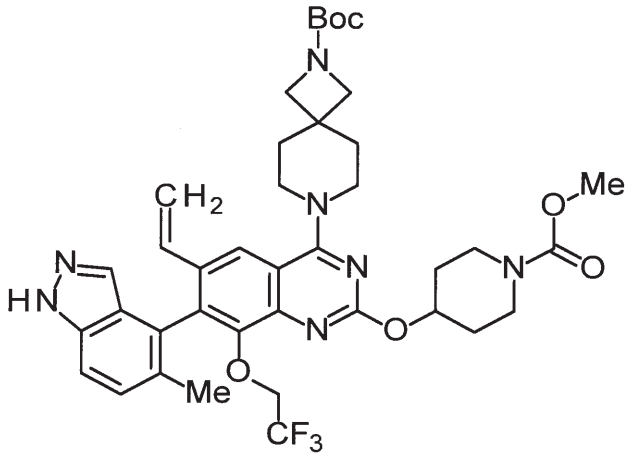
[0282]

[Table 112]

PEx	PSyn	Str	Dat
273	7		ESI+; 706.5, 708.5
274	24		ESI+; 698.7
275	235		ESI+; 786.5

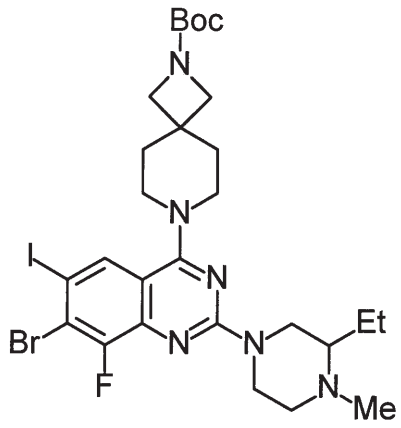
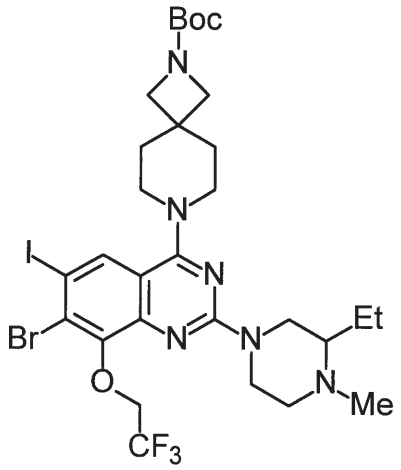
[0283]

[Table 113]

PEx	PSyn	Str	Dat
276	7		ESI+; 766.5
277	235		ESI+; 766.4

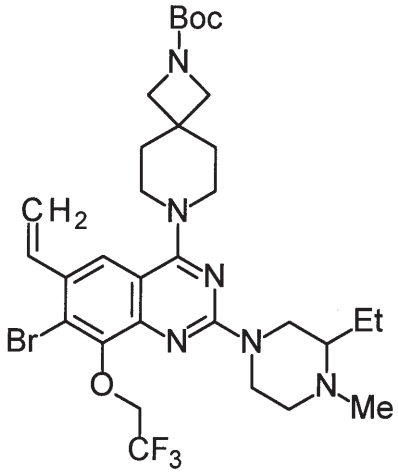
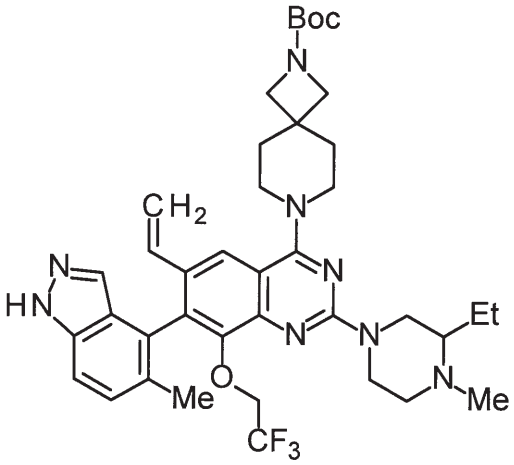
[0284]

[Table 114]

PEx	PSyn	Str	Dat
278	4		ESI+; 705.2
279	39		ESI+; 783.3

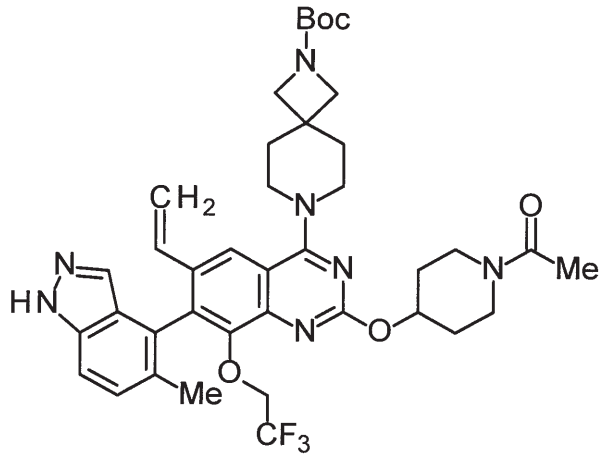
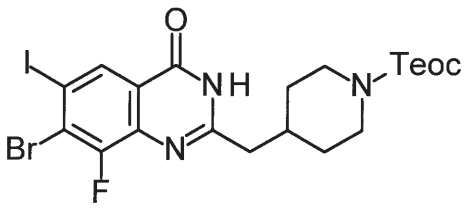
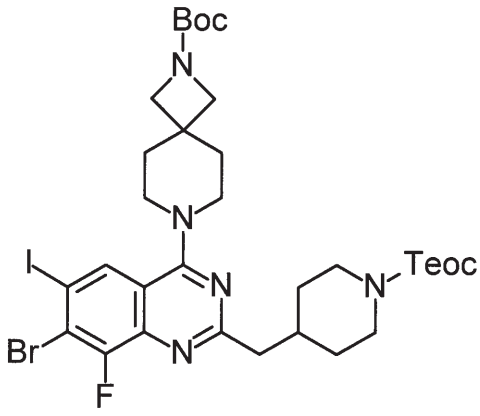
[0285]

[Table 115]

PEx	PSyn	Str	Dat
280	6		ESI+; 685.4
281	23		ESI+; 735.5

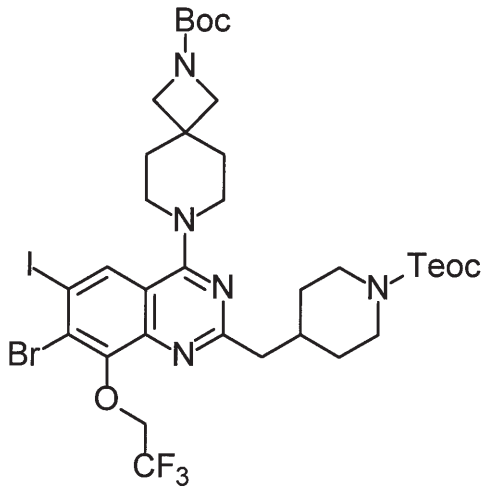
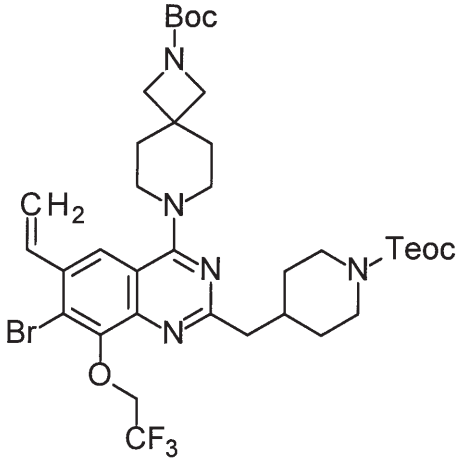
[0286]

[Table 116]

PEx	PSyn	Str	Dat
282	235		ESI+; 750.5
283	283		ESI-; 608.2
284	284		ESI+; 818.3, 820.3

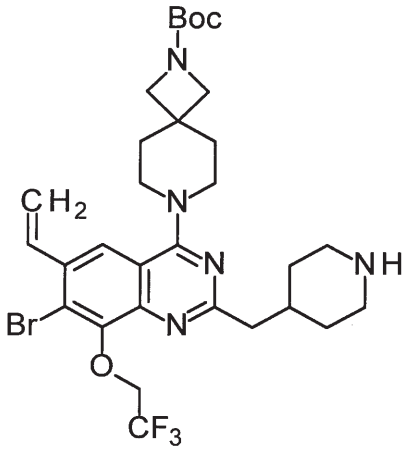
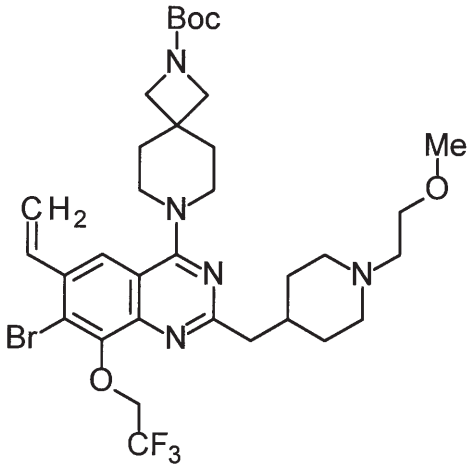
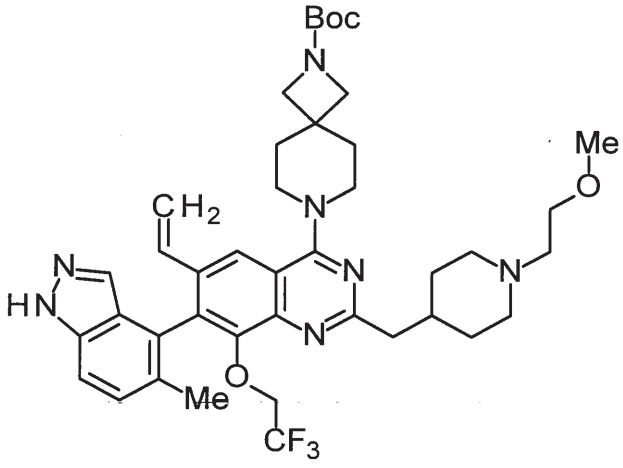
[0287]

[Table 117]

PEx	PSyn	Str	Dat
285	39		ESI+; 898.3, 900.4
286	6		ESI+; 798.5, 800.5

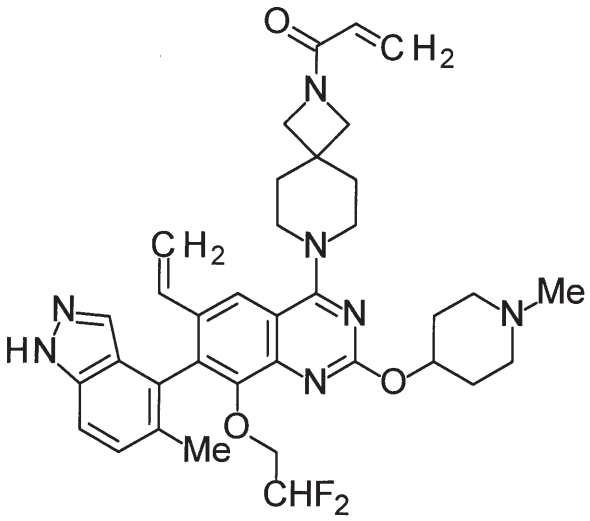
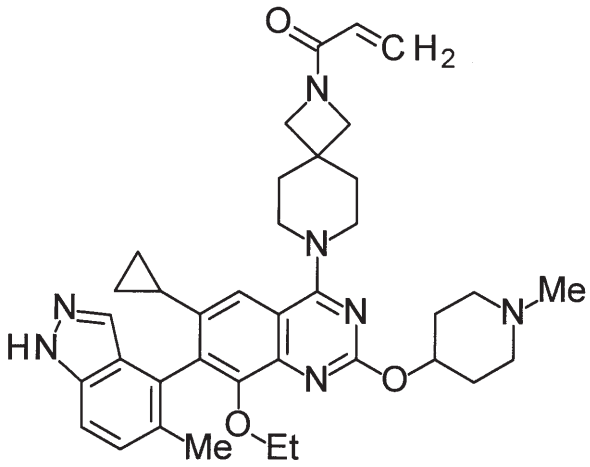
[0288]

[Table 118]

PEx	PSyn	Str	Dat
287	118		ESI+; 656.3
288	144		ESI+; 714.4
289	23		ESI+; 764.5

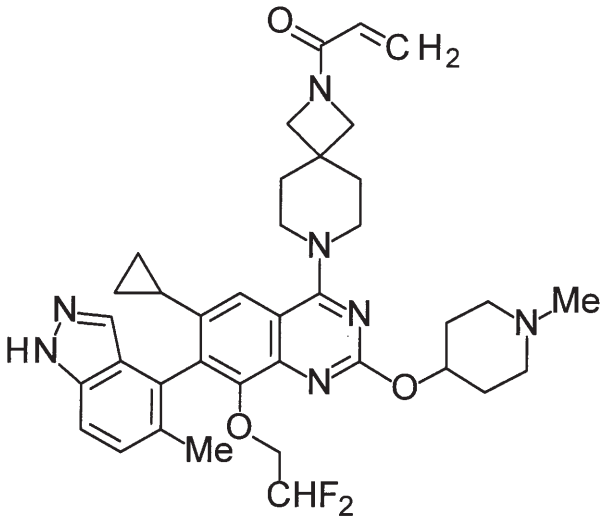
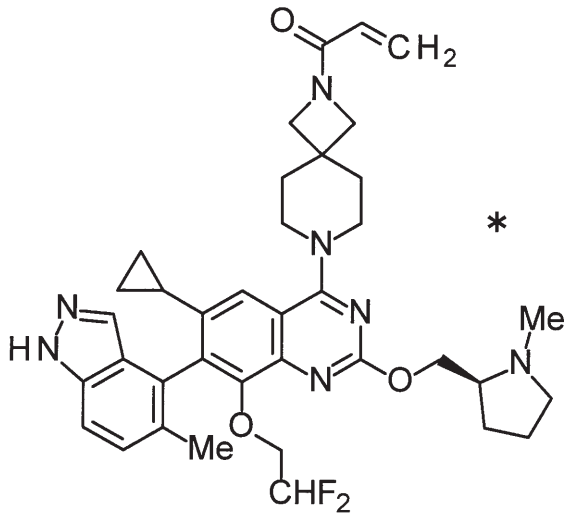
[0289]

[Table 119]

Ex	Str
1	
2	

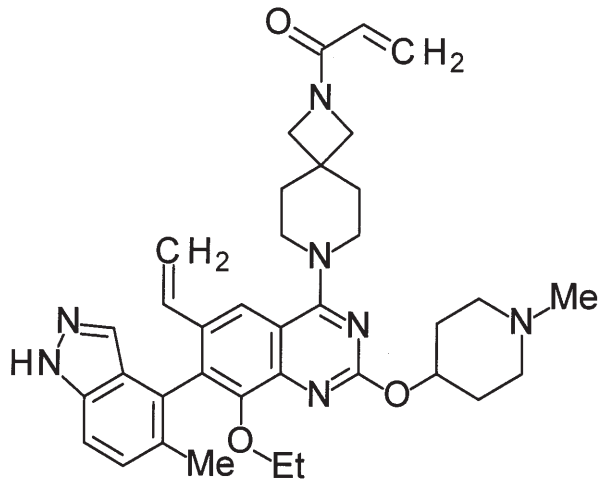
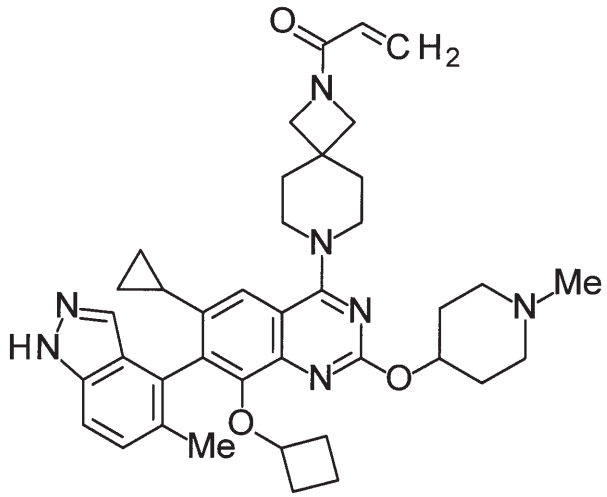
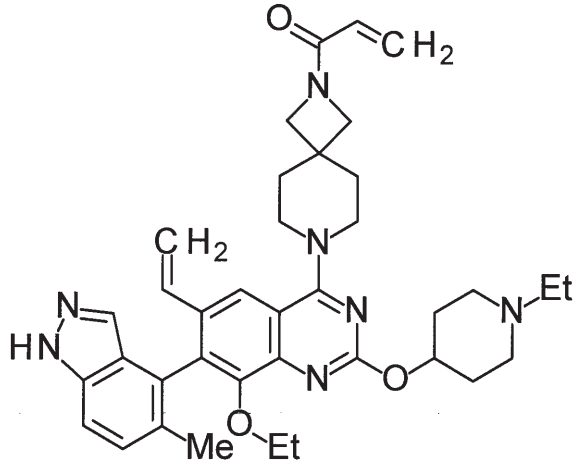
[0290]

[Table 120]

Ex	Str
3	
4	

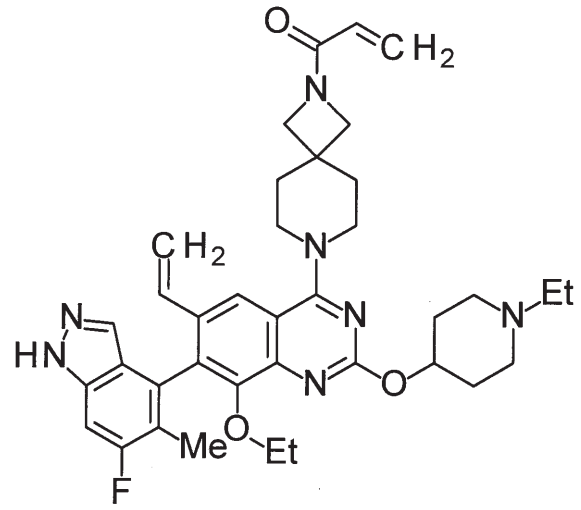
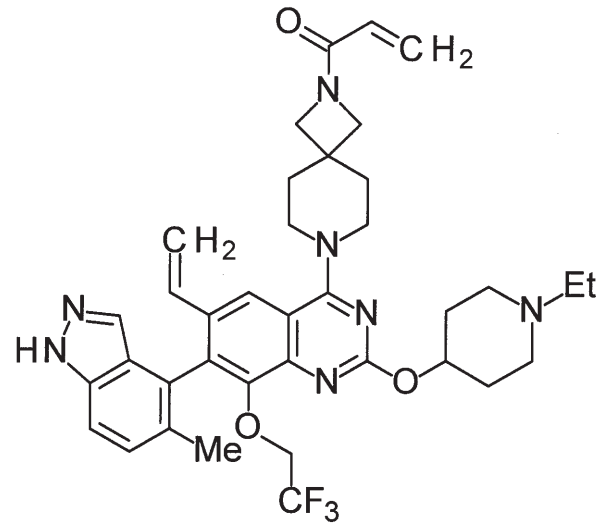
[0292]

[Table 121]

Ex	Str
5	
6	
7	

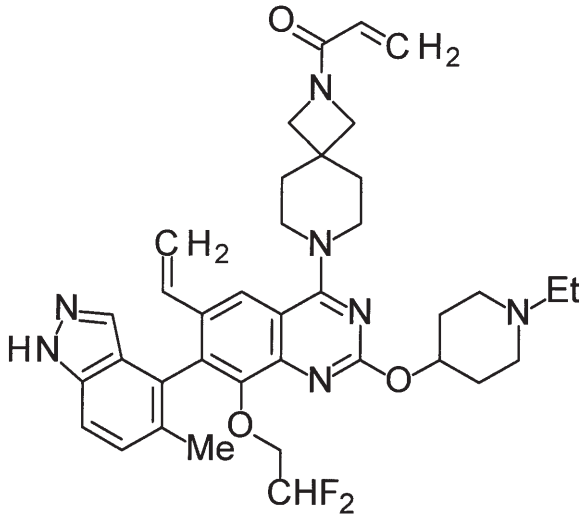
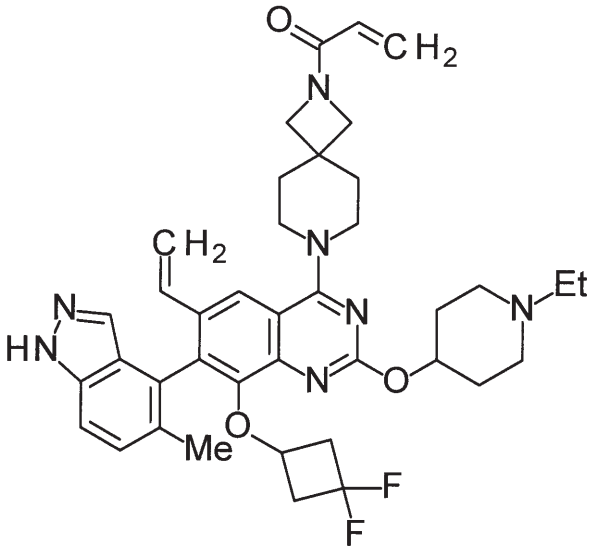
[0292]

[Table 122]

Ex	Str
8	
9	

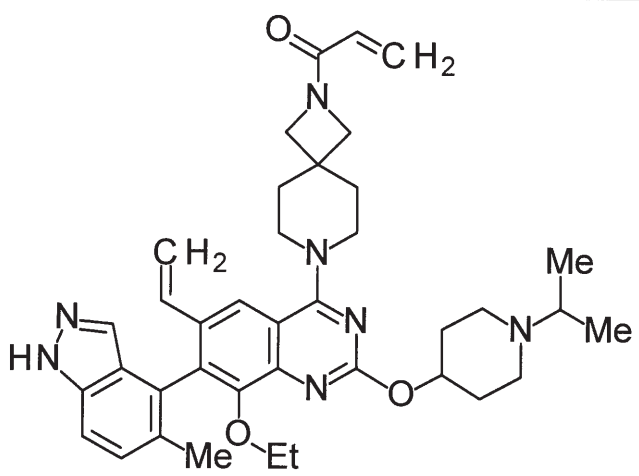
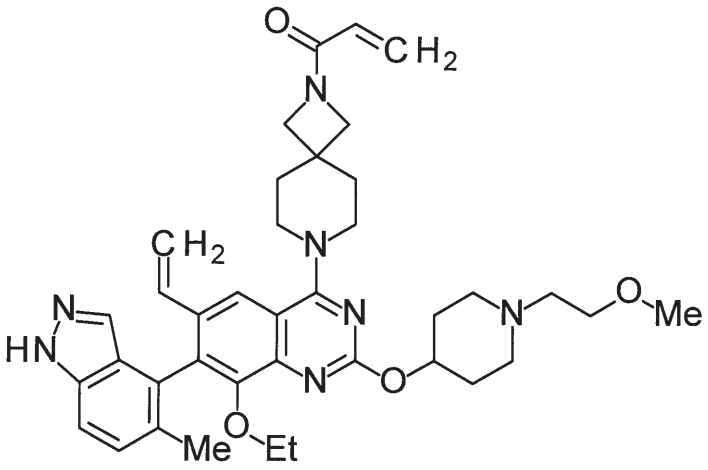
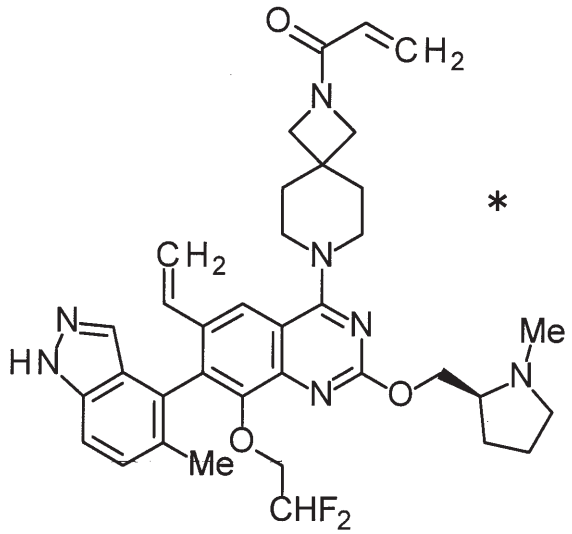
[0293]

[Table 123]

Ex	Str
10	
11	

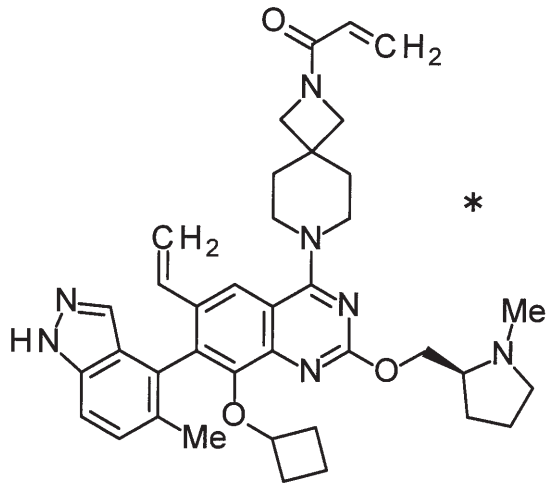
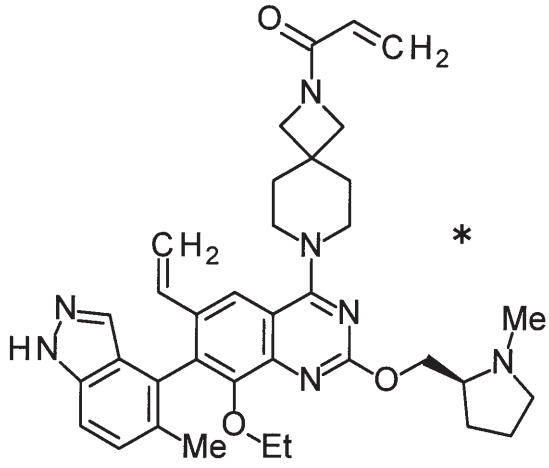
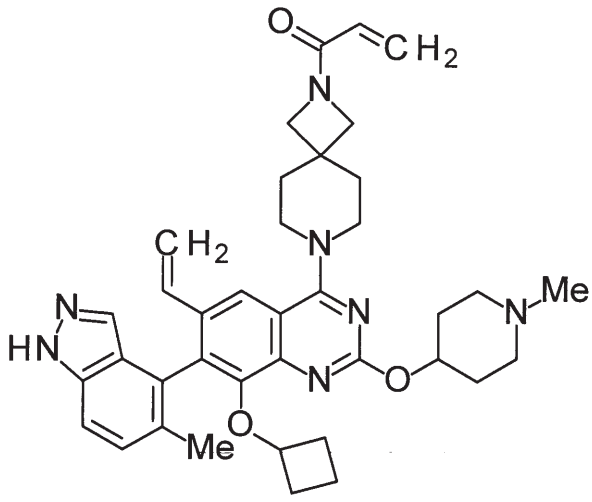
[0294]

[Table 124]

Ex	Str
12	
13	
14	

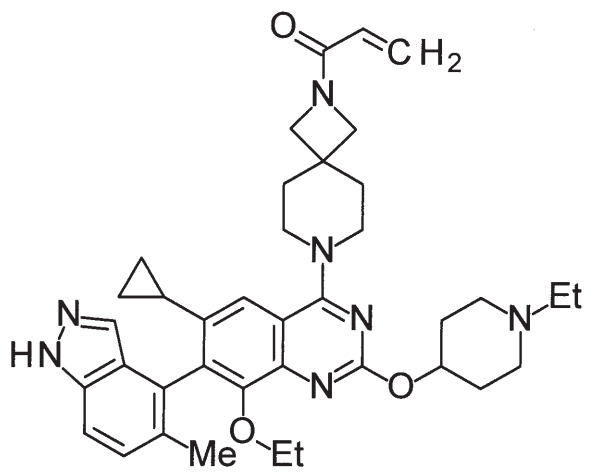
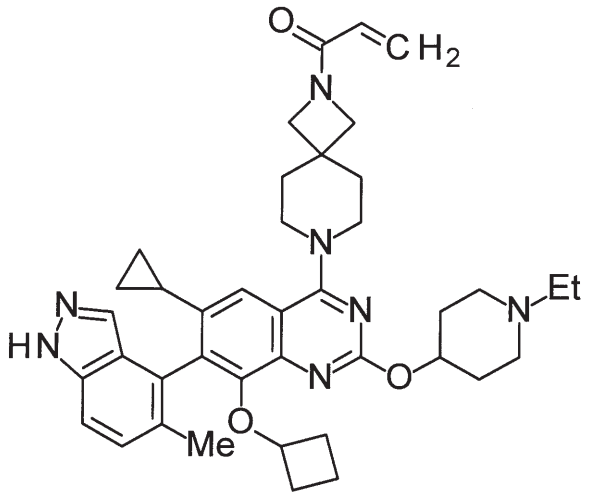
[0295]

[Table 125]

Ex	Str
15	
16	
17	

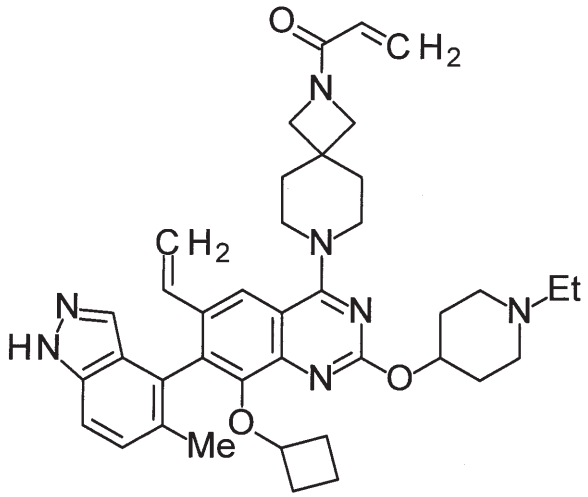
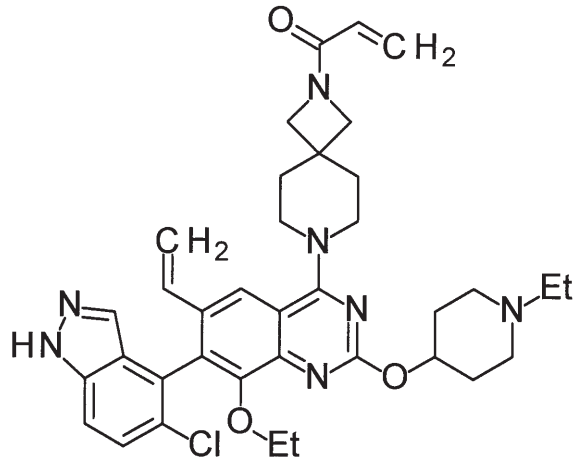
[0296]

[Table 126]

Ex	Str
18	
19	

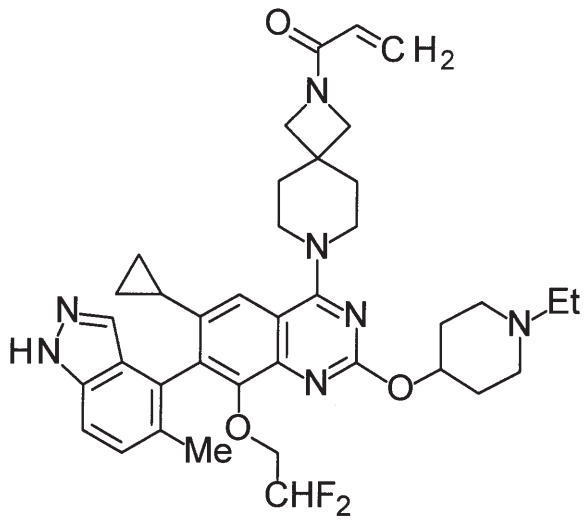
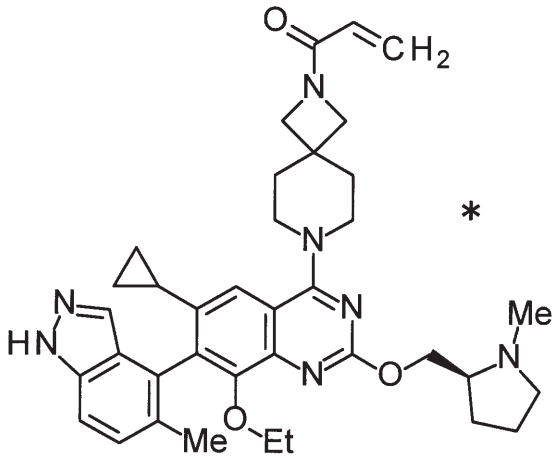
[0297]

[Table 127]

Ex	Str
20	
21	

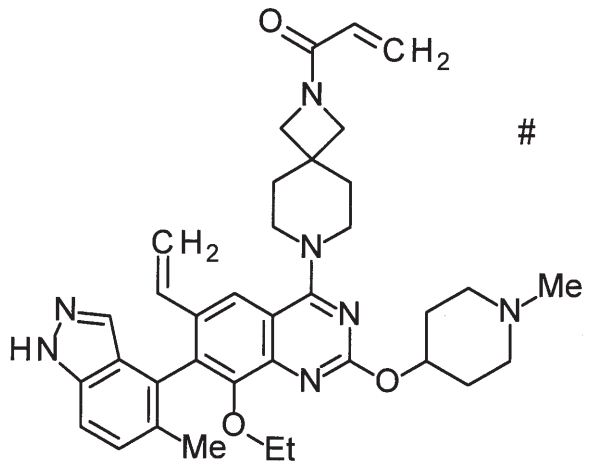
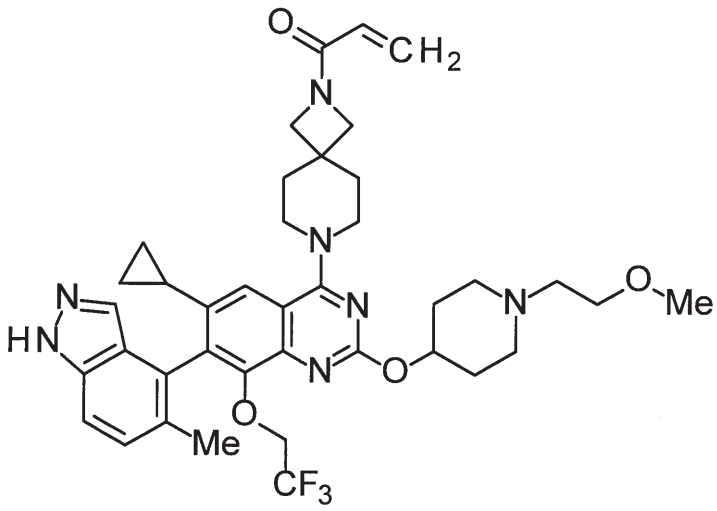
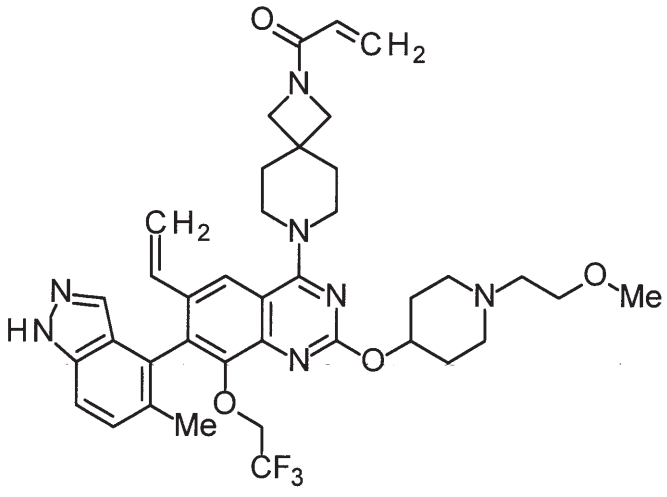
[0298]

[Table 128]

Ex	Str
22	
23	

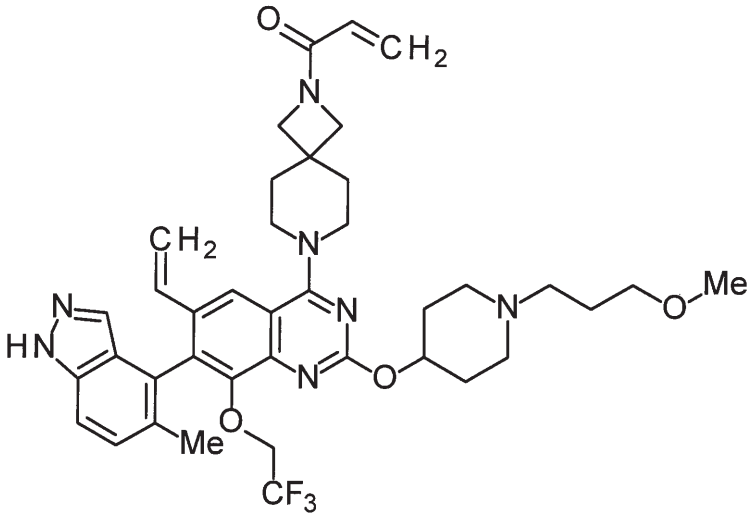
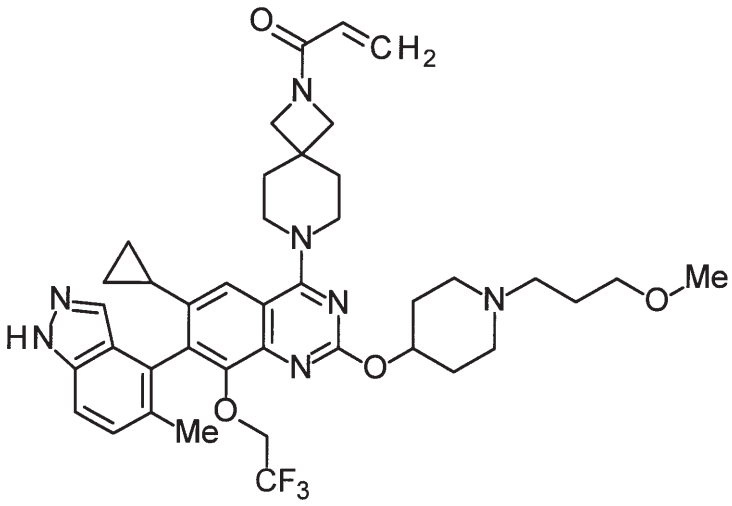
[0299]

[Table 129]

Ex	Str
24	 #
25	
26	

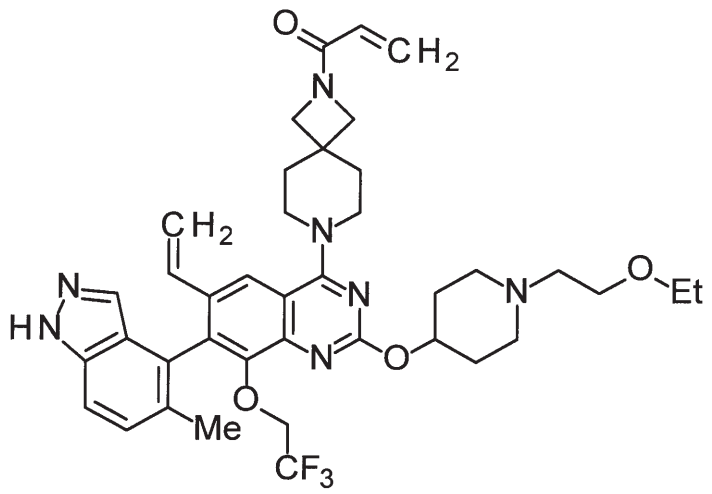
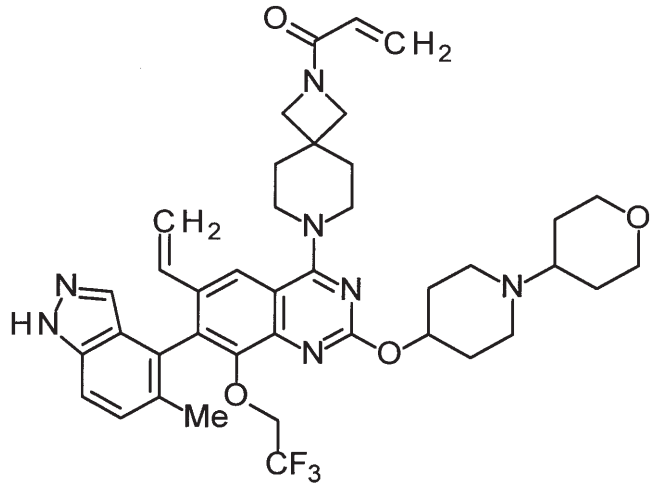
[0300]

[Table 130]

Ex	Str
27	
28	

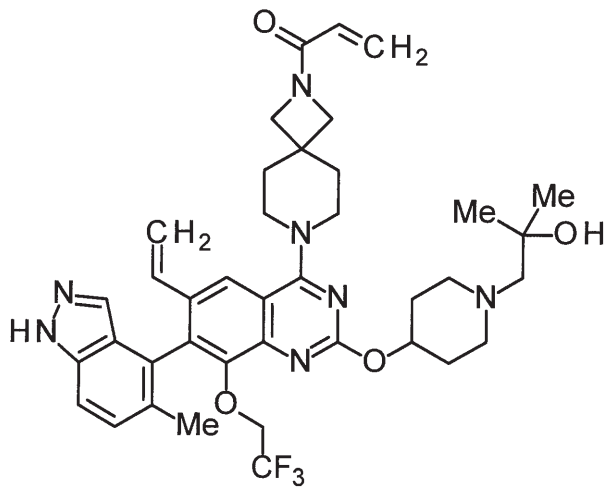
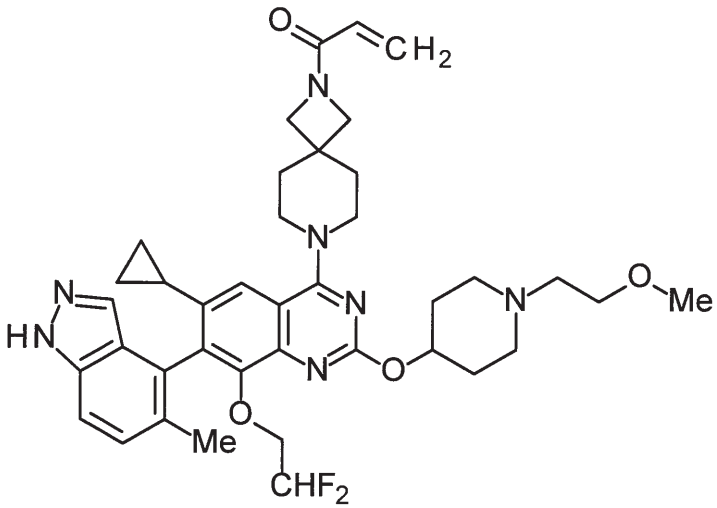
[0301]

[Table 131]

Ex	Str
29	
30	

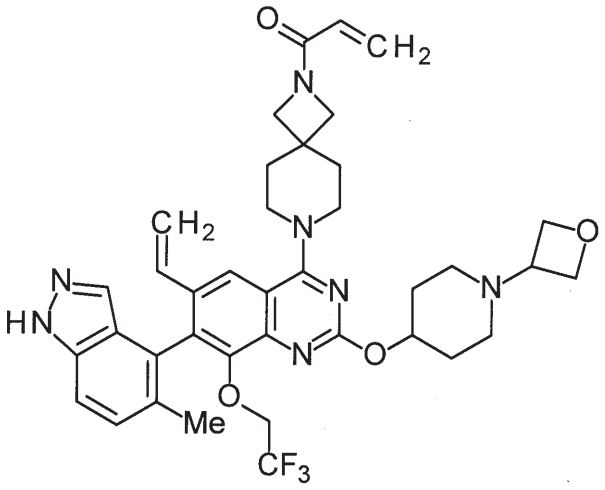
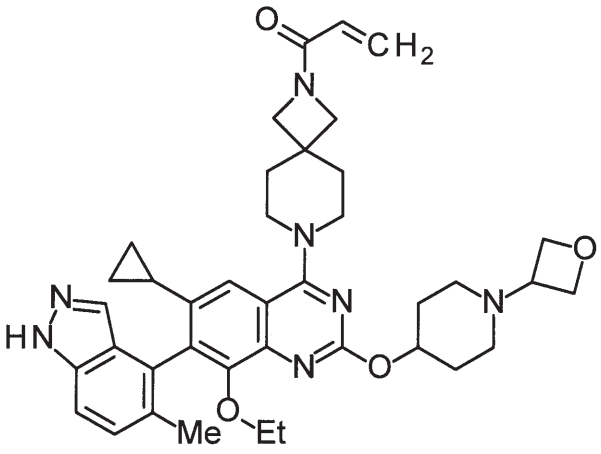
[0302]

[Table 132]

Ex	Str
31	
32	

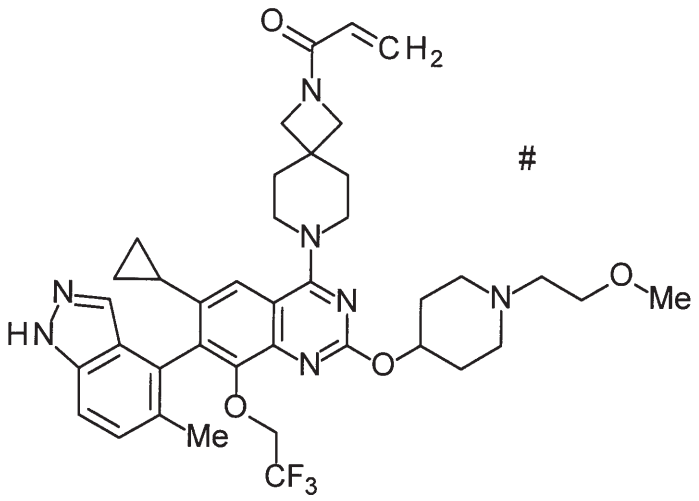
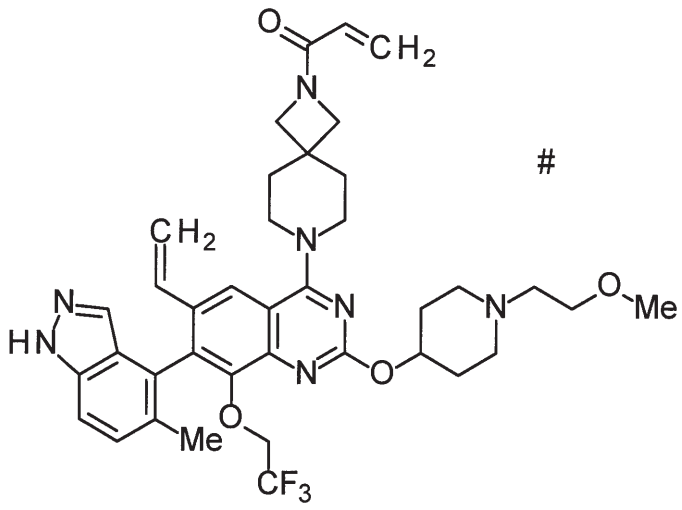
[0303]

[Table 133]

Ex	Str
33	
34	

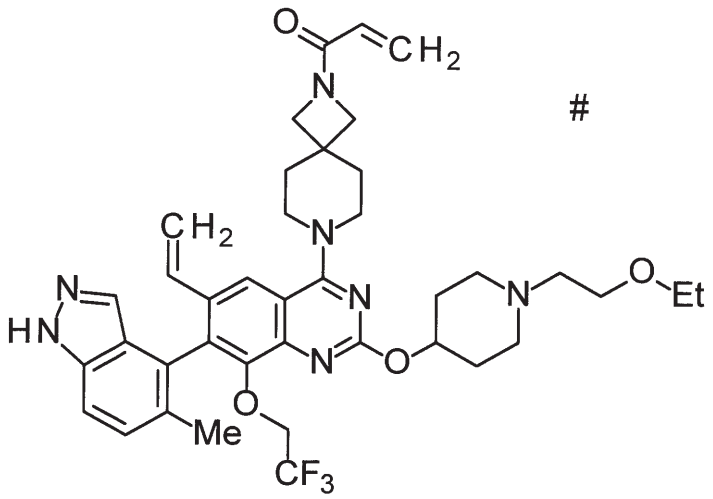
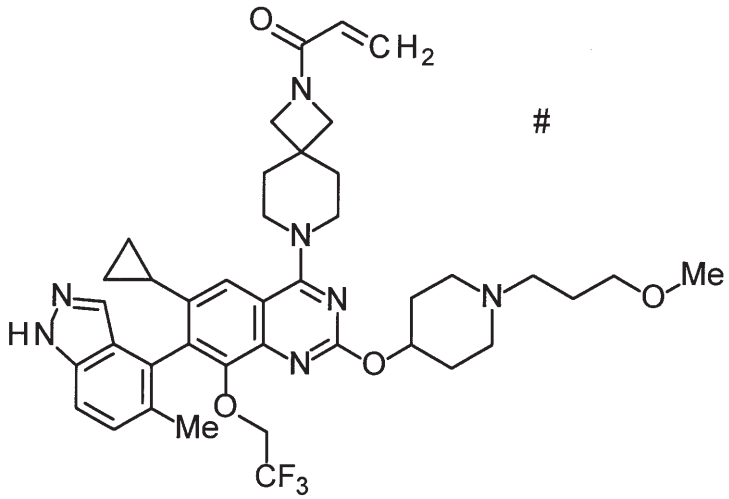
[0304]

[Table 134]

Ex	Str
35	
36	

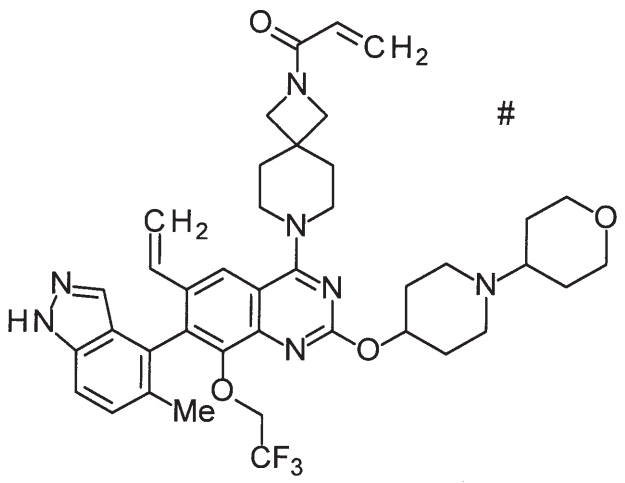
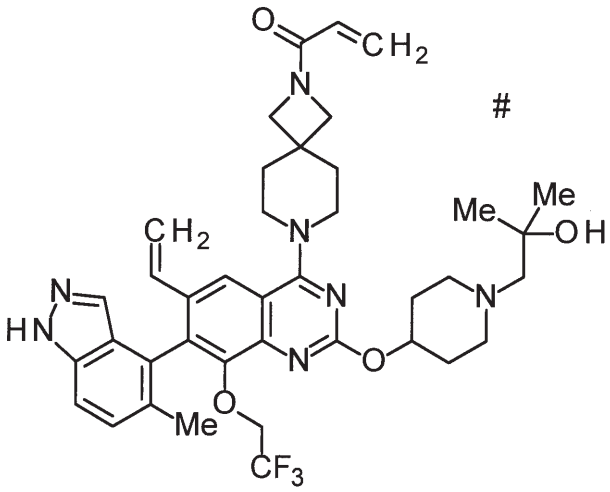
[0305]

[Table 135]

Ex	Str
37	 #
38	 #

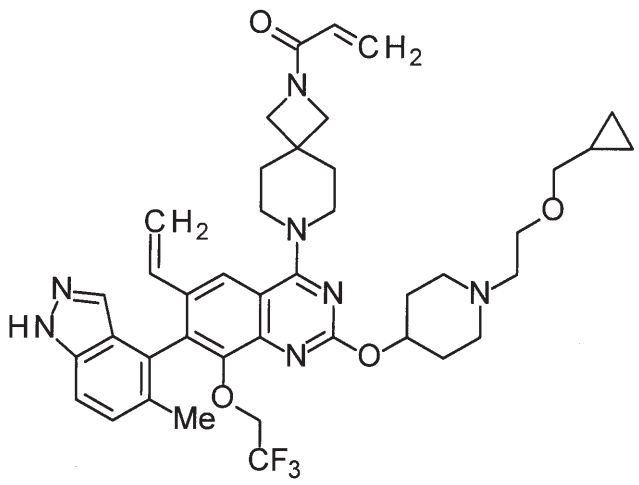
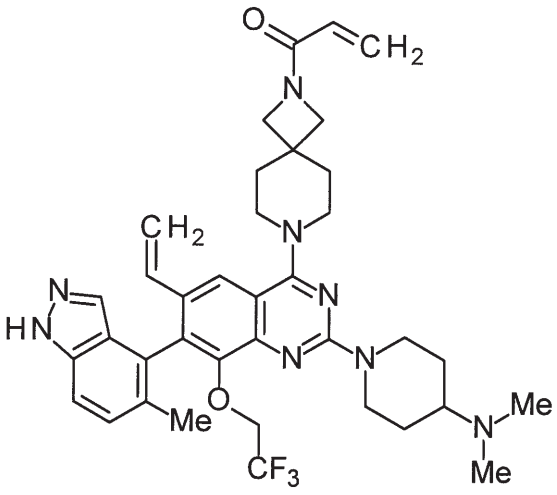
[0306]

[Table 136]

Ex	Str
39	
40	

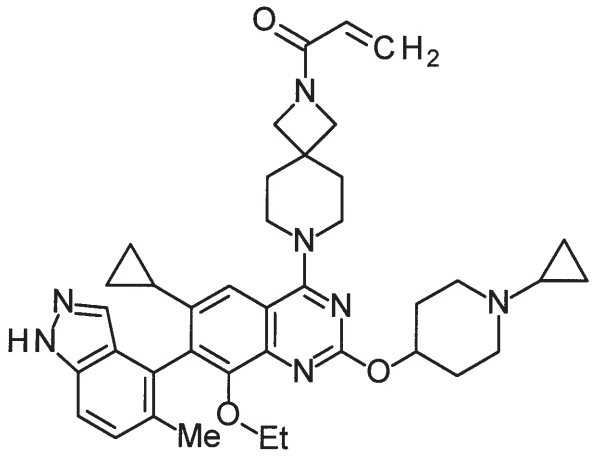
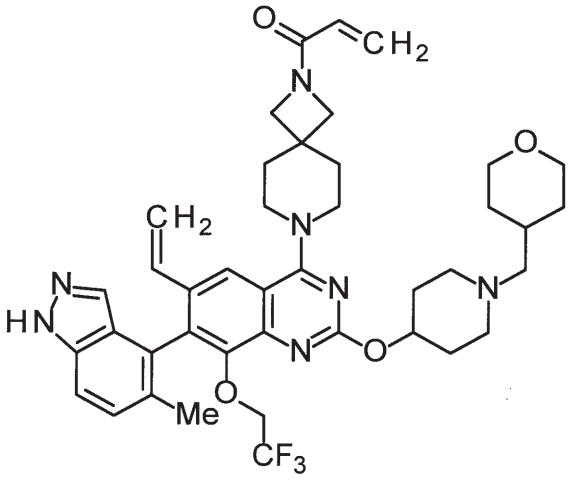
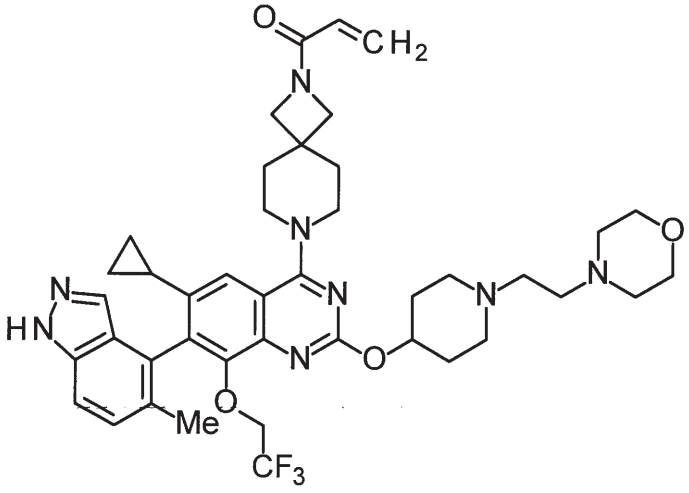
[0307]

[Table 137]

Ex	Str
41	
42	

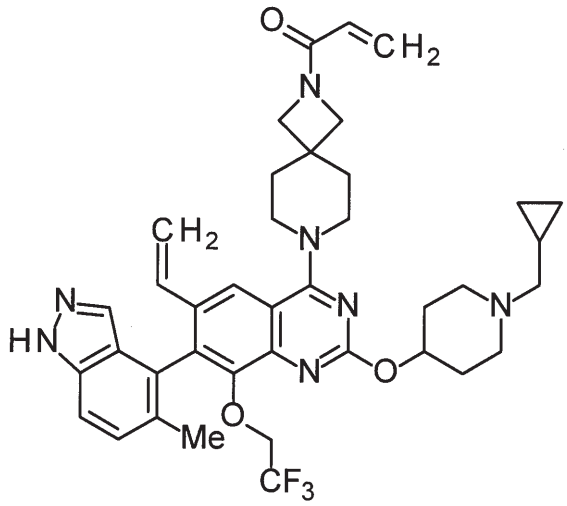
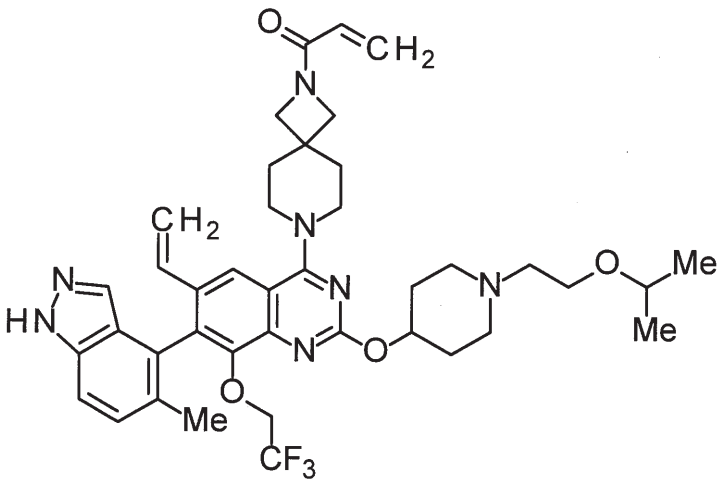
[0308]

[Table 138]

Ex	Str
43	
44	
45	

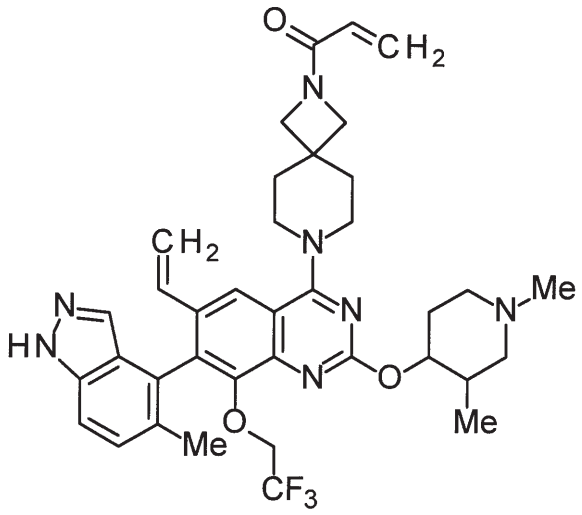
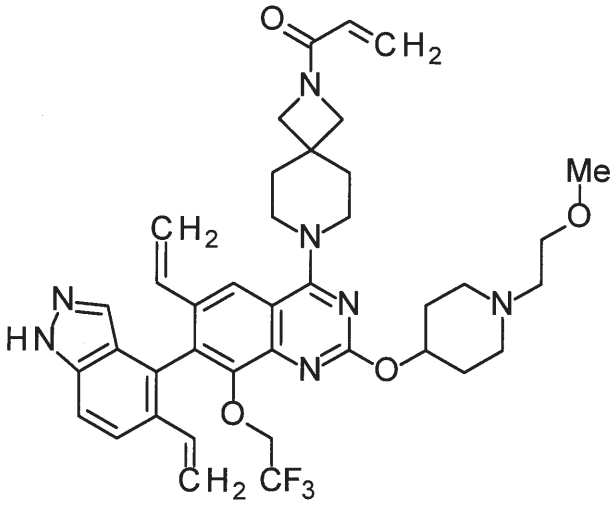
[0309]

[Table 139]

Ex	Str
46	
47	

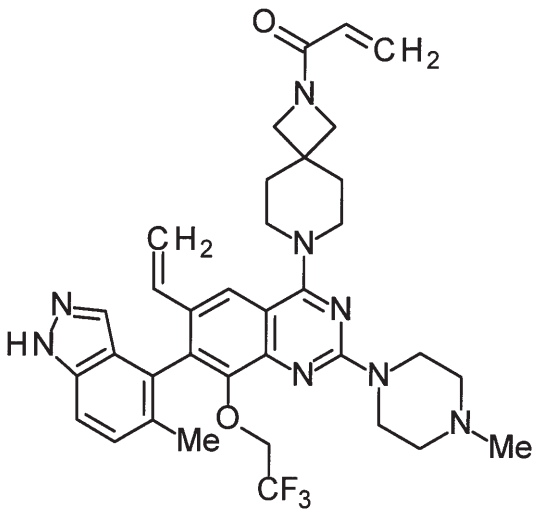
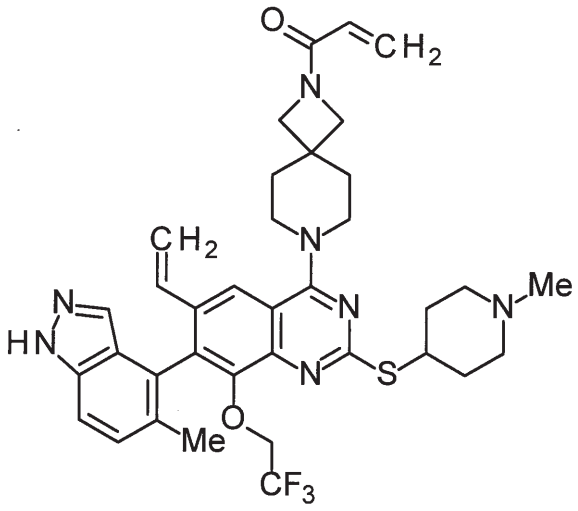
[0310]

[Table 140]

Ex	Str
48	
49	

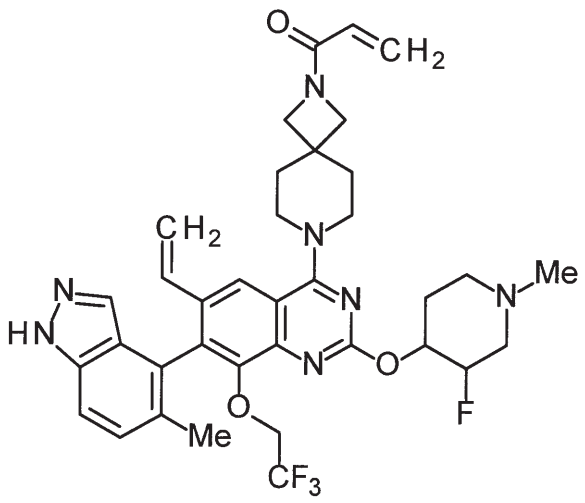
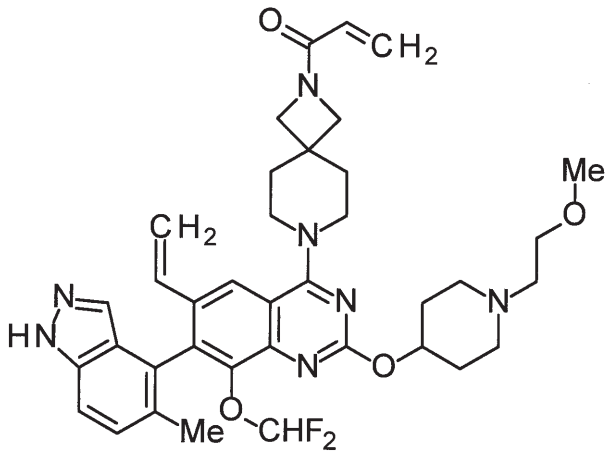
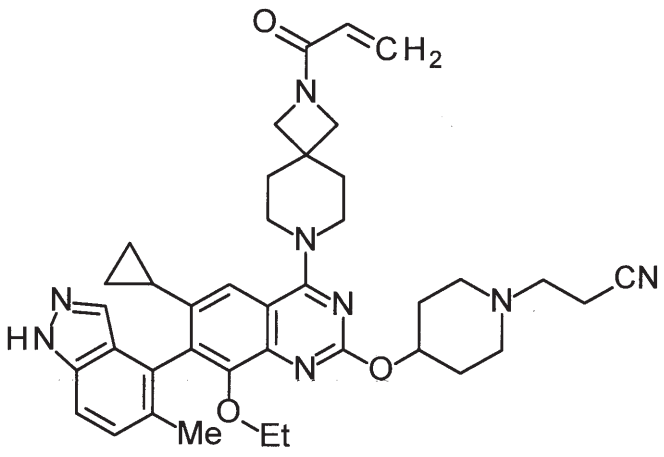
[0311]

[Table 141]

Ex	Str
50	
51	

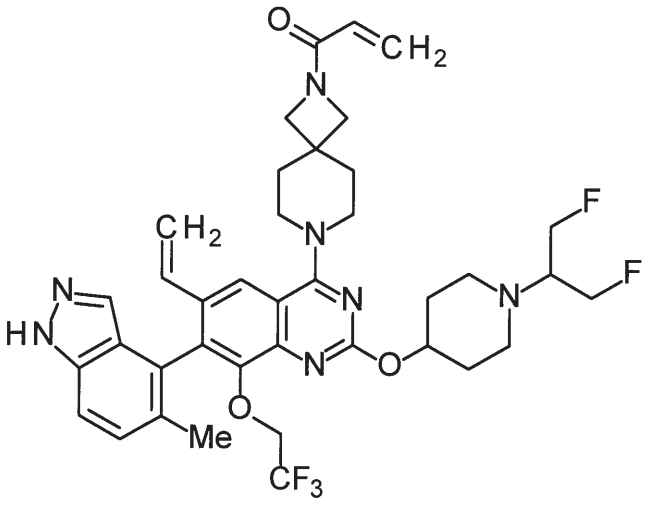
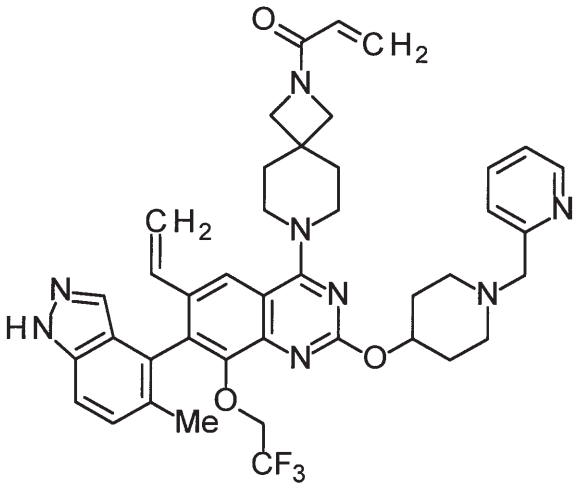
[0312]

[Table 142]

Ex	Str
52	
53	
54	

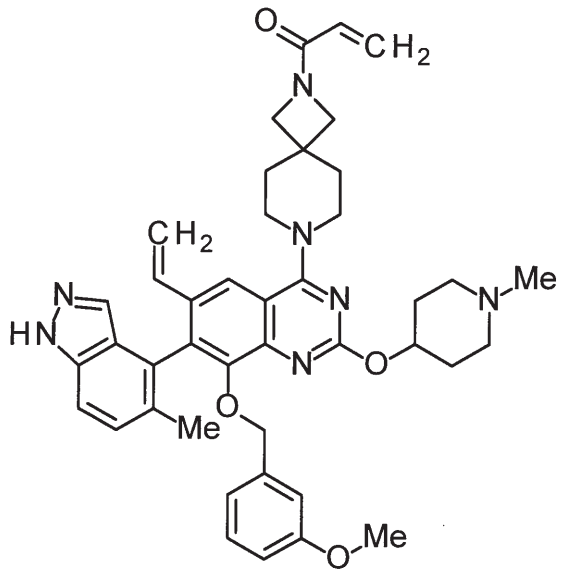
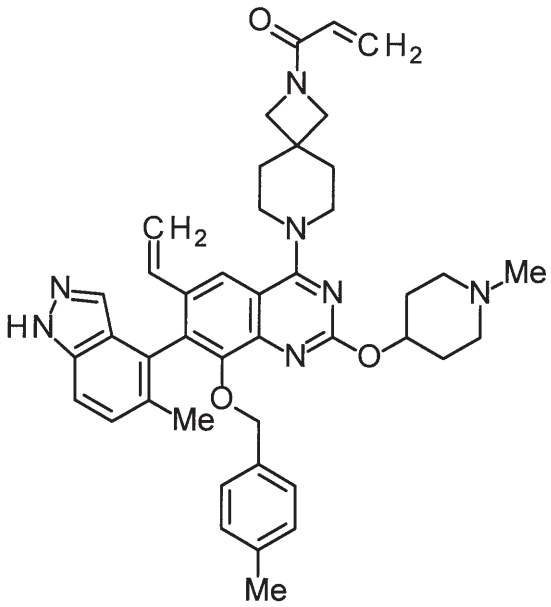
[0313]

[Table 143]

Ex	Str
55	
56	

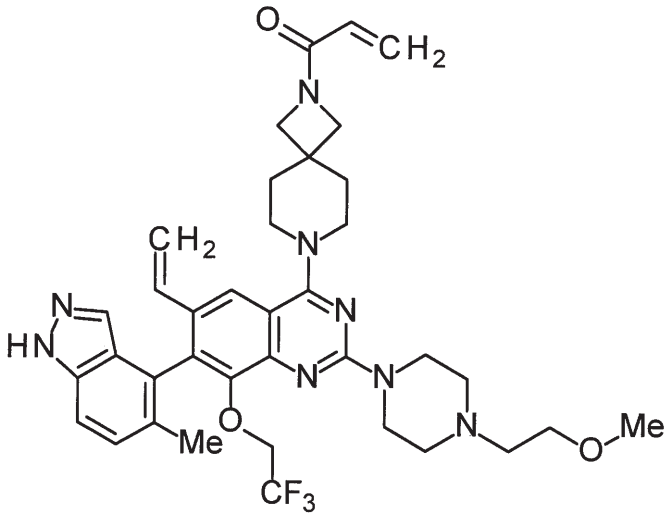
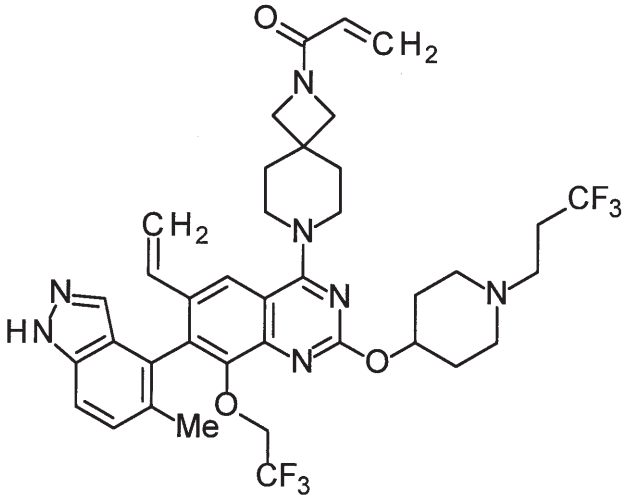
[0314]

[Table 144]

Ex	Str
57	
58	

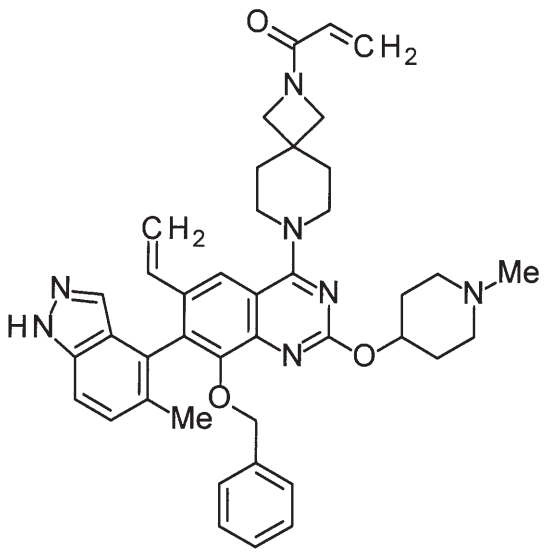
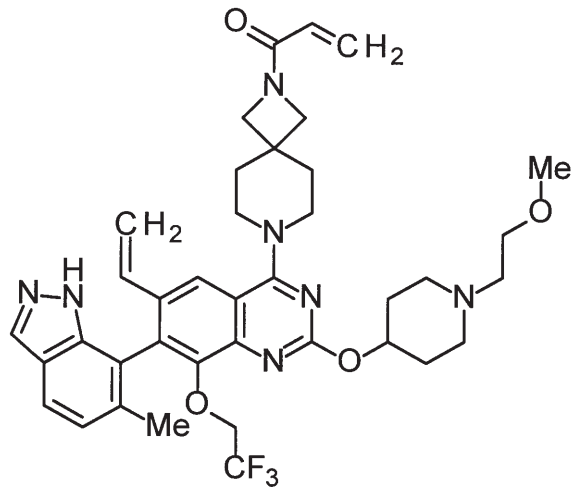
[0315]

[Table 145]

Ex	Str
59	
60	

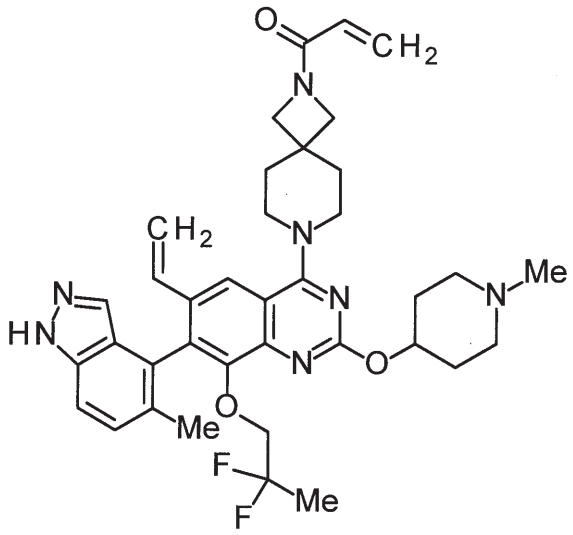
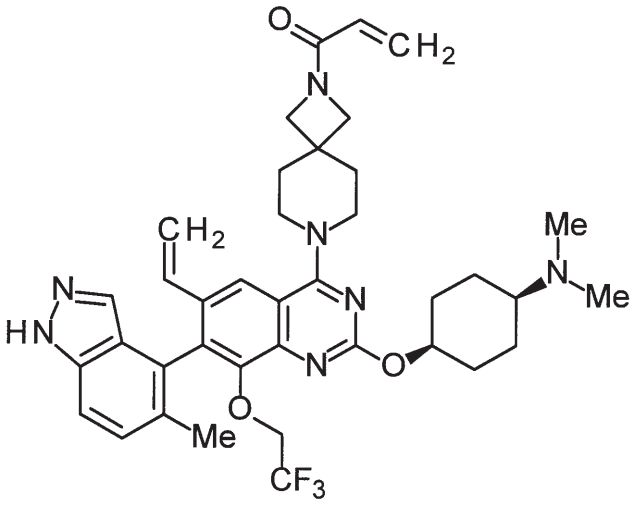
[0316]

[Table 146]

Ex	Str
61	
62	

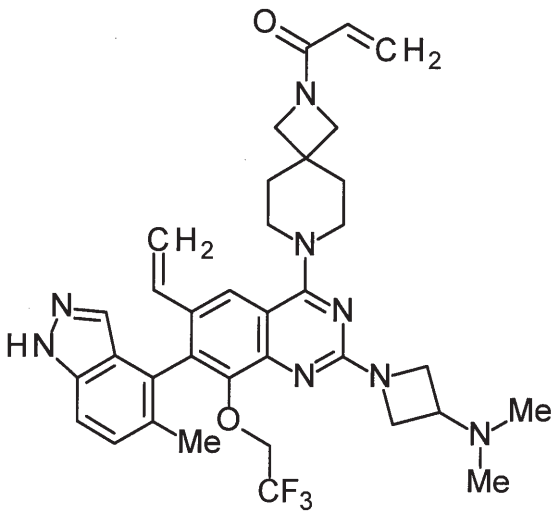
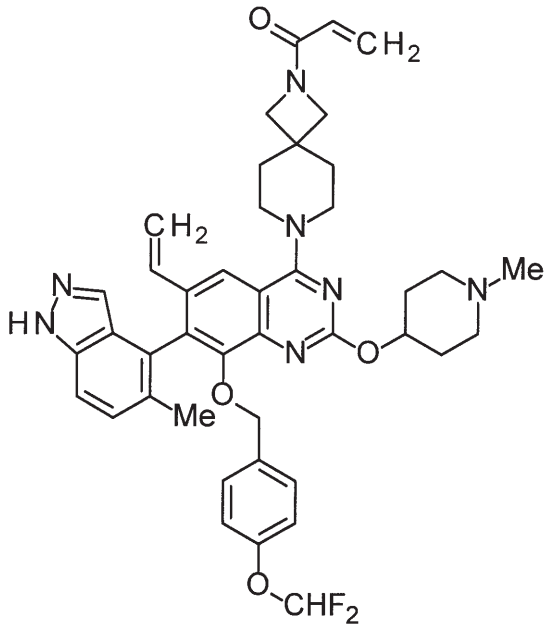
[0317]

[Table 147]

Ex	Str
63	
64	

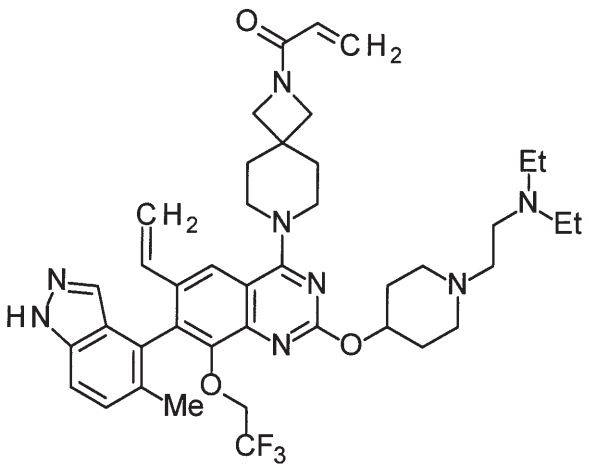
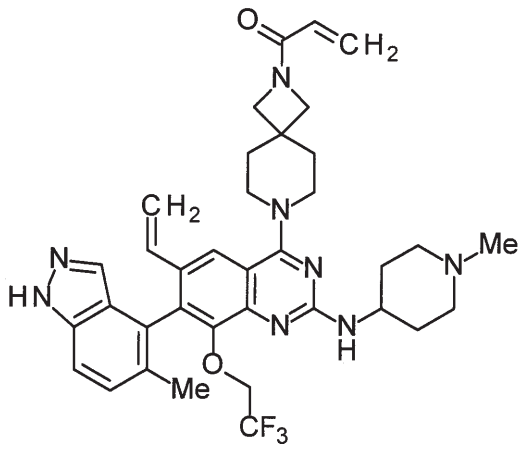
[0318]

[Table 148]

Ex	Str
65	
66	

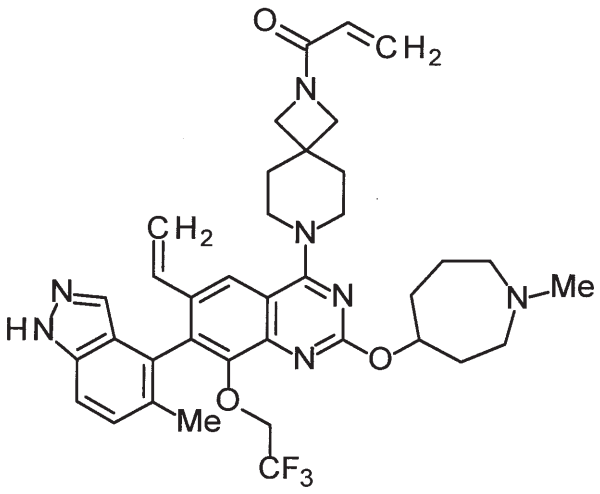
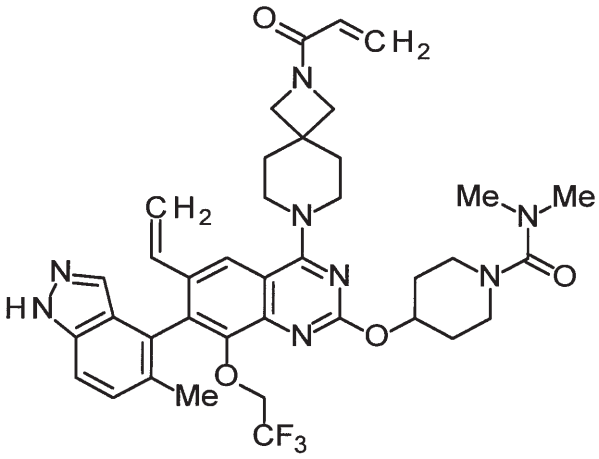
[0319]

[Table 149]

Ex	Str
67	
68	

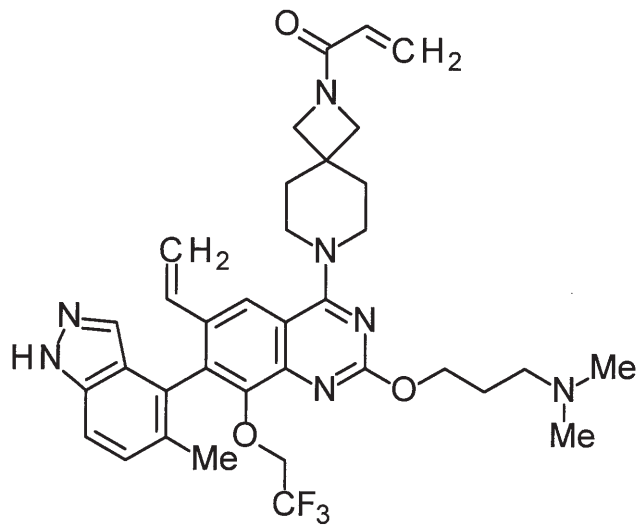
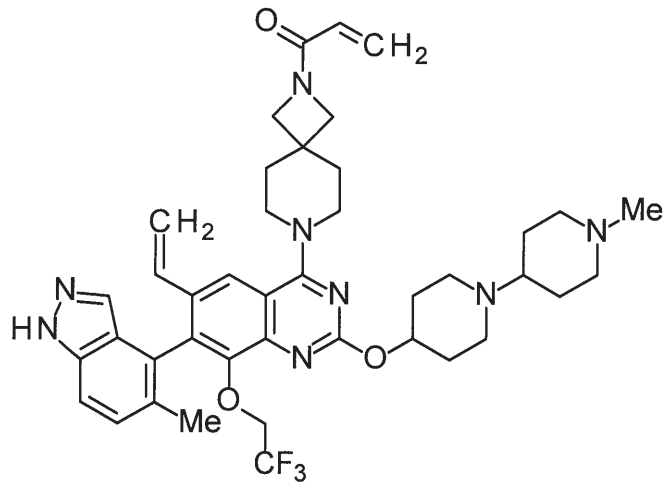
[0320]

[Table 150]

Ex	Str
69	
70	

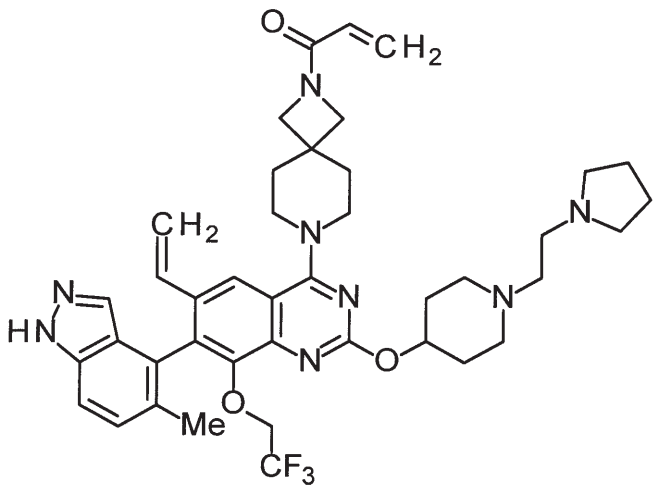
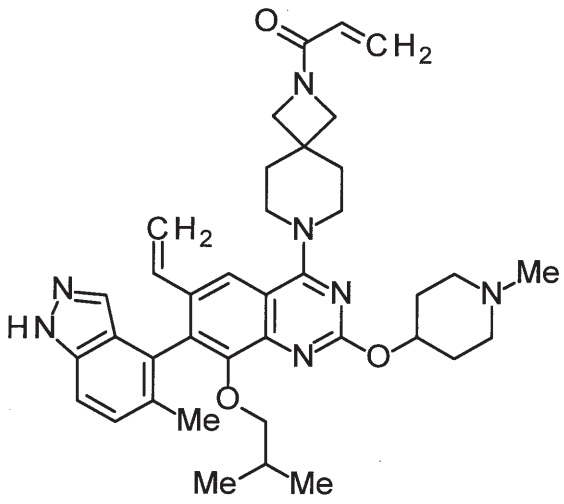
[0321]

[Table 151]

Ex	Str
71	
72	

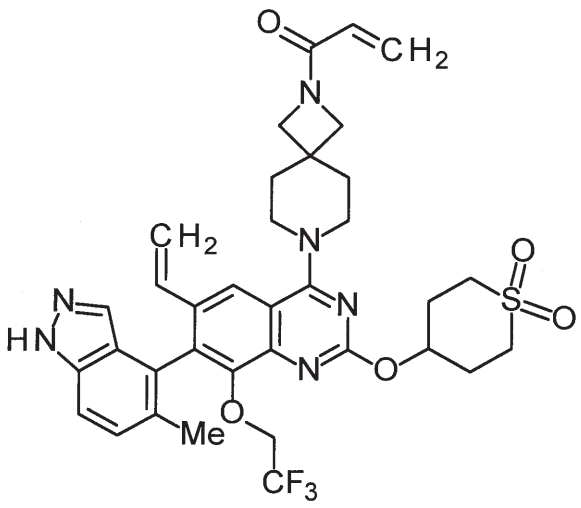
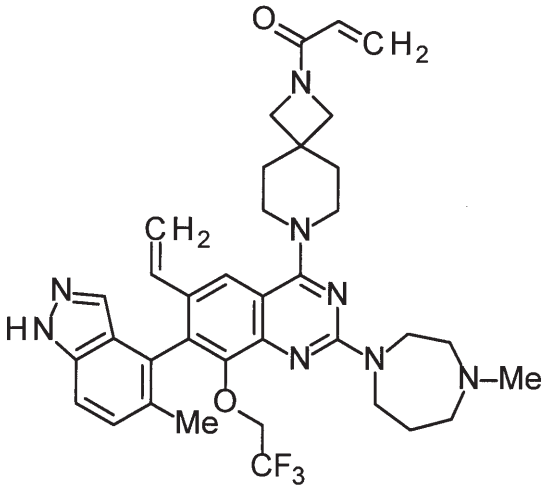
[0322]

[Table 152]

Ex	Str
73	
74	

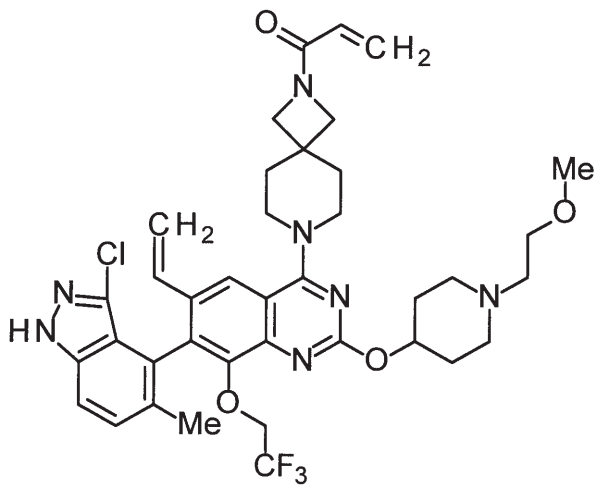
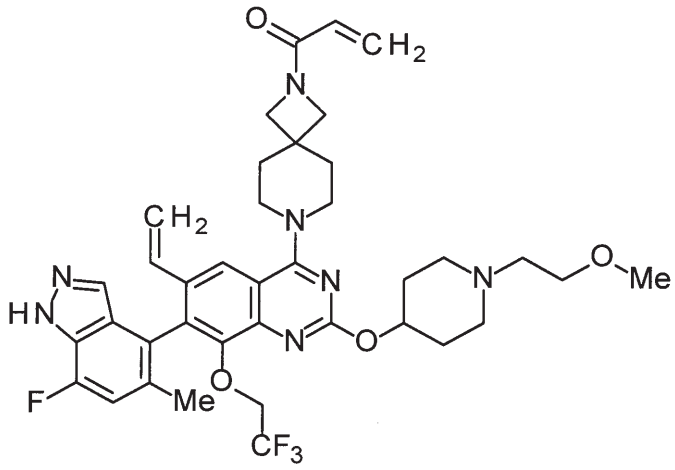
[0323]

[Table 153]

Ex	Str
75	
76	

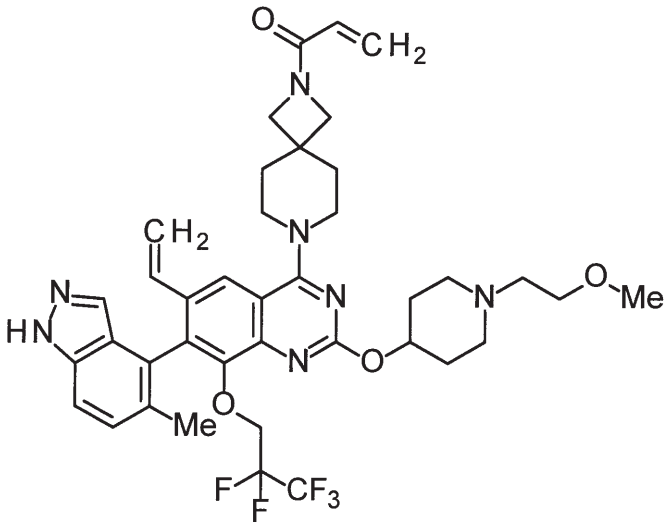
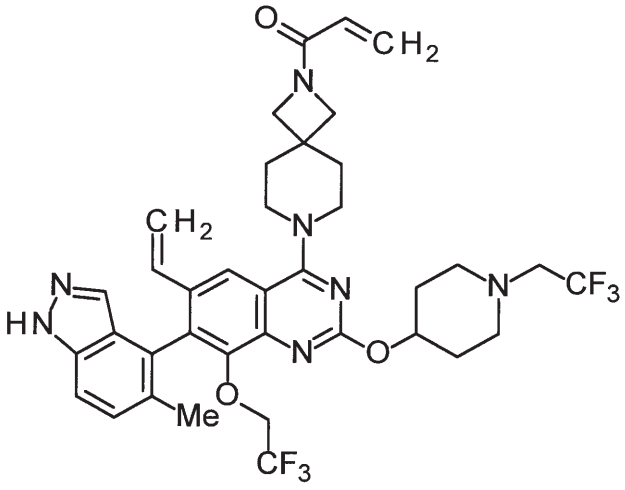
[0324]

[Table 154]

Ex	Str
77	
78	

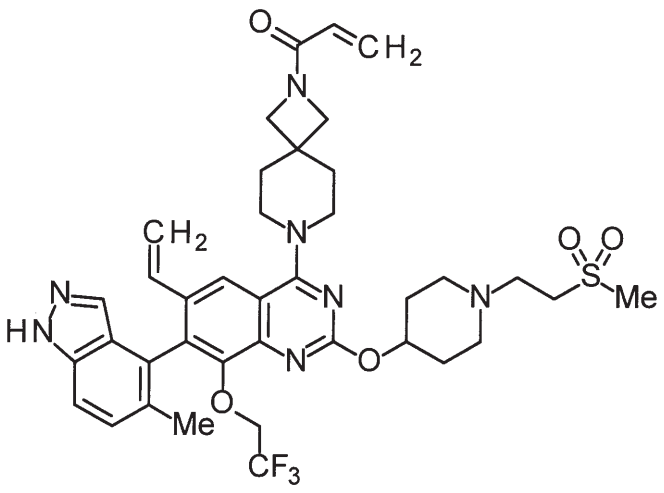
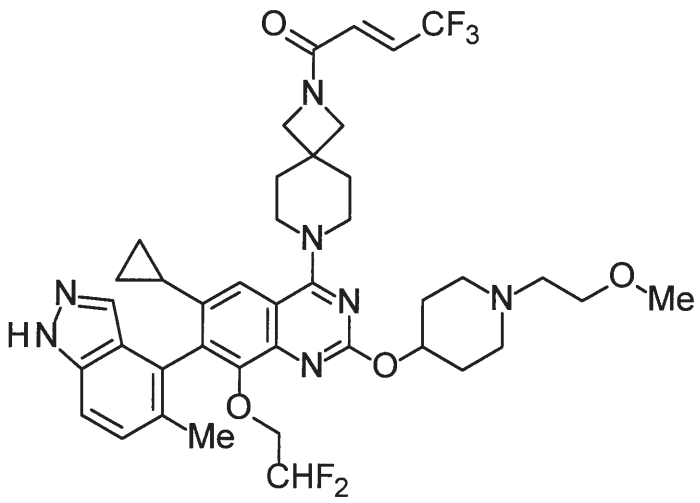
[0325]

[Table 155]

Ex	Str
79	
80	

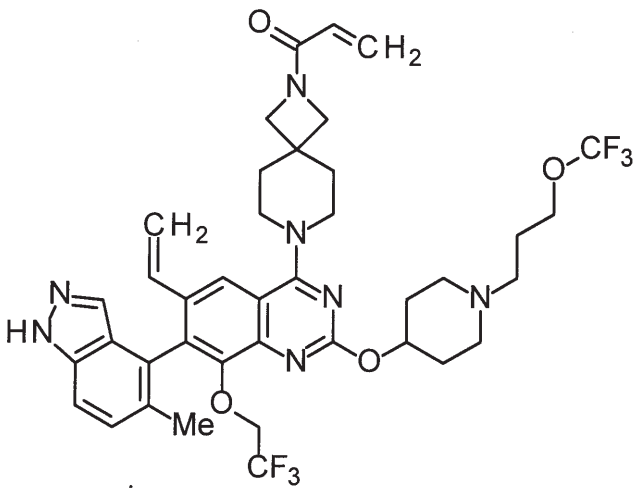
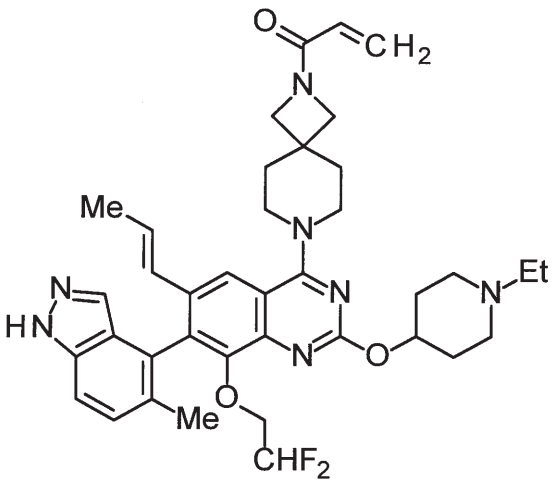
[0326]

[Table 156]

Ex	Str
81	
82	

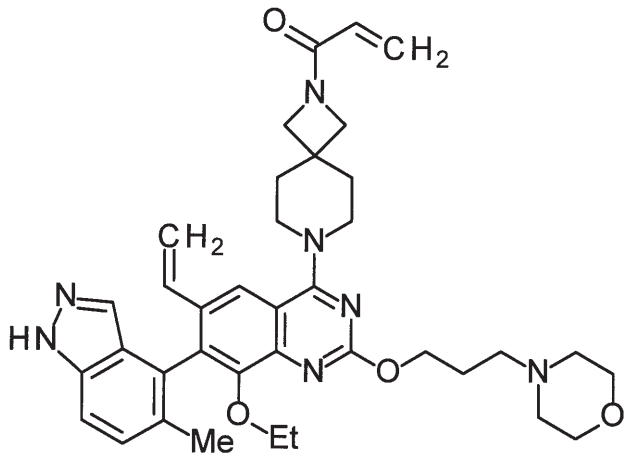
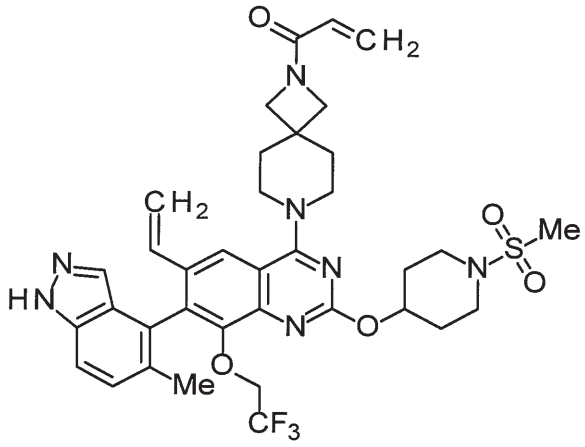
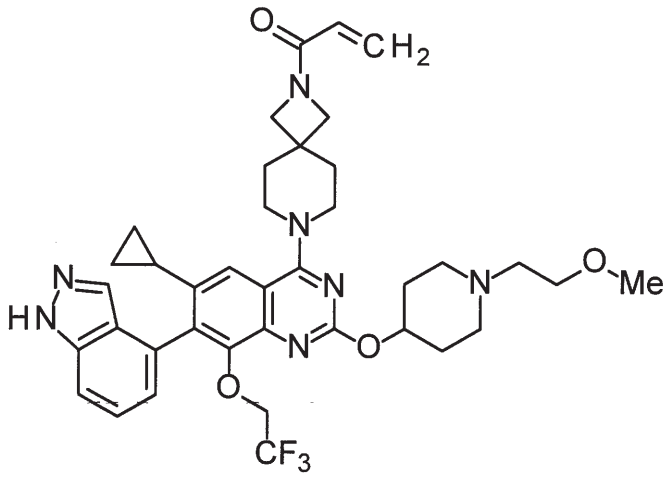
[0327]

[Table 157]

Ex	Str
83	
84	

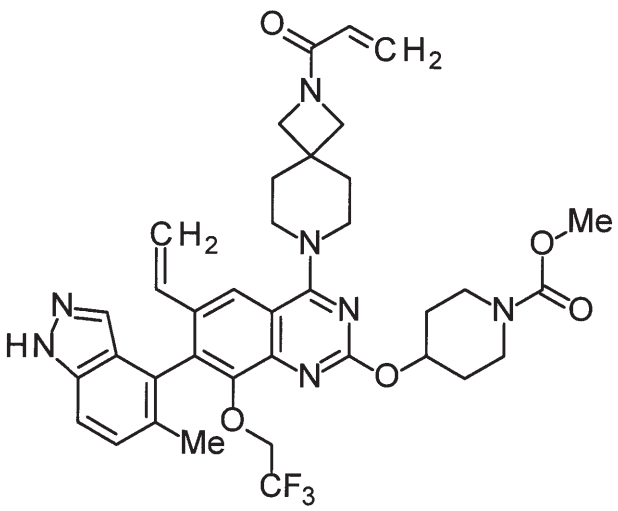
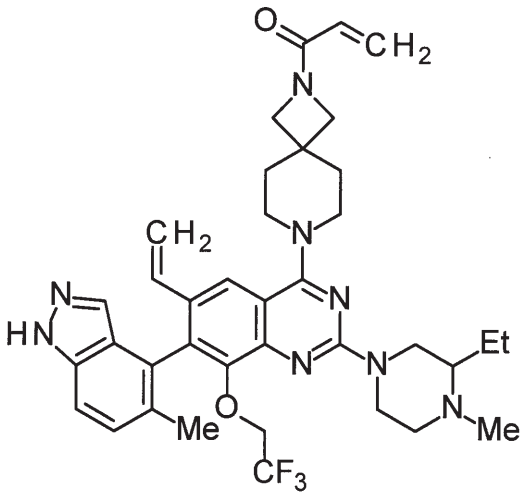
[0328]

[Table 158]

Ex	Str
85	
86	
87	

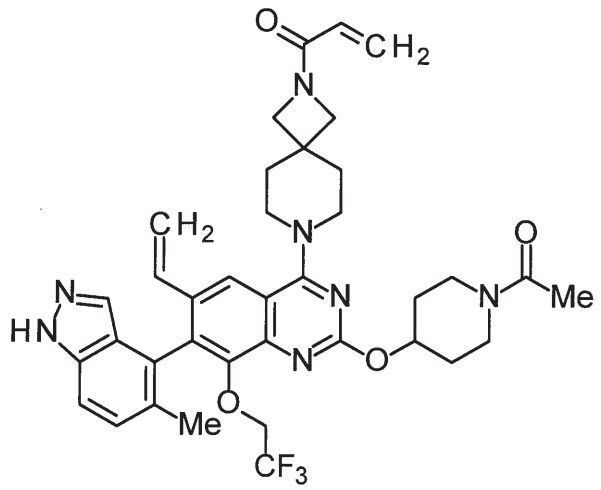
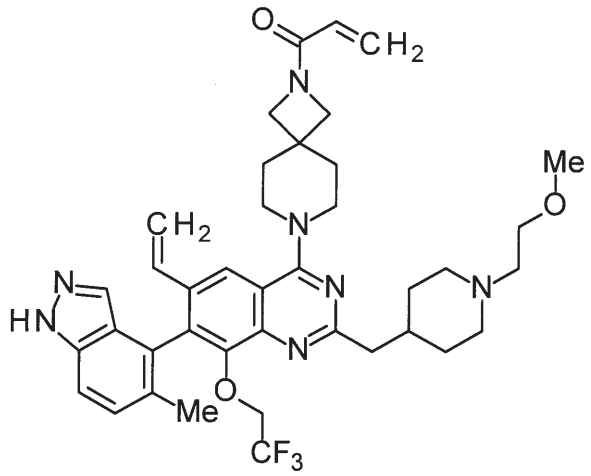
[0329]

[Table 159]

Ex	Str
88	
89	

[0330]

[Table 160]

Ex	Str
90	
91	

[0331]

[Table 161]

Ex	Syn	Dat
1	E1	ESI+; 658.5 NMR (400 MHz): 1.63 - 1.80 (2 H, m) 1.91 - 2.22 (8 H, m) 2.04 (3 H, s) 2.17 (3 H, s) 2.59 - 2.79 (2 H, m) 3.65 - 3.84 (4 H, m) 3.75 (2 H, s) 4.00 - 4.17 (1 H, m) 4.04 (2 H, s) 4.25 - 4.44 (1 H, m) 4.92 - 5.11 (2 H, m) 5.72 (1 H, tt, J=55.3, 4.0 Hz) 5.65 - 5.71 (2 H, m) 5.99 - 6.18 (2 H, m) 6.34 (1 H, dd, J=17.0, 10.4 Hz) 7.33 (1 H, d, J=8.6 Hz) 7.38 - 7.45 (1 H, m) 7.50 (1 H, d, J=8.4 Hz) 7.96 (1 H, s) 13.03 (1 H, s)
2	E2	ESI+; 636.6 NMR (500 MHz): 0.42 - 0.71 (4 H, m) 0.83 (3 H, t, J=7.0 Hz) 1.23 - 1.36 (1 H, m) 1.59 - 1.79 (2 H, m) 1.90 - 1.98 (4 H, m) 1.99 - 2.25 (4 H, m) 2.11 (3 H, s) 2.18 (3 H, s) 2.65 - 2.77 (2 H, m) 3.57 - 3.68 (4 H, m) 3.75 (2 H, s) 3.77 - 3.87 (1 H, m) 3.98 - 4.12 (1 H, m) 4.03 (2 H, s) 4.92 - 5.03 (1 H, m) 5.68 (1 H, dd, J=10.3, 2.3 Hz) 6.12 (1 H, dd, J=17.0, 2.3 Hz) 6.34 (1 H, dd, J=17.0, 10.3 Hz) 7.14 (1 H, s) 7.33 (1 H, d, J=8.6 Hz) 7.41 - 7.44 (1 H, m) 7.46 (1 H, d, J=8.6 Hz) 12.96 (1 H, s)
3	E3	ESI+; 672.6 NMR (500 MHz): 0.46 - 0.73 (4 H, m) 1.24 - 1.37 (1 H, m) 1.62 - 1.80 (2 H, m) 1.89 - 2.23 (8 H, m) 2.11 (3 H, s) 2.17 (3 H, s) 2.60 - 2.76 (2 H, m) 3.57 - 3.69 (4 H, m) 3.75 (2 H, s) 3.97 - 4.15 (1 H, m) 4.03 (2 H, s) 4.22 - 4.48 (1 H, m) 4.87 - 5.03 (1 H, m) 5.72 (1 H, tt, J=55.2, 3.8 Hz) 5.68 (1 H, dd, J=10.3, 2.3 Hz) 6.12 (1 H, dd, J=17.0, 2.3 Hz) 6.34 (1 H, dd, J=16.8, 10.3 Hz) 7.20 (1 H, s) 7.34 (1 H, d, J=8.4 Hz) 7.43 - 7.52 (2 H, m) 12.99 (1 H, s)

[0332]

[Table 162]

Ex	Syn	Dat
4	E4	ESI+; 672.6 NMR (400 MHz): 0.46 - 0.76 (4 H, m) 1.21 - 1.45 (1 H, m) 1.57 - 3.01 (14 H, m) 2.11 (3 H, s) 3.58 - 3.83 (4 H, m) 3.76 (2 H, s) 3.95 - 4.19 (1 H, m) 4.04 (2 H, s) 4.21 - 4.65 (3 H, m) 5.72 (1 H, tt, J=55.1, 3.7 Hz) 5.69 (1 H, dd, J=10.1, 2.2 Hz) 6.12 (1 H, dd, J=16.8, 2.2 Hz) 6.34 (1 H, dd, J=17.0, 10.1 Hz) 7.22 (1 H, s) 7.35 (1 H, d, J=8.6 Hz) 7.44 - 7.48 (1 H, m) 7.49 (1 H, d, J=8.6 Hz) 13.01 (1 H, s)
5	E5 E5-2	ESI+; 622.5 NMR (400 MHz): 0.83 (3 H, t, J=7.1 Hz) 1.62 - 1.83 (2 H, m) 1.87 - 2.27 (8 H, m) 2.04 (3 H, s) 2.18 (3 H, s) 2.62 - 2.78 (2 H, m) 3.63 - 3.80 (4 H, m) 3.76 (2 H, s) 3.78 - 3.91 (1 H, m) 3.98 - 4.16 (1 H, m) 4.04 (2 H, s) 4.93 - 5.08 (2 H, m) 5.60 - 5.74 (2 H, m) 6.00 - 6.17 (2 H, m) 6.34 (1 H, dd, J=17.0, 10.4 Hz) 7.32 (1 H, d, J=8.6 Hz) 7.36 - 7.41 (1 H, m) 7.49 (1 H, d, J=8.4 Hz) 7.90 (1 H, s) 13.01 (1 H, s)
6	E6	ESI+; 662.5
7	E7	ESI+; 636.5
8	E3	ESI+; 654.6
9	E1	ESI+; 690.6
10	E1	ESI+; 672.6
11	E1	ESI+; 698.6
12	E1	ESI+; 650.6
13	E1	ESI+; 666.6
14	E3	ESI+; 658.6
15	E1	ESI+; 648.6
16	E1	ESI+; 622.6
17	E1	ESI+; 648.6
18	E3	ESI+; 650.5

[0333]

[Table 163]

Ex	Syn	Dat
19	E3	ESI+; 676.5
20	E3	ESI+; 662.6
21	E3	ESI+; 656.5
22	E6	ESI+; 686.5
23	E1	ESI+; 636.5
24	E24	ESI+; 622.4 NMR (500 MHz): 0.83 (3 H, t, J=7.0 Hz) 1.64 - 1.79 (2 H, m) 1.90 - 2.23 (8 H, m) 2.04 (3 H, s) 2.17 (3 H, s) 2.65 - 2.75 (2 H, m) 3.67 - 3.75 (4 H, m) 3.76 (2 H, s) 3.79 - 3.88 (1 H, m) 4.00 - 4.13 (1 H, m) 4.04 (2 H, s) 4.94 - 5.07 (2 H, m) 5.62 - 5.72 (2 H, m) 6.06 (1 H, dd, J=17.5, 10.9 Hz) 6.12 (1 H, dd, J=17.0, 2.3 Hz) 6.35 (1 H, dd, J=17.1, 10.3 Hz) 7.32 (1 H, d, J=8.6 Hz) 7.35 - 7.41 (1 H, m) 7.49 (1 H, d, J=8.6 Hz) 7.90 (1 H, s) 13.01 (1 H, s) $[\alpha]_D^{20}$ +39.6 (c 0.35, MeOH)
25	E25	ESI+; 734.5
26	E26	ESI+; 720.5 NMR (500 MHz): 1.63 - 1.76 (2 H, m) 1.91 - 2.11 (6 H, m) 2.05 (3 H, s) 2.12 - 2.22 (2 H, m) 2.47 (2 H, t, J=5.8 Hz) 2.75 - 2.87 (2 H, m) 3.22 (3 H, s) 3.42 (2 H, t, J=5.8 Hz) 3.68 - 3.82 (4 H, m) 3.76 (2 H, s) 4.04 (2 H, s) 4.42 - 4.54 (1 H, m) 4.70 - 4.85 (1 H, m) 4.92 - 5.03 (1 H, m) 5.07 (1 H, d, J=11.8 Hz) 5.64 - 5.75 (2 H, m) 6.02 - 6.18 (2 H, m) 6.35 (1 H, dd, J=17.0, 10.3 Hz) 7.32 (1 H, d, J=8.7 Hz) 7.38 - 7.42 (1 H, m) 7.49 (1 H, d, J=8.6 Hz) 7.98 (1 H, s) 13.00 (1 H, s)
27	E5-2	ESI+; 734.5

[0334]

[Table 164]

Ex	Syn	Dat
28	E28	ESI+; 748.5 NMR (400 MHz): 0.46 - 0.78 (4 H, m) 1.24 - 1.41 (1 H, m) 1.58 - 1.77 (4 H, m) 1.87 - 2.16 (8 H, m) 2.11 (3 H, s) 2.25 - 2.36 (2 H, m) 2.70 - 2.84 (2 H, m) 3.21 (3 H, s) 3.27 - 3.37 (2 H, m) 3.59 - 3.72 (4 H, m) 3.75 (2 H, s) 4.03 (2 H, s) 4.38 - 4.53 (1 H, m) 4.69 - 4.84 (1 H, m) 4.89 - 5.03 (1 H, m) 5.68 (1 H, dd, J=10.1, 2.2 Hz) 6.12 (1 H, dd, J=17.1, 2.3 Hz) 6.34 (1 H, dd, J=17.0, 10.1 Hz) 7.22 (1 H, s) 7.33 (1 H, d, J=8.6 Hz) 7.42 - 7.51 (2 H, m) 12.96 (1 H, s)
29	E5-2	ESI+; 734.5
30	E30	ESI+; 746.6 NMR (500 MHz): 1.34 - 1.50 (2 H, m) 1.59 - 1.76 (4 H, m) 1.90 - 2.13 (6 H, m) 2.05 (3 H, s) 2.22 - 2.33 (2 H, m) 2.38 - 2.50 (1 H, m) 2.80 - 2.92 (2 H, m) 3.20 - 3.33 (2 H, m) 3.69 - 3.81 (4 H, m) 3.76 (2 H, s) 3.82 - 3.92 (2 H, m) 4.04 (2 H, s) 4.42 - 4.54 (1 H, m) 4.72 - 4.84 (1 H, m) 4.93 - 5.01 (1 H, m) 5.06 (1 H, d, J=11.9 Hz) 5.65 - 5.74 (2 H, m) 6.03 - 6.17 (2 H, m) 6.35 (1 H, dd, J=17.0, 10.4 Hz) 7.32 (1 H, d, J=8.7 Hz) 7.37 - 7.43 (1 H, m) 7.49 (1 H, d, J=8.9 Hz) 7.98 (1 H, s) 12.74 - 13.27 (1 H, m)
31	E31	ESI+; 734.5
32	E5-2	ESI+; 716.6
33	E5-2	ESI+; 718.5
34	E31	ESI+; 678.5

[0335]

[Table 165]

Ex	Syn	Dat
35	E24	ESI+; 734.5 $[\alpha]_D^{20}$ +19.7 (c 0.35, MeOH)
36	E36	ESI+; 720.5 NMR (400 MHz): 1.62 - 1.77 (2 H, m) 1.91 - 2.09 (6 H, m) 2.05 (3 H, s) 2.11 - 2.23 (2 H, m) 2.45 - 2.52 (2 H, m) 2.75 - 2.89 (2 H, m) 3.22 (3 H, s) 3.42 (2 H, t, J=5.8 Hz) 3.69 - 3.81 (4 H, m) 3.76 (2 H, s) 4.04 (2 H, s) 4.41 - 4.54 (1 H, m) 4.71 - 4.84 (1 H, m) 4.92 - 5.03 (1 H, m) 5.06 (1 H, d, J=11.7 Hz) 5.64 - 5.76 (2 H, m) 6.01 - 6.19 (2 H, m) 6.34 (1 H, dd, J=17.0, 10.4 Hz) 7.32 (1 H, d, J=8.6 Hz) 7.37 - 7.43 (1 H, m) 7.49 (1 H, d, J=8.6 Hz) 7.98 (1 H, s) 12.94 - 13.06 (1 H, m) $[\alpha]_D^{20}$ +33.2 (c 0.35, MeOH)
37	E24	ESI+; 734.5 $[\alpha]_D^{20}$ +34.2 (c 0.35, MeOH)
38	E38	ESI+; 748.5 NMR (400 MHz): 0.48 - 0.74 (4 H, m) 1.27 - 1.40 (1 H, m) 1.58 - 1.75 (4 H, m) 1.88 - 2.16 (8 H, m) 2.11 (3 H, s) 2.24 - 2.38 (2 H, m) 2.71 - 2.83 (2 H, m) 3.21 (3 H, s) 3.27 - 3.36 (2 H, m) 3.51 - 3.71 (4 H, m) 3.75 (2 H, s) 4.03 (2 H, s) 4.35 - 4.55 (1 H, m) 4.67 - 4.85 (1 H, m) 4.88 - 5.06 (1 H, m) 5.68 (1 H, dd, J=10.1, 2.2 Hz) 6.12 (1 H, dd, J=17.0, 2.2 Hz) 6.34 (1 H, dd, J=17.0, 10.1 Hz) 7.22 (1 H, s) 7.33 (1 H, d, J=8.6 Hz) 7.42 - 7.52 (2 H, m) 12.96 (1 H, s) $[\alpha]_D^{20}$ +20.0 (c 0.35, MeOH)

[0336]

[Table 166]

Ex	Syn	Dat
39	E39	ESI+; 746.5 NMR (500 MHz): 1.35 - 1.49 (2 H, m) 1.60 - 1.75 (4 H, m) 1.91 - 2.12 (6 H, m) 2.05 (3 H, s) 2.23 - 2.34 (2 H, m) 2.38 - 2.54 (1 H, m) 2.80 - 2.92 (2 H, m) 3.19 - 3.35 (2 H, m) 3.69 - 3.81 (4 H, m) 3.76 (2 H, s) 3.82 - 3.91 (2 H, m) 4.04 (2 H, s) 4.42 - 4.53 (1 H, m) 4.72 - 4.85 (1 H, m) 4.92 - 5.02 (1 H, m) 5.06 (1 H, d, J=11.8 Hz) 5.64 - 5.75 (2 H, m) 6.02 - 6.17 (2 H, m) 6.35 (1 H, dd, J=17.1, 10.3 Hz) 7.32 (1 H, d, J=8.7 Hz) 7.38 - 7.43 (1 H, m) 7.49 (1 H, d, J=8.7 Hz) 7.98 (1 H, s) 12.76 - 13.18 (1 H, m) $[\alpha]_D^{20}$ +32.7 (c 0.35, MeOH)
40	E39	ESI+; 734.5 $[\alpha]_D^{20}$ +31.2 (c 0.35, MeOH)
41	E41	ESI+; 760.5
42	E5-2	ESI+; 689.5
43	E25	ESI+; 662.5
44	E5-2	ESI+; 760.5
45	E5-2	ESI+; 789.5
46	E5-2	ESI+; 716.5
47	E5-2	ESI+; 748.5
48	E5-2	ESI+; 690.5
49	E41	ESI+; 732.5
50	E5-2	ESI+; 661.5
51	E51	ESI+; 692.4
52	E5-2	ESI+; 694.4
53	E5-2	ESI+; 688.5
54	E25	ESI+; 675.6
55	E5-2	ESI+; 740.5
56	E5-2	ESI+; 753.5
57	E5-2	ESI+; 714.5
58	E5-2	ESI+; 698.5

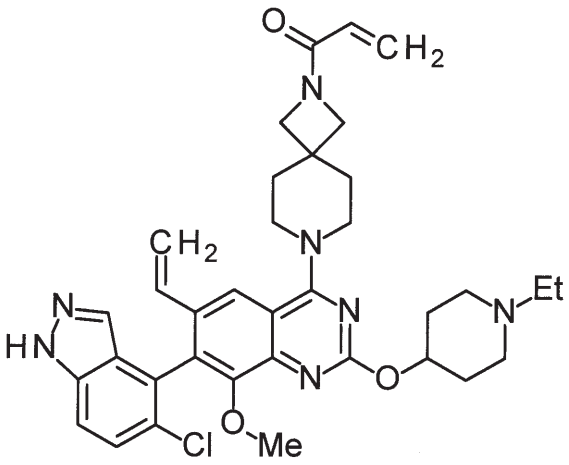
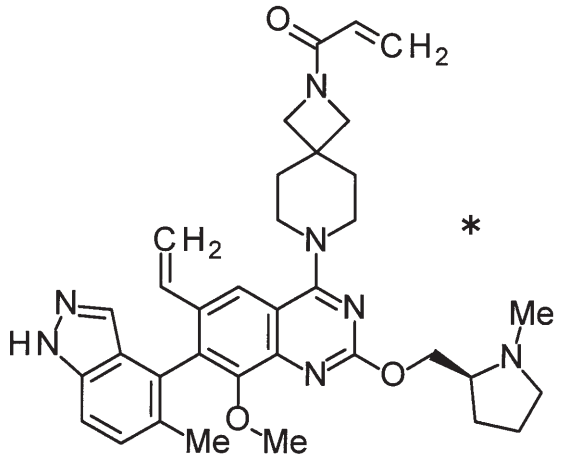
[0337]

[Table 167]

Ex	Syn	Dat
59	E5-2	ESI+; 705.5
60	E5-2	ESI+; 758.4
61	E5-2	ESI+; 684.5
62	E5-2	ESI+; 720.5
63	E5-2	ESI+; 672.5
64	E5-2	ESI+; 704.5
65	E5-2	ESI+; 661.5
66	E5-2	ESI+; 750.5
67	E41	ESI+; 761.5
68	E5-2	ESI+; 675.5
69	E5-2	ESI+; 690.5
70	E5-2	ESI+; 733.5
71	E5-2	ESI+; 664.4
72	E5-2	ESI+; 759.5
73	E41	ESI+; 759.5
74	E5-2	ESI+; 650.4
75	E5-2	ESI+; 711.4
76	E5-2	ESI+; 675.5
77	E5-2	ESI+; 754.5
78	E31	ESI+; 738.5
79	E5-2	ESI+; 770.5
80	E5-2	ESI+; 744.5
81	E5-2	ESI+; 768.4
82	E82	ESI+; 784.5
83	E41	ESI+; 788.5
84	E1	ESI+; 686.6
85	E1	ESI+; 652.5
86	E5-2	ESI+; 740.4
87	E5-2	ESI+; 720.4
88	E5-2	ESI+; 720.5
89	E5-2	ESI+; 689.5
90	E5-2	ESI+; 704.5
91	E5-2	ESI+; 718.5

[0338]

[Table 168]

Reference example 1		Syn: E3 Dat: ESI+; 642.5
Reference example 2		Syn: E3 Dat: ESI+; 608.6

Industrial Applicability

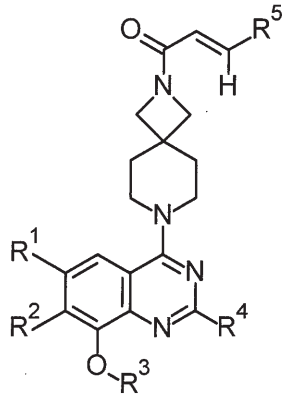
[0339]

The compound of the present invention and a salt thereof are useful as a G12C mutation KRAS inhibitor, and may be used as a pharmaceutical composition, for example, an active ingredient of a pharmaceutical composition for treating lung cancer.

Claims

[Claim 1] A compound of Formula (I) or a salt thereof:

[Chem. 9]



(I)

(in the formula,

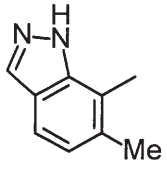
R^1 is vinyl, (E)-1-propenyl or cyclopropyl,

R^2 is Formula (II) or (III),

[Chem. 10]



(II)

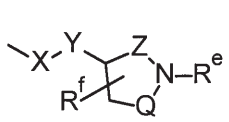


(III)

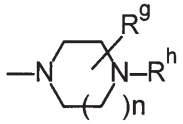
R^3 is C_{3-4} alkyl, methyl or n-propyl each of which may be substituted with two or more F's, ethyl or C_{3-4} cycloalkyl each of which may be substituted with F, benzyl which may be substituted with C_{1-3} alkyl, benzyl which may be substituted with -O-C_{1-3} alkyl, or benzyl which may be substituted with -O-(C_{1-3} alkyl which is substituted with F),

R^4 is -O-C_{3-5} alkyl which may be substituted, -O-cycloalkyl which may be substituted, or Formula (IV), (V), (VI), or (VII),

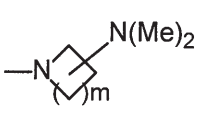
[Chem. 11]



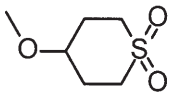
(IV)



(V)



(VI)



(VII)

R^5 is H or CF_3,

R^a is H or F,

R^b is H or F,

R^c is H, methyl, vinyl, or Cl,

R^d is H or Cl,

R^e is CO_2Me, COMe, $CON(Me)_2$, SO_2Me, C_{3-4} cycloalkyl, a nonaromatic heterocyclic group having 4 to 6 ring members which may be substituted, or C_{1-3} alkyl which may be substituted with a group selected from the Group G,
the Group G is -O-C_{1-3} alkyl, -O-(C_{1-3} alkyl which is substituted with F or C_{3-4} cycloalkyl), C_{3-4} cycloalkyl, -F, -CN, $-SO_2Me$, an aromatic heterocyclic group, a nonaromatic heterocyclic group having 4 to 6 ring members, -N(C_{1-3} alkyl)$_2$, and -$C(Me)_2OH$,
R^f is H, methyl, or F,
R^g is H, methyl, or ethyl,
R^h is C_{1-3} alkyl which may be substituted with -OMe,
X is O, NH, S, or methylene,
Y is a bond or methylene,
Z is a bond, methylene, or ethylene,
Q is methylene or ethylene,
n is an integer of 1 or 2, and
m is an integer in a range of 1 to 3.)

[Claim 2] The compound or the salt thereof according to claim 1, wherein R^2 is Formula (II).

[Claim 3] The compound or the salt thereof according to claim 2, wherein R^4 is Formula (IV).

[Claim 4] The compound or the salt thereof according to claim 3, wherein X is O.

[Claim 5] The compound or the salt thereof according to claim 4, wherein R^5 is H.

[Claim 6] The compound or the salt thereof according to claim 5, wherein R^1 is vinyl or cyclopropyl.

[Claim 7] The compound or the salt thereof according to claim 6, wherein R^a is H, R^b is H or F, R^c is methyl or Cl, and R^d is H.

[Claim 8] The compound or the salt thereof according to claim 7, wherein R^3 is C_{3-4} alkyl, methyl or n-propyl each of which is substituted with two or more F's, or ethyl or C_{3-4} cycloalkyl each of which may be substituted with F.

[Claim 9] The compound or the salt thereof according to claim 8,
wherein R^e is a nonaromatic heterocyclic group having 4 to 6 ring members which may be substituted, or C_{1-3} alkyl which may be substituted with a group selected from the Group G.

[Claim 10] The compound or the salt thereof according to claim 9,
wherein R^e is oxetanyl, tetrahydropyranyl, or C_{1-3} alkyl which may be substituted with a group selected from the group consisting of -OMe, -OEt, and $-C(Me)_2OH$.

[Claim 11] The compound or the salt thereof according to claim 1,
wherein the compound is selected from the group consisting of
(+)-1-(7-{8-ethoxy-7-(5-methyl-1H-indazol-4-yl)-2-[(1-methylpiperidin-4-yl)oxy]-6-vinylquinazolin-4-yl}-2,7-diazaspiro[3.5]non-2-yl)prop-2-en-1-one,
(+)-1-{7-[6-cyclopropyl-2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[2-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[2-{[1-(2-ethoxyethyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[6-cyclopropyl-2-{[1-(3-methoxypropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)quinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one,
(+)-1-{7-[7-(5-methyl-1H-indazol-4-yl)-2-{[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one, and
(+)-1-{7-[2-{[1-(2-hydroxy-2-methylpropyl)piperidin-4-yl]oxy}-7-(5-methyl-1H-indazol-4-yl)-8-(2,2,2-trifluoroethoxy)-6-vinylquinazolin-4-yl]-2,7-diazaspiro[3.5]non-2-yl}prop-2-en-1-one.

[Claim 12] A pharmaceutical composition, comprising:
the compound or the salt thereof according to claim1; and
a pharmaceutically acceptable excipient.

[Claim 13] The pharmaceutical composition according to claim 12 which is a pharmaceutical composition for treating lung cancer.

[Claim 14] Use of the compound or the salt thereof according to claim 1 for the manufacture of a pharmaceutical composition for treating lung cancer.

[Claim 15] The compound or the salt thereof according to claim 1 for use in the treatment of lung cancer.

[Claim 16] Use of the compound or the salt thereof according to claim 1 for treating lung cancer.

[Claim 17] A method of treating lung cancer, comprising:

administering an effective dose of the compound or the salt thereof according to claim 1 to a target.