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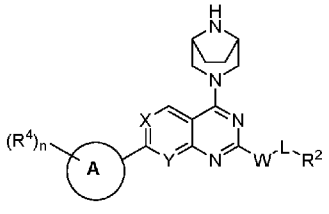

(I)

(57) Abstract: The present embodiments provide compounds of Formula (I), compositions of the compounds, and methods for treating diseases such as cancer.

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SELECTIVE KRAS INHIBITORS

BACKGROUND

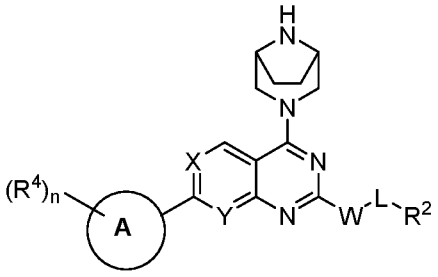
[0001] Embodiments herein relate to compounds, compositions and methods for the treatment of RAS-mediated disease. In particular, embodiments herein relate to compounds and methods for treating diseases such as cancer via targeting oncogenic mutants of the K-RAS isoform.

[0002] Ras proteins are small guanine nucleotide-binding proteins that act as molecular switches by cycling between active GTP-bound and inactive GDP-bound conformations. Ras signaling is regulated through a balance between activation by guanine nucleotide exchange factors (GEFs), most commonly son of sevenless (SOS), and inactivation by GTPase-activating proteins (GAPs) such as neurofibromin or p120GAP. The Ras proteins play an important role in the regulation of cell proliferation, differentiation, and survival. Dysregulation of the Ras signaling pathway is almost invariably associated with disease. Hyper-activating somatic mutations in Ras are among the most common lesions found in human cancer. Most of these mutations have been shown to decrease the sensitivity of Ras to GAP stimulation and decrease its intrinsic GTPase activity, leading to an increase in the active GTP-bound population. Although mutation of any one of the three Ras isoforms (K-Ras, N-Ras, or H-Ras) has been shown to lead to oncogenic transformation, K-Ras mutations are by far the most common in human cancer. For example, K- Ras mutations are known to be often associated with pancreatic, colorectal and non-small-cell lung carcinomas. Similarly, H-Ras mutations are common in cancers such as papillary thyroid cancer, lung cancers and skin cancers. Finally, N-Ras mutations occur frequently in hepatocellular carcinoma.

[0003] K-Ras is the most frequently mutated oncoprotein in human cancers, and the G12D mutation is among the most prevalent. Accordingly, there is a need to develop selective inhibitors of KRAS G12D. The present embodiments meet this and other needs.

SUMMARY

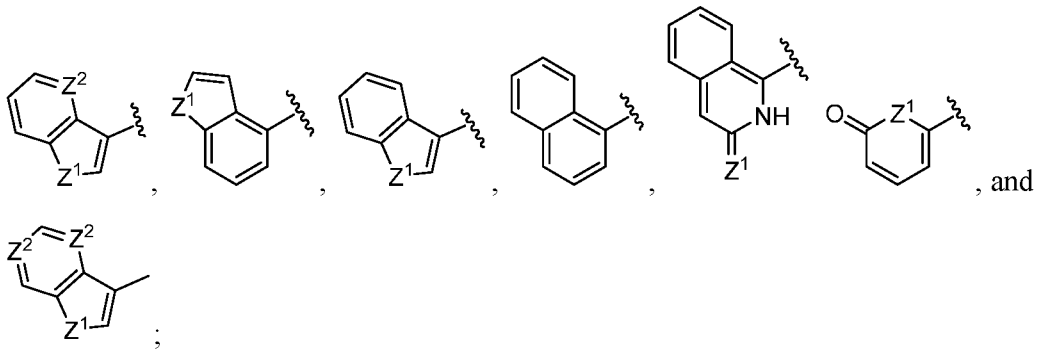
[0004] In one aspect, the present embodiments provide compounds of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

ring A is selected from



;

W is O, NR^3, S, or absent;

X is CR^1 or N;

Y is CR^1 or N;

Z^1 is O, N(C_1-C_4 alkyl), NH, or S;

each Z^2 is independently CH or N;

L is C_{1-3} alkyl or absent;

each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl

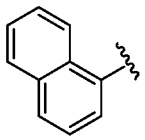
R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

R^3 is H or C_{1-4} alkyl;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, -NH_2; and,

n is 0, 1, 2, 3, or 4.

[0005] In an embodiment, when X is N of Formula (I), ring A is not



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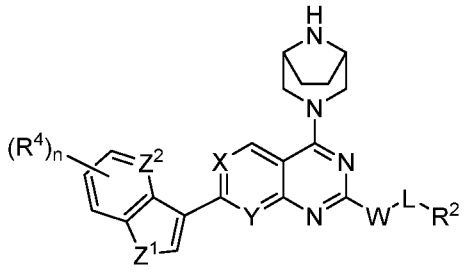
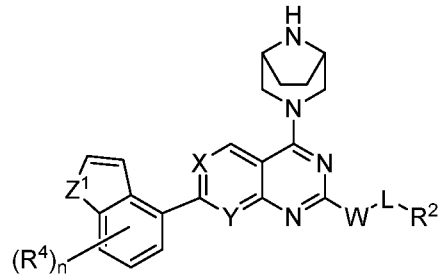
[0006] In an embodiment, the present application provides compounds of Formula (Ia):



(Ia)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

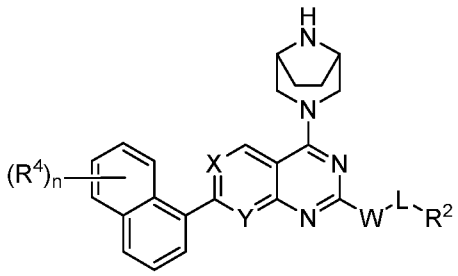
[0007] In an embodiment, the present application provides compounds of Formula (Ib):



(Ib)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

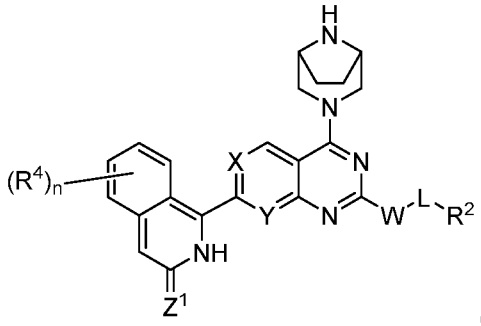
[0008] In an embodiment, the present application provides compounds of Formula (Ic):



(Ic)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

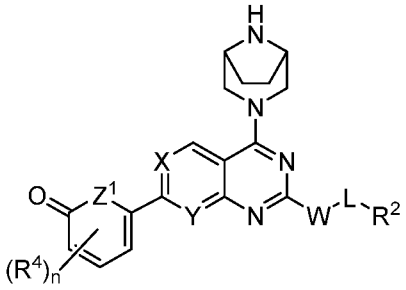
[0009] In an embodiment, the present application provides compounds of Formula (Id):



(Id)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

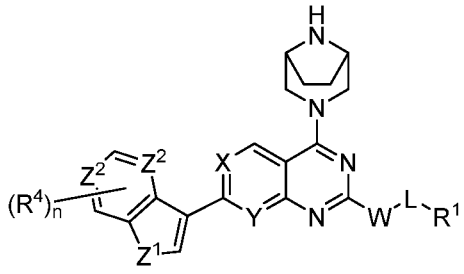
[0010] In an embodiment, the present application provide compounds of Formula (Ie):



(Ie)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

[0011] In an embodiment, the present application provides compounds of Formula (If):



(If)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof.

[0012] In another aspect, the present embodiments provide a pharmaceutical composition comprising a pharmaceutically effective amount of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0013] In another embodiment, the present embodiments provide a method of treating a subject having cancer, the cancer characterized by the presence of a KRAS G12D

mutation, the method comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein.

[0014] In another embodiment, the present embodiments provide a method for manufacturing a medicament for treating a subject having cancer, the cancer characterized by the presence of a KRAS G12D mutation, the medicament comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a a pharmaceutical composition as disclosed herein, is used.

[0015] In another embodiment, the present embodiments provide for the use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a a pharmaceutical composition as disclosed herein, for the manufacture of a medicament for the treatment of cancer in a subject, the cancer characterized by the presence of a KRAS G12D mutation.

[0016] In another embodiment, the present embodiments provide the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, or a a pharmaceutical composition as disclosed herein, for use in the treatment of cancer in a subject, the cancer characterized by a KRAS G12D mutation.

DETAILED DESCRIPTION

I. GENERAL

[0017] The present embodiments provide selective inhibitors of KRAS G12D exhibiting good selectivity over wild-type KRAS and are useful for treating a cancer characterized by a KRAS G12D mutation.

II. DEFINITIONS

[0018] Unless specifically indicated otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the embodiments belong. In addition, any method or material similar or equivalent to a method or material described herein can be used in the practice of the present embodiments. For purposes of the present embodiments, the following terms are defined.

[0019] "A," "an," or "the" as used herein not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms "a,"

"an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the agent" includes reference to one or more agents known to those skilled in the art, and so forth.

[0020] "Alkyl" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{1-7}, C_{1-8}, C_{1-9}, C_{1-10}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. For example, C_{1-6} alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can also refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Alkyl groups can be substituted or unsubstituted.

[0021] "Alkylene" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated, and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkylene can be linked to the same atom or different atoms of the alkylene group. For instance, a straight chain alkylene can be the bivalent radical of $-(CH_2)_n-$, where n is 1, 2, 3, 4, 5 or 6. Representative alkylene groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene and hexylene. Alkylene groups can be substituted or unsubstituted.

[0022] "Alkenyl" refers to a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one double bond. Alkenyl can include any number of carbons, such as C_2, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{2-7}, C_{2-8}, C_{2-9}, C_{2-10}, C_3, C_{3-4}, C_{3-5}, C_{3-6}, C_4, C_{4-5}, C_{4-6}, C_5, C_{5-6}, and C_6. Alkenyl groups can have any suitable number of double bonds, including, but not limited to, 1, 2, 3, 4, 5 or more. Examples of alkenyl groups include, but are not limited to, vinyl (ethenyl), propenyl, isopropenyl, 1-butenyl, 2-butenyl, isobutenyl, butadienyl, 1-pentenyl, 2-pentenyl, isopentenyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,5-hexadienyl, 2,4-hexadienyl, or 1,3,5-hexatrienyl. Alkenyl groups can be substituted or unsubstituted.

[0023] "Alkenylene" refers to an alkenyl group, as defined above, linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkenylene can be linked to the same atom or different atoms of the alkenylene. Alkenylene groups include, but are not limited to, ethenylene, propenylene,

isopropenylene, butenylene, isobutenylene, sec-butenylene, pentenylene and hexenylene. Alkenylen groups can be substituted or unsubstituted.

[0024] "Alkynyl" refers to either a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one triple bond. Alkynyl can include any number of carbons, such as C_2, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{2-7}, C_{2-8}, C_{2-9}, C_{2-10}, C_3, C_{3-4}, C_{3-5}, C_{3-6}, C_4, C_{4-5}, C_{4-6}, C_5, C_{5-6}, and C_6. Examples of alkynyl groups include, but are not limited to, acetylenyl, propynyl, 1-butynyl, 2-butynyl, butadiynyl, 1-pentynyl, 2-pentynyl, isopentynyl, 1,3-pentadiynyl, 1,4-pentadiynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1,3-hexadiynyl, 1,4-hexadiynyl, 1,5-hexadiynyl, 2,4-hexadiynyl, or 1,3,5-hexatriynyl. Alkynyl groups can be substituted or unsubstituted.

[0025] "Alkynylene" refers to an alkynyl group, as defined above, linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkynylene can be linked to the same atom or different atoms of the alkynylene. Alkynylene groups include, but are not limited to, ethynylene, propynylene, isopropynylene, butynylene, sec-butynylene, pentynylene and hexynylene. Alkynylene groups can be substituted or unsubstituted.

[0026] "Alkoxy" refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: alkyl-O-. As for alkyl group, alkoxy groups can have any suitable number of carbon atoms, such as C_{1-6}. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc. The alkoxy groups can be further substituted with a variety of substituents described within. Alkoxy groups can be substituted or unsubstituted.

[0027] "Alkoxyalkyl" refers to a radical having an alkyl component and an alkoxy component, where the alkyl component links the alkoxy component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the alkoxy component and to the point of attachment. The alkyl component can include any number of carbons, such as C_{0-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. The alkoxy component is as defined above. Examples of the alkoxyalkyl group include, but are not limited to, 2-ethoxy-ethyl and methoxymethyl.

[0028] "Alkylhydroxy" or "hydroxyalkyl" refers to an alkyl group, as defined above, where at least one of the hydrogen atoms is replaced with a hydroxy group. As for the alkyl group, alkylhydroxy groups can have any suitable number of carbon atoms, such as C_{1-6}. Exemplary alkylhydroxy groups include, but are not limited to, hydroxy-methyl, hydroxyethyl (where the hydroxy is in the 1- or 2-position), hydroxypropyl (where the hydroxy is in the 1-, 2- or 3-position), hydroxybutyl (where the hydroxy is in the 1-, 2-, 3- or 4-position), hydroxypentyl (where the hydroxy is in the 1-, 2-, 3-, 4- or 5-position), hydroxyhexyl (where the hydroxy is in the 1-, 2-, 3-, 4-, 5- or 6-position), 1,2-dihydroxyethyl, and the like.

[0029] "Halogen" or "halo" refers to fluorine, chlorine, bromine and iodine. "Haloalkyl" refers to alkyl, as defined above, where some or all of the hydrogen atoms are replaced with halogen atoms. As for alkyl group, haloalkyl groups can have any suitable number of carbon atoms, such as C_{1-6}. For example, haloalkyl includes trifluoromethyl, flouromethyl, etc. In some instances, the term "perfluoro" can be used to define a compound or radical where all the hydrogens are replaced with fluorine. For example, perfluoromethyl refers to 1,1,1-trifluoromethyl.

[0030] "Haloalkoxy" refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for an alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as C_{1-6}. The alkoxy groups can be substituted with 1, 2, 3, or more halogens. When all the hydrogens are replaced with a halogen, for example by fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2,-trifluoroethoxy, perfluoroethoxy, etc.

[0031] "Cycloalkyl" refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as C_{3-6}, C_{4-6}, C_{5-6}, C_{3-8}, C_{4-8}, C_{5-8}, C_{6-8}, C_{3-9}, C_{3-10}, C_{3-11}, and C_{3-12}. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double or triple bonds in the ring. Representative cycloalkyl groups that are partially unsaturated include, but are not

limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. When cycloalkyl is a saturated monocyclic C_{3-8} cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. When cycloalkyl is a saturated monocyclic C_{3-6} cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyl groups can be substituted or unsubstituted.

[0032] "Cycloalkylene" refers to a cycloalkyl group having the number of carbon atoms indicated, and linking at least two other groups, *i.e.*, a divalent radical. The two moieties linked to the cycloalkylene can be linked to the same atom or different atoms of the cycloalkylene group. Examples of cycloalkylene rings include cyclopropylene, cyclobutylene, cyclopentylene and cyclohexylene, among others. Cycloalkylene groups can be linked 1,1, 1,2, 1,3, or 1,4. The cyclohexylene ring, for example, can adopt a number of conformations, including the boat and chair conformations. The chair conformation of cyclohexylene can have substituents in an axial or equatorial orientation. The divalent nature of the cycloalkylenes results in *cis* and *trans* formations where *cis* refers to both substituents being on the same side (top or bottom) of the cycloalkylene ring, and where *trans* refers to the substituents being on on opposite sides of the cycloalkylene ring. For example, *cis*-1,2- and *cis*-1,4-cyclohexylene can have one substituent in the axial orientation and the other substituent in the equatorial orientation, while *trans*-1,2- and *trans*-1,4-cyclohexylene have both substituents in the axial or equatorial orientation. *cis*-1,3-cyclohexylene have both substituents in the axial or equatorial orientation, and *trans*-1,3-cyclohexylene can have one substituent in the axial orientation and the other substituent in the equatorial orientation. Cycloalkylene groups can be substituted or unsubstituted.

[0033] "Alkyl-cycloalkyl" refers to a radical having an alkyl component and a cycloalkyl component, where the alkyl component links the cycloalkyl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the cycloalkyl component and to the point of attachment. In some instances, the alkyl component can be absent. The alkyl component can include any number of carbons, such as C_{1-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{2-3},

C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. The cycloalkyl component is as defined within. Exemplary alkyl-cycloalkyl groups include, but are not limited to, methyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl and methyl-cyclohexyl.

[0034] "Heterocycloalkyl" or "heterocyclyl" refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can also be oxidized, such as, but not limited to, -S(O)- and -$S(O)_2$-. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, dithiane, and hexahydro-1H-pyrrolizine. The heterocycloalkyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline. Heterocycloalkyl groups can be unsubstituted or substituted. For example, heterocycloalkyl groups can be substituted with C_{1-6} alkyl or oxo (=O), among many others.

[0035] The heterocycloalkyl groups can be linked via any position on the ring. For example, aziridine can be 1- or 2-aziridine, azetidine can be 1- or 2- azetidine, pyrrolidine can be 1-, 2- or 3-pyrrolidine, piperidine can be 1-, 2-, 3- or 4-piperidine, pyrazolidine can be 1-, 2-, 3-, or 4-pyrazolidine, imidazolidine can be 1-, 2-, 3- or 4-imidazolidine, piperazine can be 1-, 2-, 3- or 4-piperazine, tetrahydrofuran can be 1- or 2-tetrahydrofuran, oxazolidine can be 2-, 3-, 4- or 5-oxazolidine, isoxazolidine can be 2-, 3-, 4- or 5-isoxazolidine, thiazolidine can be 2-, 3-, 4- or 5-thiazolidine, isothiazolidine can be 2-, 3-, 4- or 5- isothiazolidine, and morpholine can be 2-, 3- or 4-morpholine.

[0036] When heterocycloalkyl includes 3 to 8 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine,

piperazine, oxazolidine, isoxzoalidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocycloalkyl can also form a ring having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine, piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, and hexahydro-1H-pyrrolizine.

[0037] "Heterocyclalkylene" refers to a heterocyclalkyl group, as defined above, linking at least two other groups. The two moieties linked to the heterocyclalkylene can be linked to the same atom or different atoms of the heterocyclalkylene. Heterocycloalkylene groups can be substituted or unsubstituted.

[0038] "Alkyl-heterocycloalkyl" refers to a radical having an alkyl component and a heterocycloalkyl component, where the alkyl component links the heterocycloalkyl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the heterocycloalkyl component and to the point of attachment. The alkyl component can include any number of carbons, such as C_{0-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. In some instances, the alkyl component can be absent. The heterocycloalkyl component is as defined above. Alkyl-heterocycloalkyl groups can be substituted or unsubstituted.

[0039] "Aryl" refers to an aromatic ring system having any suitable number of ring atoms and any suitable number of rings. Aryl groups can include any suitable number of ring atoms, such as, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, as well as from 6 to 10, 6 to 12, or 6 to 14 ring members. Aryl groups can be monocyclic, fused to form bicyclic or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, having a methylene linking group. Some aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl. Some other aryl groups have 6 ring members, such as phenyl. Aryl groups can be substituted or unsubstituted.

[0040] "Alkyl-aryl" refers to a radical having an alkyl component and an aryl component, where the alkyl component links the aryl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is

at least divalent, an alkylene, to link to the aryl component and to the point of attachment. The alkyl component can include any number of carbons, such as C_{0-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. In some instances, the alkyl component can be absent. The aryl component is as defined above. Examples of alkyl-aryl groups include, but are not limited to, benzyl and ethyl-benzene. Alkyl-aryl groups can be substituted or unsubstituted.

[0041] "Arylene" refers to an aryl group, as defined above, linking at least two other groups. The two moieties linked to the aryl can be linked to the same atom or different atoms of the aryl. Arylene groups can be substituted or unsubstituted.

[0042] "Heteroaryl" refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can also be oxidized, such as, but not limited to, -S(O)- and $-S(O)_2-$. Heteroaryl groups can include any number of ring atoms, such as, 5 to 6, 5 to 8, 6 to 8, 5 to 9, 5 to 10, 5 to 11, or 5 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted.

[0043] The heteroaryl groups can be linked via any position on the ring. For example, pyrrole includes 1-, 2- and 3-pyrrole, pyridine includes 2-, 3- and 4-pyridine, imidazole includes 1-, 2-, 4- and 5-imidazole, pyrazole includes 1-, 3-, 4- and 5-pyrazole, triazole

includes 1-, 4- and 5-triazole, tetrazole includes 1- and 5-tetrazole, pyrimidine includes 2-, 4-, 5- and 6- pyrimidine, pyridazine includes 3- and 4-pyridazine, 1,2,3-triazine includes 4- and 5-triazine, 1,2,4-triazine includes 3-, 5- and 6-triazine, 1,3,5-triazine includes 2-triazine, thiophene includes 2- and 3-thiophene, furan includes 2- and 3-furan, thiazole includes 2-, 4- and 5-thiazole, isothiazole includes 3-, 4- and 5-isothiazole, oxazole includes 2-, 4- and 5-oxazole, isoxazole includes 3-, 4- and 5-isoxazole, indole includes 1-, 2- and 3-indole, isoindole includes 1- and 2-isoindole, quinoline includes 2-, 3- and 4-quinoline, isoquinoline includes 1-, 3- and 4-isoquinoline, quinazoline includes 2- and 4-quinoazoline, cinnoline includes 3- and 4-cinnoline, benzothiophene includes 2- and 3-benzothiophene, and benzofuran includes 2- and 3-benzofuran.

[0044] Some heteroaryl groups include those having from 5 to 10 ring members and from 1 to 3 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include those having from 5 to 8 ring members and from 1 to 3 heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Some other heteroaryl groups include those having from 9 to 12 ring members and from 1 to 3 heteroatoms, such as indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, benzofuran and bipyridine. Still other heteroaryl groups include those having from 5 to 6 ring members and from 1 to 2 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole.

[0045] Some heteroaryl groups include from 5 to 10 ring members and only nitrogen heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, and cinnoline. Other heteroaryl groups include from 5 to 10 ring members and only oxygen heteroatoms, such as furan and benzofuran. Some other heteroaryl groups include from 5 to 10 ring members and only sulfur heteroatoms, such as thiophene and benzothiophene. Still other heteroaryl

groups include from 5 to 10 ring members and at least two heteroatoms, such as imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiazole, isothiazole, oxazole, isoxazole, quinoxaline, quinazoline, phthalazine, and cinnoline.

[0046] "Heteroarylene" refers to a heteroaryl group, as defined above, linking at least two other groups. The two moieties linked to the heteroaryl are linked to different atoms of the heteroaryl. Heteroarylene groups can be substituted or unsubstituted.

[0047] "Alkyl-heteroaryl" refers to a radical having an alkyl component and a heteroaryl component, where the alkyl component links the heteroaryl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the heteroaryl component and to the point of attachment. The alkyl component can include any number of carbons, such as C_{0-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. In some instances, the alkyl component can be absent. The heteroaryl component is as defined within. Alkyl-heteroaryl groups can be substituted or unsubstituted.

[0048] The groups defined above can optionally be substituted by any suitable number and type of subsituents. Representative substituents include, but are not limited to, halogen, haloalkyl, haloalkoxy, -OR',
=O, -OC(O)R', -(O)R', -O_2R', -ONR'R", -OC(O)NR'R", =NR',
=N-OR', -NR'R", -NR"C(O)R', -NR'-(O)NR"R"', -NR"C(O)OR', -NH-(NH_2)=NH, -NR'C(NH_2)=NH, -NH-(NH_2)=NR', -SR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -NR'$S(O)_2$R", -N_3 and -NO_2. R', R" and R"' each independently refer to hydrogen, unsubstituted alkyl, such as unsubstituted C_{1-6} alkyl. Alternatively, R' and R", or R" and R"', when attached to the same nitrogen, are combined with the nitrogen to which they are attached to form a heterocycloalkyl or heteroaryl ring, as defined above.

[0049] "Salt" refers to acid or base salts of the compounds, which can be used in the methods disclosed herein. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical

Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

[0050] Pharmaceutically acceptable salts of the acidic compounds disclosed herein are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

[0051] Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids, e.g., hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

[0052] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present embodiments.

[0053] Certain compounds disclosed herein possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present embodiments.

[0054] "Hydrate" refers to a compound that is complexed to at least one water molecule. The compounds disclosed herein can be complexed with from 1 to 10 water molecules.

[0055] "Composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product, which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and deleterious to the recipient thereof.

[0056] "Pharmaceutically acceptable excipient" refers to a substance that aids the administration of an active agent to and absorption by a subject. Pharmaceutical excipients useful in the present embodiments include, but are not limited to, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors. One of skill in

the art will recognize that other pharmaceutical excipients are useful in the present embodiments.

[0057] "Treat", "treating" and "treatment" refers to any indicia of success in the treatment or amelioration of an injury, pathology, condition, or symptom (e.g., pain), including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the symptom, injury, pathology or condition more tolerable to the patient; decreasing the frequency or duration of the symptom or condition; or, in some situations, preventing the onset of the symptom. The treatment or amelioration of symptoms can be based on any objective or subjective parameter; including, e.g., the result of a physical examination.

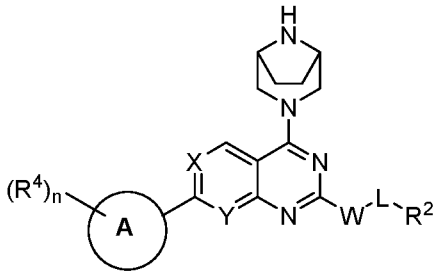
[0058] "Administering" refers to oral administration, administration as a suppository, topical contact, parenteral, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, intrathecal administration, or the implantation of a slow-release device e.g., a mini-osmotic pump, to the subject.

[0059] "Therapeutically effective amount or dose" or "therapeutically sufficient amount or dose" or "effective or sufficient amount or dose" refer to a dose that produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). In sensitized cells, the therapeutically effective dose can often be lower than the conventional therapeutically effective dose for non-sensitized cells.

[0060] "Subject" refers to animals such as mammals, including, but not limited to, primates (*e.g.,* humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In certain embodiments, the subject is a human.

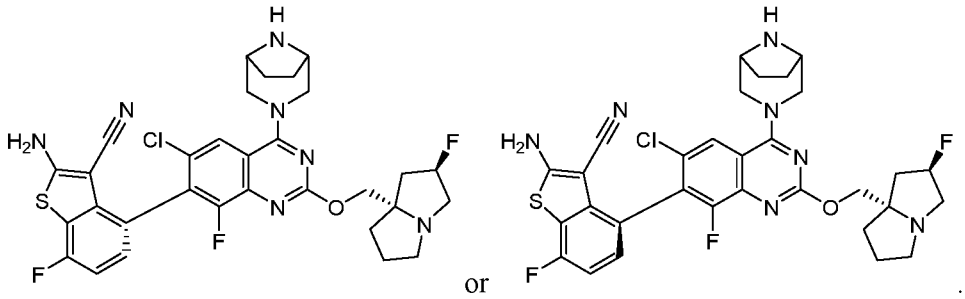
III. COMPOUNDS

[0061] The present embodiments provide compounds, and pharmaceutically acceptable salts thereof, of Formula (I):

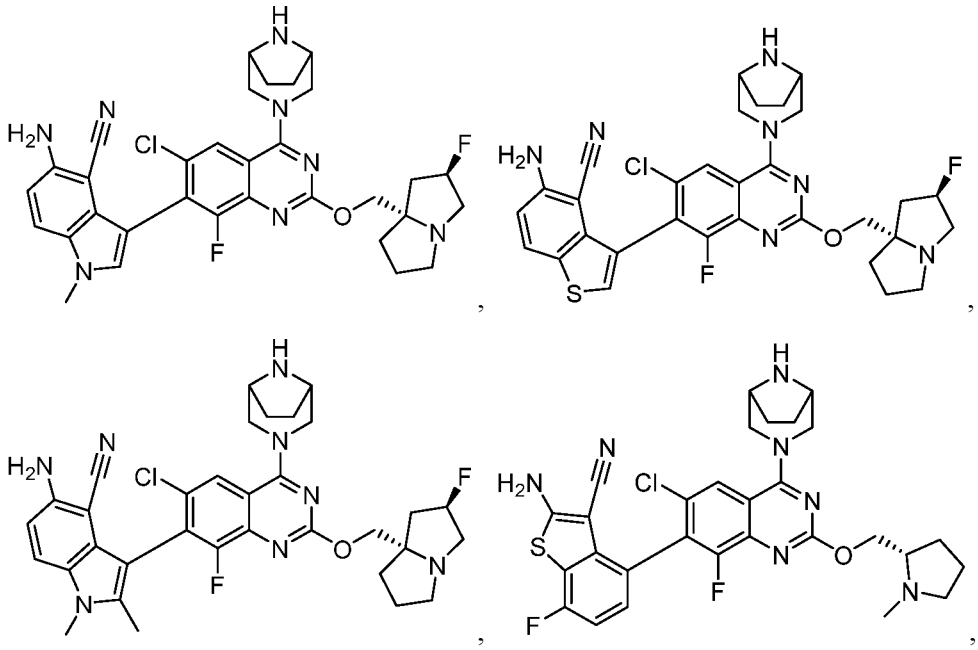


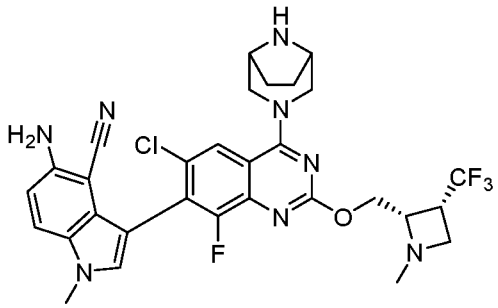
(I).

[0062] In some embodiments, the compound is a single atropisomer of Formula (I):



[0063] In some embodiments, the compound is:

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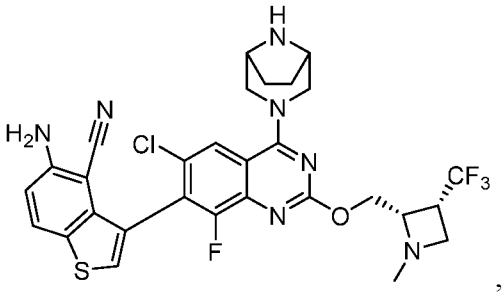
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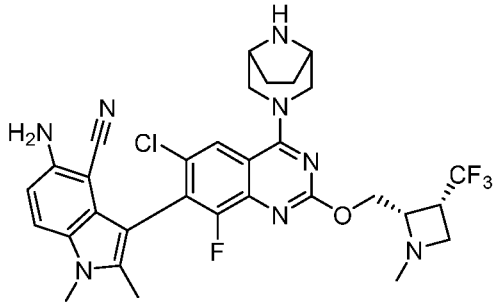
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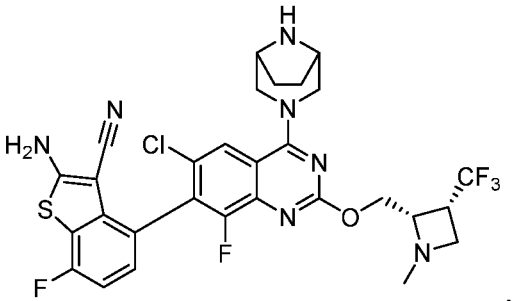
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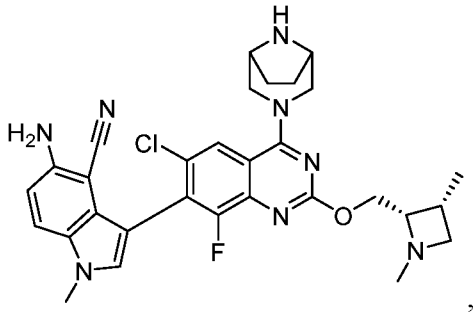
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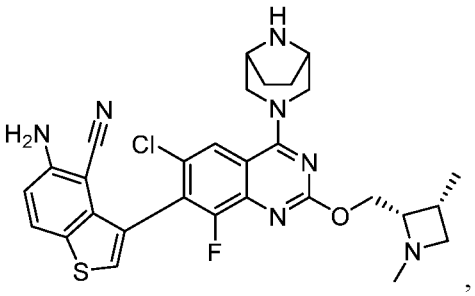
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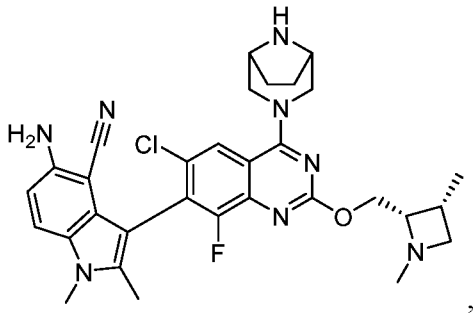
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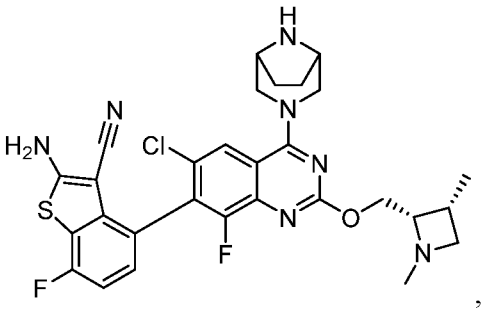
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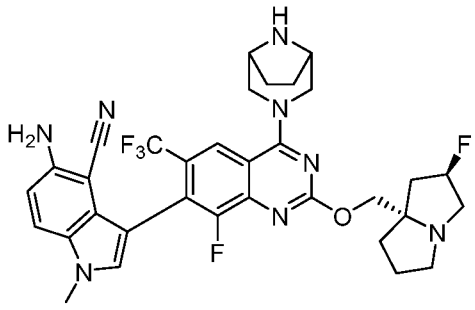
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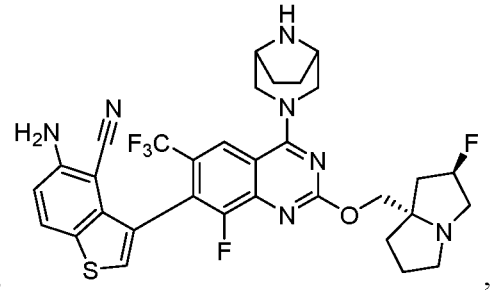
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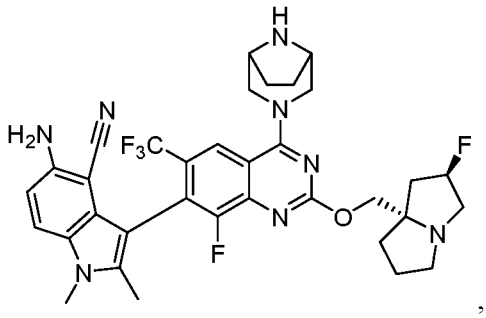
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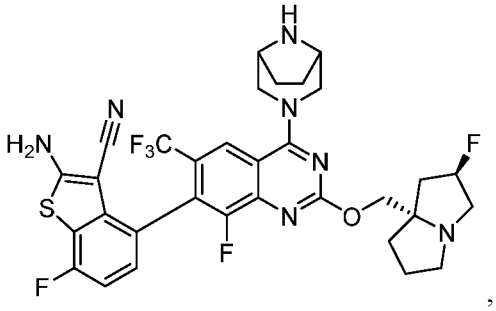
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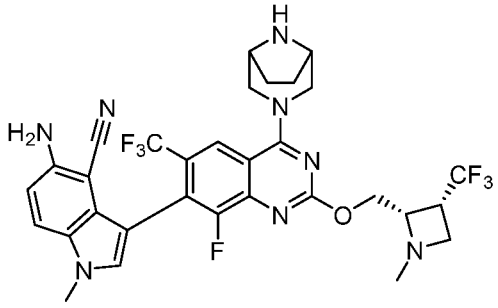
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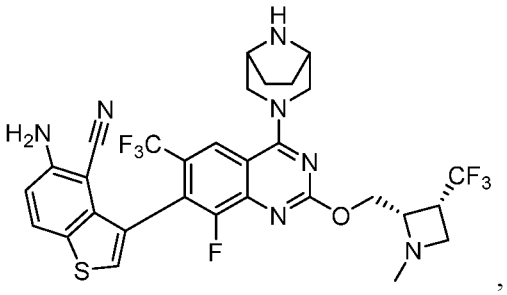
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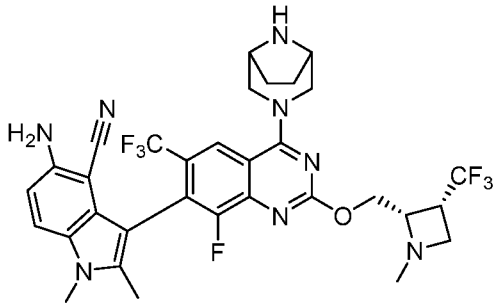
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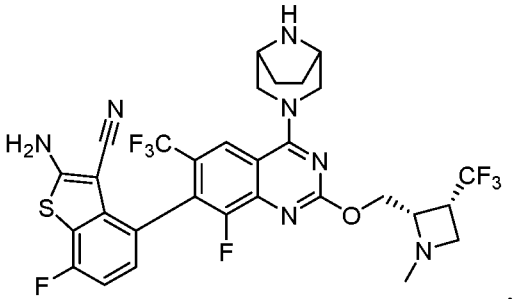
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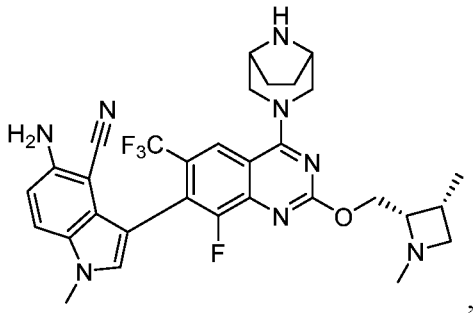
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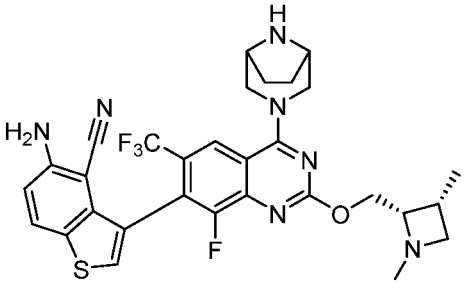
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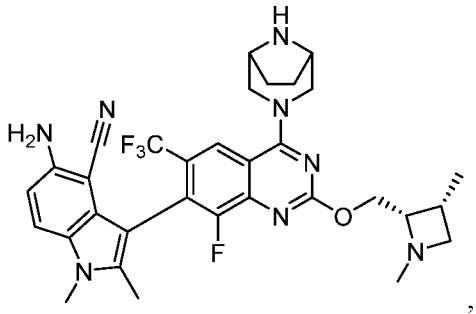
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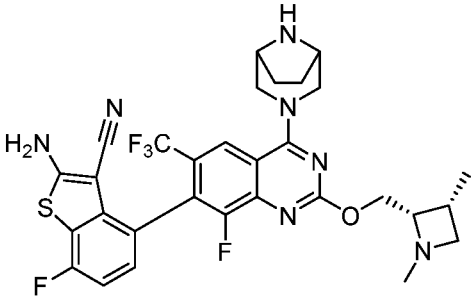
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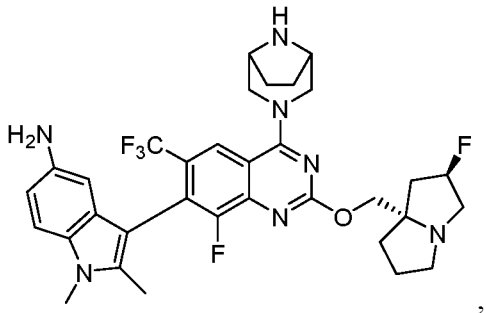
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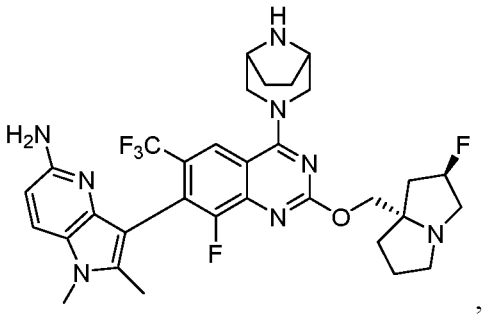
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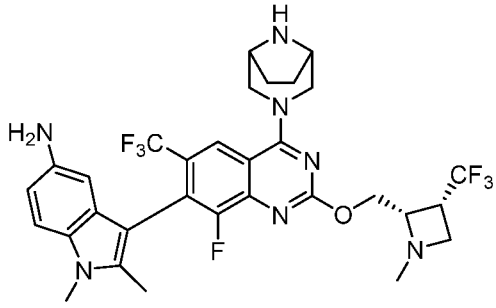
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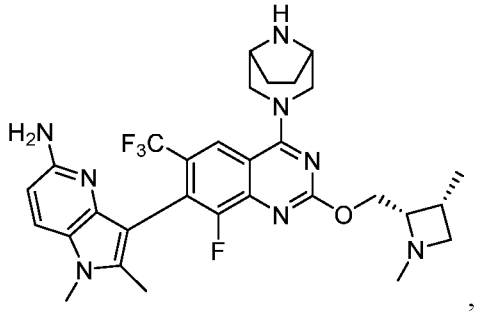
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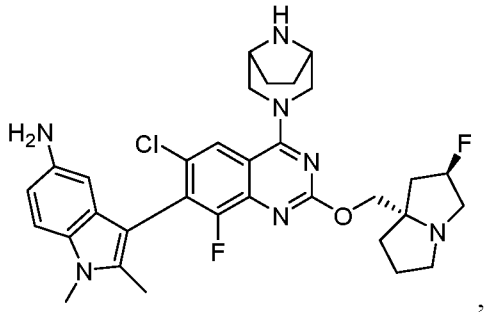
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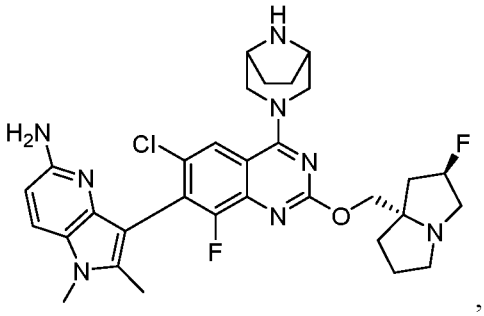
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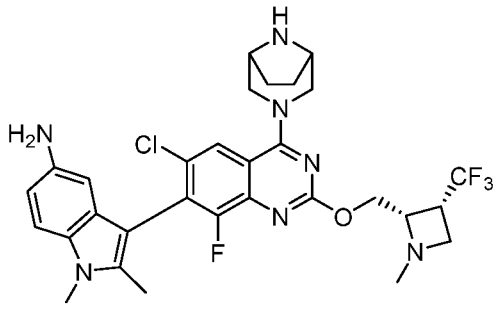
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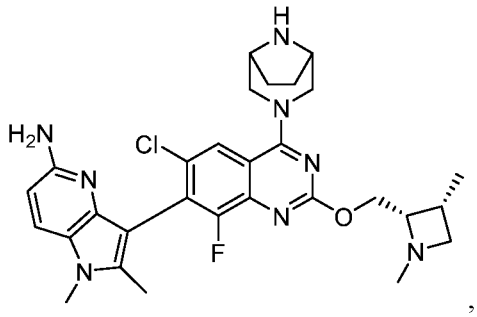
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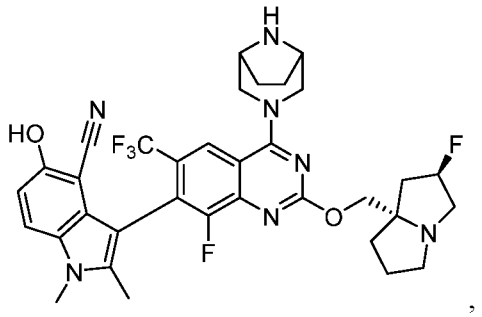
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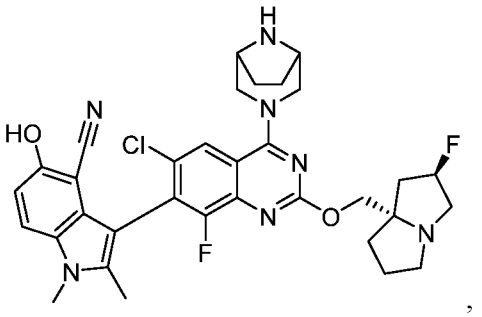
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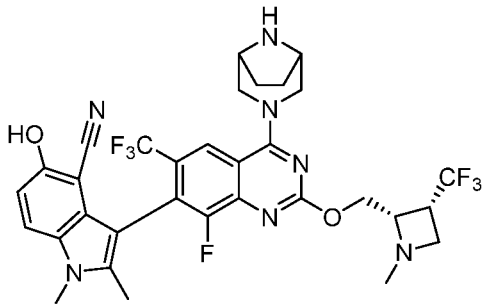
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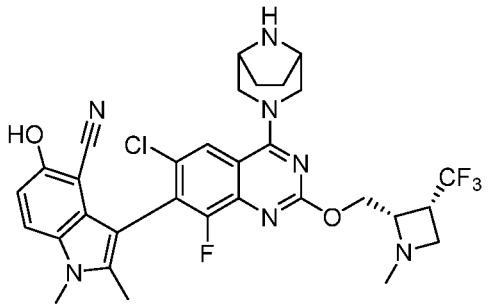
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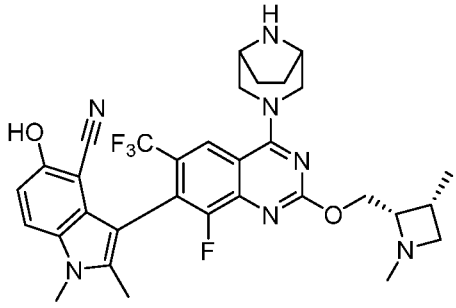
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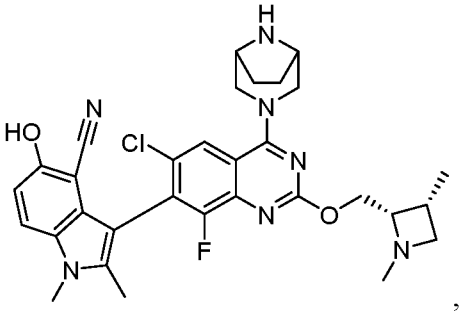
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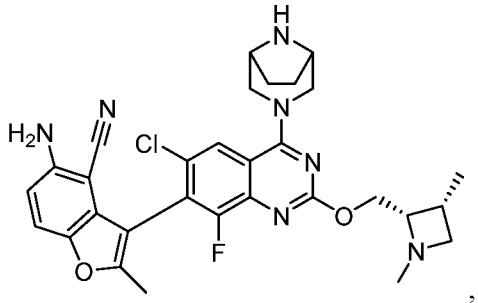
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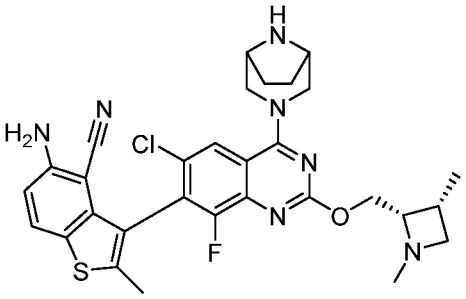
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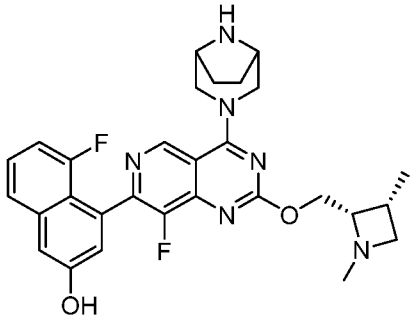
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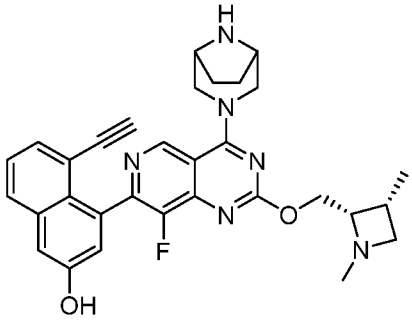
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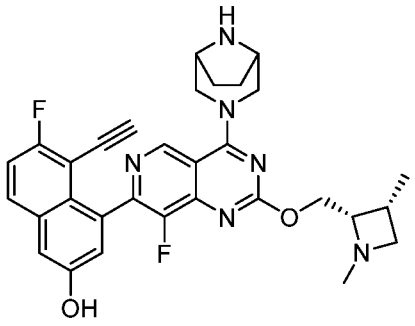
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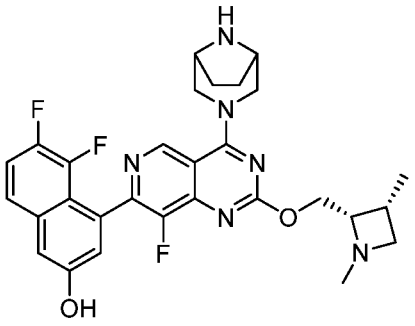
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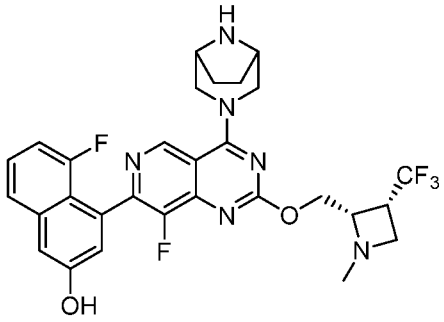
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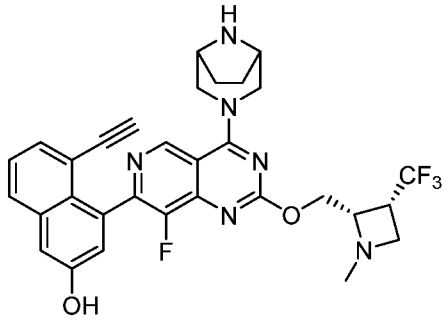
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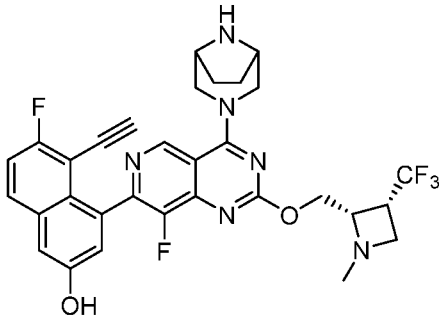
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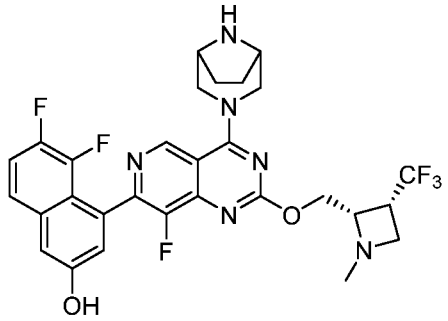
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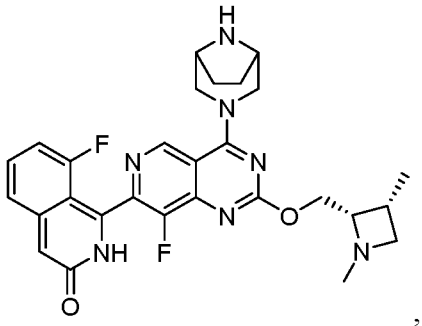
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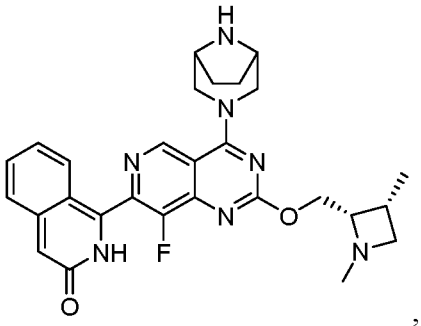
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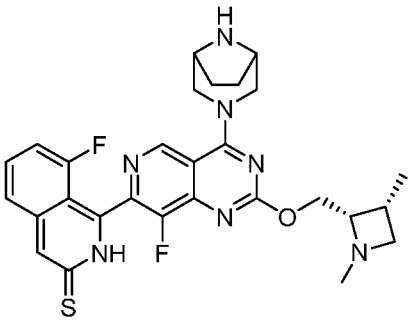
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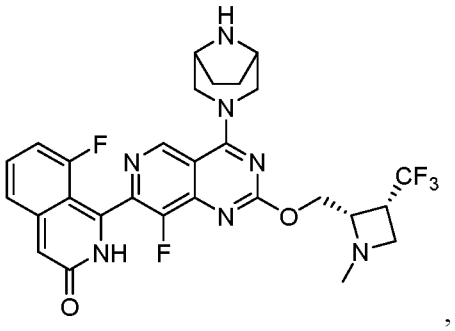
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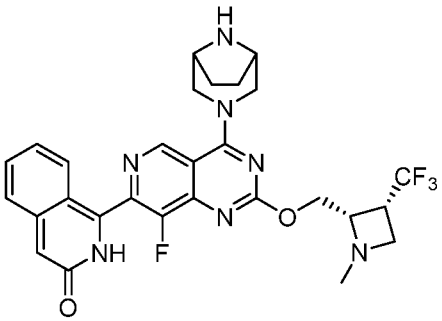
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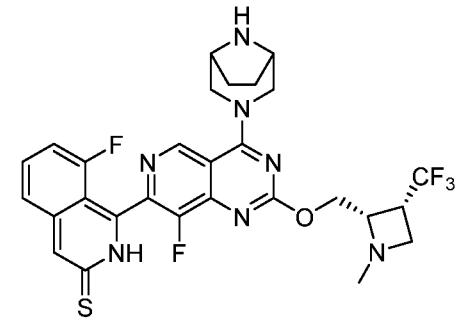
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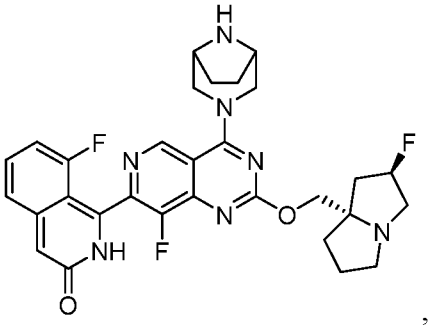
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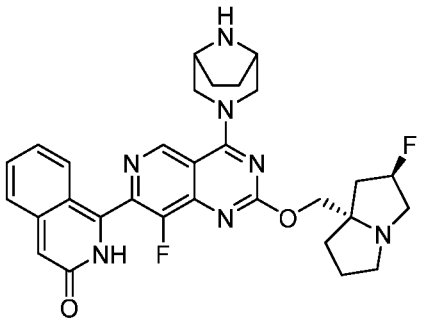
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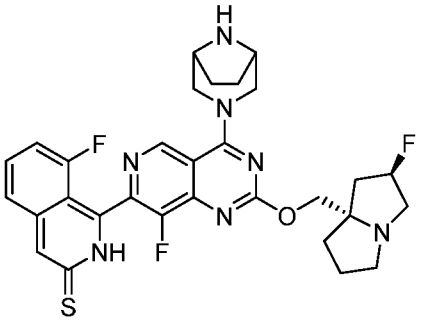
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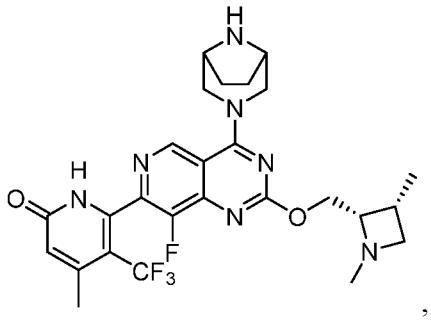
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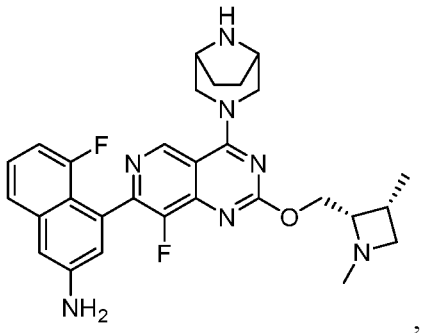
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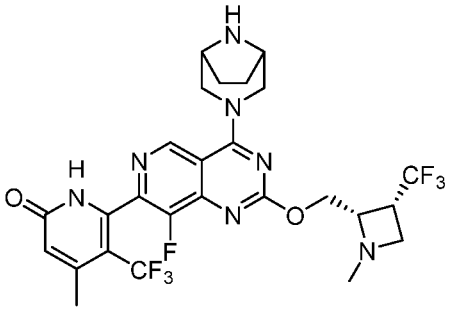
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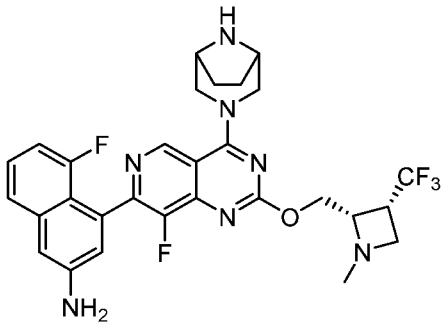
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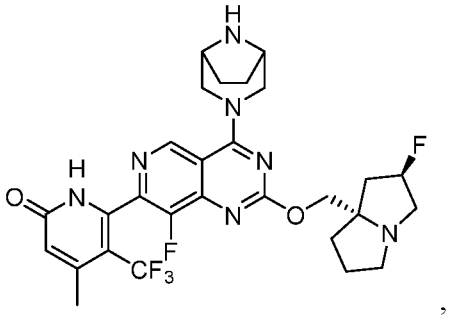
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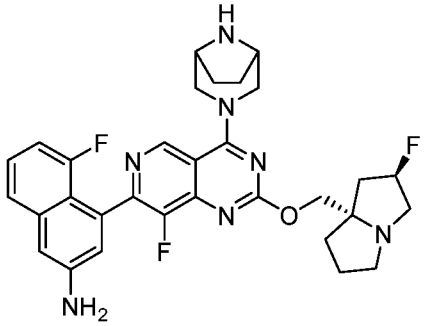
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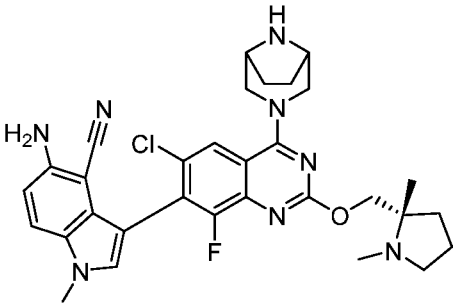
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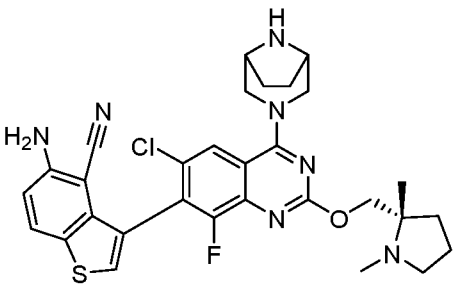
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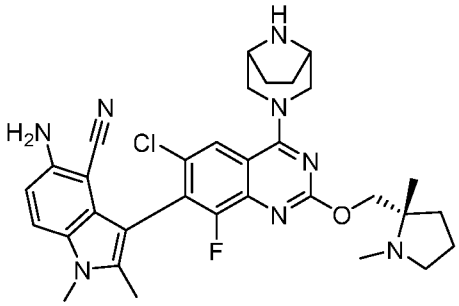
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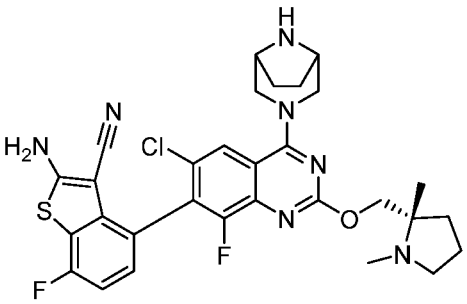
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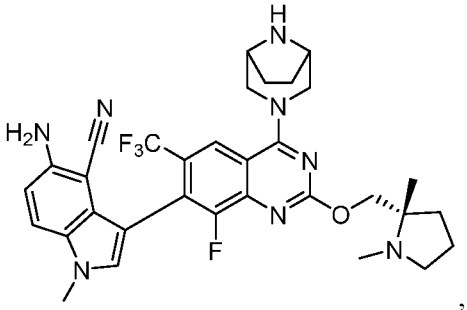
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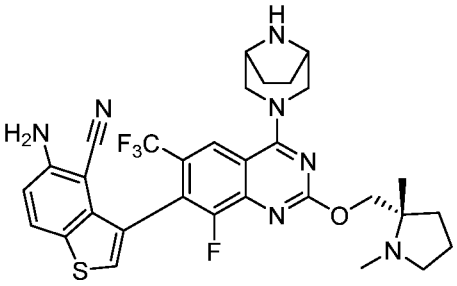
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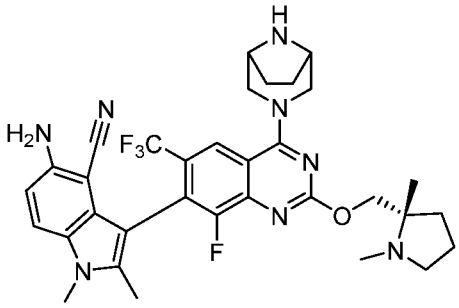
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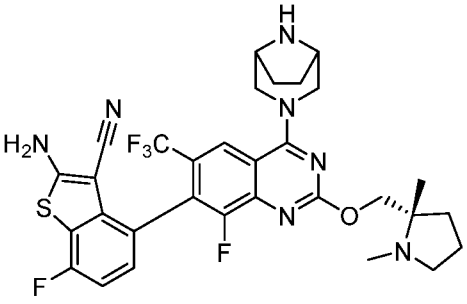
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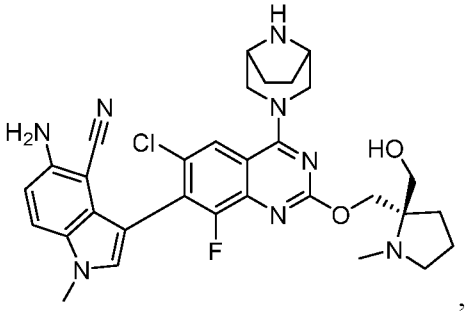
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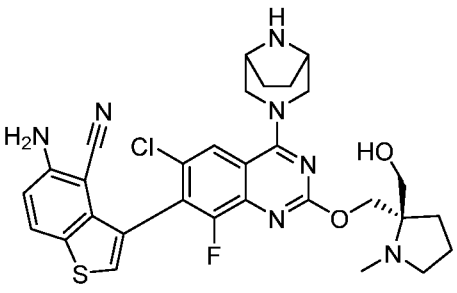
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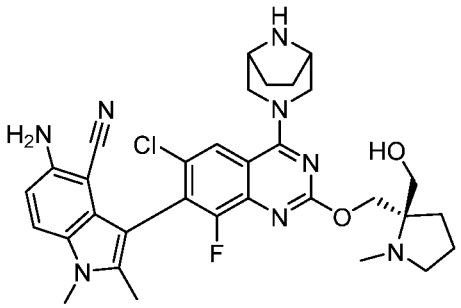
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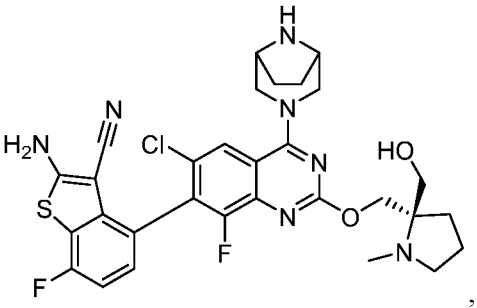
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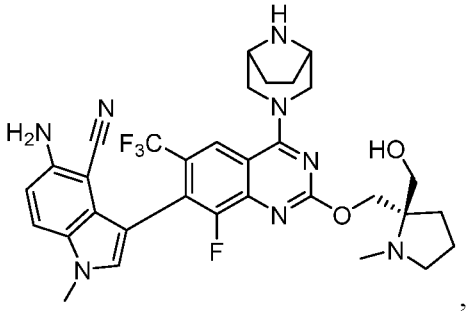
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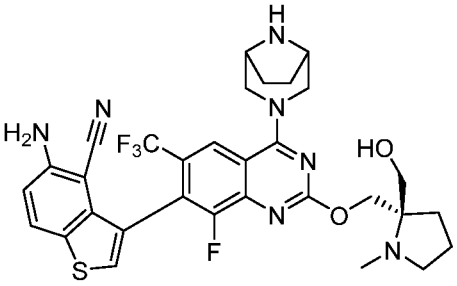
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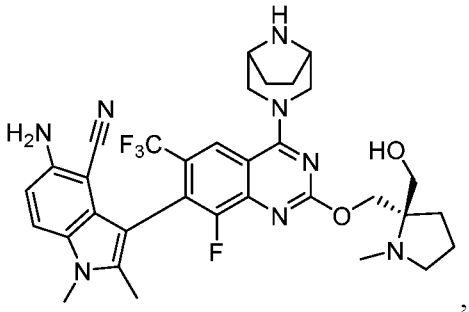
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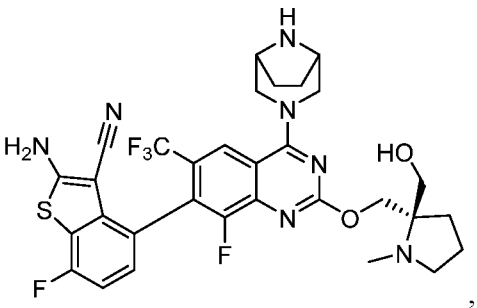
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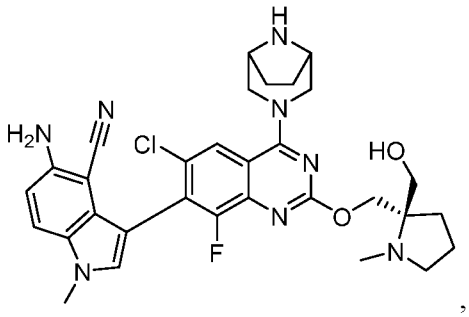
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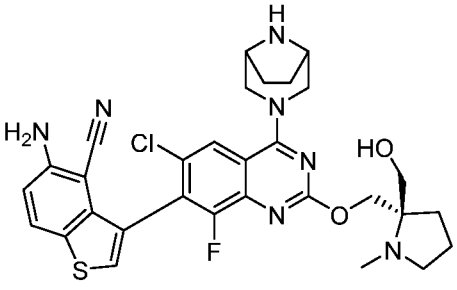
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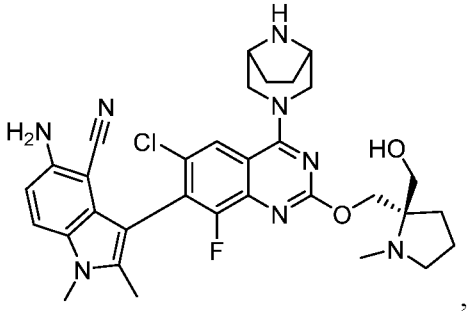
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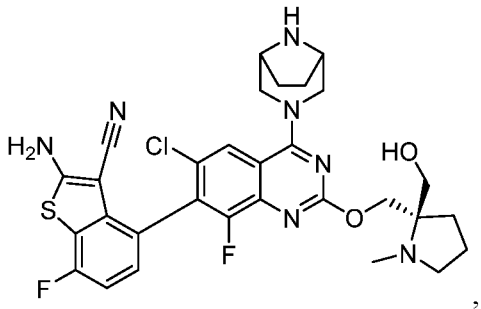
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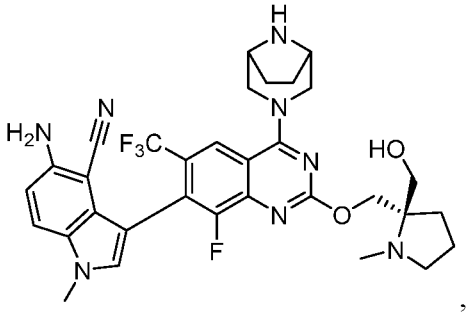
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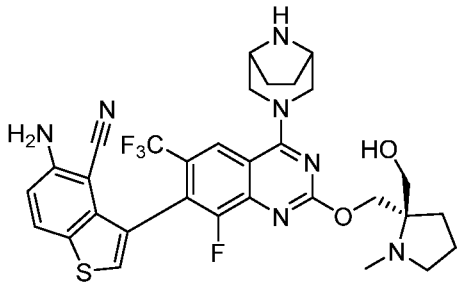
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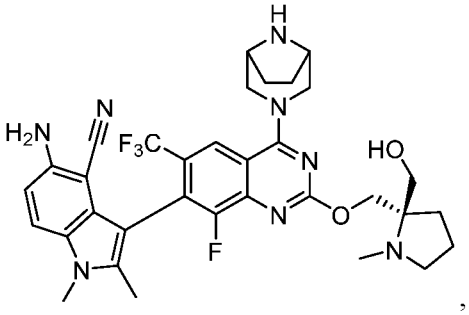
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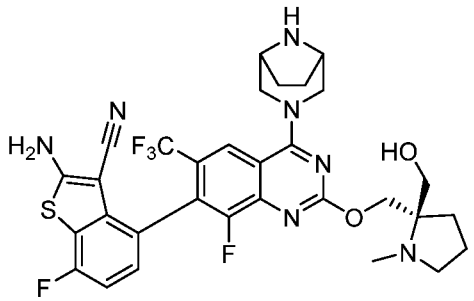
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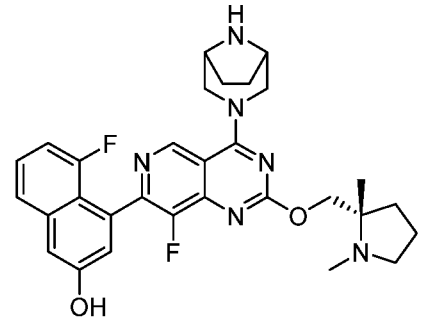
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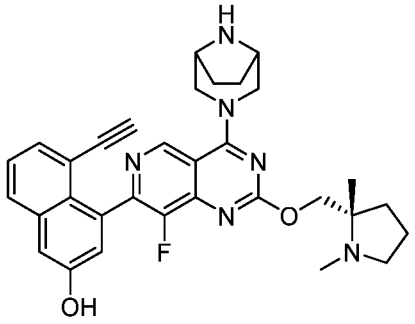
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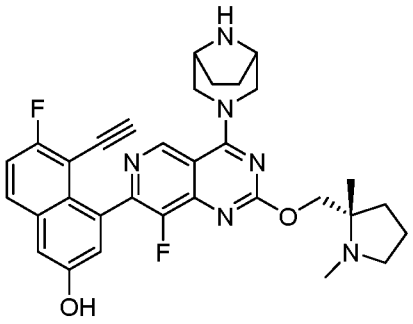
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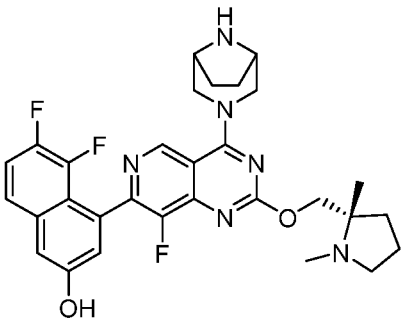
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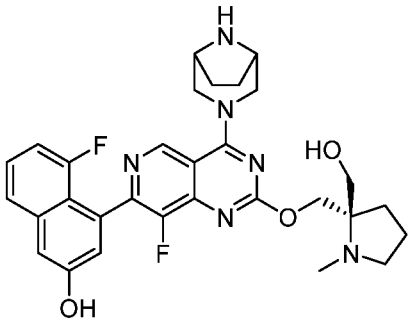
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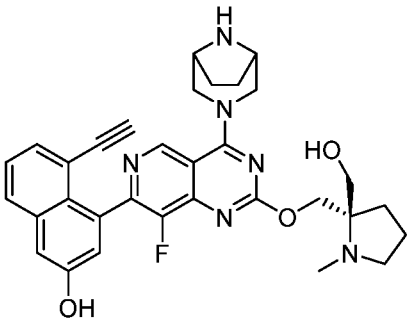
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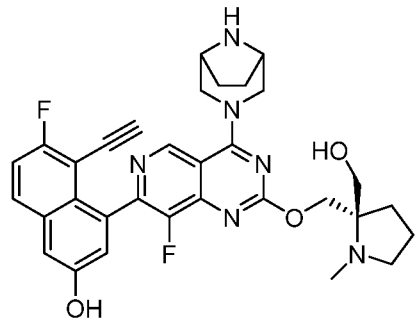
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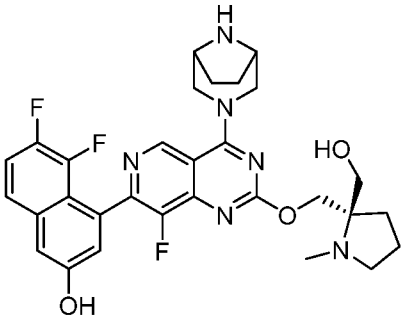
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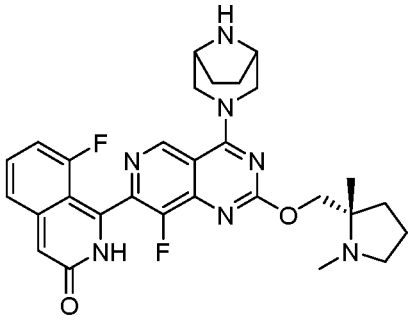
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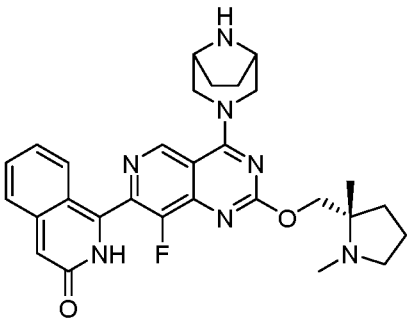
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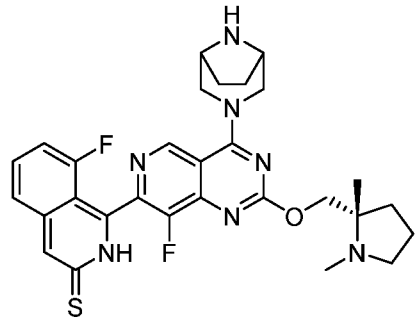
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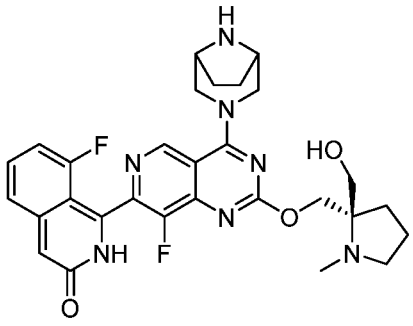
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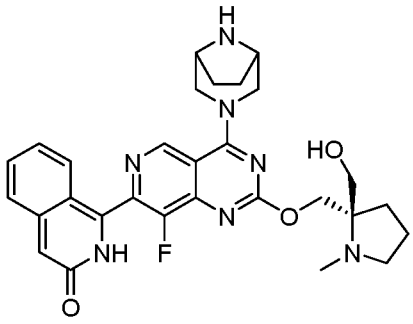
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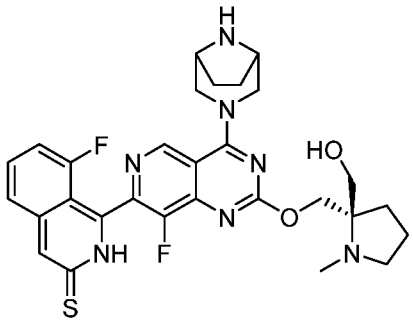
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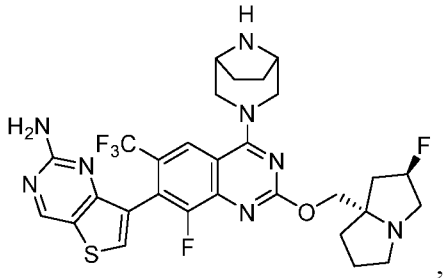
[0064] In some embodiments, the compound is: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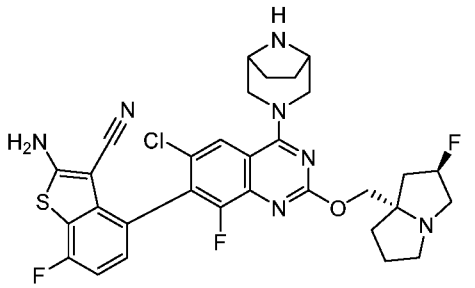
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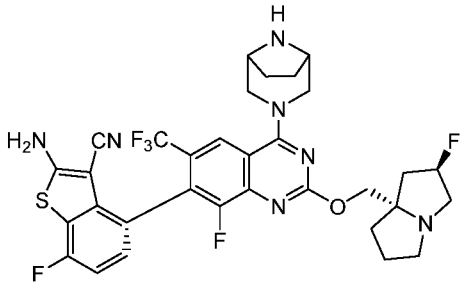
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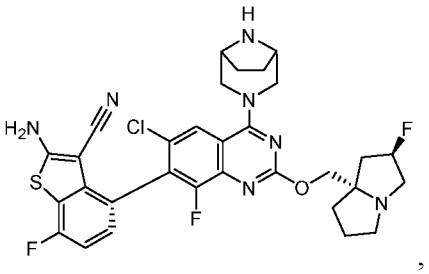
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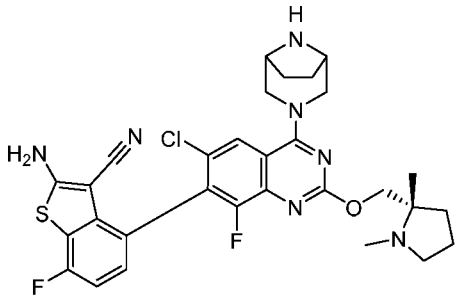
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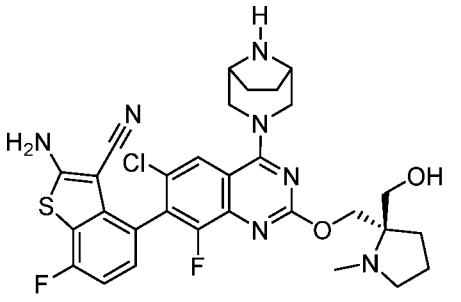
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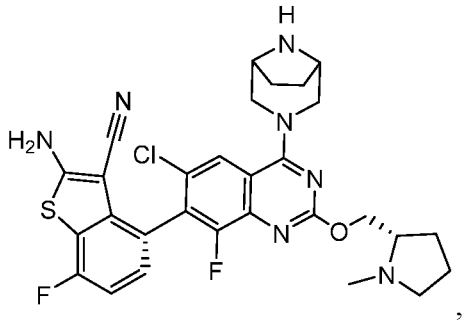
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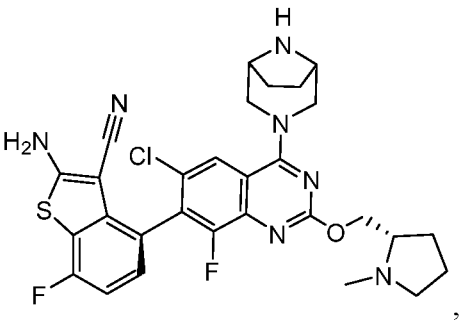
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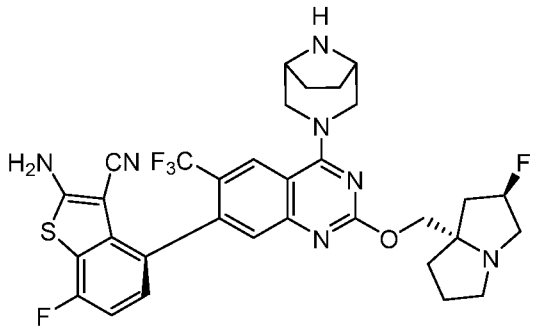
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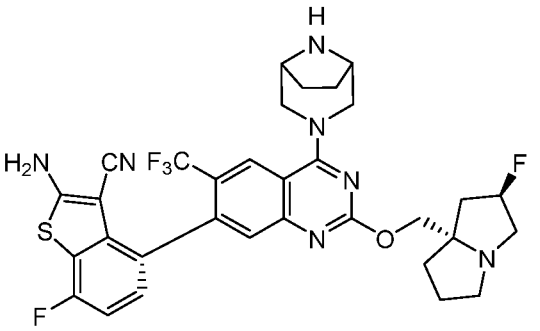
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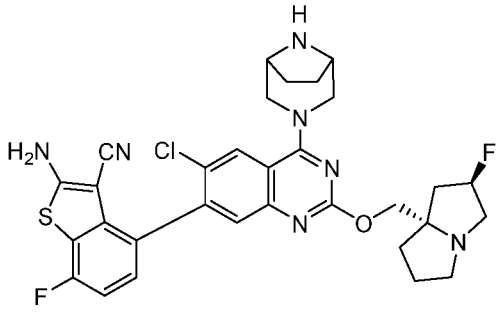
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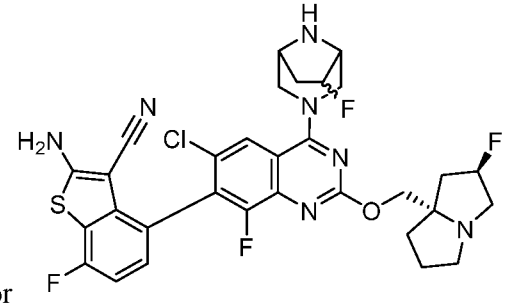
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[0065] The compounds disclosed herein can exist as salts. The present embodiments include such salts, which can be pharmaceutically acceptable salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino

acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds disclosed herein contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds disclosed herein contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0066] Other salts include acid or base salts of the compounds used in the methods of the present embodiments. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, and quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

[0067] Pharmaceutically acceptable salts includes salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds disclosed herein contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or

magnesium salt, or a similar salt. When compounds disclosed herein contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds disclosed herein contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0068] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0069] Certain compounds disclosed herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present embodiments. Certain compounds disclosed herein may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present embodiments and are intended to be within the scope of the present embodiments.

[0070] Certain compounds disclosed herein possess asymmetric carbon atoms (optical centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present embodiments. The compounds disclosed herein do not include those which are known in art to be too unstable to synthesize and/or isolate. The present embodiments are meant to include compounds in racemic and optically pure

forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. The compounds disclosed herein can be provided as a mixture of atropisomers or can be pure atropisomers.

[0071] Isomers include compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0072] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the embodiments.

[0073] Unless otherwise stated, the compounds disclosed herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds disclosed herein may be labeled with radioactive or stable isotopes, such as for example deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I), fluorine-18 (^{18}F), nitrogen-15 (^{15}N), oxygen-17 (^{17}O), oxygen-18 (^{18}O), carbon-13 (^{13}C), or carbon-14 (^{14}C). All isotopic variations of the compounds disclosed herein, whether radioactive or not, are encompassed within the scope of the present embodiments.

[0074] In addition to salt forms, the present embodiments provide compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds disclosed herein. Additionally, prodrugs can be converted to the compounds disclosed herein by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds disclosed herein when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0075] Compounds disclosed herein can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's *Reagents for Organic Synthesis*; Wiley & Sons: New York, vol. 1-21; R. C.

LaRock, *Comprehensive Organic Transformations*, 2nd edition Wiley-VCH, New York **1999**; *Comprehensive Organic Synthesis*, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, **1991**; *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees (Eds.) Pergamon, Oxford **1984**, vol. 1-9; *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford **1996**, vol. 1-11; and *Organic Reactions*, Wiley & Sons: New York, **1991**, vol. 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds disclosed herein can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained herein.

[0076] For illustrative purposes, reaction Schemes below provide routes for synthesizing the compounds disclosed herein as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used. Although some specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be substituted to provide a variety of derivatives or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[0077] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0078] Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about −78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C, and most preferably and conveniently at about room (or ambient) temperature, or, about 20 °C.

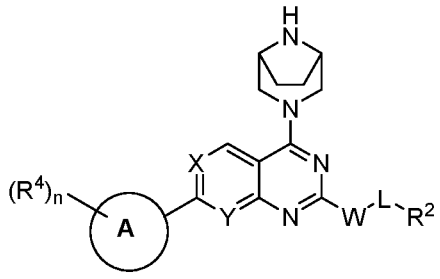
[0079] Some compounds in following schemes are depicted with generalized substituents; however, one skilled in the art will immediately appreciate that the nature of the substituents can varied to afford the various compounds contemplated in the present

embodiments. Moreover, the reaction conditions are exemplary and alternative conditions are well known. The reaction sequences in the following examples are not meant to limit the scope of the embodiments as set forth in the claims.

IV. PHARMACEUTICAL FORMULATIONS

[0080] In some embodiments, pharmaceutical compositions comprise a compound of any one of the compounds disclosed herein and a pharmaceutically acceptable excipient.

[0081] In some embodiments, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of any one of Formula (I),



(I)

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0082] In some embodiments, the pharmaceutical composition further comprises an additional therapeutic agent.

[0083] In some embodiments, the additional therapeutic agent is a chemotherapeutic agent. In some embodiments, the chemotherapeutic agent is an anti-microtubule agent, a platinum coordination complex, a alkylating agent, an antibiotic agent, a topoisomerase II inhibitor, a antimetabolite, a topoisomerase I inhibitor, a hormone or hormonal analogue, a signal transduction pathway inhibitor, a non-receptor tyrosine kinase angiogenesis inhibitor, a immunotherapeutic agent, a proapoptotic agent, an inhibitor of LDH-A, an inhibitor of fatty acid biosynthesis, a cell cycle signalling inhibitor, a HDAC inhibitor, a proteasome inhibitor, or an inhibitor of cancer metabolism. In some embodiments, the chemotherapeutic agent is cisplatin, carboplatin, doxorubicin, ionizing radiation, docetaxel or paclitaxel.

[0084] The compounds disclosed herein can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. The compounds disclosed herein can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds described

herein can be administered by inhalation, for example, intranasally. Additionally, the compounds disclosed herein can be administered transdermally. The compounds disclosed herein can also be administered by in intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, *J. Clin. Pharmacol.* 35:1187-1193, 1995; Tjwa, *Ann. Allergy Asthma Immunol.* 75:107-111, 1995). Accordingly, the present embodiments also provide pharmaceutical compositions including one or more pharmaceutically acceptable carriers and/or excipients and either a compound of Formula I, or a pharmaceutically acceptable salt of a compound of Formula I.

[0085] For preparing pharmaceutical compositions from the compounds disclosed herein, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, surfactants, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton PA ("Remington's").

[0086] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties and additional excipients as required in suitable proportions and compacted in the shape and size desired.

[0087] The powders, capsules and tablets preferably contain from 5% or 10% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other exceipients, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0088] Suitable solid excipients are carbohydrate or protein fillers including, but not limited to sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn,

wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0089] Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the compounds disclosed herein mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the compounds disclosed herein may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[0090] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0091] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0092] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid

(e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[0093] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0094] Oil suspensions can be formulated by suspending the compounds disclosed herein in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

[0095] The compounds disclosed herein can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0096] The compounds disclosed herein can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug -containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months.

[0097] The pharmaceutical formulations of the compounds disclosed herein can be provided as a salt and can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

[0098] The pharmaceutical formulations of the compounds disclosed herein can be provided as a salt and can be formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

[0099] In some embodiments, the formulations of the compounds disclosed herein can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the GR modulator into the target cells in vivo. (See, e.g., Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

[0100] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0101] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0102] The dosage regimen also takes into consideration pharmacokinetics parameters well known in the art, i.e., the rate of absorption, bioavailability, metabolism, clearance, and the like (see, e.g., Hidalgo-Aragones (1996) *J. Steroid Biochem. Mol. Biol.* 58:611-617; Groning (1996) *Pharmazie* 51:337-341; Fotherby (1996) *Contraception* 54:59-69; Johnson (1995) *J. Pharm. Sci.* 84:1144-1146; Rohatagi (1995) *Pharmazie* 50:610-613; Brophy (1983) *Eur. J. Clin. Pharmacol.* 24:103-108; the latest Remington's, *supra*). The state of the art allows the clinician to determine the dosage regimen for each individual patient, GR and /or MR modulator and disease or condition treated.

[0103] Single or multiple administrations of the compounds disclosed herein formulations can be administered depending on the dosage and frequency as required and tolerated by the patient. The formulations should provide a sufficient quantity of active agent to effectively treat the disease state. Thus, in one embodiment, the pharmaceutical formulations for oral administration of the compounds disclosed herein is in a daily amount of between about 0.5 to about 30 mg per kilogram of body weight per day. In an alternative embodiment, dosages are from about 1 mg to about 20 mg per kg of body weight per patient per day are used. Lower dosages can be used, particularly when the drug is administered to an anatomically secluded site, such as the cerebral spinal fluid (CSF) space, in contrast to administration orally, into the blood stream, into a body cavity or into a lumen of an organ. Substantially higher dosages can be used in topical administration. Actual methods for preparing formulations including the compounds disclosed herein for parenteral administration are known or apparent to those skilled in the

art and are described in more detail in such publications as Remington's, supra. See also Nieman, In "Receptor Mediated Antisteroid Action," Agarwal, et al., eds., De Gruyter, New York (1987).

[0104] The compounds described herein can be used in combination with one another, with other active agents known to be useful in modulating a glucocorticoid receptor, or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0105] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In some embodiments, the active agents can be formulated separately. In some embodiments, the active and/or adjunctive agents may be linked or conjugated to one another.

[0106] After a pharmaceutical composition including a compound disclosed herein has been formulated in one or more acceptable carriers, it can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of the compounds of Formula I, such labeling would include, e.g., instructions concerning the amount, frequency and method of administration.

[0107] In some embodiments, the compositions disclosed herein are useful for parenteral administration, such as intravenous (IV) administration or administration into a body cavity or lumen of an organ. The formulations for administration will commonly comprise a solution of the compositions disclosed herein dissolved in one or more pharmaceutically acceptable carriers. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by conventional, well known sterilization

techniques. The formulations may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, tonicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of the compositions in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

[0108] In some embodiments, the formulations of the compositions disclosed herein can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions disclosed herein into the target cells in vivo. (See, e.g., Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

V. METHODS

[0109] In some embodiments, there is provided a method of treating a disorder or condition in a subject, the method comprising administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein.

[0110] In some embodiments, there is provided a method for inhibiting KRAS G12D activity in a cell, comprising contacting the cell in which inhibition of KRAS G12D activity is desired with an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof.

[0111] In some embodiments, there is provided a method for inhibiting KRAS G12D activity in a cell, comprising contacting the cell in which inhibition of KRAS G12D activity is desired with the pharmaceutical composition disclosed herein.

[0112] In some embodiments, there is provided a method for treating a KRAS G12D-associated cancer comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[0113] In some embodiments, there is provided a method for treating a KRAS G12D-associated cancer comprising administering to a patient in need thereof the pharmaceutical composition disclosed herein.

[0114] In some embodiments, there is provided a method of treating a subject having cancer, the cancer characterized by the presence of a KRAS G12D mutation, the method comprising administering to the human a therapeutically effective amount of a compound of any one of Formula (I), or a pharmaceutically acceptable salt thereof, or a a pharmaceutical composition as disclosed herein.

[0115] In some embodiments, there is provided a method for manufacturing a medicament for treating a subject having cancer, the cancer characterized by the presence of a KRAS G12D mutation, the compound comprising Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition.

[0116] In some embodiments, there is provided a use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a a pharmaceutical composition as disclosed herein, for the manufacture of a medicament for the treatment in a human having cancer, the cancer characterized by the presence of a KRAS G12D mutation.

[0117] In some embodiments, there are provided compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a a pharmaceutical composition as disclosed herein, for use in the treatment of a subject having cancer, the cancer characterized by the presence of a KRAS G12D mutation.

[0118] In some embodiments, there is provided a method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with a KRAS G12D mutation (*e.g.*, a KRAS G12D- associated cancer); and (b) administering to the patient a therapeutically effective amount of a compound disclosed herein.

[0119] In some embodiments, there is provided a method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with a KRas G12D mutation (*e.g.*, a KRAS G12D- associated cancer); and (b) administering to the patient the pharmaceutical composition disclosed herein.

[0120] In some embodiments, the cancer is Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial

'carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; or Adrenal glands: neuroblastoma.

[0121] In some embodiments, the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer, or pancreatic cancer.

[0122] In certain embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0123] The compounds of Formula (I) or a pharmaceutically acceptable salt thereof, can be inhibitors of KRAS G12D. For example, the inhibition constant (Ki) of the compounds disclosed herein can be less than about 50 μM, or less than about 40, 30, 20, 10, 9, 8, 7, 6, 5, 4, 3, 2, or less than about 1 μM. The inhibition constant (Ki) of the compounds disclosed herein can be less than about 1,000 nM, or less than about 900, 800, 700, 600, 500, 400, 300, 200, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 9, 8, 7, 6, 5, 4, 3, 2, or less than about 1 nM. The inhibition constant (Ki) of the compounds disclosed herein can be less than about 1 nM, or less than about 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or less than about 0.1 nM.

[0124] The compounds of Formula (I) or a pharmaceutically acceptable salt thereof, can be selective inhibitors of KRAS G12D. For example, KRAS G12D inhibition constant (IC50) of the compounds disclosed herein can be at least 2-fold less than the inhibition constant of one or more of KRAS wild-type, or NRAS, or HRAS, or at least 3, 4, 5, 6, 7,

8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100-fold less. The KRAS g12D inhibition constant (Ki) of the compounds disclosed herein can also be at least 100-fold less than the inhibition constant of one or more of KRAS wild-type, or NRAS, or HRAS, or at least 200, 300, 400, 500, 600, 700, 800, 900, 1000, or 10,000-fold less.

A. Cancer Combination Therapies

[0125] The compounds disclosed herein or salts thereof may be employed alone or in combination with other agents for treatment. For example, the second agent of the pharmaceutical combination formulation or dosing regimen may have complementary activities to the compounds disclosed herein such that they do not adversely affect each other. The compounds may be administered together in a unitary pharmaceutical composition or separately. In one embodiment a compound or a pharmaceutically acceptable salt can be co-administered with a cytotoxic agent to treat proliferative diseases and cancer.

[0126] The term "co-administering" refers to either simultaneous administration, or any manner of separate sequential administration, of a compound disclosed herein or a salt thereof, and a further active pharmaceutical ingredient or ingredients, including cytotoxic agents and radiation treatment. If the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

[0127] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound disclosed herein, in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[0128] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with embodiments herein. For example, a compound disclosed herein may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present embodiments

provide a single unit dosage form comprising a compound of Formula (I), an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0129] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. In certain embodiments, compositions disclosed herein are formulated such that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive can be administered.

[0130] Typically, any agent that has activity against a disease or condition being treated may be co-administered. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved.

[0131] In one embodiment, the treatment method includes the co-administration of a compound disclosed herein or a pharmaceutically acceptable salt thereof and at least one cytotoxic agent. The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); chemotherapeutic agents; growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof.

[0132] Exemplary cytotoxic agents can be selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, inhibitors of LDH-A; inhibitors of fatty acid biosynthesis; cell cycle signalling inhibitors; HDAC inhibitors, proteasome inhibitors; and inhibitors of cancer metabolism.

[0133] "Chemotherapeutic agent" includes chemical compounds useful in the treatment of cancer. Examples of chemotherapeutic agents include erlotinib (TARCEVA®,

Genentech/OSI Pharm.), bortezomib (VELCADE®, Millennium Pharm.), disulfiram , epigallocatechin gallate, salinosporamide A, carfilzomib, 17-AAG(geldanamycin), radicicol, lactate dehydrogenase A (LDH-A), fulvestrant (FASLODEX®, AstraZeneca), sunitib (SUTENT®, Pfizer/Sugen), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®., Novartis), finasunate (VATALANIB®, Novartis), oxaliplatin (ELOXATIN®, Sanofi), 5-FU (5-fluorouracil), leucovorin, Rapamycin (Sirolimus, RAPAMUNE®, Wyeth), Lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), Lonafamib (SCH 66336), sorafenib (NEXAVAR®, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), AG1478, alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including topotecan and irinotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); adrenocorticosteroids (including prednisone and prednisolone); cyproterone acetate; 5α-reductases including finasteride and dutasteride); vorinostat, romidepsin, panobinostat, valproic acid, mocetinostat dolastatin; aldesleukin, talc duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlomaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin γ1I and calicheamicin ω1I (*Angew Chem. Intl. Ed. Engl.* **1994** 33:183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and

deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamnol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE® (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.), and TAXOTERE® (docetaxel, doxetaxel; Sanofi-Aventis); chloranmbucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0134] Chemotherapeutic agent also includes (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, iodoxyfene , 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; buserelin, tripterelin, medroxyprogesterone acetate, diethylstilbestrol, premarin, fluoxymesterone, all transretionic acid, fenretinide, as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN®, rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN®; ABARELIX® rmRH; and (ix) pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0135] Chemotherapeutic agent also includes antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds disclosed herein include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab,

matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti–interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length $IgG_1 \lambda$ antibody genetically modified to recognize interleukin-12 p40 protein.

[0136] Chemotherapeutic agent also includes "EGFR inhibitors," which refers to compounds that bind to or otherwise interact directly with EGFR and prevent or reduce its signaling activity, and is alternatively referred to as an "EGFR antagonist." Examples of such agents include antibodies and small molecules that bind to EGFR. Examples of antibodies which bind to EGFR include MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528 (ATCC CRL 8509) (see, US Patent No. 4,943, 533, Mendelsohn *et al.*) and variants thereof, such as chimerized 225 (C225 or Cetuximab; ERBUTIX®) and reshaped human 225 (H225) (see, WO 96/40210, Imclone Systems Inc.); IMC-11F8, a fully human, EGFR-targeted antibody (Imclone); antibodies that bind type II mutant EGFR (US Patent No. 5,212,290); humanized and chimeric antibodies that bind EGFR as described in US Patent No. 5,891,996; and human antibodies that bind EGFR, such as ABX-EGF or Panitumumab (see WO98/50433, Abgenix/Amgen); EMD 55900 (Stragliotto *et al. Eur. J. Cancer* 32A:636-640 (1996)); EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR that competes with both EGF and TGF-alpha for EGFR binding (EMD/Merck); human EGFR antibody, HuMax-EGFR (GenMab); fully human antibodies known as E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6. 3 and E7.6. 3 and described in US 6,235,883; MDX-447 (Medarex Inc); and mAb 806 or humanized mAb 806 (Johns *et al., J. Biol. Chem.* 279(29):30375-30384 (2004)). The anti-EGFR antibody may be conjugated with a cytotoxic agent, thus generating an immunoconjugate (see, *e.g.*, EP659,439A2, Merck Patent GmbH). EGFR antagonists include small molecules such as compounds described in US Patent Nos: 5,616,582, 5,457,105, 5,475,001, 5,654,307, 5,679,683, 6,084,095, 6,265,410, 6,455,534, 6,521,620, 6,596,726, 6,713,484, 5,770,599, 6,140,332, 5,866,572, 6,399,602, 6,344,459,

6,602,863, 6,391,874, 6,344,455, 5,760,041, 6,002,008, and 5,747,498, as well as the following PCT publications: WO98/14451, WO98/50038, WO99/09016, and WO99/24037. Particular small molecule EGFR antagonists include OSI-774 (CP-358774, erlotinib, TARCEVA® Genentech/OSI Pharmaceuticals); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSA®) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenyl-amino)-quinazoline, Zeneca); BIBX-1382 (N8-(3-chloro-4-fluoro-phenyl)-N2-(1-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, Boehringer Ingelheim); PKI-166 ((R)-4-[4-[(1-phenylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol); (R)-6-(4-hydroxyphenyl)-4-[(1-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine); CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butenamide) (Wyeth); AG1478 (Pfizer); AG1571 (SU 5271; Pfizer); dual EGFR/HER2 tyrosine kinase inhibitors such as lapatinib (TYKERB®, GSK572016 or N-[3-chloro-4-[(3 fluorophenyl)methoxy]phenyl]-6[5[[[2methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine).

[0137] Chemotherapeutic agents also include "tyrosine kinase inhibitors" including the EGFR-targeted drugs noted in the preceding paragraph; small molecule HER2 tyrosine kinase inhibitor such as TAK165 available from Takeda; CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from Glaxo-SmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-1 signaling; non-HER targeted TK inhibitors such as imatinib mesylate (GLEEVEC®, available from Glaxo SmithKline); multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT®, available from Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG); MAPK extracellular regulated kinase I inhibitor CI-1040 (available from Pharmacia);

quinazolines, such as PD 153035,4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; PD-0183805 (Warner-Lamber); antisense molecules *(e.g.* those that bind to HER-encoding nucleic acid); quinoxalines (US Patent No. 5,804,396); tryphostins (US Patent No. 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); imatinib mesylate (GLEEVEC®); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone), rapamycin (sirolimus, RAPAMUNE®); or as described in any of the following patent publications: US Patent No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378 (Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca).

[0138] Chemotherapeutic agents also include dexamethasone, interferons, colchicine, metoprine, cyclosporine, amphotericin, metronidazole, alemtuzumab, alitretinoin, allopurinol, amifostine, arsenic trioxide, asparaginase, BCG live, bevacuzimab, bexarotene, cladribine, clofarabine, darbepoetin alfa, denileukin, dexrazoxane, epoetin alfa, elotinib, filgrastim, histrelin acetate, ibritumomab, interferon alfa-2a, interferon alfa-2b, lenalidomide, levamisole, mesna, methoxsalen, nandrolone, nelarabine, nofetumomab, oprelvekin, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, plicamycin, porfimer sodium, quinacrine, rasburicase, sargramostim, temozolomide, VM-26, 6-TG, toremifene, tretinoin, ATRA, valrubicin, zoledronate, and zoledronic acid, and pharmaceutically acceptable salts thereof.

[0139] Chemotherapeutic agents also include hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate,

prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (feG) (IMULAN BioTherapeutics, LLC); anti-rheumatic drugs such as azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomideminocycline, sulfasalazine, tumor necrosis factor alpha (TNFα) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers such as anakinra (Kineret), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-13) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway blockers such as Anti-M1 prime; Secreted homotrimeric LTa3 and membrane bound heterotrimer LTa1/β2 blockers such as Anti-lymphotoxin alpha (LTa); radioactive isotopes (e.g., At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18- OCH_3, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; autophagy inhibitors such as chloroquine; delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; acetylcamptothecin, scopolectin, and 9-aminocamptothecin); podophyllotoxin; tegafur (UFTORAL®); bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine; perifosine, COX-2 inhibitor (*e.g.* celecoxib or etoricoxib), proteosome inhibitor (*e.g.* PS341); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASAR™); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin,

vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU and leucovorin.

[0140] Chemotherapeutic agents also include non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory effects. NSAIDs include non-selective inhibitors of the enzyme cyclooxygenase. Specific examples of NSAIDs include aspirin, propionic acid derivatives such as ibuprofen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin and naproxen, acetic acid derivatives such as indomethacin, sulindac, etodolac, diclofenac, enolic acid derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam and isoxicam, fenamic acid derivatives such as mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, and COX-2 inhibitors such as celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib. NSAIDs can be indicated for the symptomatic relief of conditions such as rheumatoid arthritis, osteoarthritis, inflammatory arthropathies, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic.

[0141] In certain embodiments, chemotherapeutic agents include, but are not limited to, doxorubicin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, interferons, platinum derivatives, taxanes (e.g., paclitaxel, docetaxel), vinca alkaloids (e.g., vinblastine), anthracyclines (e.g., doxorubicin), epipodophyllotoxins (e.g., etoposide), cisplatin, an mTOR inhibitor (e.g., a rapamycin), methotrexate, actinomycin D, dolastatin 10, colchicine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents (e.g., chlorambucil), 5-fluorouracil, campthothecin, cisplatin, metronidazole, and imatinib mesylate, among others. In other embodiments, a compound disclosed herein is administered in combination with a biologic agent, such as bevacizumab or panitumumab.

[0142] In certain embodiments, compounds disclosed herein, or a pharmaceutically acceptable composition thereof, are administered in combination with an antiproliferative or chemotherapeutic agent selected from any one or more of abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, BCG live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin,

carmustine, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, elotinib, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine, fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, or zoledronic acid.

[0143] Chemotherapeutic agents also include treatments for Alzheimer's Disease such as donepezil hydrochloride and rivastigmine; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating multiple sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), glatiramer acetate, and mitoxantrone; treatments for asthma such as albuterol and montelukast sodium; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as

corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[0144] Additionally, chemotherapeutic agents include pharmaceutically acceptable salts, acids or derivatives of any of chemotherapeutic agents, described herein, as well as combinations of two or more of them.

VI. EXAMPLES

[0145] Abbreviations:

ACN - acetonitrile

AC_2O - acetyl acetate

BINAP - (+/-)-2,2'-bis(diphenylphosphino)-l,r-binaphthyl

Boc_2O - di-tert-butyl dicarbonate

BOP - (benzotriazol-l-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

DBU - l,8-diazabicyclo[5.4.0]undec-7-ene

DCE- 1,2-dichloroethane

DCM - dichloromethane

DIEA or DIPEA - *N,N*-diisopropylethylamine

DMA - *N,N*-dimethylacetamide

DMAc - *N,N*-dimethylacetamide

DMAP - 4-dimethylaminopyridine

DMF - *N,N*-dimethylformamide

DMSO - dimethyl sulfoxide

EA - ethyl acetate

EtOAc - ethyl acetate

EtOH - ethanol

HATU -2-(7-azabenzotriazol-l -yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

HFIP - hexafluoroisopropanol

HOAc - acetic acid

iPrOAc - isopropyl acetate

KF - potassium fluoride

KOAc - potassium acetate

LDA - lithium diisopropylamide

LiHMDS - lithium bis(trimethylsilyl)amide

mCPBA -3-chloroperoxybenzoic acid

MeCN - acetonitrile

MeI - iodomethane

MeOH - methanol

MeONa - sodium methoxide or sodium methanolate

MTBE - methyl tert-butyl ether

MW - microwave

$NaBH(OAc)_3$ - sodium triacetoxyborohydride

NIS - *N*-iodosuccinimide

$P(Cy)_3$ or PCy_3 - tricyclohexylphosphine

$P(t\text{-}Bu)_3HBF_4$ - tri-tert-buty lphosphonium tetrafluoroborate

Pd/C - palladium on carbon

$Pd_2(dba)_3$ - tris(dibenzylideneacetone)dipalladium(0)

$Pd_2(dba)_3CHCl_3$ - tris(dibenzylidenacetone)dipalladium(0) chloroform

$Pd(dppf)Cl_2.CH_2Cl_2$ - [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) or dichloro[1.1'-bis(diphenylphosphino)ferrocene]palladium(II), complexed with dichloromethane

$Pd(PPh_3)_4$ - tetrakis(triphenylphosphine)palladium(0)

$Pd(PPh_3)_2Cl_2$ - bis(triphenylphosphine)palladium(II) dichloride

PE - petroleum ether

PMBCl - 4-methoxybenzylchloride

pTsA - p-toluenesulfbnic acid

r.t. - room temperature

$Sn_2(n\text{-}Bu)_6$ - hexabutylditin

TBSCl - tert-butyldimethylsilyl chloride or tert-butyldimethylchlorosilane

$[Rh(COD)Cl]_2$ - chloro(l,5-cyclooctadiene)rhodium(I) dimer

TEA - triethylamine

TFA- trifluoroacetic acid or 2,2,2-trifluoroacetic acid

THF - tetrahydrofuran

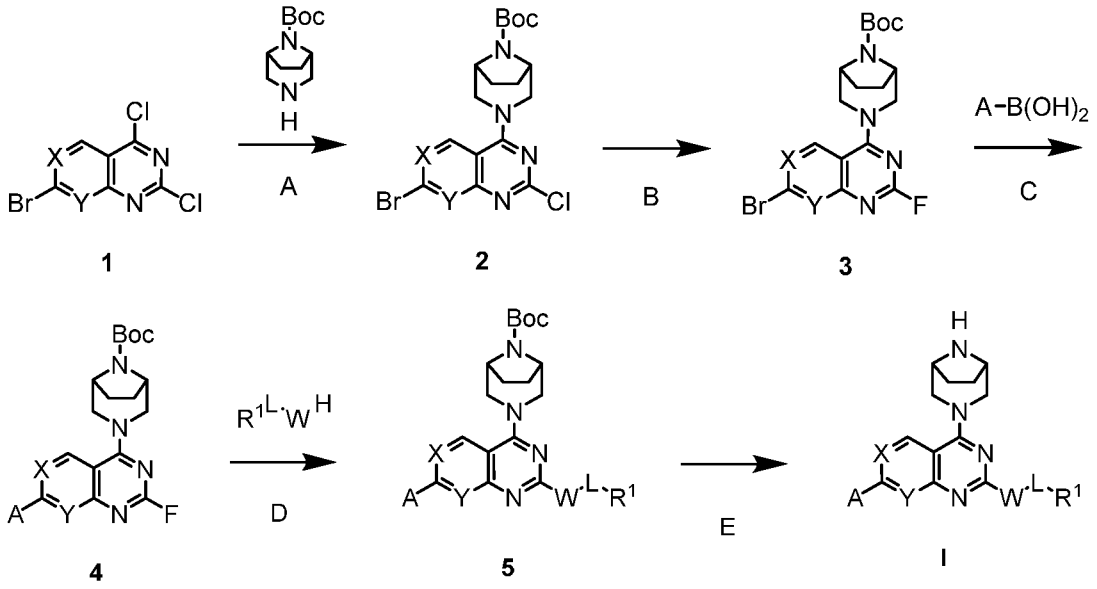
THP - tetrahydropyran

TsOH - p-toluenesulfonic acid

A. Synthetic Procedures

General Procedure

[0146] The compounds of Formulae I, Ia, Ib, Ic, Id, and Ie may be prepared from commercially available reagents using the synthetic methods and reaction schemes herein, or using other reagents and conventional methods well known to those skilled in the art. For instance, compounds of the present invention may be prepared according to the general reaction Scheme I:

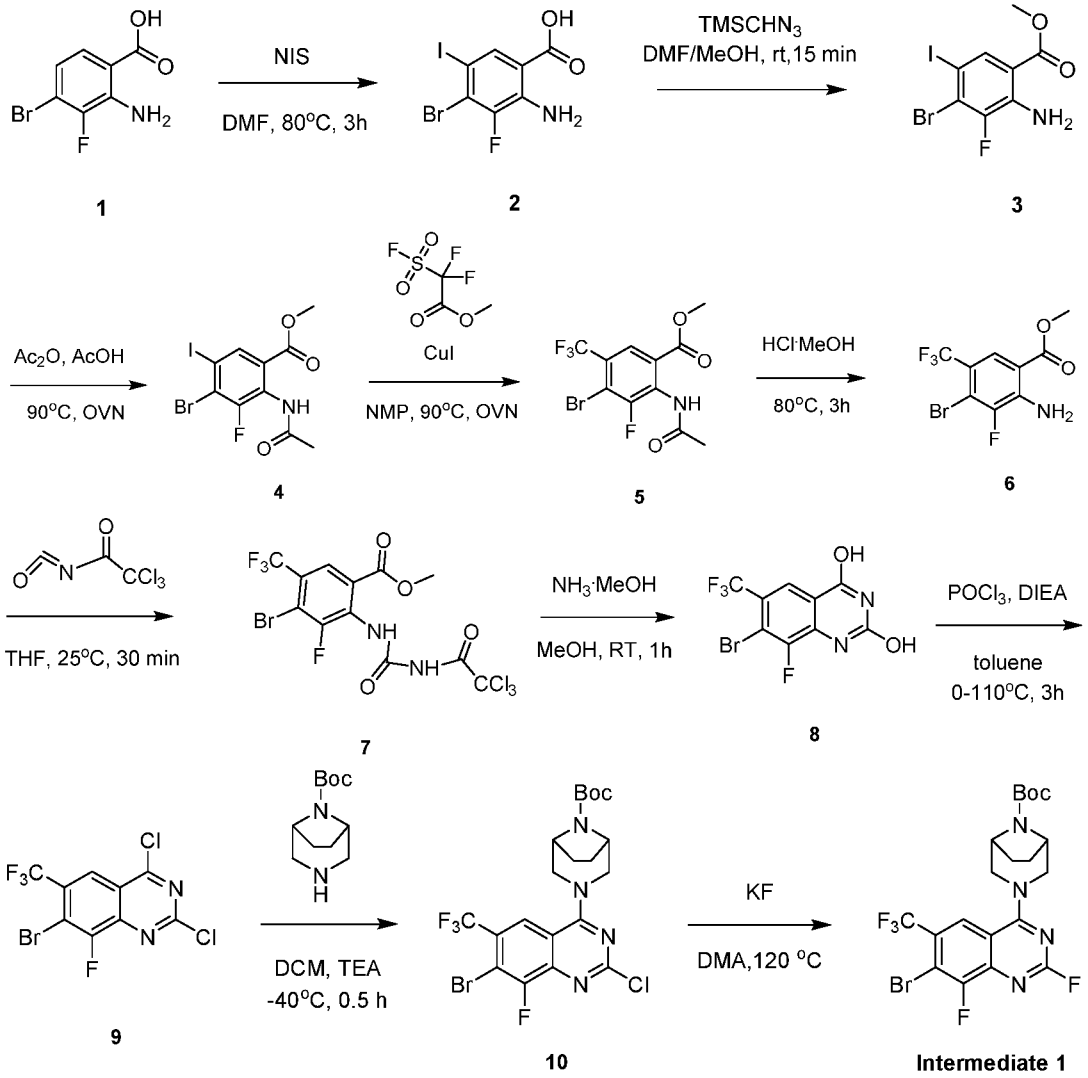


SCHEME I

[0147] Compounds of Formula (I) wherein all the substituents are as defined for Formula I, with the exception of Y other than absent, can be prepared according to Scheme I. In step A, compound (1) undergoes a S_NAr reaction with mono-Boc protected diazabicyclo[3,3,1]octane in a solvent such as dichloromethane and in the presence of a base such as triethylamine to afford compound (2). In step B, compound (2) is treated with KF in a solvent such as *N*,*N*-dimethylacetamide to generate compound (3). In step C, compound (3) is treated with a boronic acid following Suzuki reaction conditions to afford compound (3). In step D, the substituent -W-L-R^1 is introduced by substitution of the fluoride with a nucleophile with the formula H-W-L-R^1 in a solvent such as acetonitrile in the presence of a base such as diisopropylethylamine to provide compound (5). In step E, the Boc group of compound (5) is removed using conditions known in the art, for example

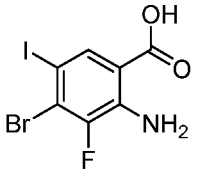
with trifluoroacetic acid, to provide compound of Formula (I). Atropisomers, when present, may be separated by conventional methods, such as chiral HPLC.

[0148] Synthesis of tert-butyl (1R,5S)-3-(7-bromo-2,8-difluoro-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate **(Intermediate 1)**



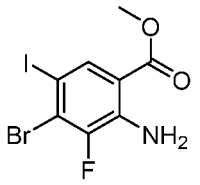
SCHEME II

[0149] **Step 1:** 2-amino-4-bromo-3-fluoro-5-iodobenzoic acid



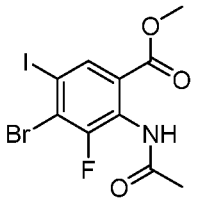
[0150] To a solution of 2-amino-4-bromo-3-fluoro-benzoic acid (32 g, 136.74 mmol) in DMF (300 mL) at room temperature was added 1-iodopyrrolidine-2,5-dione (36.92 g, 164.09 mmol). The mixture was stirred at 80 °C for 2h. The mixture was diluted with water (500 ml), the precipitate was filtered, washed with water and dried to afford the desired product (47 g, 130.59 mmol, 95.50% yield) as a brown solid. ESI-MS: 359.9, 361.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 6.88 (s, 2H).

[0151] **Step 2:** Methyl 2-amino-4-bromo-3-fluoro-5-iodobenzoate



[0152] To a solution of 2-amino-4-bromo-3-fluoro-5-iodo-benzoic acid (13 g, 36.12 mmol) in DCM/MeOH (120 mL) at room temperature was dropwise added $TMSCHN_2$ (36.12 mmol). The mixture was stirred at RT for 15 min. The mixture was removed in vacuo and the resultant crude residue was diluted with EtOAc (200 ml), washed with brine and dried over sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography (eluent: PE/EtOAc = 20/1) to afford the title compound (11 g, 29.42 mmol, 81.44% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 1.8 Hz, 1H), 6.85 (s, 2H), 3.82 (s, 3H).

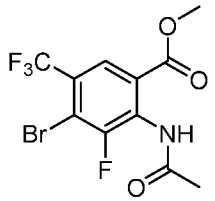
[0153] **Step 3:** Methyl 2-acetamido-4-bromo-3-fluoro-5-iodobenzoate



[0154] A solution of methyl 2-amino-4-bromo-3-fluoro-5-iodo-benzoate (47 g, 125.69 mmol) in Ac_2O (90 mL) and AcOH (150 mL) was stirred at 90 °C overnight. The mixture

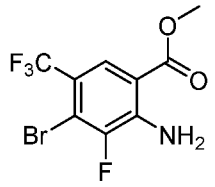
was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc = 4/1) to afford title product (42.6 g, 102.41 mmol, 81.48% yield) as an off-white solid. ESI-MS Calcd: 415.9, 417.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.03 (d, J = 1.7 Hz, 1H), 3.77 (s, 3H), 2.04 (s, 3H).

[0155] **Step 4:** Methyl 2-acetamido-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate



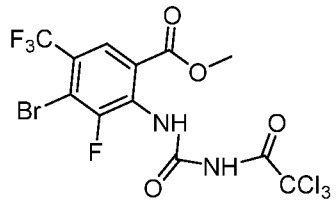
[0156] To a mixture of methyl 2-acetamido-4-bromo-3-fluoro-5-iodo-benzoate (19 g, 45.68 mmol) in NMP (150 mL) was added CuI (2.61 g, 13.70 mmol) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (17.55 g, 91.35 mmol). The mixture was stirred at 90 °C overnight. The mixture was diluted with water (200 mL) and extracted with EtOAc (500 mL). The organic phase was washed with brine, dried over sodium sulfate. After filtration and concentration, the residue was purified by silica gel column chromatography (eluent: PE/EtOAc = 5/2) to afford the desired product (13.5 g, 37.70 mmol, 82.54% yield) as an off-yellow solid. ESI-MS: 358.0, 360.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.89 (s, 1H), 3.80 (s, 3H), 2.10 (s, 3H).

[0157] **Step 5**: Methyl 2-amino-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate



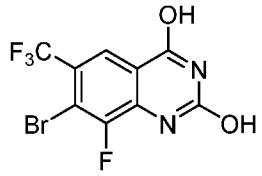
[0158] A solution of methyl 2-acetamido-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (13.5 g, 37.81 mmol) in HCl in MeOH (3M, 100 mL) was stirred at 80 °C for 3h. The mixture was concentrated in vacuo and the resultant crude residue was triturated with MTBE (100 mL) to afford the desired product (10.3 g, 32.70 mmol, 86.4% yield) as a white solid. ESI-MS: 316.0, 318.0$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.40 (s, 2H), 3.85 (s, 3H).

[0159] **Step 6**: Methyl 4-bromo-3-fluoro-2-(3-(2,2,2-trichloroacetyl)ureido)-5-(trifluoromethyl)benzoate



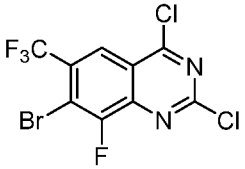
[0160] To a solution of methyl 2-amino-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (10 g, 31.75 mmol) in THF (80 mL) was added 2,2,2-trichloroacetyl isocyanate (11.87 g, 63.49 mmol) at rt. The reaction mixture was stirred at rt for 0.5 h. The mixture was concentrated in vacuo and the resultant crude residue was triturated with MTBE (100 mL) to afford the desired product (13 g, 25.90 mmol, 81.59% yield) as a white solid. ESI-MS: 502.9, 504.9$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.33 (s, 1H), 8.02 (s, 1H), 3.86 (s, 3H).

[0161] **Step 7**: 7-bromo-8-fluoro-6-(trifluoromethyl)quinazoline-2,4-diol



[0162] To a solution of methyl 4-bromo-3-fluoro-2-(3-(2,2,2-trichloroacetyl)ureido)-5-(trifluoromethyl)benzoate (13 g, 25.90 mmol) in MeOH (200 mL) at room temperature was added NH_3·MeOH (40 mL). The mixture was stirred at RT for 1 h. The mixture was concentrated in vacuo and the resultant crude residue was triturated with MTBE (150 mL) to afford the desired product (7.55 g, 23.16 mmol, 90.0% yield) as a white solid. ESI-MS: 324.9, 326.9$[M-H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 2H), 7.90 (s, 1H).

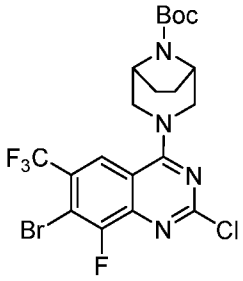
[0163] **Step 8:** 7-bromo-2,4-dichloro-8-fluoro-6-(trifluoromethyl)quinazoline



[0164] To a mixture of 7-bromo-8-fluoro-6-(trifluoromethyl)quinazoline-2,4-diol (7.55 g, 23.16 mmol) in toluene (60 mL) at room temperature, was added N-ethyl-N-isopropyl-

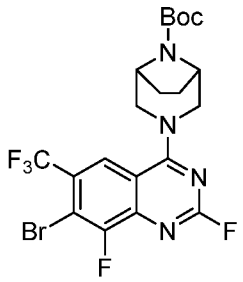
propan-2-amine (8.98 g, 69.48 mmol) and $POCl_3$ (10.65 g, 69.48 mmol) at 0 °C. The mixture was stirred at 110 °C for 3 h under nitrogen. The mixture was removed in vacuo and the resultant crude residue was diluted with EtOAc (50 mL). The organic phase was washed with brine and dried and concentrated. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc = 4/1) to afford title product (7 g, 22.11 mmol, 59.61% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H).

[0165] **Step 9**: tert-butyl (1R,5S)-3-(7-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



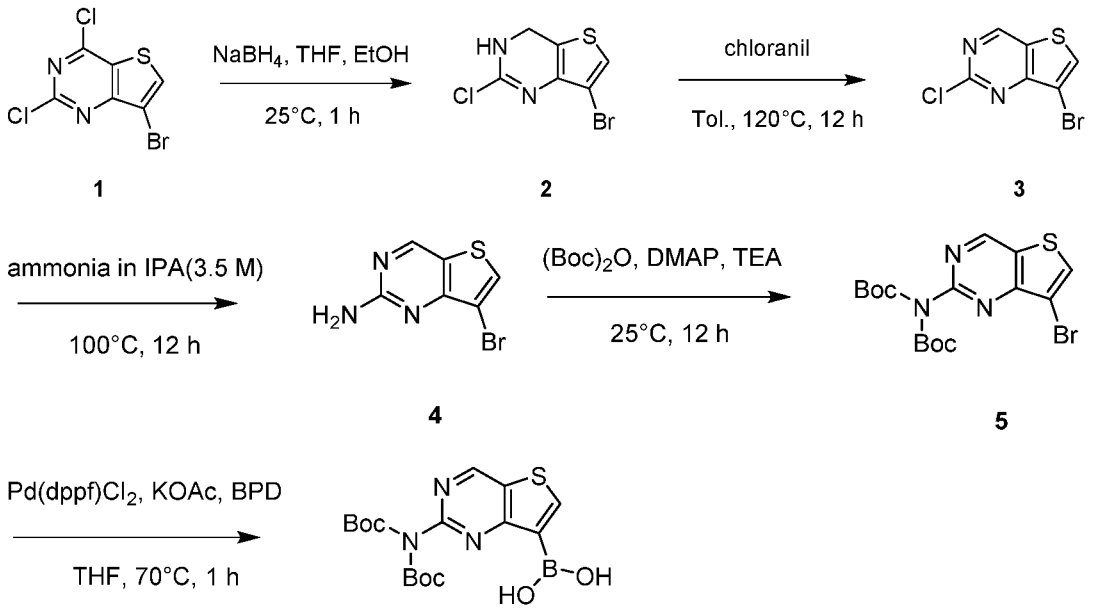
[0166] To a solution of 7-bromo-2,4-dichloro-8-fluoro-6-(trifluoromethyl)quinazoline (7 g, 22.11 mmol) in DCM (50 mL) was added N,N-diethylethanamine (6.70 g, 66.33 mmol, 6.30 mL) at rt. Then tert-butyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.75 g, 17.69 mmol) was added at -40 °C. The mixture was stirred at -40 °C for 0.5 h. The mixture was diluted with brine (100 mL) and extracted with DCM (80 mL x 3). The organic phase was dried over Na_2SO_4 and filtered and concentrated. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc = 8/1) to afford title product (7.24 g, 13.45 mmol, 60.86% yield) as a yellow solid. ESI-MS: 539.0, 541.0 $[M+H]^+$.

[0167] **Step 10**: *tert*-butyl (1R,5S)-3-(7-bromo-2,8-difluoro-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**Intermediate 1**).



[0168] To a solution of tert-butyl (1R,5S)-3-[7-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (8.6 g, 15.93 mmol) in DMA (80 mL) at room temperature was added CsF (46.29 g, 796.67 mmol). The mixture was stirred at 120 °C overnight. The mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluent: PE/EtOAc = 20/1) to afford the desired product (2 g, 3.82 mmol, 23.99% yield) as a white solid. ESI-MS: 523.2，525.2[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 4.43 (d, J = 12.2 Hz, 2H), 4.26 (s, 2H), 3.69 (d, J = 11.6 Hz, 2H), 1.77 (s, 2H), 1.61 (d, J = 7.4 Hz, 2H), 1.46 (s, 9H).

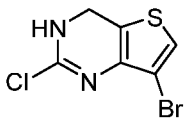
[0169] Synthesis of [2-[bis(*tert*-butoxycarbonyl)amino]thieno[3,2-d]pyrimidin-7-yl]boronic acid **(Intermediate 2)**



Intermediate 2

SCHEME III

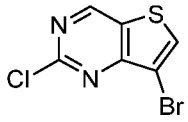
[0170] **Step 1**: 7-bromo-2-chloro-3,4-dihydrothieno[3,2-d]pyrimidine



[0171] To a solution of 7-bromo-2,4-dichloro-thieno[3,2-d]pyrimidine (2 g, 7.04 mmol, 1 *eq*) in ethanol (30 mL) and tetrahydrofuran (30 mL) was added sodium borohydride

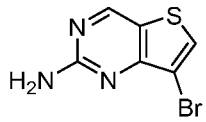
(1.74 g, 45.99 mmol, 6.53 *eq*). The mixture was stirred at 25 °C for 1 hour. LCMS showed the reaction was completed. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (20 mL x 2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product (1.6 g, 6.36 mmol, 90% yield) as a yellow solid, which was used into next step without further purification. LCMS (ESI, m/z): 252.8 $[M+1]^+$.

[0172] Step 2: 7-bromo-2-chloro-thieno[3,2-d]pyrimidine



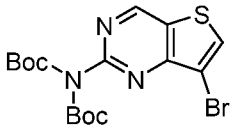
[0173] To a solution of 7-bromo-2-chloro-3,4-dihydrothieno[3,2-d]pyrimidine (1.6 g, 6.36 mmol, 1 *eq*) in toluene (60 mL) was added chloranil (1.56 g, 6.36 mmol, 1 *eq*). The mixture was stirred at 110 °C for 12 hours. LCMS showed the reaction was completed. The reaction mixture was diluted with **toluene (60** mL), then washed with 0.5 N sodium hydroxide solution **(60** mL) and water (60 mL), dried over anhydrous sodium sulfate**,** filtered and concentrated under reduced pressure to give a residue which was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 20/1 to 10/1) to afford the desired product (600 mg, 2.40 mmol, 38% yield) as a white solid. LCMS: (ESI, m/z): 250.8 $[M+1]^+$.

[0174] **Step 3**: 7-bromothieno[3,2-d]pyrimidin-2-amine



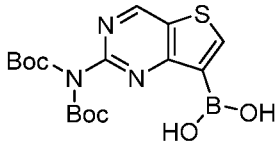
[0175] To a solution of 7-bromo-2-chloro-thieno[3,2-d]pyrimidine (1.8 g, 7.21 mmol, 1 *eq*) in isopropanol (2 mL) was added ammonia (3.5 M in isopropanol, 27 mL, 13.10 *eq*). Then the mixture was stirred at 100 °C for 12 hours. LCMS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC (column: Phenomenex Luna C8 250*50mm*10um;mobile phase: [water(FA)-ACN];B%: 5%-35%,20min) to give the desired product (540 mg, 2.35 mmol, 33% yield) as a yellow solid.

[0176] **Step 4**: *tert*-butyl N-(7-bromothieno[3,2-d]pyrimidin-2-yl)-N-tert-butoxycarbonyl-carbamate



[0177] To a solution of 7-bromothieno[3,2-d]pyrimidin-2-amine (880 mg, 3.82 mmol, 1 *eq*) in dichloromethane (30 mL) was added dimethylaminopyridine (47 mg, 0.38 mmol, 0.1 *eq*) , triethylamine (774 mg, 7.65 mmol, 1.1 mL, 2 *eq*) and di-*tert*-butyl dicarbonate (2.0 g, 9.18 mmol, 2.1 mL, 2.4 *eq*). The mixture was stirred at 25 °C for 12 hours. LCMS showed the reaction was completed. The solution was added water (40 mL), extracted by ethyl acetate (80 mL x 3). The combined organic layers were washed with brine (150 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get the residue which was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 100/1 to 1/1) to generate the desired product (1.1 g, 2.56 mmol, 67% yield) as a white solid. LCMS: (ESI, m/z): 429.8 $[M+1]^+$. ^1H NMR: (400 MHz, DMSO-d_6) *δ:* 9.63 (s, 1H), 8.80 (s, 1H), 1.41 (s, 18H).

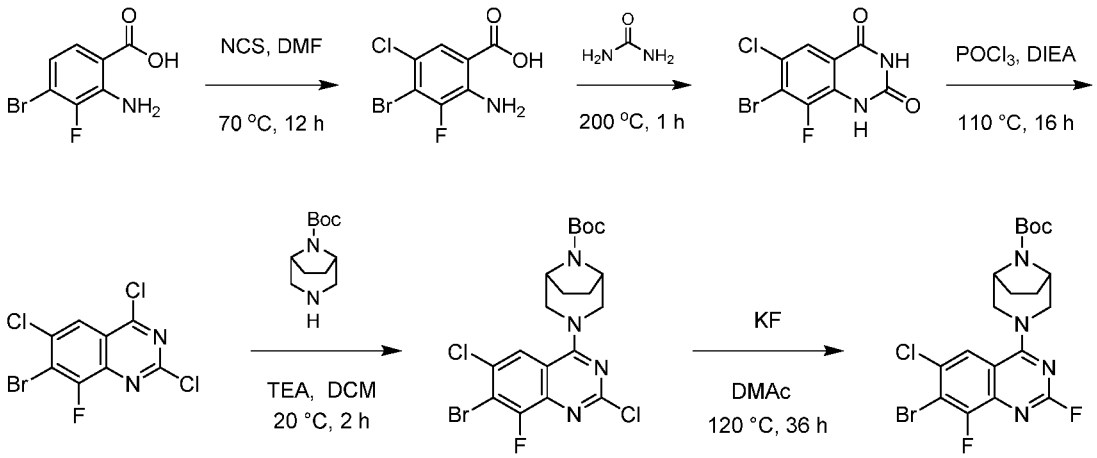
[0178] **Step 5**: [2-[bis(*tert*-butoxycarbonyl)amino]thieno[3,2-d]pyrimidin-7-yl]boronic acid



[0179] A mixture of *tert*-butyl *N*-(7-bromothieno[3,2-d]pyrimidin-2-yl)-N-tert-butoxycarbonyl-carbamate (300 mg, 0.73 mmol, 1 *eq*), potassium acetate (138 mg, 1,1 mmol, 2 *eq*), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50 mg, 0.075 mmol, 0.1 *eq*) and bis(pinacolato)diboron (265 mg, 1.05 mmol, 1.5 *eq*) in tetrahydrofuran (5 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 70 °C for 5 hour under nitrogen. LCMS showed the reaction was completed. The reaction mixture was filtered, and the filtrate was added water (10 mL) before extracted by ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to get a residue which was purified by prep-TLC (50% ethyl acetate in petroleum

ether) to afford the desired product (127 mg, 0.32 mmol, 46% yield) was obtained as a colorless oil. LCMS: (ESI, m/z): 396.1 $[M+1]^+$.

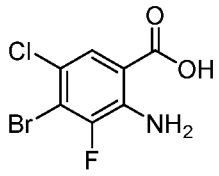
[0180] Synthesis of *tert*-butyl 3-(7-bromo-6-chloro-2,8-difluoro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate **(Intermediate 3)**



Intermediate 3

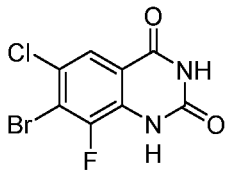
SCHEME IV

[0181] **Step 1:** 2-amino-4-bromo-5-chloro-3-fluoro-benzoic acid



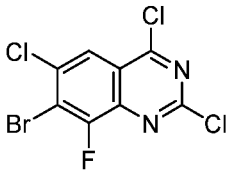
[0182] To a solution of 2-amino-4-bromo-3-fluoro-benzoic acid (25 g, 106.83 mmol, 1 *eq*) in *N*,*N*-dimethylformamide (400 mL) was added *N*-chlorosuccinimide (15.69 g, 117.51 mmol, 1.1 *eq*). The mixture was stirred at 70 °C for 12 hours. The mixture was cooled to 25 °C, and then poured into water (2000 mL). The resultant mixture was filtered and the filter cake was collected, dried under reduced pressure to get the crude product (28 g, 104.30 mmol, 97% yield) as a yellow solid, which was used for next step directly. ^{1}H NMR**:** (400 MHz, DMSO-d_6) δ: 13.48 (s,1H), 7.68 (s, 1H), 6.90 (s, 2H).

[0183] **Step 2**: 7-bromo-6-chloro-8-fluoro-1H-quinazoline-2,4-dione



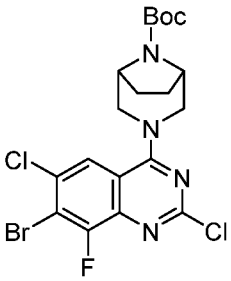
[0184] A mixture of 2-amino-4-bromo-5-chloro-3-fluoro-benzoic acid (29 g, 108.0 mmol, 1 *eq*) in urea (64.87 g, 1.08 mol, 10 *eq*) was stirred at 200 °C for 1 hour. LCMS showed that the desired mass was detected. The mixture was cooled to 25 °C, diluted with water (800 mL) and stirred at 25 °C for 1 hour. The mixture was filtered and the solid was dried in vacuum to give the crude product (31 g, 105.63 mmol, 97% yield) as a brown solid, which was used for next step directly. LCMS (ESI, m/z): 293.9 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.24 (s, 1H).

[0185] **Step 3**: 7-bromo-2,4,6-trichloro-8-fluoro-quinazoline



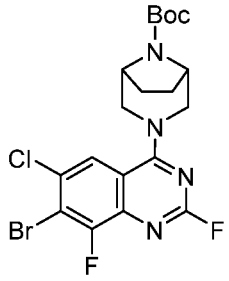
[0186] To a solution of 7-bromo-6-chloro-8-fluoro-1H-quinazoline-2,4-dione (31 g, 105.6 mmol, 1 *eq*) in phosphoryl chloride (360 mL) was added *N,N*-diisopropylethylamine (310.0 mmol, 54 mL, 2.94 *eq*), the mixture was stirred at 110 °C for 16 hours. LCMS showed that the reactant was consumed completely. The mixture was concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography eluted by petroleum ether/tetrahydrofuran = 40/1 to give the product (24 g, 72.65 mmol, 68% yield) as a yellow solid. ^{1}H NMR**:** (400 MHz, DMSO-d_6) δ: 8.03 (s, 1H).

[0187] **Step 4:** *tert*-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0188] To a solution of *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.93 g, 9.08 mmol, 1 *eq*) in dichloromethane (40 mL) was added triethylamine (2.76 g, 27.24 mmol, 3.8 mL, 3 *eq*) and 7-bromo-2,4,6-trichloro-8-fluoro-quinazoline (3 g, 9.08 mmol, 1 *eq*). The mixture was stirred at 20 °C for 2 hours. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. Water (50 mL) was added before the mixture was extracted by dichloromethane (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 30/1 to 10/1) to give the product (3.6 g, 7.11 mmol, 78 % yield) as a white solid. LCMS (ESI, m/z): 507.2 $[M+1]^+$. ^{1}H NMR: (400 MHz, CHLOROFORM-d) δ: 7.75 (d, J = 2.0 Hz, 1H), 4.40 (s, 4H), 3.80 - 3.52 (m, 2H), 2.02 - 1.92 (m, 2H), 1.80 - 1.68 (m, 2H), 1.53 (s, 9H).

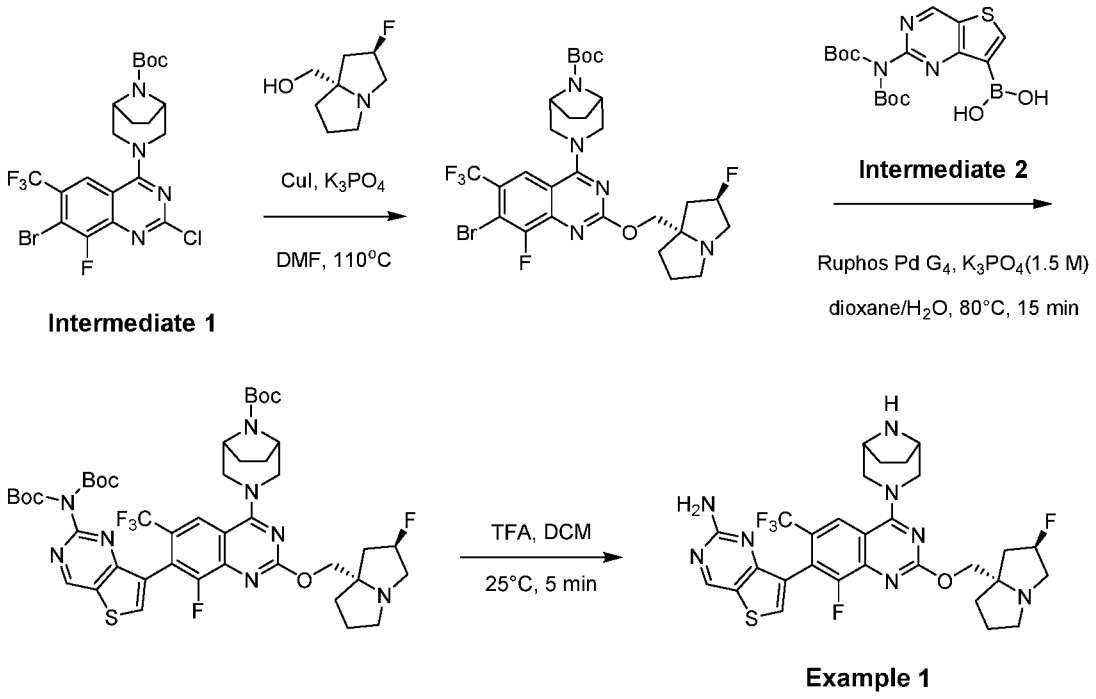
[0189] **Step 5:** *tert*-butyl 3-(7-bromo-6-chloro-2,8-difluoro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0190] To a solution of *tert*-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.5 g, 6.91 mmol, 1 *eq*) in *N*,*N*-dimethylacetamide (50 mL) was added potassium fluoride (12.05 g, 207.43 mmol, 4.9 mL, 30 *eq*). The mixture was stirred at 120 °C for 36 hours. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. Water (500 mL) was added before the mixture was extracted by ethyl acetate (250 mL x 3). The combined organic layers were washed with brine (500 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 1/0 to 5/1) to give the product (1.9 g, 3.88 mmol, 56% yield) as a white solid. LCMS (ESI, m/z): 491.2 $[M+1]^+$. ^{1}H NMR: (400 MHz, CHLOROFORM-d)

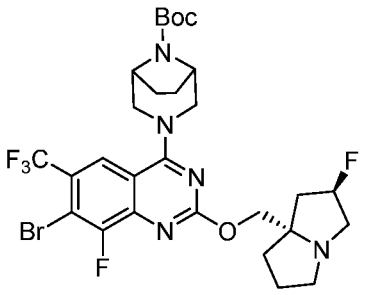
δ: 7.80 (d, J = 0.8 Hz, 1H), 4.52 - 4.29 (m, 4H), 3.85 - 3.53 (m, 2H), 2.02 - 1.86 (m, 2H), 1.81 - 1.67 (m, 2H), 1.53 (s, 9H).

[0191] Synthesis of 7-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]thieno[3,2-d]pyrimidin-2-amine **(Example 1)**



SCHEME V

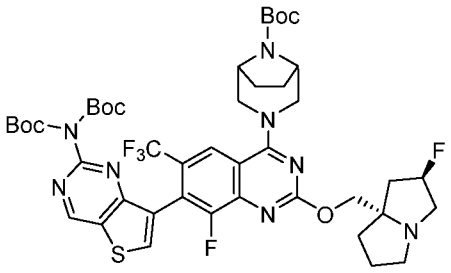
[0192] **Step 1**: *tert*-buty l(1R,5S)-3-(7-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0193] [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (162.22 mg, 1.02 mmol), K_3PO_4 (393.28 mg, 1.85 mmol) and CuI (35.28 mg, 185.27 µmol) were

added to a solution of tert-butyl 3-[7-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 926.36 μmol) in DMF (20 mL) at rt, then the mixture was stirred for 16 h at 110°C under nitrogen atmosphere. The mixture was diluted with EtOAc (150 mL). The organic phase was washed with water (50 mL x 3), dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with PE/EtOAc= 1/1 to afford the desired product (200 mg, crude) as a white solid. ESI-MS: 662.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 6.87 (s, 1H), 5.29 (d, J = 53.9 Hz, 1H), 4.38 (d, J = 12.2 Hz, 2H), 4.14 (d, J = 9.8 Hz, 1H), 4.05 (d, J = 10.3 Hz, 1H), 3.59 (d, J = 12.3 Hz, 2H), 3.11 (s, 2H), 3.03 (br s, 1H), 2.85 (br s, 1H), 2.18 (br s, 1H), 2.13 (br s, 1H), 2.06 (br s, 1H), 2.01 - 1.87 (m, 2H), 1.78 (s, 4H), 1.62 (d, J = 7.4 Hz, 2H), 1.46 (s, 9H).

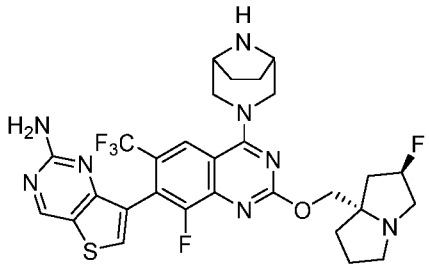
[0194] **Step 2**: *tert*-butyl 3-[7-[2-[bis(*tert*-butoxycarbonyl)amino]thieno[3,2-d]pyrimidin-7-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0195] A mixture of [2-[bis(tert-butoxycarbonyl)amino]thieno[3,2-d]pyrimidin-7-yl]boronic acid (14 mg, 0.03 mmol, 1.2 *eq*), *tert*-butyl 3-[7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.03 mmol, 1 *eq*), methanesulfonato(2-dicyclohexylphosphino-2,6-di-i-propoxy-1,1-biphenyl)(2-methylamino-1,1-biphenyl-2-yl)palladium(ii) (8 mg, 0.01 mmol, 0.3 *eq*), potassium phosphate (1.5 M, 0.06 mL, 3 *eq*) in dioxane (1 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 15 minutes under nitrogen. LCMS showed the reaction was completed. The reaction mixture was diluted with water (10 mL), extracted by dichloromethane (5 mL x 3). The combined organic

layers were washed with brine (10 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (9% methanol in dichloromethane) to give the desired product (10 mg, 0.004 mmol, 35% yield) as a white solid. LCMS: (ESI, m/z): 932.9 $[M]^+$.

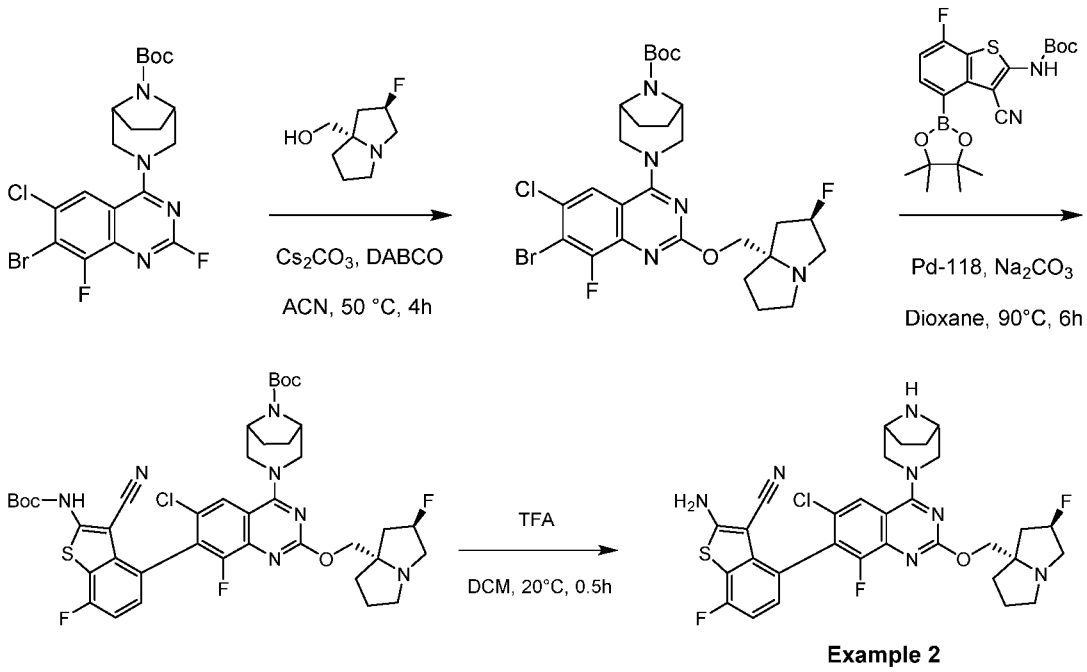
[0196] **Step 3**: 7-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]thieno[3,2-d]pyrimidin-2-amine



Example 1

[0197] To a solution of *tert*-butyl 3-[7-[2-[bis(*tert*-butoxycarbonyl)amino]thieno[3,2-d]pyrimidin-7-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (31 mg, 0.03 mmol, 1 *eq*) in dichloromethane (1 mL) was added trifluoroacetic acid. The mixture was stirred at 25 °C for 5 minutes. LCMS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 μm;mobile phase: [water(FA)-ACN];B%: 1%-20%,10min) to afford the desired product (13.51 mg, 0.02 mmol, 57% yield, 96% purity, formate) as a white solid. LCMS: (ESI, m/z): 633.2 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO -d_6) *δ:* 9.02 (s, 1H), 8.28 (s, 1H), 8.24 - 8.20 (m, 1H), 8.10 (s, 1H), 6.63 (s, 2H), 5.38 - 5.18 (m, 1H), 4.40 - 4.22 (m, 2H), 4.14 - 4.00 (m, 2H), 3.63 - 3.52 (m, 3H), 3.07 (br d, J = 1.6 Hz, 1H), 3.03 - 2.98 (m, 1H), 2.86 - 2.78 (m, 1H), 2.13 (br d, J = 3.6 Hz, 1H), 2.06 - 1.99 (m, 2H), 1.88 - 1.73 (m, 4H), 1.69 - 1.56 (m, 6H).

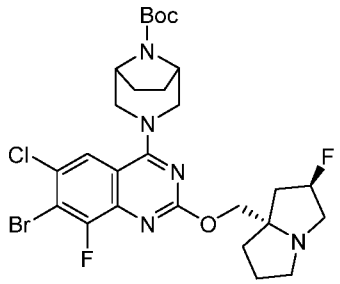
[0198] Synthesis of 2-amino-4-[6-chloro-4-(3,8-diazabicyclo[3.2.1]octan- 3-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Example 2**)



Example 2

SCHEME VI

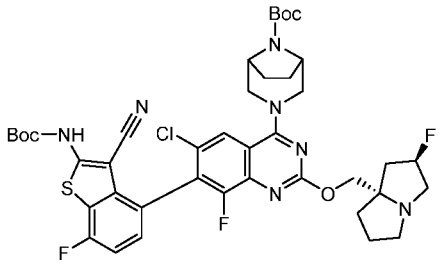
[0199] **Step 1**: *tert*-butyl 3-[7-bromo-6-chloro -8-fluoro-2-[[(2R,8S)- 2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0200] To a mixture of *tert*-butyl 3-(7-bromo-6-chloro-2,8-difluoro-quinazolin-4-yl)-3,8- diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 1.02 mmol, 1 *eq*) and [(2R,8S)-2-fluoro- 1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (179 mg, 1.12 mmol, 1.1 *eq*) in acetonitrile (5 mL) was added cesium carbonate (665 mg, 2.04 mmol, 2 *eq*) and 1,4-diazabicyclo[2.2.2]octane (11 mg, 0.1 mmol, 0.1 *eq*). The mixture was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 50 °C for 4 hours. The mixture was filtered and concentrated to give a residue which was purified by prep-TLC (silicon dioxide, Dichloromethane/Methanol = 10/1) to afford the desired product

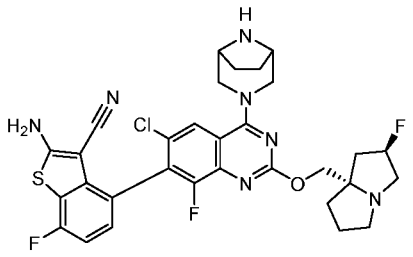
(500 mg, 0.79 mmol, 78% yield) as a white solid. LCMS: (ESI, m/z): 630.1[M+1]$^+$. ^{1}H NMR: (400MHz, CHLOROFORM-d) δ: 7.69 (d, J = 2.0 Hz, 1H), 5.37 - 5.19 (m, 1H), 4.38 - 4.28 (m, 3H), 4.26 - 4.20 (m, 1H), 4.16 - 4.09 (m, 1H), 3.71 - 3.39 (m, 2H), 3.27 - 3.15 (m, 2H), 3.04 - 2.93 (m, 1H), 2.29 - 2.21 (m, 1H), 2.19 - 2.12 (m, 1H), 1.99 - 1.87 (m, 4H), 1.76 (d, J = 7.6 Hz, 2H), 1.52 (s, 9H), 1.26 (s, 3H), 0.94 - 0.79 (m, 2H).

[0201] **Step 2**: *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-3-cyano-7- fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0202] To a solution of *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7- hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 0.29 mmol, 1 *eq*) and *tert*-butyl *N*-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate (239 mg, 0.57 mmol, 2 *eq*) in dioxane (5 mL) was added sodium carbonate (91 mg, 0.86 mmol, 3 *eq*). The mixture was purged with nitrogen for 3 times and ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (19 mg, 0.03 mmol, 0.1 *eq*) was added into the mixture, the mixture was stirred at 90 °C for 6 hours. The mixture was filtered and then concentrated to get a residue which was purified by prep-TLC (silicon dioxide, Petroleum ether/Ethyl acetate/triethylamine= 1/1/0.01) to afford the desired product (40 mg, 0.048 mmol, 17% yield) as a yellow oil. LCMS: (ESI, m/z): 839.7[M]$^+$.

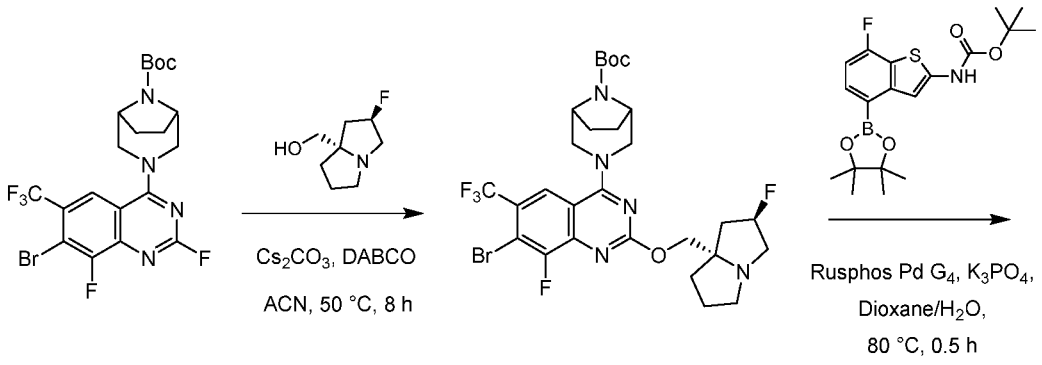
[0203] **Step 3**: 2-amino-4-[6-chloro-4-(3,8-diazabicyclo[3.2.1]octan- 3-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile

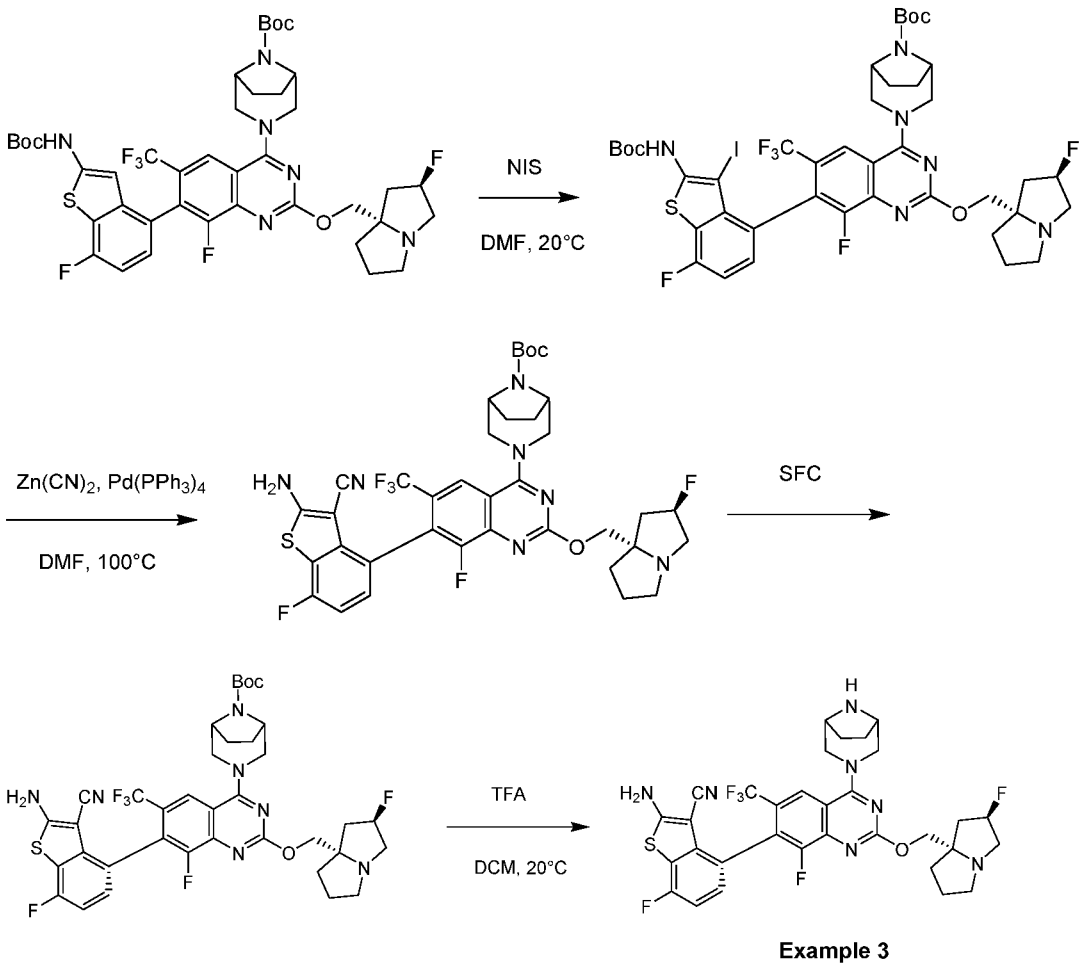


Example 2

[0204] To a solution of *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30 mg, 0.036 mmol, 1 *eq*) in dichloromethane (1 mL) was added trifluoroacetic acid (0.3 mL). Then the mixture was stirred at 20 °C for 0.5 hour. The mixture was concentrated under reduced pressure to get a residue which was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 5%-29%,12min) to afford the desired product (11.31 mg, 0.016 mmol, 48% yield, 95% purity, formate [1]) as a yellow solid. LCMS: (ESI, m/z): 640.0 $[M]^+$. ^{1}H NMR: (400MHz, DMSO-d_6) δ: 8.25 (s, 1H), 8.10 (s, 2H), 7.84 (s, 1H), 7.30 - 7.21 (m, 1H), 7.20 - 7.09 (m, 1H), 5.37 - 5.18 (m, 1H), 4.32 - 4.22 (m, 2H), 4.10 - 4.06 (m, 1H), 4.01 - 3.97 (m, 1H), 3.56 (m, 4H), 3.13 - 2.98 (m, 4H), 2.85 - 2.78 (m, 1H), 2.18 - 2.10 (m, 1H), 2.08 - 1.97 (m, 2H), 1.86 - 1.73 (m, 3H), 1.69 - 1.56 (m, 4H).

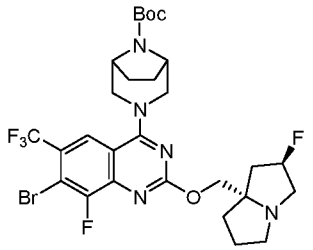
[0205] Synthesis of 2-amino-(S)-4-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (Example 3)





Example 3

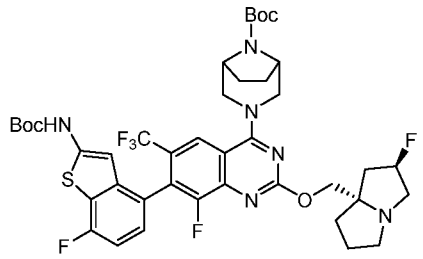
[0206] **Step 1**: *tert*-butyl 3-[7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0207] To a solution of [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (365 mg, 2.29 mmol, 2.00 *eq*) in acetonitrile (10 mL) was added *tert*-butyl 3-[7-bromo-2,8-difluoro-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (600 mg, 1.15 mmol, 1.00 *eq*), cesium carbonate (747 mg, 2.29 mmol, 2.00

eq) and 1,4-diazabicyclo[2.2.2]octane (25.72 mg, 0.23 mmol, 0.1 mL, 0.20 *eq*) at 50 °C. The mixture was stirred at 50 °C for 5 h. Thin layer chromatography (dichloromethane: methanol = 10:1) showed the reaction was completed. The mixture was filtered and then concentrated under reduced pressure to give a residue which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 5:1 to 1:1) to give the desired product (1.50 g, 2.26 mmol, 66% yield) as a light-yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 5.35 - 5.05 (m, 1H), 4.28 (s, 4H), 4.20 - 4.12 (m, 1H), 4.10 - 4.03 (m, 1H), 3.69 - 3.40 (m, 2H), 3.26 - 3.02 (m, 3H), 2.95 - 2.84 (m, 1H), 2.25 - 2.03 (m, 3H), 1.89 - 1.77 (m, 5H), 1.71 - 1.60 (m, 2H), 1.45 (s, 9H).

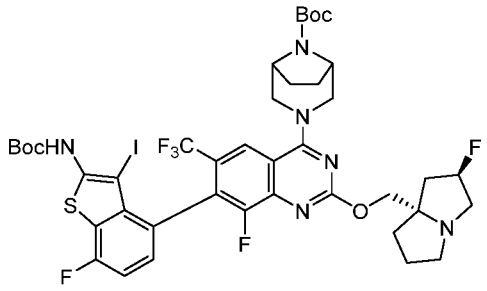
[0208] **Step 2**: *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-7-fluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0209] To a solution of *tert*-butyl 3-[7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 0.75 mmol, 1.00 *eq*) in dioxane (12 mL) and water (3 mL) was added RuPhos Pd G4 (189 mg, 0.23 mmol, 0.30 *eq*) and *tert*-butyl N-[7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate (445 mg, 1.13 mmol, 1.50 *eq*), potassium phosphate (481 mg, 2.26 mmol, 3.00 *eq*) at 80 °C under nitrogen and the mixture was stirred at 80 °C for 20 min. LCMS showed the reaction was completed. The mixture was diluted with water (150 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL), brine (80 mL), dried over sodium sulfate and then concentrated under reduced pressure to give a residue which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 10:1 to 1:1) to give a yellow solid, which was further purified by preparative high performance liquid chromatography (column: Phenomenex luna C18 (250*70mm,10 um);mobile phase: [water(FA)-ACN];B%: 45%-65%,15min) to afford the desired product (2.00 g, 2.36 mmol, 69% yield) as a light yellow solid. LCMS (ESI, m/z):

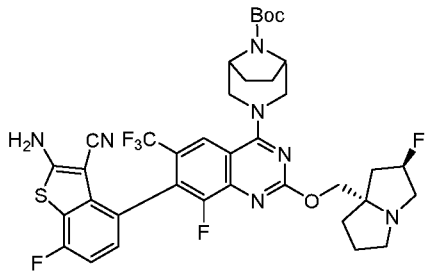
849.2[M+1]$^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 11.15 - 10.53 (m, 1H), 8.25 (s, 1H), 7.31 - 7.23 (m, 1H), 7.22 - 7.15 (m, 1H), 6.33 (d, J = 3.2 Hz, 1H), 5.80 - 5.40 (m, 1H), 4.66 - 4.53 (m, 3H), 4.49 - 4.26 (m, 3H), 3.85 - 3.57 (m, 5H), 3.41 - 3.20 (m, 2H), 2.65 - 2.56 (m, 1H), 2.37 - 2.27 (m, 1H), 2.23 - 2.01 (m, 3H), 1.89 - 1.62 (m, 4H), 1.47 (d, J = 4.0 Hz, 18H).

[0210] **Step 3**: *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-7-fluoro-3-iodo-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



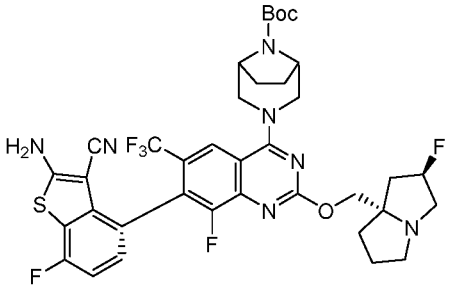
[0211] To a solution of *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-7-fluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 1.18 mmol, 1.00 *eq*) in dimethyl formamide (15 mL) was added *N*-Iodosuccinimide (530 mg, 2.36 mmol, 2.00 *eq*) at 20 °C under nitrogen and the mixture was stirred at 20 °C for 6 h. LCMS and HPLC showed the reaction was completed. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with water (80 mL), brine (40 mL), dried over sodium sulfate and then concentrated under reduced pressure to give a residue which was purified by preparative high performance liquid chromatography (column: Phenomenex Synergi Max-RP 250*50mm*10 um;mobile phase: [water(FA)-ACN];B%: 50%-80%,21min) to give the desired product (1.30 g, 1.33 mmol, 57% yield) as a yellow solid. LCMS (ESI, m/z): 975.0[M+1] $^+$

[0212] **Step 4:** *tert*-butyl 3-[7-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



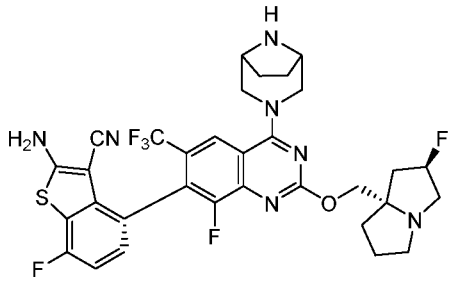
[0213] To a solution of *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-7-fluoro-3-iodo-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (700 mg, 0.72 mmol, 1.00 *eq*) in dimethyl formamide (10 mL) was added zinc cyanide (354 mg, 3.01 mmol, 0.2 mL, 4.20 *eq*), tetratriphenylphosphopalladium (250 mg, 0.22 mmol, 0.3 *eq*) at 100 °C under nitrogen and the mixture was stirred at 100 °C for 6 h. LCMS showed the reaction was completed. The mixture were diluted with water (40 mL) and extracted with ethyl acetate (40 mL). The organic layer was washed with water (40 mL), brine (40 mL), dried over sodium sulfate and then concentrated under reduced pressure to give a residue. The water phase was added sodium hydroxide to adjust pH=14 and quenched by sodium hypochlorite solution (50 mL) and discarded. The mixture was purified by preparative high performance liquid chromatography (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 28%-58%,10min) to give *tert*-butyl 3-[7-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.06 mmol, 9% yield) as a white solid. LCMS (ESI, m/z): 774.2$[M+1]^+$.

[0214] **Step 5**: *tert*-butyl 3-[7-((S)-2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0215] The mixture of atropisomers (*tert*-butyl 3-[7-((S)-2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl 3-[7-((R)-2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate) (150 mg, 0.19 mmol, 1.00 *eq*) was separated by SFC (column: DAICEL CHIRALPAK IC(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 50%-50%,5.3min), and the first eluent was identified as the desired atropisomer *tert*-butyl 3-[7-((S)-2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.08 mmol, 40% yield) as a white solid. LCMS (ESI, m/z): 774.1$[M+1]^+$.

[0216] **Step 6**: 2-amino-(S)-4-[4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (Example 3)

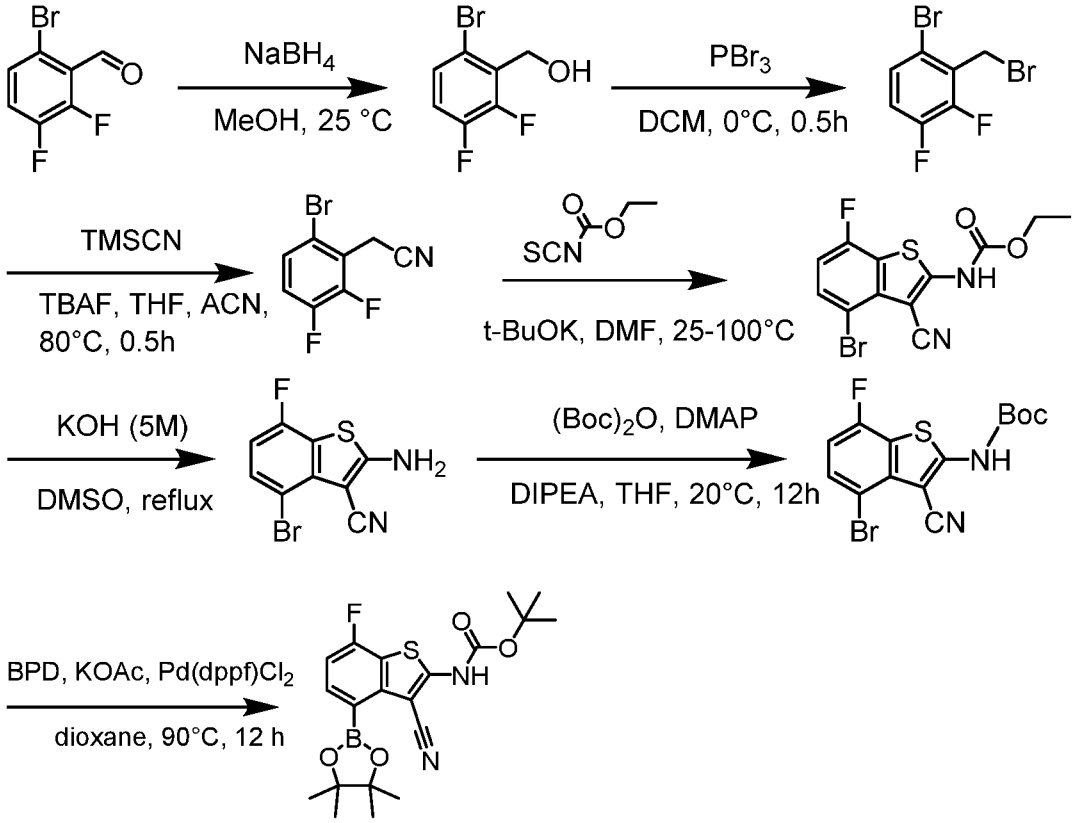


Example 3

[0217] To a solution of *tert*-butyl 3-[7-((S)-2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (60.00 mg, 0.08 mmol, 1.00 *eq*) in dichloromethane (5 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol, 1.0 mL, 174.18 *eq*) at 20 °C and the mixture was stirred at 20 °C for 0.5 h. LCMS showed the reaction was completed. The mixture was concentrated under reduced pressure to give a residue which was purified by preparative high layer chromatography (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 5%-35%,10min) to give the desired product (37.22 mg, 0.05 mmol, 67% yield, 100%

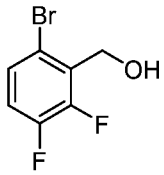
purity, formate[1]) as an off-white solid. LCMS (ESI, m/z): 674.2[M+1]$^+$. ^{1}H NMR: (400 MHz, DMSO-d$_6$) δ: 8.17 (s, 1H), 8.12 - 8.02 (m, 3H), 7.29 - 7.21 (m, 1H), 7.18 - 7.09 (m, 1H), 5.39 - 5.17 (m, 1H), 4.41 - 4.30 (m, 2H), 4.16 - 4.10 (m, 1H), 4.06 - 4.00 (m, 1H), 3.78 - 3.70 (m, 4H), 3.09 (d, J = 6.0 Hz, 2H), 3.02 (s, 1H), 2.87 - 2.79 (m, 1H), 2.16 - 1.99 (m, 3H), 1.87 - 1.63 (m, 7H).

[0218] Synthesis of *tert*-butyl N-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)benzothiophen-2-yl]carbamate **(Intermediate 4)**



Intermediate 4

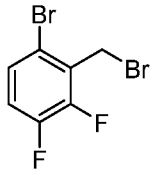
[0219] Step 1: (6-bromo-2,3-difluoro-phenyl)methanol



[0220] To a solution of 6-bromo-2,3-difluoro-benzaldehyde (50 g, 226.25 mmol, 1 *eq*) in methanol (500 mL) was added sodium borohydride (17.12 g, 452.49 mmol, 2 *eq*) at 0

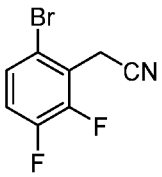
°C. Then the mixture was stirred at 20 °C for 0.5 h. TLC (Petroleum ether/Ethyl acetate = 5/1) showed 6-bromo-2,3-difluoro-benzaldehyde was consumed completely. The mixture was poured into saturated aqueous ammonium chloride (500 mL) at 0 °C, extracted with ethyl acetate (500 mL x 2). The organic layer was washed with brine (300 mL), dried over sodium sulfate, filtered and then concentrated under reduced pressure to afford the desired crude product (50 g, 44.84 mmol, 99% yield) as a white solid, which was used into the next step directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.31 (m, 1H), 7.14 - 6.98 (m, 1H), 4.94 - 4.82 (m, 2H), 2.21 (t, J = 6.8 Hz, 1H).

[0221] **Step 2**: 1-bromo-2-(bromomethyl)-3,4-difluoro-benzene



[0222] To a solution of (6-bromo-2,3-difluoro-phenyl)methanol (50 g, 224.20 mmol, 1 *eq*) in dichloromethane (500 mL) was added phosphorus tribromide (24.28 g, 89.68 mmol, 0.4 *eq*) at 0 °C. Then the mixture was stirred at 20 °C for 0.5 h. TLC (Petroleum ether/Ethyl acetate = 10/1) showed (6-bromo-2,3-difluoro-phenyl)methanol was consumed completely. The mixture was quenched with saturated aqueous sodium bicarbonate (500 mL), extracted with ethyl acetate (500 mL x 2). The organic layer washed with brine (300 mL), dried over sodium sulfate, filtered and then concentrated under reduced pressure to afford the desired product (52 g, 4.55 mmol, 82% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.33 (m, 1H), 7.13 - 7.03 (m, 1H), 4.86 (s, 2H).

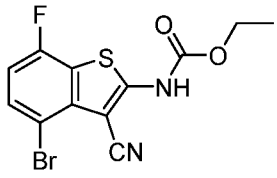
[0223] **Step 3**: 2-(6-bromo-2,3- difluoro-phenyl)acetonitrile



[0224] To a solution of 1-bromo-2-(bromomethyl)-3,4-difluoro-benzene (45 g, 157.39 mmol, 1 *eq*) and trimethylchlorosilane (17.18 g, 173.13 mmol, 1.1 *eq*) in acetonitrile (300 mL) was added tetrabutylammonium fluoride (1 M, 173.13 mL, 1.1 *eq*) at 0 °C. Then the mixture was stirred at 80 °C for 0.5 h. TLC (Petroleum ether/Ethyl acetate = 5/1) showed 1-bromo-2-(bromomethyl)-3,4-difluoro-benzene was consumed completely. The mixture

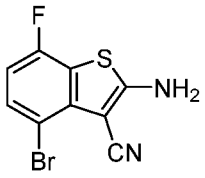
was concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (silicon dioxide, Petroleum ether/Ethyl acetate = 30/1 to 5/1) to afford the desired product (35 g, 150.85 mmol, 96% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.33 (m, 1H), 7.13 - 7.03 (m, 1H), 4.86 (s, 2H).

[0225] **Step 4**: Ethyl N-(4-bromo-3-cyano-7-fluoro-benzothiophen-2-yl) carbamate



[0226] To a solution of 2-(6-bromo-2,3-difluoro-phenyl)acetonitrile (35 g, 150.85 mmol, 1 *eq*) in *N*,*N*-dimethylformamide (300 mL) was added potassium *tert*-butoxide (20.31 g, 181.02 mmol, 1.2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 10 min. Ethyl N-(thioxomethylene)carbamate (21.76 g, 165.93 mmol, 1.1 *eq*) was added into the mixture and stirred at 25 °C for 50 min. The mixture was stirred at 100 °C for 0.5 h. TLC (Petroleum ether/Ethyl acetate = 3/1) showed 2-(6-bromo-2,3-difluoro-phenyl)acetonitrile was consumed completely. The mixture was poured into ice water (1500 mL), filtered to afford the product (75 g, crude) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 12.11 (d, J = 1.2 Hz, 1H), 7.68 (m, J = 4.8, 8.6 Hz, 1H), 7.21 (t, J = 8.8 Hz, 1H), 4.29 (m, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H).

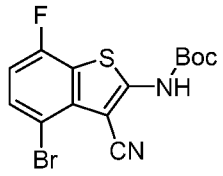
[0227] **Step 5**: 2-amino-4-bromo-7-fluoro- benzothiophene-3-carbonitrile



[0228] To a solution of ethyl N-(4-bromo-3-cyano-7-fluoro-benzothiophen-2-yl) carbamate (40 g, 116.56 mmol, 1 *eq*) in dimethyl sulfoxide (200 mL) was added sodium hydroxide (5 M, 180 mL, 7.72 *eq*). Then the mixture was stirred at 125 °C for 12 h. TLC (Dichloromethane/Petroleum ether = 2/1) showed ethyl N-(4-bromo-3-cyano-7-fluoro-benzothiophen-2-yl) carbamate was consumed completely and a new spot was detected. The mixture was cooled to 20 °C, poured into ice water (500 mL), filtered to afford the desired product (28 g, 103.28 mmol, 89% yield) as a yellow solid, which was used into the

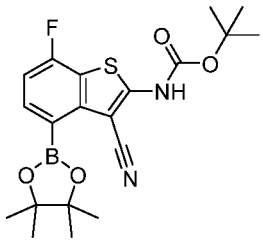
next step directly. ^{1}H NMR (400 MHz, DMSO) δ 7.53 - 7.41 (m, 1H), 6.94 (t, *J* = 8.8 Hz, 1H).

[0229] **Step 6**: *tert*-butyl N-(4-bromo-3-cyano-7-fluoro-benzothiophen-2-yl)carbamate



[0230] To a solution of 2-amino-4-bromo-7-fluoro-benzothiophene-3-carbonitrile (50 g, 184.43 mmol, 1 *eq*) and di-tert-butyl dicarbonate (44.28 g, 202.87 mmol, 1.1 *eq*) in tetrahydrofuran (500 mL) was added *N*,*N*-diisopropylethylamine (47.67 g, 368.86 mmol, 2 *eq*) and dimethylaminopyridine (2.25 g, 18.44 mmol, 0.1 *eq*). The mixture was stirred at 20 °C for 12 h. TLC (Dichloromethane/Petroleum ether = 2/1) showed 2-amino-4-bromo-7-fluoro-benzothiophene-3-carbonitrile was consumed completely and a new spot was detected. The mixture was diluted with ethyl acetate (300 mL) and water (200 mL), extracted with ethyl acetate (300 mL x 2). The organic layer was washed with brine (200 mL), dried over sodium sulfate, filtered and then concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (silicon dioxide, dichloromethane/ petroleum ether = 1/0) to afford the desired product (52 g, 140.08 mmol, 76% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.81 (s, 1H), 7.69 (m, *J* = 4.8, 8.8 Hz, 1H), 7.21 (t, *J* = 9.2 Hz, 1H), 1.54 (s, 9H).

[0231] **Step 7**: *tert*-butyl N-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzothiophen-2-yl]carbamate

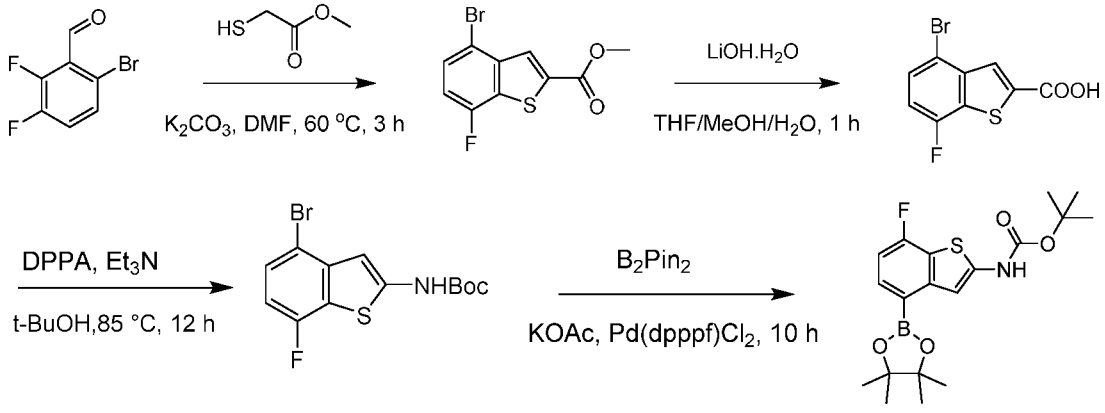


Intermediate 4

[0232] To a solution of *tert*-butyl N-(4-bromo-3-cyano-7-fluoro-benzothiophen-2-yl)carbamate (12 g, 32.32 mmol, 1 *e*) and bis(pinacolato)diboron (9.86 g, 38.80 mmol, 1.2 *eq*) in dioxane (300 mL) was added potassium acetate (9.52 g, 96.9 mmol, 3 *eq*). Then the

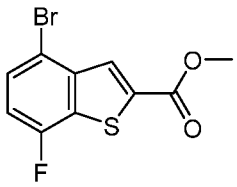
mixture was purged with nitrogen for 3 times. [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(ii) (2.36 g, 3.24 mmol, 0.1 *eq*) was added into the mixture and stirred at 80 °C for 12 h. TLC (Petroleum ether/Ethyl acetate = 3/1) showed *tert*-butyl N-(4-bromo-3-cyano-7-fluoro- benzothiophen-2-yl) carbamate was consumed completely and several new spots were detected. The mixture was filtered and then concentrated under reduced pressure to get a residue. The residue was purified by column chromatography (silicon dioxide, Petroleum ether/Ethyl acetate = 50/1 to 3/1) to afford the desired product (9.6 g, 22.95 mmol, 71% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 7.89 (s, 1H), 7.77 - 7.70 (m, 1H), 6.96 - 6.90 (m, 1H), 1.51 (s, 9H), 1.37 - 1.35 (m, 12H).

[0233] Synthesis of *tert*-butyl N-[7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate **(Intermediate 5)**



intermediate 5

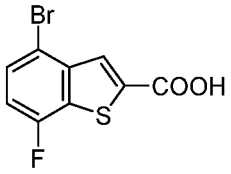
[0234] **Step 1**: methyl 4-bromo-7-fluoro-benzothiophene-2-carboxylate



[0235] To a solution of 6-bromo-2,3-difluoro-benzaldehyde (50.00 g, 226.25 mmol, 1.00 *eq*) in dimethyl formamide (500 mL) was added potassium carbonate (62.54 g, 452.49 mmol, 2.00 *eq*) under nitrogen atmosphere. Then methyl 2-sulfanylacetate (26.74 g, 251.92 mmol, 22.8 mL, 1.11 *eq*) was added into the mixture. The mixture was stirred at 60 °C for 3 h. The reaction mixture was diluted with water (1000 mL) and extracted with ethyl acetate (400 mL x 3). The combined organic layers were washed with brine (500

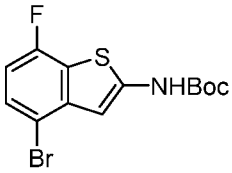
mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with the mixed solvent of petroleum ether and ethyl acetate (v/v = 10:1, 300 mL) to get the desired product (55.00 g, 182.62 mmol, 81% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 3.2 Hz, 1H), 7.61 - 7.46 (m, 1H), 7.05 (t, *J* = 8.8 Hz, 1H), 3.99 (s, 3H).

[0236] **Step 2**: 4-bromo-7-fluoro-benzothiophene-2-carboxylic acid



[0237] A mixture of methyl 4-bromo-7-fluoro-benzothiophene-2-carboxylate (50.00 g, 172.94 mmol, 1.00 *eq*) and lithium hydroxide monohydrate (25.00 g, 595.81 mmol, 3.45 *eq*) in tetrahydrofuran (200 mL) , methanol (200 mL) and water (100 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 20 C for 1 h under nitrogen atmosphere. The mixture was diluted with water (1000 mL) and the pH was adjusted to 3 with 4M hydrochloric acid and extracted with ethyl acetate (500 mL x 2). The combined organic layers were washed with brine (1000 ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the desired product (45.00 g, 163.58 mmol, 95% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, *J* = 3.2 Hz, 1H), 7.74 - 7.56 (m, 1H), 7.32 (t, *J* = 9.2 Hz, 1H).

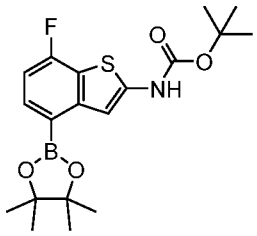
[0238] **Step 3**: *tert*-butyl N-(4-bromo-7-fluoro-benzothiophen-2-yl)carbamate



[0239] To a solution of 4-bromo-7-fluoro-benzothiophene-2-carboxylic acid (15.00 g, 54.53 mmol, 1.00 *eq*) in tertiary butanol (200 mL) was added diphenylphosphoryl azide (19.51 g, 70.88 mmol, 15.4 mL, 1.30 *eq*) and diisopropylethylamine (14.09 g, 109.05 mmol, 19.0 mL, 2.00 *eq*). The mixture was stirred at 85 °C for 12 h. The mixture was diluted with water (500 mL) and extracted with ethyl acetate (250 mL x 2). The combined organic layers were washed with brine (500ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get a residue. The residue was

purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 1:0 to 20:1) to get *tert*-butyl N-(4-bromo-7-fluoro-benzothiophen-2-yl)carbamate (15.00 g, 43.33 mmol, 79% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.56 - 7.41 (m, 1H), 6.99 (t, J = 9.2 Hz, 1H), 6.80 (d, J = 3.6 Hz, 1H), 1.50 (s, 9H).

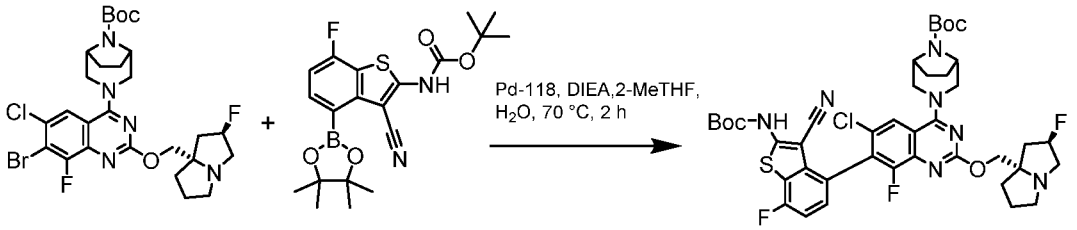
[0240] **Step 4**: *tert*-butyl N-[7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate

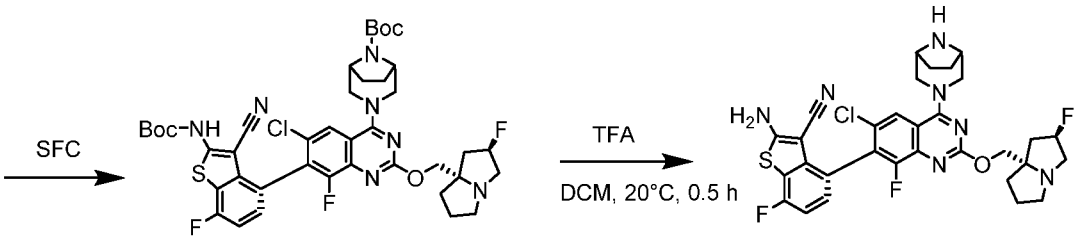


Intermediate 5

[0241] A mixture of *tert*-butyl N-(4-bromo-7-fluoro-benzothiophen-2-yl)carbamate (25.00 g, 72.21 mmol, 1.00 *eq*), bis(pinacolato)diboron(26.04 g, 102.54 mmol, 1.40 *eq*), [1,1-bis(diphenylphosphina)ferrocene]dichloropalladium(II) (10.57 g, 14.44 mmol, 0.20 eq) and potassium acetate (21.26 g, 216.63 mmol, 3.00 eq) in dioxane (300 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 100 °C for 10 h under nitrogen atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 20:1 to 10:1) to get the desired product (20.00 g, 50.85 mmol, 70% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.67 (dd, J = 6.0, 8.0 Hz, 1H), 7.39 (d, J = 4.0 Hz, 1H), 7.01 (dd, J = 8.0, 10.4 Hz, 1H), 1.50 (s, 9H), 1.33 (s, 12H).

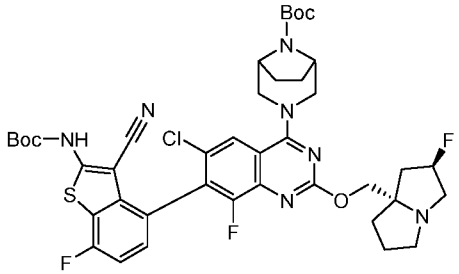
[0242] Synthesis of (R)-4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile **(Example 4)**





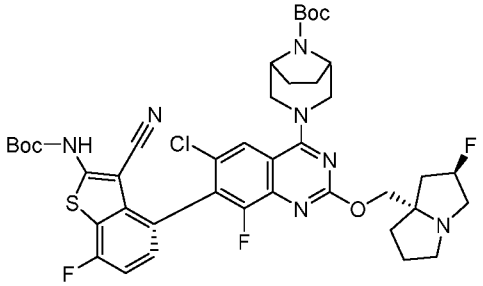
Example 4

[0243] **Step 1:** tert-butyl (1R,5S)-3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



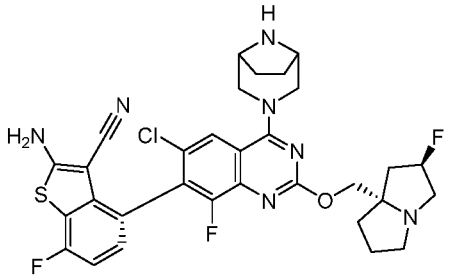
[0244] To a solution of *tert*-butyl *N*-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)benzothiophen-2-yl]carbamate (6.4 g, 15.28 mmol, 1.2 *eq*) and *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (8 g, 12.72 mmol, 1 *eq*) in 2-methyltetrahydrofuran (80 mL) and water (20 mL) was added di*tert*-butyl(cyclopentyl)phosphane;dichloropalladium;iron (829 mg, 1.27 mmol, 0.1 *eq*). The mixture was purged with nitrogen for 3 times, and then *N,N*-diisopropylethylamine (4.92 g, 38.16 mmol, 3 *eq*) was added into the mixture. The mixture was stirred at 70 °C for 2 hours. The mixture was filtered and then concentrated to get a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm,10 um);mobile phase: [water(FA)-ACN];B%: 50%-70%,15min). *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)- 3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.6 g, 5.42 mmol, 50% yield, 99% purity) was obtained as a yellow oil. LCMS (ESI, m/z): 840.1[M]$^+$.

[0245] **Step 2:** tert-butyl (1R,5S)-3-(7-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0246] *Tert*-butyl (1R,5S)-3-(7-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen- 4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.6 g, 5.47 mmol, 1.0 eq) was purified by SFC (Rt = 0.898 min, 1.172 min; column: DAICEL CHIRALPAK IC(250mm*30mm,10um); mobile phase: [0.1%NH_3H_2O ETOH]; B%: 45%-45%,4;140min) to get product. Compound tert-butyl (1R,5S)-3-(7-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.1 g, 2.50 mmol, 46% yield) was obtained as a yellow oil.

[0247] **Step 3:** (R)-4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile

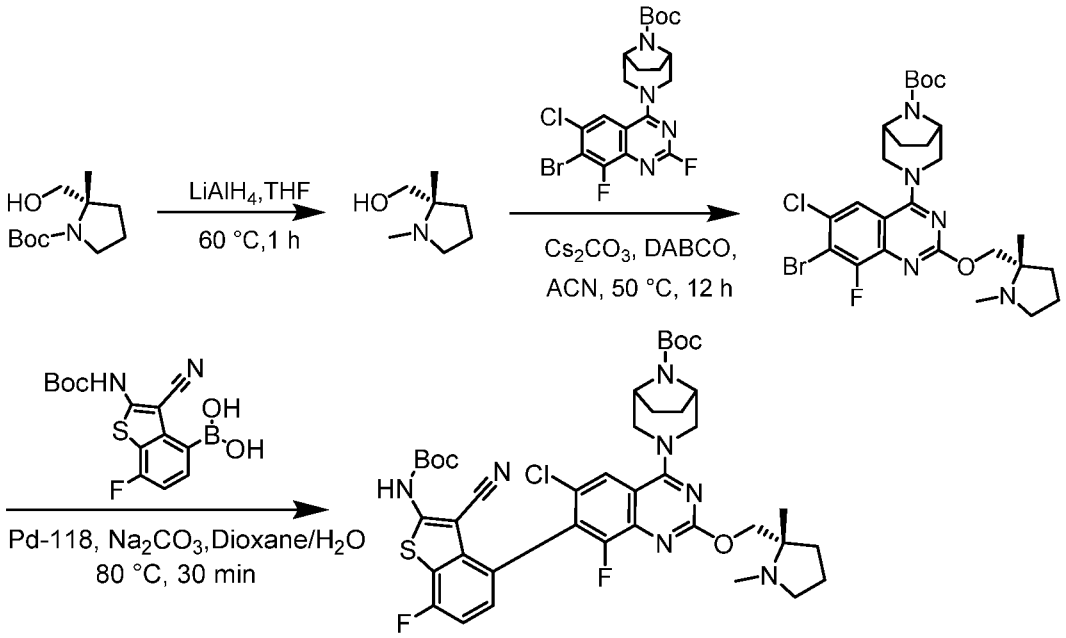


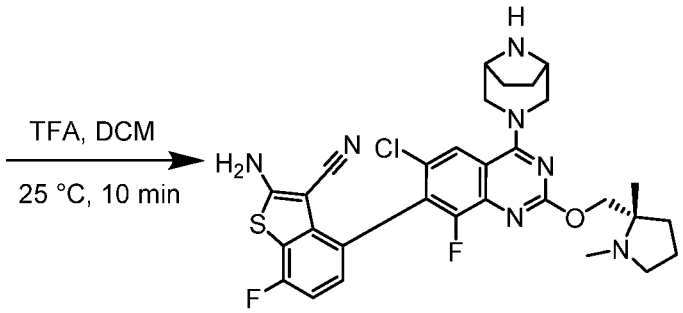
Example 4

[0248] To a solution of tert-butyl (1R,5S)-3-(7-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-

1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.0 g, 2.40 mmol, 1 *eq*) in dichloromethane (20 mL) was added trifluoroacetic acid (5 mL). Then the mixture was stirred at 20 °C for 0.5 hour. LCMS showed the desired mass was detected. The mixture was concentrated under reduced pressure to get a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm,10 um);mobile phase: [water(FA)-ACN];B%: 10%-40%,20min). (R)-4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (1.4 g, 2.00 mmol, 84% yield, 98% purity, formate[1]) was obtained as a yellow solid. LCMS (ESI, m/z): 640.3 $[M]^+$. ^1H NMR: (400MHz, DMSO-d_6) δ: 8.15 (s, 1H), 8.13 (s, 2H), 7.91 (s, 1H), 7.28 - 7.20 (m, 1H), 7.20 - 7.12 (m, 1H), 5.44 - 5.21 (m, 1H), 4.52 (d, J = 13.2 Hz, 1H), 4.36 (d, J = 13.2 Hz, 1H), 4.24 - 4.05 (m, 4H), 3.85 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.23 - 3.12 (m, 3H), 2.95 - 2.85 (m, 1H), 2.28 - 2.01 (m, 3H), 1.96 - 1.77 (m, 7H).

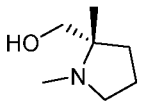
[0249] Synthesis of 2-amino-4-[6-chloro-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[(2S)-1,2-dimethylpyrrolidin-2-yl]methoxy]-8-fluoro-quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile **(Example 5)**





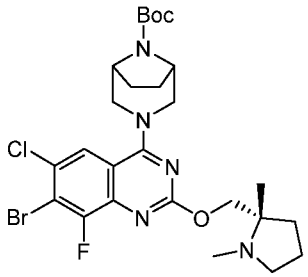
Example 5

[0250] **Step 1**: [(2S)-1,2-dimethylpyrrolidin-2-yl]methanol



[0251] To a solution of lithium aluminum hydride (2.64 g, 69.67 mmol) in tetrahydrofuran (25 mL) was added a solution of *tert*-butyl (2S)-2-(hydroxymethyl)-2-methyl-pyrrolidine-1-carboxylate (5 g, 23.22 mmol) in tetrahydrofuran (25 mL) at 0°C. Then the mixture was stirred at 60 °C for 1 h. Thin layer chromatography (dichloromethane: methanol = 10:1) showed the reaction was completed. The mixture was quenched with water (8 mL) and dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to get [(2S)-1, 2-dimethylpyrrolidin-2-yl]methanol (2.50 g, 19.35 mmol, 83% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 3.37 - 3.20 (m, 2H), 3.03 (td, J = 5.2, 9.2 Hz, 1H), 2.55 (q, J = 8.8 Hz, 1H), 2.19 (s, 3H), 2.10 - 2.01 (m, 1H), 1.76 - 1.65 (m, 2H), 1.57 - 1.40 (m, 2H), 0.85 (s, 3H).

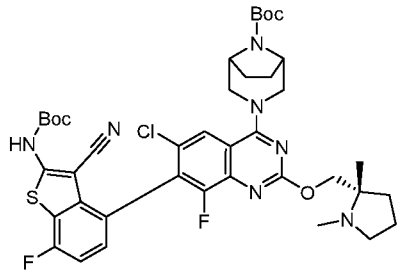
[0252] **Step 2**: *tert*-butyl 3-[7-bromo-6-chloro-2-[[(2S)-1,2-dimethylpyr rolidin-2-yl]methoxy]-8-fluoro-quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0253] To a solution of *tert*-butyl 3-(7-bromo-6-chloro-2,8-difluoro-quinazolin-4-yl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (1.5 g, 3.06 mmol) and [(2S)-1,2-dimethyl pyrrolidin-2-yl]methanol (791 mg, 6.13 mmol) in acetonitrile (30 mL) was added cesium

carbonate (2 g, 6.13 mmol) and 1,4-diazabicyclo[2.2.2]octane (34 mg, 0.3 mmol). The mixture was stirred at 50 °C for 12 h. LCMS showed the reaction was completed. The mixture was filtered and the filtrate was concentrated under reduced pressure to get a residue. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to get a residue. The residue was purified by preparative high performance liquid chromatography (column: Phenomenex luna C18 150*40mm*15um; mobile phase: [water(FA)-ACN];B%: 23%-53%,10min) to get the desired product (220 mg, 0.36 mmol, 12% yield) as a yellow solid. LCMS (ESI, m/z): 598.2, 600.2 $[M+H]^+$.

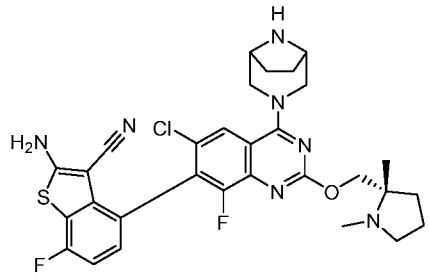
[0254] **Step 3**: *tert*-butyl 3-[7-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-2-[[(2S)-1,2-dimethylpyrrolidin-2-yl]methoxy]-8-fluoro-quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0255] A mixture of *tert*-butyl 3-[7-bromo-6-chloro-2-[[(2S)-1,2-dimethylpyrrolidin-2-yl]methoxy]-8-fluoro-quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0.18 g, 0.30 mmol), *tert*-butyl N-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate (251 mg, 0.60 mmol), ditertbutyl(cyclopentyl)phosphane;dichloro palladium;iron (19 mg, 0.03 mmol), sodium carbonate (95 mg, 0.90 mmol) in dioxane (3 mL) and water (0.6 mL) was degassed and purged with nitrogen for 3 times, then the mixture was stirred at 80 °C for 30 min under nitrogen atmosphere. LCMS showed the reaction was completed. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative high performance liquid chromatography (column: Phenomenex Synergi Polar-RP 100*25mm*4um;mobile phase: [water(TFA)-

ACN];B%: 58%-78%,7min) to afford the desired product (30 mg, 0.03 mmol, 12% yield) as a white solid. LCMS (ESI, m/z): 810.1 $[M+H]^+$.

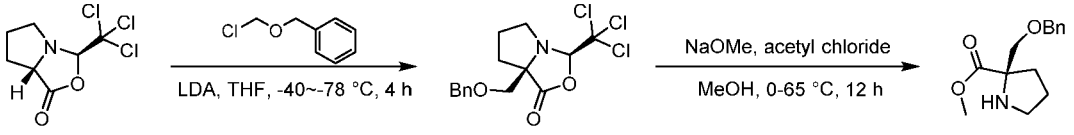
[0256] **Step 4**: 2-amino-4-[6-chloro-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[(2S)-1,2-dimethylpyrrolidin-2-yl]methoxy]-8-fluoro-quinazolin-7-yl]-7-fluoro-benzothi ophene-3-carbonitrile.

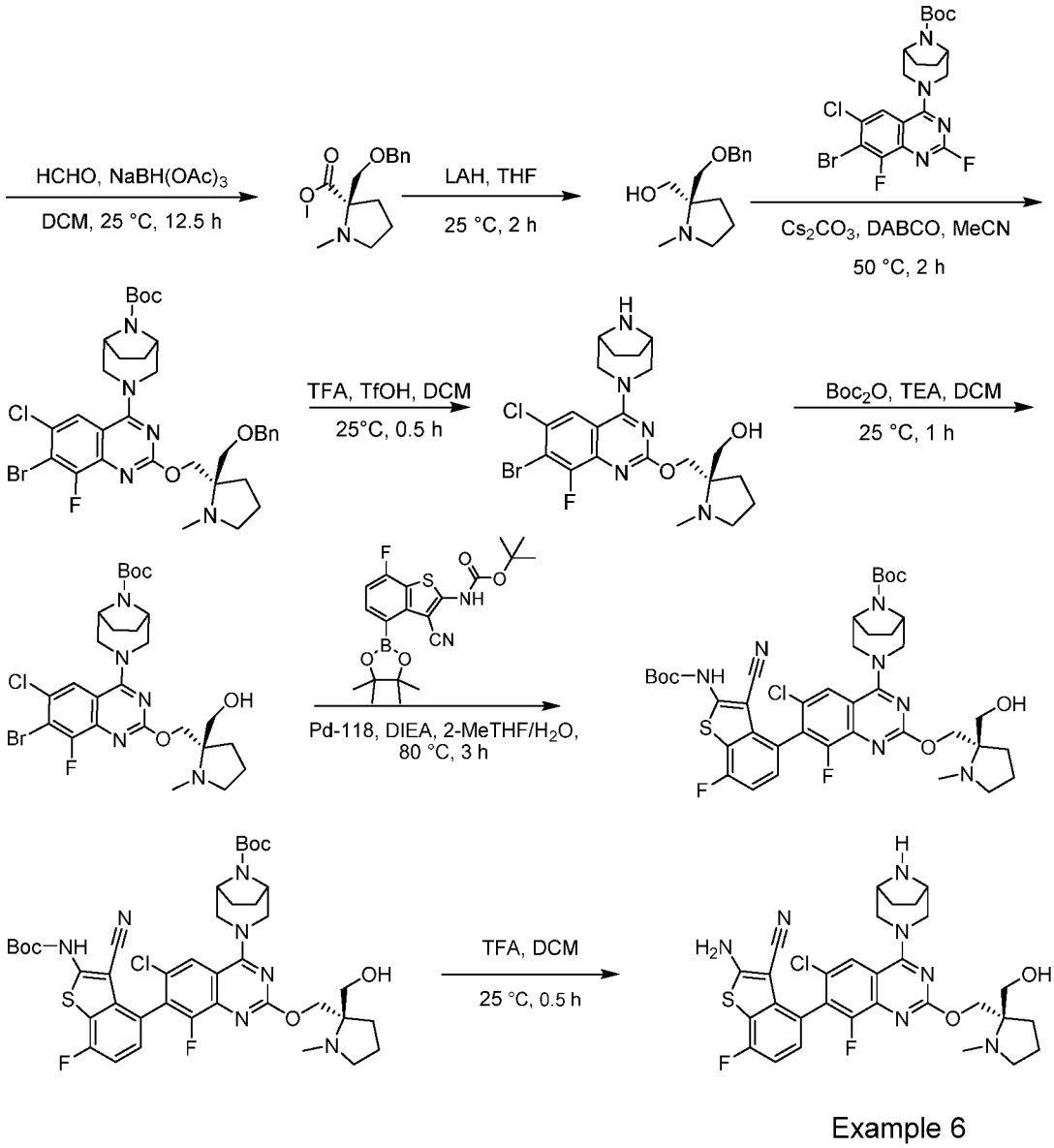


Example 5

[0257] To a solution of *tert*-butyl 3-[7-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-2-[[(2S)-1,2-dimethylpyrrolidin-2-yl]methoxy]-8-fluoro-quinazolin-4-yl]-3,8–diazabicyclo [3.2.1]octane-8-carboxylate (25 mg, 0.03 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (3.08 g, 27.01 mmol, 2 mL). The mixture was stirred at 25 °C for 10 min. Thin layer chromatography (dichloromethane: methanol = 10:1) showed the reaction was completed. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by preparative high performance liquid chromatography (column: Phenomenex C18 75*30mm*3um;mobile phase: [water(FA)-ACN];B%: 8%-38%,7min) to give the product (4 mg, 0.01 mmol, 19% yield, formate [2]) as a yellow solid. LCMS (ESI, m/z): 610.2$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.28 (s, 2H), 8.13 (s, 2H), 7.86 (s, 1H), 7.26 (dd, J = 5.2, 8.4 Hz, 1H), 7.20 - 7.11 (m, 1H), 4.42 - 4.24 (m, 2H), 4.22 - 4.15 (m, 2H), 3.56 - 3.27 (m, 5H), 2.95 - 2.81 (m, 1H), 2.62 (q, J = 8.4 Hz, 1H), 2.30 (s, 3H), 1.93 (td, J = 7.2, 12.4 Hz, 1H), 1.79 - 1.56 (m, 7H), 1.11 - 1.02 (m, 3H).

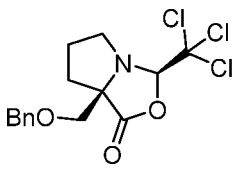
[0258] Synthesis of 2-amino-4-[6-chloro-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-[[(2R)-2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile **(Example 6)**





Example 6

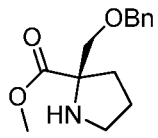
[0259] **Step 1**: (3R,7aR)-7a-(benzyloxymethyl)-3-(trichloromethyl)-3,5,6,7-tetrahydropyrrolo[1,2-c]oxazol-1-one



[0260] A mixture of (3R,7aS)-3-(trichloromethyl)-5,6,7,7a-tetrahydro-3H-pyrrolo[1,2-c]oxazol-1-one (30.00 g, 122.70 mmol), chloromethoxymethylbenzene (38.43 g, 245.40 mmol) , lithium;di(propan-2-yl)azanide (2 M, 92 mL) in tetrahydrofuran (300 mL) was

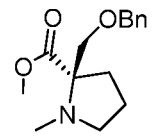
degassed and purged with nitrogen for 3 times at -78 °C, and then the mixture was stirred at -40 °C for 4 h under nitrogen atmosphere. The reaction mixture was quenched by the slowly addition of water (300 mL), and then the mixture was extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc = 5/1) to give (3R,7aR)-7a-(benzyloxymethyl)-3-(trichloromethyl)-3,5,6,7-tetrahydropyrrolo[1,2-c]oxazol-1-one (21 g, 58.14 mmol, 47% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.17 (m, 5H), 4.92 (s, 1H), 4.55 (d, J = 1.6 Hz, 2H), 3.66 (s, 2H), 3.30 - 3.22 (m, 1H), 3.21 - 3.14 (m, 1H), 2.24 (ddd, J = 7.2, 9.6, 13.2 Hz, 1H), 2.09 - 2.01 (m, 1H), 1.95 - 1.87 (m, 1H), 1.65 - 1.60 (m, 1H).

[0261] **Step 2**: methyl (2R)-2-(benzyloxymethyl)pyrrolidine-2-carboxylate



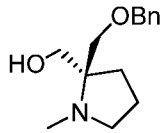
[0262] To a solution of (3R,7aR)-7a-(benzyloxymethyl)-3-(trichloromethyl)-3,5,6,7-tetrahydropyrrolo[1,2-c]oxazol-1-one (5 g, 13.71 mmol) in methanol (100 mL) was added sodium methylate (518 mg, 9.60 mmol). The mixture was stirred at rt for 12 h. Then acetyl chloride (22 g, 280.26 mmo) was added at 0 °C. The mixture was stirred at 65 °C for 1 h. The mixture was concentrated in vacuo. The residue was added saturated sodium carbonate solution (100 ml), extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give methyl (2R)-2-(benzyloxymethyl)pyrrolidine-2-carboxylate (2.2 g, 8.82 mmol, 64% yield) as a yellow oil, which was used into the next step without further purification. LCMS (ESI, m/z): 250.0 $[M+H]^+$. ^{1}H NMR (400 MHz, CDCl3) δ 7.36 - 7.28 (m, 5H), 4.64 - 4.59 (m, 1H), 4.52 - 4.47 (m, 1H), 3.76 (d, *J* = 8.8 Hz, 1H), 3.73 (s, 3H), 3.45 (d, *J* = 8.8 Hz, 1H), 3.10 - 2.96 (m, 2H), 2.67 (s, 1H), 2.10 - 2.01 (m, 1H), 1.83 - 1.67 (m, 3H).

[0263] **Step 3**: methyl (2R)-2-(benzyloxymethyl)-1-methyl-pyrrolidine-2-carboxylate



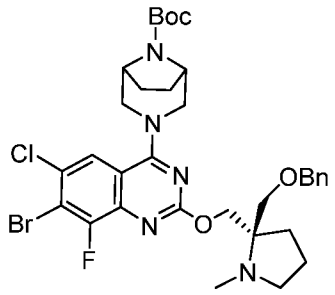
[0264] A mixture of methyl (2R)-2-(benzyloxymethyl)pyrrolidine-2-carboxylate (2.2 g, 8.82 mmol, 1.00 eq), formaldehyde (2.86 g, 35.30 mmol, 37% purity) in dichloromethane (100 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at rt for 0.5 h under nitrogen atmosphere. Then sodium triacetoxyborohydride (3.74 g, 17.65 mmol) added to the mixture, the mixture was stirred at 25 °C for 12 h. LCMS that the reaction was completed. The reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate (100 mL), extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative high performance liquid chromatography (column: Phenomenex luna C18 250*50mm*10 um;mobile phase: [water(FA)-ACN];B%: 1%-30%,20min) to give the desired product (1.30 g, 4.94 mmol, 56% yield) as a colorless oil. LCMS (ESI, m/z): 264.3 $[M+H]^+$.

[0265] **Step 4**: [(2S)-2-(benzyloxymethyl)-1-methyl-pyrrolidin-2-yl]methanol



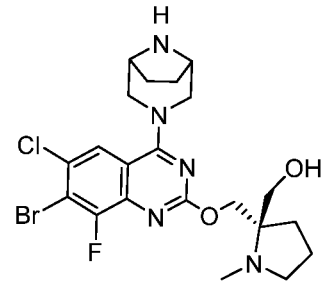
[0266] A mixture of methyl (2R)-2-(benzyloxymethyl)-1-methyl-pyrrolidine-2-carboxylate (1.30 g, 4.94 mmol) in tetrahydrofuran (30 mL) was degassed and purged with nitrogen for 3 times, and then lithium aluminum hydride (562 mg, 14.81 mmol) was added to the reaction mixture at 0 °C, the mixture was stirred at rt for 2 h under nitrogen atmosphere. It was quenched by the addition of water (1 mL), aqueous sodium hydroxide (15%, 2 ml), water (3 ml) at 25 °C, and then filtered to remove the insoluble fraction. The filtrate was concentrated under reduced pressure to remove the solvent to give a residue. The residue was purified by preparative high performance liquid chromatography (column: Phenomenex luna C18 150*40mm* 15um;mobile phase: [water(FA)-ACN];B%: 2%-32%,10min) to afford the product as a colorless oil. LCMS (ESI, m/z): 236.5 $[M+H]^+$.

[0267] **Step 5**: *tert*-butyl 3-[2-[[(2R)-2-(benzyloxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]-7-bromo-6-chloro-8-fluoro-quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



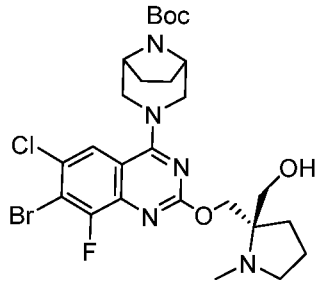
[0268] To a solution of [(2S)-2-(benzyloxymethyl)-1-methyl-pyrrolidin-2-yl]methanol (216 mg, 0.9 mmol), *tert*-butyl 3-(7-bromo-6-chloro-2,8-difluoro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 0.6 mmol) in acetonitrile (10 mL) was added 1,4-diazabicyclo[2.2.2]octane (7 mg, 0.06 mmol) and cesium carbonate (599 mg, 1.84 mmol). The mixture was stirred at 50 °C for 2 h. The reaction mixture was filtered to remove the insoluble byproduct. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (9% methanol in dichloromethane) to afford the desired product (200 mg, 0.28 mmol, 46% yield) as a yellow solid. LCMS (ESI, m/z): 704.1, 706.0$[M+H]^+$.

[0269] **Step 6**: [(2R)-2-[[7-bromo-6-chloro-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-quinazolin-2-yl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methanol



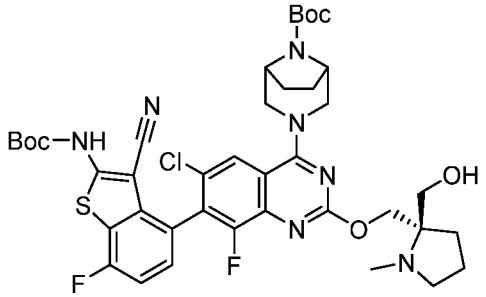
[0270] To a solution of *tert*-butyl 3-[2-[[(2R)-2-(benzyloxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]-7-bromo-6-chloro-8-fluoro-quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.28 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (3.66 g, 32.08 mmol) and trifluoromethanesulfonic acid (212 mg, 1.42 mmol). The mixture was stirred at rt for 0.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent to afford the product (140 mg, 0.27 mmol, 96% yield) as a yellow oil, which was used into the next step without further purification. LCMS (ESI, m/z): 514.2, 516.1$[M+H]^+$.

[0271] **Step 7**: *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[(2R)-2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0272] To a solution of [(2R)-2-[[7-bromo-6-chloro-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-quinazolin-2-yl]oxymethyl]-1-methyl-pyrrolidin-2-yl]methanol (140 mg, 0.27 mmol) in dichloromethane (8 mL) was added di-*tert*-butyl dicarbonate (178 mg, 0.82 mmol) and triethylamine (82 mg, 0.82 mmol). The mixture was stirred at rt for 1 h. The reaction mixture was quenched by water (10 mL) at 25 °C, and then extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (9% methanol in dichloromethane) to afford the desired product (105 mg, 0.17 mmol, 62% yield) as a white solid. LCMS (ESI, m/z): 613.9, 615.8$[M+H]^+$

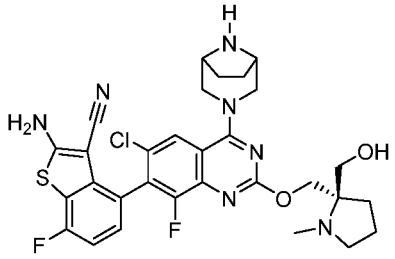
[0273] **Step 8**: *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2R)-2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0274] A mixture of *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[(2R)-2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (105 mg, 0.17 mmol, 1.00 eq), *tert*-butyl N-[3-

cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate (93 mg, 0.22 mmol), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (11 mg, 0.02 mmol), diisopropylethylamine (66 mg, 0.51 mmol) in 2-methyltetrahydrofuran (2 mL), water (0.2 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 3 h under nitrogen atmosphere. The reaction mixture was quenched by water (10 mL) at 25°C, extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative high layer chromatography (column: Phenomenex Synergi Polar-RP 100*25mm*4um;mobile phase: [water(TFA)-ACN];B%: 67%-87%,7min) to afford the desired product (18 mg, 0.02 mmol, 13% yield) as a yellow solid. LCMS (ESI, m/z): 826.0 $[M]^+$.

[0275] **Step 9**: 2-amino-4-[6-chloro-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-[[(2R)-2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile

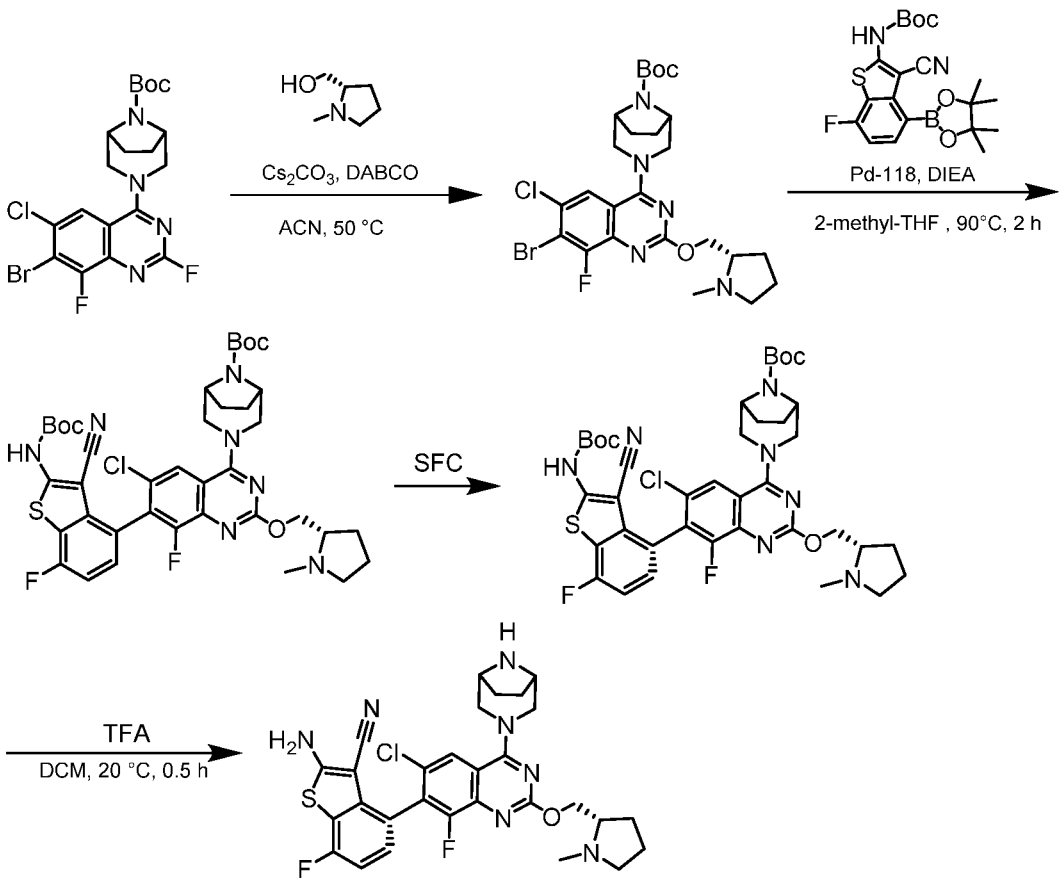


Example 6

[0276] To a solution of *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2R)-2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (18 mg, 0.02 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent to give a residue. The residue was purified by preparative high layer chromatography (column: Unisil 3-100 C18 Ultra 150*50mm*3 um;mobile phase: [water(FA)-ACN];B%: 3%-33%,10min) to give the desired product

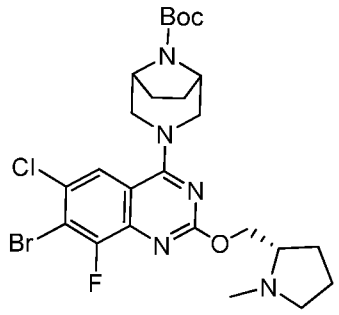
(6.05 mg, 0.01 mmol, 41% yield, 100% purity, formate[1]) as a white solid. LCMS (ESI, m/z): 626.2 $[M]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.18 (s, 1H), 8.10 (s, 2H), 7.85 (s, 1H), 7.27 (dd, J = 5.2, 8.4 Hz, 1H), 7.18 - 7.13 (m, 1H), 4.33 - 4.24 (m, 4H), 3.64 (d, J = 5.6 Hz, 5H), 2.83 - 2.76 (m, 3H), 2.42 (s, 3H), 2.03 - 1.97 (m, 1H), 1.81 (dd, J = 2.8, 8.0 Hz, 1H), 1.71 - 1.66 (m, 4H), 1.26 - 1.23 (m, 4H).

[0277] Synthesis of 4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile **(Example 7)**



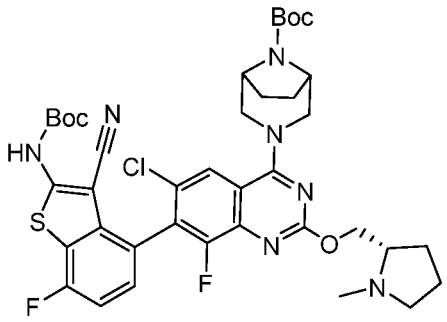
Example 7

[0278] **Step 1**: *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



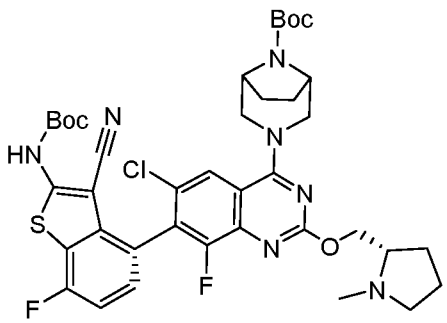
[0279] To a solution of *tert*-butyl 3-(7-bromo-6-chloro-2,8-difluoro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.2 mmol, 1 *eq*) and [(2S)-1-methylpyrrolidin-2-yl]methanol (23 mg, 0.2 mmol, 1 *eq*) in acetonitrile (5 mL) was added *N*,*N*-diisopropylethylamine (79 mg, 0.6 mmol, 3 *eq*). The mixture was stirred at 70 °C for 12 h. Thin layer chromatography (dichloromethane: methanol = 10:1) showed the starting material was consumed completely. Water (10 mL) was added before the mixture was extracted by ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate concentrated and purified by prep-TLC (9% methanol in dichloromethane) to afford the title compound (51 mg, 0.05 mmol, 26% yield) as a white solid. LCMS (ESI, m/z): 584.1, 586.1[M+1]$^+$. ^{1}H NMR (400 MHz, DMSO) δ = 7.97 (s, 1H), 4.33 (d, *J* = 11.6 Hz, 2H), 4.21 (s, 2H), 4.10 (d, *J* = 4.4 Hz, 2H), 3.62 - 3.49 (m, 2H), 3.17 (d, *J* = 3.6 Hz, 6H), 2.27 - 2.15 (m, 1H), 2.00 - 1.89 (m, 1H), 1.77 (s, 2H), 1.70 - 1.61 (m, 4H), 1.45 (s, 9H).

[0280] **Step 2**: *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



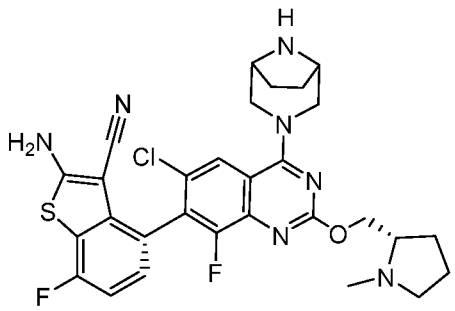
[0281] A mixture of *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.08 mmol, 1 *eq*), *tert*-butyl N-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate (50 mg, 0.1 mmol, 1.4 *eq*), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (6 mg, 0.01 mmol, 0.1 *eq*), *N*,*N*-diisopropylethylamine (33 mg, 0.26 mmol, 3 *eq*) in tetrahydrofuran (4 mL) and water (1 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 70 °C for 2 h under nitrogen atmosphere. Thin layer chromatography (dichloromethane: methanol = 10:1) and LCMS showed the starting material was consumed completely. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by prep-TLC (9% methanol in dichloromethane) to afford the desired product (30 mg, 0.03 mmol, 38% yield) as a yellow solid. LCMS (ESI, m/z): 438.4 $[M+1]^+$.

[0282] **Step 3**: *tert*-butyl (3-((R)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



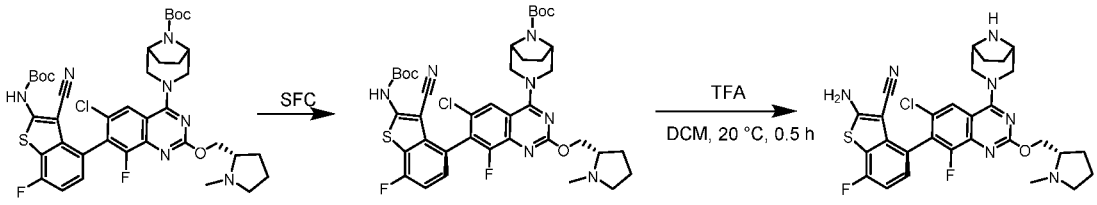
[0283] The mixture of atropisomers *tert*-butyl (3-((R)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl (3-((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (177 mg, 0.22 mmol, 1 eq) was separated by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1% ammonium hydroxide ethanol]; B%: 30%-30%, 5.9 min), and the first eluent was identified as the desired atropisomer *tert*-butyl (3-((R)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (61 mg, 0.7 mmol, 34% yield) as a white solid.

[0284] **Step 4**: 4-((R)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



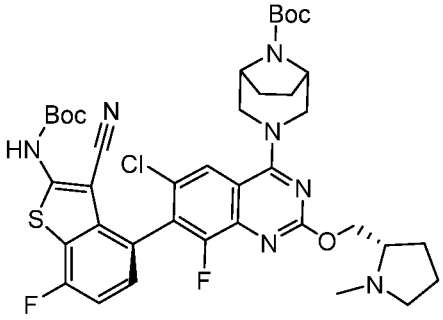
Example 7

[0285] Synthesis of 4-((S)-4-((3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile **(Example 8)**



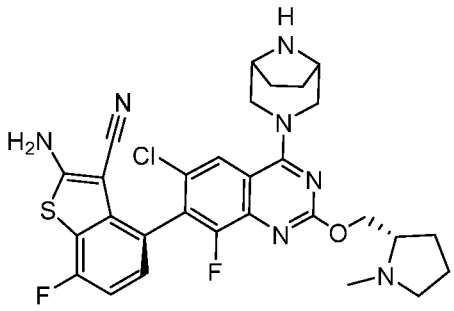
Example 8

[0286] **Step 1**: *tert*-butyl (3-((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0287] The mixture of atropisomers *tert*-butyl (3-((R)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl (3-((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (177 mg, 0.22 mmol, 1 eq) was separated by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1% ammonium hydroxide ethanol]; B%: 30%-30%, 5.9 min), and the second eluent was identified as the desired atropisomer *tert*-butyl (3-((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (67 mg, 0.08 mmol, 38% yield) as a white solid.

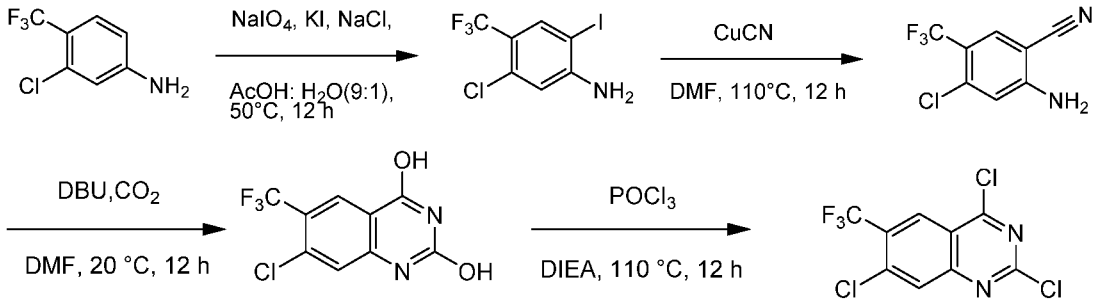
[0288] **Step 2**: 4-((S)-4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile

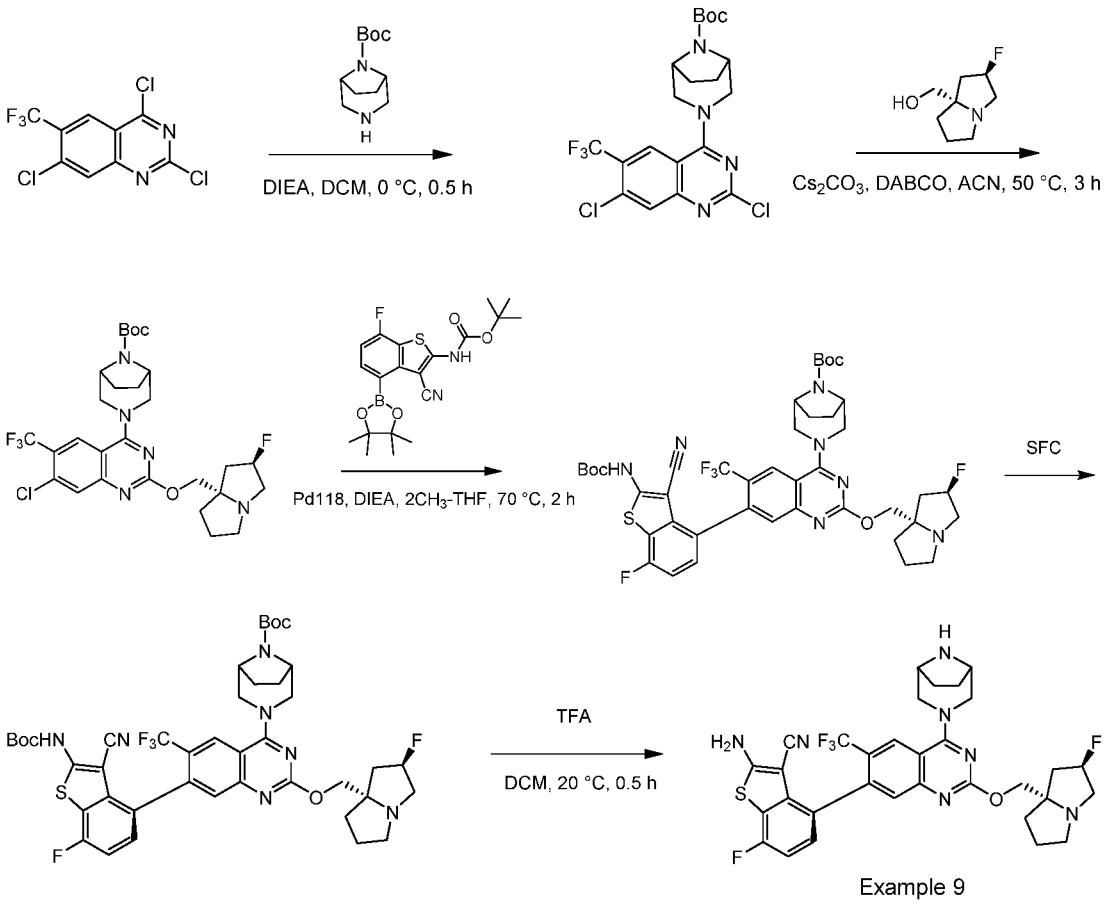


Example 8

[0289] To a solution of *tert*-butyl (3-((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (67 mg, 0.08 mmol, 1 *eq*) in dichloromethane (2 mL) was added trifluoroacetic acid (719. mg, 6 mmol, 75 *eq*). The mixture was stirred at 20 °C for 0.5 h. HPLC showed the starting material was consumed completely. The reaction mixture was bubbled by nitrogen gas to remove dichloromethane. The residue was purified by preparative high layer chromatography (column: Phenomenex Synergi C18 150*25mm* 10um; mobile phase: [water (formic acid) - acetonitrile]; B%: 3%-33%,10min) to afford the desired product (36 mg, 0.06 mmol, 72% yield) as a white solid. LCMS (ESI, m/z): 596.2 $[M]^+$. ^1H NMR (400 MHz, DMSO) δ = 8.15 (d, J = 2.4 Hz, 1H), 8.11 (s, 2H), 7.88 (s, 1H), 7.25 (dd, J = 3.2, 8.0 Hz, 1H), 7.19 - 7.11 (m, 1H), 4.40 (d, J = 11.6 Hz, 2H), 4.33 - 4.29 (m, 1H), 4.25 - 4.22 (m, 1H), 3.83 (d, J = 3.6 Hz, 2H), 3.71 - 3.68 (m, 3H), 3.05 - 3.01 (m, 2H), 2.73 (s, 2H), 2.32 (dd, J = 2.0, 5.6 Hz, 1H), 1.98 (s, 1H), 1.80 - 1.69 (m, 7H)

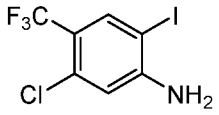
[0290] Synthesis of R-4-(4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile **(Example 9)**





Example 9

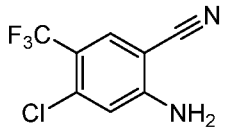
[0291] **Step 1**: 5-chloro-2-iodo-4-(trifluoromethyl)aniline



[0292] To a solution of 3-chloro-4-(trifluoromethyl)aniline (20 g, 102.27 mmol, 1 eq), sodium periodate (21.87 g, 102.27 mmol, 1 eq), sodium chloride (11.95 g, 204.53 mmol, 2 eq) in acetate (360 mL) was slowly added potassium iodide (16.98 g, 102.27 mmol, 1 eq) in water (40 mL). The mixture was stirred at 50 °C for 12 h. The mixture was poured into ice water (1000 mL), and then diluted with ethyl acetate (1000 mL) and washed with saturated aqueous sodium thiosulfate (500 mL x 5). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 1:0 to 20:1) to afford the desired product (32 g, 89.59 mmol, 87%

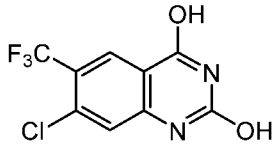
yield, 90% purity) as a brown solid. LCMS (ESI, m/z): 322.0[M+1]$^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 7.83 (s, 1H), 6.88 (s, 1H), 6.21 (s, 2H)

[0293] **Step 2**: 2-amino-4-chloro-5-(trifluoromethyl)benzonitrile



[0294] To a solution of 5-chloro-2-iodo-4-(trifluoromethyl)aniline (8 g, 24.89 mmol, 1 eq) in *N,N*-dimethylformamide (80 mL) was added cuprous cyanide (4.46 g, 49.77 mmol, 2 eq). The mixture was stirred at 110 °C for 12 h. Thin layer chromatography (petroleum ether: ethyl acetate = 3: 1) indicated the starting material was consumed completely. The reaction mixture was diluted with ethyl acetate (1000 mL) and filtered. The filtrate was washed with brine (400 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 30:1 to 10:1) to afford the desired product (9.22 g, crude) as a brown solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 7.92 (s, 1H), 7.07 (s, 2H), 7.00 (s, 1H).

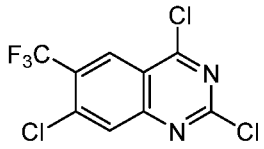
[0295] **Step 3**: 7-chloro-6-(trifluoromethyl)-1H-quinazoline-2,4-dione



[0296] To a solution of 2-amino-4-chloro-5-(trifluoromethyl)benzonitrile (9.3 g, 42.16 mmol, 1 eq) in *N,N*-dimethylformamide (100 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (51.35 g, 337.29 mmol, 8 eq) under carbon dioxide. The mixture was stirred at 20 °C for 12 h under carbon dioxide. Thin layer chromatography (petroleum ether: ethyl acetate = 1: 1) indicated 20% of the starting material was remained, and one major new spot was detected. The reaction mixture was diluted with water (20 mL) and quenched by the addition of aqueous hydrogen chloride (1 M, 15 mL). The mixture was filtered and the filter cake was wash with water (15ml x 3), and concentrated under reduced pressure to get the crude product. The crude product was triturated with the mixed solvent of petroleum ether and ethyl acetate (v/v = 1/1, 40 mL) at

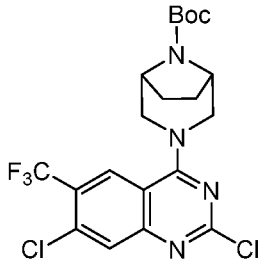
25 °C for 10 min. Then the solution was filtered and the filter cake was collected to afford the desired product (6.2 g, 23.43 mmol, 55% yield) as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 11.74 - 11.55 (m, 2H), 8.15 (s, 1H), 7.36 (s, 1H)

[0297] **Step 4**: 2,4,7-trichloro-6-(trifluoromethyl)quinazoline



[0298] To a solution of 7-chloro-6-(trifluoromethyl)-1H-quinazoline-2,4-dione (2.00 g, 7.56 mmol, 1 eq) in phosphorus oxychloride (25 mL) was slowly added *N*,*N*-diisopropylethylamine (2.93 g, 22.68 mmol, 3 eq) at 25°C. The mixture was stirred at 110 °C for 12 h. Thin layer chromatography (petroleum ether: ethyl acetate = 3: 1) indicated the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 1:0 to 20:1) to afford the desired product (1.66 g, 5.51 mmol, 72% yield) as a white solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 8.34 (s, 1H), 7.97 (s, 1H)

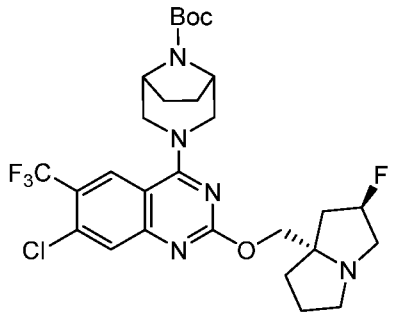
[0299] **Step 5**: *tert*-butyl-3-(2,7-dichloro-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0300] To a solution of 2,4,7-trichloro-6-(trifluoromethyl)quinazoline (1.66 g, 5.51 mmol, 1 eq) in dichloromethane (25 mL) was added *N*,*N*-diisopropylethylamine (2.13 g, 16.52 mmol, 3 eq) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.17 g, 5.51 mmol, 1 eq). The mixture was stirred at 0 °C for 30 min. Thin layer chromatography (petroleum ether: ethyl acetate = 3: 1) indicated the starting material was consumed completely. The reaction mixture was partitioned between dichloromethane (20 mL) and water (20 mL). The organic phase was separated, washed with brine (20 mL x 3), dried

over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with the mixed solvent of petroleum ether and ethyl acetate (v/v = 3/1, 40mL) at 25 °C for 30 min to afford the desired product (2.38 g, 4.99 mmol, 90 % yield) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$-d) δ: 8.17 (s, 1H), 7.90 (s, 1H), 4.57 - 4.26 (m, 4H), 3.87 - 3.49 (m, 2H), 2.03 - 1.88 (m, 2H), 1.80 - 1.65 (m, 2H), 1.53 (s, 9H)

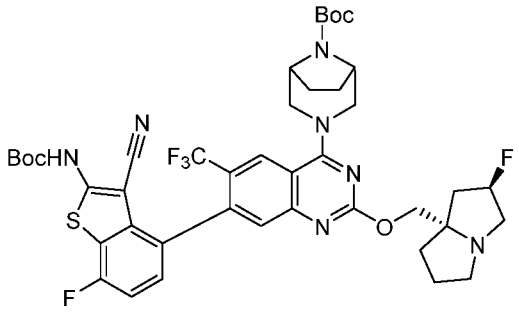
[0301] **Step 6**: *tert*-butyl-3-(7-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0302] To a solution of *tert*-butyl-3-(2,7-dichloro-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (500 mg, 1.05 mmol, 1 eq) and [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (250 mg, 1.58 mmol, 1.5 eq) in acetonitrile (8 mL) was added 1,4-diazabicyclo[2.2.2]octane (12 mg, 0.10 mmol, , 0.1 eq) and cesium carbonate (684 mg, 2.10 mmol, 2 eq). The mixture was stirred at 50 °C for 3 h. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was partitioned between water (20 mL) and ethyl acetate (20 mL). The organic phase was separated, washed with brine (15 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (silicon dioxide, dichloromethane: methanol = 10: 1) to afford the desired product (200 mg, 0.33 mmol, 31% yield) as a white solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.78 (s, 1H), 5.40 - 5.18 (m, 1H), 4.32 - 4.17 (m, 2H), 4.36 (d, J = 12.4 Hz, 2H), 4.14 - 4.08 (m, 1H), 4.06 - 3.99 (m, 1H), 3.57 (d, J = 12.8 Hz, 2H), 3.13 - 2.99 (m, 2H), 2.88 - 2.78 (m, 1H), 2.17 - 1.92 (m, 3H), 1.89 - 1.72 (m, 5H), 1.62 (d, J = 7.6 Hz, 2H), 1.45 (s, 9H)

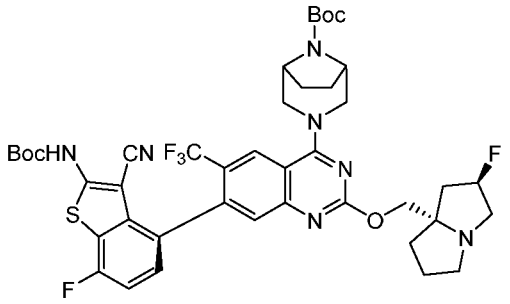
[0303] **Step 7:** *tert*-butyl-3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



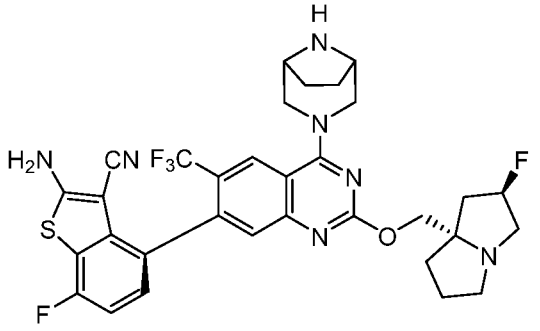
[0304] A mixture of *tert*-butyl-3-(7-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (91 mg, 0.21 mmol, 1.3 eq), *N*,*N*-diisopropylethylamine (64 mg, 0.49 mmol, 3 eq), ditert-butyl(cyclopentyl)phosphane; dichloropalladium;iron (11 mg, 0.016 mmol, 0.1 eq) in tetrahydrofuran (4 mL) and water (1 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 70 °C for 2 h under nitrogen atmosphere. LCMS showed the starting material was consumed completely. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic phase was separated, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative high performance liquid chromatography (column: Phenomenex Synergi C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 34%-64%,10min) to afford the desired product (35 mg, 0.040 mmol, 24 % yield, 99% purity) as a white solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 8.28 (s, 1H), 7.46 (s, 1H), 7.31 - 7.09 (m, 2H), 5.50 - 5.28 (m, 1H), 4.39 (d, J = 12.4 Hz, 2H), 4.33 - 4.14 (m, 4H), 3.73 - 3.56 (m, 2H), 3.34 - 3.29 (m, 4H), 3.07 - 2.90 (m, 1H), 2.31 - 2.08 (m, 3H), 2.03 - 1.76 (m, 5H), 1.71 - 1.57 (m, 2H), 1.46 (d, J = 2.0 Hz, 18H).

[0305] **Step 8**: *tert*-butyl-3-(7-((R)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0306] The mixture of atropisomers *tert*-butyl-3-(7-((R)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl-3-(7-((S)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (45 mg, 0.052 mmol, 1 eq) was separated by SFC(column: DAICEL CHIRALPAK IE(250mm*30mm,10um);mobile phase: [ACN/IPA(0.1%NH_3H_2O)];B%: 70%-70%,10.9min), and the first eluent was identified as the desired atropisomer *tert*-butyl-3-(7-((R)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.023 mmol, 44% yield, 99% purity) as a colorless oil.

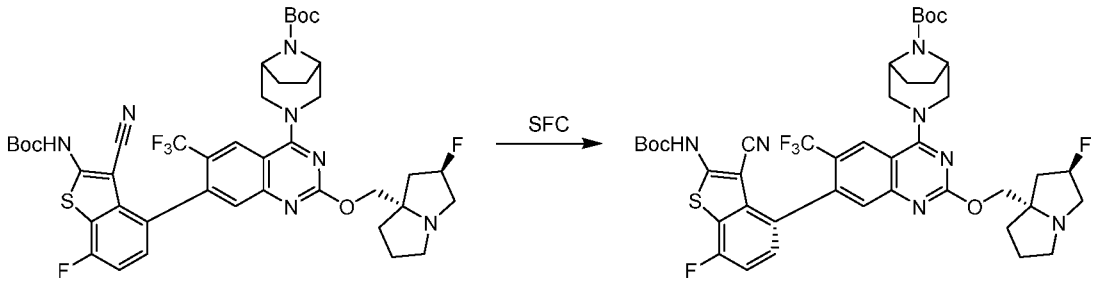
[0307] **Step 9**: R-4-(4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile

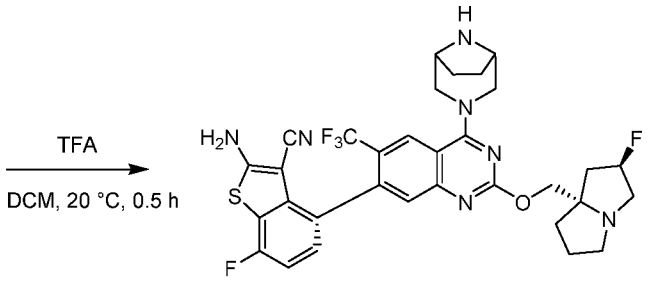


Example 9

[0308] To a solution of *tert*-butyl-3-(7-((R)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.023 mmol, 1 eq) in dichloromethane (5 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol, 578.00 eq). The mixture was stirred at 20 °C for 0.5 h. LCMS showed the starting material was consumed completely. The reaction mixture was bubbled by nitrogen gas to remove dichloromethane at 20 °C. The residue was diluted with *N,N*-dimethylformamide (2 mL), purified by preparative high layer chromatography (column: Phenomenex Synergi C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 7%-37%,10min) to afford the desired product (7.91 mg, 0.012 mmol, 51% yield, 100% purity, formate[1]) as a white solid. LCMS: MS (ESI) *m/z*: 656.3 $[M+1]^+$. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 8.20 (s, 2H), 7.98 (s, 2H), 7.40 (s, 1H), 7.20 (m, J = 5.2, 8.0 Hz, 1H), 7.12 - 7.04 (m, 1H), 5.37 - 5.19 (m, 1H), 4.41 - 4.32 (m, 1H), 4.25 (d, J = 12.4 Hz, 1H), 4.11 - 3.98 (m, 2H), 3.64 - 3.56 (m, 4H), 3.11 - 3.05 (m, 2H), 3.01 (s, 1H), 2.86 - 2.79 (m, 2H), 2.17 - 1.97 (m, 4H), 1.85 - 1.73 (m, 3H), 1.67 (s, 3H), 1.56 (d, J = 2.0 Hz, 1H)

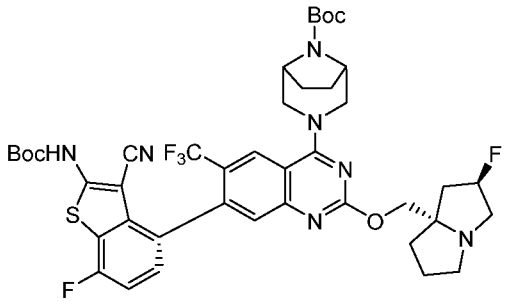
[0309] Synthesis of S-4-(4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile **(Example 10)**





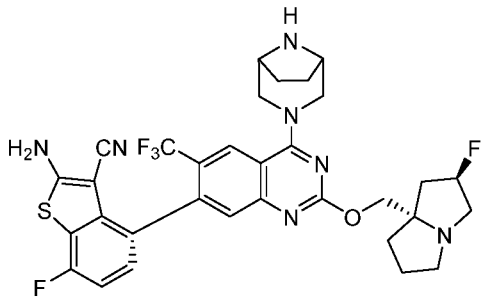
Example 10

[0310] **Step 1**: *tert*-butyl-3-(7-((S)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0311] The mixture of atropisomers *tert*-butyl-3-(7-((R)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl-3-(7-((S)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (45 mg, 0.052 mmol, 1 eq) was separated by SFC(column: DAICEL CHIRALPAK IE(250mm*30mm,10um);mobile phase: [ACN/IPA(0.1%NH3H2O)];B%: 70%-70%,10.9min),and the second eluent was identified as the desired atropisomer *tert*-butyl-3-(7-((S)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.023 mmol, 44% yield, 99% purity) as a colorless oil.

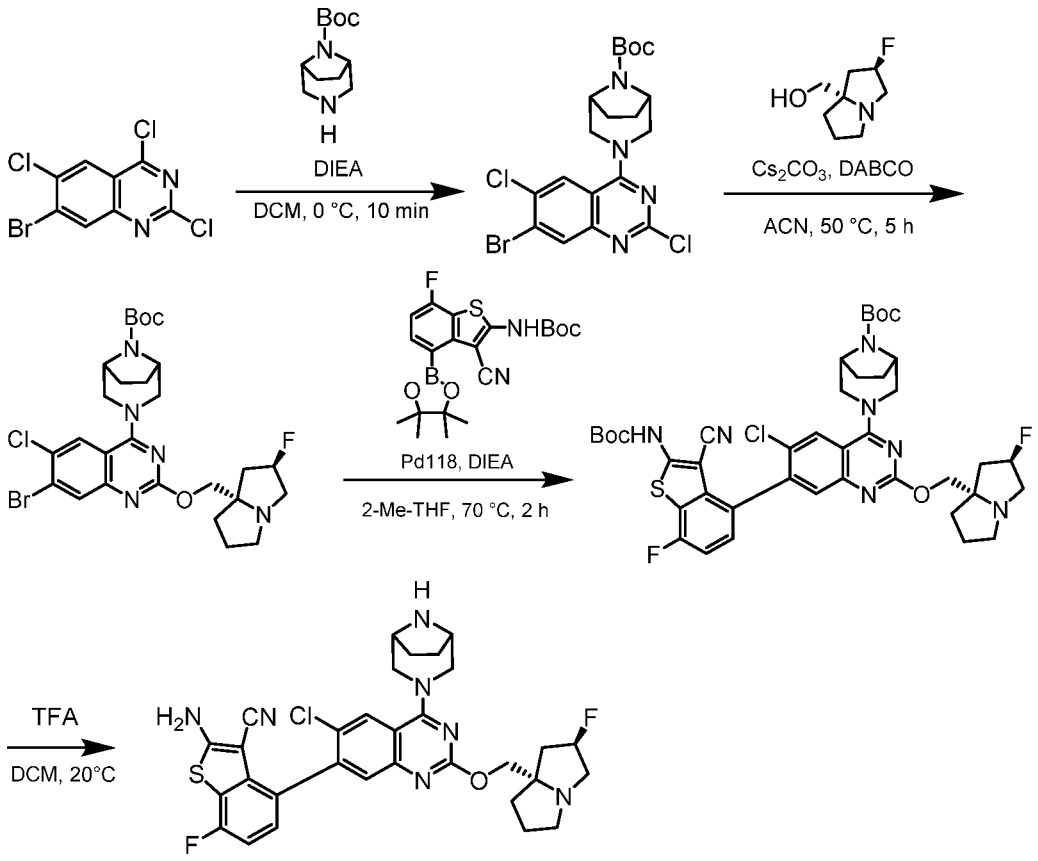
[0312] **Step 2**: S-4-(4-(-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile



Example 10

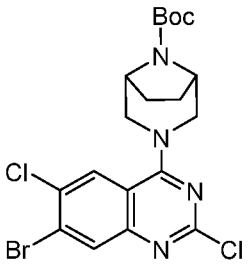
[0313] To a solution of *tert*-butyl-3-(7-((S)-2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.023 mmol, 1 eq) in dichloromethane (5 mL) was added trifluoroacetic acid (1.54 g, 13.51 mmol, 578.00 eq). The mixture was stirred at 20 °C for 0.5 h. LCMS showed the starting material was consumed completely. The reaction mixture was bubbled by nitrogen gas to remove dichloromethane at 20 °C. The residue was diluted with *N,N*-dimethylformamide (2 mL). The residue was purified by preparative high layer chromatography (column: Phenomenex Synergi C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 6%-36%,10min) to afford the desired product (6.82 mg, 0.010 mmol, 44% yield, 100% purity) as a white solid. LCMS: MS (ESI) *m/z*: 656.3 $[M+1]^+$.. ^{1}H NMR: (400 MHz, DMSO-d_6) δ: 8.21 (s, 2H), 7.98 (s, 2H), 7.41 (s, 1H), 7.24 - 7.16 (m, 1H), 7.12 - 7.04 (m, 1H), 5.37 - 5.17 (m, 1H), 4.40 - 4.24 (m, 2H), 4.11 - 3.98 (m, 2H), 3.66 - 3.58 (m, 4H), 3.14 - 3.06 (m, 2H), 3.03 - 2.98 (m, 1H), 2.86 - 2.78 (m, 1H), 2.16 - 1.93 (m, 4H), 1.86 - 1.73 (m, 3H), 1.68 (s, 3H), 1.62 - 1.53 (m, 1H)

[0314] Synthesis of 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile **(Example 11)**



Example 11

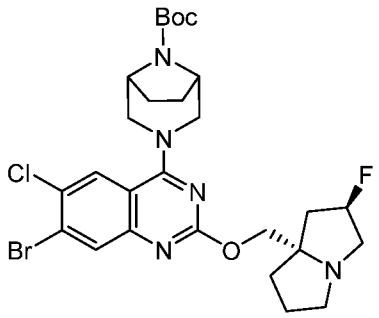
[0315] **Step 1**: *tert*-butyl 3-(7-bromo-2,6-dichloro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0316] To a solution of 7-bromo-2,4,6-trichloro-quinazoline (500 mg, 1.60 mmol, 1 eq) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (340 mg, 1.60 mmol, 1 eq) in dichloromethane (3 mL) was added *N,N*-diisopropylethylamine (621 mg, 4.80 mmol, 3 eq). The mixture was stirred at 0 °C for 10 min. LCMS showed the starting material was consumed completely. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (10 mL),

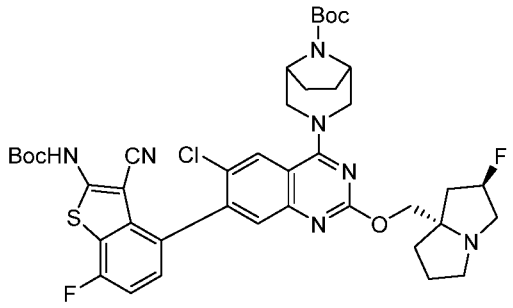
dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 10:1 to 3:1) to afford the desired compound (704 mg, 1.30 mmol, 81 % yield) as a white solid. LCMS (ESI, m/z): 487.2, 489.1 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO) δ = 8.22 (s, 1H), 8.11 (s, 1H), 4.37 (d, *J* = 11.2 Hz, 2H), 4.23 (s, 2H), 3.62 (d, *J* = 12.0 Hz, 2H), 1.77 (d, *J* = 4.4 Hz, 2H), 1.60 (d, *J* = 8.0 Hz, 2H), 1.46 (s, 9H).

[0317] **Step 2**: *tert*-butyl-3-(7-bromo-6-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



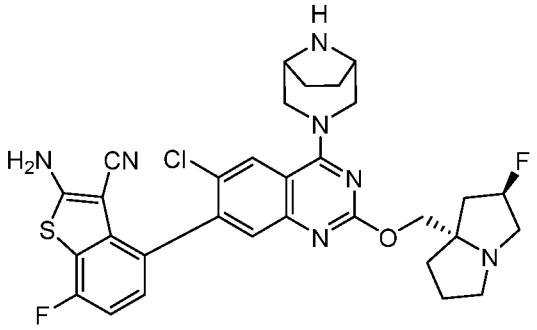
[0318] To a solution of *tert*-butyl 3-(7-bromo-2,6-dichloro-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.8 mmol, 1 eq) and [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (261 mg, 1.64 mmol, 2 eq) in acetonitrile (5 mL) was added cesium carbonate (534 mg, 1.64 mmol, 2 eq) and 1,4-diazabicyclo[2.2.2]octane (9.2 mg, 0.09 mmol, 0.1 eq). The mixture was stirred at 50 °C for 5 h. LCMS showed the starting material was consumed completely. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium and filtered. The filtrate was concentrated and purified by prep-TLC (9% methanol in dichloromethane) to afford the desired product (336 mg, 0.48 mmol, 59% yield) as a white solid. LCMS (ESI, m/z): 610.2, 612.2$[M+1]^+$. ^{1}H NMR (400 MHz, DMSO) δ = 8.07 (s, 1H), 7.92 - 7.90 (m, 1H), 5.38 - 5.17 (m, 1H), 4.31 (d, *J* = 11.6 Hz, 2H), 4.22 (s, 2H), 4.08 (d, *J* = 10.4 Hz, 1H), 4.03 - 3.95 (m, 1H), 3.52 (d, *J* = 12.4 Hz, 2H), 3.16 (s, 2H), 3.11 (d, *J* = 5.2 Hz, 2H), 3.03 (s, 1H), 2.90 - 2.80 (m, 1H), 2.15 - 2.10 (m, 1H), 2.05 (s, 1H), 1.84 - 1.75 (m, 4H), 1.63 (d, *J* = 8.0 Hz, 2H), 1.45 (s, 9H).

[0319] **Step 3**: *tert*-butyl-3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0320] A mixture of *tert*-butyl-3-(7-bromo-6-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (236 mg, 0.39 mmol, 1 eq), *tert*-butyl N-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate (242.37 mg, 579.43 umol, 1.5 eq) , *N*,*N*-diisopropylethylamine (150 mg, 1.16 mmol, 3 eq), ditert-butyl(cyclopentyl)-phosphane;dichloropalladium;iron (25 mg, 0.04 mmol, 0.1 eq) in tetrahydrofuran (2 mL) and water (0.5 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 70 °C for 2 hours under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium and filtered. The filtrate was concentrated and purified by preparative high performance liquid chromatography (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(formic acid)- acetonitrile];B%: 37%-67%,2min) to afford the desired product (272 mg, 0.3 mmol, 86%) as a white solid. LCMS (ESI, m/z): 822.0[M] $^{+}$. ^{1}H NMR (400 MHz, DMSO) δ = 8.14 (s, 1H), 8.05 (s, 1H), 7.53 (s, 1H), 7.24 (s, 2H), 5.49 - 5.28 (m, 1H), 4.49 - 4.36 (m, 1H), 4.35 - 4.12 (m, 5H), 3.72 - 3.62 (m, 1H), 3.58 - 3.48 (m, 1H), 3.30 (s, 4H), 3.06 - 2.94 (m, 1H), 2.24 - 2.17 (m, 1H), 2.16 - 2.08 (m, 1H), 2.02 - 1.77 (m, 5H), 1.72 - 1.63 (m, 2H), 1.47 (s, 18H).

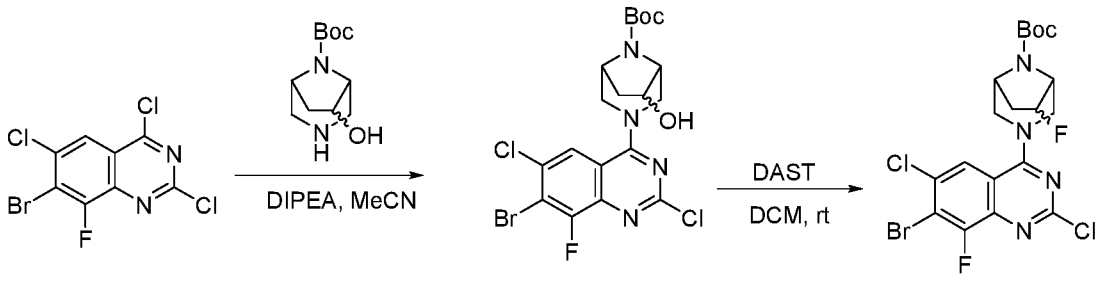
[0321] **Step 4**: 4-(4-(3,8-diazabicyclo[3.2.1]octan-3-yl)-6-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile

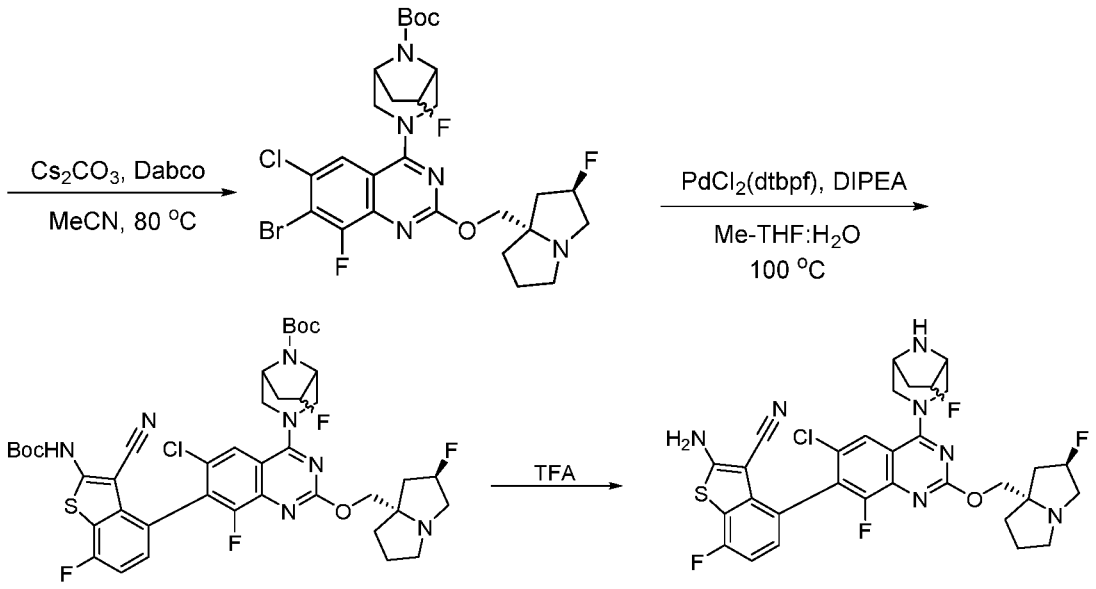


Example 11

[0322] To a solution of *tert*-butyl-3-(7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (116 mg, 0.14 mmol, 1 eq) in dichloromethane (3 mL) was added trifluoroacetic acid (1.21 g, 11 mmol, 75 eq). The mixture was stirred at 25 °C for 1 h. LCMS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by preparative high performance liquid chromatography (column: Phenomenex luna C18 150*25mm* 10 um; mobile phase: [water (formic acid) - acetonitrile]; B%: 0%-30%, 2min) to afford the desired product (44 mg, 0.07 mmol, 49% yield) as a white solid. LCMS (ESI, m/z): 622.3[M] $^{+}$. ^{1}H NMR (400 MHz, DMSO) δ =8.23 - 8.18 (m, 1H), 8.02 (s, 1H), 7.95 (s, 1H), 7.47 (s, 1H), 7.20 (dd, *J* = 5.6, 8.0 Hz, 1H), 7.14 - 7.06 (m, 1H), 5.37 - 5.16 (m, 1H), 4.27 (d, *J* = 13.2 Hz, 2H), 4.06 (d, *J* = 10.4 Hz, 1H), 3.97 (dd, *J* = 2.8, 10.4 Hz, 1H), 3.63 - 3.54 (m, 6H), 3.11 - 3.06 (m, 2H), 3.01 (s, 1H), 2.82 (dd, *J* = 8.4, 14.8 Hz, 2H), 2.15 - 2.09 (m, 1H), 2.05 (s, 1H), 1.99 (s, 1H), 1.78 (dd, *J* = 7.6, 12.4 Hz, 2H), 1.66 (s, 3H).

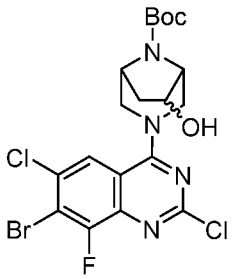
[0323] Synthesis of 2-amino-4-[6-chloro-8-fluoro-4-(6-fluoro-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile **(Example 12)**





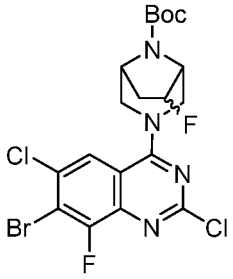
Example 12

[0324] **Step 1**: *tert*-butyl 3-[7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



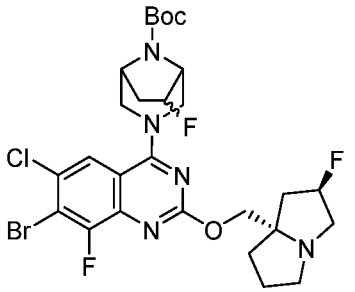
[0325] To a solution of 7-bromo-2,4,6-trichloro-8-fluoro-quinazoline (732.26 mg, 2.216 mmol, 1.10 *eq*) and *tert*-butyl 6-hydroxy-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (460 mg, 2.015 mmol, 1.00 *eq*) in acetonitrile (10 mL) was added *N,N*-diisopropylethylamine (1.06 mL, 6.045 mmol, 3.00 *eq*). The resulting solution was stirred at room temperature for 1 hour before concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography eluted by dichloromethane: ethyl acetate to give the desired product (720 mg, 1.3788 mmol, 68.43% yield). LCMS (ESI, m/z): 523.0 $[M+1]^+$.

[0326] **Step 2**: *tert*-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-quinazolin-4-yl)-6-fluoro-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



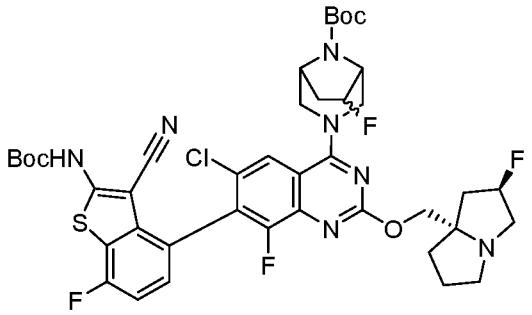
[0327] To a solution of tert-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-quinazolin-4-yl)-6-hydroxy-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, 0.766 mmol, 1.00 *eq*) in dichloromethane (5 mL) was added diethylaminosulfur trifluoride (740.82 mg, 4.5959 mmol, 6.00 *eq*). The resulting solution was stirred at room temperature for 30 min before concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography eluted by hexanes: ethyl acetate to give the desired product (210 mg, 0.401 mmol, 52.31% yield). LCMS (ESI, m/z): 525.1[M+1]$^+$.

[0328] **Step 3**: *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[rac-(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-6-fluoro-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



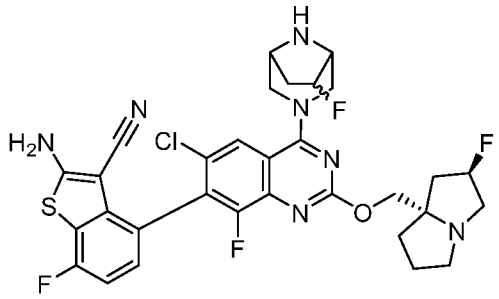
[0329] A mixture of *tert*-butyl 3-(7-bromo-2,6-dichloro-8-fluoro-quinazolin-4-yl)-6-fluoro-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (210 mg, 0.400 mmol, 1.00 *eq*), [(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (191.34 mg, 1.202 mmol, 3.00 *eq*), caesium carbonate (391.59 mg, 1.2019 mmol, 3.00 *eq*), and 1,4-diazabicyclo[2.2.2]octane (134.81 mg, 1.2019 mmol, 3.00 *eq*) was stirred at 80 °C for 1 hour. After cooling down, the mixture was concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography eluted by dichloromethane: methanol to give the impure product, which was further purified by prep-HPLC (acetonitrile/water/1% formic acid) to give the desired product (75 mg, 0.1159 mmol, 28.94% yield) as a light-yellow solid. LCMS (ESI, m/z): 646.1 [M+1]$^+$.

[0330] **Step 4:** *tert*-butyl 3-[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-6-fluoro-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0331] A mixture of *tert*-butyl 3-[7-bromo-6-chloro-8-fluoro-2-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-6-fluoro-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (45 mg, 0.070 mmol, 1.00 *eq*), *tert*-butyl N-[3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzothiophen-2-yl]carbamate (58.2 mg, 0.139 mmol, 2.00 *eq*), [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (10 mg, 0.0139 mmol, 0.20 *eq*) in 2-methyltetrahydrofuran (4 mL) and water (1 mL) under nitrogen atmosphere was added *N*,*N*-diisopropylethylamine (0.06 mL, 0.347 mmol, 5.00 *eq*). The resulting mixture was stirred at 100 °C for 30 minutes. After cooling down, the mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (acetonitrile/water/1% formic acid) to give the desired product (15.03 mg, 0.0175 mmol, 25.17% yield) as a light-yellow solid. LCMS (ESI, m/z): 858.3 $[M+1]^+$.

[0332] **Step 5**: 2-amino-4-[6-chloro-8-fluoro-4-(6-fluoro-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile



Example 12

[0333] To a solution of *tert*-butyl 3-[7-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-6-chloro-8-fluoro-2-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-4-yl]-6-fluoro-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (12.03 mg, 0.014 mmol, 1.00 *eq*) at room temperature was added trifluoroacetic acid (1.0 mL) slowly. The mixture was stirred for 30 min before concentrated under reduced pressure to give a residue which was purified by prep-HPLC (acetonitrile/water/1% formic acid) to give the desired product (4.80 mg, 0.0073 mmol, 52.17% yield) as a light-yellow solid. LCMS (ESI, m/z): 658.2 $[M+1]^+$. ^1H NMR: (400 MHz, CD_3OD) δ 8.00 (d, 1H), 7.13 (m, 1H), 6.96 (t, 1H), 5.52-5.43 (m, 2H), 4.58-4.18 (m, 5 H), 3.92-3.80 (m, 5H), 3.40-3.35 (m, 1H), 2.62-222 (m, 8H), 1.25-1.18 (m, 1H).

B. Assays & Activity Data

[0334] KRAS G12D and Wild-type KRAS enzyme assays were carried out as follows:

KRAS G12D and Wild-type KRAS- In-Vitro RAS-RAF Binding Assay (RRB)

[0335] Biotinylated KRAS protein amino acids 1-169 (produced at Erasca) was labeled with streptavidin-terbium (lanthanide cryptate donor fluorophore) in assay buffer (50 mM HEPES, pH 7.5, 100 mM NaCl, 1 mM $MgCl_2$, 1 mM DTT) at a final concentration of 30nM. In a separate reaction mixture, 30nM cRAF (RBD) (Abcam, Cambridge MA) was labeled with anti-GST d2 (acceptor fluorophore). Labeling reactions were incubated for one hour at room temperature.

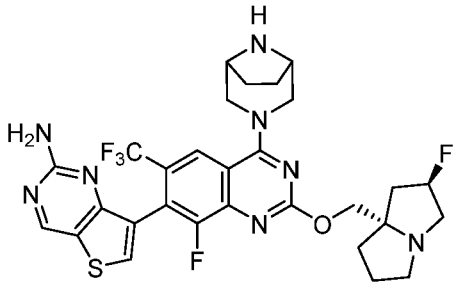
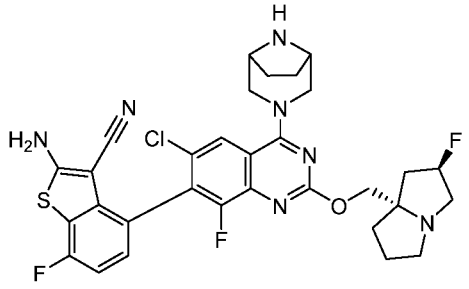
[0336] Compounds of interest were incubated with the labeled-KRAS for 60 minutes at room temperature at a final DMSO concentration of 5% in a black ½ area microtiter plate (50 µL final reaction volume). Following the compound incubation, SOS1 catalytic domain (produced at Erasca) and GTPgS were added to the reaction to initiate nucleotide exchange (60 minutes exchange reaction). Once in the GTP state KRAS will bind to

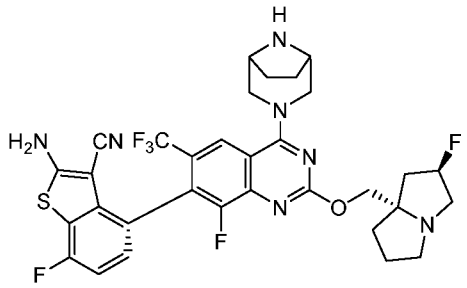
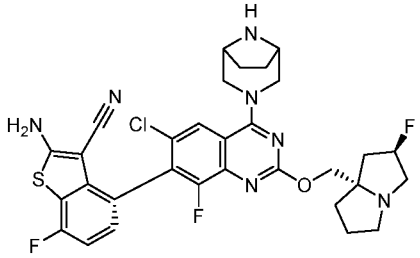
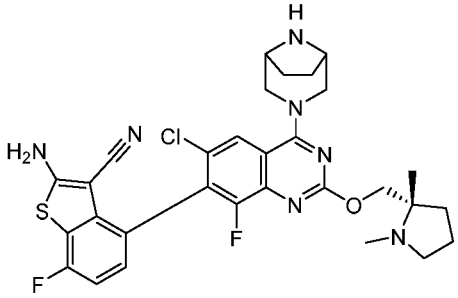
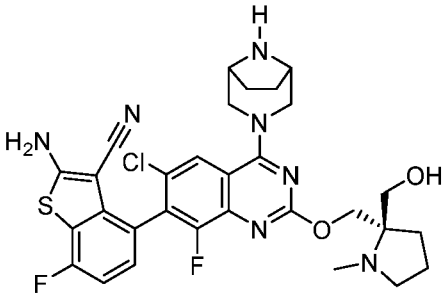
cRAF. No binding will occur if KRAS remains in the GDP state. Compounds may block nucleotide exchange or may create a steric obstruction to cRAF-KRAS interaction by binding to the RAS effector site.

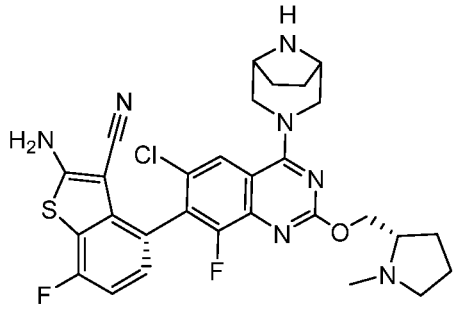
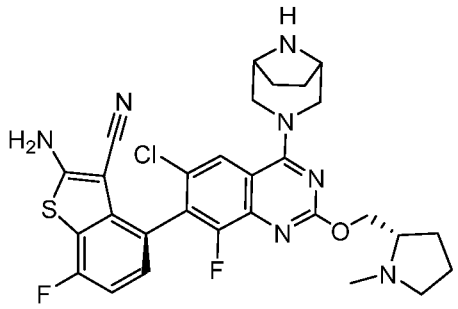
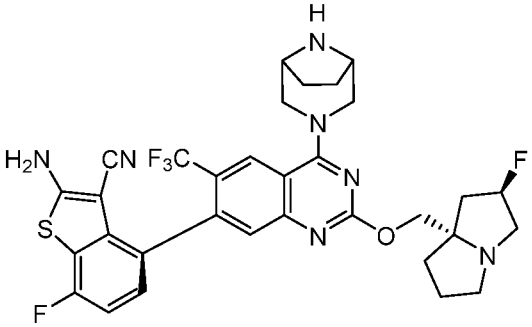
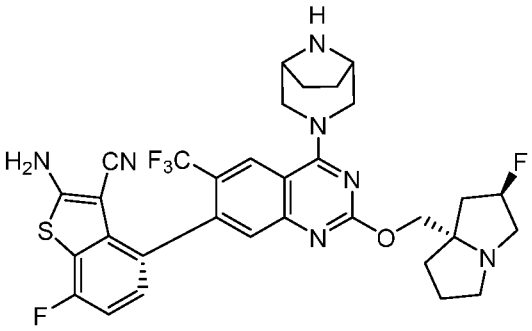
[0337] Following the exchange reaction, the labeled KRAS and cRAF were mixed in equal volume (30 µL each) and incubated for 30-60 minutes at room temperature. A portion of this mixture was transferred to a white 384-well plate (20 µL per well in duplicate) and read on an HTRF compatible plate reader (ClarioSTAR). Fluorescent resonance energy transfer (FRET) was measured at equilibrium. FRET signal will be high if KRAS-cRAF binding occurs. FRET signal will be low if KRAS-cRAF binding is inhibited by the test compound. The results for exemplary compounds are shown below in **Table 1**.

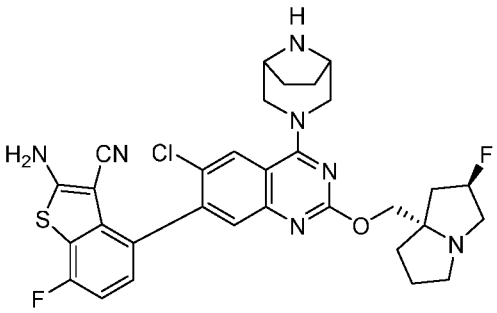
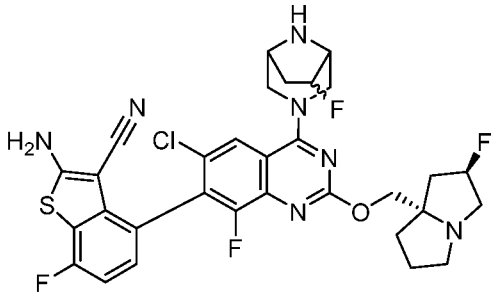
Table 1

Inhibition of RAS-RAF Binding (*in-vitro*)

Compound	KRAS (WT) IC_{50} (nM)	KRAS (G12D) IC_{50} (nM)
 Example 1	>10,000	45
 Example 2	35	12

 Example 3	12	8
 Example 4	14	8
 Example 5	76	21
 Example 6	55	11

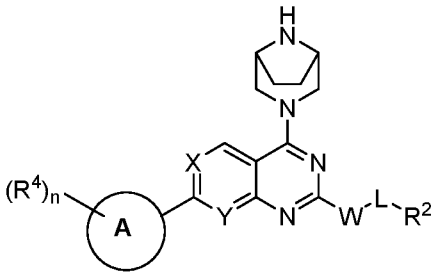
 Example 7	1862	440
 Example 8	19	8
 Example 9	50	20
 Example 10	25	11

 Example 11	31	10
 Example 12	43	18

[0338] Although the foregoing embodiments have been described in some detail by way of illustration and Example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

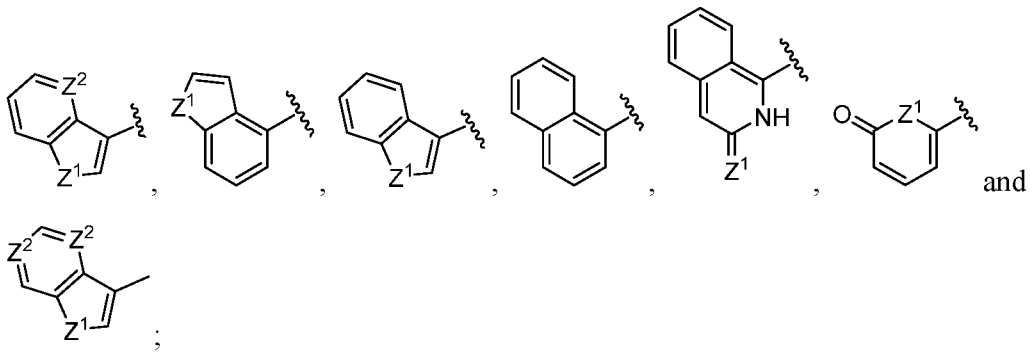
1. A compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

ring A is selected from



;

W is O, NR^3, S, or absent;

X is CR^1 or N;

Y is CR^1 or N;

Z^1 is O, N(C_1-C_4 alkyl), NH, or S;

each Z^2 is independently CH or N;

L is C_{1-3} alkyl or absent;

each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl;

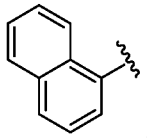
R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

R^3 is H or C_{1-4} alkyl;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, -NH_2; and,

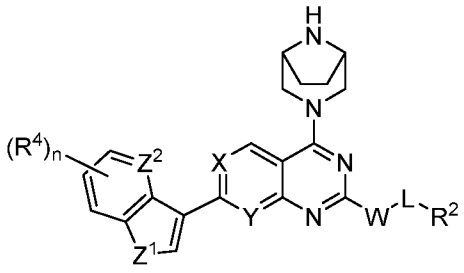
n is 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein when X is N, ring A is not



.

3. The compound of claim 1 having Formula (Ia):



(Ia)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

W is O, NR^3, S, or absent;

X is CR^1 or N;

Y is CR^1 or N;

Z^1 is O, N(C_1-C_4 alkyl), NH, or S;

Z^2 is CH or N;

L is C_{1-3} alkyl or absent;

each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl;

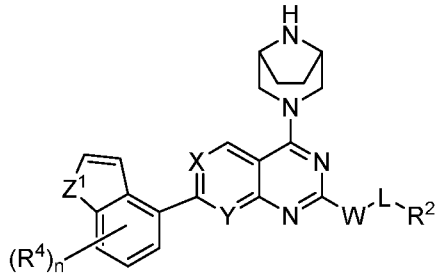
R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

R^3 is H or C_{1-4} alkyl;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, -NH_2; and,

n is 0, 1, 2, 3, or 4.

4. The compound of claim 1 having Formula (Ib):



(Ib)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

W is O, NR^3, S, or absent;

X is CR^1 or N;

Y is CR^1 or N;

Z^1 is O, N(C_1-C_4 alkyl), NH, or S;

L is C_{1-3} alkyl or absent;

each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl;

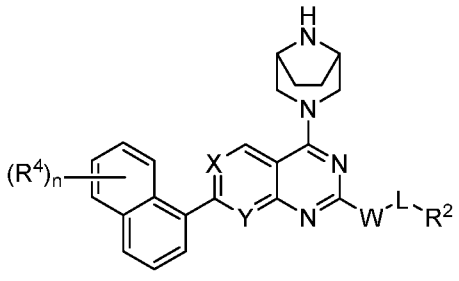
R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

R^3 is H or C_{1-4} alkyl;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, -NH_2; and,

n is 0, 1, 2, 3, or 4.

5. The compound of claim 1 having Formula (Ic)



(Ic)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

W is O, NR^3, S, or absent;

X is CR^1;

Y is CR^1 or N;

L is C_{1-3} alkyl or absent;

each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl;

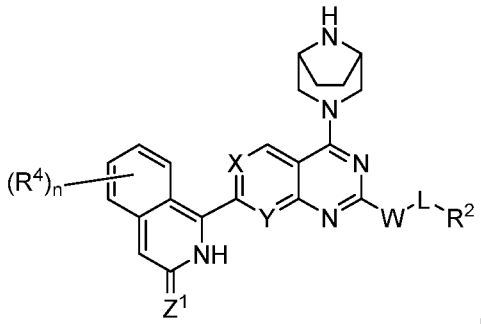
R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

R^3 is H or C_{1-4} alkyl;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, $-NH_2$; and,

n is 0, 1, 2, 3, or 4.

6. The compound of claim 1 having Formula (Id)



(Id)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

W is O, NR^3, S, or absent;

X is CR^1 or N;

Y is CR^1 or N;

Z^1 is O, N(C_1-C_4 alkyl), NH, or S;

L is C_{1-3} alkyl or absent;

each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl;

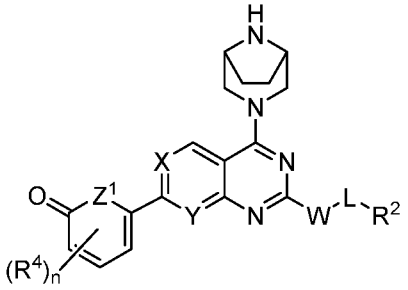
R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

R^3 is H or C_{1-4} alkyl;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, $-NH_2$; and,

n is 0, 1, 2, 3, or 4.

7. The compound of claim 1 having Formula (Ie)



(Ie)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

W is O, NR^3, S, or absent;

X is CR^1 or N;

Y is CR^1 or N;

Z^1 is O, N(C_1-C_4 alkyl), NH, or S;

L is C_{1-3} alkyl or absent;

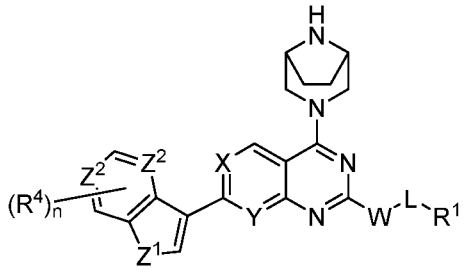
each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, -NH_2; and,

n is 0, 1, 2, 3, or 4.

8. The compound of claim 1 having Formula (If):



(If)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof, wherein:

W is O, NR^3, S, or absent;

X is CR^1 or N;

Y is CR^1 or N;

Z^1 is O, N(C_1-C_4 alkyl), NH, or S;

each Z^2 is independently CH or N;

L is C_{1-3} alkyl or absent;

each R^1 is independently H, halo, C_{1-6} alkyl or C_{3-6} cycloalkyl;

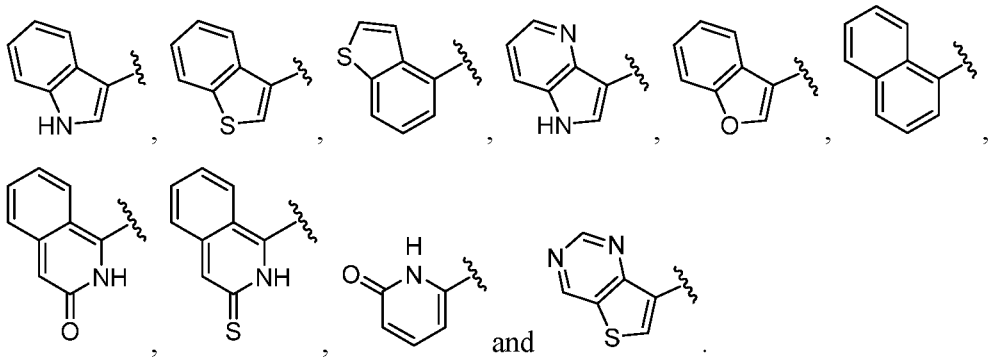
R^2 is 4-10 membered heterocyclyl, 3-10 membered cycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl, wherein said heterocyclyl, cycloalkyl, aryl and heteroaryl are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH;

R^3 is H or C_{1-4} alkyl;

each R^4 is independently selected from -OH, halo, C_{1-3} alkyl, C_2-C_4 alkynyl, C_{1-3} haloalkyl, -CN, -NH_2; and,

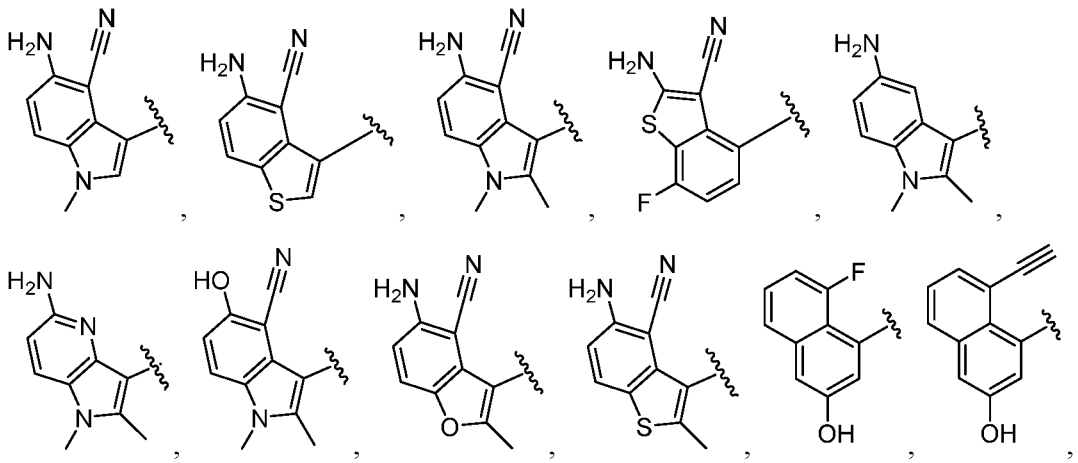
n is 0, 1, 2, 3, or 4.

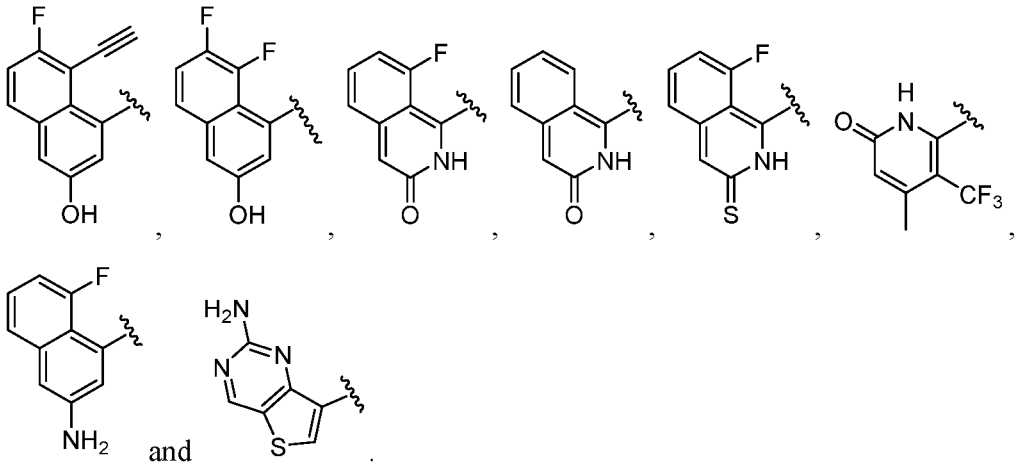
9. The compound of claim 1, wherein ring A is selected from:



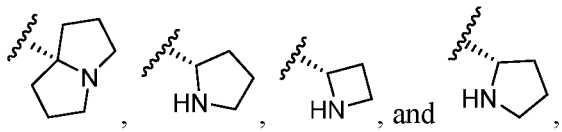
and

10. The compound of claim 1, wherein n is 1, 2, 3, or 4 and ring A is selected from:



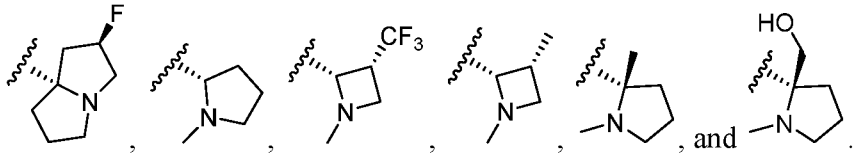


11. The compound of claim 1, wherein R^2 is selected from:

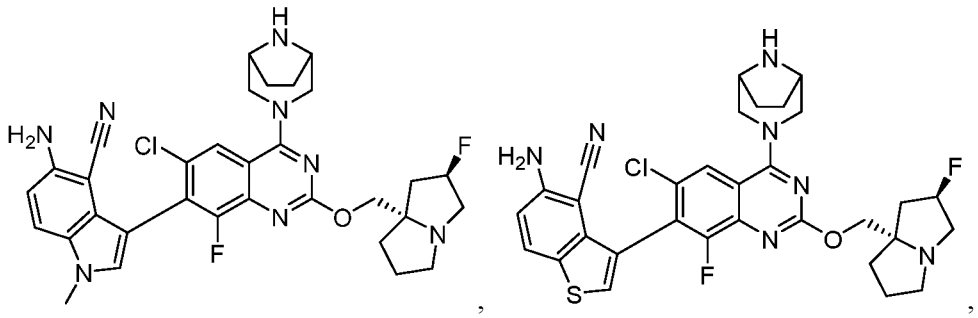


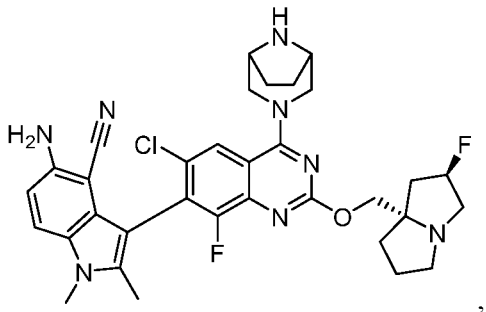
wherein each are optionally substituted with OH, halo, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-3} alkyl-OH.

12. The compound of claim 1, wherein R^2 is selected from:



13. A compound selected from:

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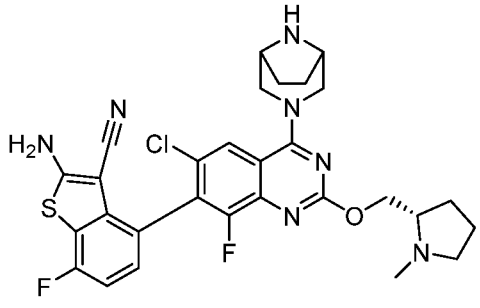
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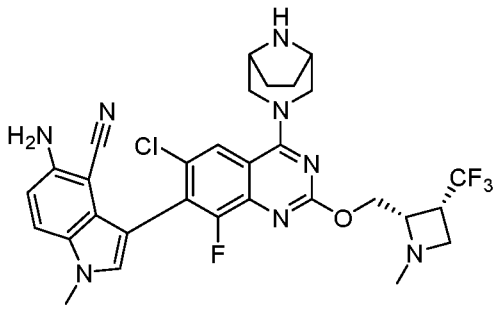
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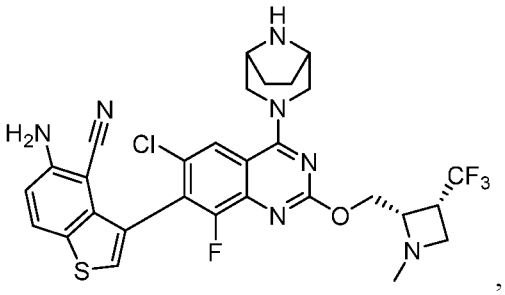
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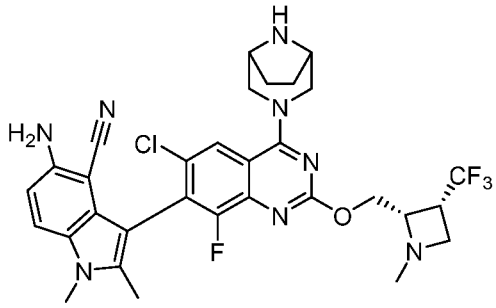
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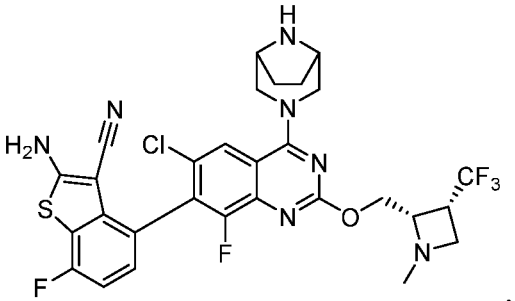
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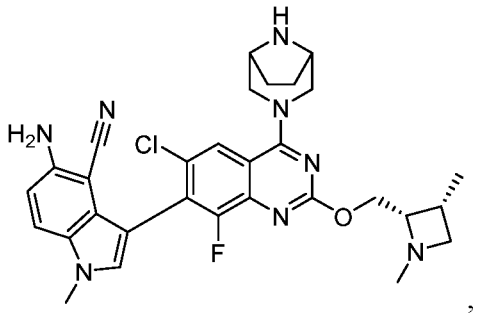
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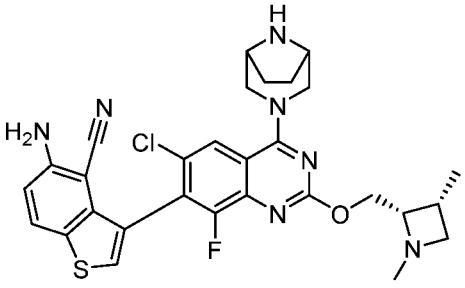
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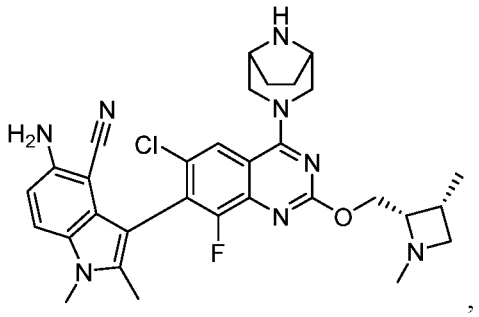
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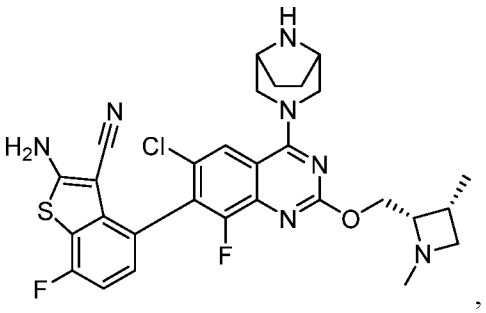

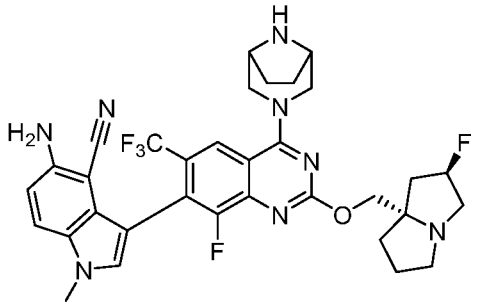
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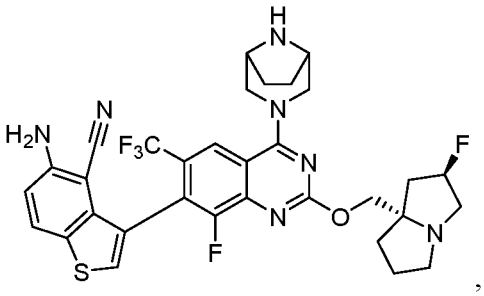
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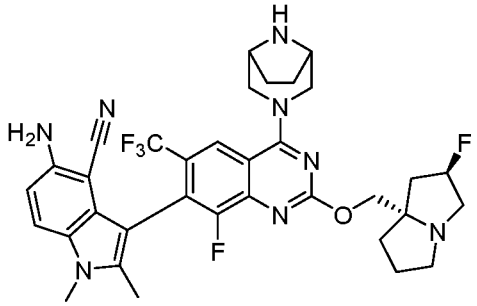
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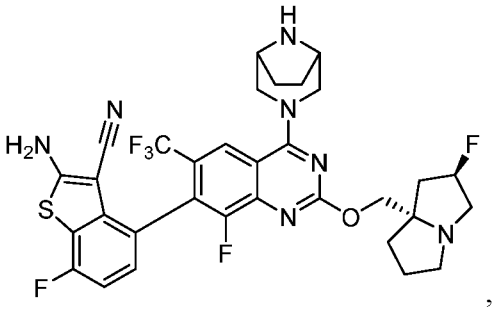
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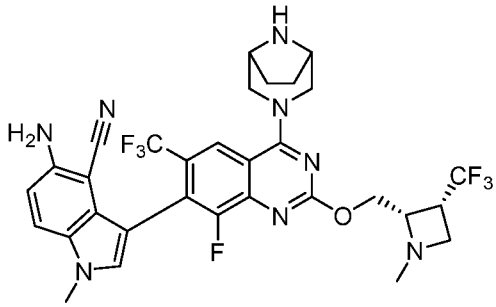
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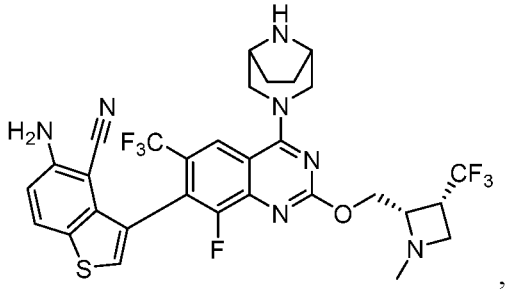
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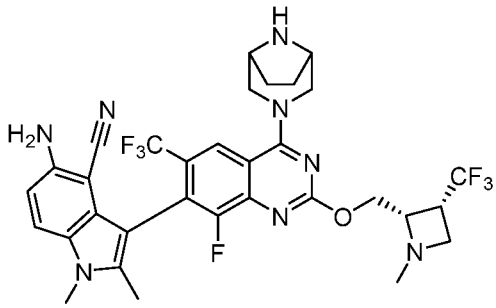
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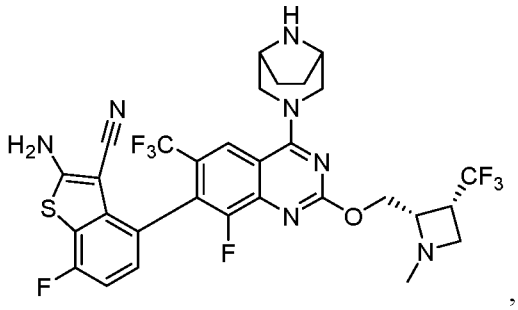
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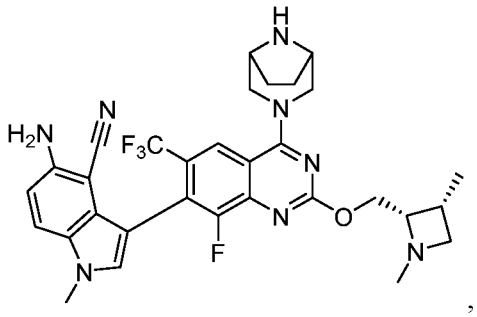
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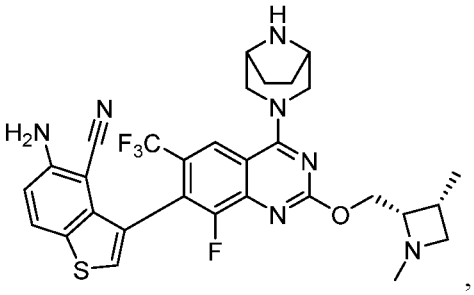
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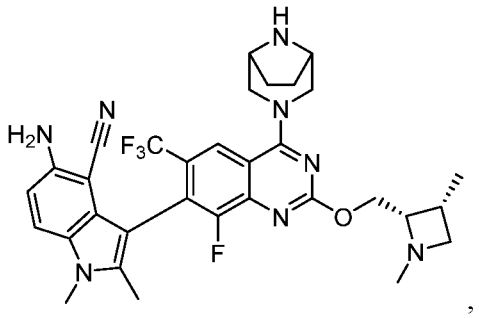
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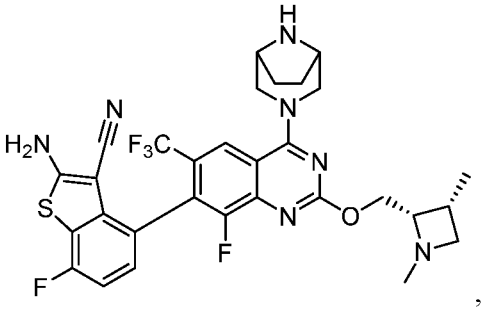
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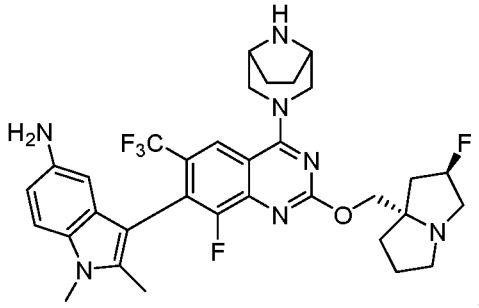
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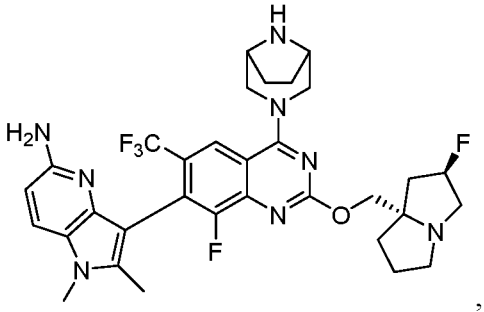
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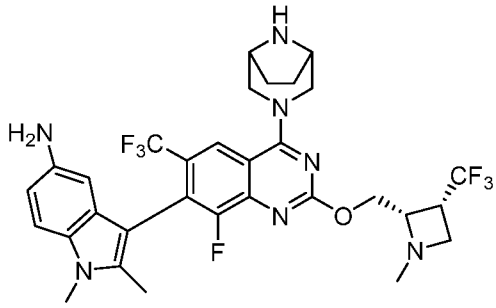
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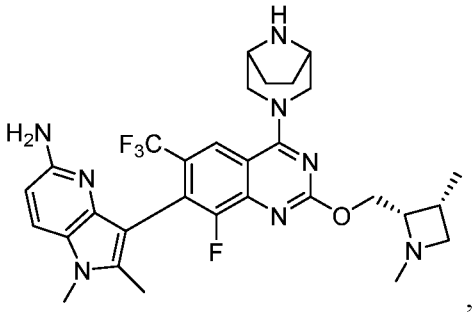
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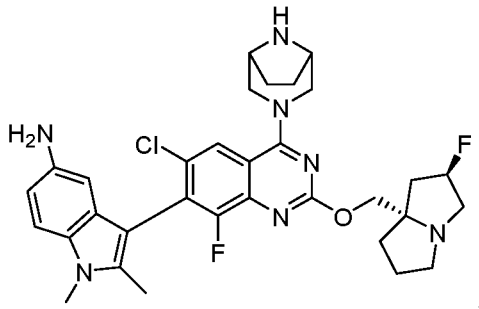
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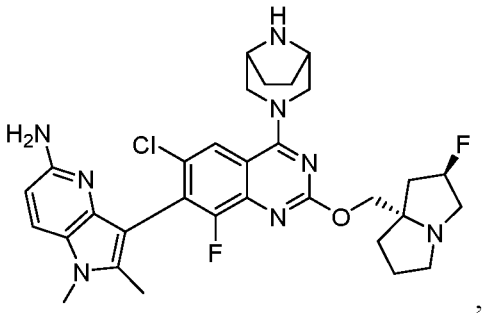
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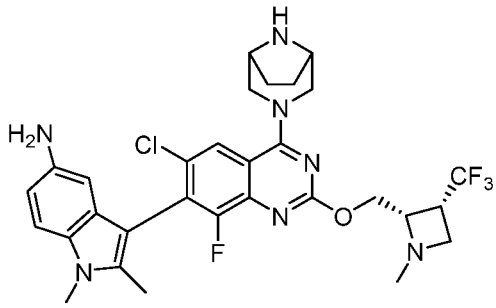
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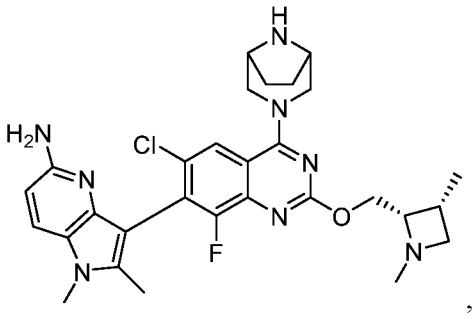
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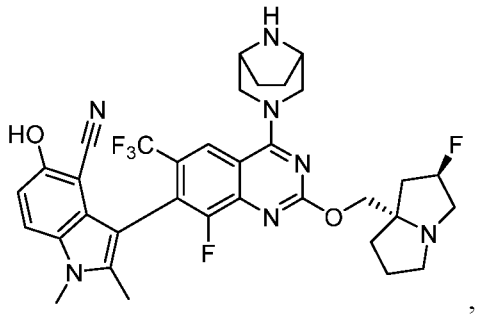
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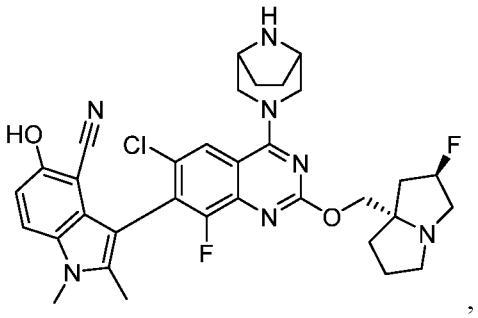
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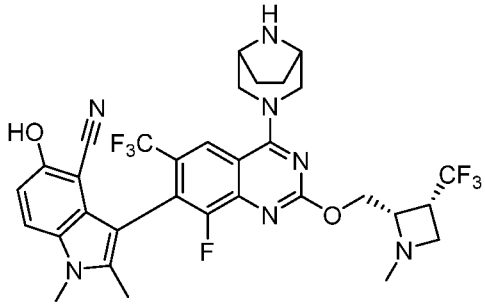
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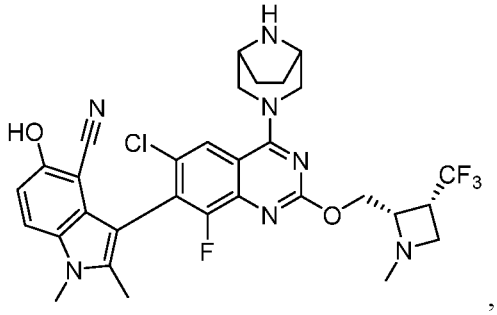
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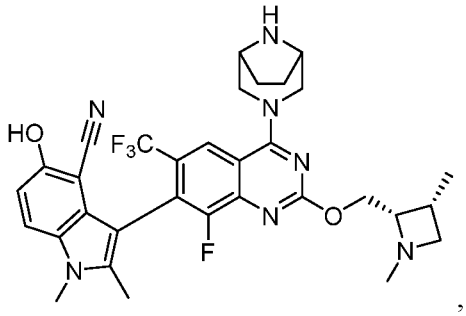
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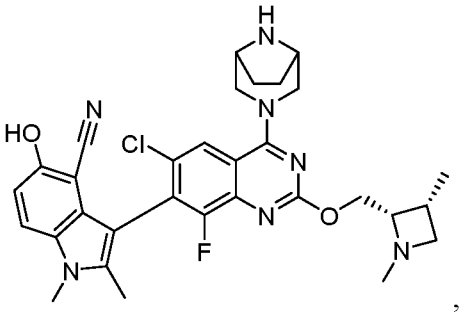
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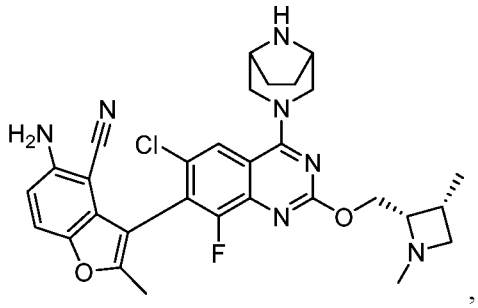
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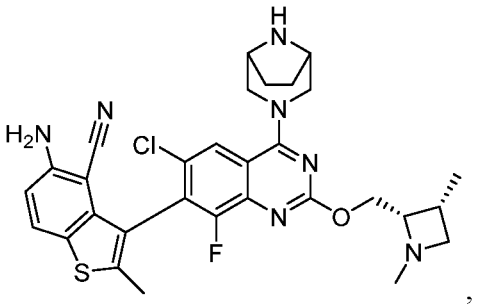
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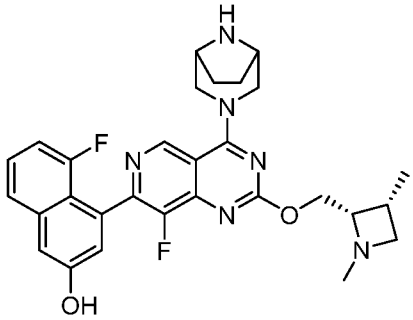
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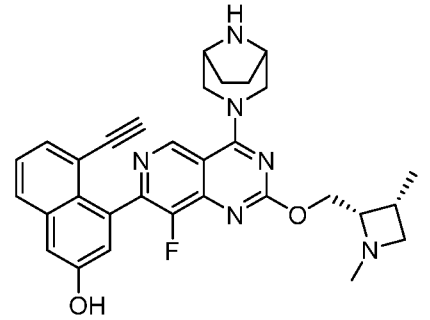
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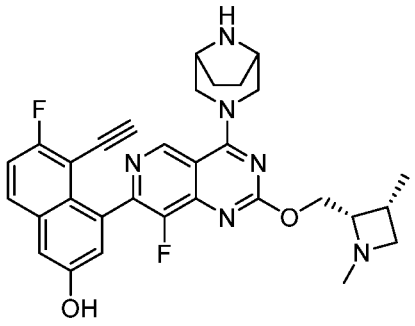
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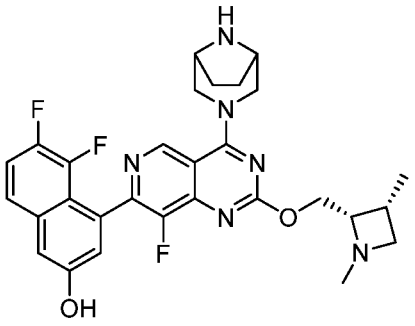
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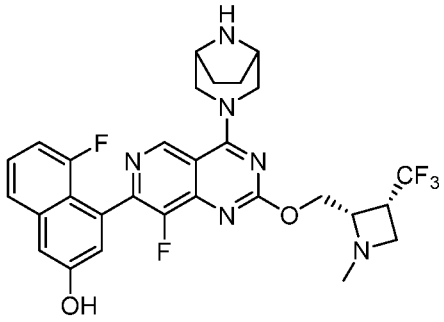
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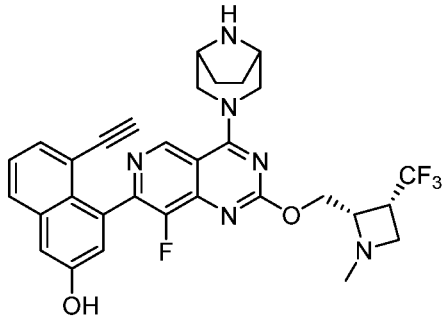
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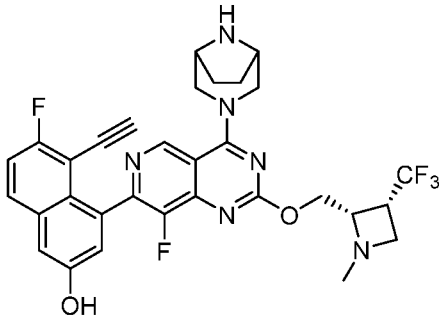
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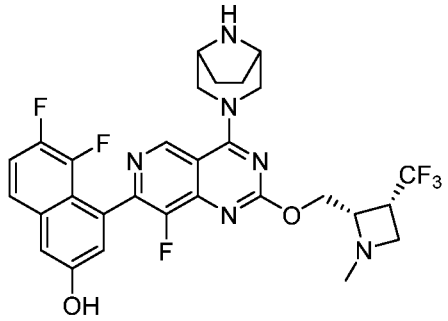
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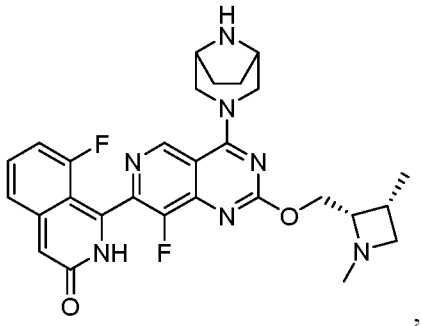
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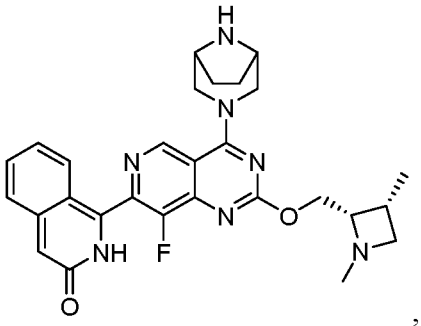
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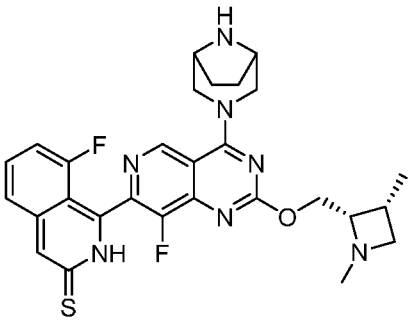
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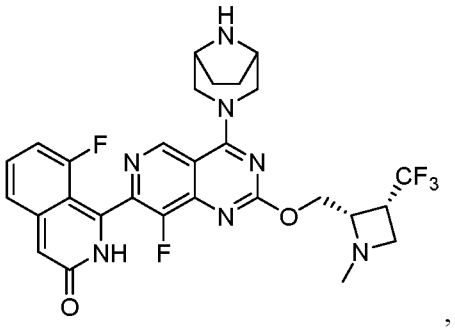
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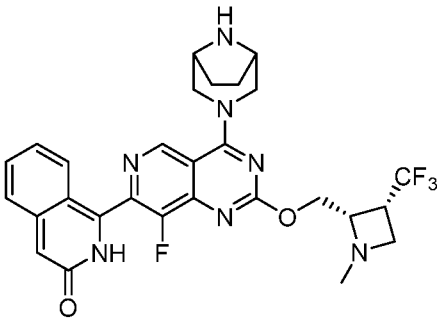
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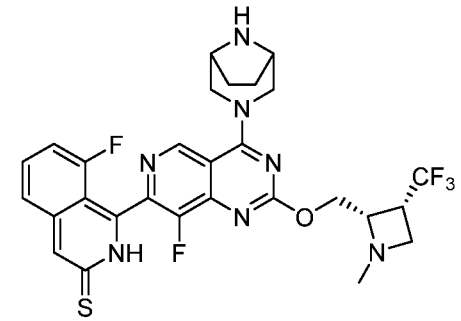
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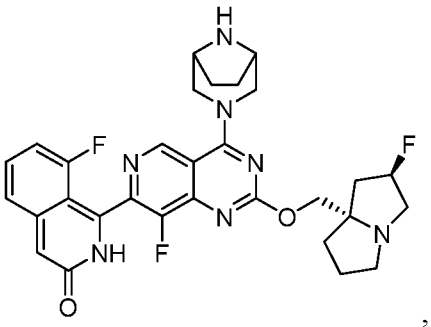
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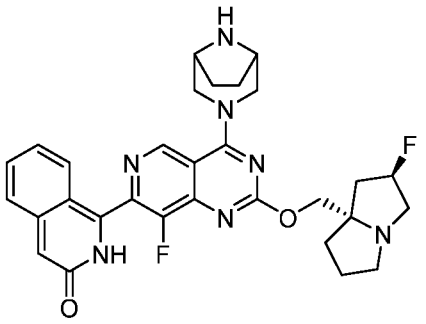
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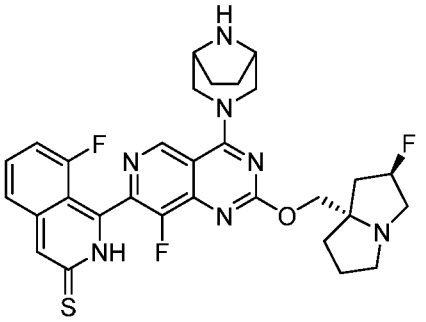
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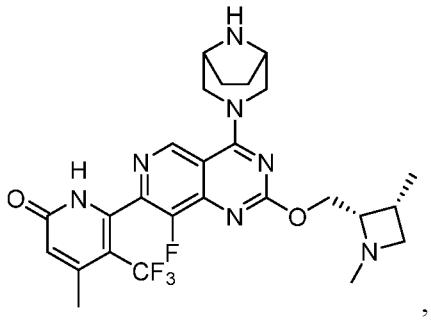
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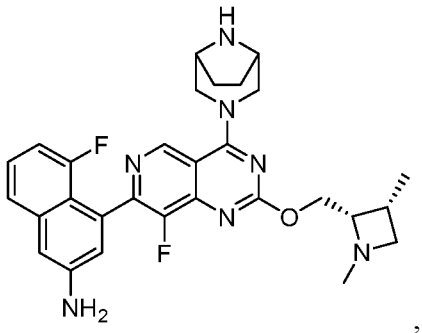
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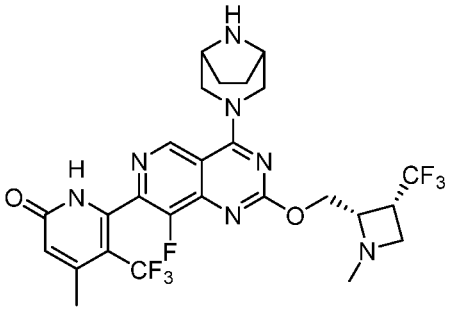
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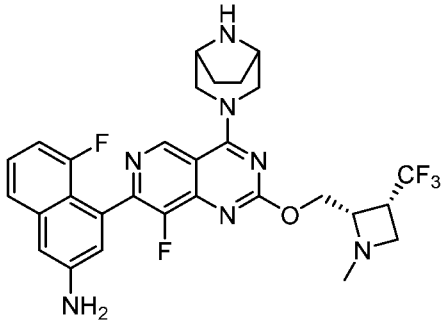
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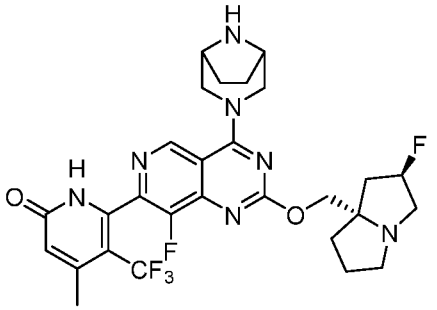
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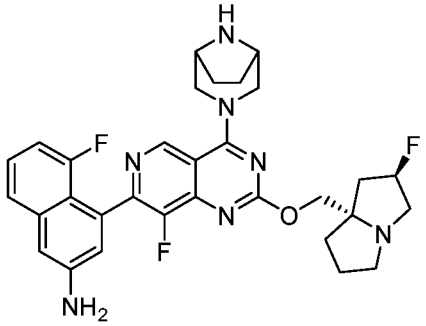
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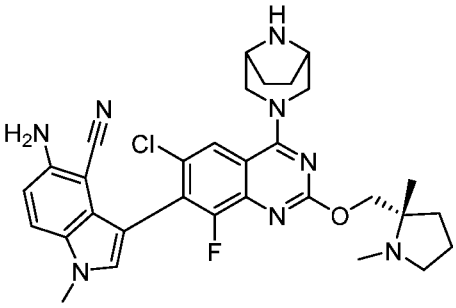
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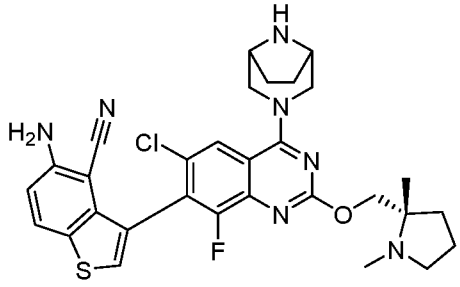
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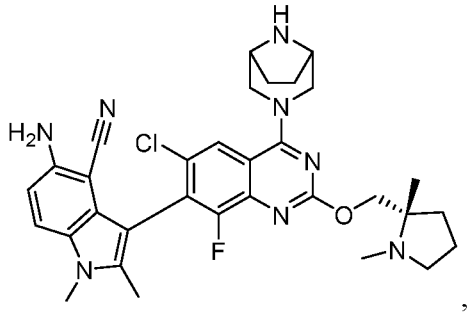
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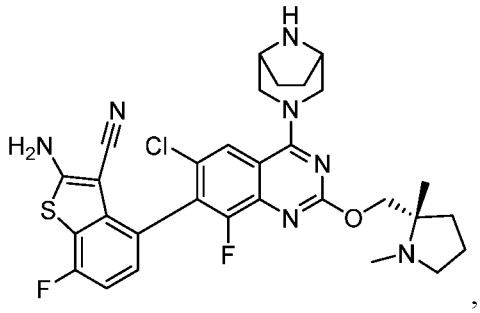
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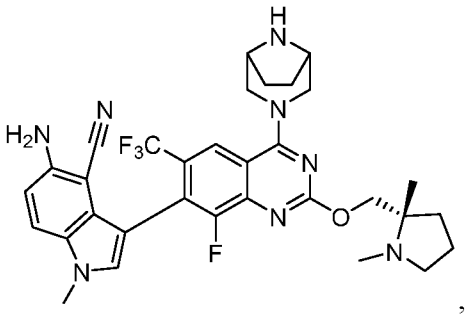
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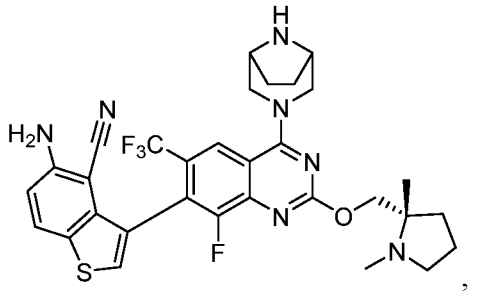
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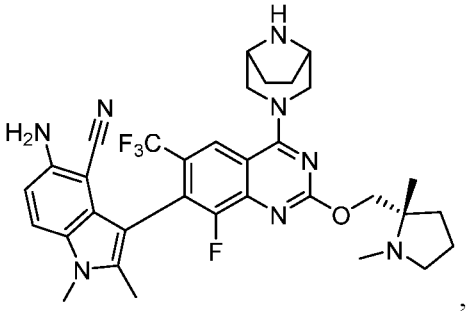
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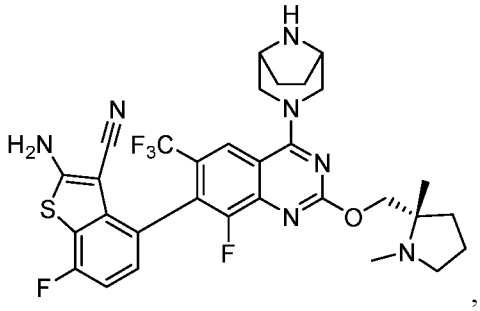
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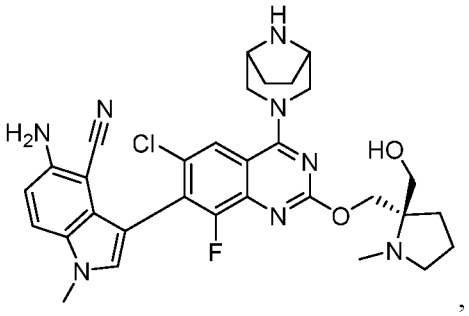
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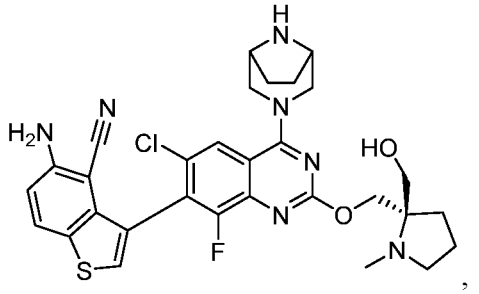
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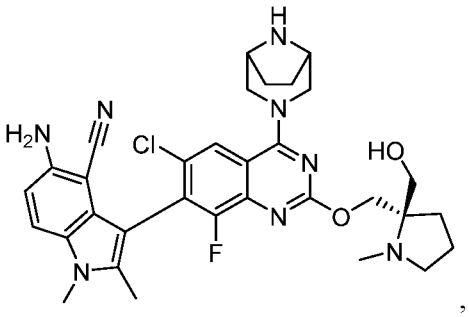
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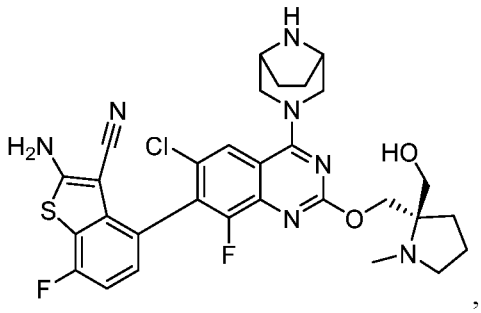
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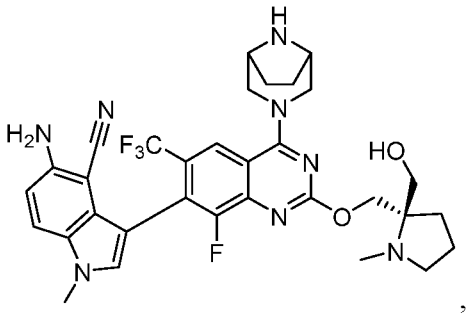
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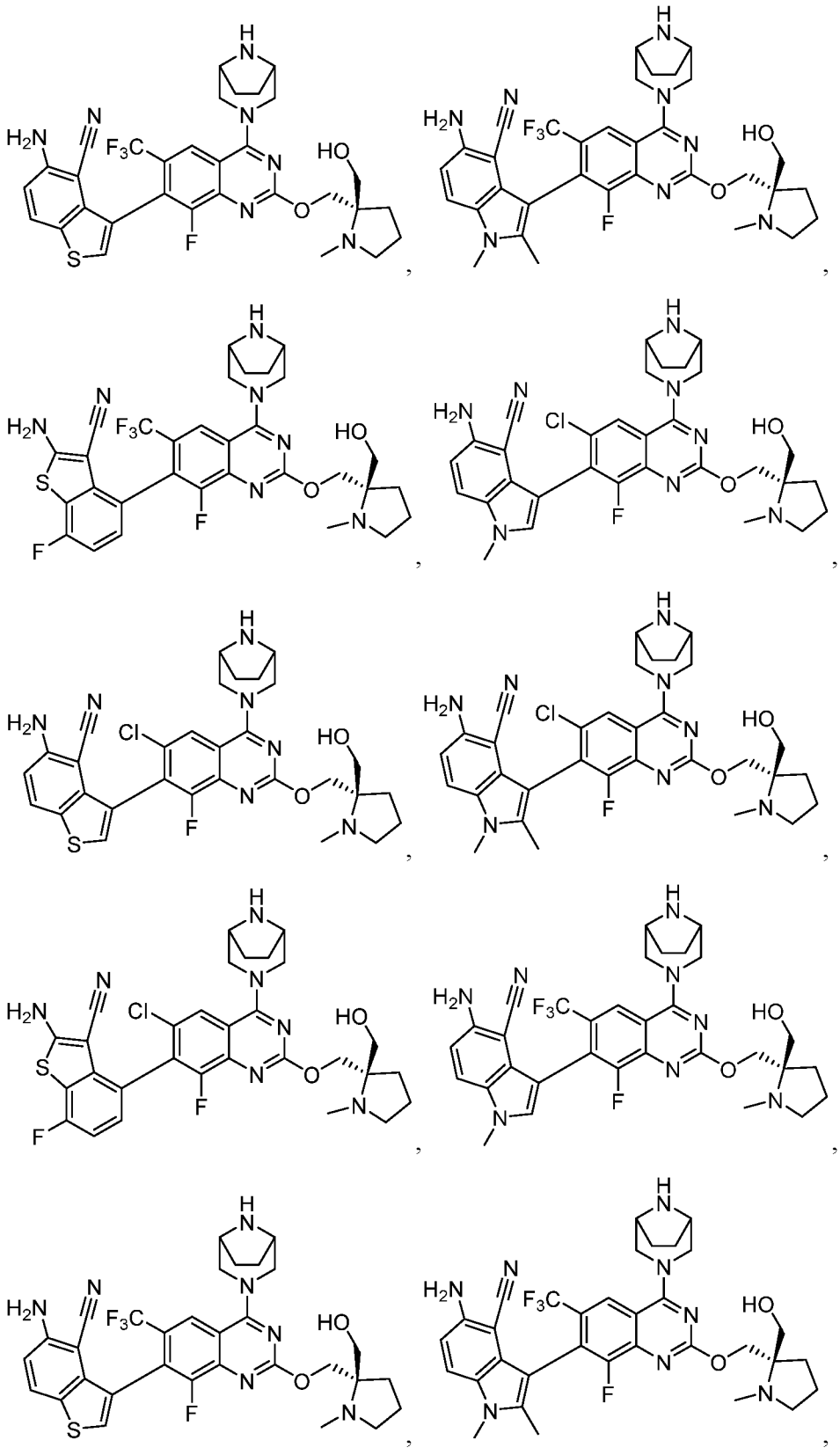

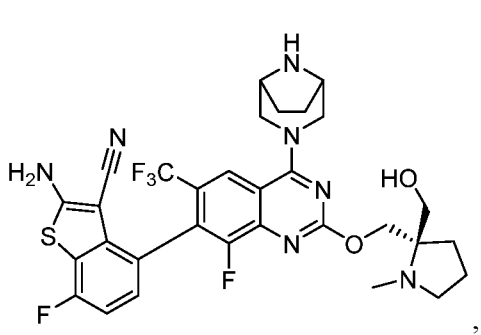
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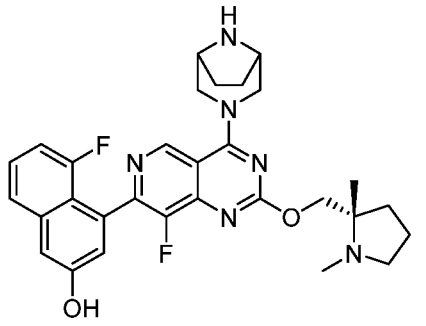
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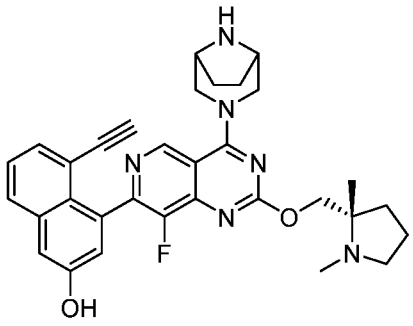
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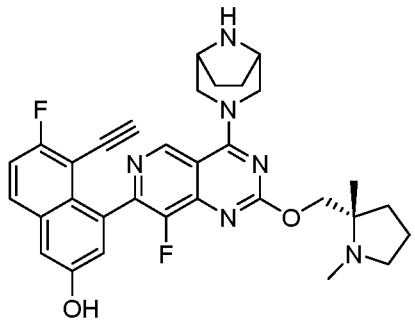
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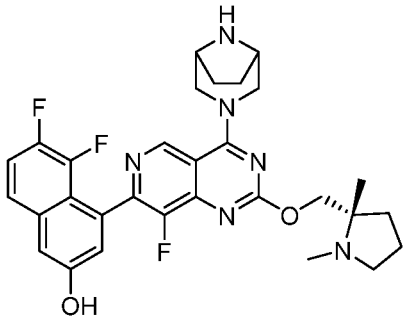
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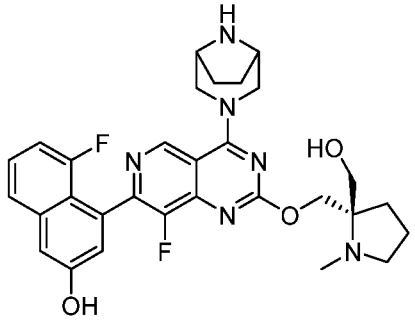
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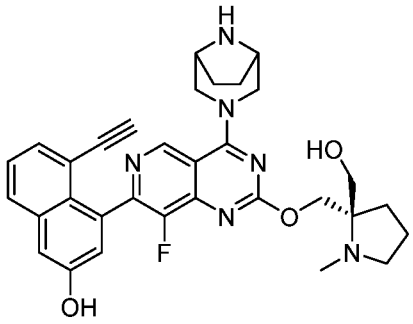
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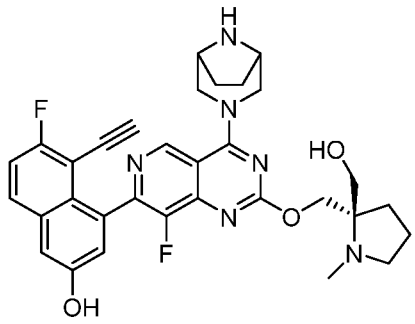
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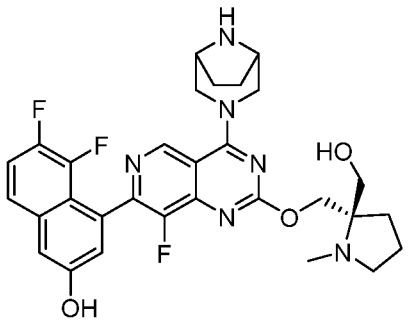
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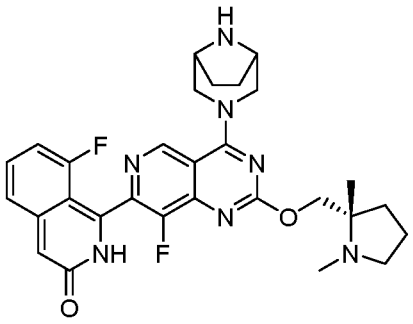
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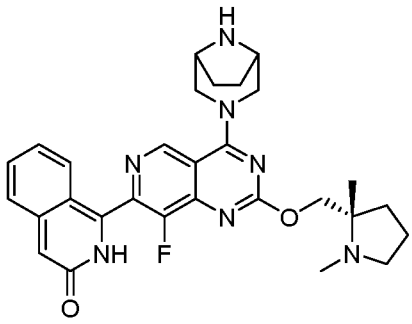
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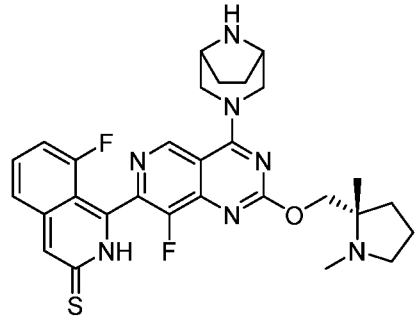
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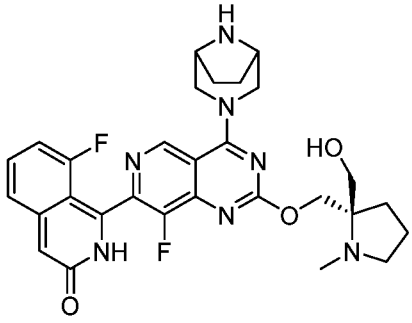
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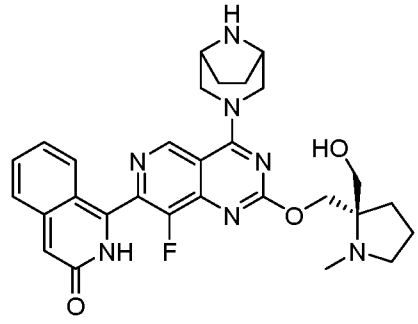
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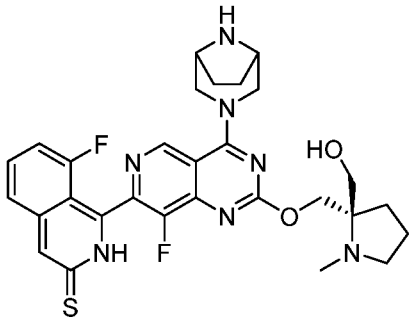
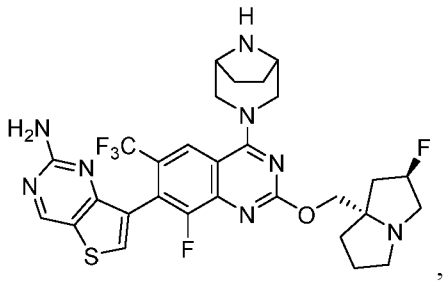

; or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

14. A compound selected from: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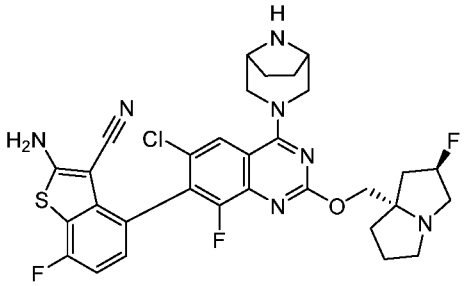
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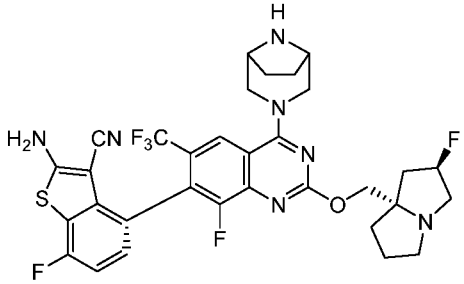
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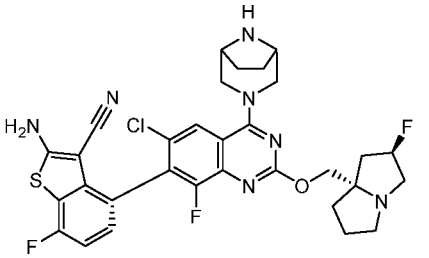
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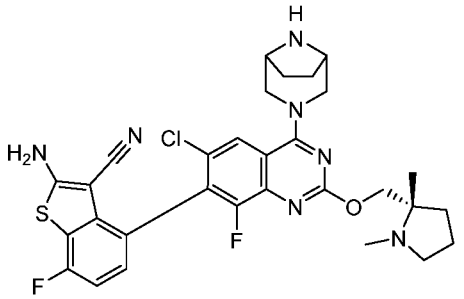
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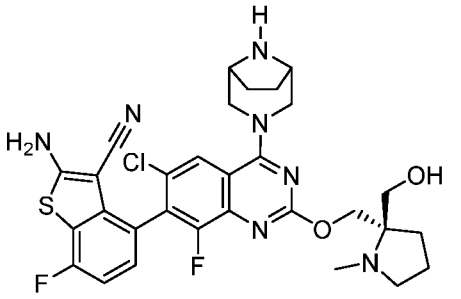
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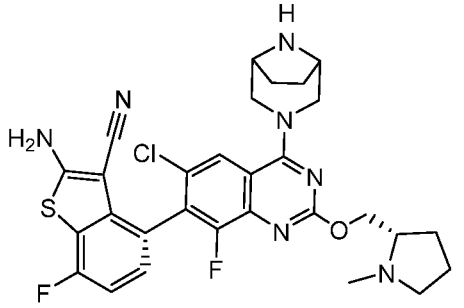
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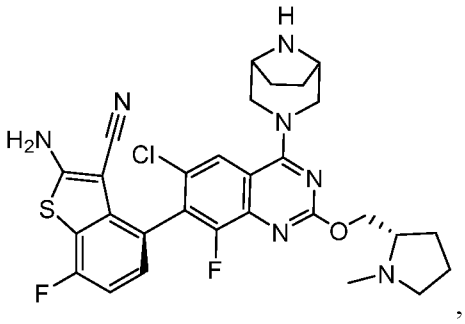
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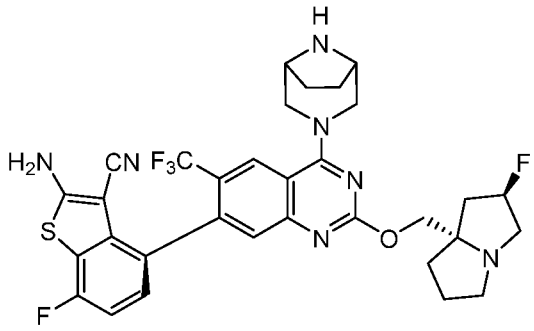
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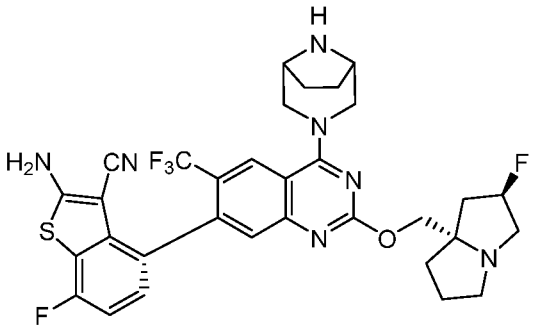
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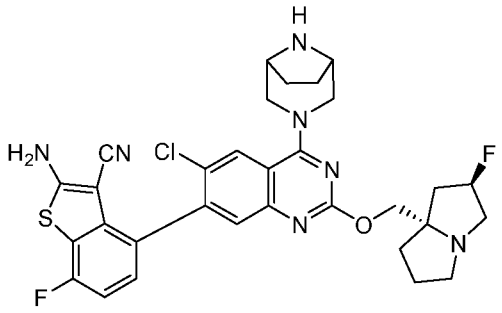
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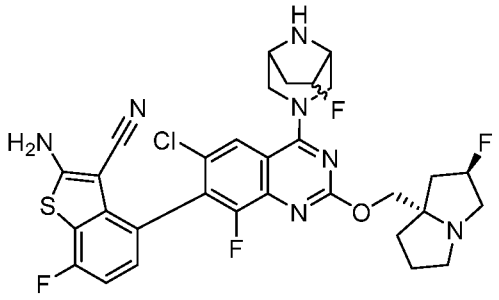
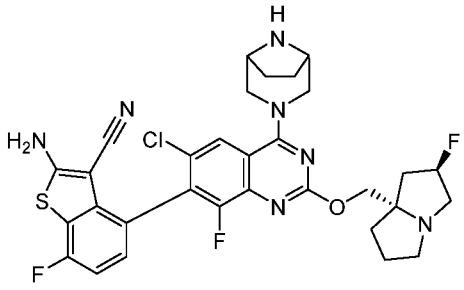

;

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

15. A compound having the structure:


or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

17. The pharmaceutical composition of claim 16, further comprising an additional therapeutic agent.

18. A method of treating a subject having cancer, the cancer characterized by the presence of a KRAS G12D mutation, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

19. The method of claim 18, wherein the cancer is Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial 'carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell

carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; or Adrenal glands: neuroblastoma.

20. The method of claim 18, wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer, or pancreatic cancer.

21. Use of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or a a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of cancer in a subject, the cancer characterized by the presence of a KRAS G12D mutation.

22. The use of claim 21, wherein the cancer is Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma,

cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial 'carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; or Adrenal glands: neuroblastoma.

23. The method of claim 21, wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer, or pancreatic cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/039808

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/08 C07D519/00 A61P35/00 A61K31/517 A61K31/519
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/041671 A1 (MIRATI THERAPEUTICS INC [US]; ARRAY BIOPHARMA INC [US]) 4 March 2021 (2021-03-04)	1-5,8-23
Y	exemplary compounds on page 865 (2nd to 6th); exemplary compound on page 848 (10th) for claim 11; claims 1,45,46,49,52,53; examples A-C	6,7
X	WO 2021/106231 A1 (TAIHO PHARMACEUTICAL CO LTD [JP]; ASTEX THERAPEUTICS LTD [GB]) 3 June 2021 (2021-06-03) compound 16 on page 136, compound 26 on page 139, compound 27 on page 140, compounds 31 and 32 on page 141; Test Example 1; Table 2 on page 146; claims 1,10,17,19,29,30,34	1,5,9, 12,16, 18-23

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2022	24/10/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Guspanová, Jana

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/039808

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2020/331911 A1 (MARX MATTHEW ARNOLD [US] ET AL) 22 October 2020 (2020-10-22) compound 107 on page 314; paragraphs [0007] - [0027], [0073]; claims 1,2,7	6,7
X,P	WO 2022/061251 A1 (PLEXXIKON INC [US]) 24 March 2022 (2022-03-24) exemplary compound P-0154 on page 232 for claims 2 and 3; exemplary compound P-0184 on page 238 for claim 4; compound P-0378 on page 285 for claim 6 exemplary compound P-0666 on page 352 for claim 8; exemplary compound P-0714 on page 362 for claim 11 exemplary compound P-0729 on page 365 for claim 12; paragraph [0539]; claims 1,26-30; table 2	1-4,6,8, 9,11,12, 16-23
X,P	WO 2022/148422 A1 (BEIGENE LTD [GB]; JI QI [CN]) 14 July 2022 (2022-07-14) exemplary compounds E104 and E106 on page 432 and E111, E115 and E116 on page 433, especially for claim 4; claims 1,24,39,40; table 3	1,2,4,9, 12,16, 18-23
E	WO 2022/193871 A1 (YA THERAPEUTICS INC [CN]) 22 September 2022 (2022-09-22) compound 77 on page 43, especially for claim 6; claims 1,8,9	1-23

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/039808

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		WO 2020146613 A1	16-07-2020
		WO 2021141628 A1	15-07-2021
WO 2022061251 A1	24-03-2022	NONE	
WO 2022148422 A1	14-07-2022	NONE	
WO 2022193871 A1	22-09-2022	NONE	