KRAS INHIBITORS

Background

[0001] The MAPK/ERK signaling pathway relays extracellular stimuli to the nucleus, thereby regulating diverse cellular responses including cell proliferation, differentiation, and apoptosis. KRas protein is an initiator of the MAPK/ERK signaling pathway and functions as a switch responsible for inducing cell division. In its inactive state, KRas binds guanosine diphosphate (GDP), effectively sending a negative signal to suppress cell division. In response to an extracellular signal, KRas is allosterically activated allowing for nucleotide exchange of GDP for guanosine triphosphate (GTP). In its GTP-bound active state, KRas recruits and activates proteins necessary for the propagation of growth factor induced signaling, as well as other cell signaling receptors. Examples of the proteins recruited by KRas-GTP are c-Raf and PI3-kinase. KRas, as a GTP-ase, converts the bound GTP back to GDP, thereby returning itself to an inactive state, and again propagating signals to suppress cell division. KRas gain of function mutations exhibit an increased degree of GTP binding and a decreased ability to convert GTP into GDP. The result is an increased MAPK/ERK signal which promotes cancerous cell growth. Missense mutations of KRas at codon 12 are the most common mutations and markedly diminish GTPase activity.

[0002] Oncogenic KRas mutations have been identified in approximately 30% of human cancers and have been demonstrated to activate multiple downstream signaling pathways. Despite the prevalence of KRas mutations, it has been a difficult therapeutic target. (Cox, A.D. *Drugging the Undruggable RAS: Mission Possible?* Nat. Rev. Drug Disc. 2014, 13, 828-851; Pylayeva-Gupta, y et al. *RAS Oncogenes: Weaving a Tumorigenic Web.* Nat. Rev. Cancer 2011, 11, 761-774).

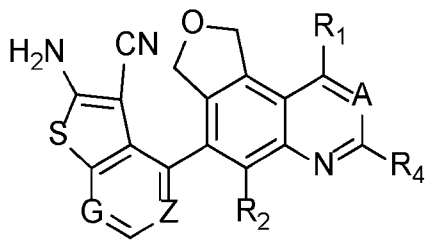
[0003] Thus far, work has focused on KRas G12C mutant inhibitors (e.g., WO2019/099524, WO2020/081282, WO2020/101736, WO2020/146613, and WO2021/118877 disclose KRas G12C inhibitors), whereas WO2021/041671 discloses small molecules inhibitors of KRas G12D and WO2017/011920 discloses small molecule inhibitors of KRas G12C, G12D, and G12V.

[0004] There remains a need to provide alternative, small molecule KRas inhibitors. In particular, there is a need to provide more potent, orally deliverable KRas inhibitors that are useful for treating cancer. More particularly, there is a need to provide small molecule inhibitors that specifically inhibit KRas GTP activity. Further, there is a desire to provide KRas inhibitors that exhibit better

pharmacokinetic/pharmacodynamic properties. Also, there is a need to provide more potent KRas inhibitors that exhibit increased efficacy with reduced or minimized untoward or undesired effects. Further, there is a need to provide more potent KRas inhibitors that exhibit selective inhibition preference for KRas G12D mutant over KRas wild-type. Further, there is also a need to provide more potent KRas inhibitors that exhibit selective inhibition preference for KRas G12C, G12D, and/or G12V mutants over HRAS or NRAS. Even further, there is also a need to provide more potent KRas inhibitors that exhibit selective inhibition preference for KRas G12C, G12D, and G12V mutants over HRAS or NRAS. These panKRas inhibitors could also be KRas wild-type inhibitors or they could be selective over KRas wild-type. The present invention addresses one or more of these needs by providing novel KRas inhibitors.

Summary

[0005] Compounds of Formula I are provided herein:



Formula I

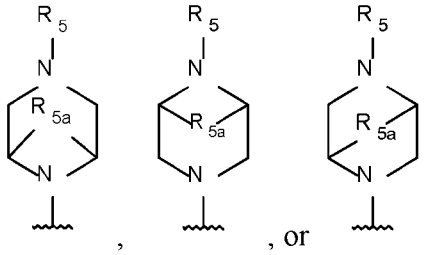
wherein

A is -C(H)- or -N-;

Z is -C(R_{3c})- or -N-;

G is -C(R_{3b})- or -N-;

R_1 is H, or a group of the formula

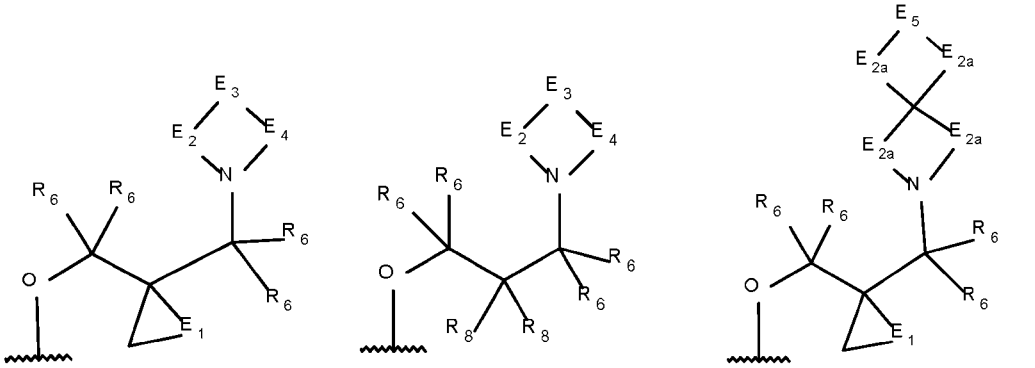


, , or ;

R_2 is H, halogen, or methyl;

R_{3b}, and R_{3c} are each independently H, halogen, or methyl;

R_4 is a N-linked cyclic amine or a group of the formula



, , or ;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, morpholine, diazepane, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen; hydroxyl; -$NR_{6a}R_{6a}$; (1-methylpiperidin-4-yl)oxy; C_{1-3} alkoxy optionally substituted with -$NR_{6a}R_{6a}$; C_{1-3} alkyl optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or hydroxyl; an imidazole optionally substituted with a methyl; a monocyclic ring selected from azetidine, piperidine, piperazine, morpholine, oxazepane, or diazepane; a bicycle selected from hexahydro-1H-furo[3,4-c]pyrrole, octahydropyrrolo[3,4-c]pyrrole, or octahydropyrrolo[1,2-a]pyrazine; or a spirocycle selected from 4,7-diazaspiro[2.5]octane, 2-oxa-7-azaspiro[3.5]nonane, 2,6-diazaspiro[3.4]octane, or 2-azaspiro[3.3]heptane; wherein the monocyclic ring is optionally bridged by a C_{1-3} alkylene, and can optionally be substituted with one or more halogen, hydroxyl, -

CN, C_{1-3} alkoxy, $-NR_{10}R_{10}$, cyclopropyl, oxetane, $-CO-C_{1-3}$ alkyl, or a C_{1-3} alkyl optionally substituted with hydroxyl, C_{1-3} alkoxy, $-NR_{10}R_{10}$, halogen, or $-CF_3$; and wherein the bicyclo or spirocyclo is each optionally substituted with a methyl or a halogen; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, hexahydro-1H-furo[3,4-b]pyrrole, octahydro-1H-pyrrolo[3,2-b]pyridine, (3as,6as)-tetrahydro-1H,4H-3a,6a-(methanooxymethano)pyrrolo[3,4-c]pyrrole, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, 2-oxa-6-azaspiro[3.4]octane, 2,7-diazaspiro[4.4]nonane, 2-oxa-6-azaspiro[3.4]octane or1-oxa-7-azaspiro[4.4]nonane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$ or hydroxyl;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$;

R_{4b} is H, hydroxyl, or C_{1-3} alkyl;

R_{4c} is independently cyclopropyl, or oxetane;

R_{4d} is independently C_{1-3} alkyl;

R_5 is trideuteromethyl, oxetane, or a C_{1-4} alkyl optionally substituted with one or more halogen, trifluoromethyl, hydroxyl, methoxy, trifluoromethoxy, difluoromethoxy, trideuteromethoxy, oxetane, cyclopropyl, imidazole, pyrazole, $-CO-NR_{6a}R_{6a}$, $-O-(CH_2)_2-OR_{6a}$, or $-O-CO-C_{1-3}$ alkyl, wherein the cyclopropyl is optionally substituted with a hydroxyl, or hydroxymethyl,

and the imidazole, or pyrazole are each optionally substituted with a hydroxyl, or a C_{1-3} alkyl substituted with one or more hydroxyl;

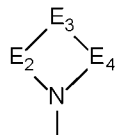
R_{5a} is C_{1-3} alkylene;

each R_6 is independently H or deuterium;

each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, a N-methyl pyrrolidine, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, bicyclo[1.1.1]pentan-1-ol, or a C_{1-3} alkyl optionally substituted with one or more deuterium, hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran, -CO-NHMe, or -CO-NH_2, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl;

E_1 is -O-C_{1-3} alkylene, or C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl, C_{1-3} alkoxy or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene; and E_3 is -O-, -CR_7R_7-, -NR_9-, or -CO-NR_{6a}-; or

the ring 

is hexahydro-1H-furo[3,4-c]pyrrole;

Each E_{2a} is independently a C_{1-3} alkylene optionally substituted with one or more hydroxyls;

E_5 is -O-, -CR_7R_7-, or -NR_9-;

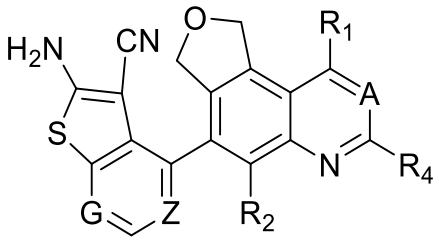
Each R_7 is independently H, halogen, CN, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls;

each R_8 is independently a C_{1-3} alkyl;

R_9 is each independently H, optionally substituted C_{1-3} alkyl or -CO-C_{1-3} alkyl; wherein the optionally substituted C_{1-3} alkyl is optionally substituted with one or more halogens; and

R_{10} is H or C_{1-3} alkyl optionally substituted with one or more deuterium; or a pharmaceutically acceptable salt thereof.

[0005a] In an aspect of the present disclosure, there is provided a compound of the formula:



wherein:

A is -C(H)- or -N-;

Z is -C(R_{3c})- or -N-;

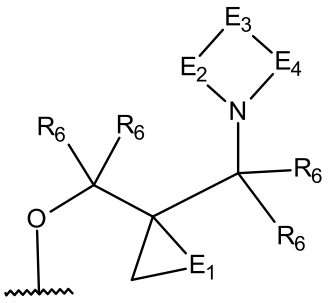
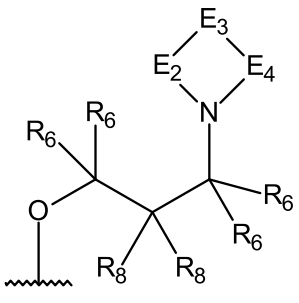
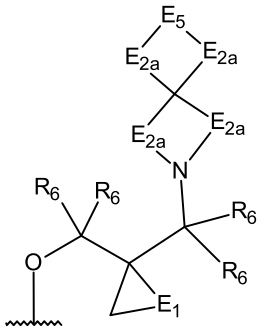
G is -C(R_{3b})- or -N-;

R_1 is H;

R_2 is H, halogen, or methyl;

R_{3b}, and R_{3c} are each independently H, halogen, or methyl;

R_4 is a N-linked cyclic amine or a group of the formula


, 
, or 
;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, morpholine, diazepane, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen; hydroxyl; -$NR_{6a}R_{6a}$; (1-methylpiperidin-4-yl)oxy; C_{1-3}

alkoxy optionally substituted with -$NR_{6a}R_{6a}$; C_{1-3} alkyl optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or hydroxyl; an imidazole optionally substituted with a methyl; a monocyclic ring selected from azetidine, piperidine, piperazine, morpholine, oxazepane, or diazepane; a bicycle selected from hexahydro-1H-furo[3,4-c]pyrrole, octahydropyrrolo[3,4-c]pyrrole, or octahydropyrrolo[1,2-a]pyrazine; or a spirocycle selected from 4,7-diazaspiro[2.5]octane, 2-oxa-7-azaspiro[3.5]nonane, 2,6-diazaspiro[3.4]octane, or 2-azaspiro[3.3]heptane; wherein the monocyclic ring is optionally bridged by a C_{1-3} alkylene, and can optionally be substituted with one or more halogen, hydroxyl, -CN, C_{1-3} alkoxy, -$NR_{10}R_{10}$, cyclopropyl, oxetane, -CO-C_{1-3} alkyl, or a C_{1-3} alkyl optionally substituted with hydroxyl, C_{1-3} alkoxy, -$NR_{10}R_{10}$, halogen, or -CF_3; and wherein the bicyclo or spirocyclo is each optionally substituted with a methyl or a halogen; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, hexahydro-1H-furo[3,4-b]pyrrole, octahydro-1H-pyrrolo[3,2-b]pyridine, (3as,6as)-tetrahydro-1H,4H-3a,6a-(methanooxymethano)pyrrolo[3,4-c]pyrrole, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, 2-oxa-6-azaspiro[3.4]octane, 2,7-diazaspiro[4.4]nonane, 2-oxa-6-azaspiro[3.4]octane or1-oxa-7-azaspiro[4.4]nonane; each of which is optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with -$NR_{6a}R_{6a}$ or hydroxyl;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or -$NR_{6a}R_{6a}$;

R_{4b} is H, hydroxyl, or C_{1-3} alkyl;

R_{4c} is independently cyclopropyl, or oxetane;

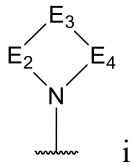
R_{4d} is independently C_{1-3} alkyl;

each R_6 is independently H or deuterium;

each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, a N-methyl pyrrolidine, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, bicyclo[1.1.1]pentan-1-ol, or a C_{1-3} alkyl optionally substituted with one or more deuterium, hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran, -CO-NHMe, or -CO-NH_2, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl;

E_1 is -O-C_{1-3} alkylene, or C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl, C_{1-3} alkoxy or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene; and E_3 is -O-, -CR_7R_7-, -NR_9-, or -CO-NR_{6a}-; or

the ring 

is hexahydro-1H-furo[3,4-c]pyrrole;

each E_{2a} is independently a C_{1-3} alkylene optionally substituted with one or more hydroxyls;

E_5 is -O-, -CR_7R_7-, or -NR_9-;

each R_7 is independently H, halogen, CN, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls;

each R_8 is independently a C_{1-3} alkyl;

R_9 is each independently H, optionally substituted C_{1-3} alkyl or -CO-C_{1-3} alkyl; wherein the optionally substituted C_{1-3} alkyl is optionally substituted with one or more halogens; and

R_{10} is H or C_{1-3} alkyl optionally substituted with one or more deuterium; or a pharmaceutically acceptable salt thereof.

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

[0006] Also provided herein are methods of using the compounds of Formula I, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, to treat cancer, in particular for the treatment of lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer. The methods include administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

[0007] Further provided herein, are compounds of Formula I, and pharmaceutically acceptable salts thereof, for use in therapy. Additionally provided herein, are the compounds of Formula I, and pharmaceutically acceptable salts thereof, for use in the treatment of cancer, in particular for the treatment of lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer. Also additionally provided herein is the use of compounds of Formula I, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating cancer, in particular for the treatment of lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

[0007a] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

[0007b] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

[0007c] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient with a cancer that has a KRas G12C, G12D, and/or G12V mutation.

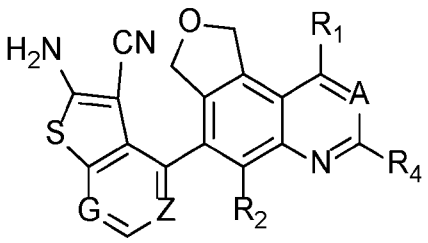
[0007d] In another aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, for use in therapy.

[0007e] In a further aspect of the present disclosure, there is provided a use of the compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, in the manufacture of a medicament for the treatment of cancer

Detailed Description

[0008] Novel inhibitors of the KRas gain of function mutation G12C, G12D, and/or G12V are described herein. These new compounds could address the needs noted above for inhibitors of KRas GTP activity in gain of function mutants in the treatment of cancers such as lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma or esophageal cancer. Some of these new KRas inhibitor compounds are selective to KRas G12D mutants over wild-type KRas (and likely other mutant types such as G12C or G12V). Additionally, some of these new KRas inhibitor compounds are non-selective and inhibit both wild-type KRas and KRas G12D mutants (and/or possibly other mutant types such as G12C or G12V). Also, some of these new KRas inhibitor compounds are non-selective and inhibit both wild-type KRas and Kras G12C, G12D, and/or G12V mutants.

[0009] The present invention provides a compound of Formula I:

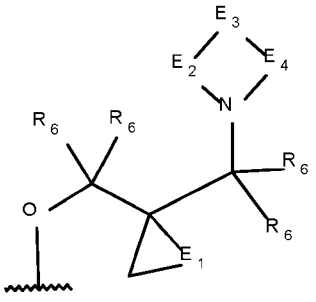


Formula I

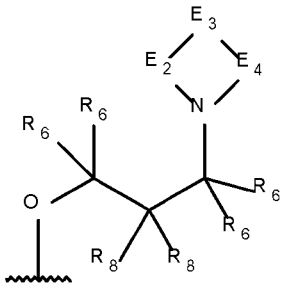
wherein A, Z, G, R_1, R_2, and R_4 are as defined above, or a pharmaceutically acceptable salt thereof.

[0010] As used herein, the term halogen means fluoro (F), chloro (Cl), bromo (Br), or iodo (I). As used herein, the term alkyl means saturated linear or branched-chain monovalent hydrocarbon radicals of one to a specified number of carbon atoms, e.g., "C_{1-4} alkyl" or "C_{1-3} alkyl." Examples of alkyls include, but are not limited to, methyl, ethyl, propyl, 1-propyl, isopropyl, butyl, and iso-butyl. As used herein, the term alkylene means saturated linear or branched-chain bivalent hydrocarbon radicals of one to a specified number of carbon atoms, e.g., "C_{1-3} alkylene." Examples of alkylenes include, but are not limited to, methylene, ethylene, propylene, 1-propylene, and isopropylene. Examples of C_{1-3} alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, 1-propoxy, and isopropoxy.

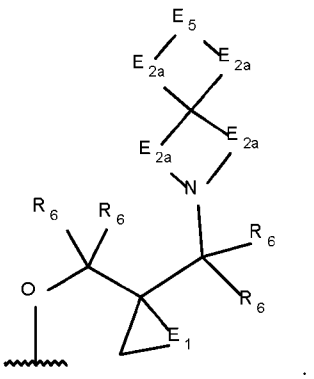
[0011] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine or a group of the formula



,



, or



;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

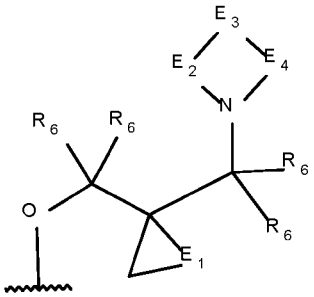
ii. pyrrolidine, piperidine, piperazine, morpholine, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, C_{1-3} alkoxy, $-NR_{6a}R_{6a}$, azetidine, piperazine, morpholine, a C_{1-3} alkyl, or an imidazole optionally substituted with a methyl; wherein the azetidine is optionally substituted with hydroxyl or C_{1-3} alkoxy; the piperazine is optionally substituted with a methyl, and the C_{1-3} alkyl is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or hydroxyl; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, or 2-oxa-6-azaspiro[3.4]octane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$;

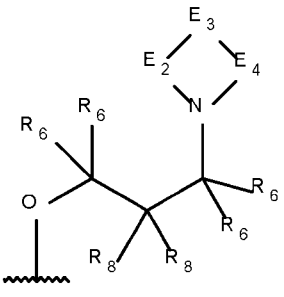
R_{4a} is $-NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$; and

each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, or a C_{1-3} alkyl optionally substituted with one or more hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran, -CO-NHMe, or $-CO-NH_2$, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl.

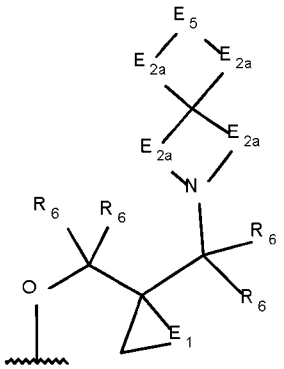
[0012] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine or a group of the formula



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, or



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wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

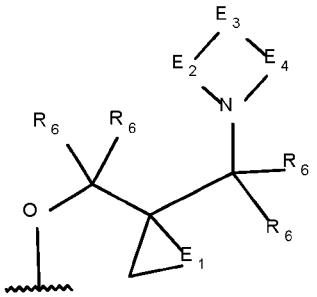
ii. pyrrolidine, piperidine, piperazine, morpholine, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, C_{1-3} alkoxy, $-NR_{6a}R_{6a}$, azetidine, a C_{1-3} alkyl, or an imidazole optionally substituted with a methyl; wherein the azetidine is optionally substituted with hydroxyl or C_{1-3} alkoxy; and the C_{1-3} alkyl is optionally substituted with halogen-$NR_{6a}R_{6a}$ or hydroxyl; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-6-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, or 5-azaspiro[2.4]heptane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$;

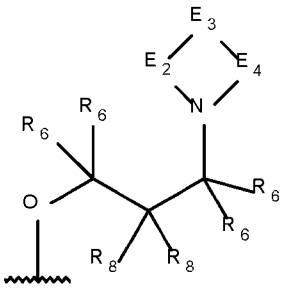
R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$;

and each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl or a C_{1-3} alkyl optionally substituted with hydroxyl.

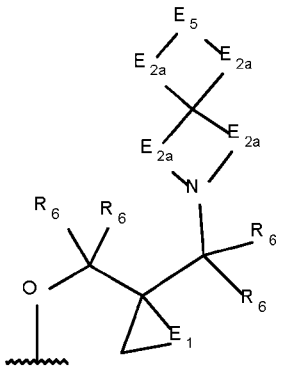
[0013] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_{3b}, and R_{3c} are each independently H or halogen, and R_4 is a N-linked cyclic amine or a group of the formula



,



, or



;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, or morpholine; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, $-NR_{6a}R_{6a}$, imidazole or a C_{1-3} alkyl; wherein the imidazole is optionally substituted with a methyl; and the C_{1-3} alkyl is optionally substituted with $-NR_{6a}R_{6a}$ or hydroxyl; or

iii. octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,4-c]pyrrole, 1,6-diazaspiro[3.3]heptane, or 1,6-diazaspiro[3.4]octane; each of which is optionally substituted with one or more halogen, or a C_{1-3} alkyl;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, morpholine, wherein the cyclopropyl, azetidine, pyrrolidine or morpholine is optionally substituted with halogen, or $-NR_{6a}R_{6a}$;

R_{4b} is H, or C_{1-3} alkyl;

R_{4c} is independently cyclopropyl, or oxetane;

R_{4d} is independently C_{1-3} alkyl;

R_5 is trideuteromethyl, oxetane, or a C_{1-4} alkyl optionally substituted with one or more halogen, trifluoromethyl, hydroxyl, methoxy, trifluoromethoxy, difluoromethoxy, trideuteromethoxy, oxetane, cyclopropyl, imidazole, pyrazole, -CO-$NR_{6a}R_{6a}$, -O-$(CH_2)_2$-OR_{6a}, or -O-CO-C_{1-3} alkyl, wherein the cyclopropyl is optionally substituted with a hydroxyl, or hydroxymethyl, and the imidazole, or pyrazole are each optionally substituted with a hydroxyl, or a C_{1-3} alkyl substituted with one or more hydroxyl;

R_{5a} is C_{1-3} alkylene;

each R_6 is independently H or deuterium;

each R_{6a} is independently H or C_{1-3} alkyl;

E_1 is -O-C_{1-3} alkylene, or C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene;

each E_{2a} is independently a C_{1-3} alkylene optionally substituted with one or more hydroxyls;

E_3 is -O-, -CR_7R_7-, -NR_9-, or -CO-NR_{6a}-;

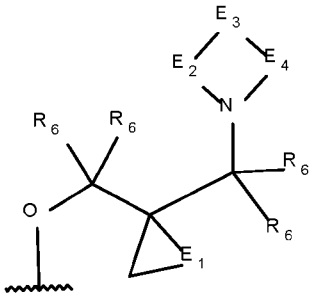
E_5 is -O-, -CR_7R_7-, or -NR_9-;

each R_7 is independently H, halogen, CN, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls;

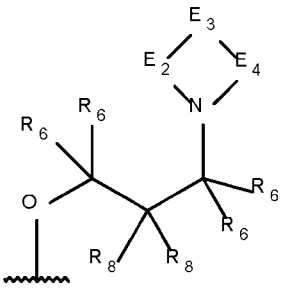
each R_8 is independently a C_{1-3} alkyl; and

R_9 is each independently H, optionally substituted C_{1-3} alkyl or -CO-C_{1-3} alkyl; wherein the optionally substituted C_{1-3} alkyl is optionally substituted with one or more halogens.

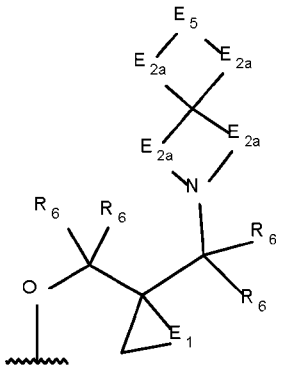
[0014] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_{3b}, and R_{3c} are each independently H or halogen, and R_4 is a group of the formula



,



, or



;

E_1 is C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyls, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene;

E_3 is -O-, $-CR_7R_7$-, $-NR_9$-, or $-CO-NR_{6a}$-;

each R_{6a} is independently H or C_{1-3} alkyl;

each R_7 is independently H, halogen, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls; and

R_9 is each independently H, C_{1-3} alkyl or $-CO-C_{1-3}$ alkyl.

[0015] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -N-.

[0016] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(R3b)-.

[0017] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(R3b)-, wherein R3b is H or halogen.

[0018] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(F)-.

[0019] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(Cl)-.

[0020] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(H)-.

[0021] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(CH3)-.

[0022] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, Z is -N-.

[0023] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, Z is -C(R3c)-.

[0024] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, Z is -C(R3c)-, wherein R3c is H or halogen.

[0025] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, Z is -C(H)-.

[0026] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, Z is -C(F)-.

[0027] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -N-, and Z is -C(R3c)-.

[0028] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -N-, and Z is -C(H)-.

[0029] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -N-, and Z is -C(F)-.

[0030] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(R3b)-, and Z is -N-.

[0031] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(R3b)-, wherein R3b is H or halogen, and Z is -N-.

[0032] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(F)-, and Z is -N-.

[0033] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(Cl)-, and Z is -N-.

[0034] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(H)-, and Z is -N-.

[0035] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, G is -C(CH3)-, and Z is -N-.

[0036] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R3b, and R3c are each independently H or halogen.

[0037] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-.

[0038] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-.

[0039] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R2 is F or Cl.

[0040] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -N-, and R2 is F.

[0041] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -N-, and R2 is F.

[0042] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -N-, and R2 is F.

[0043] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -N-, and R2 is F.

[0044] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -N-, and R2 is F.

[0045] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -N-, and R2 is F.

[0046] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(H)-, and R2 is F.

[0047] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(H)-, and R2 is F.

[0048] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(H)-, and R2 is F.

[0049] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(H)-, and R2 is F.

[0050] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(H)-, and R2 is F.

[0051] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(H)-, and R2 is F.

[0052] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(F)-, and R2 is F.

[0053] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(F)-, and R2 is F.

[0054] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(F)-, and R2 is F.

[0055] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(F)-, and R2 is F.

[0056] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(F)-, and R2 is F.

[0057] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(F)-, and R2 is F.

[0058] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -N-, and R2 is Cl.

[0059] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -N-, and R2 is Cl.

[0060] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -N-, and R2 is Cl.

[0061] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -N-, and R2 is Cl.

[0062] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -N-, and R2 is Cl.

[0063] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -N-, and R2 is Cl.

[0064] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(H)-, and R2 is Cl.

[0065] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(H)-, and R2 is Cl.

[0066] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(H)-, and R2 is Cl.

[0067] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(H)-, and R2 is Cl.

[0068] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(H)-, and R2 is Cl.

[0069] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(H)-, and R2 is Cl.

[0070] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(F)-, and R2 is Cl.

[0071] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(F)-, and R2 is Cl.

[0072] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(F)-, and R2 is Cl.

[0073] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(F)-, and R2 is Cl.

[0074] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(F)-, and R2 is Cl.

[0075] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(F)-, and R2 is Cl.

[0076] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R1 is H.

[0077] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -N-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0078] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -N-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0079] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -N-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0080] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -N-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0081] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -N-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0082] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -N-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0083] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(H)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0084] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(H)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0085] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(H)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0086] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(H)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0087] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(H)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0088] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(H)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0089] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(F)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0090] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(F)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0091] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(F)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0092] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(F)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0093] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(F)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0094] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(F)-, R2 is F, R1 is H, and R4 is a N-linked cyclic amine.

[0095] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -N-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0096] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -N-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0097] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -N-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0098] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -N-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0099] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -N-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0100] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -N-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0101] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(H)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0102] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(H)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0103] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(H)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0104] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(H)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0105] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(H)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0106] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(H)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0107] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(F)-, G is -C(F)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0108] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(F)-, G is -C(F)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

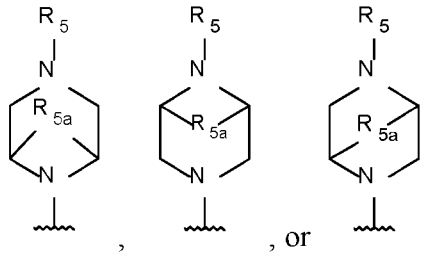
[0109] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -C(H)-, G is -C(F)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0110] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -C(H)-, G is -C(F)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0111] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -C(H)-, Z is -N-, G is -C(F)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

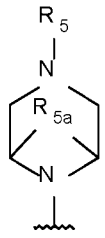
[0112] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, A is -N-, Z is -N-, G is -C(F)-, R2 is Cl, R1 is H, and R4 is a N-linked cyclic amine.

[0113] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is a group of the formula



, , or .

[0114] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is a group of the formula

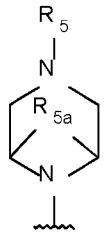


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[0115] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_5 is a C_{1-4} alkyl optionally substituted with one or more hydroxyl, methoxy or oxetane.

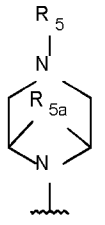
[0116] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_5 is a C_{1-4} alkyl optionally substituted with one or more hydroxyl, or methoxy.

[0117] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is a group of the formula



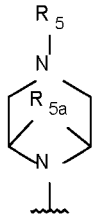
, wherein R_{5a} is ethylene.

[0118] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is a group of the formula



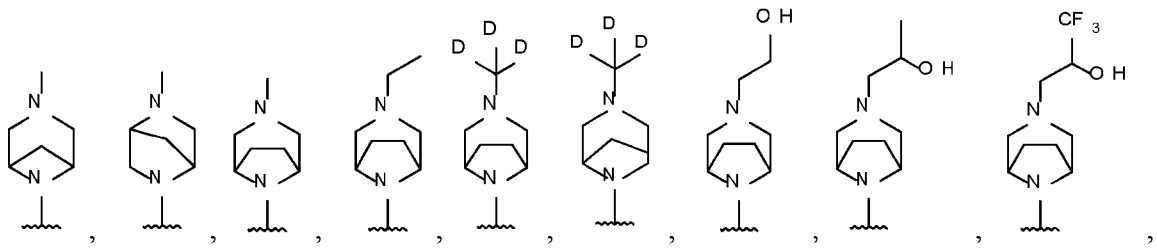
, wherein R_5 is a C_{1-4} alkyl optionally substituted with one or more hydroxyl, methoxy or oxetane and preferably R_{5a} is ethylene.

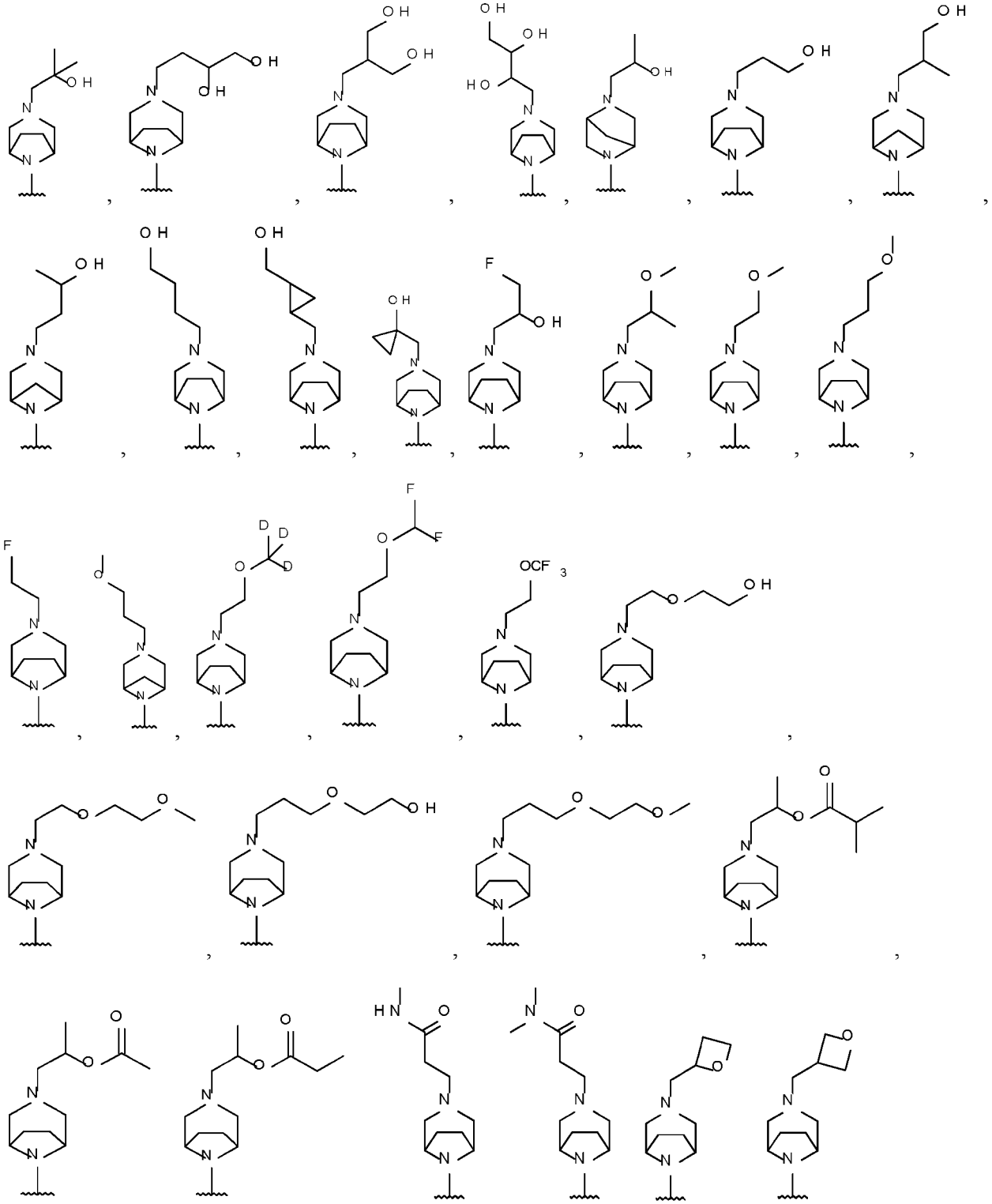
[0119] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is a group of the formula

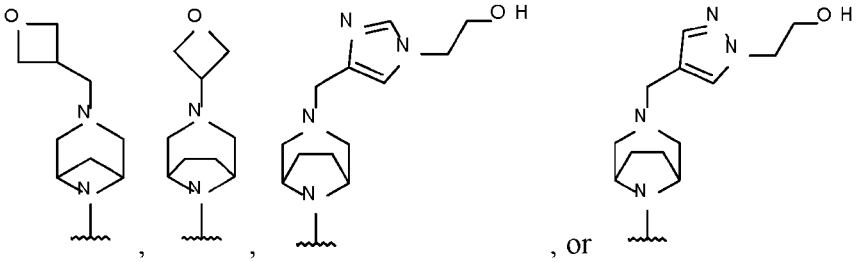


, wherein R_5 is a C_{1-4} alkyl optionally substituted with one or more hydroxyl, or methoxy and preferably R_{5a} is ethylene.

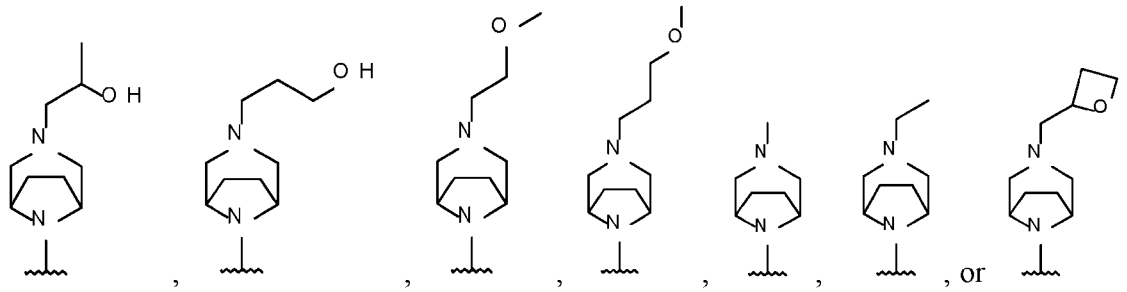
[0120] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is selected from



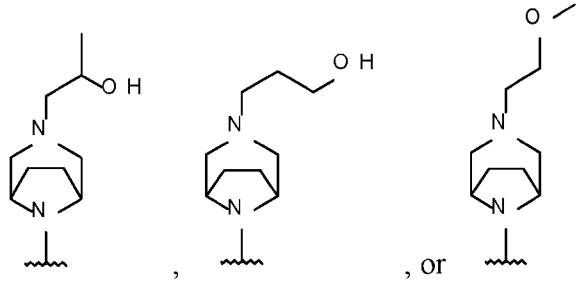




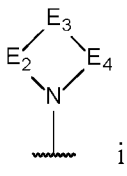
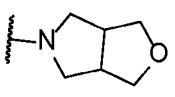
[0121] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is selected from



[0122] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_1 is selected from



[0123] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof,

the ring  is hexahydro-1H-furo[3,4-c]pyrrole:  .

[0124] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked azetidine substituted with R_{4a} and R_{4b}.

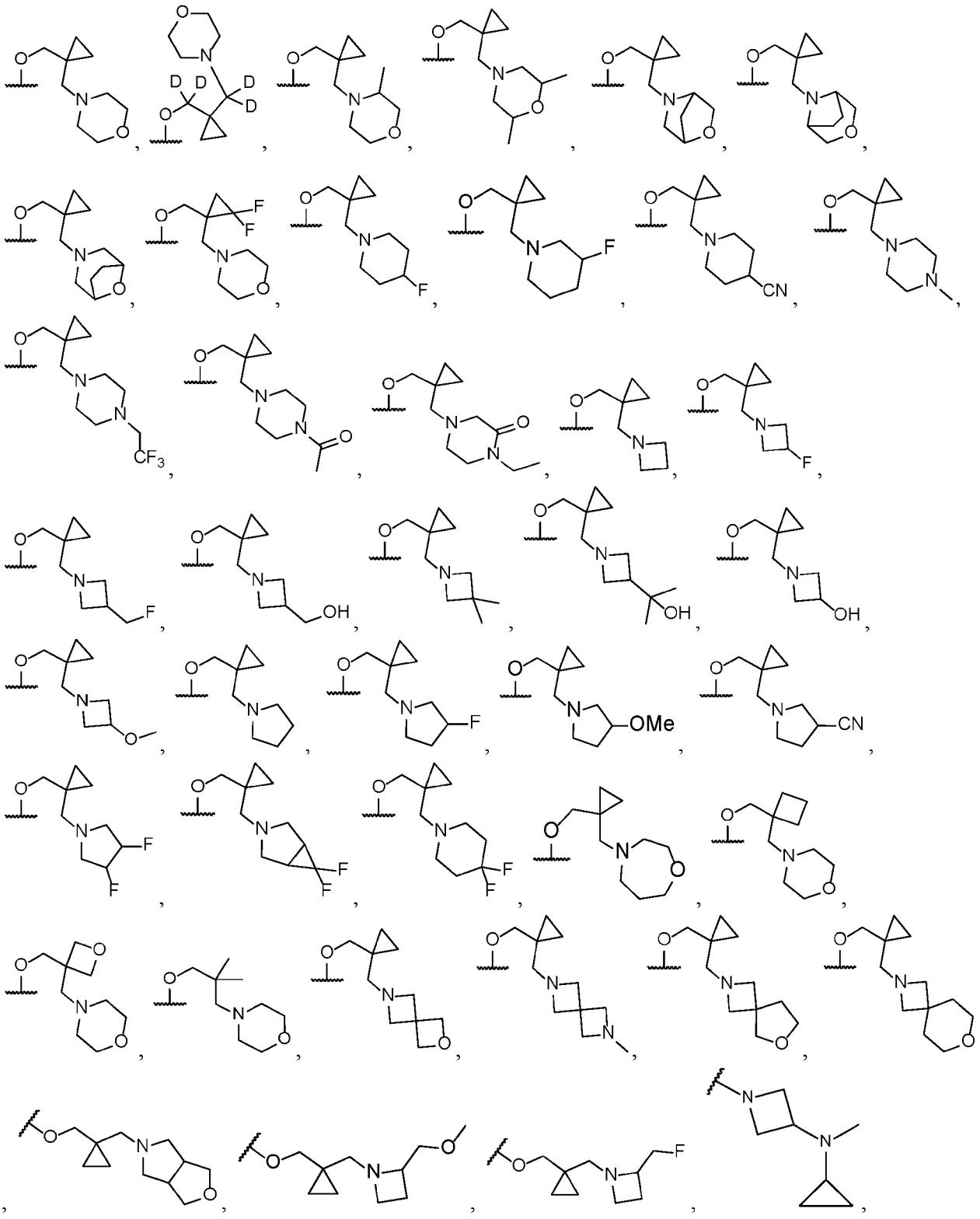
[0125] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked pyrrolidine, piperidine, piperazine, or morpholine; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, -$NR_{6a}R_{6a}$, imidazole or a C_{1-3} alkyl; wherein the imidazole is optionally substituted with a methyl; and the C_{1-3} alkyl is optionally substituted with -$NR_{6a}R_{6a}$ or hydroxyl.

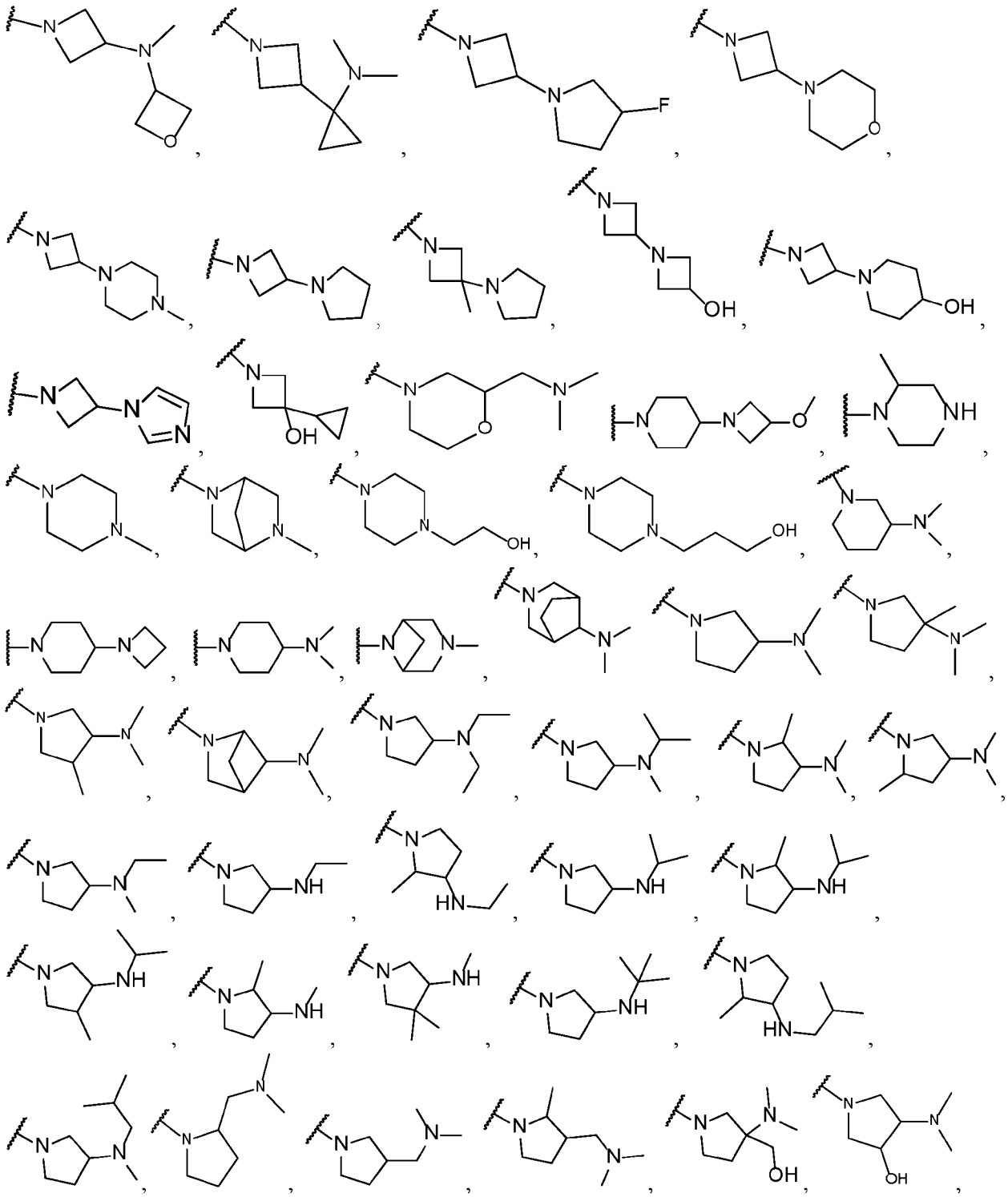
[0126] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,4-c]pyrrole, 1,6-diazaspiro[3.3]heptane, or 1,6-diazaspiro[3.4]octane; each of which is optionally substituted with one or more halogen, or a C_{1-3} alkyl.

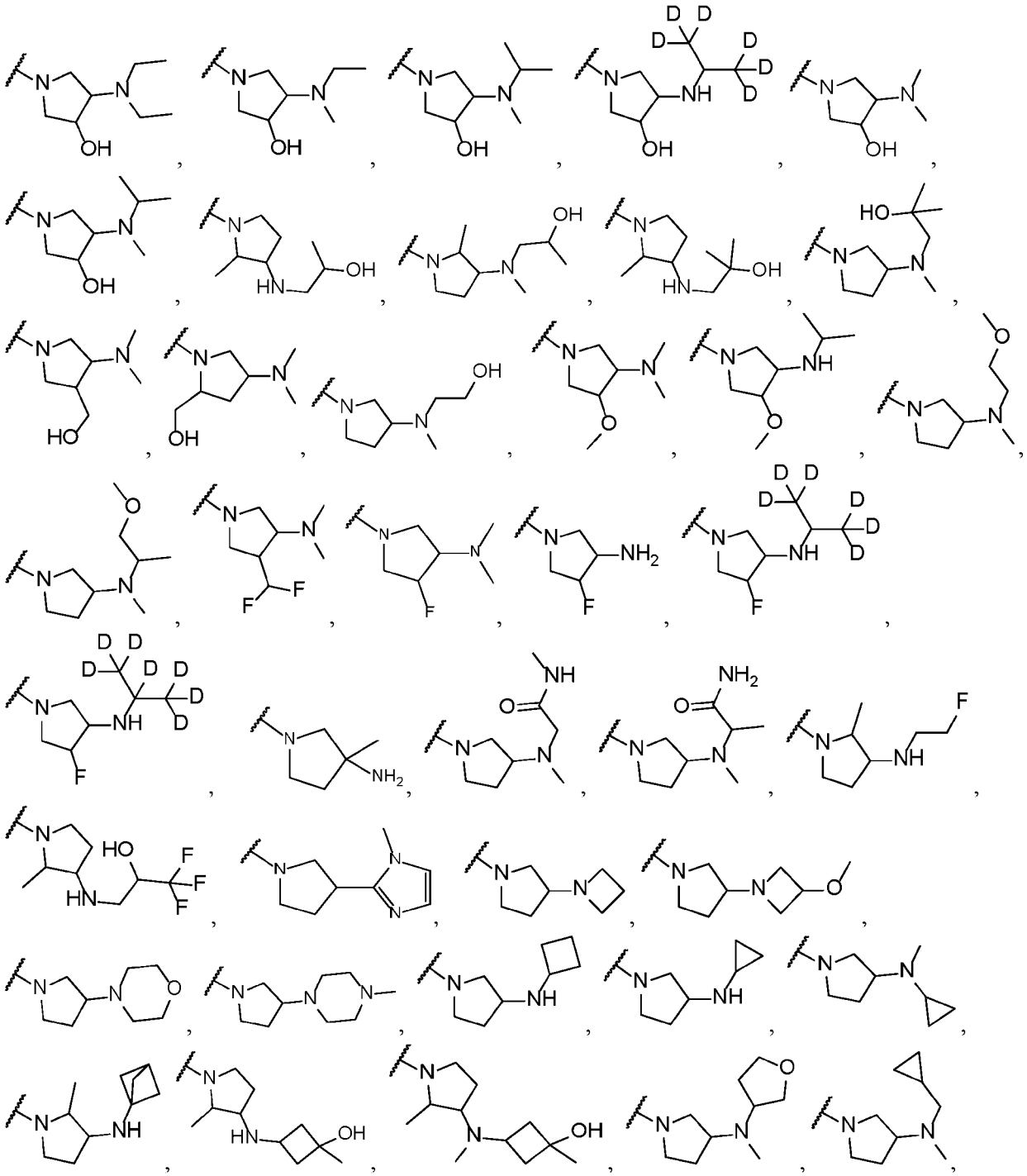
[0127] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked pyrrolidine, piperidine, piperazine, morpholine, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, C_{1-3} alkoxy, -$NR_{6a}R_{6a}$, azetidine, a C_{1-3} alkyl, or an imidazole optionally substituted with a methyl; the azetidine is optionally substituted with hydroxyl or C_{1-3} alkoxy; and the C_{1-3} alkyl is optionally substituted with -$NR_{6a}R_{6a}$ or hydroxyl.

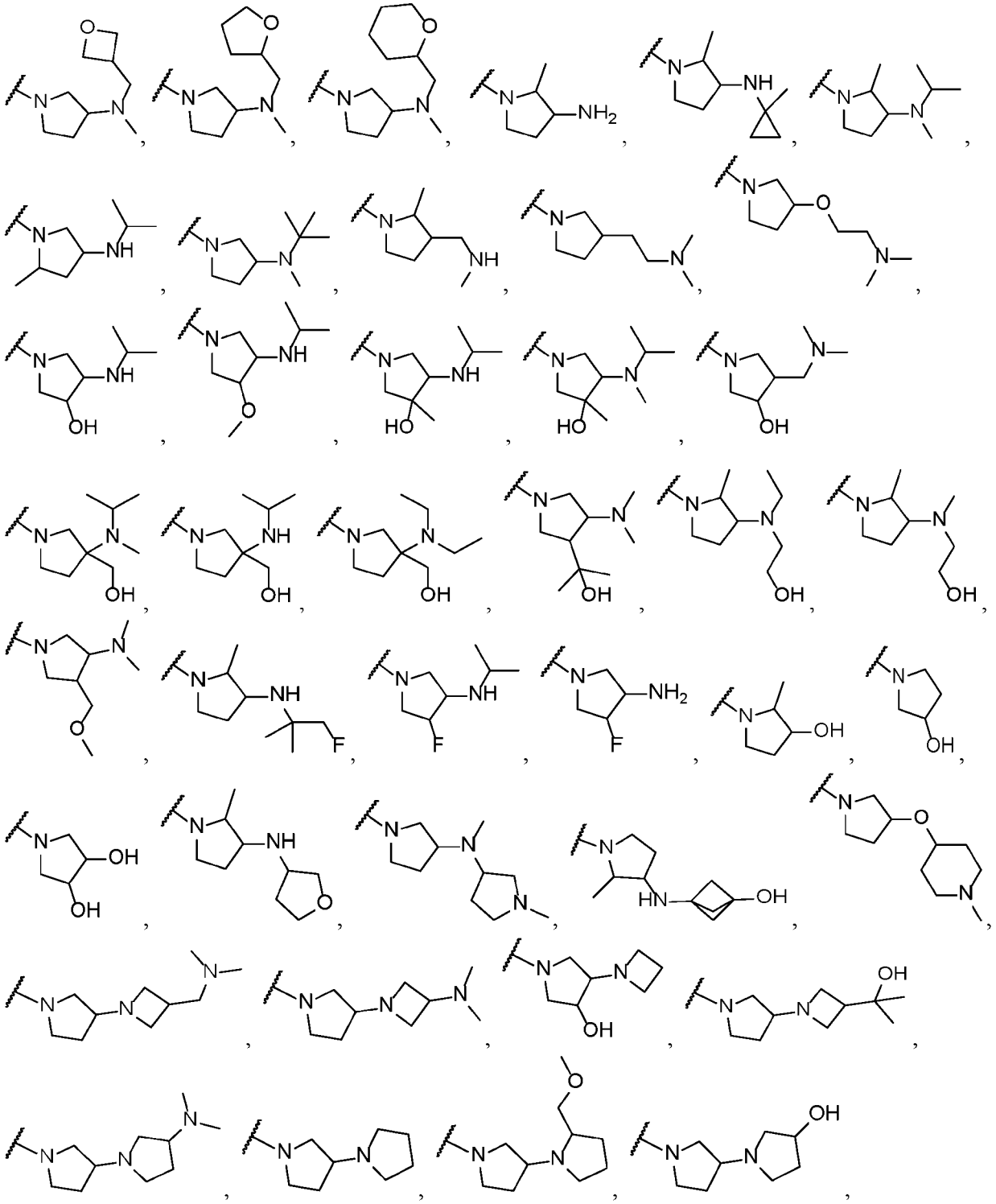
[0128] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-6-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, or 5-azaspiro[2.4]heptane; each of which is optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with -$NR_{6a}R_{6a}$.

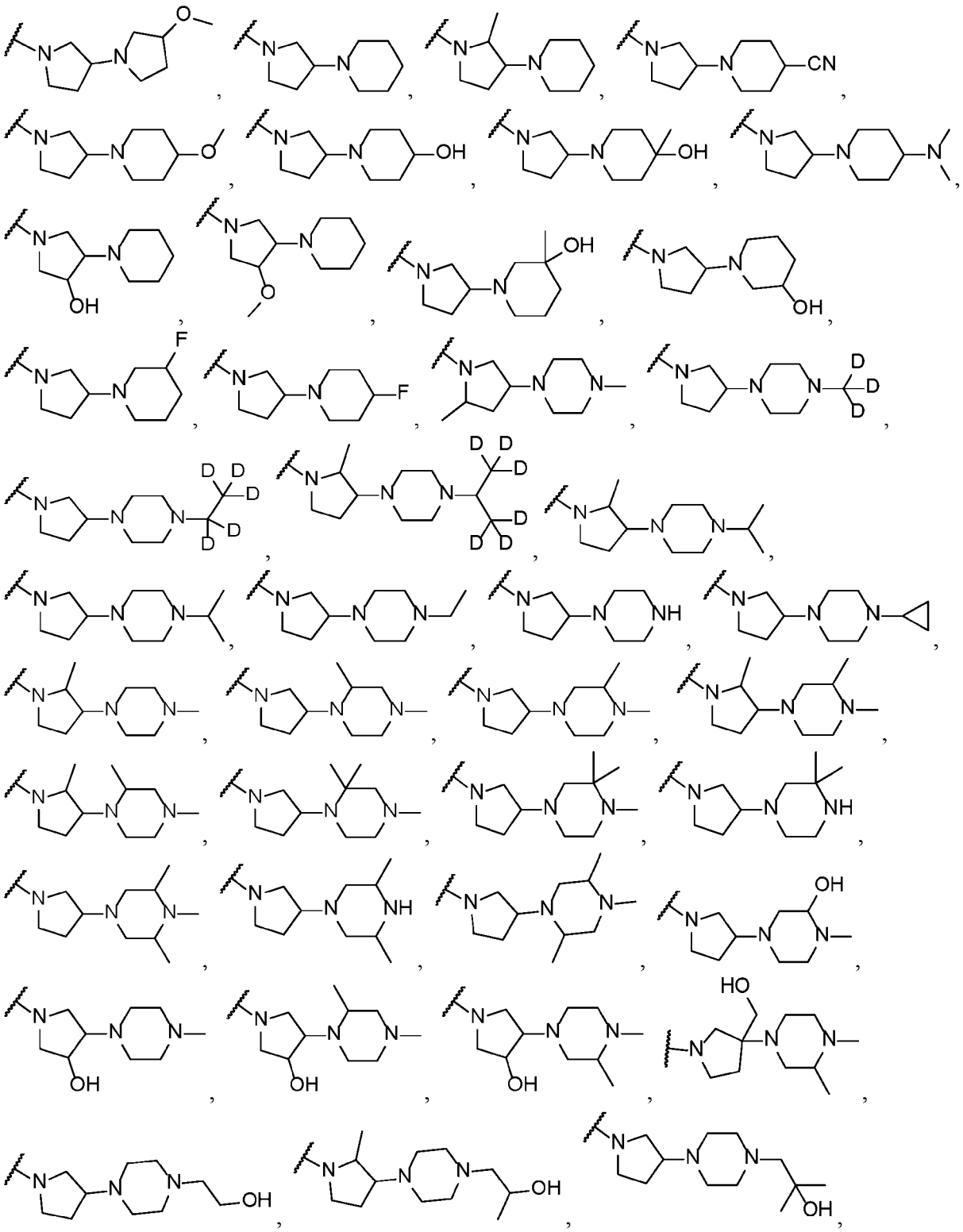
[0129] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

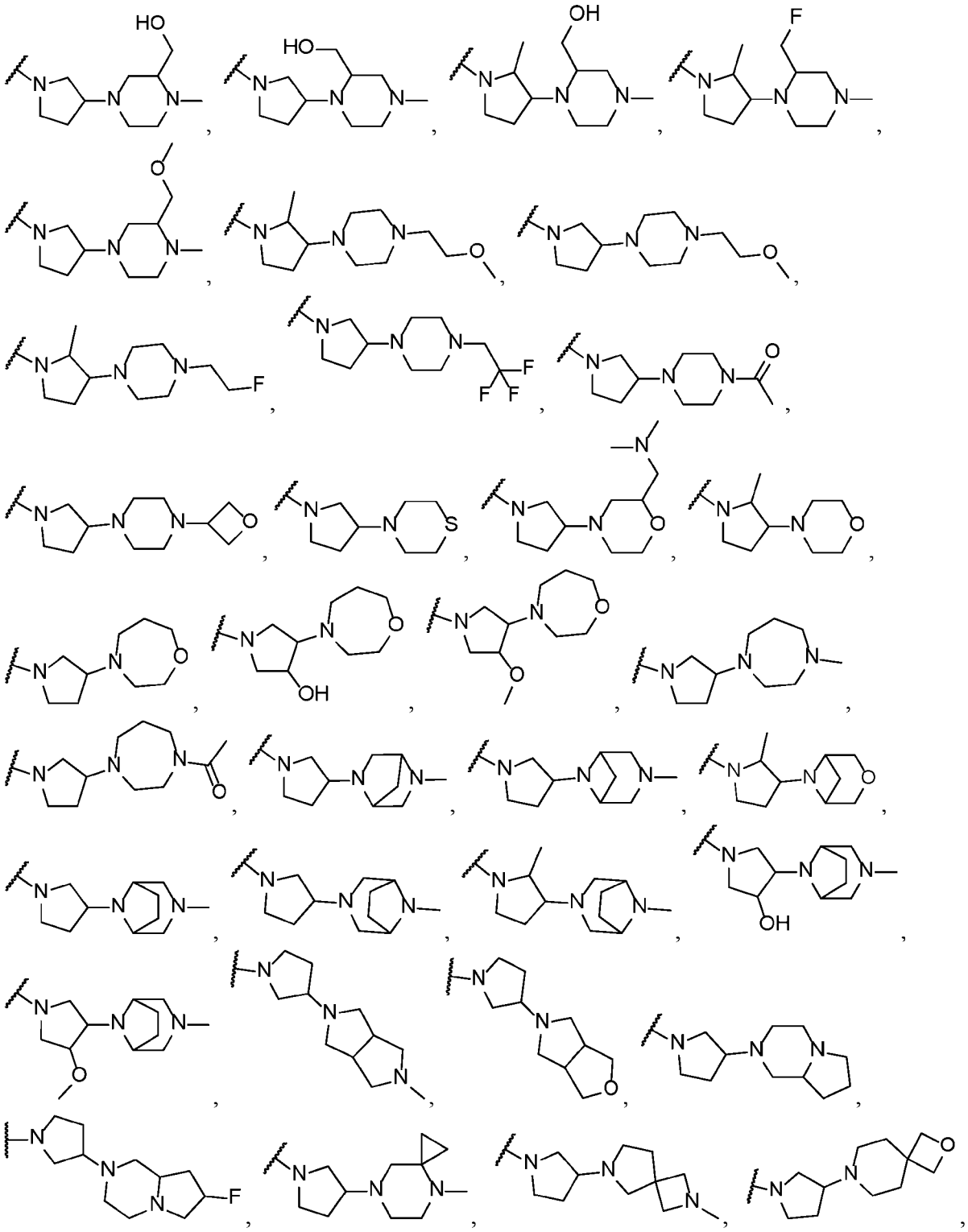


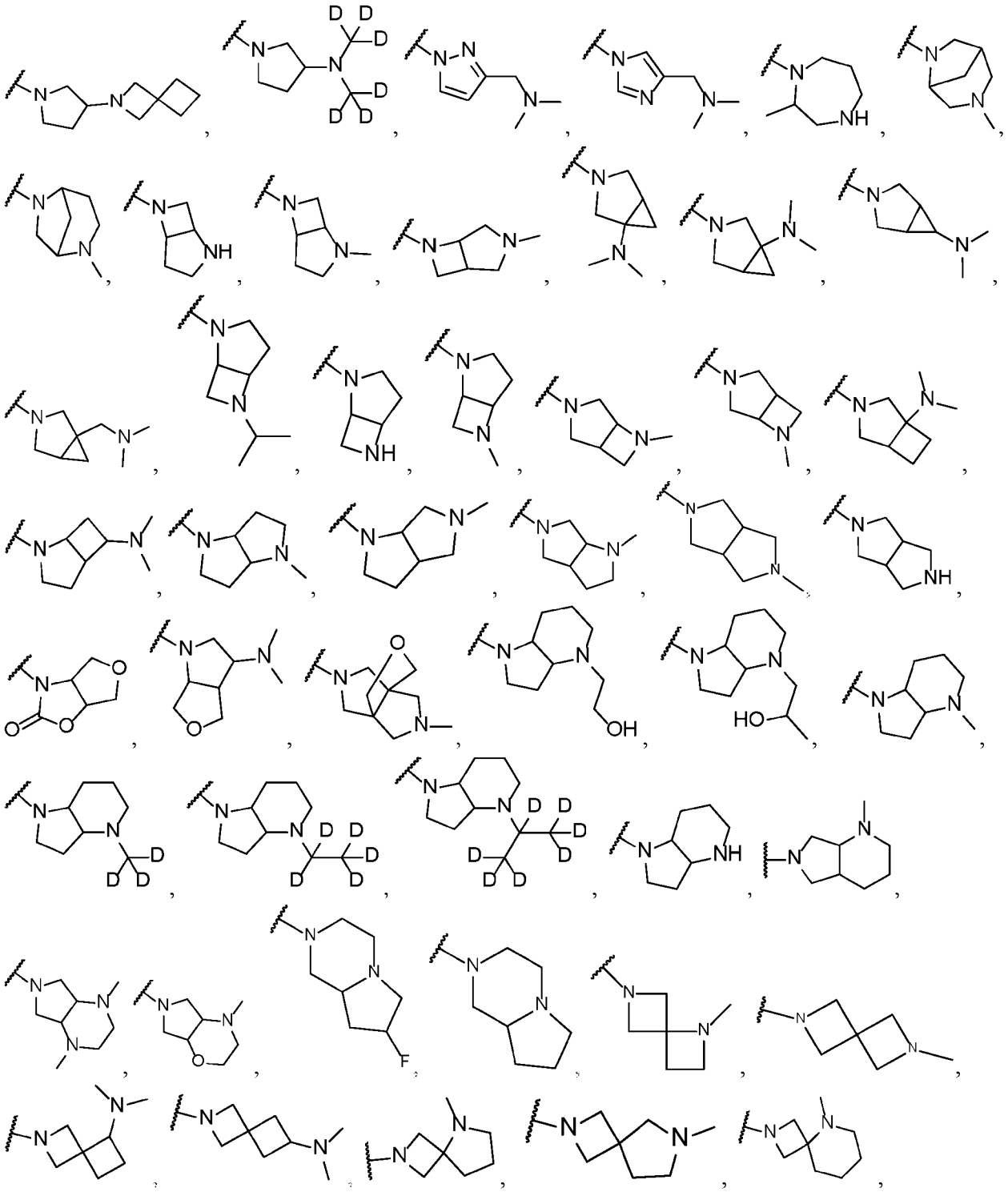


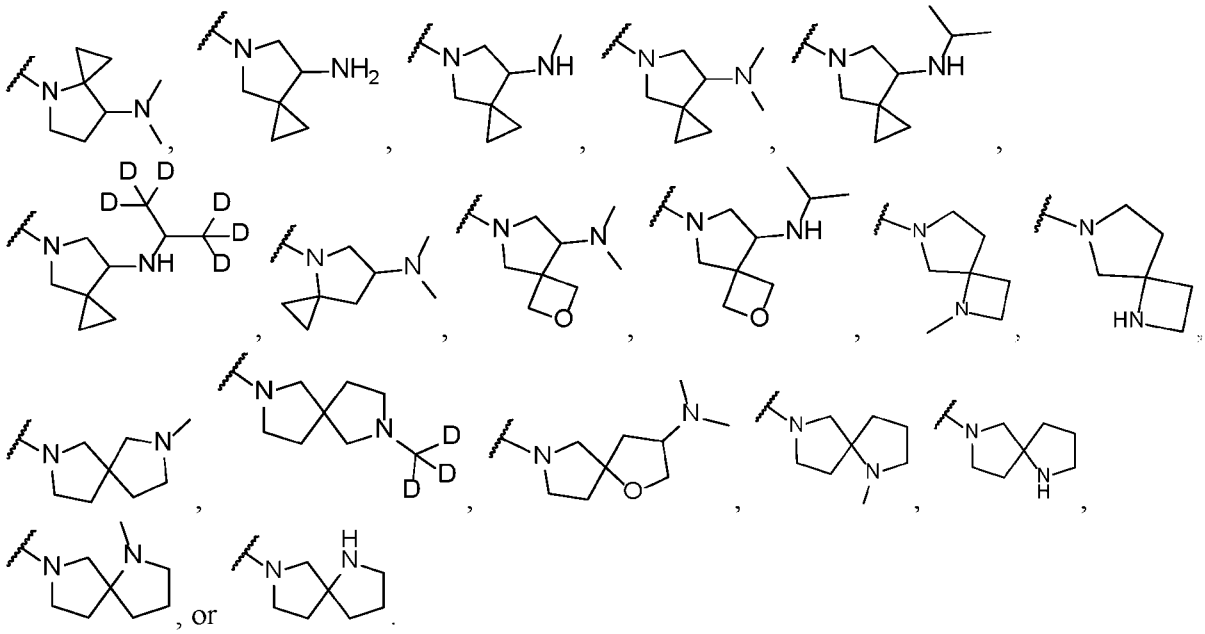






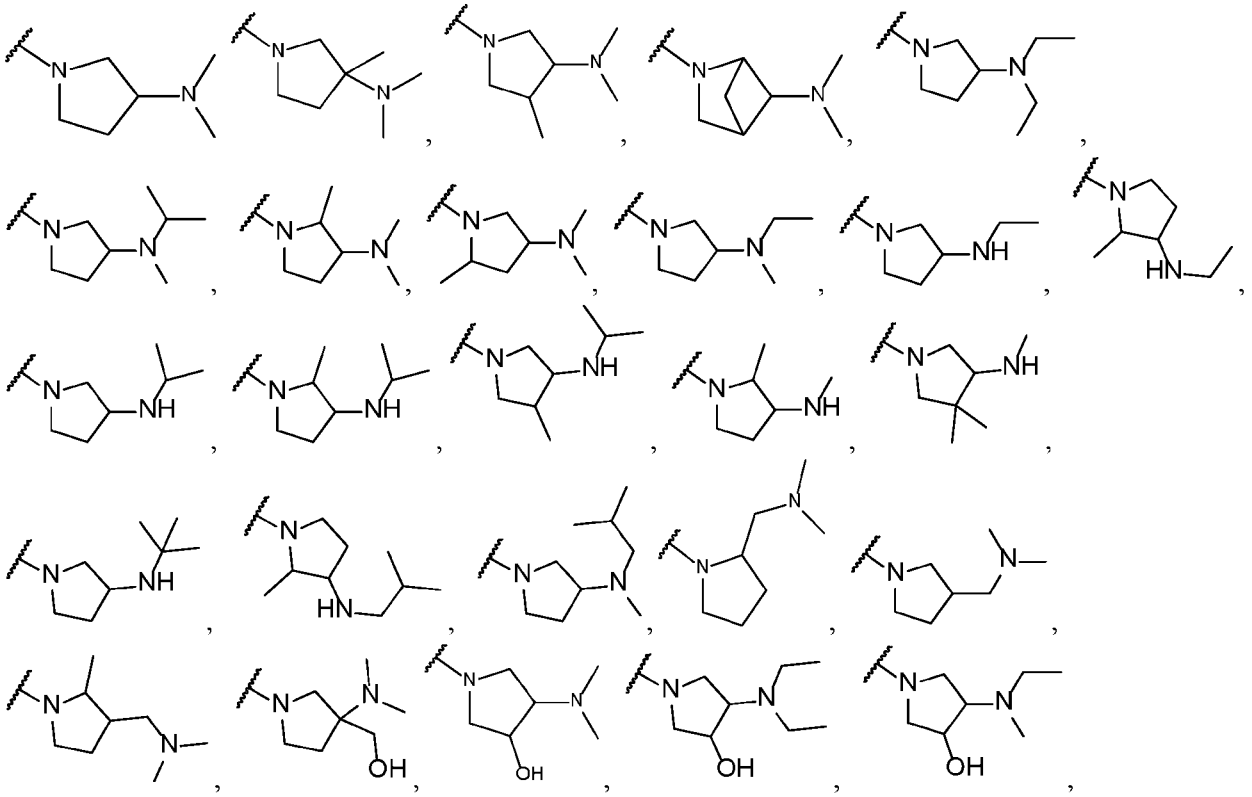


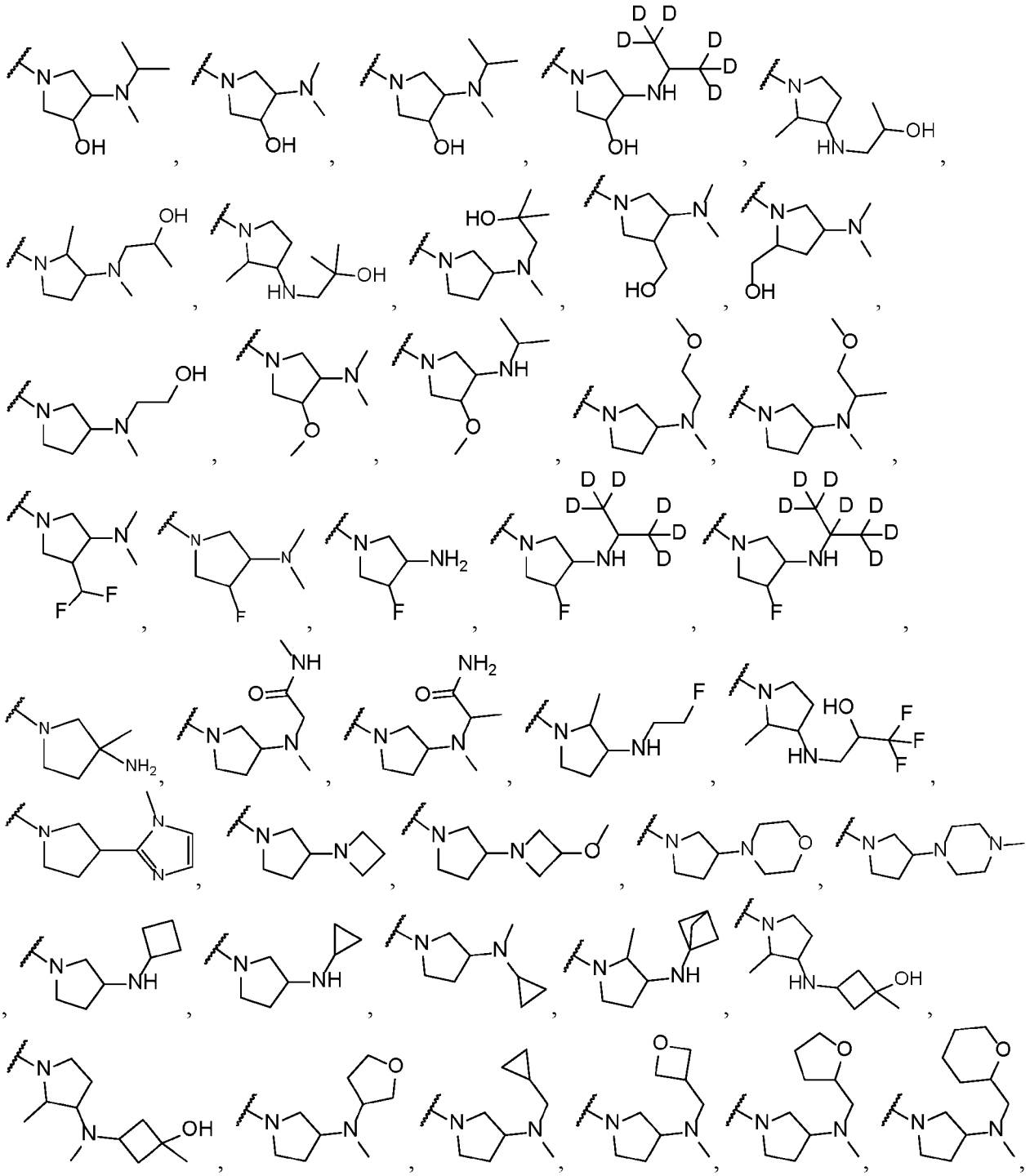


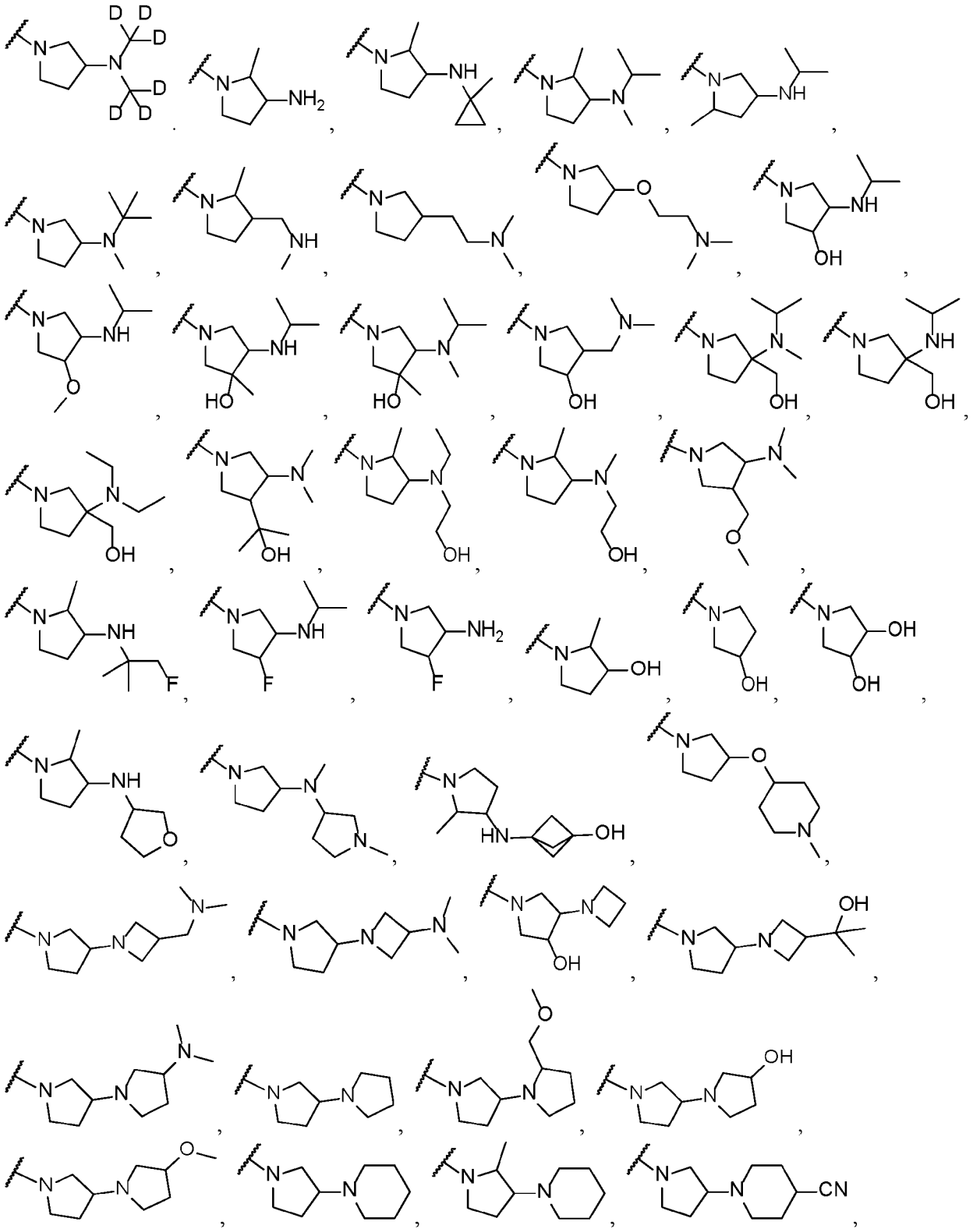


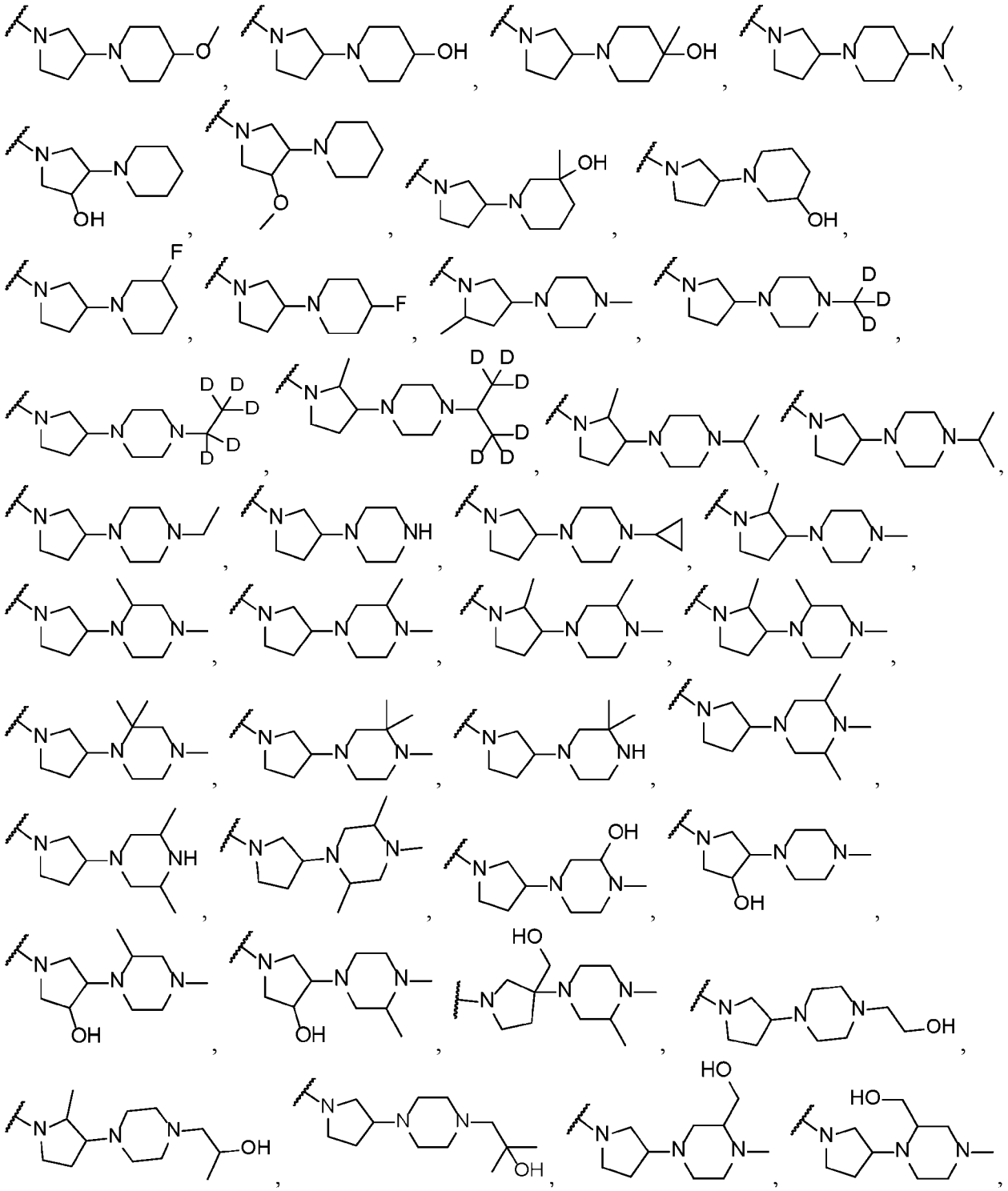
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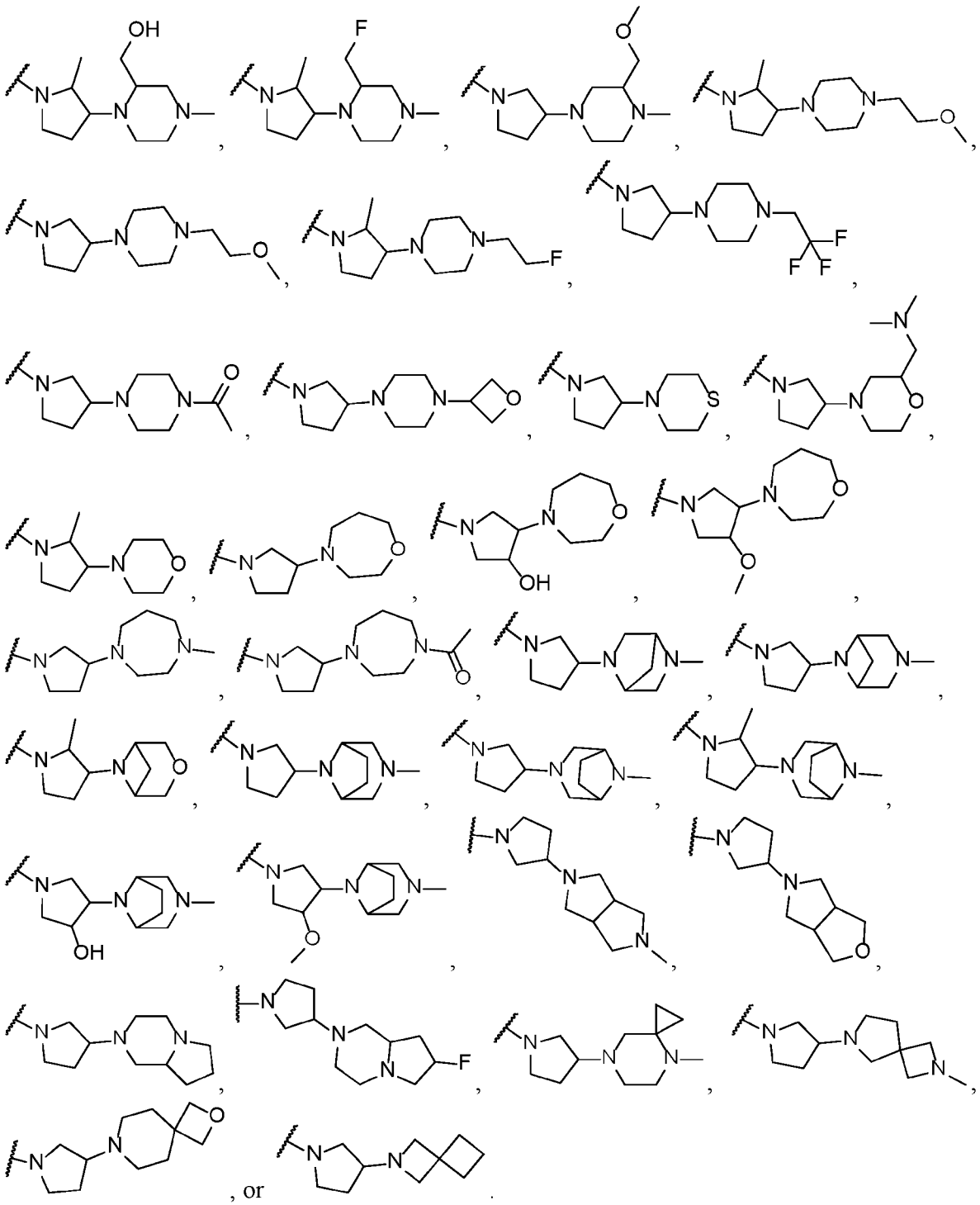
[0130] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from



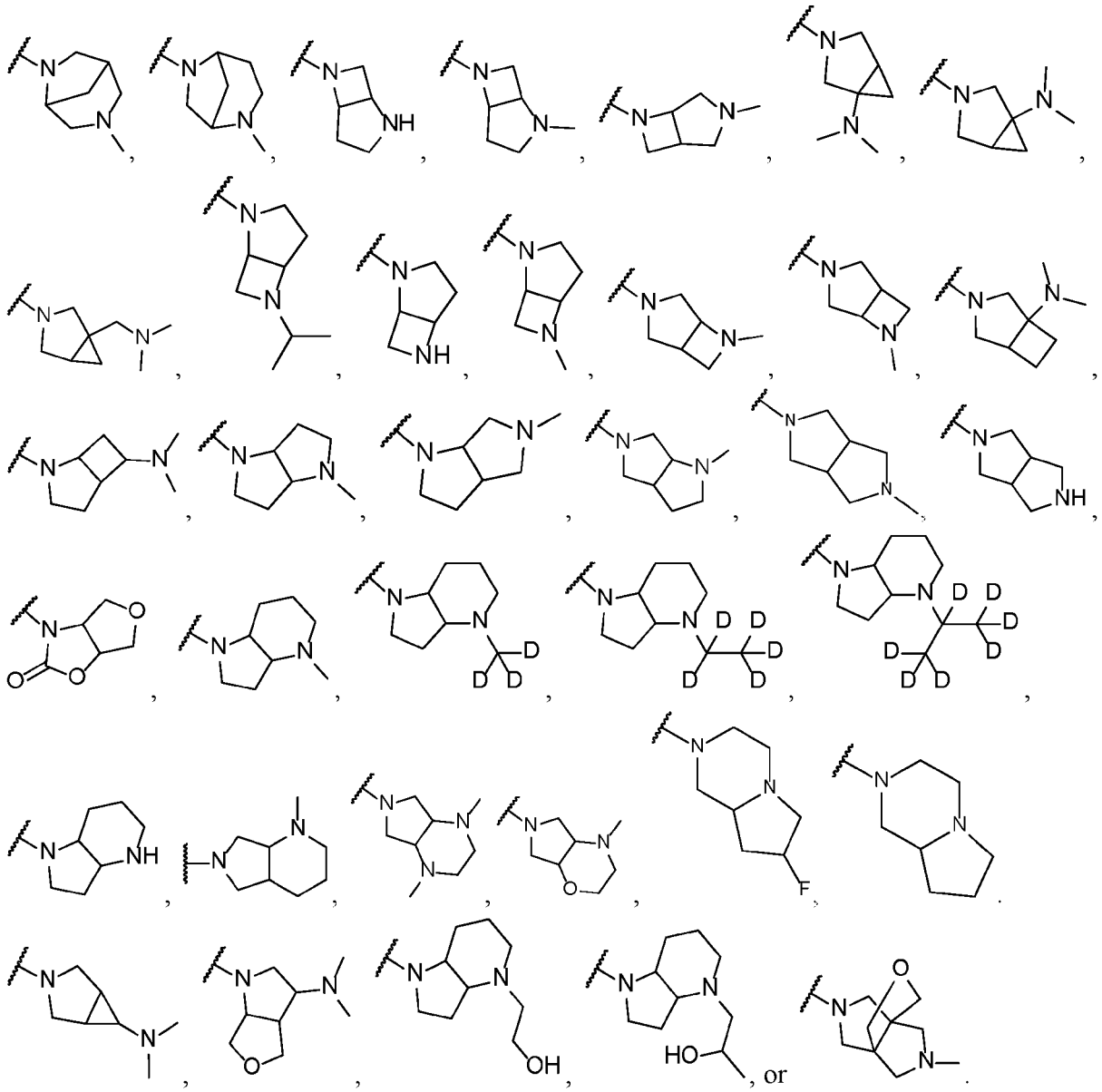




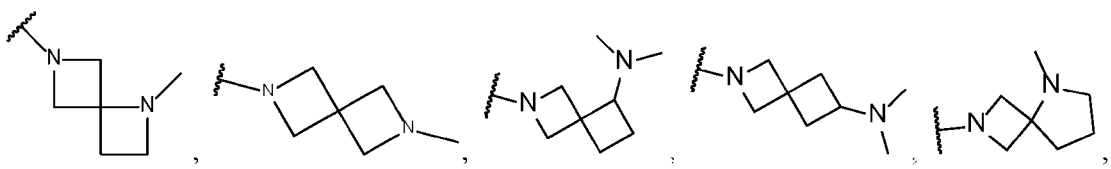


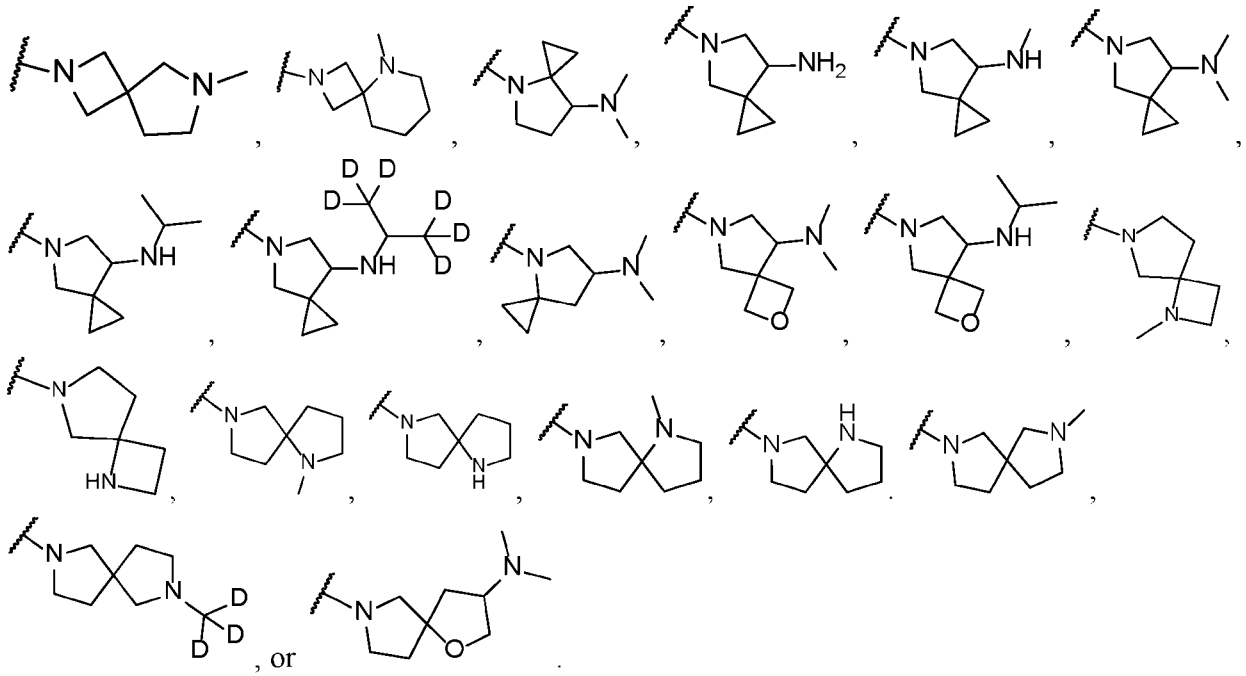


[0131] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from



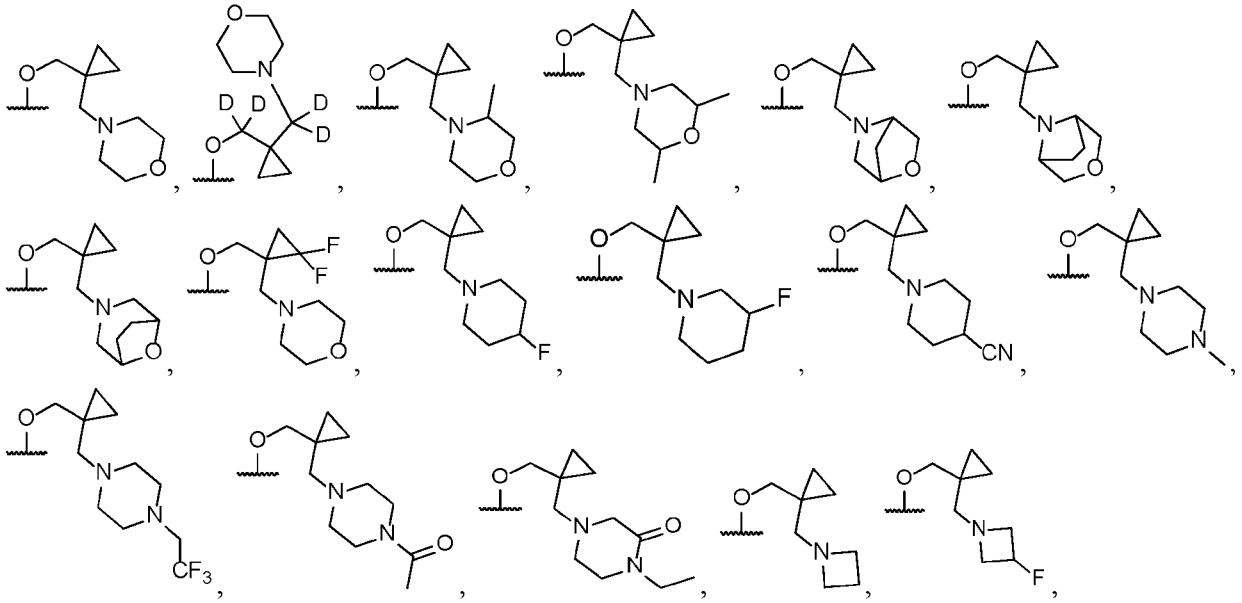
[0132] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

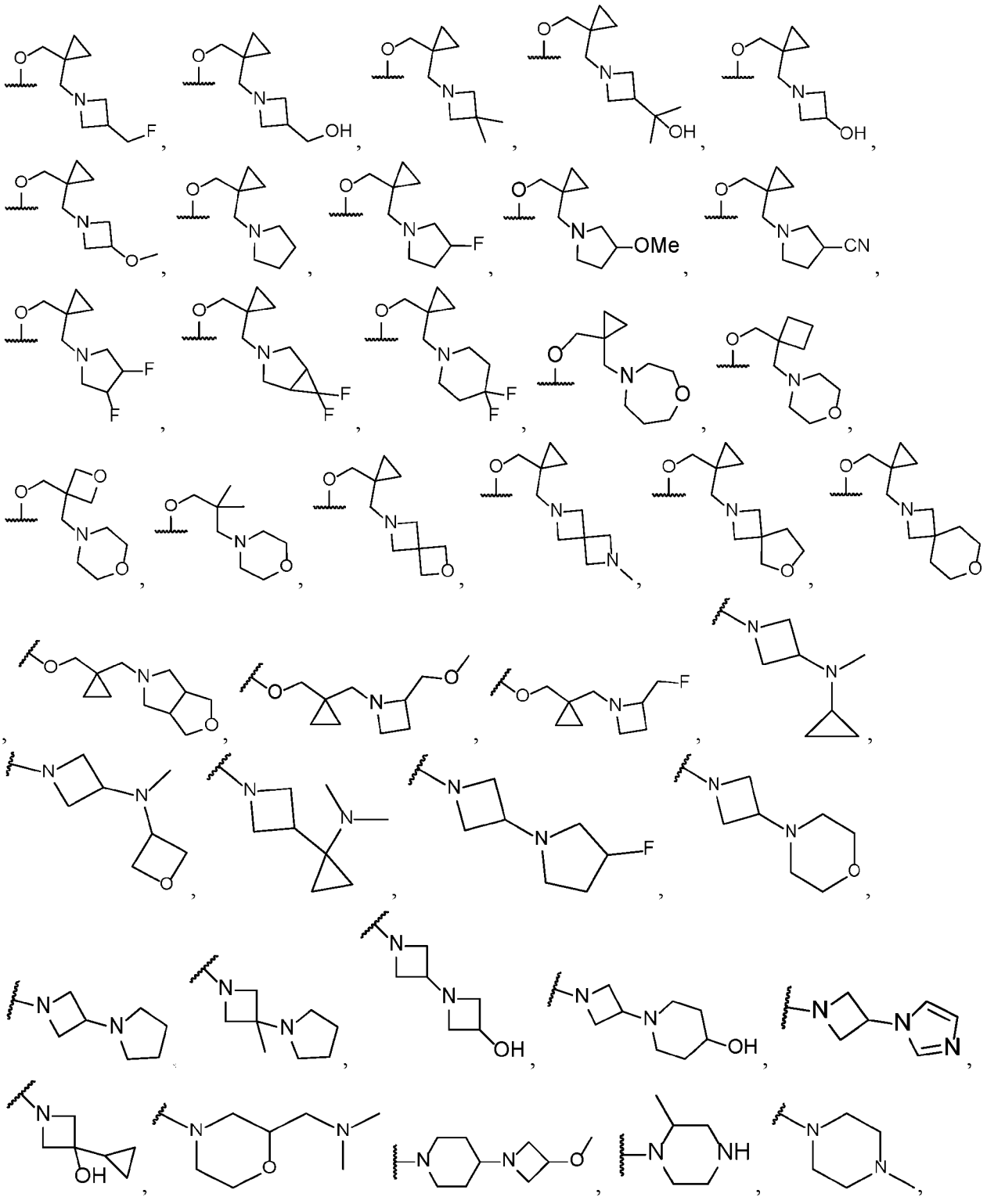


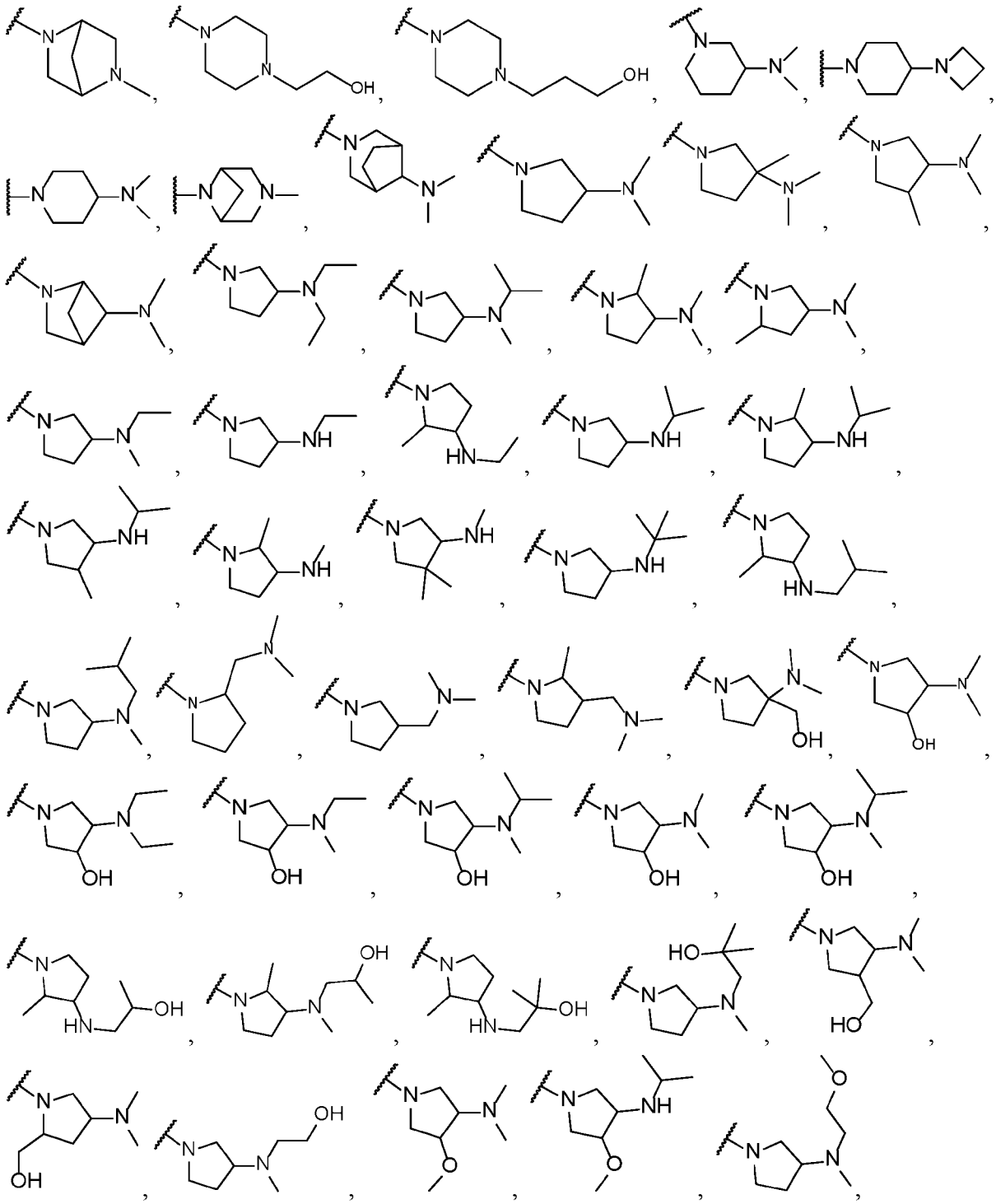


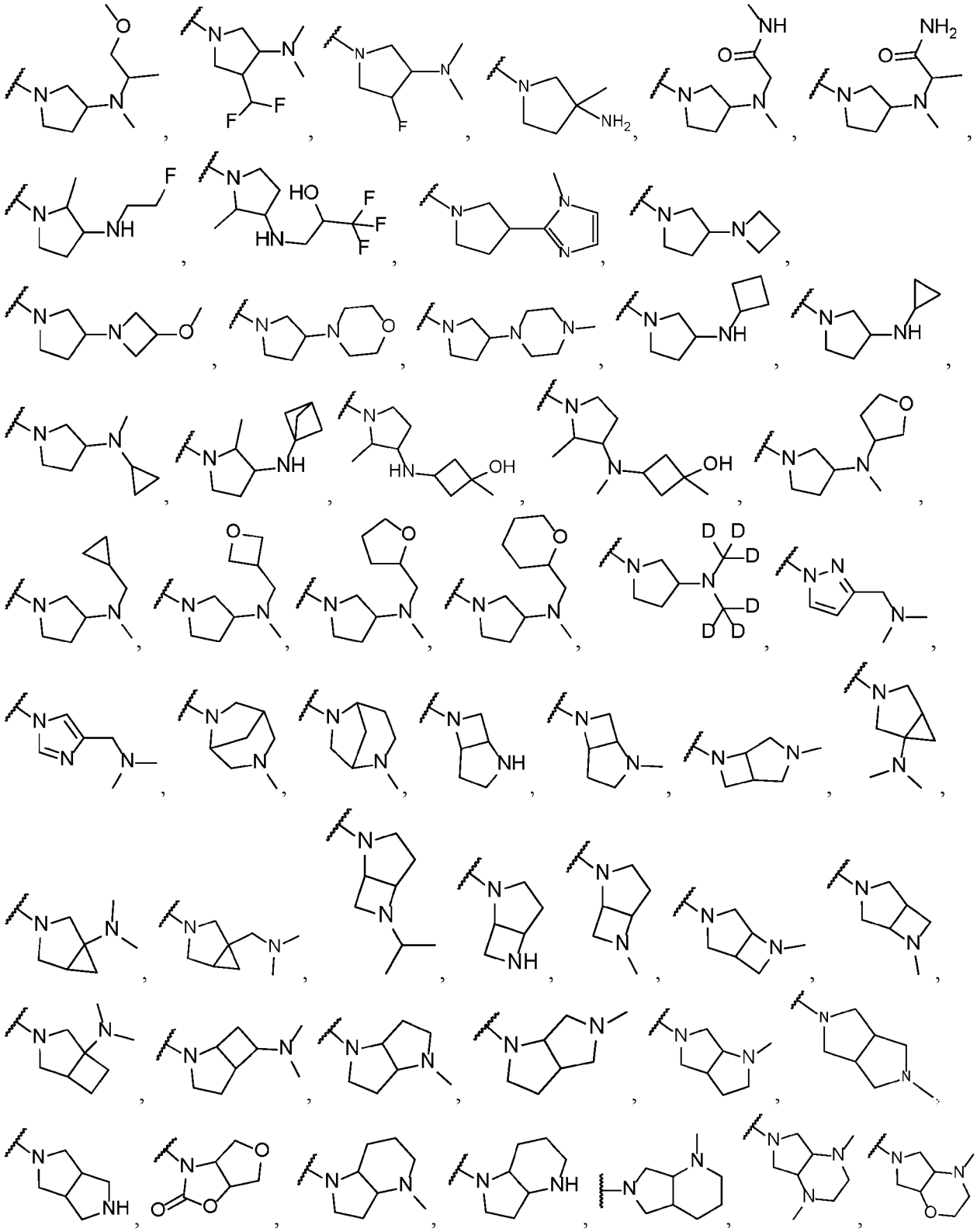
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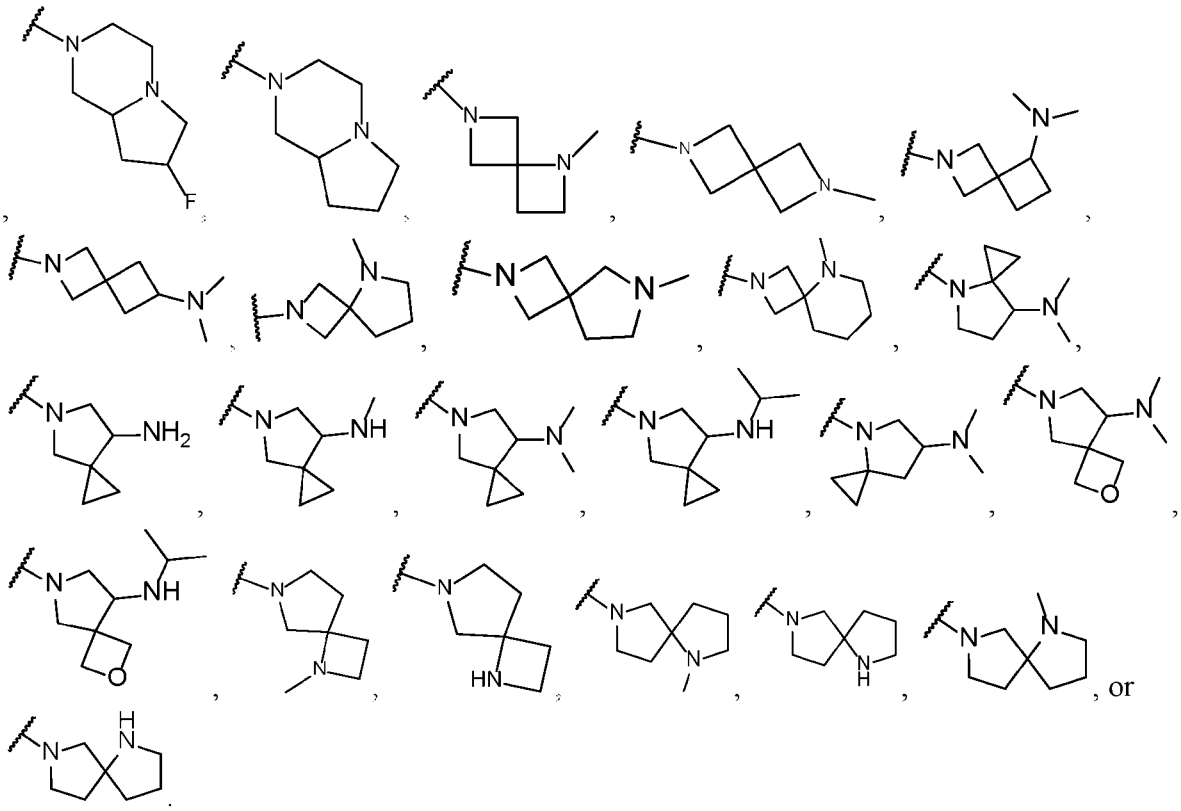
[0133] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from



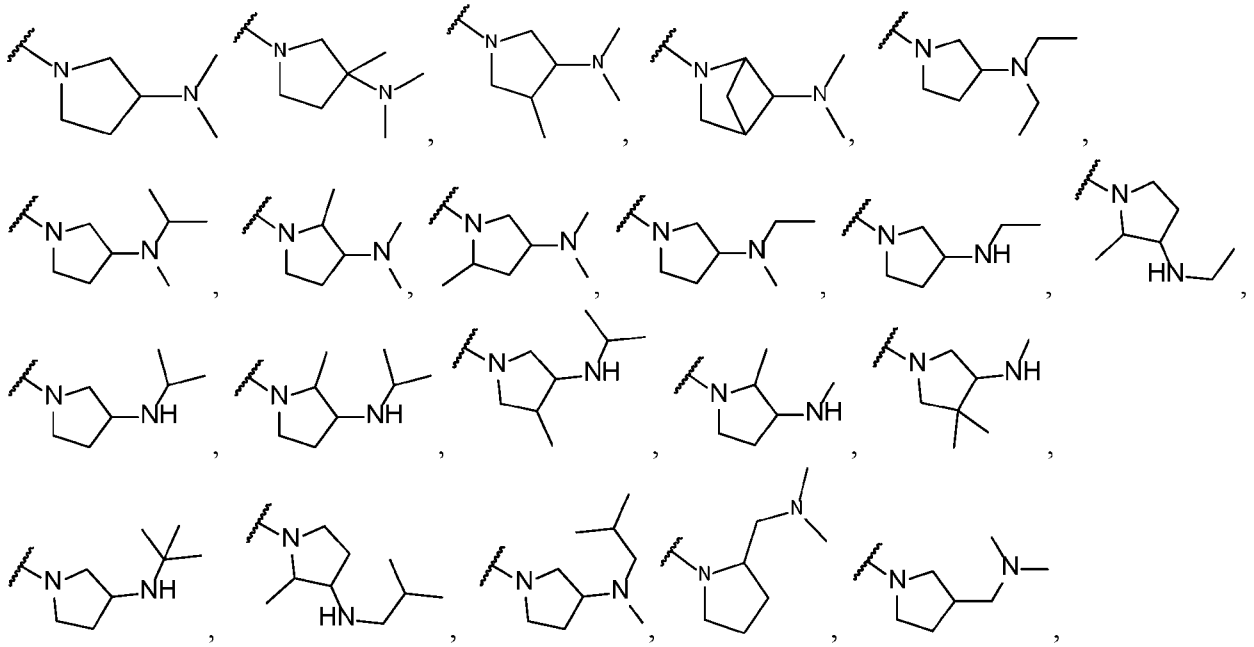


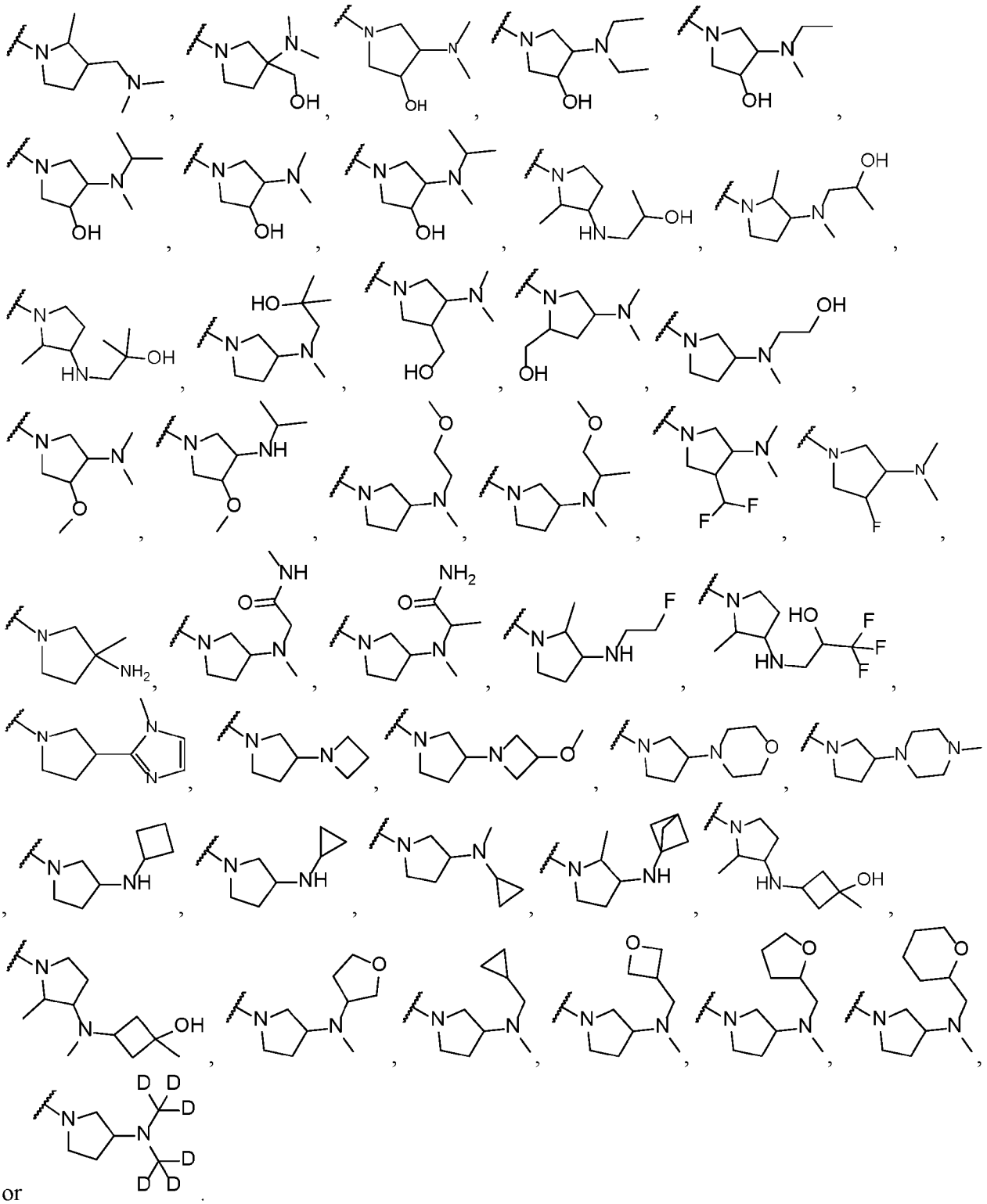






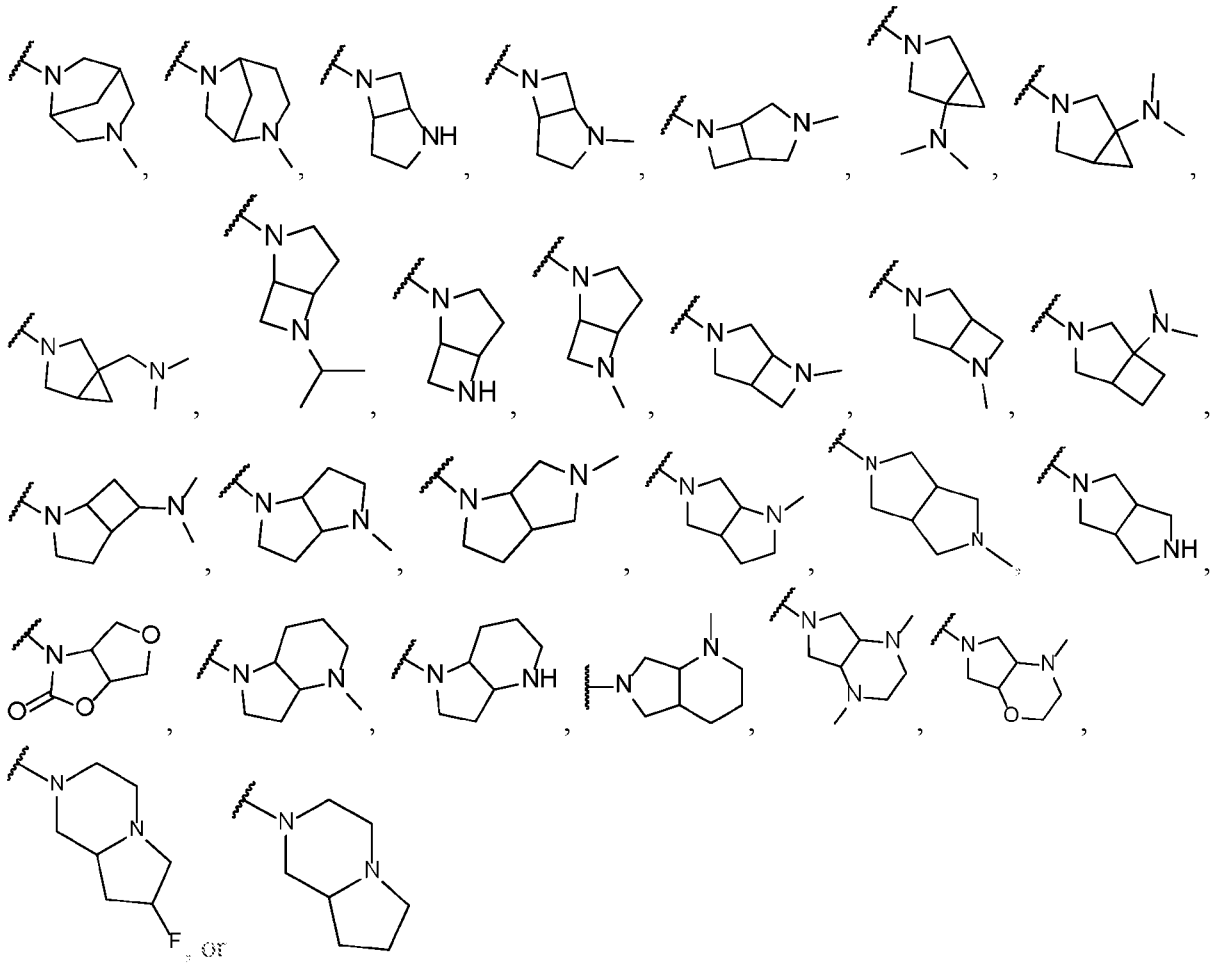
[0134] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from



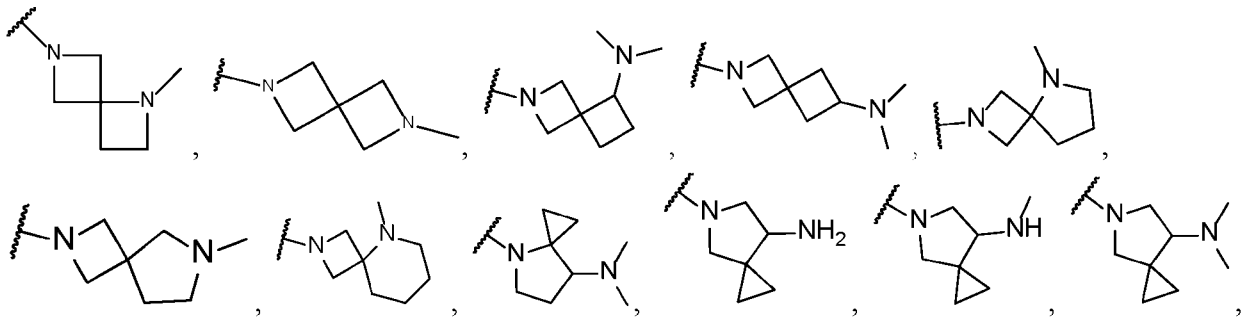


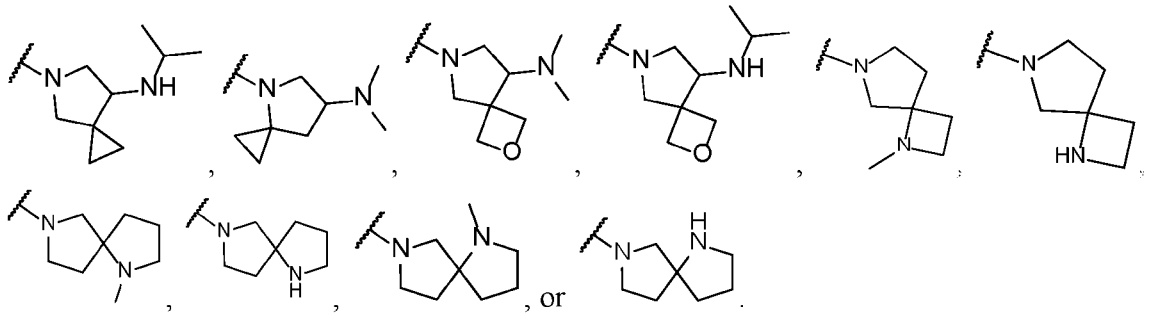
or

[0135] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

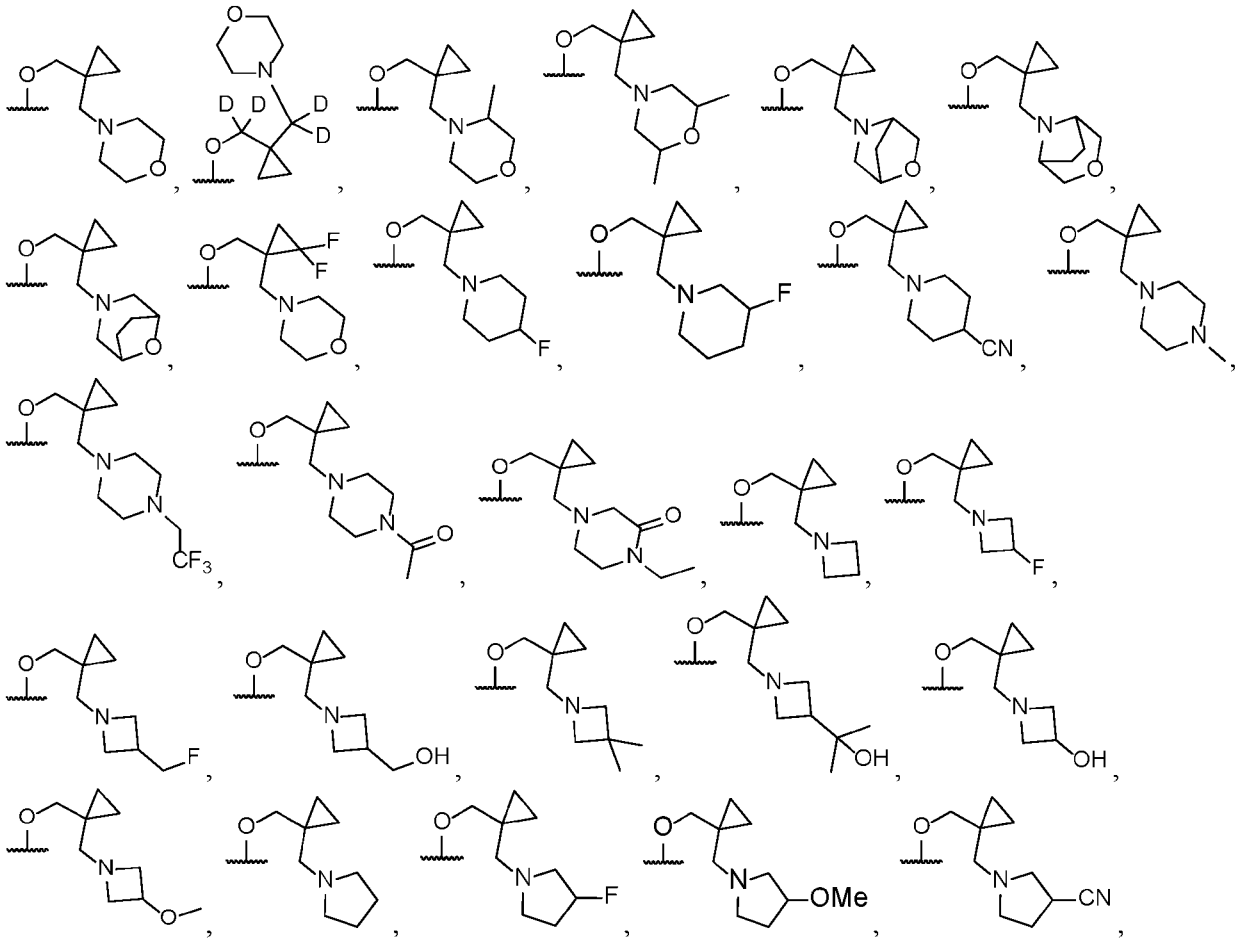


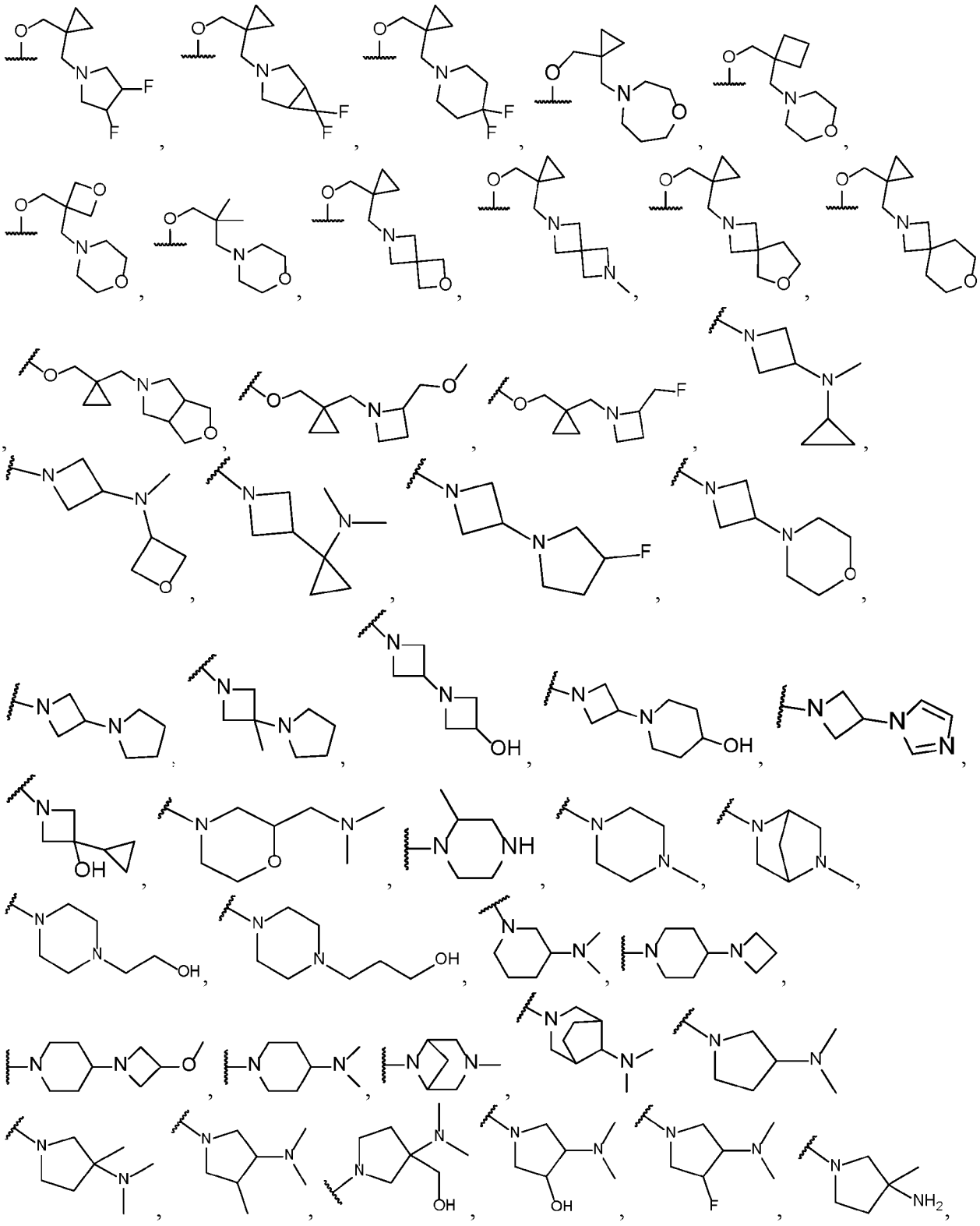
[0136] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

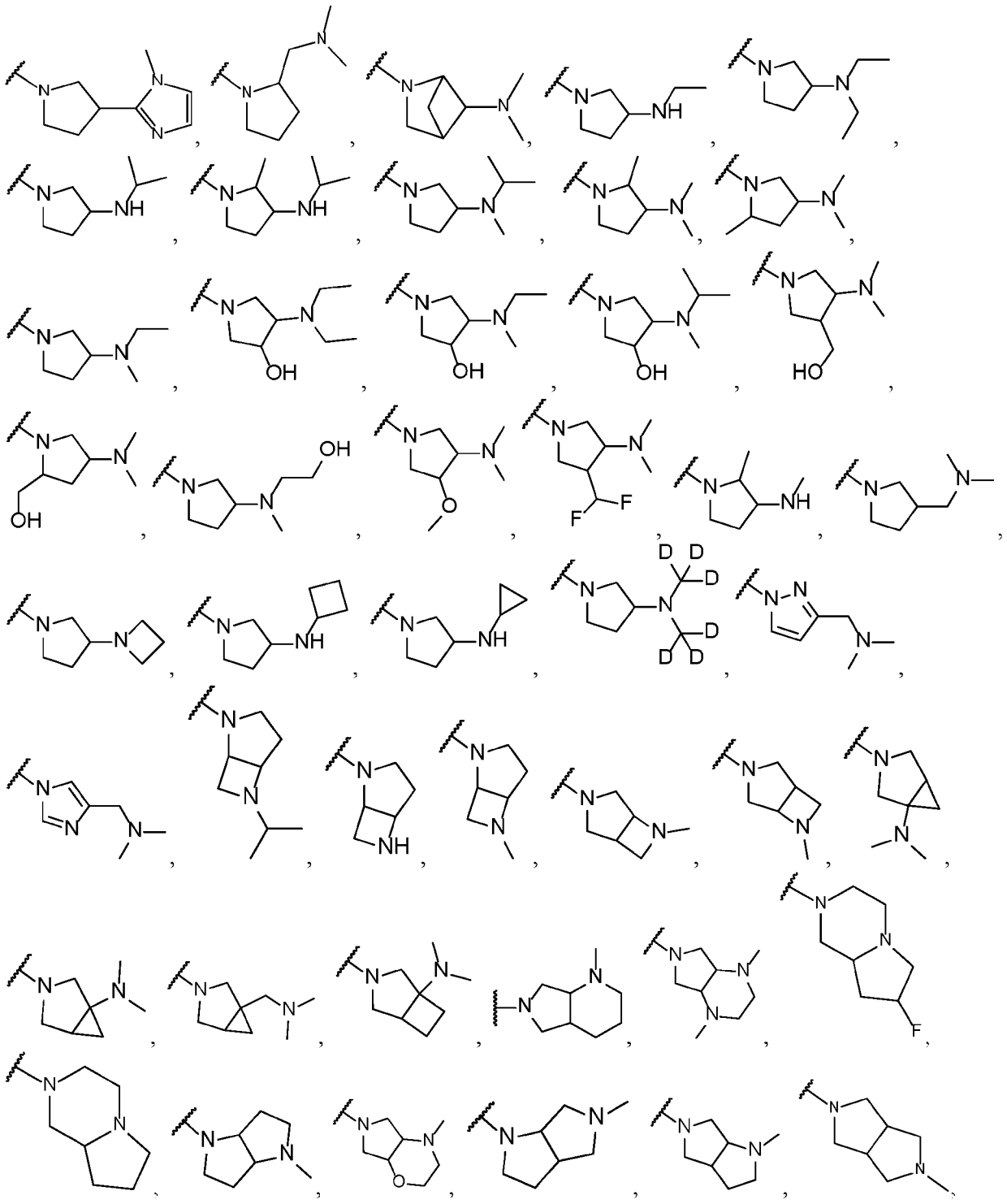


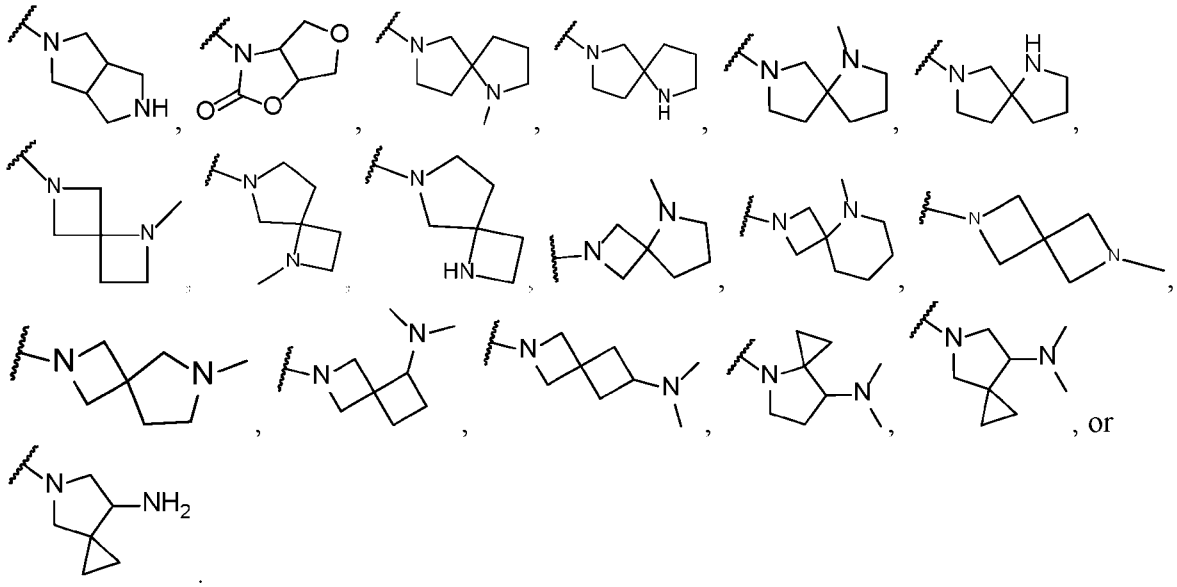


[0137] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from





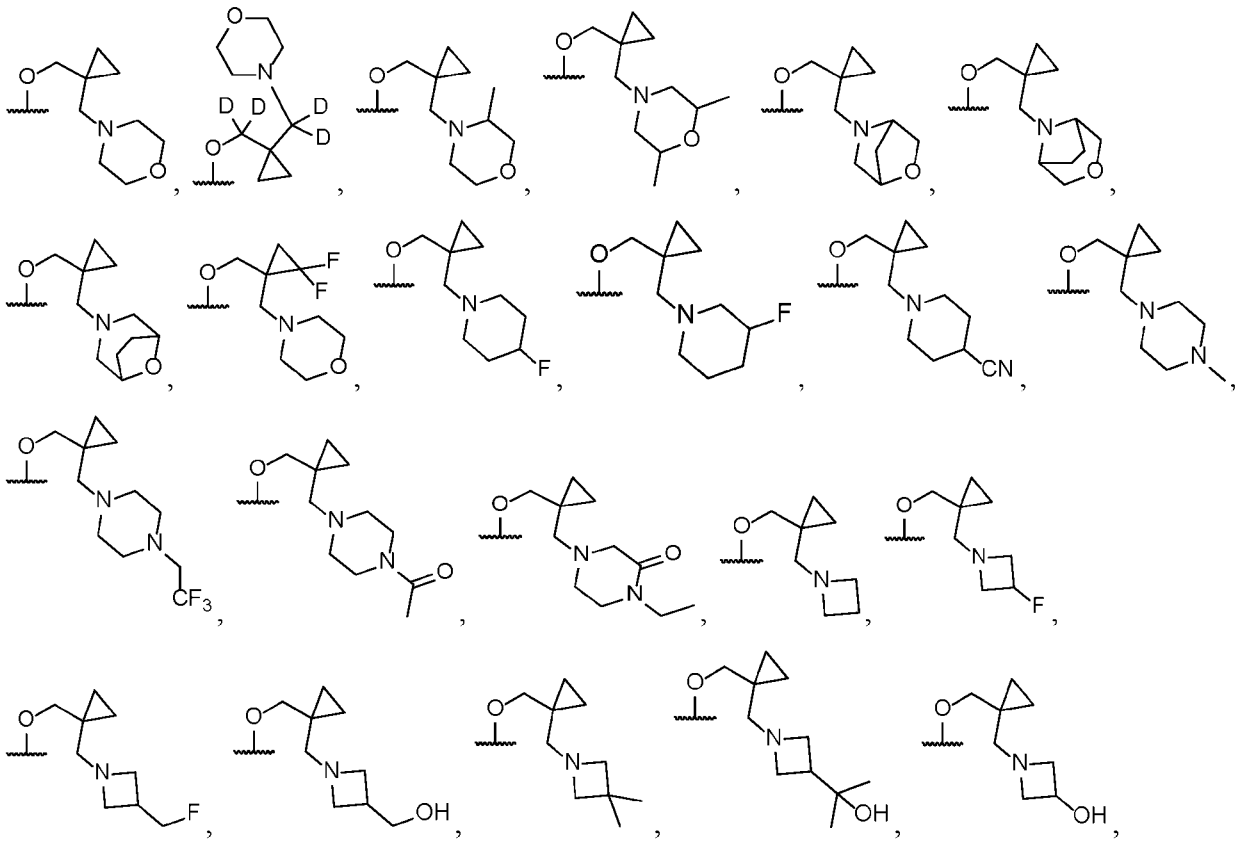


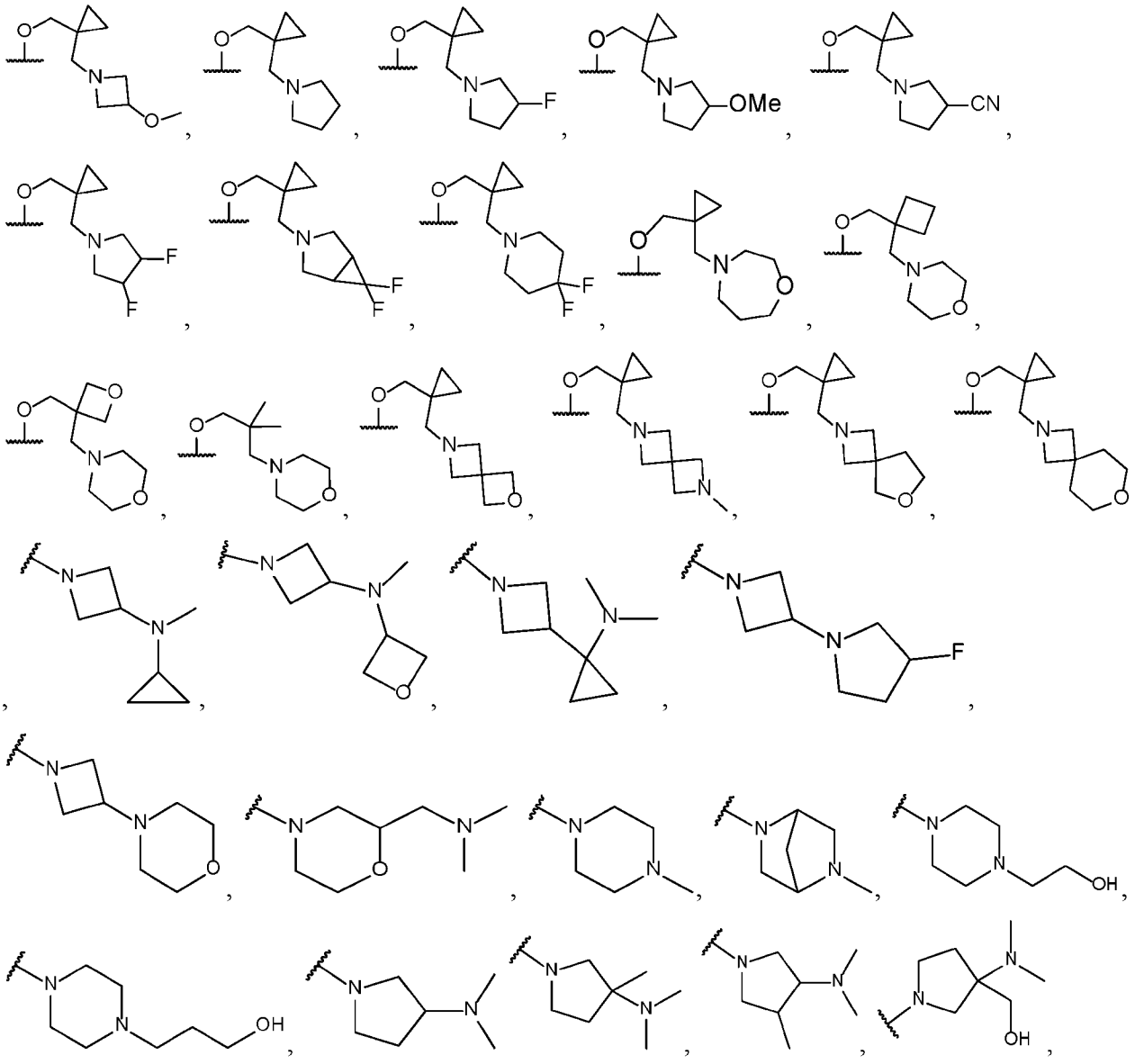


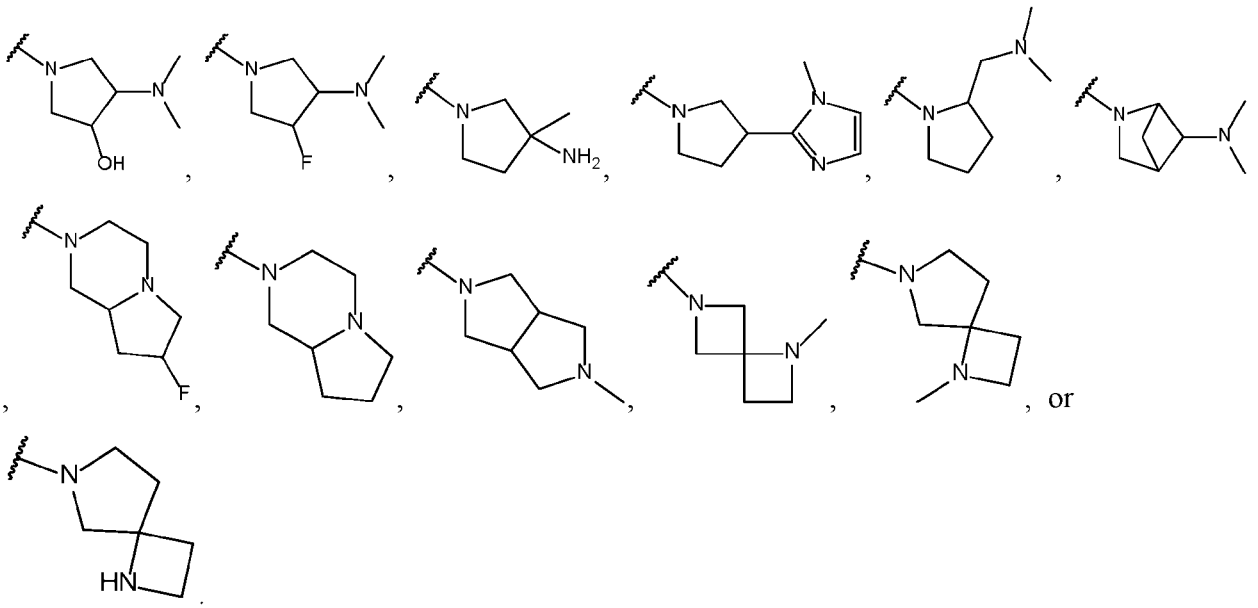
, or

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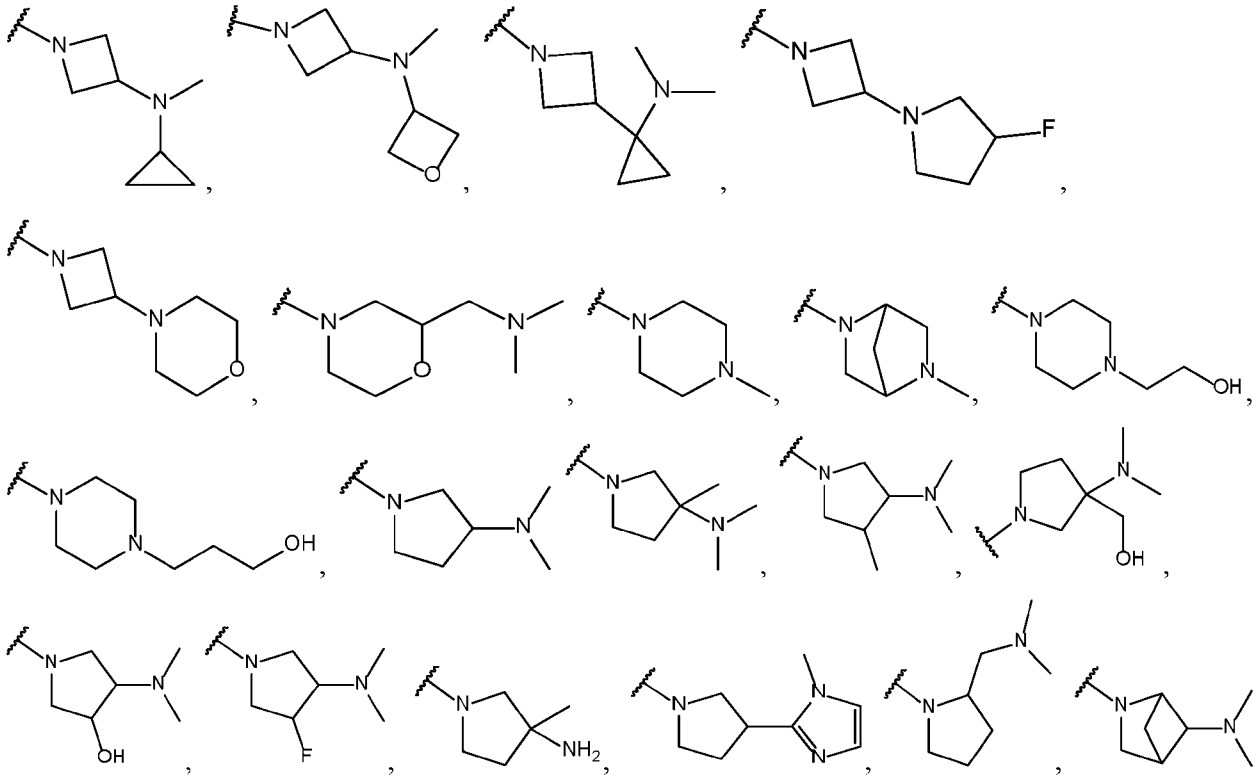
[0138] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

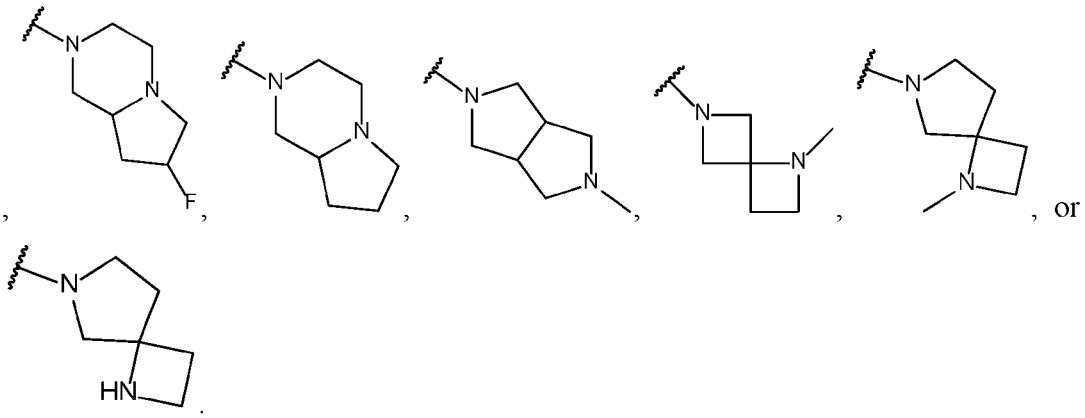




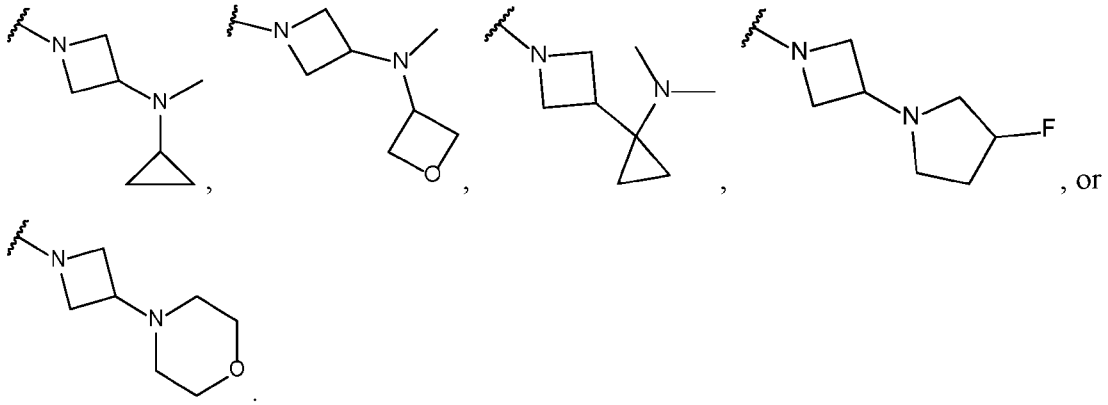


[0139] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

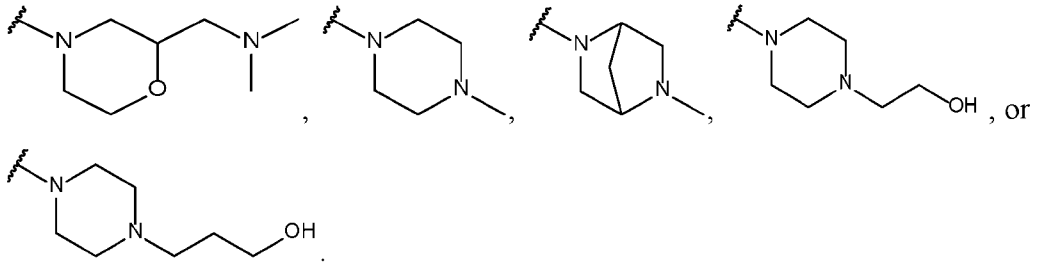




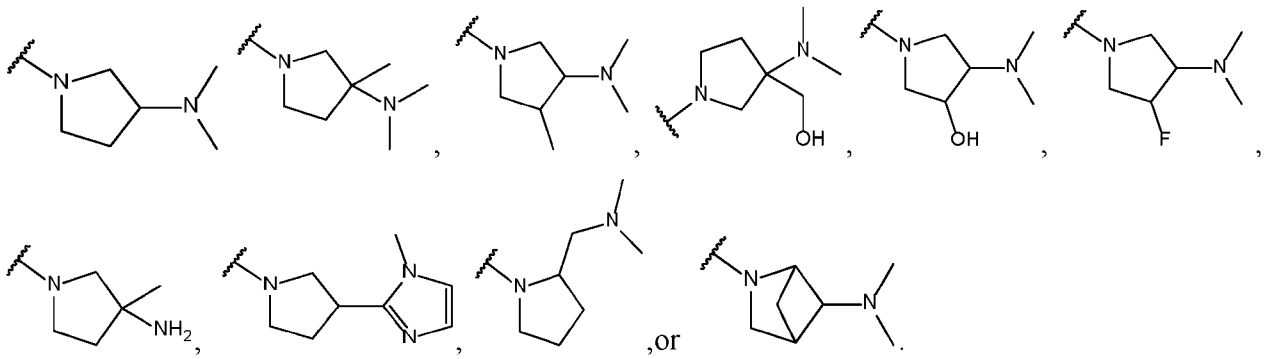
[0140] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from



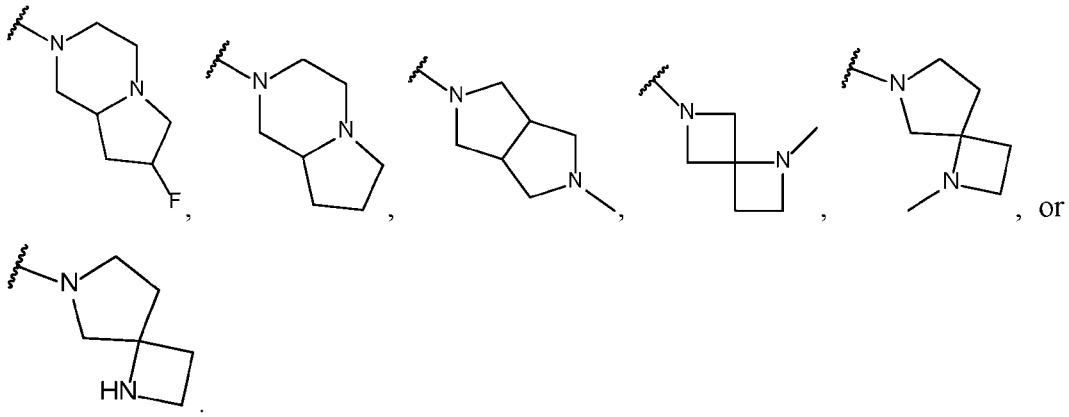
[0141] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from



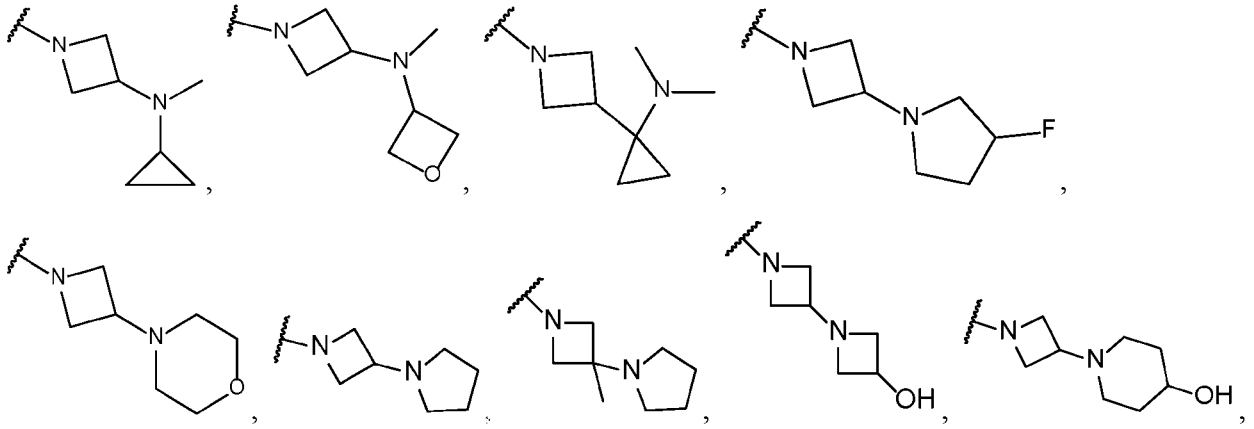
[0142] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

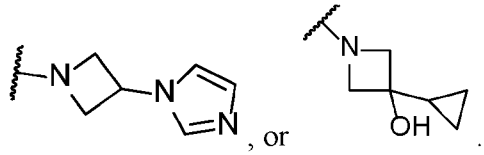


[0143] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

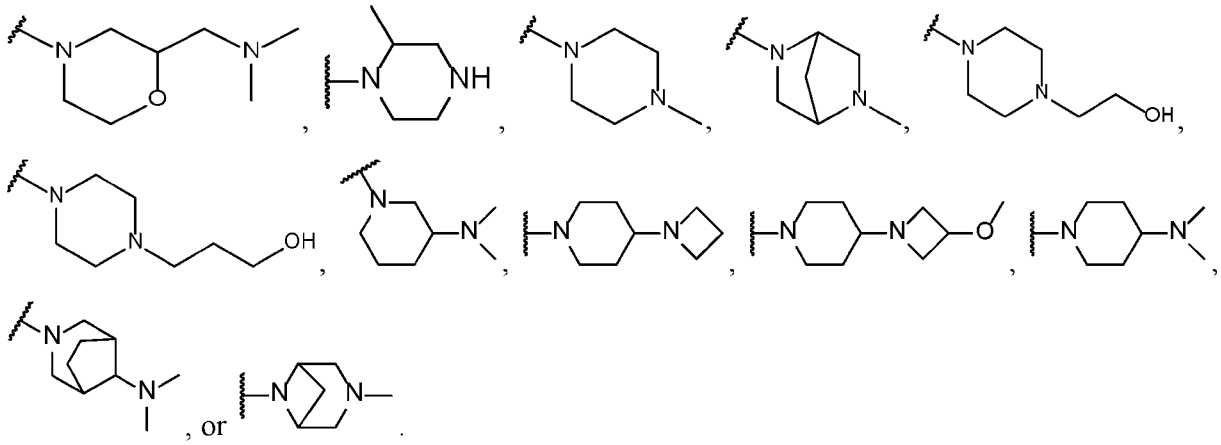


[0144] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

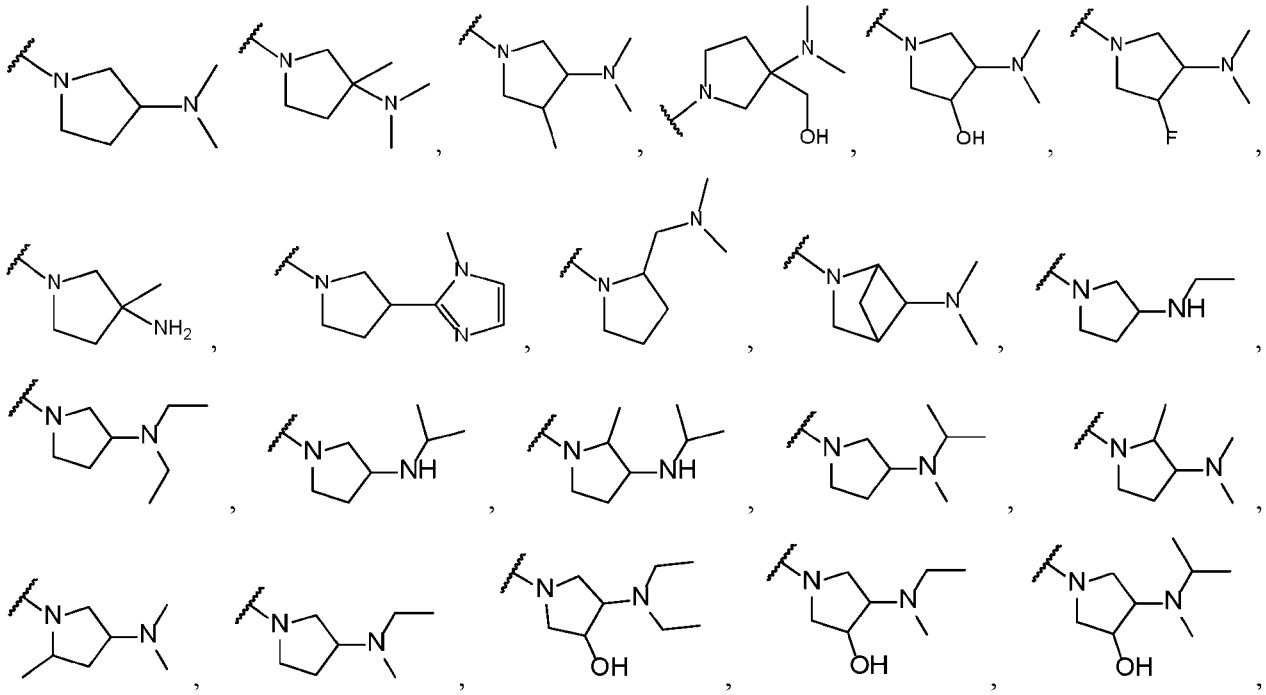


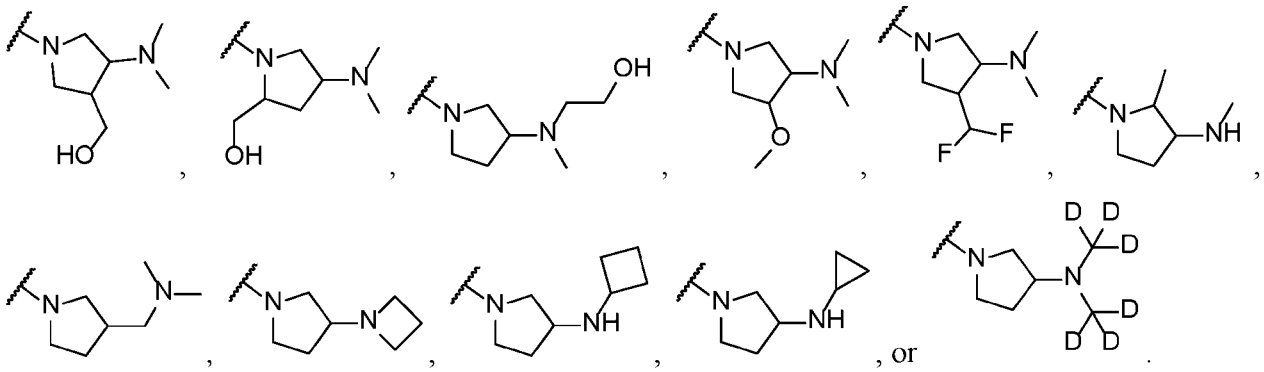


[0145] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

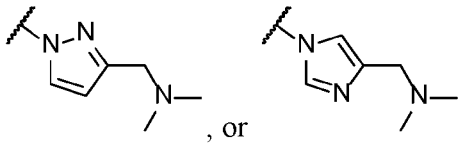


[0146] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

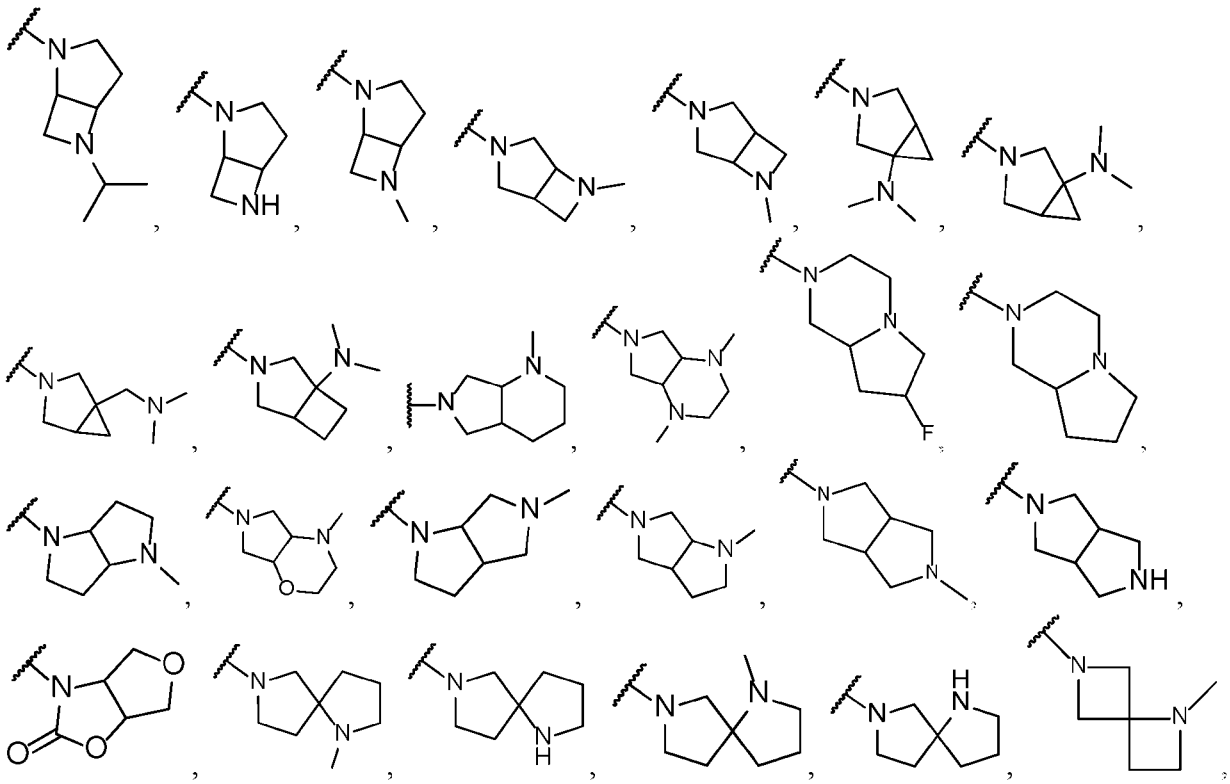


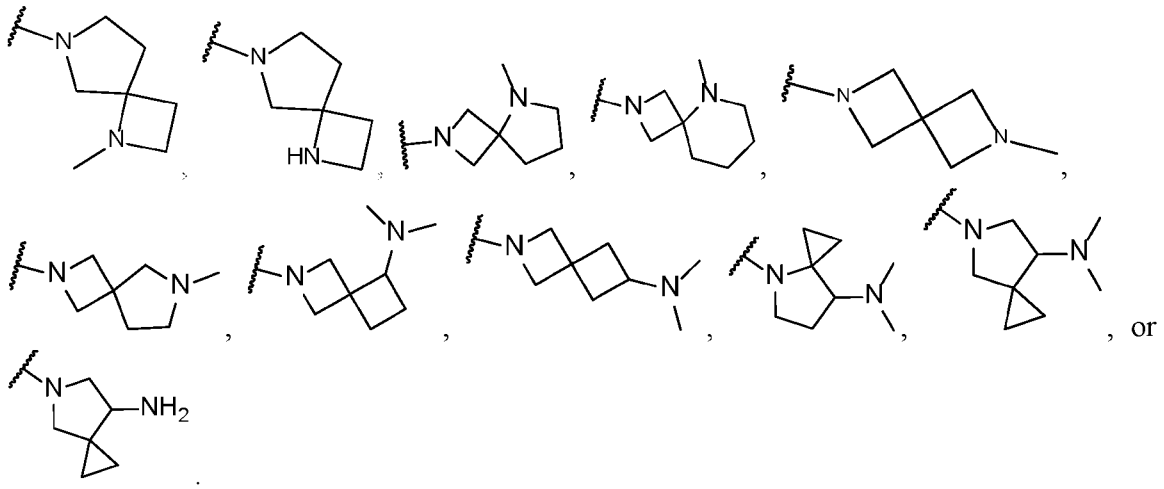


[0147] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from

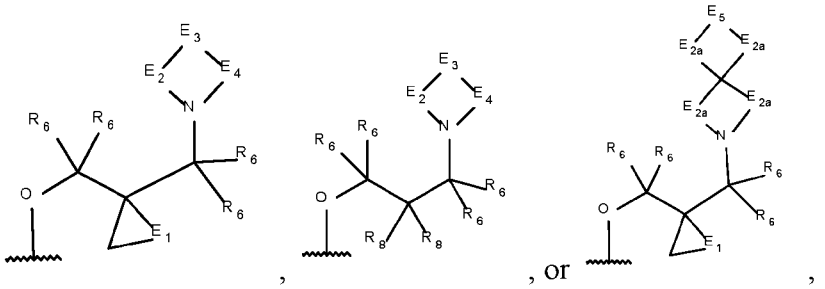


[0148] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is a N-linked cyclic amine selected from





[0149] In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R_4 is a group of the formula



a) A is -C(H)-, Z is -C(F)-, G is -N-, and R_2 is F, and R_1 is H;

b) A is -N-, Z is -C(F)-, G is -N-, R_2 is F, and R_1 is H;

c) A is -C(H)-, Z is -C(H)-, G is -N-, R_2 is F, and R_1 is H;

d) A is -N-, Z is -C(H)-, G is -N-, R_2 is F, and R_1 is H;

e) A is -C(H)-, Z is -N-, G is -N-, R_2 is F, and R_1 is H;

f) A is -N-, Z is -N-, G is -N-, R_2 is F, and R_1 is H;

g) A is -C(H)-, Z is -C(F)-, G is -C(H)-, R_2 is F, and R_1 is H;

h) A is -N-, Z is -C(F)-, G is -C(H)-, R_2 is F, and R_1 is H;

i) A is -C(H)-, Z is -C(H)-, G is -C(H)-, R_2 is F, and R_1 is H;

j) A is -N-, Z is -C(H)-, G is -C(H)-, R_2 is F, and R_1 is H;

k) A is -C(H)-, Z is -N-, G is -C(H)-, R_2 is F, and R_1 is H;

l) A is -N-, Z is -N-, G is -C(H)-, R_2 is F, and R_1 is H;

m) A is -C(H)-, Z is -C(F)-, G is -C(F)-, R_2 is F, and R_1 is H;

n) A is -N-, Z is -C(F)-, G is -C(F)-, R_2 is F, and R_1 is H;

o) A is -C(H)-, Z is -C(H)-, G is -C(F)-, R_2 is F, and R_1 is H;

p) A is -N-, Z is -C(H)-, G is -C(F)-, R_2 is F, and R_1 is H;

q) A is -C(H)-, Z is -N-, G is -C(F)-, R_2 is F, and R_1 is H;

r) A is -N-, Z is -N-, G is -C(F)-, R_2 is F, and R_1 is H;

s) A is -C(H)-, Z is -C(F)-, G is -N-, R_2 is Cl, and R_1 is H;

t) A is -N-, Z is -C(F)-, G is -N-, R_2 is Cl, and R_1 is H;

u) A is -C(H)-, Z is -C(H)-, G is -N-, R_2 is Cl, and R_1 is H;

v) A is -N-, Z is -C(H)-, G is -N-, R_2 is Cl, and R_1 is H;

w) A is -C(H)-, Z is -N-, G is -N-, R_2 is Cl, and R_1 is H;

x) A is -N-, Z is -N-, G is -N-, R_2 is Cl, and R_1 is H;

y) A is -C(H)-, Z is -C(F)-, G is -C(H)-, R_2 is Cl, and R_1 is H;

z) A is -N-, Z is -C(H)-, G is -C(H)-, R_2 is Cl, and R_1 is H;

aa) A is -N-, Z is -C(H)-, G is -C(H)-, R_2 is Cl, and R_1 is H;

bb) A is -C(H)-, Z is -N-, G is -C(H)-, R_2 is Cl, and R_1 is H;

cc) A is -N-, Z is -N-, G is -C(H)-, R_2 is Cl, and R_1 is H;

dd) A is -C(H)-, Z is -C(F)-, G is -C(F)-, R_2 is Cl, and R_1 is H;

ee) A is -N-, Z is -C(F)-, G is -C(F)-, R_2 is Cl, and R_1 is H;

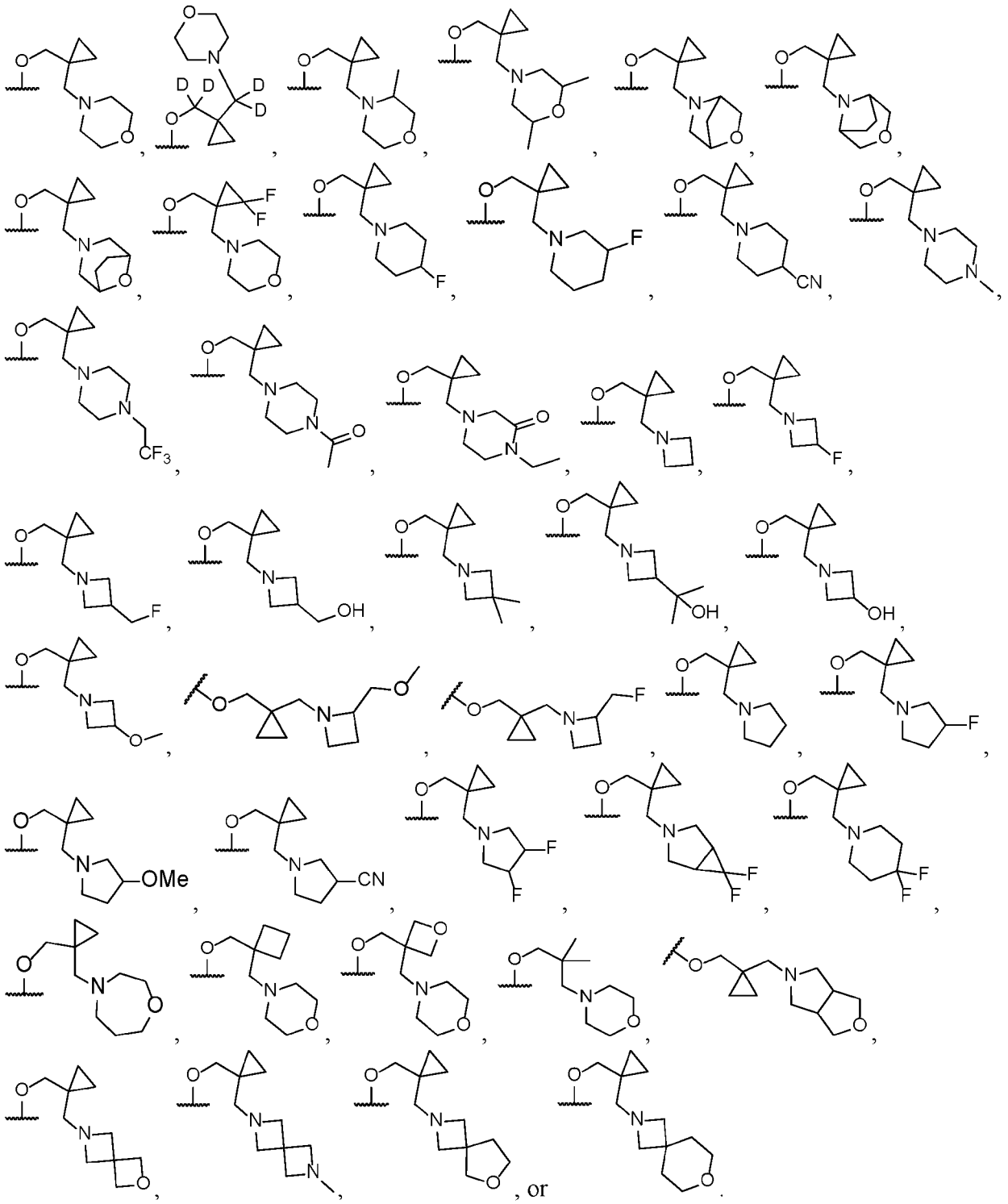
ff) A is -C(H)-, Z is -C(H)-, G is -C(F)-, R_2 is Cl, and R_1 is H;

gg) A is -N-, Z is -C(H)-, G is -C(F)-, R_2 is Cl, and R_1 is H;

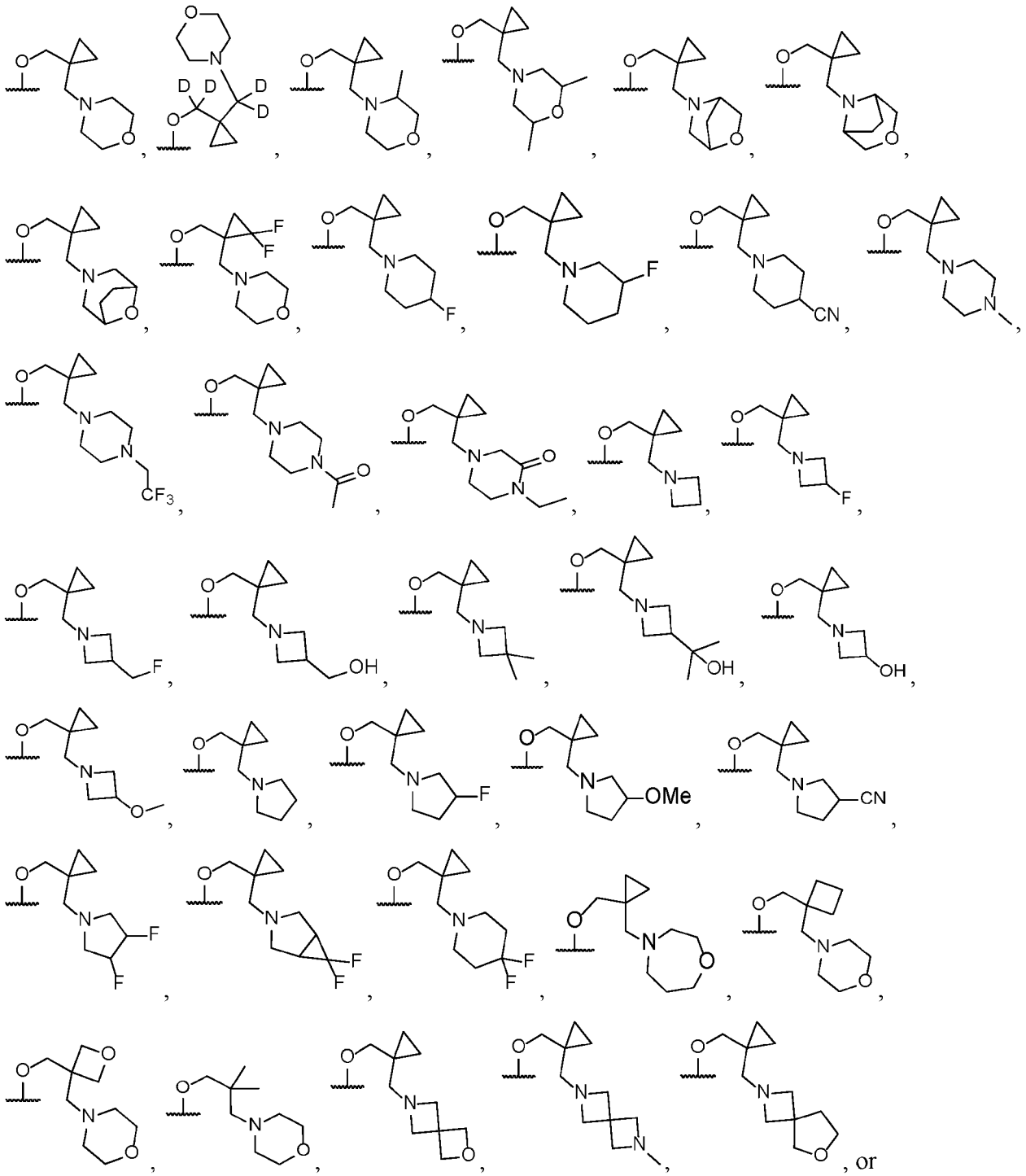
hh) A is -C(H)-, Z is -N-, G is -C(F)-, R_2 is Cl, and R_1 is H; or

ii) A is -N-, Z is -N-, G is -C(F)-, R_2 is Cl, and R_1 is H.

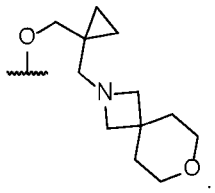
[0150] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from



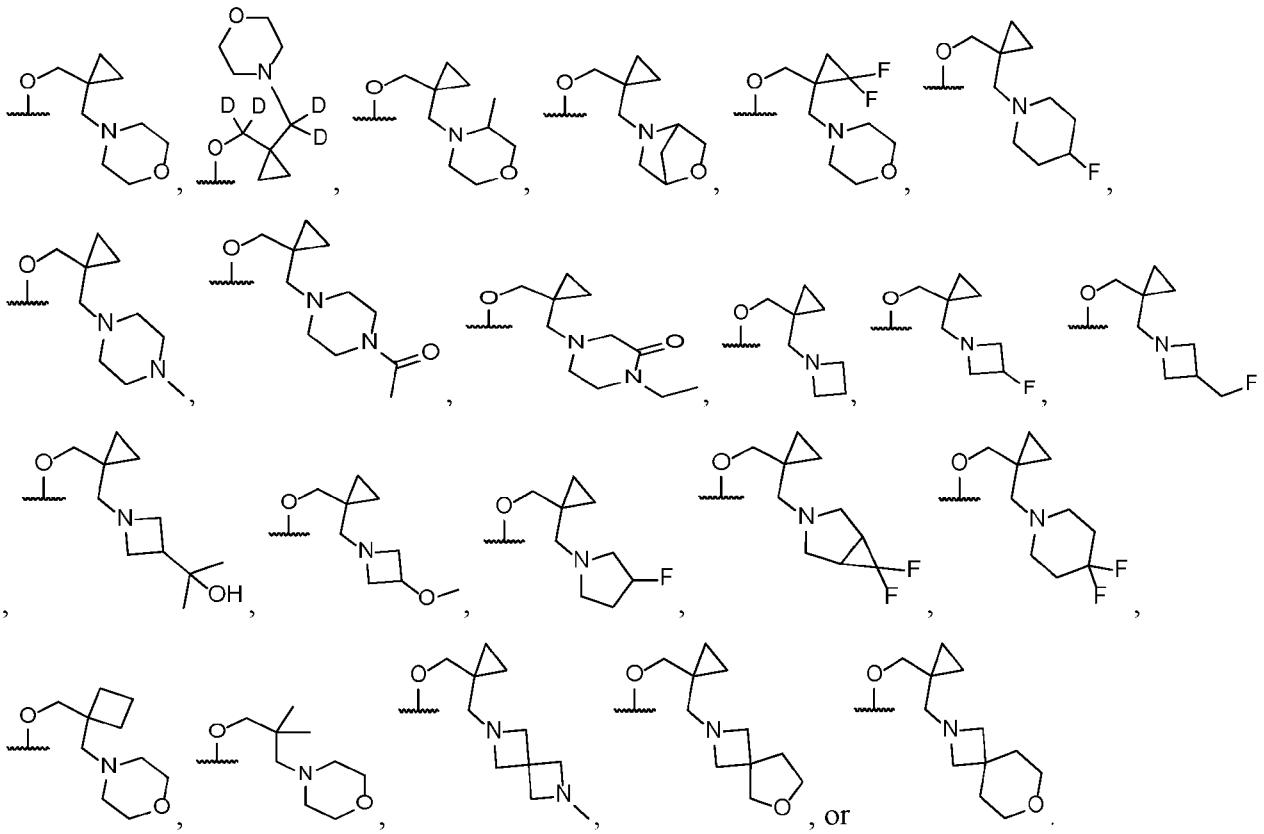
[0151] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from



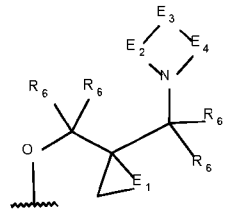
, or



[0152] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

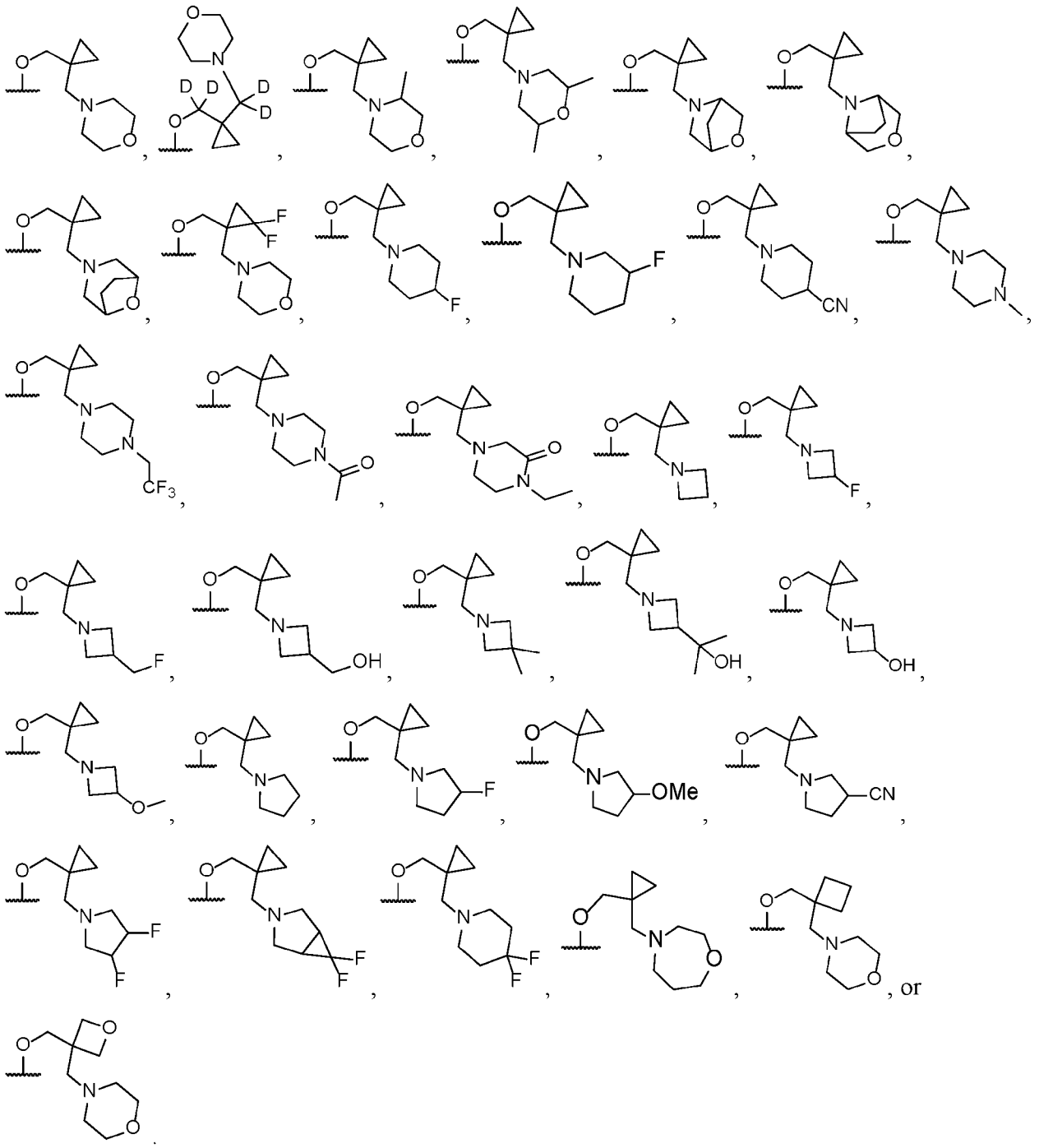


[0153] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is

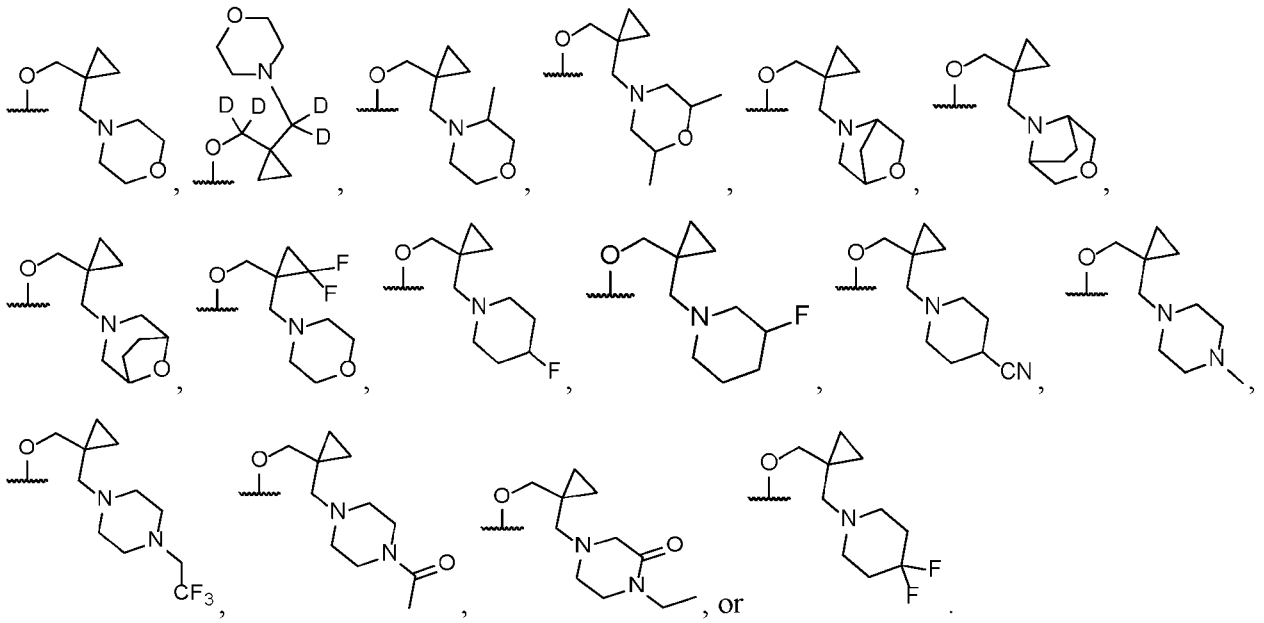


, wherein preferably each R_6 is H.

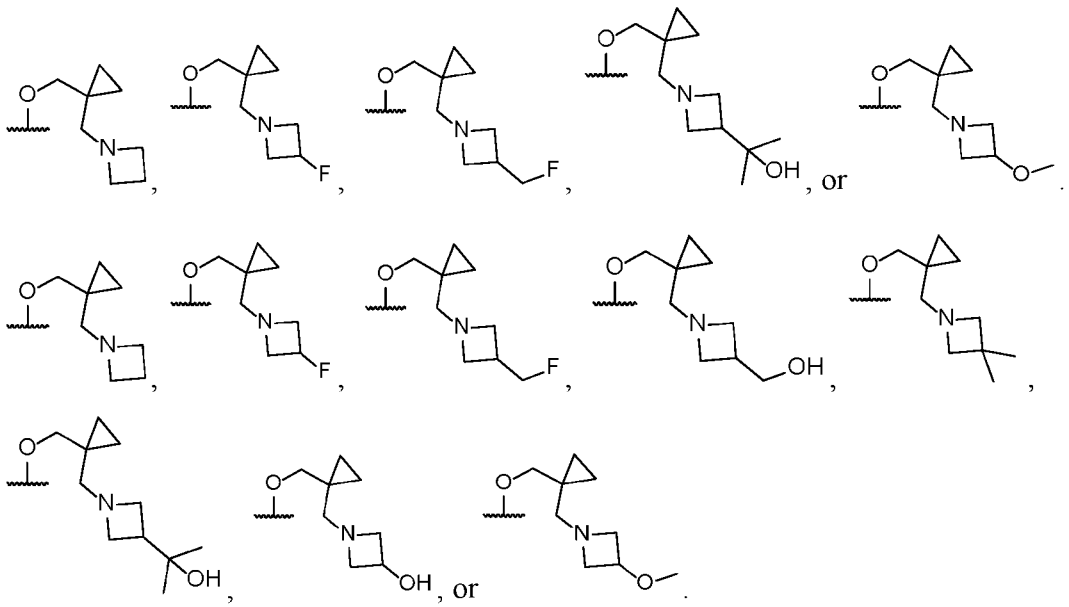
[0154] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from



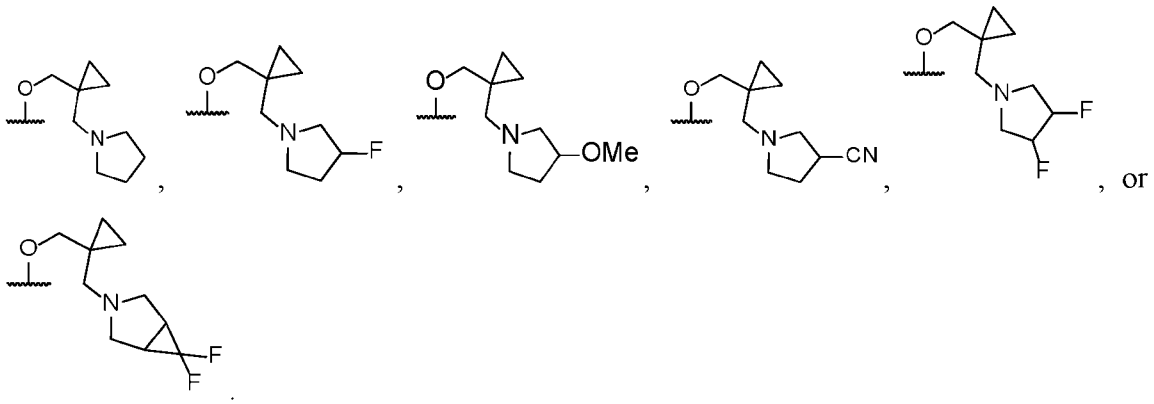
[0155] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from



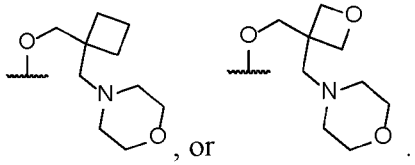
[0156] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from



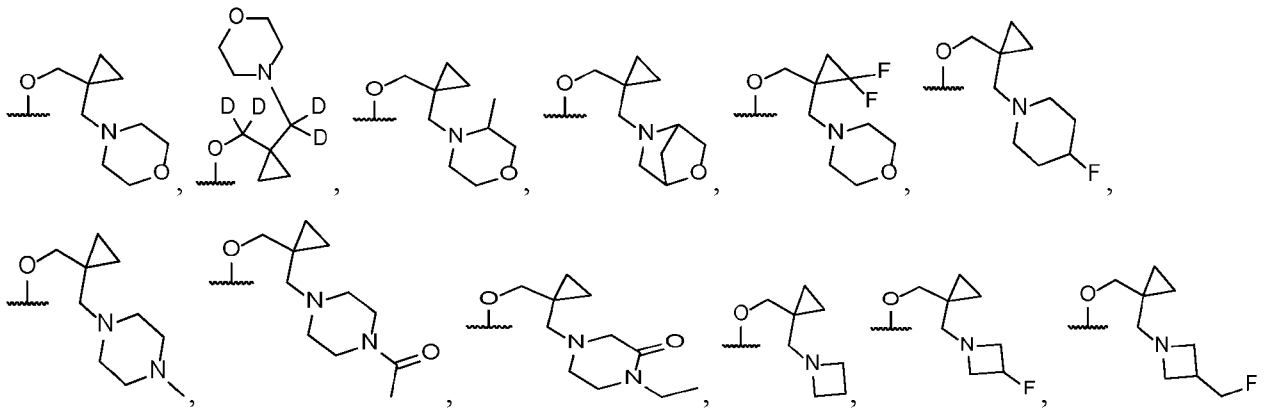
[0157] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

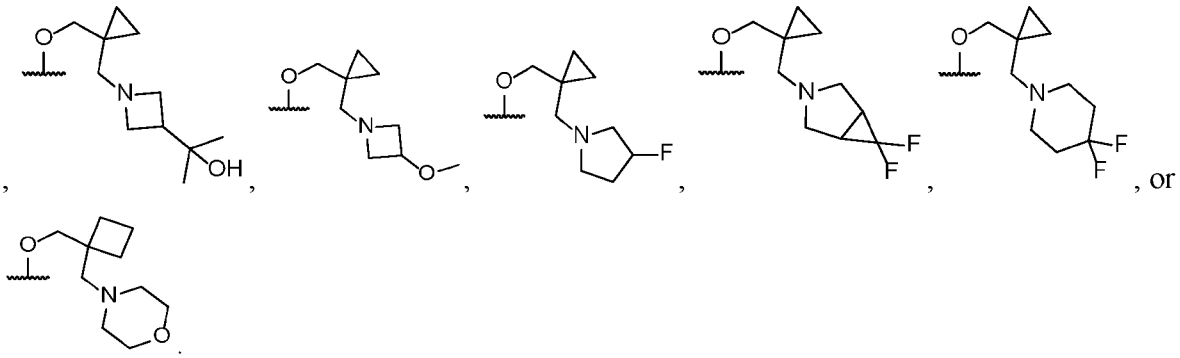


[0158] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is

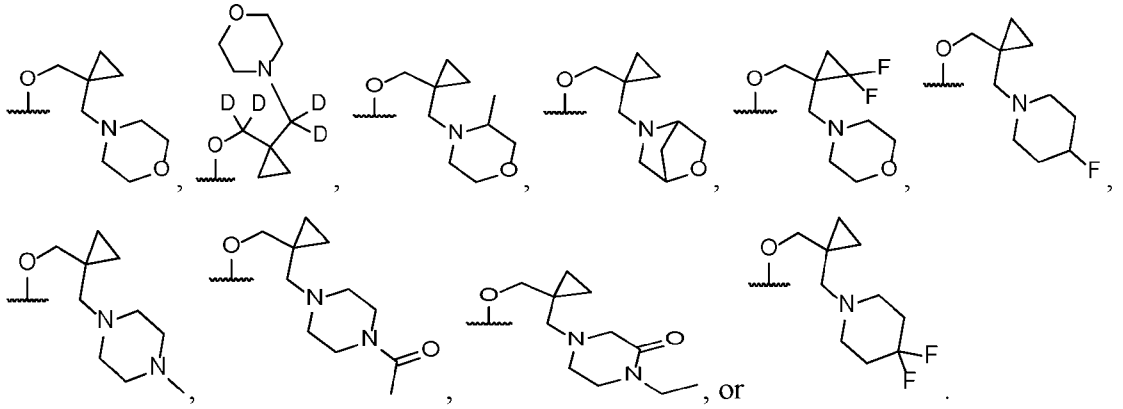


[0159] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

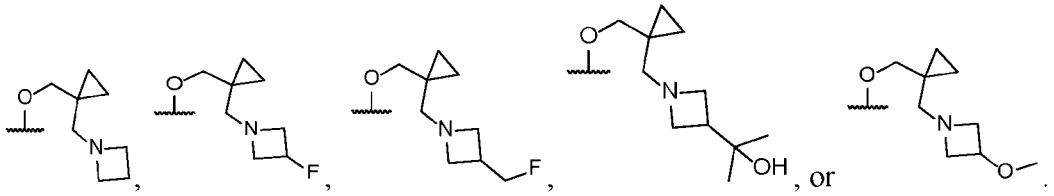




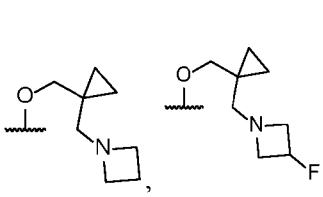
[0160] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

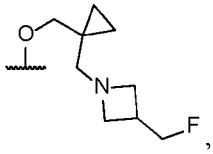
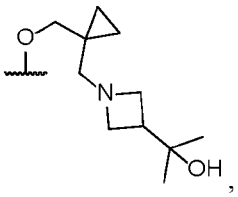
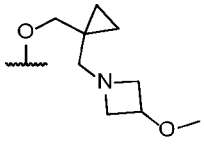
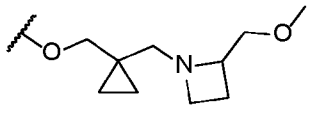
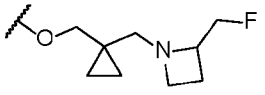


[0161] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

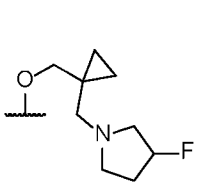
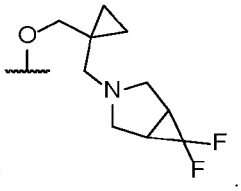


[0162] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

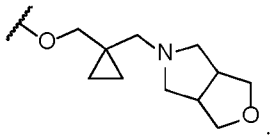






, or

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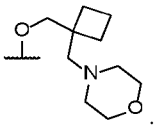
[0163] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from


or

.

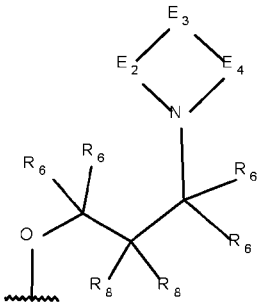
[0164] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is


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[0165] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is

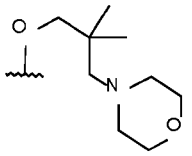

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[0166] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is



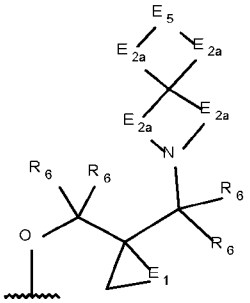
, wherein preferably each R_6 is H.

[0167] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is



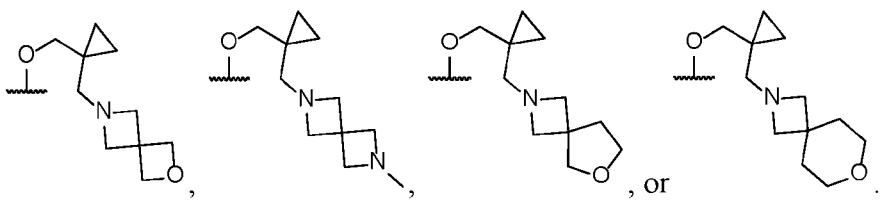
.

[0168] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is



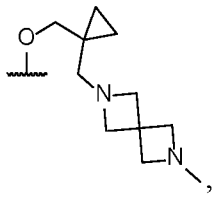
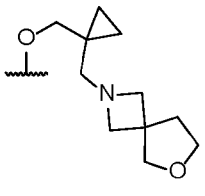
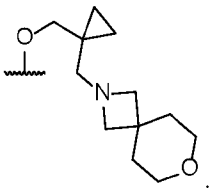
, wherein preferably each R_6 is H.

[0169] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

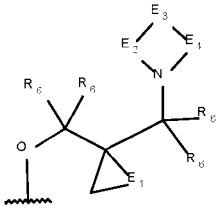
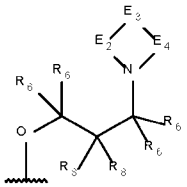


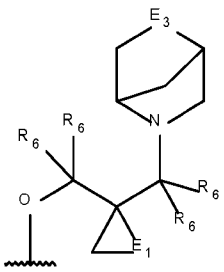
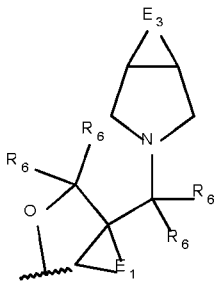
.

[0170] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, R_4 is selected from

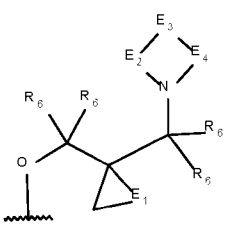
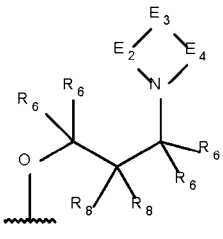

, 
, or 
.

[0171] In the above embodiments of the compounds of Formula I, or a pharmaceutically acceptable salt thereof, R_4 is a group of the formula

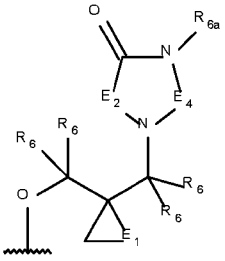

, or 
, wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene. Examples of these compounds of Formula I are shown below:


, or 
, or a pharmaceutically acceptable salt thereof.

[0172] In the above embodiments of the compounds of Formula I, or a pharmaceutically acceptable salt thereof, R_4 is a group of the formula


, or 
, wherein E_3 can be -CO-NR_{6a}-.

Examples of these compounds of Formula I are shown below:



, or a pharmaceutically acceptable salt thereof.

[0173] In the above embodiments of the compounds of Formula I, the chemical drawings are shown flat without chiral information. These compounds often have multiple chiral centers and are contemplated to exist is various forms with various combinations of chiral centers. Additionally, these compounds have various enantiomers, diastereomers, and atropisomers that can exist and are included herein.

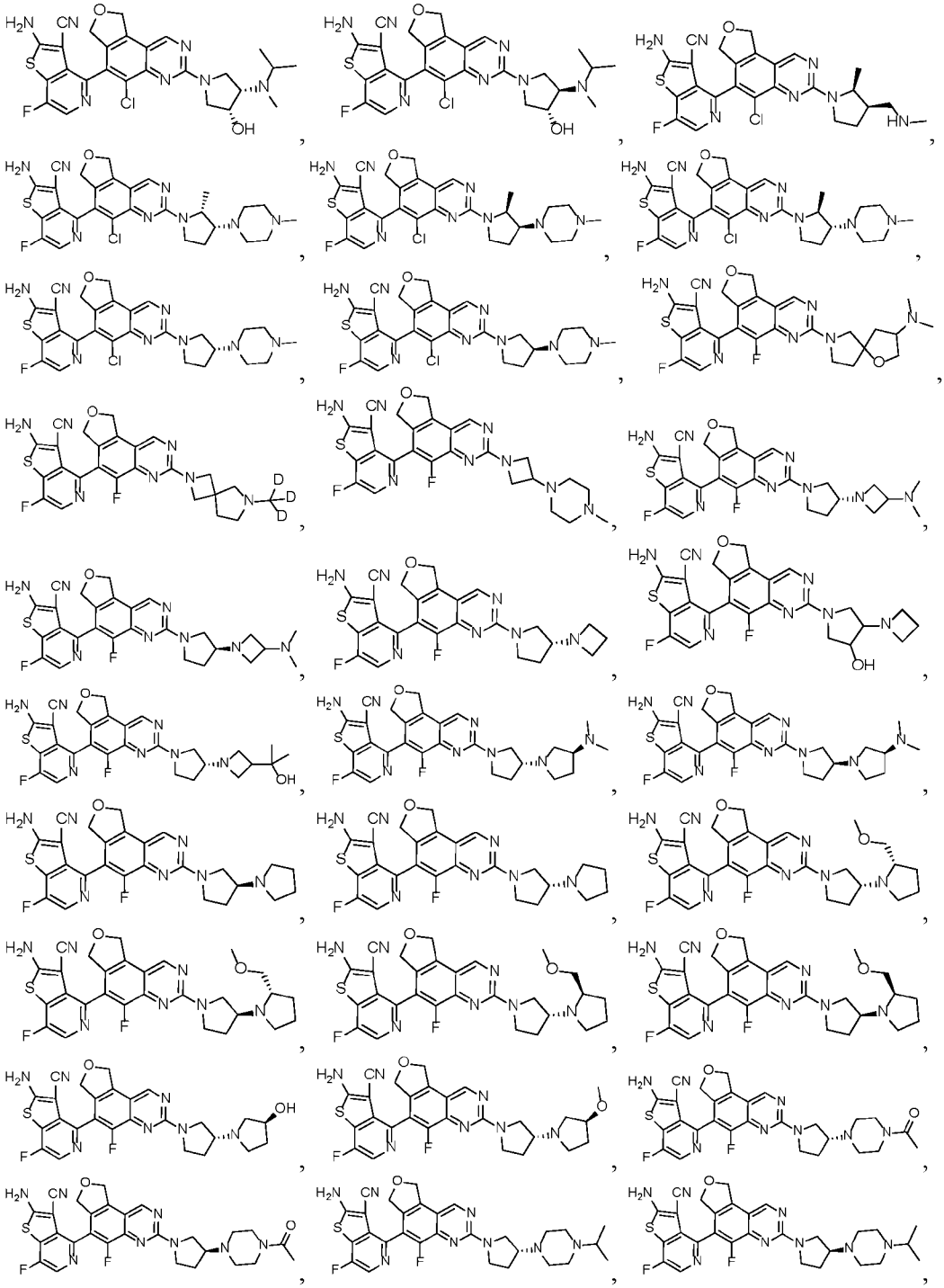
[0174] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is an isotopic derivative of any one of the compounds described herein or a pharmaceutically acceptable salt thereof.

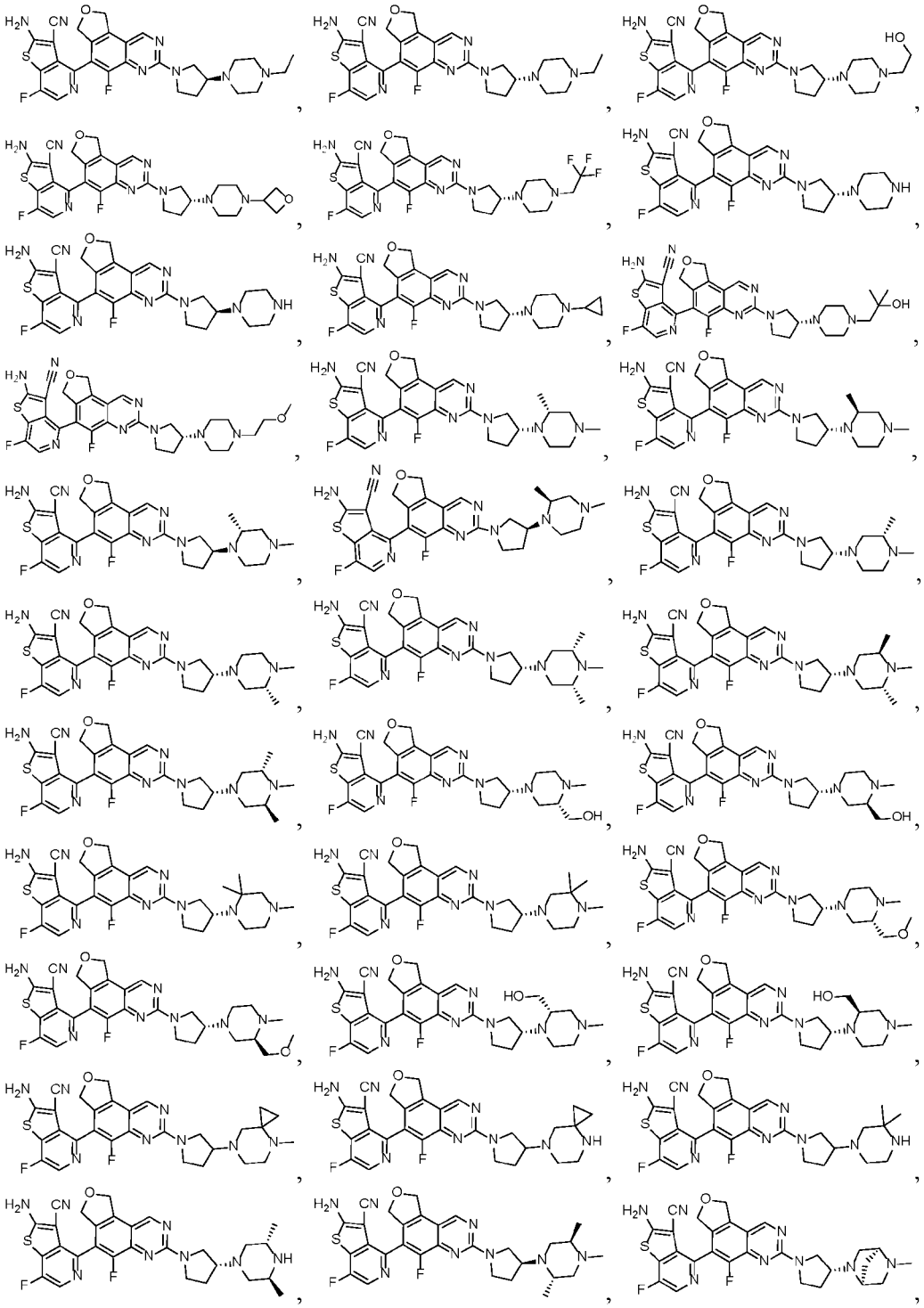
[0175] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivatives can generally be prepared by carrying out the procedures disclosed in the schemes and/or in the examples described herein or a pharmaceutically acceptable salt thereof, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

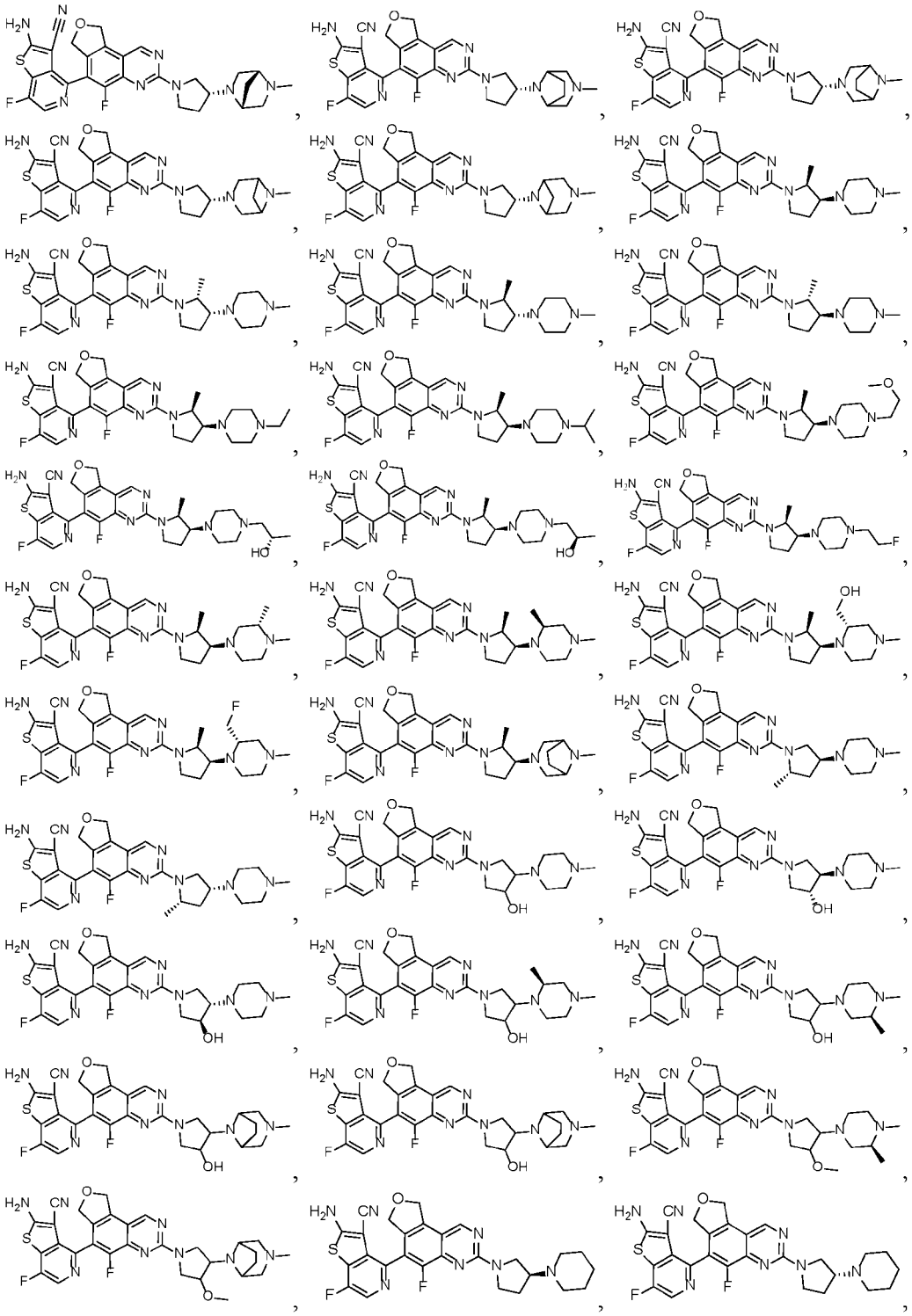
[0176] In an embodiment of a compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is a deuterium labeled compound of any one of the compounds described herein and pharmaceutically acceptable salts thereof.

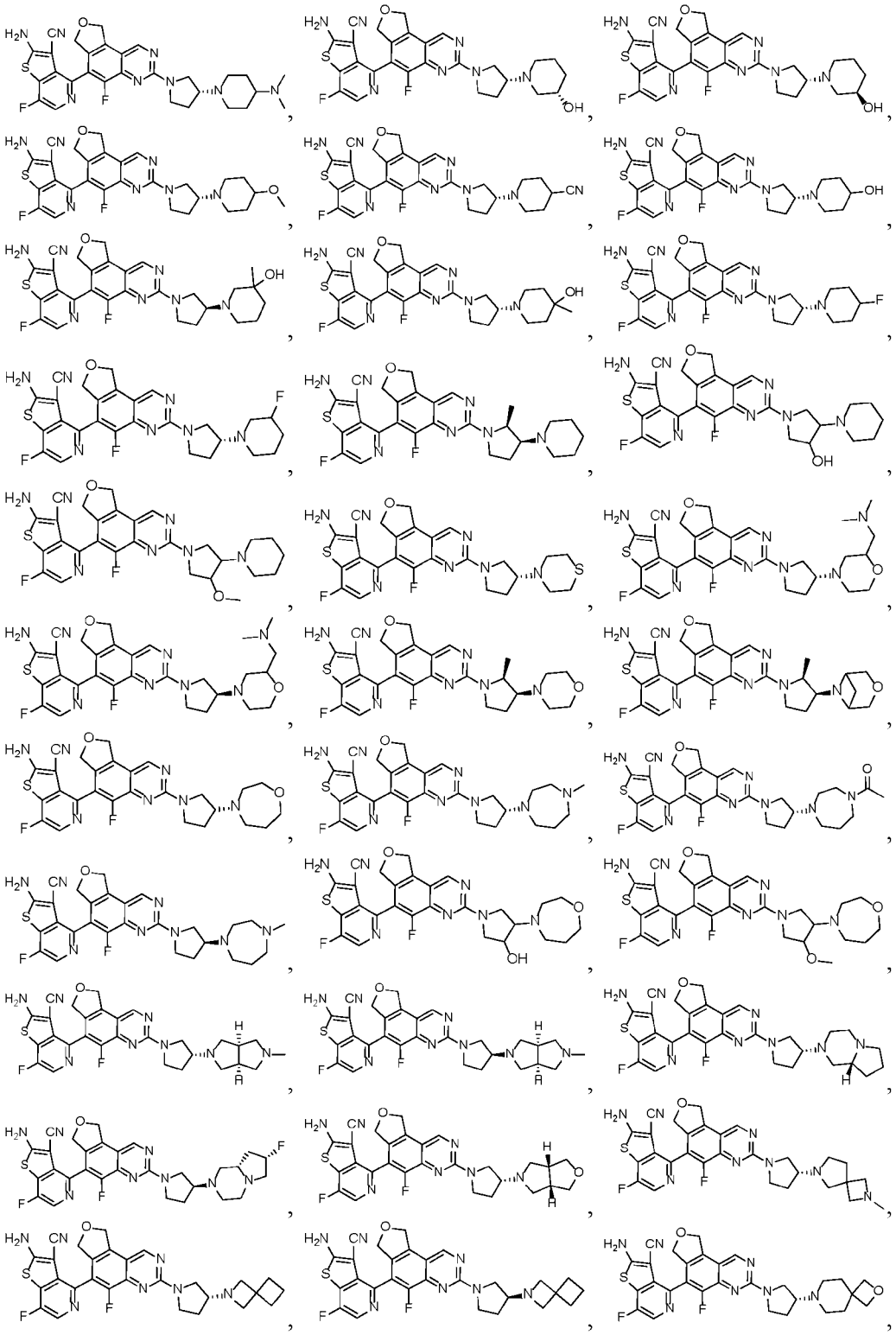
[0177] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when an atom is designated specifically as "H" or "hydrogen", the atom is understood to have hydrogen at its natural abundance isotopic composition. Also, unless otherwise stated, when an atom is designated specifically as "D" or "deuterium", the atom is understood to have deuterium at an abundance substantially greater than the natural abundance of deuterium, which is 0.015%.

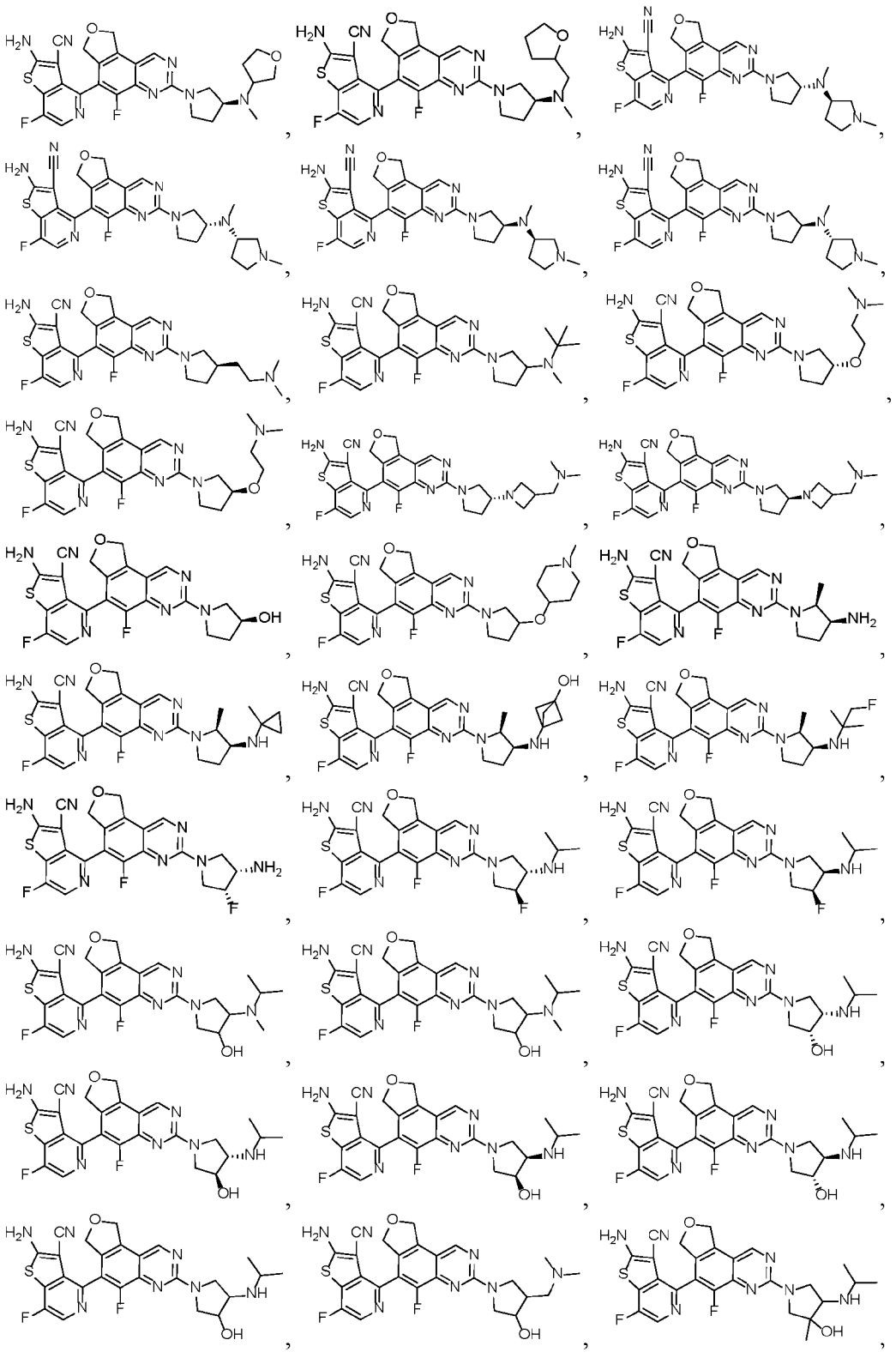
[0178] A compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is selected from

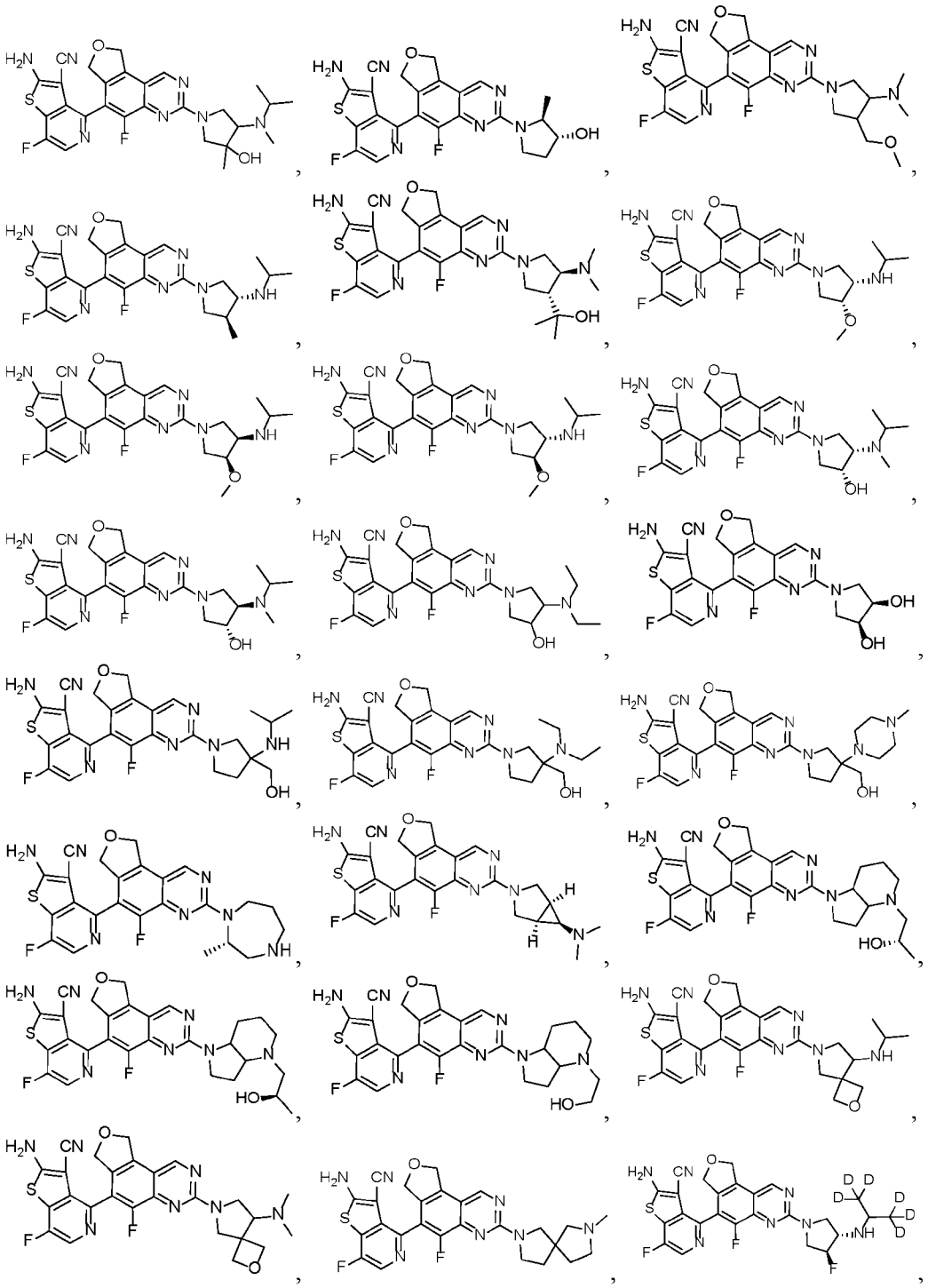


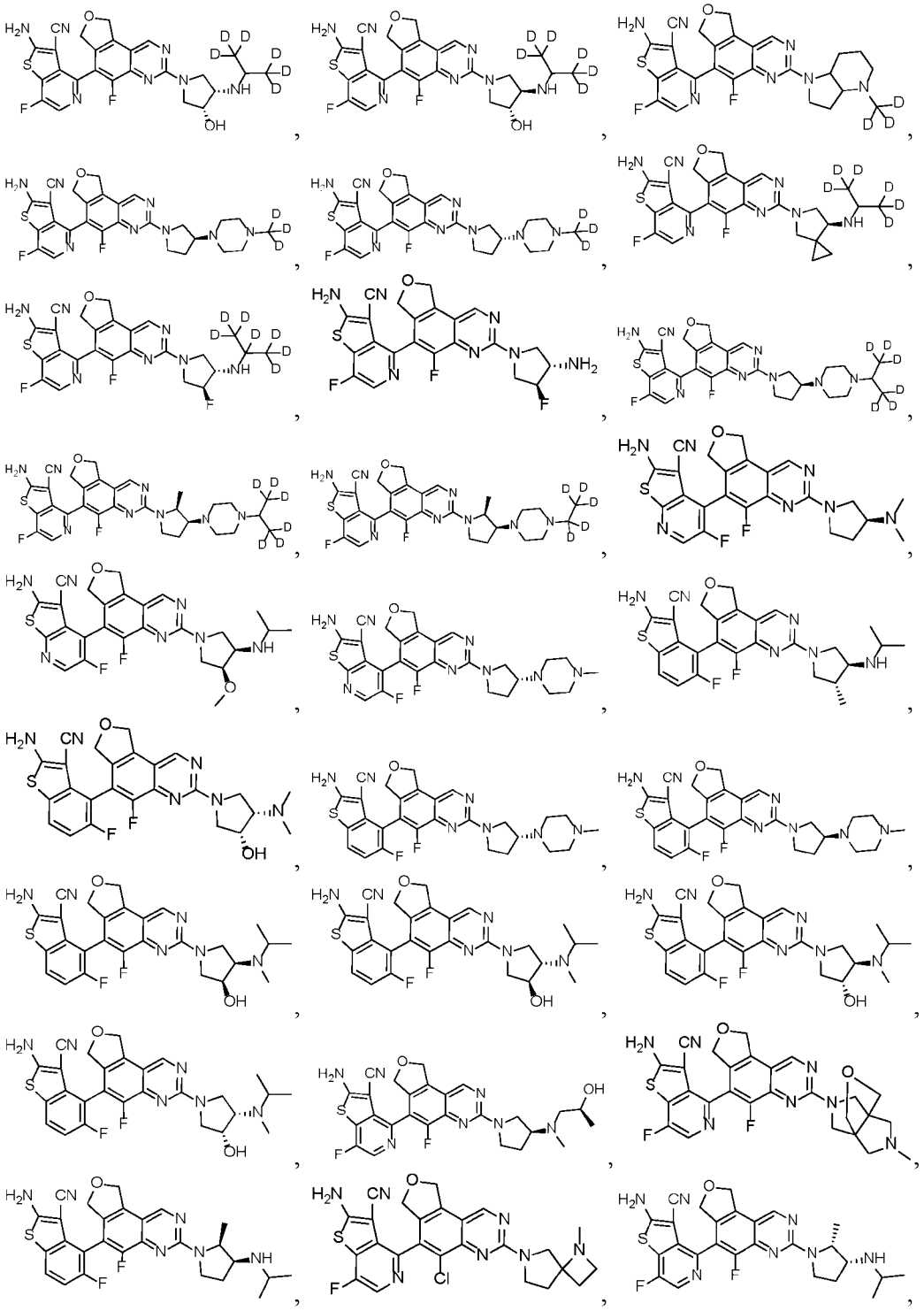


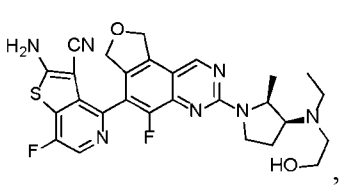
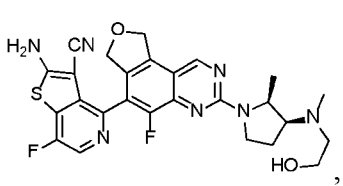
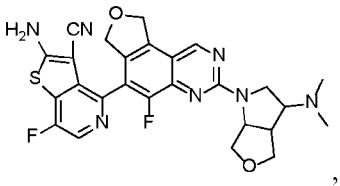
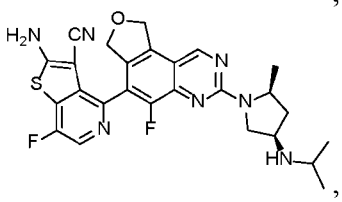
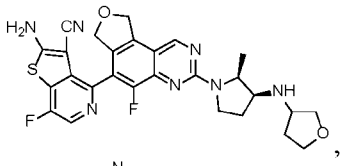
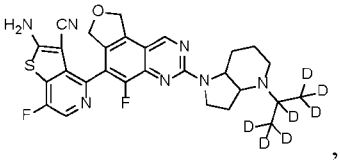
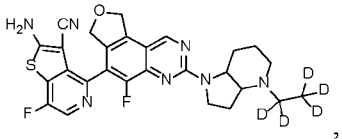
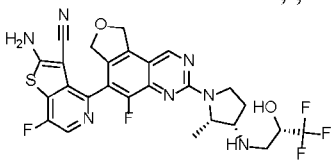




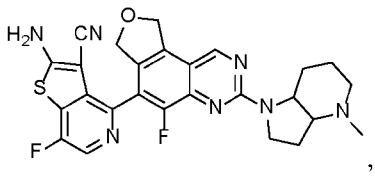
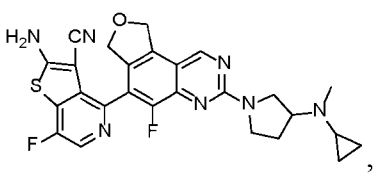
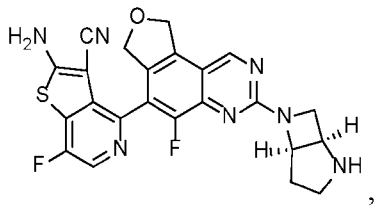
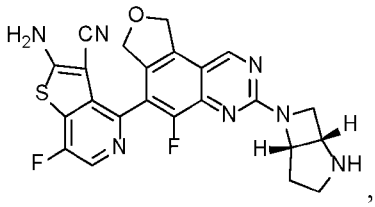
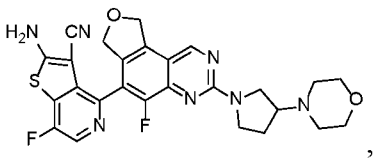
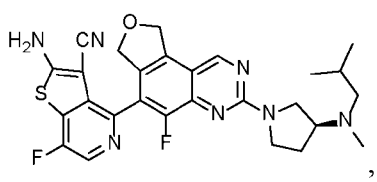
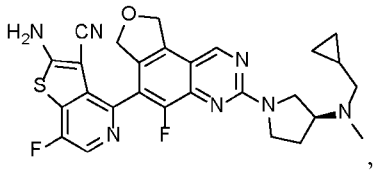
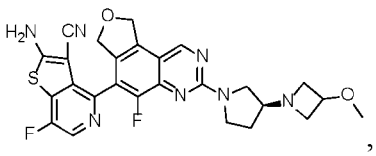
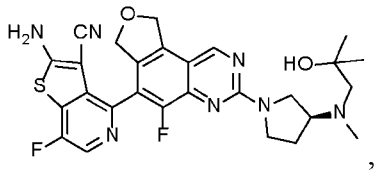


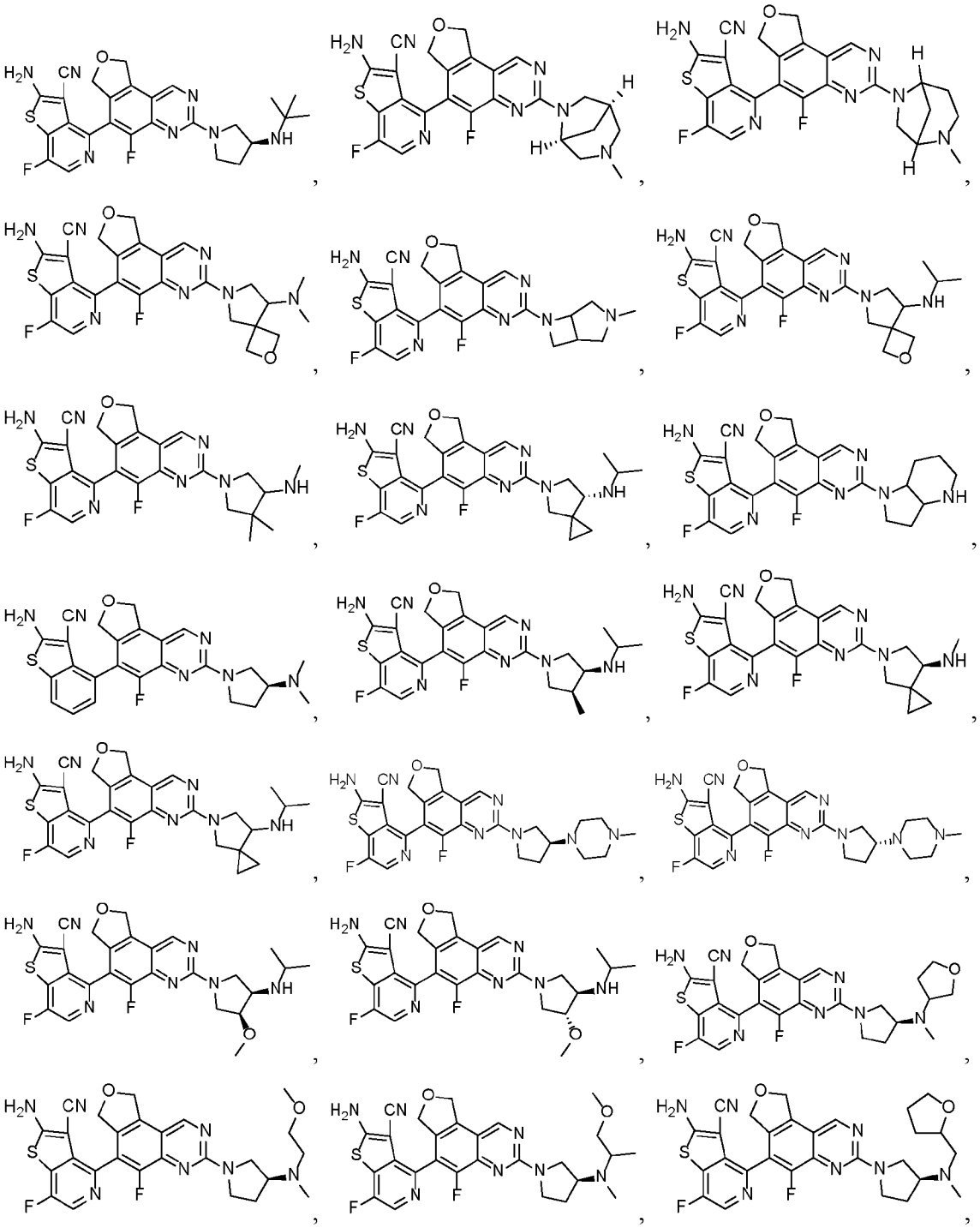


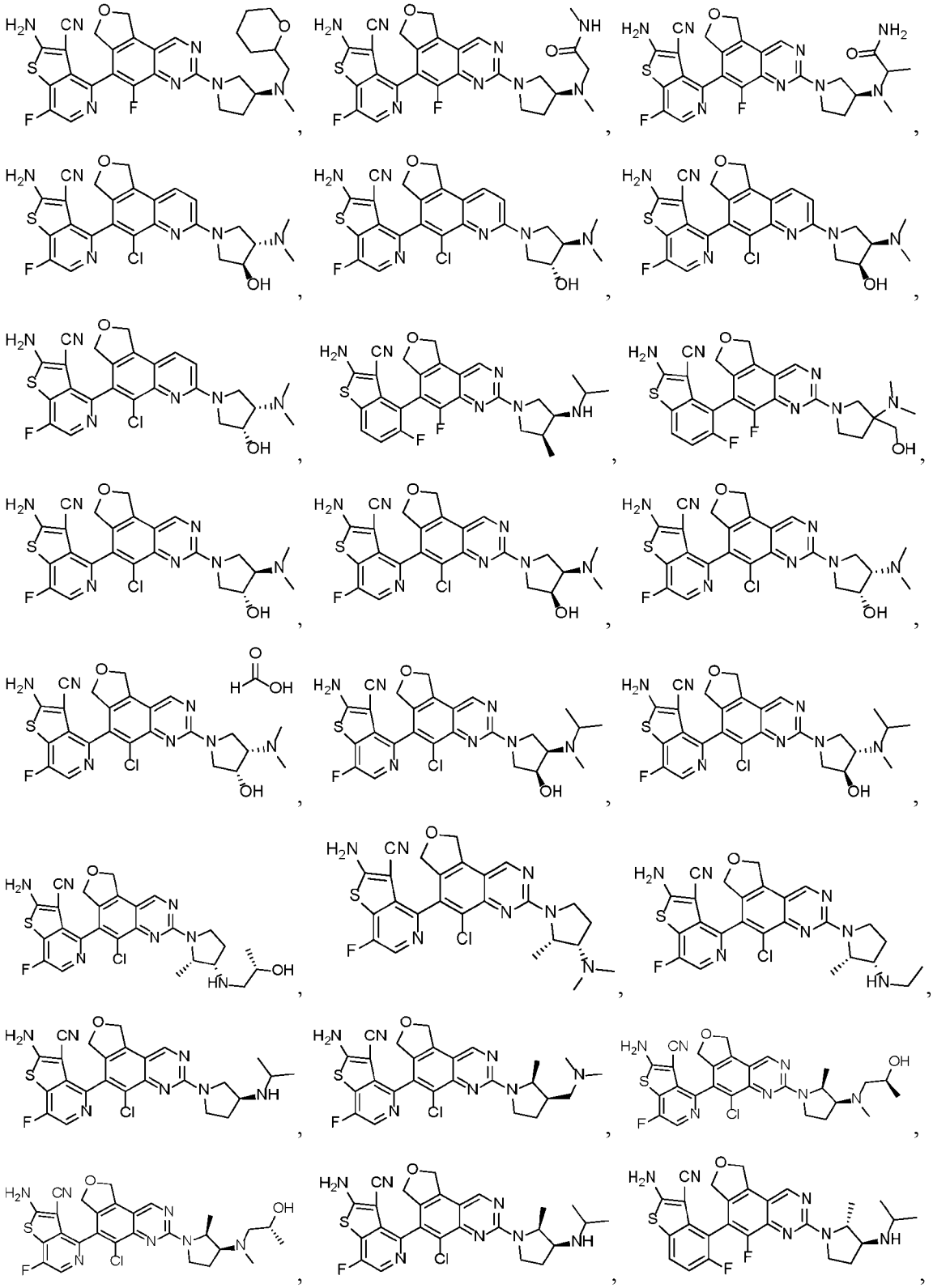


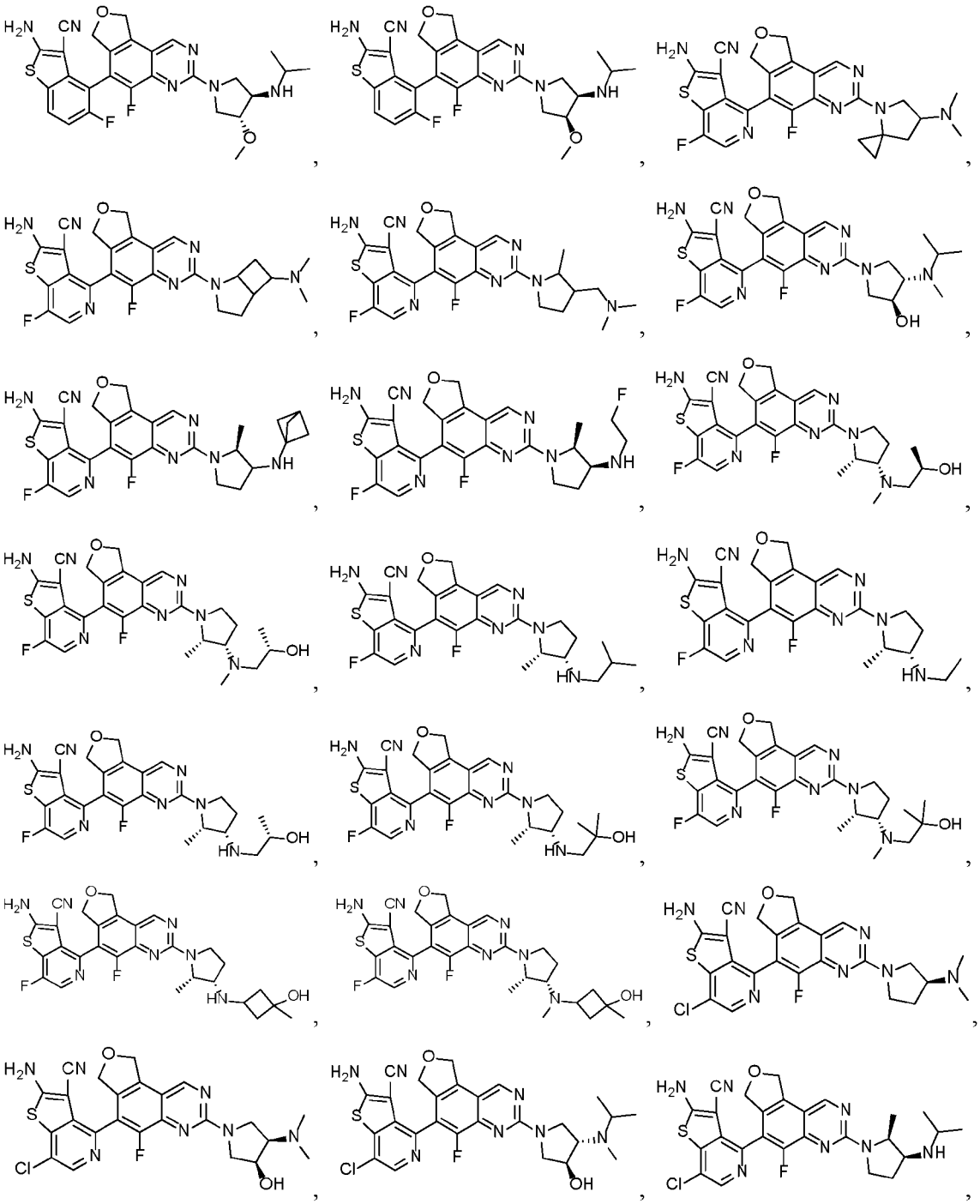

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, or a pharmaceutically acceptable salt thereof.

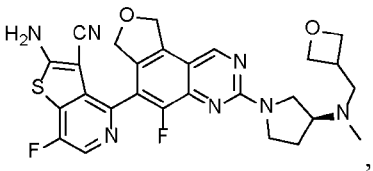
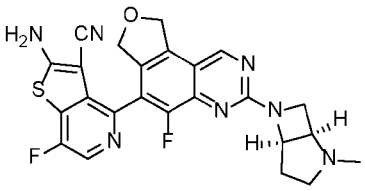
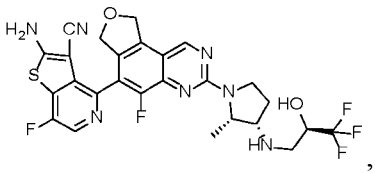
[0179] A compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is selected from


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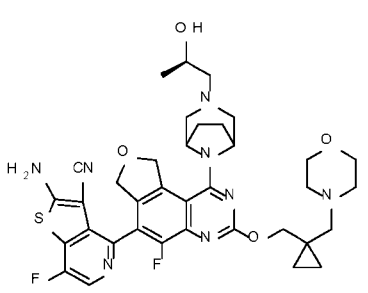
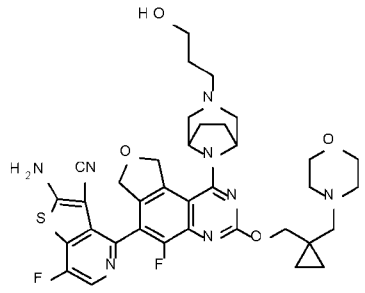
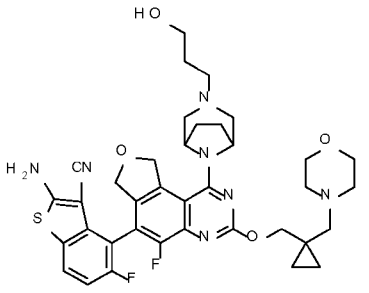


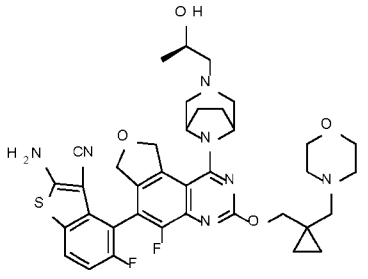
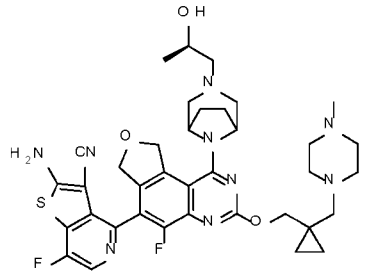
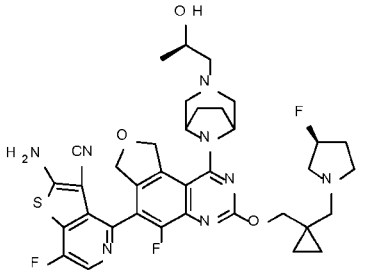


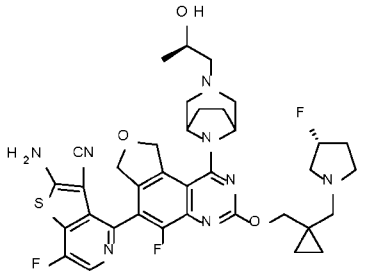
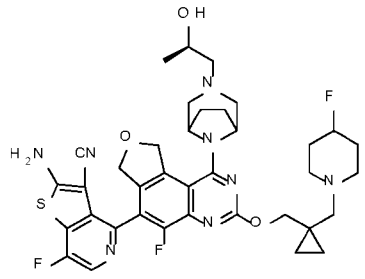
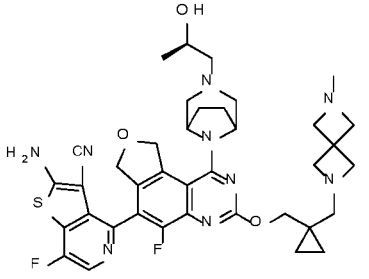


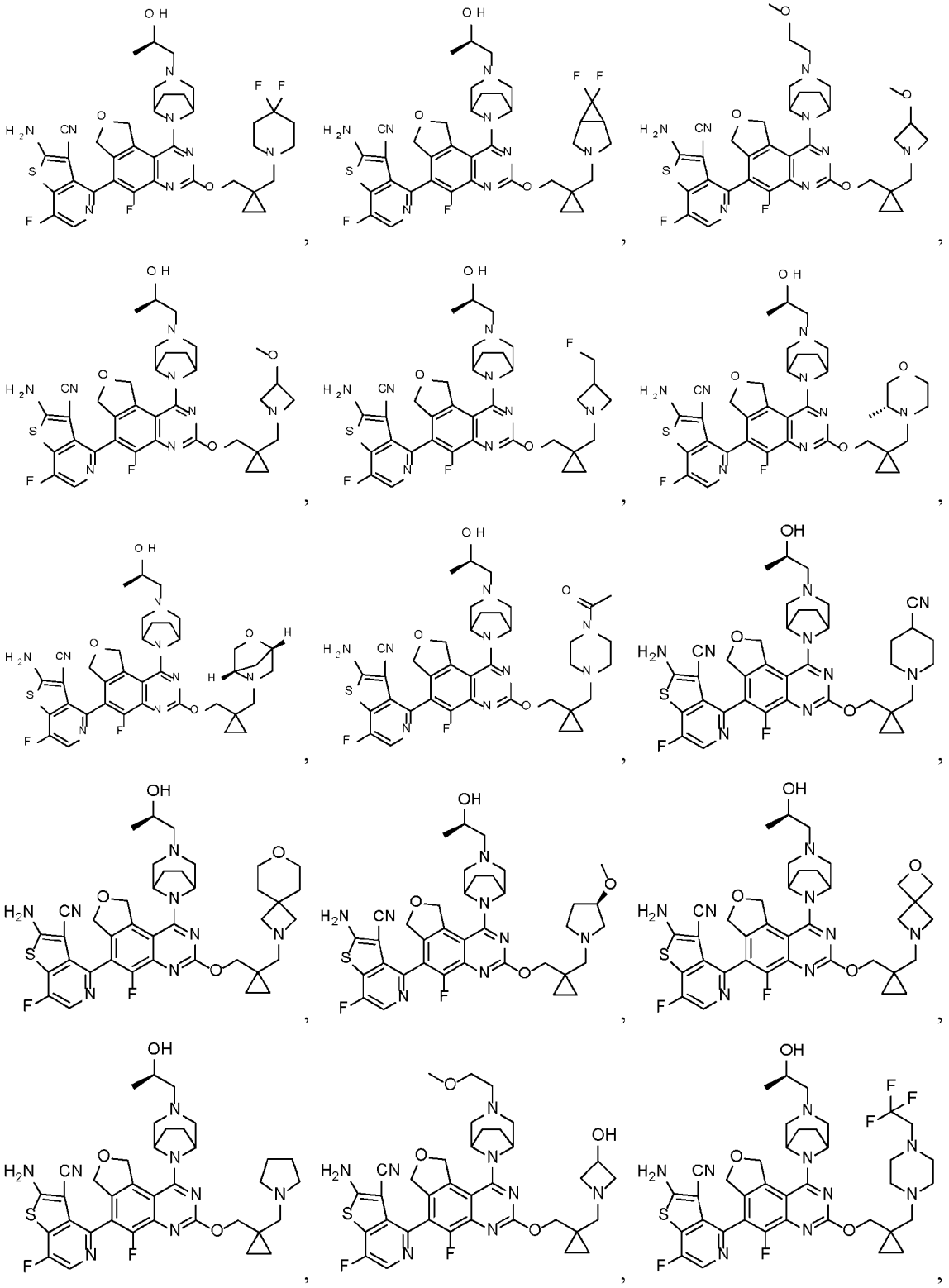

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, and

, or a pharmaceutically acceptable salt thereof.

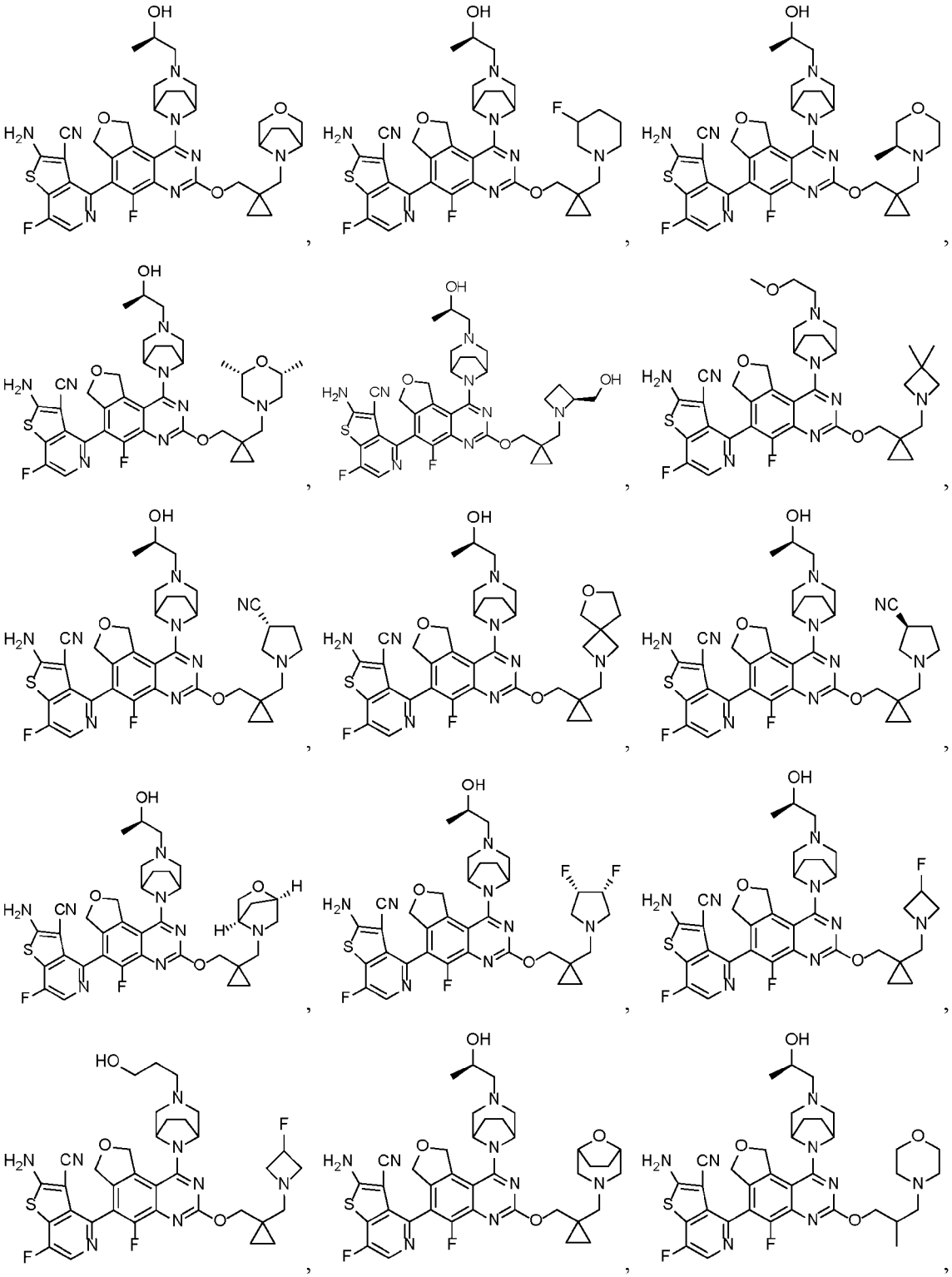
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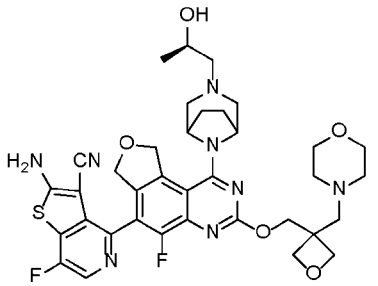
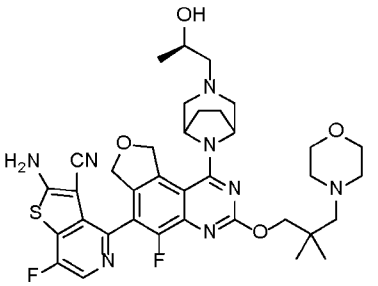
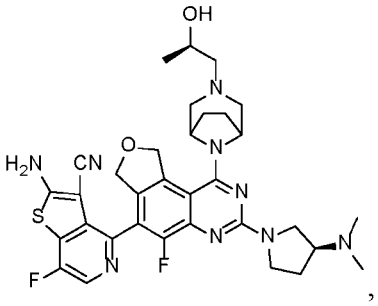
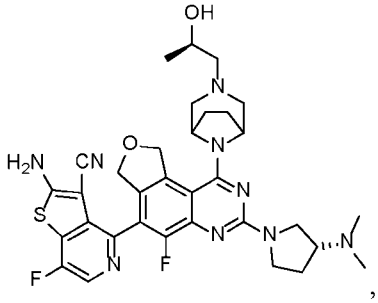
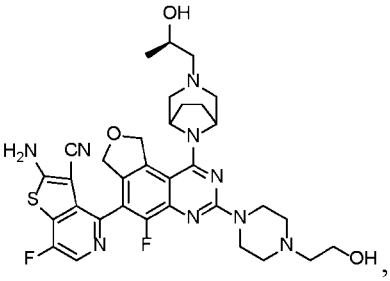
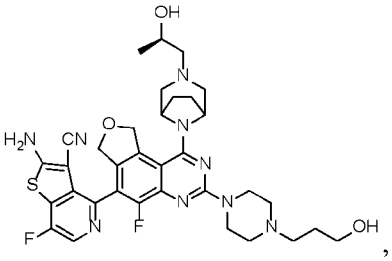
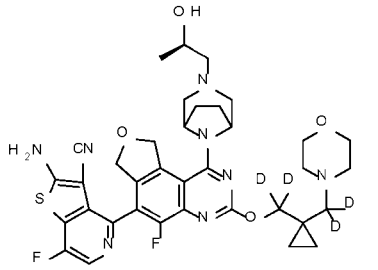
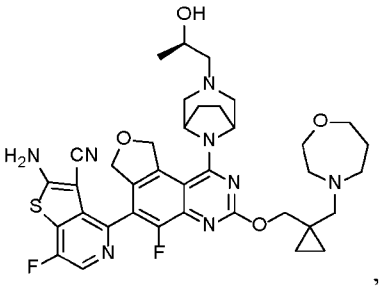
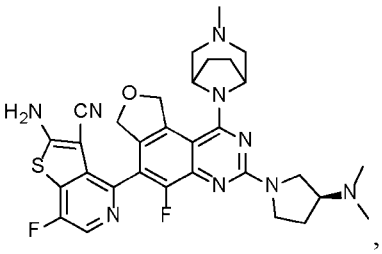
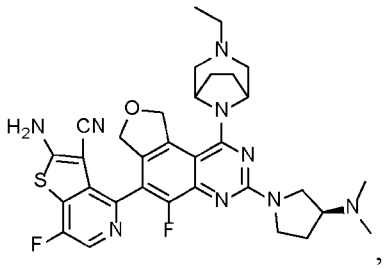
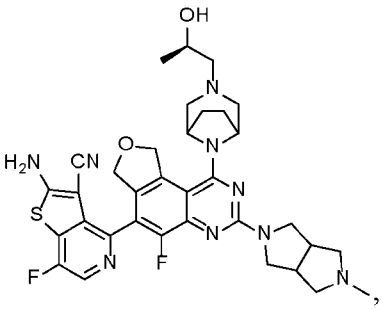
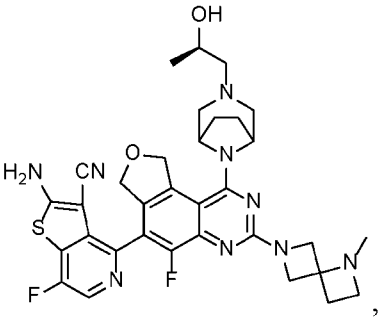
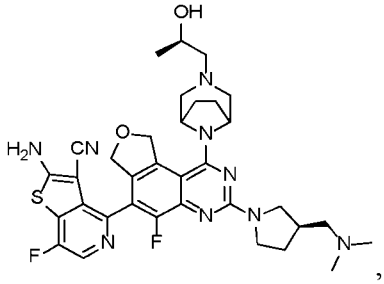
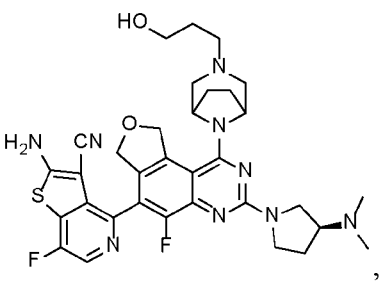
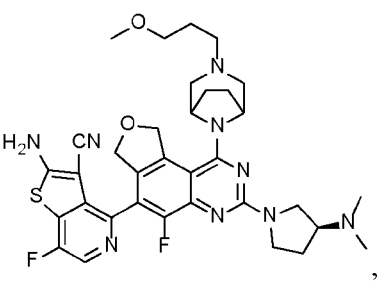

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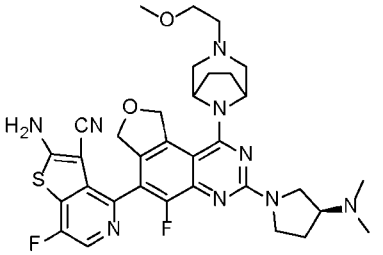
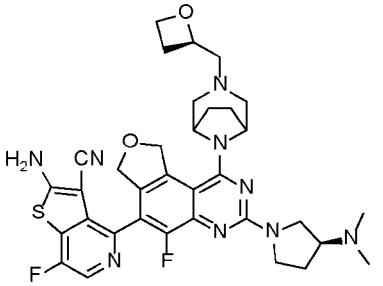
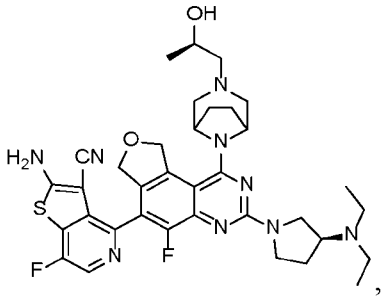
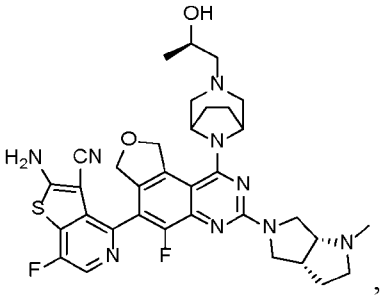
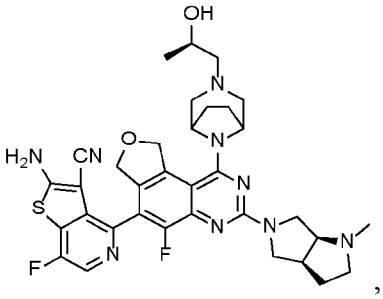
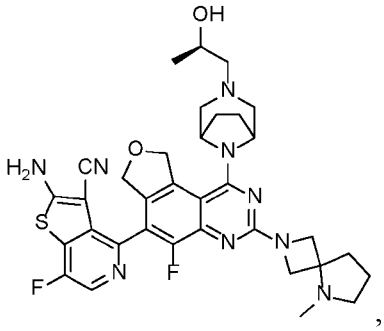
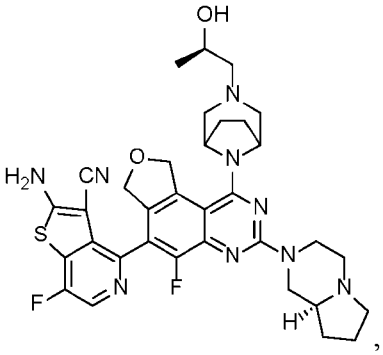
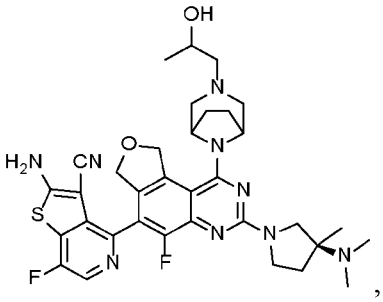
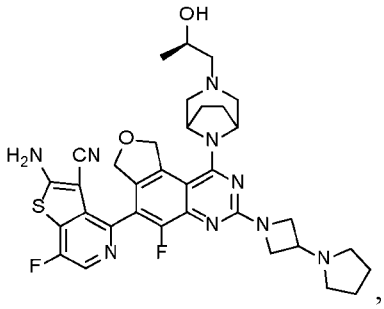
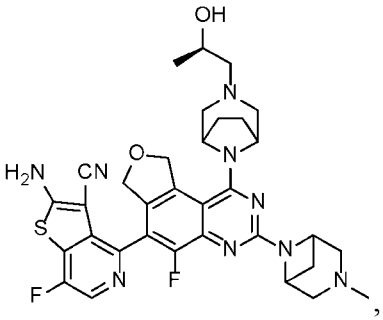
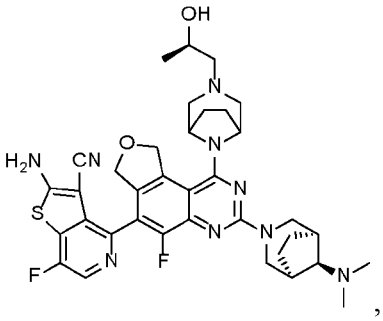
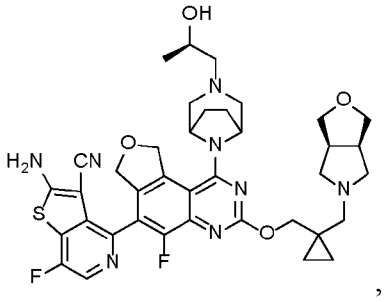

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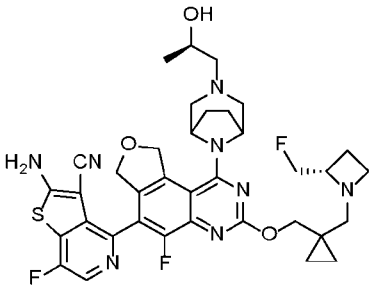
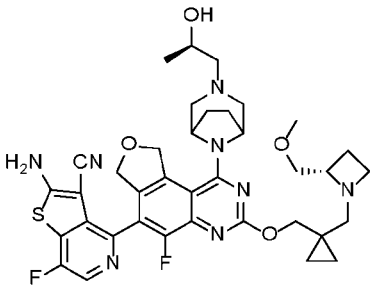
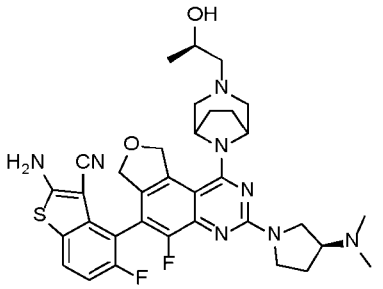
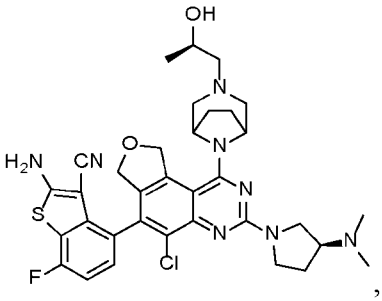
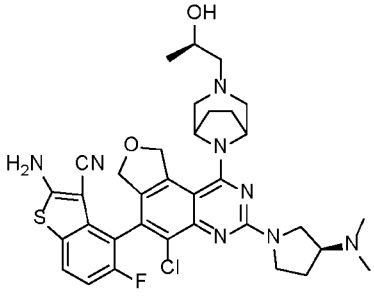

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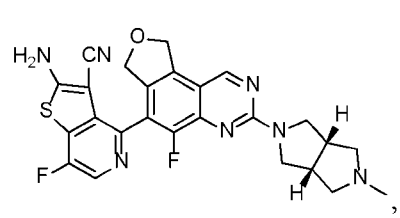
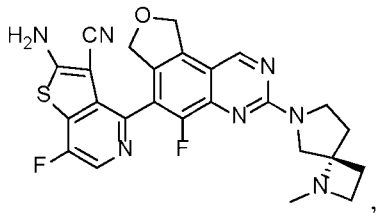
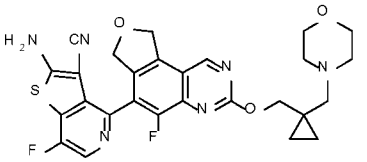
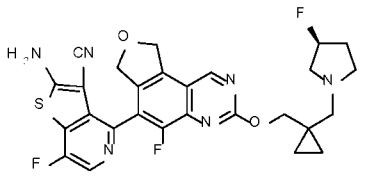
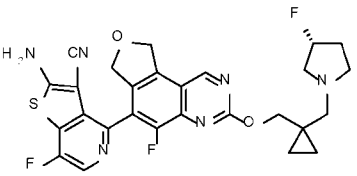
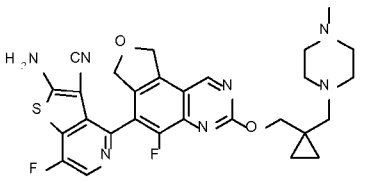
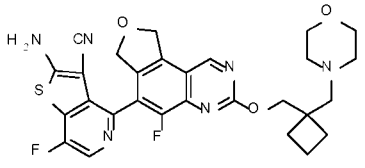
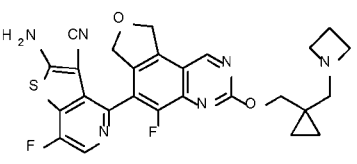
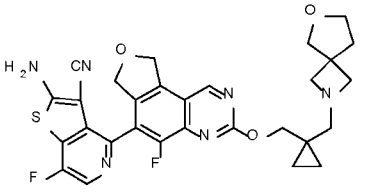


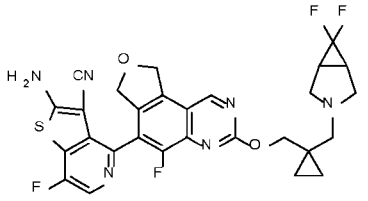
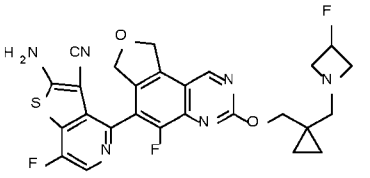
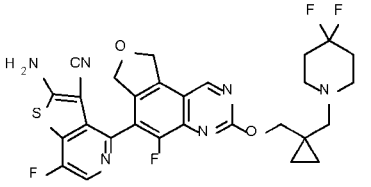
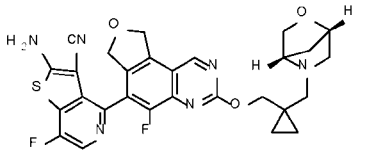
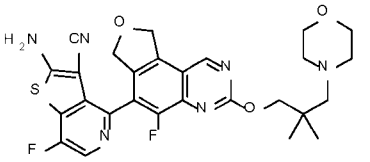
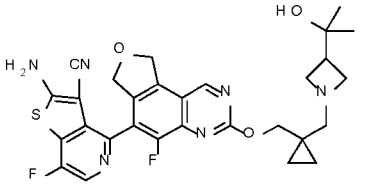
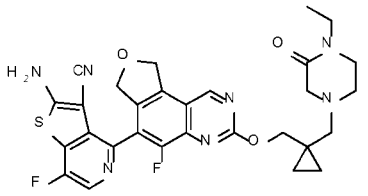
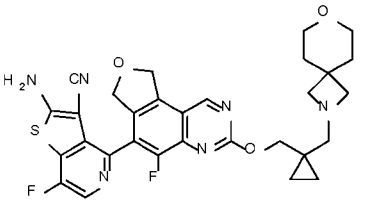
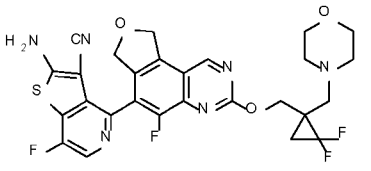
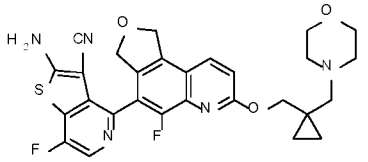
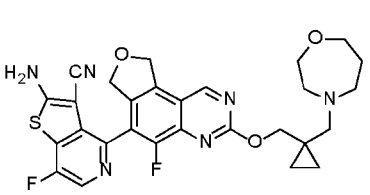
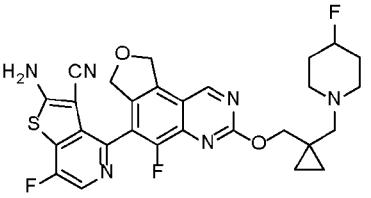
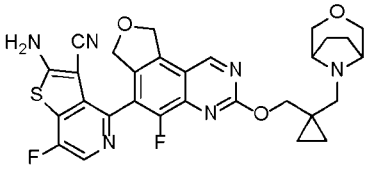
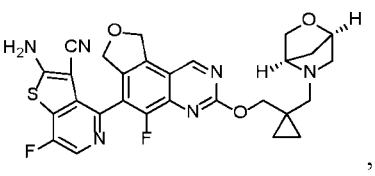

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[0181] A compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is selected from


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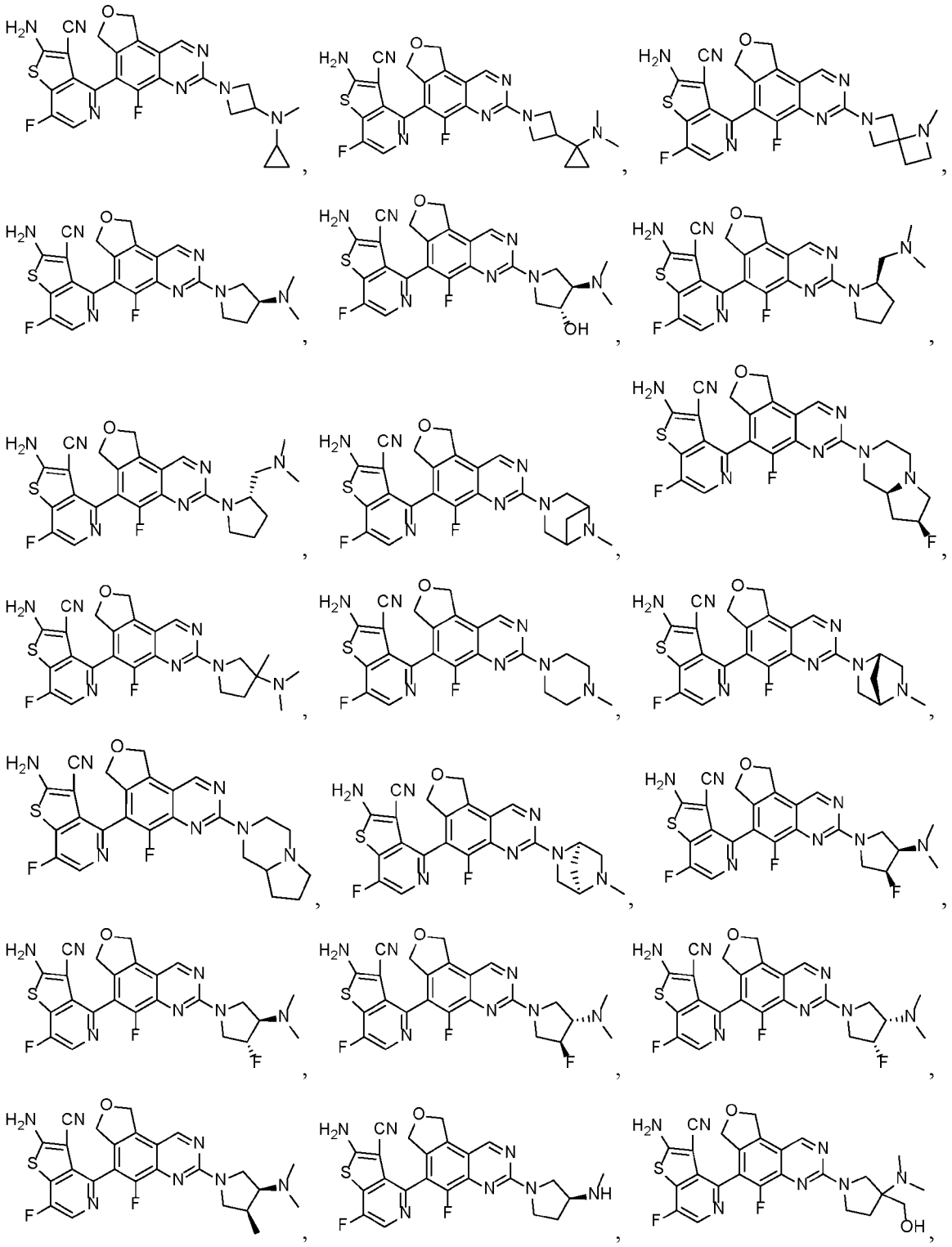
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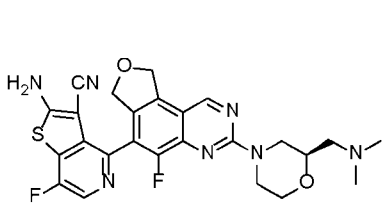
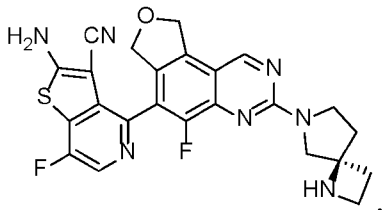
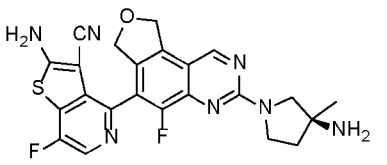
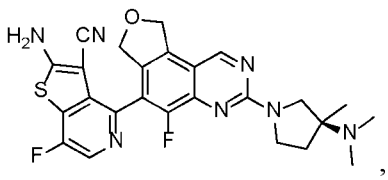
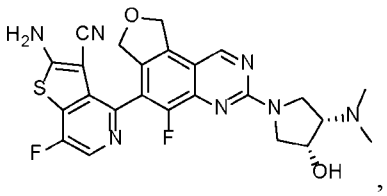
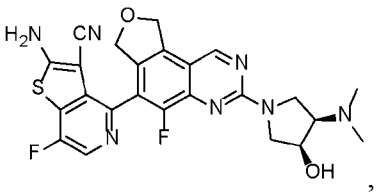
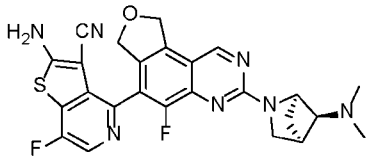
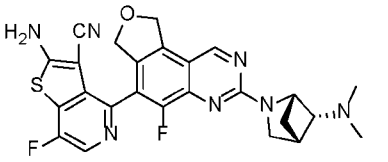
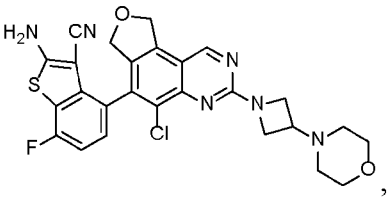
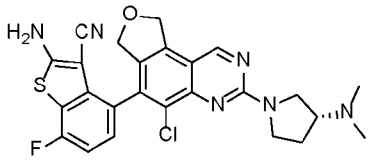
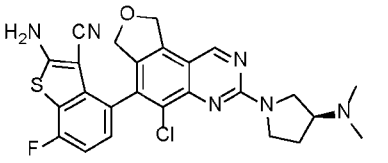
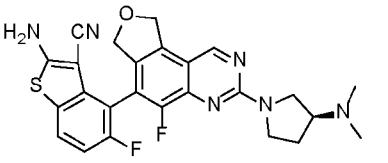
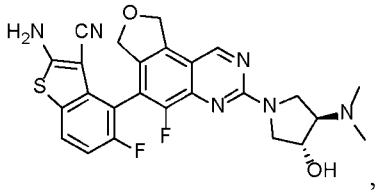
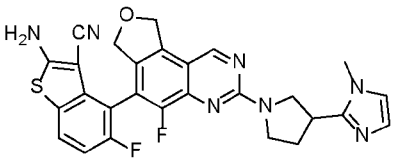
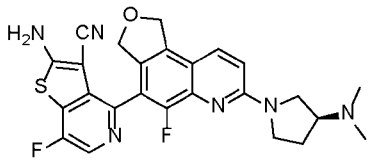
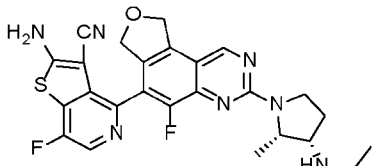
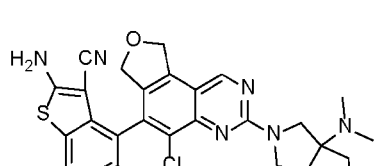
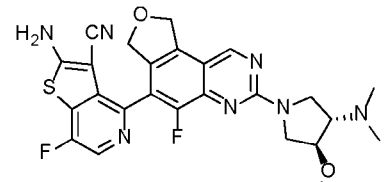
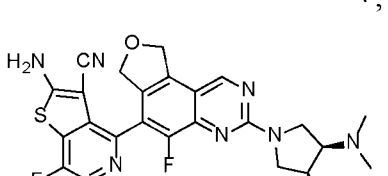
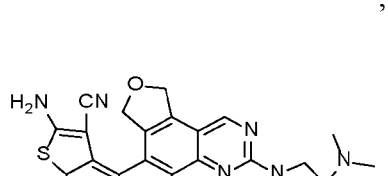
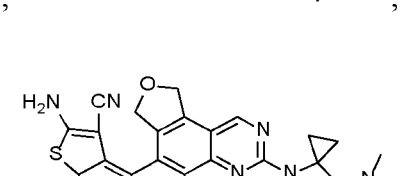
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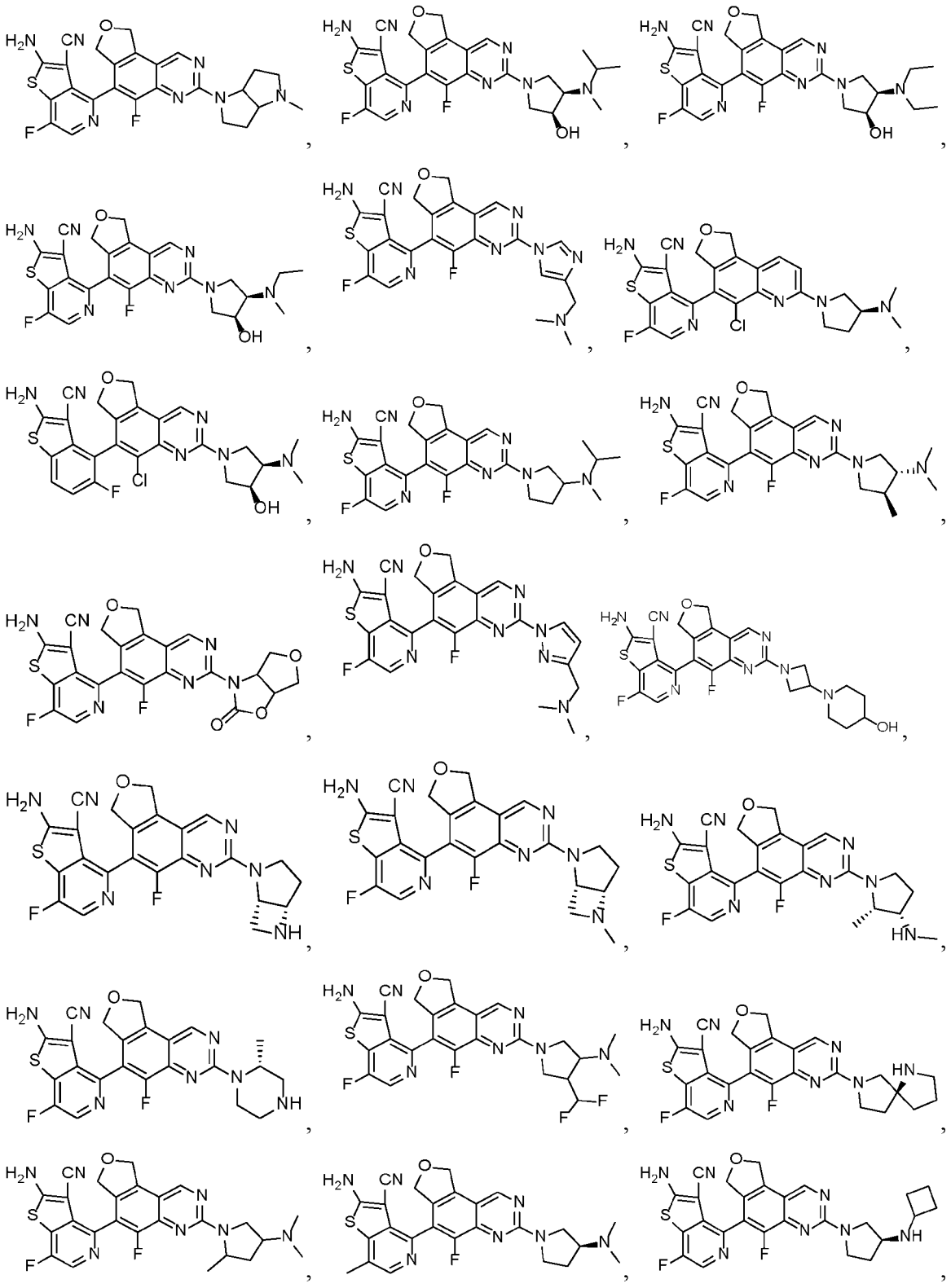


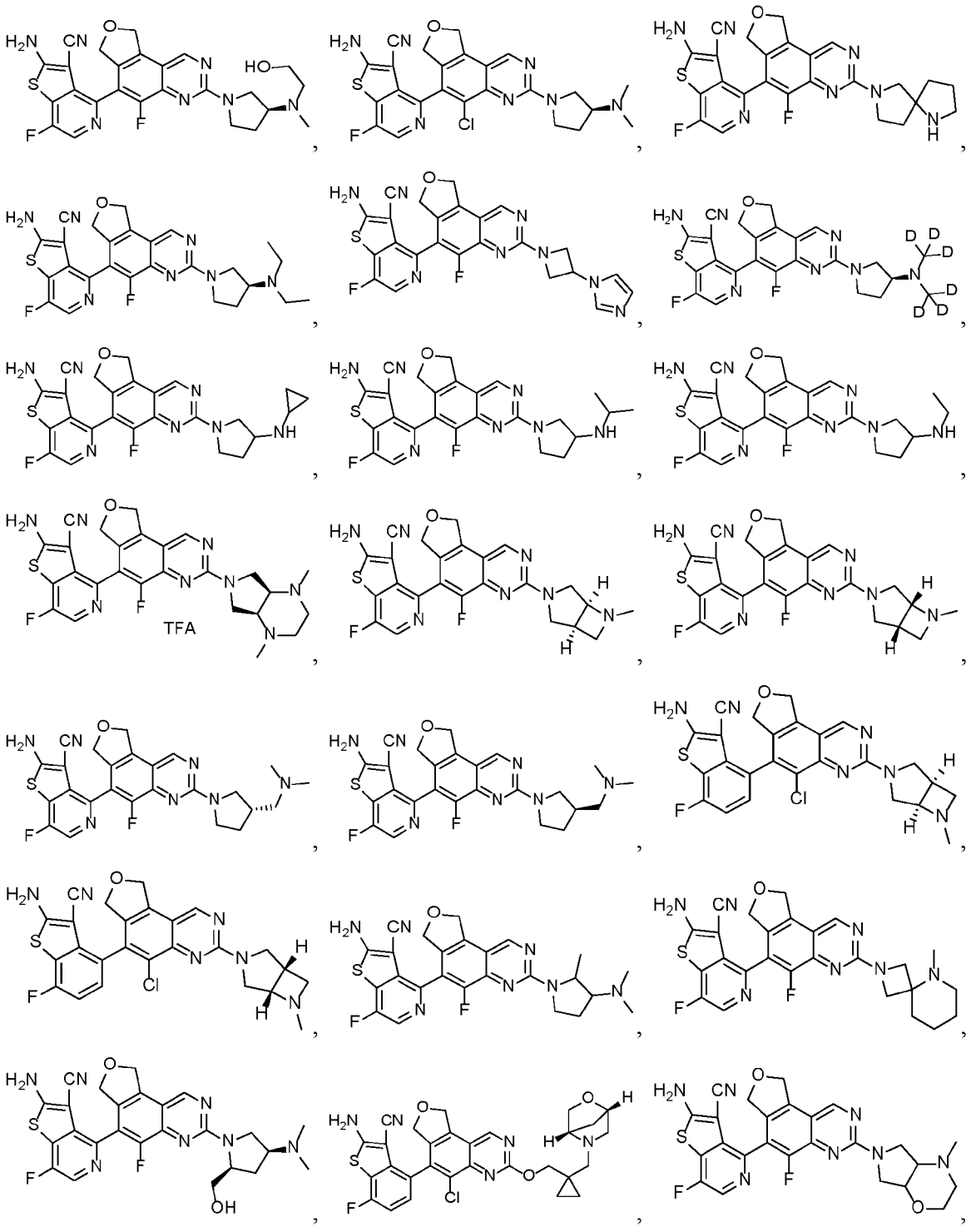

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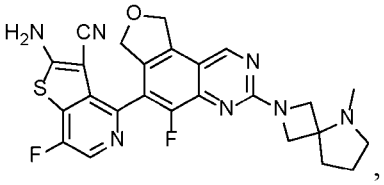
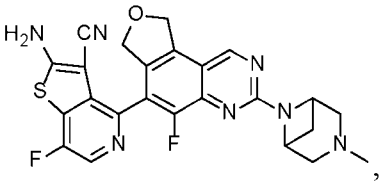
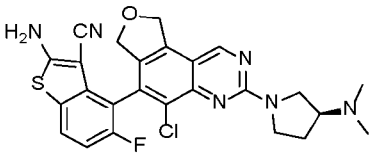
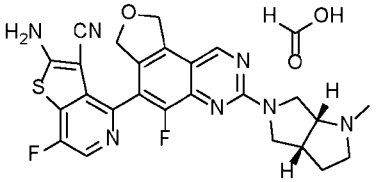
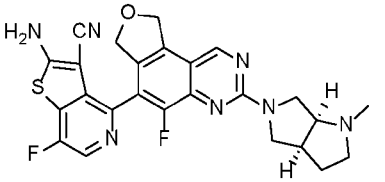
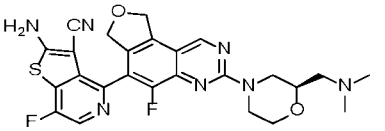
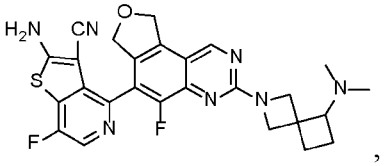
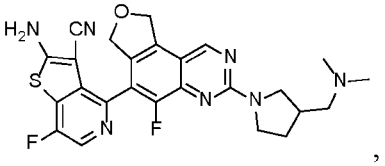
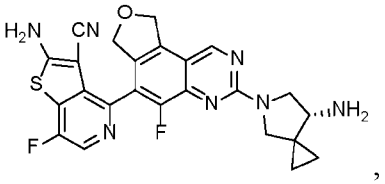
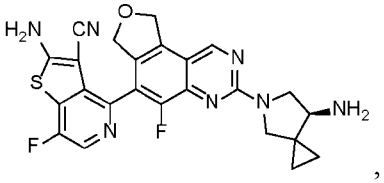
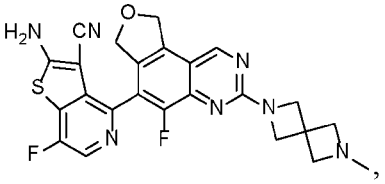
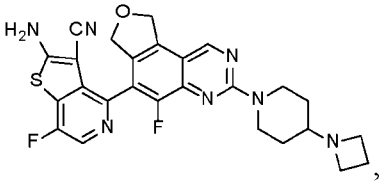
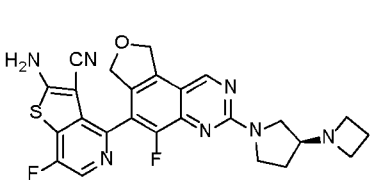
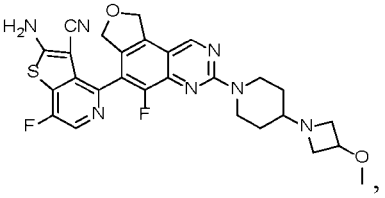
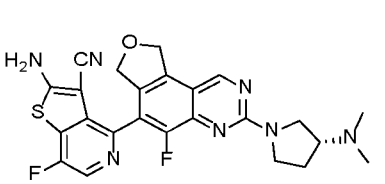
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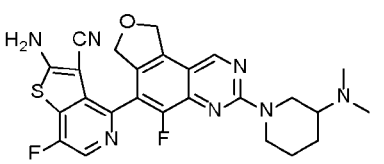
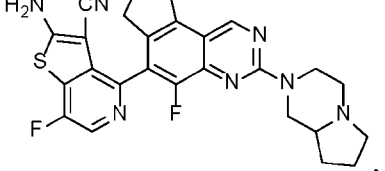
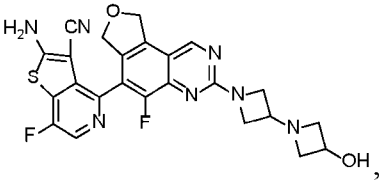
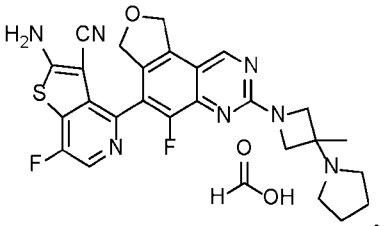
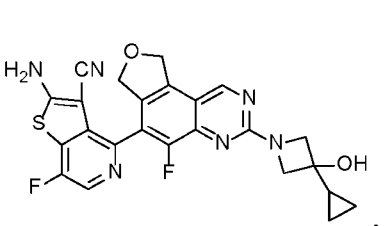
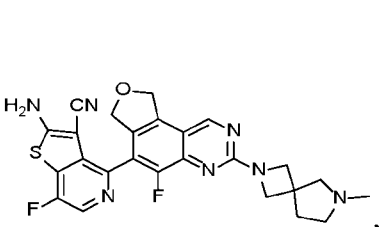



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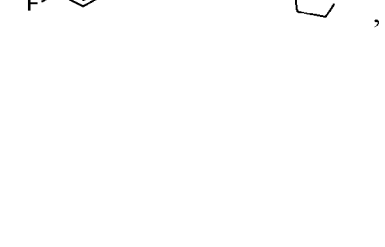

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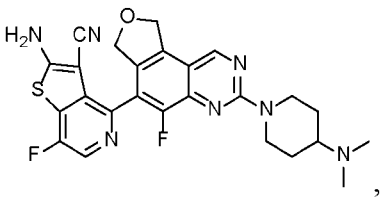
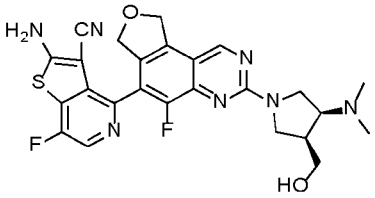
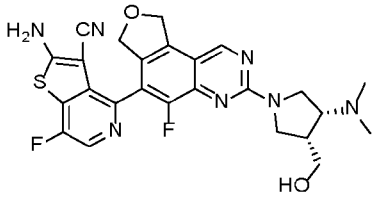
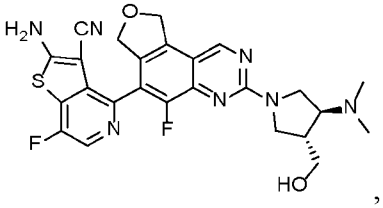
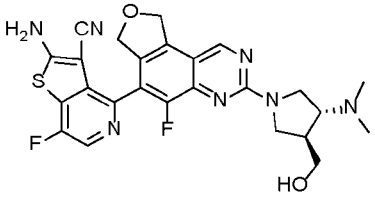
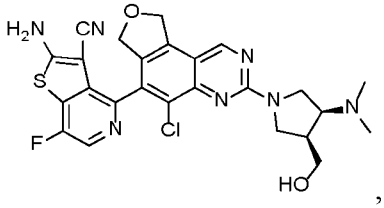
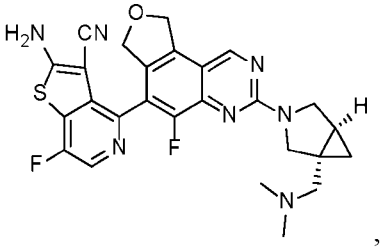
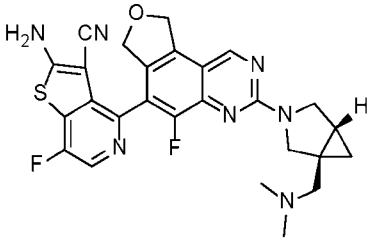
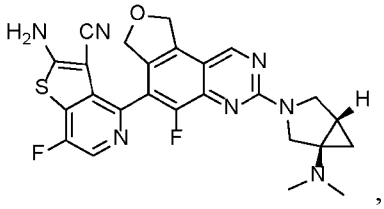
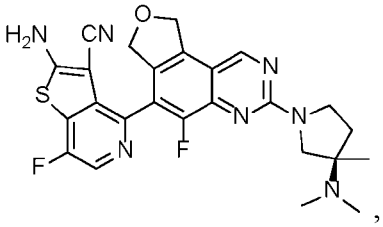
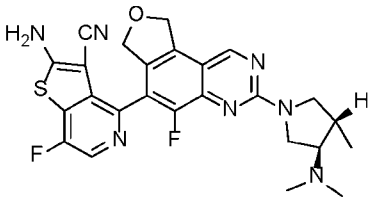
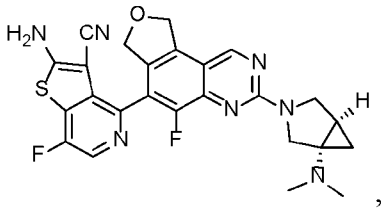
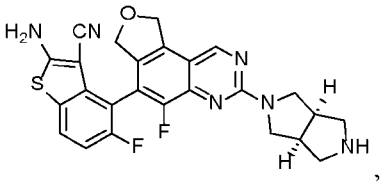
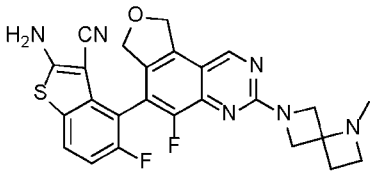
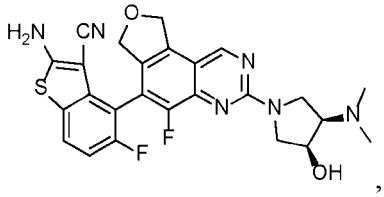
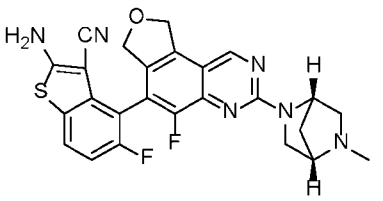
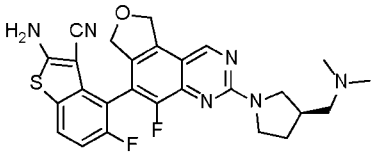
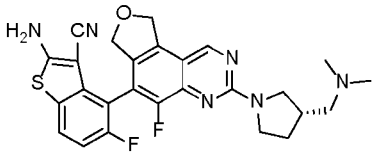
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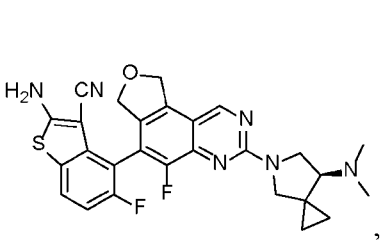
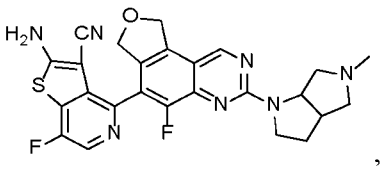
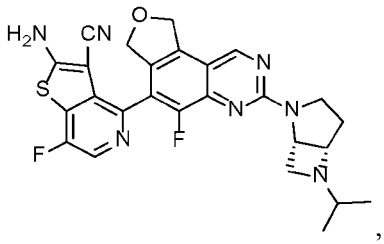
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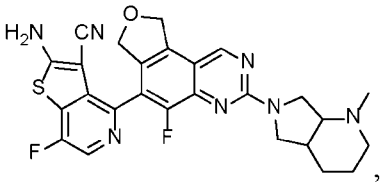
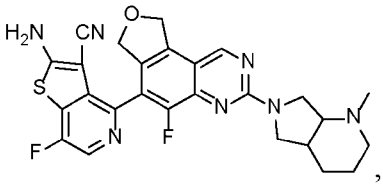
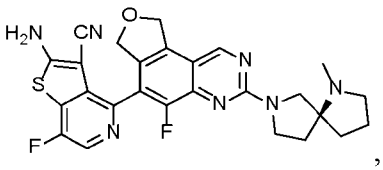

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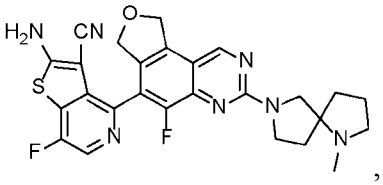
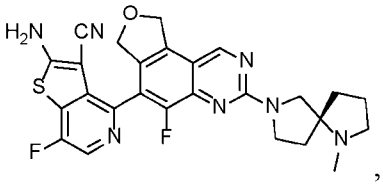
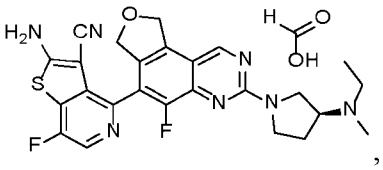
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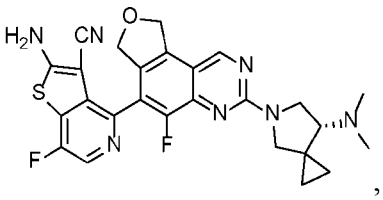
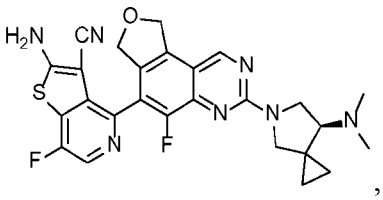
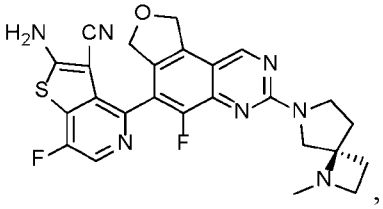
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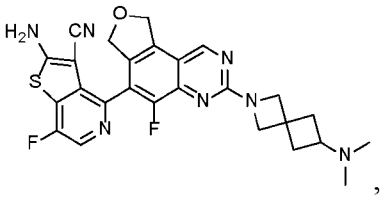
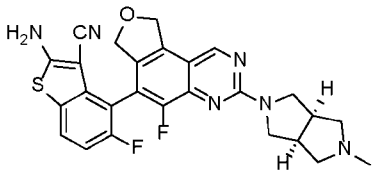
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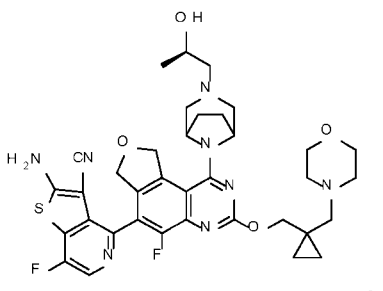
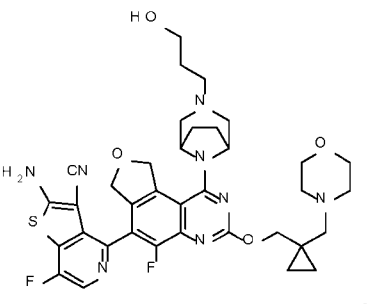
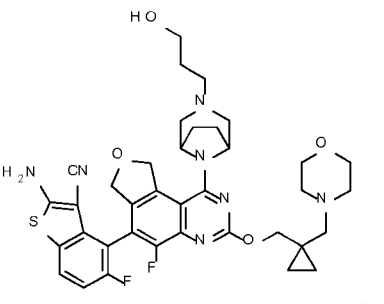
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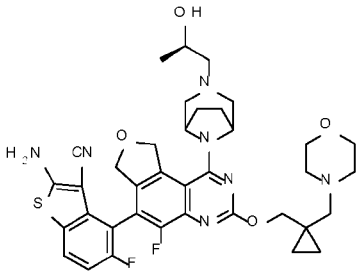
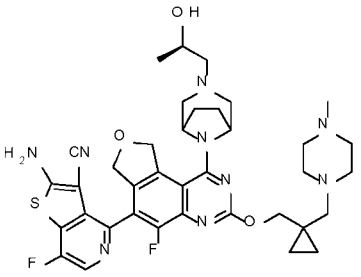
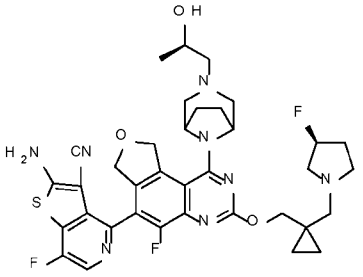
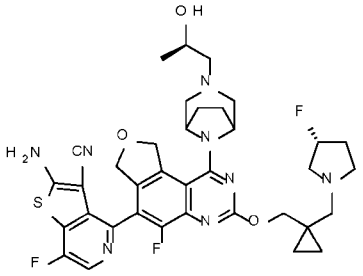
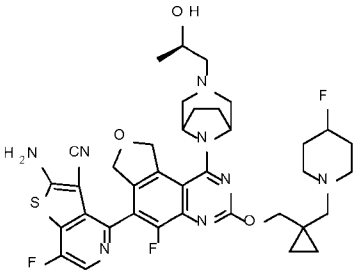
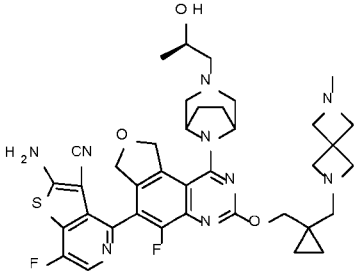
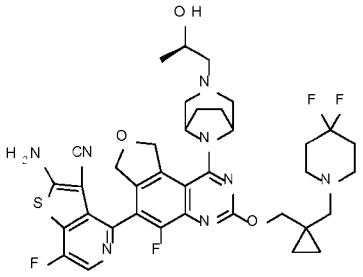
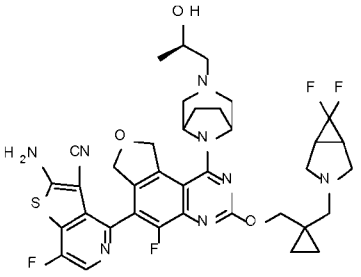
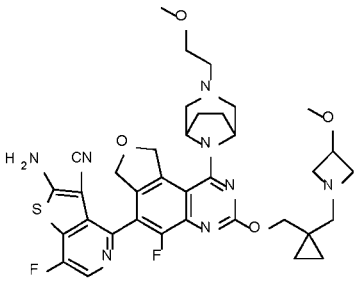
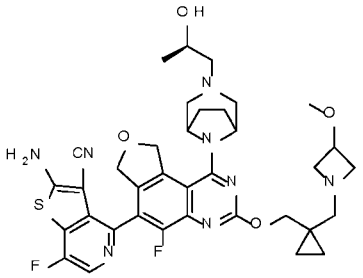
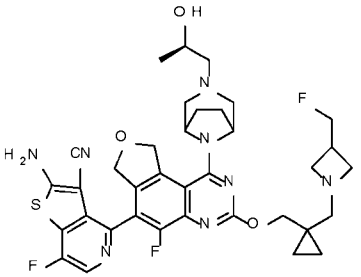
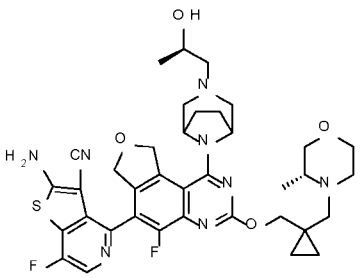
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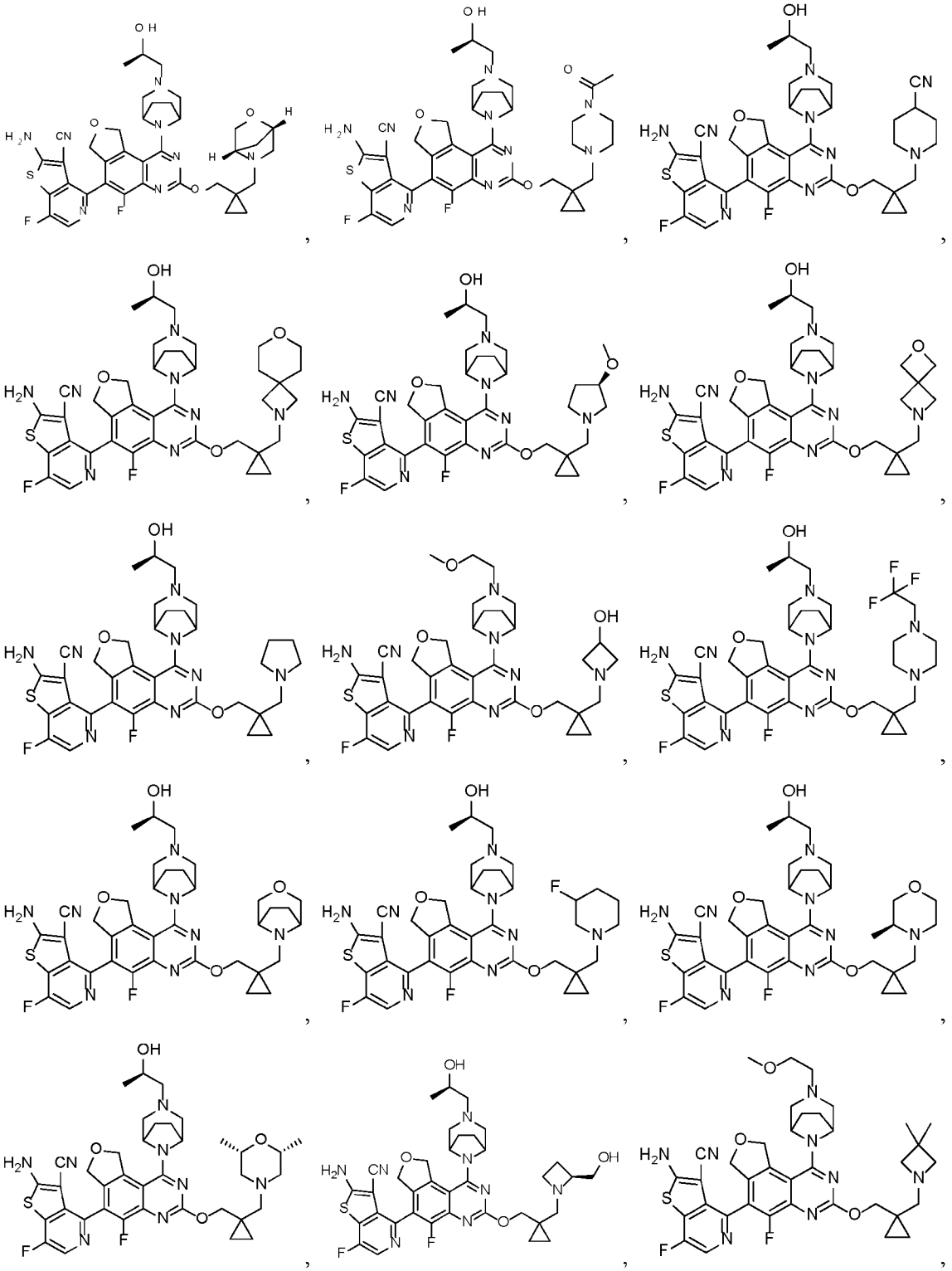
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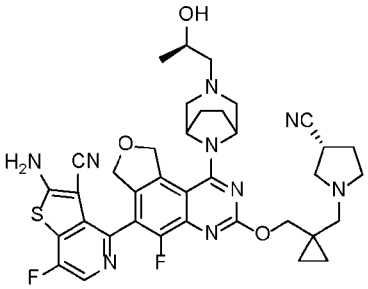
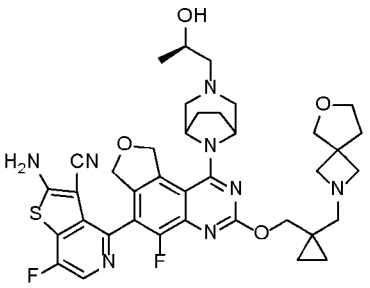
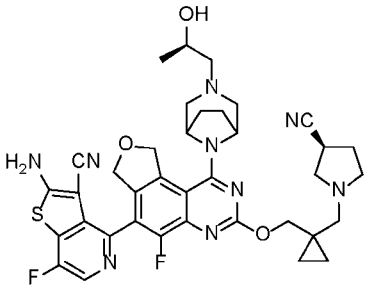
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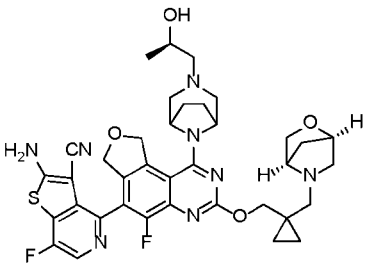
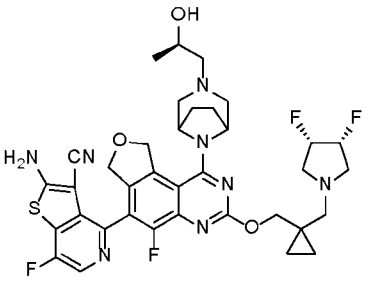
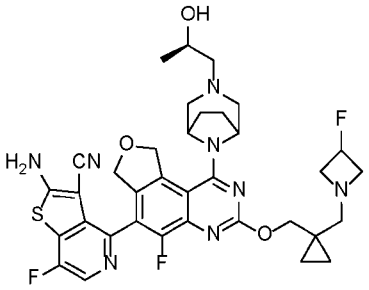
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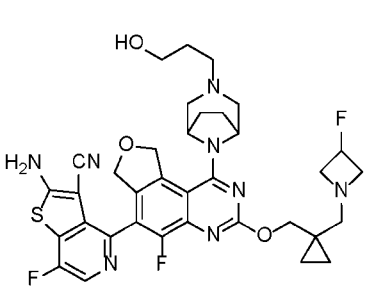
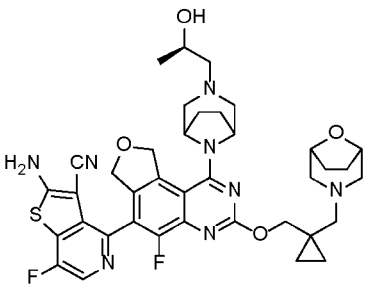
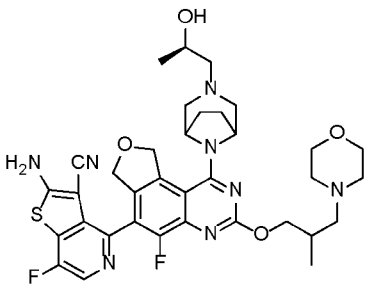
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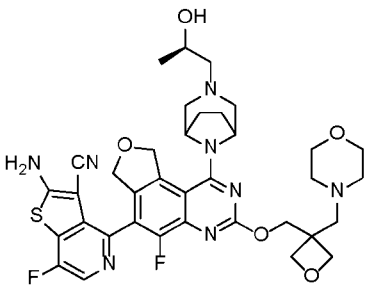
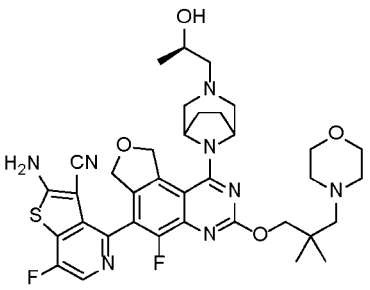
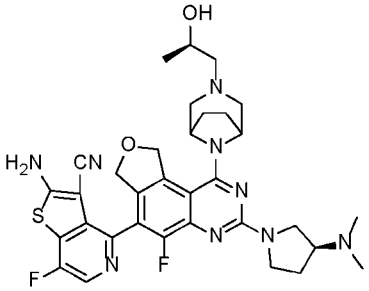

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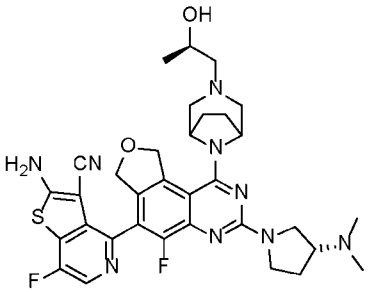
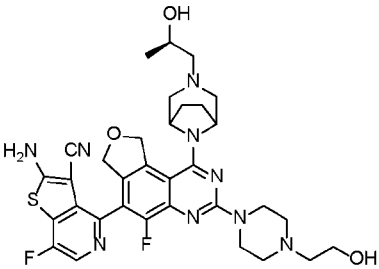
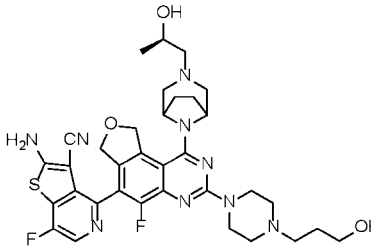


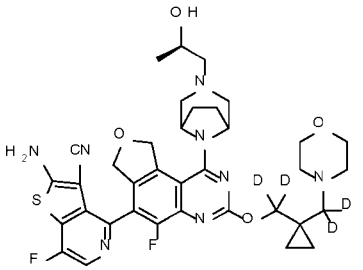
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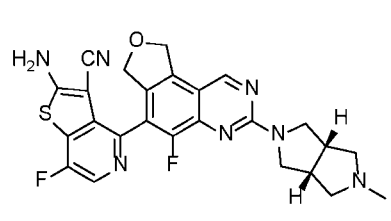
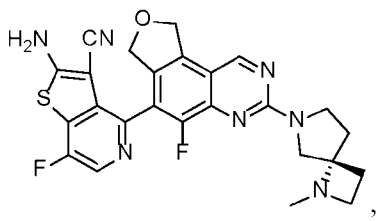
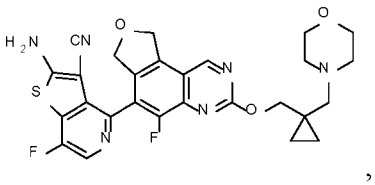
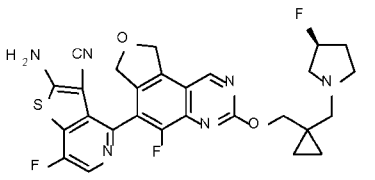
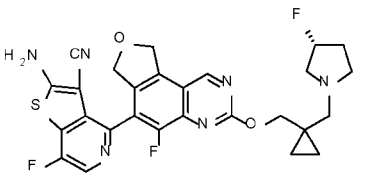
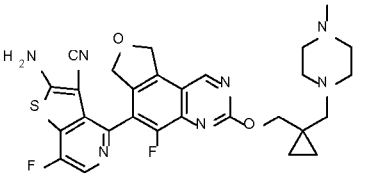
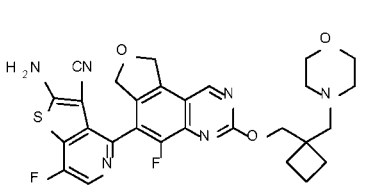
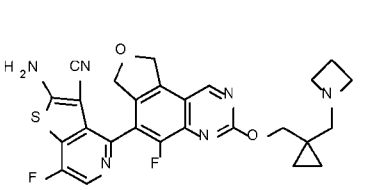
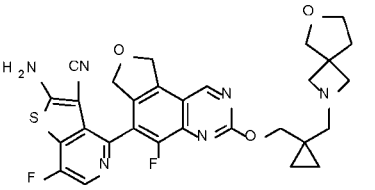
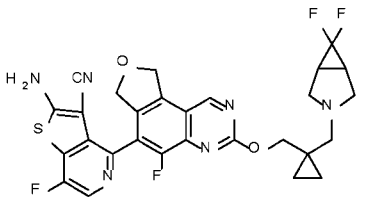
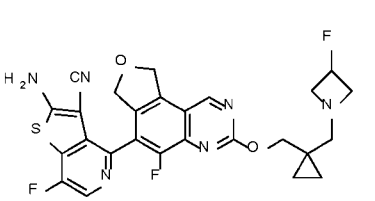
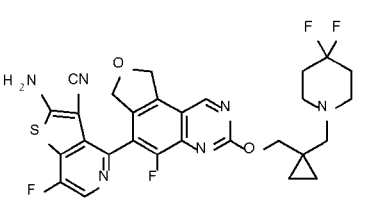
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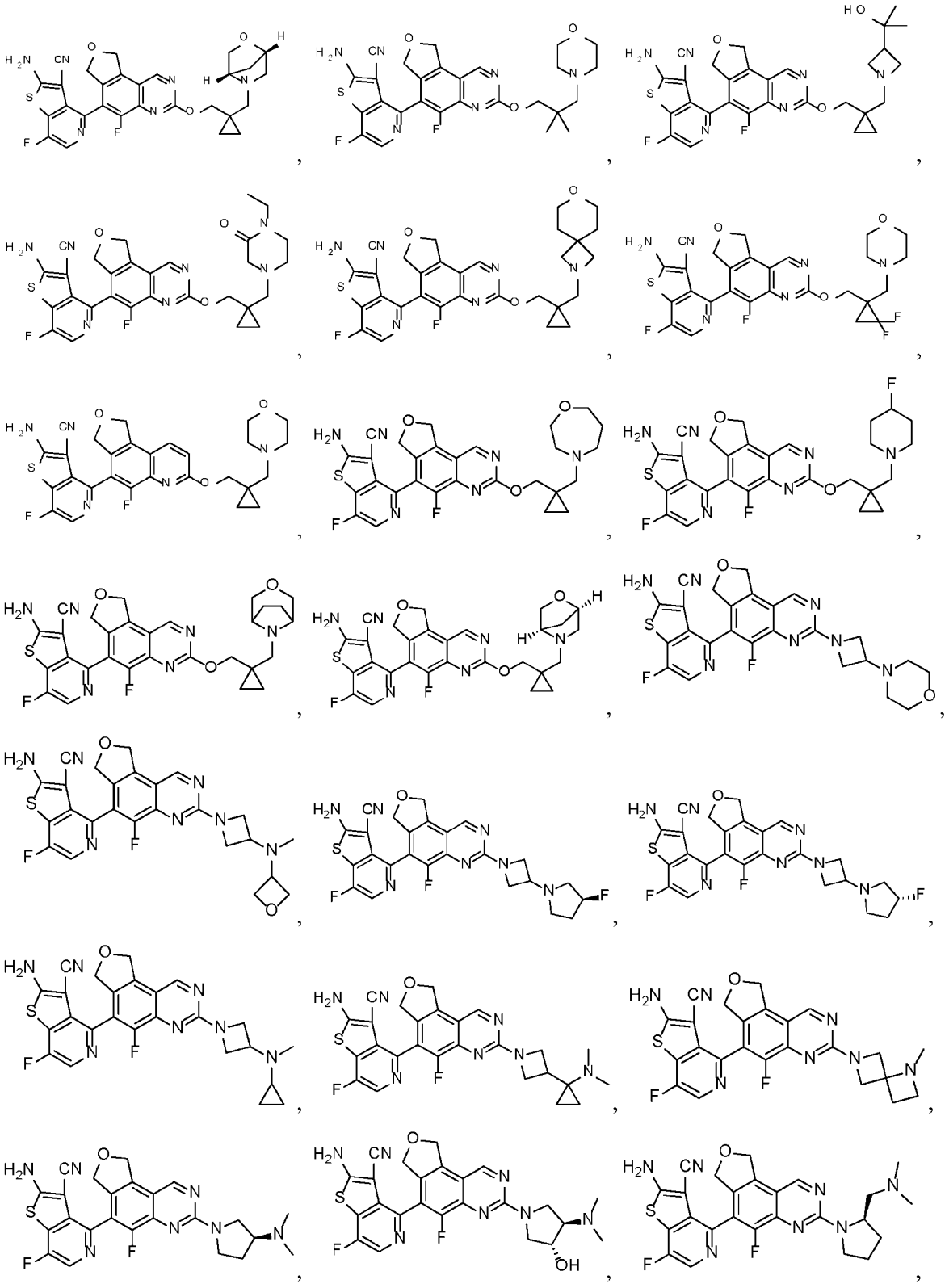
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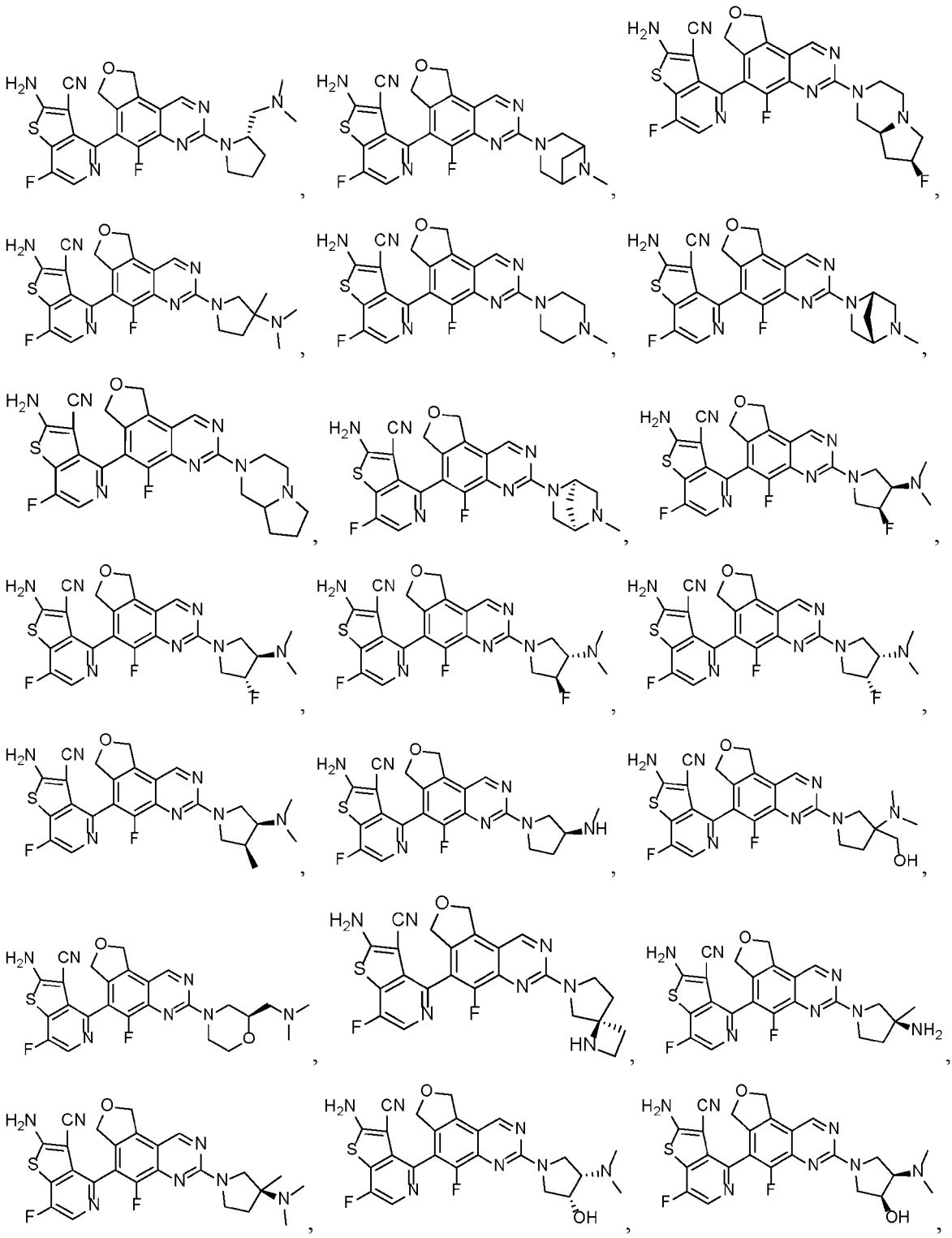
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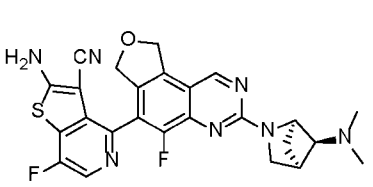
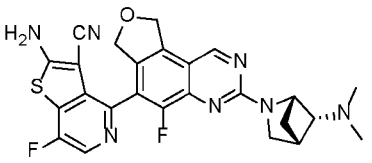
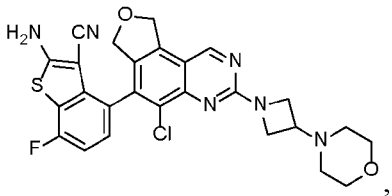
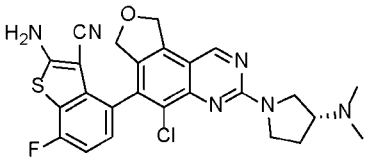
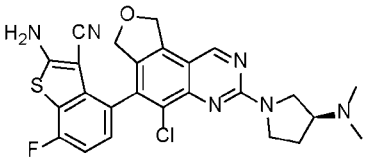
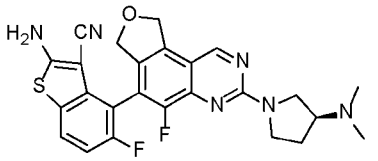
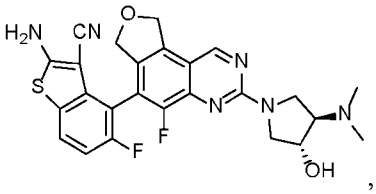
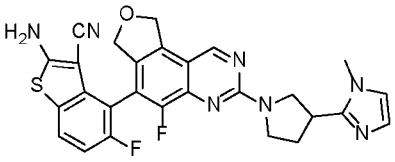
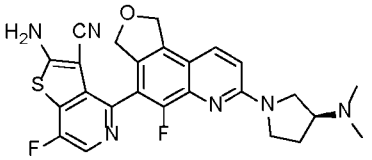

, or a pharmaceutically acceptable salt thereof.

[0183] A compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is selected from

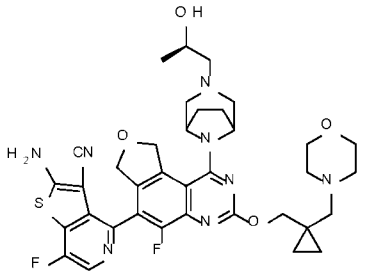
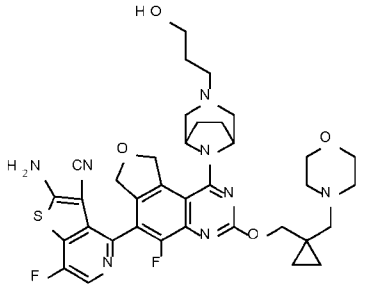
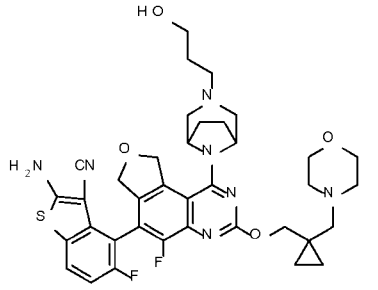
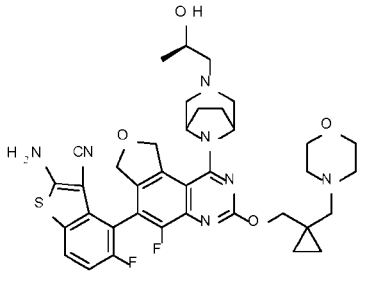
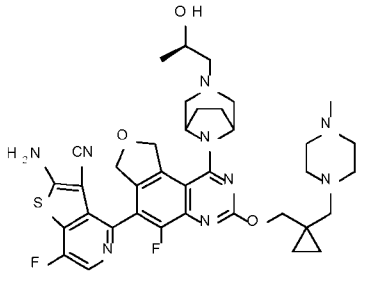
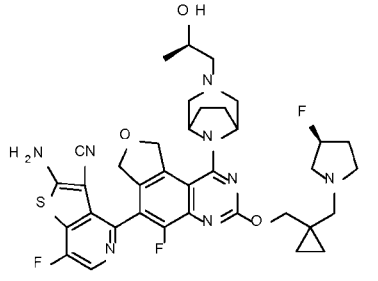

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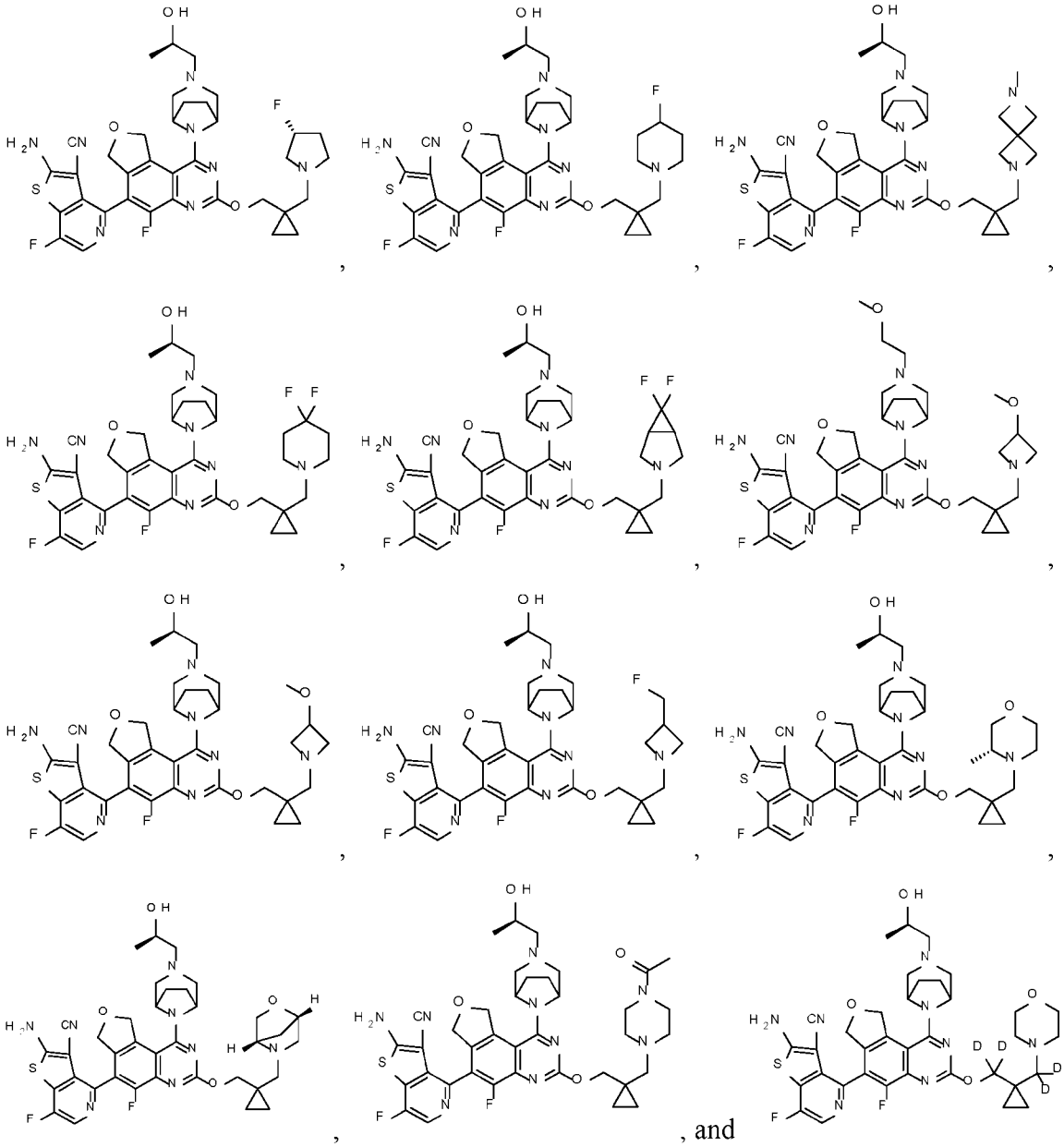





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, or a pharmaceutically acceptable salt thereof.

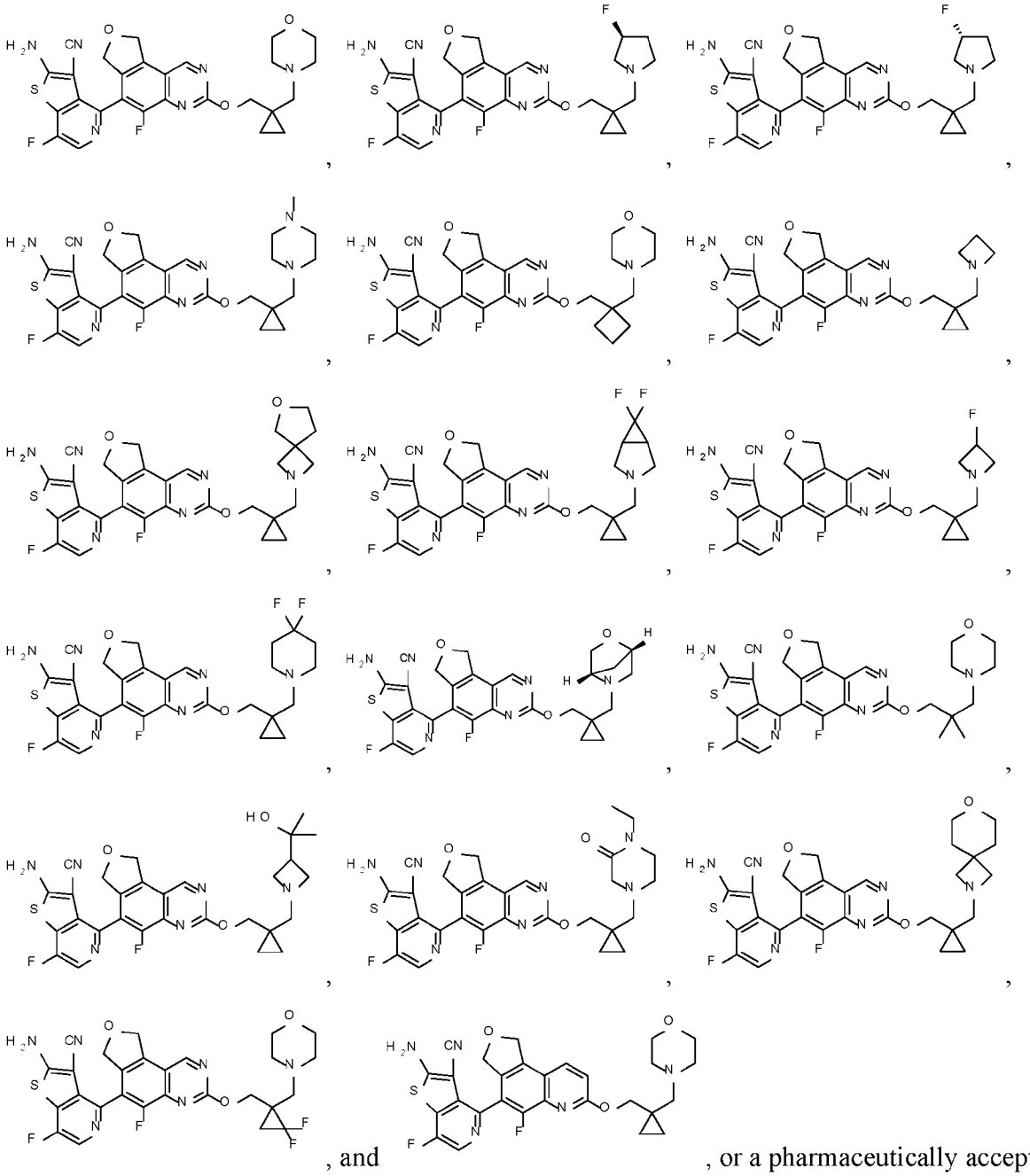
[0184] A compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is selected from


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pharmaceutically acceptable salt thereof.

[0185] A compound of Formula I or a pharmaceutically acceptable salt thereof, the compound is selected from



, or a pharmaceutically acceptable salt thereof.

[0186] The chemical drawings in the compounds above contain indications of chiral aspects of the specific compounds shown. However, the chemical drawings in the compounds above do not contain all the possible chiral features of these compounds and the chiral indications shown are not

intended to exclude changes to the chiral aspects shown. Thus, alternate chiral versions of the compounds as well as different combinations of chiral attributes are contemplated and included herein.

[0187] Also provided herein are pharmaceutical compositions comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, examples of which include, but are not limited to, the compounds disclosed herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0188] Further provided herein are methods of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof. In this method, the cancer can be lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, gastric, or esophageal cancer. In this method, the cancer can more specifically be non-small cell lung cancer, pancreatic cancer, or colorectal cancer. In an embodiment the cancer can be non-small cell lung cancer. In an embodiment the cancer can be pancreatic cancer. In an embodiment the cancer can be colorectal cancer.

[0189] Also provided herein is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12D protein. In this method, the cancer can be non-small cell lung cancer, pancreatic cancer, or colorectal cancer, in which the cancer has one or more cells that express a KRas G12D mutant protein. In an embodiment, the cancer is non-small cell lung carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein. In an embodiment, the cancer is mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. In an embodiment, the cancer is colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. Also provided herein is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. In this method, the cancer can be non-small cell lung cancer, pancreatic cancer, or colorectal cancer, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. In an embodiment, the cancer is non-small cell lung carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant

protein. In an embodiment, the cancer is mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. In an embodiment, the cancer is colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0190] Further provided herein is a method of treating a patient with a cancer that has a KRas G12D mutation comprising administering to a patient in need thereof an effective amount of a compound according to Formula I or a pharmaceutically acceptable salt thereof. In this method, the cancer that has a KRas G12D mutation can be KRas G12D mutant lung cancer, KRas G12D mutant pancreatic cancer, KRas G12D mutant cervical cancer, KRas G12D mutant esophageal cancer, KRas G12D mutant endometrial cancer, KRas G12D mutant ovarian cancer, KRas G12D mutant cholangiocarcinoma, and KRas G12D mutant colorectal cancer. In an embodiment the cancer that has a KRas G12D mutation can be KRas G12D mutant non-small cell lung cancer. In an embodiment the cancer that has a KRas G12D mutation can be KRas G12D mutant pancreatic cancer. In an embodiment the cancer that has a KRas G12D mutation can be KRas G12D mutant colorectal cancer.

[0191] Further provided herein is a method of treating a patient with a cancer that has a KRas G12C, G12D, and/or G12V mutation comprising administering to a patient in need thereof an effective amount of a compound according to Formula I or a pharmaceutically acceptable salt thereof. In this method, the cancer that has a KRas G12C, G12D, and/or G12V mutation can be KRas G12C, G12D, and/or G12V mutant lung cancer, KRas G12C, G12D, and/or G12V mutant pancreatic cancer, KRas G12C, G12D, and/or G12V mutant cervical cancer, KRas G12C, G12D, and/or G12V mutant esophageal cancer, KRas G12C, G12D, and/or G12V mutant endometrial cancer, KRas G12C, G12D, and/or G12V mutant ovarian cancer, KRas G12C, G12D, and/or G12V mutant cholangiocarcinoma, and KRas G12C, G12D, and/or G12V mutant colorectal cancer. In an embodiment the cancer that has a KRas G12C, G12D, and/or G12V mutation can be KRas G12C, G12D, and/or G12V mutant non-small cell lung cancer. In an embodiment the cancer that has a KRas G12C, G12D, and/or G12V mutation can be KRas G12C, G12D, and/or G12V mutant pancreatic cancer. In an embodiment the cancer that has a KRas G12C, G12D, and/or G12V mutation can be KRas G12C, G12D, and/or G12V mutant colorectal cancer.

[0192] Additionally provided herein is a method of modulating a mutant KRas G12D enzyme in a patient in need thereof, by administering a compound according to Formula I, or a pharmaceutically acceptable salt thereof. In one embodiment this method comprises inhibiting a human mutant KRas G12D enzyme. Additionally provided herein is a method of modulating a mutant KRas G12C, G12D, and/or G12V enzyme in a patient in need thereof, by administering a compound according to Formula I, or a pharmaceutically acceptable salt thereof. In one embodiment this method comprises inhibiting a human mutant KRas G12C, G12D, and/or G12V enzyme.

[0193] Also provided herein is a method of treating cancer in a patient in need thereof, wherein the patient has a cancer that was determined to express the KRas G12D mutant protein. The method comprises administering to a patient an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof. Also provided herein is a method of treating cancer in a patient in need thereof, wherein the patient has a cancer that was determined to express the KRas G12C, G12D, and/or G12V mutant protein. The method comprises administering to a patient an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof. The G12C, G12D, and/or G12V mutational status of one or more cancer cells can be determined by a number of assays known in the art. Typically, one or more biopsies containing one or more cancer cells are obtained, and subjected to sequencing and/or polymerase chain reaction (PCR). Circulating cell-free DNA can also be used, e.g. in advanced cancers. Non-limiting examples of sequencing and PCR techniques used to determine the mutational status (e.g., G12C, G12D, and/or G12V mutational status, in one or more cancer cells or in circulating cell-free DNA) include direct sequencing, next-generation sequencing, reverse transcription polymerase chain reaction (RT-PCR), multiplex PCR, and pyrosequencing and multi-analyte profiling.

[0194] Further provided herein is a compound or a pharmaceutically acceptable salt thereof according to Formula I for use in therapy. The compound or a pharmaceutically acceptable salt thereof, can be for use in treating cancer. For this use in treating cancer, the cancer can be lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, or esophageal cancer. The cancer can more specifically be non-small cell lung cancer, pancreatic cancer, or colorectal cancer. In an embodiment, the cancer is non-small cell lung cancer. In an embodiment, the cancer is pancreatic cancer. In an embodiment, the cancer is colorectal cancer. The cancer can have one or more cancer cells that express the mutant KRas G12D protein such

as KRas G12D mutant lung cancer, KRas G12D mutant pancreatic cancer, KRas G12D mutant cervical cancer, KRas G12D mutant esophageal cancer, KRas G12D mutant endometrial cancer, KRas G12D mutant ovarian cancer, KRas G12D mutant cholangiocarcinoma, and KRas G12D mutant colorectal cancer. In these uses, the cancer is selected from: KRas G12D mutant non-small cell lung cancer, KRas G12D mutant colorectal cancer, and KRas G12D mutant pancreatic cancer. Additionally, the cancer can be non-small cell lung cancer, and one or more cells express KRas G12D mutant protein. Further, the cancer can be colorectal cancer, and one or more cells express KRas G12D mutant protein. Additionally, the cancer can be pancreatic cancer, and one or more cells express KRas G12D mutant protein. The patient can have a cancer that was determined to have one or more cells expressing the KRas G12D mutant protein prior to administration of the compound or a pharmaceutically acceptable salt thereof. The cancer can have one or more cancer cells that express the mutant KRas G12C, G12D, and/or G12V protein such as KRas G12C, G12D, and/or G12V mutant lung cancer, KRas G12C, G12D, and/or G12V mutant pancreatic cancer, KRas G12C, G12D, and/or G12V mutant cervical cancer, KRas G12C, G12D, and/or G12V mutant esophageal cancer, KRas G12C, G12D, and/or G12V mutant endometrial cancer, KRas G12C, G12D, and/or G12V mutant ovarian cancer, KRas G12C, G12D, and/or G12V mutant cholangiocarcinoma, and KRas G12C, G12D, and/or G12V mutant colorectal cancer. In these uses, the cancer is selected from: KRas G12C, G12D, and/or G12V mutant non-small cell lung cancer, KRas G12C, G12D, and/or G12V mutant colorectal cancer, and KRas G12C, G12D, and/or G12V mutant pancreatic cancer. Additionally, the cancer can be non-small cell lung cancer, and one or more cells express KRas G12C, G12D, and/or G12V mutant protein. Further, the cancer can be colorectal cancer, and one or more cells express KRas G12C, G12D, and/or G12V mutant protein. Additionally, the cancer can be pancreatic cancer, and one or more cells express KRas G12C, G12D, and/or G12V mutant protein. The patient can have a cancer that was determined to have one or more cells expressing the KRas G12C, G12D, and/or G12V mutant protein prior to administration of the compound or a pharmaceutically acceptable salt thereof. The patient may have been treated with a different course of treatment prior to being treated as described herein.

[0195] The compounds provided herein according to Formula I, or a pharmaceutically acceptable salt thereof, may also be used in the manufacture of a medicament for treating cancer. When used in the manufacture of a medicament, the cancer can be lung cancer, colorectal cancer, pancreatic cancer,

bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, or esophageal cancer. The cancer can more specifically be non-small cell lung cancer, pancreatic cancer, or colorectal cancer. In an embodiment, the cancer is non-small cell lung cancer. In an embodiment, the cancer is pancreatic cancer. In an embodiment, the cancer is colorectal cancer. The cancer can have one or more cancer cells that express the mutant KRas G12D protein. When the cancer cells express KRas G12D protein, the cancer can be selected from KRas G12D mutant non-small cell lung cancer, KRas G12D mutant colorectal cancer, and KRas G12D mutant pancreatic cancer. The cancer can have one or more cancer cells that express the mutant KRas G12C, G12D, and/or G12V protein. When the cancer cells express KRas G12C, G12D, and/or G12V protein, the cancer can be selected from KRas G12C, G12D, and/or G12V mutant non-small cell lung cancer, KRas G12C, G12D, and/or G12V mutant colorectal cancer, and KRas G12C, G12D, and/or G12V mutant pancreatic cancer.

[0196] Also provided herein is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and one or more of a PD-1 inhibitor, a PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor, an Aurora A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof, in which the cancer has one or more cells that express a mutant KRas G12D protein. Also provided herein is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and one or more of a PD-1 inhibitor, a PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor, an Aurora A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided herein is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with one or more of a PD-1 or PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor, an Aurora A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof, in the treatment of cancer. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and one or more of a PD-1 or PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor, an Aurora

A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof, for simultaneous, separate, or sequential use in the treatment of cancer.

[0197] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a PD-1 or PD-L1 inhibitor, in which the cancer has one or more cells that express a mutant KRas G12D protein. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a PD-1 or PD-L1 inhibitor, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with a PD-1 or PD-L1 inhibitor, for use in the treatment of cancer. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a PD-1 or PD-L1 inhibitor, for simultaneous, separate, or sequential use in the treatment of cancer. As used herein, the PD-1 or PD-L1 inhibitor can be pembrolizumab; the PD-1 or PD-L1 inhibitor can be nivolumab; the PD-1 or PD-L1 inhibitor can be cemiplimab; the PD-1 or PD-L1 inhibitor can be sintilimab ; the PD-1 or PD-L1 inhibitor can be atezolizumab; the PD-1 or PD-L1 inhibitor can be avelumab; the PD-1 or PD-L1 inhibitor can be durvalumab; or the PD-1 or PD-L1 inhibitor can be lodapilimab. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein; or the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; or the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0198] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12D protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. As used herein, the CDK4/CDK6 inhibitor can be abemaciclib; the CDK4/CDK6 inhibitor can be palbociclib; or the CDK4/CDK6 inhibitor can be ribociclib. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a CDK4/CDK6 inhibitor, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. As used herein, the

CDK4/CDK6 inhibitor can be abemaciclib; the CDK4/CDK6 inhibitor can be palbociclib; or the CDK4/CDK6 inhibitor can be ribociclib. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0199] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12D protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer. Additional provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of cancer. As used herein, the EGFR inhibitor can be erlotinib; the EGFR inhibitor can be afatinib; the EGFR inhibitor can be gefitinib; the EGFR inhibitor can be cetuximab. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein; or the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins.

[0200] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with an EGFR inhibitor, or a pharmaceutically

acceptable salt thereof, for the treatment of cancer. Additional provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of cancer. As used herein, the EGFR inhibitor can be erlotinib; the EGFR inhibitor can be afatinib; the EGFR inhibitor can be gefitinib; the EGFR inhibitor can be cetuximab. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; or the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0201] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an ERK inhibitor, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12D protein. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an ERK inhibitor, or a pharmaceutically acceptable salt thereof, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an Aurora A inhibitor, in which the cancer has one or more cells that express a mutant KRas G12D protein. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an Aurora A inhibitor, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with an Aurora A inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or

sequential combination with an Aurora A inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with an ERK inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with an ERK inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an ERK inhibitor, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of cancer. As used herein, the ERK inhibitor can be LY3214996; the ERK inhibitor can be LTT462; or the ERK inhibitor can be KO-947. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0202] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an Aurora A inhibitor, in which the cancer has one or more cells that express a mutant KRas G12D protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with an Aurora A

inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an Aurora A inhibitor, for simultaneous, separate, or sequential use in the treatment of cancer. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an Aurora A inhibitor, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with an Aurora A inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and an Aurora A inhibitor, for simultaneous, separate, or sequential use in the treatment of cancer. As used herein, the Aurora A inhibitor can be alisertib, tozasertib, (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid, (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : 2-methylpropan-2-amine (1:1) salt, and (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : amine (1:1) salt, or a pharmaceutically acceptable salt thereof. In one embodiment, the Aurora A inhibitor is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein;

the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0203] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a SHP2 inhibitor, in which the cancer has one or more cells that express a mutant KRas G12D protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with a SHP2 inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a SHP2 inhibitor, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with a SHP2 inhibitor, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a SHP2 inhibitor, for simultaneous, separate, or sequential use in the treatment of cancer. As used herein, the SHP2 inhibitor, or a pharmaceutically acceptable salt thereof, can be a Type I SHP2 Inhibitor or a Type II SHP2 Inhibitor. Examples of Type I SHP2 inhibitors include, but are not limited to, PHPS1, GS-493, NSC-87877, NSC-117199, and Cefsulodin, and pharmaceutically acceptable salts thereof. Examples of Type II SHP2 inhibitors include, but are not limited to, JAB-3068, JAB-3312, RMC-4550, RMC-4630, SHP099, SHP244, SHP389, SHP394, TNO155, RG-6433, and RLY-1971, and pharmaceutically acceptable salts thereof. Additional examples of SHP2 inhibitors include, but are not limited to, BBP-398, IACS-15509, IACS-13909, X37, ERAS-601, SH3809, HBI-2376, ETS-001, and PCC0208023, and pharmaceutically acceptable salts thereof. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be mutant

pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0204] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a platinum agent, in which the cancer has one or more cells that express a mutant KRas G12D protein. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a platinum agent, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with a platinum agent, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and a platinum agent, for simultaneous, separate, or sequential use in the treatment of cancer. As used herein, the platinum agent can be cisplatin; the platinum agent can be carboplatin; or the platinum agent can be oxaliplatin. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. As used herein, the platinum agent can be cisplatin; the platinum agent can be carboplatin; or the platinum agent can be oxaliplatin. As described herein, the cancer can be non-small cell lung carcinoma, in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be colorectal

carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein; the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0205] Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and pemetrexed, in which the cancer has one or more cells that express a mutant KRas G12D protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with pemetrexed, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and pemetrexed, for simultaneous, separate, or sequential use in the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12D protein. As described herein, the cancer has one or more cells that express a KRas G12D mutant protein. Further, a platinum agent can also be administered to the patient (and the platinum agent can be cisplatin, carboplatin, or oxaliplatin). As described herein, the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12D mutant protein or the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12D mutant protein. This method also includes treating KRas G12D mutant bearing cancers of other origins. Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and pemetrexed, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Further provided is a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for use in simultaneous, separate, or sequential combination with pemetrexed, for the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. Additionally provided is a combination comprising a compound according to Formula I, or a pharmaceutically acceptable salt thereof, and pemetrexed, for simultaneous, separate, or sequential use in the treatment of cancer, in which the cancer has one or more cells that express a mutant KRas G12C, G12D, and/or G12V protein. As described herein, the cancer has one or more cells that express a KRas G12C, G12D, and/or

G12V mutant protein. Further, a platinum agent can also be administered to the patient (and the platinum agent can be cisplatin, carboplatin, or oxaliplatin). As described herein, the cancer can be colorectal carcinoma in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein or the cancer can be mutant pancreatic cancer in which the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein. This method also includes treating KRas G12C, G12D, and/or G12V mutant bearing cancers of other origins.

[0206] The term "pharmaceutically acceptable salt" as used herein refers to a salt of a compound considered to be acceptable for clinical and/or veterinary use. Examples of pharmaceutically acceptable salts and common methodology for preparing them can be found in "Handbook of Pharmaceutical Salts: Properties, Selection and Use" P. Stahl, *et al.*, 2nd Revised Edition, Wiley-VCH, 2011 and S.M. Berge, *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Sciences*, 1977, 66(1), 1-19. In an embodiment of a compound of Formula I, or a pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt is a mineral acid salt. Examples of mineral acids include, but are not limited to HCl, H_2SO_4, H_3PO_4 and HNO_3. In another embodiment, the pharmaceutically acceptable salt is a sulfonic acid salt. Examples of sulfonic acids include, but are not limited to para-toluenesulfonic acid, benzenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, propane sulfonic acid and trifluoromethanesulfonic acid.

[0207] Pharmaceutical compositions containing the compounds of Formula I as described herein may be prepared using pharmaceutically acceptable additives. The term "pharmaceutically acceptable additive(s)" as used herein for the pharmaceutical compositions, refers to one or more carriers, diluents, and excipients that are compatible with the other additives of the composition or formulation and not deleterious to the patient. Examples of pharmaceutical compositions and processes for their preparation can be found in "Remington: The Science and Practice of Pharmacy", Loyd, V., *et al.* Eds., 22nd Ed., Mack Publishing Co., 2012. Non-limiting examples of pharmaceutically acceptable carriers, diluents, and excipients include the following: saline, water, starch, sugars, mannitol, and silica derivatives; binding agents such as carboxymethyl cellulose, alginates, gelatin, and polyvinyl-pyrrolidone; kaolin and bentonite; and polyethyl glycols.

[0208] As used herein, the term "effective amount" refers to an amount that is a dosage, which is effective in achieve a desired therapeutic result such as treating a disorder or disease, like a cancerous lesion or progression of abnormal cell growth and/or cell division. Factors considered in the

determination of an effective amount or dose of a compound include: whether the compound or its salt will be administered; the co-administration of other agents, if used; the species of patient to be treated; the patient's size, age, gender, and general health; the degree of involvement or stage and/or the severity of the disorder; the response of the individual patient; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of other concomitant medication.

[0209] A treating physician, veterinarian, or other medical person will be able to determine an effective amount of the compound for treatment of a patient in need. Pharmaceutical compositions can be formulated as a tablet or capsule for oral administration, a solution for oral administration, or an injectable solution. The tablet, capsule, or solution can include a compound of the present invention in an amount effective for treating a patient in need of treatment for cancer.

[0210] As used herein, the terms "treating", "to treat", or "treatment", includes slowing, controlling, delaying, reducing, stopping, reversing, preventing, or ameliorating the progression or severity of an existing symptom, disorder, condition, which can include specifically slowing the growth of a cancerous lesion or progression of abnormal cell growth and/or cell division. Treating does not necessarily indicate a total elimination of all disorder or disease symptoms.

[0211] As used herein, the term "patient" refers to a mammal in need of treatment. Specifically, the patient can be a human that is in need of treatment for cancer, for example, KRas G12C, G12D and/or G12V mutant bearing cancers.

[0212] Certain abbreviations are defined as follows: "ACN" refers to acetonitrile; "AcOH" or "HOAc" refer to acetic acid; AIBN" refers to azobisisobutyronitrile; "Alloc" refers to the allyloxycarbonyl group; "aq." refers to aqueous; "atm" refers to atmosphere or atmospheres; "Boc-Gly-OH" refers to *N*-(*tert*-butoxycarbonyl)glycine; "BrettPhos" refers to 2-dicyclohexylphosphino-3,6-dimethoxy- 2',4',6'-triisopropyl-1,1'-biphenyl; "BroP" refers to bromo tris(dimethylamino) phosphonium hexafluorophosphate; "Cbz" refers to the benzyloxycarbonyl group; "Cbz-Cl" refers to benzyl chloroformate; "conc." refers to concentrated; "CSI" refers to chlorosulfonyl isocyanate; "CV" refers to column volumes; "DCM" refers to dichloromethane; "DIAD" refers to diisopropyl azodicarboxylate; "DIBAL-H" refers to diisobutylaluminum hydride; "DIEA" and "DIPEA" refer to N,N-diisopropyl ethylamine; "(dippf)Rh(cod)BF_4" refers to [1,4-bis(diphenylphosphino)butane](1,5-cyclooctadiene)rhodium(I) tetrafluoroborate; "DMAP" refers to 4-dimethylaminopyridine; "DMEA"

refers to N,N-dimethylethylamine; "DMEM" refers to Dulbecco's modified Eagle's medium; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to dimethylsulfoxide; "DNA" refers to deoxyribonucleic acid; "DPEPhosPdCl$_2$" refers to dichlorobis(diphenylphosphinophenyl)ether palladium (II); "DTT" refers to dithiothreitol; "EDTA" refers to ethylenediaminetetraacetic acid; "EGTA" refers to ethylene glycol-bis(b-aminoethyl ether)-N,N,N',N'-tetraacetic acid; "ELISA" refers to enzyme-linked immunosorbent assay; "ERK" refers to extracellular signal-regulated kinases; "EtOAc" refers to ethyl acetate; "Et$_2$O" refers to diethyl ether; "EtOH" refers to ethanol; "FA" refers to formic acid; "FBS" refers to fetal bovine serum; "Fmoc" refers to the fluorenylmethyloxycarbonyl group; "GDP" refers to guanosine diphosphate; "GTP" refers to guanosine triphosphate; "h" refers to hour or hours; "HATU" refers to 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; "Hex" or "hex" refers to hexane or hexanes; "HPLC" refers to high-performance liquid chromatography; "HRP" refers to horseradish peroxidase; "IPA" refers to isopropyl alcohol; "IPAm" refers to isopropyl amine; "KOAc" refers to potassium acetate; "LC-ES/MS" refers to liquid chromatograph-electrospray mass spectrometry; "LC-MS" refers to liquid chromatography mass spectrometry; "LiHMDS" refers to lithium bis(trimethylsilyl)amide; "L-prolinol" refers to [(2S)-pyrrolidin-2yl]methanol; "MAPK" refers to mitogen-activated protein kinases; "*m*CPBA" refers to 3-chloro-peroxybenzoic acid; "Me" refers to a methyl group; "MeOH" refers to methanol; "min" refers to minute or minutes; "MTBE" refers to methyl *tert*-butyl ether; "NaBH(OAc)$_3$ refers to sodium triacetoxyborohydride; "NaOMe" refers to sodium methoxide; "NBS" refers to N-bromosuccinimide; "NCS" refers to N-chlorosuccinimide; "N-methyl-L-prolinol" refers to [(2S)-1-methylpyrrolidin-2-yl]methanol; "NMM" refers to N-methylmorpholine; "NMP" refers to 1-methylpyrrolidin-2-one; "NIS" refers to N-iodosuccinimide; "PCR" refers to polymerase chain reaction; "Pd-117" refers to dichloro[bis(2-(diphenylphosphino)phenyl)ether]palladium(II), CAS 205319-06-8; "Pd-118" refers to 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride, CAS 95408-45-0; "Pd$_2$(dba)$_3$" refers to tris(dibenzylideneacetone)dipalladium(0); "Pd(dppf)Cl$_2$" refers to [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II); "Pd(OAc)$_2$ refers to palladium (II) acetate; Pd(PPh$_3$)$_4$ refers to tetrakis(triphenylphosphine)palladium(0); "PE" refers to petroleum ether or diethyl ether; "Ph" refers to phenyl; "RBF" refers to round bottom flask; "RPMI" refers to Roswell Park Memorial Institute; "RT" refers to room temperature; "RuPhos" refers to 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl, CAS 787618-22-8; "sat." refers to saturated;

"SCX" refers to strong cation exchange; "Selectfluor™" refers to 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), "SPE" refers to solid phase extraction; "SPhos" refers to 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl; "TBAF" refers to tetrabutylammonium fluoride; "TBDMSCl" refers to *tert*-butyldimethylsilyl chloride; "TBDMS" refers to the *tert*-butyldimethylsilyl group; "*t*Bu" refers to the *tert*-butyl group; "*t*-BuOH" refers to *tert*-butanol or *tert*-butyl alcohol; A" refers to triethylamine; "TES" refers to triethylsilane; "Tf_2O" refers to trifluoromethanesulfonic anhydride; "TFA" refers to trifluoracetic acid; "THF" refers to tetrahydrofuran; "TMEDA" refers to tetramethylethylenediamine; "t_R" refers to retention time; "XantPhos" refers to 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; "XPhos" refers to 2-(dicyclohexylphosphino)-2',4',6'-tri-isopropyl-1,1'-biphenyl; "XPhos Palladacycle G2" refers to chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II), CAS 1310584-14-5; "XPhos Palladacycle Gen.4" or "XPhos Pd G4" refer to methanesulfonato(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II), CAS 1599466-81-5.

[0213] Individual isomers, enantiomers, diastereomers, and atropisomers may be separated or resolved at any convenient point in the synthesis of compounds listed below, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," *Stereochemistry of Organic Compounds*", Wiley-Interscience, 1994). The molecules described herein include compounds that are atropisomers and which can exist in different conformations or as different rotomers. Atropisomers are compounds that exist in different conformations arising from restricted rotation about a single bond. Atropisomers can be isolated as separate chemical species if the energy barrier to rotation about the single bond is sufficiently high that the rate of interconversion is slow enough to allow the individual rotomers to be separated from each other. This description is intended to include all of the isomers, enantiomers, diastereomers, and atropisomers possible for the compounds disclosed herein or that could be made using the compounds disclosed herein. In the molecules described herein, only molecules in which the absolute conformation of a chiral center (or atropisomer conformation) is known have used naming conventions or chemical formula that are drawn to indicate the chirality or atropisomerism. Those of skill in the art

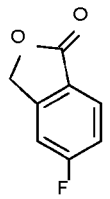
will readily understand when other chiral centers are present in the molecules described herein and be able to identify the same.

[0214] Compounds of any one of Formula I that are chemically capable of forming salts are readily converted to and may be isolated as a pharmaceutically acceptable salt. Salt formation can occur upon the addition of a pharmaceutically acceptable acid to form the acid addition salt. Salts can also form simultaneously upon deprotection of a nitrogen or oxygen, *i.e.*, removing the protecting group. Examples, reactions and conditions for salt formation can be found in Gould, P.L., "Salt selection for basic drugs," *International Journal of Pharmaceutics*, 33: 201-217 (1986); Bastin, R.J., *et al.* "Salt Selection and Optimization Procedures for Pharmaceutical New Chemical Entities," *Organic Process Research and Development*, 4: 427-435 (2000); and Berge, S.M., *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, 66: 1-19, (1977).

[0215] The compounds of the present invention, or salts thereof, may be prepared by a variety of procedures, some of which are illustrated in the Schemes, Preparations, and Examples below. The specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different routes, to prepare compounds or salts of the present invention. The products of each step in the Preparations below can be recovered by conventional methods, including extraction, evaporation, precipitation, chromatography, filtration, trituration, and crystallization.

Preparation 1

5-Fluoroisobenzofuran-1(3H)-one

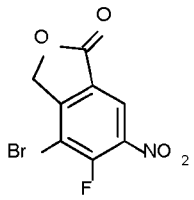


[0216] To a stirred mixture of (2-bromo-5-fluorophenyl)methanol 500 g, 2.44 mol) and TEA (474.6 mL, 3.41 mol, 1.4 eq.) in ACN (2500 mL) was added $Pd(OAc)_2$ (10.95 g, 48.77 mmol, 0.02 eq.) and XantPhos (42.33 g, 73.16 mmol, 0.03 equiv.) at RT, then stirred for 3 days at 120 °C under 10 atm of carbon monoxide. The reaction was cooled to RT and concentrated. The residue was diluted with H_2O

(1,000 mL), then extracted with EtOAc (2 x 2000 mL). The combined organic layers were washed with brine (2 x 1,000 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was triturated with 10:1 hexanes/EtOAc (1,100 mL) and then filtered. The filter cake was dried at 50 °C for ~18 h to obtain the title compound as a yellow solid (300 g, 81%). MS (ES) *m/z*=153 (M+1).

Preparation 2

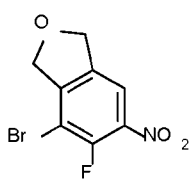
4-Bromo-5-fluoro-6-nitroisobenzofuran-1(3H)-one



[0217] To a stirred mixture of 5-fluoroisobenzofuran-1(3H)-one (300 g, 1.97 mol) in H_2SO_4 (1,500 mL) was added HNO_3 (273.38 g, 4.348 mol, 2.2 eq.) dropwise at 65 °C. The reaction was stirred for 1 h then cooled to RT. 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (2,255.43 g, 7.88 mol, 4 eq.) was added in portions over 20 min and was stirred at RT for ~18 h. The mixture was poured onto ice/water (pre-treated with 3 kg Na_2SO_3) and filtered. The filter cake was dissolved in EtOAc (3,000 mL), washed with sat. aq. Na_2CO_3 (2 x 1,000 mL), brine (2 x 1,000 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was triturated with 10:1 hexanes/EtOAc (660 mL) and was filtered and dried at 50 °C for ~18 h to obtain the title compound as a yellow solid (270 g, 49%) which was used in a subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.58 (s, 1H), 5.51 (s, 2H).

Preparation 3

4-Bromo-5-fluoro-6-nitro-1,3-dihydroisobenzofuran

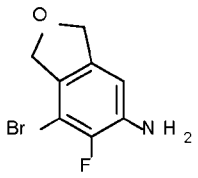


[0218] To a stirred mixture of 4-bromo-5-fluoro-6-nitroisobenzofuran-1(3H)-one (270 g, 978 mmol) in DCM (2,500 mL) was added DIBAL-H (1M in THF, 1,467 mL, 1.467 mol, 1.5 eq.) dropwise at -

78 °C under N_2. The reaction was stirred for 5 h at -78 °C, then was quenched with 5N NaOH (300 mL) at -78 °C. The resulting mixture was allowed to warm to RT, then was concentrated. The residue was diluted with EtOAc (2,500 mL), washed with brine (2 x 1,000 mL) and dried over anhydrous Na_2SO_4 and concentrated. The residue was triturated with 10:1 hexanes/EtOAc (550 mL) and filtered. The solids were dried (190 g, 683.4 mmol) then dissolved in DCM (1,500 mL) and treated dropwise with Et_3SiH (662 mL, 4.10 mol, 6 eq.) at 0 °C. The reaction was stirred for 20 min at 0 °C. TFA (152 mL, 2.05 mol, 3 eq.) was added dropwise at 0 °C. The ice bath was removed, and the reaction was stirred at RT for ~18 h. The reaction was concentrated to an oil, which was diluted with EtOAc (2,000 mL), washed with sat. aq. Na_2CO_3 (2 x 500 mL) and brine (2 x 500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the title compound (110 g, 42%) which was used in a subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J= 6.2 Hz, 1H), 5.18 – 5.15 (m, 2H), 5.11 – 5.06 (m, 2H).

Preparation 4

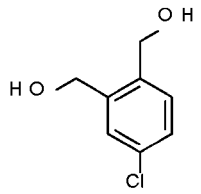
7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-amine



[0219] To a stirred mixture of 4-bromo-5-fluoro-6-nitro-1,3-dihydroisobenzofuran (110 g, 420 mmol) and NH_4Cl (112.3 g, 2.10 mol, 5 eq.) in EtOH (1,000 mL) and H_2O (200 mL) was added Fe (117.22 g, 2.09 mol, 5 eq.) in portions at RT, then stirred for ~ 18 h at 80 °C. The mixture was filtered and concentrated. The mixture was diluted with H_2O (500 mL) and extracted with EtOAc (2 x 1,000 mL). The combined organic layers were washed with brine (2 x 500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica (25% to 50% EtOAc/Hex) to afford the title compound (70 g, 72%) as a yellow solid. MS (ES) m/z=231 (M+1).

Preparation 5

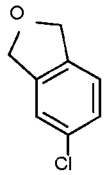
(4-Chloro-1,2-phenylene)dimethanol



[0220] To a stirred mixture of $LiAlH_4$ (1.9 L, 2.74 mol, 2 eq., 2.5 M in THF) in THF (1 L) was added 4-chlorophthalic anhydride (250 g, 1.34 mol, 1.00 eq.) in THF (500 mL) dropwise at -20 °C under N_2. The resulting mixture was stirred for 30 min at 45 °C under N_2. The reaction was quenched by the addition of H_2O (1.5 L) and 15% NaOH (500 mL) at RT. The mixture was filtered, and the filter cake was washed with MTBE (3 x 250 mL). The filtrate was extracted with MTBE (3 x 1.5 L). The combined organic layers were washed with brine (2 x 2 L) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to obtain the title compound (219.5 g, 93%) as an off-white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.45 – 7.36 (m, 2H), 7.28 (dd, J=8.2 Hz, 1H), 5.40 – 5.13 (m, 2H), 4.54 (s, 2H), 4.49 (s, 2H).

Preparation 6

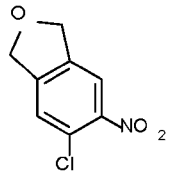
5-Chloro-1,3-dihydroisobenzofuran



[0221] To a stirred mixture of (4-chloro-1,2-phenylene)dimethanol (219.5 g, 1.271 mol) and dimethyl carbonate (458.2 g, 5.082 mol, 4 eq.) in ACN (3 L) was added NaOMe (137.4 g, 2.544 mol, 2 eq.) in portions at RT. The resulting mixture was stirred for ~18 h at 80 °C under N_2. The mixture was concentrated under reduced pressure, diluted with H_2O (2 L) and extracted with EtOAc (3 x 2 L). The combined organic layers were washed with brine (2 x 2 L) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified on silica (10:1 to 8:1 hex/EtOAc) to obtain the title compound (165 g, 82%) as a light-brown solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.42 – 7.37 (m, 1H), 7.33 (d, J=1.4 Hz,2H), 4.99 (s, 4H).

Preparation 7

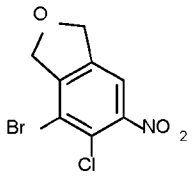
5-Chloro-6-nitro-1,3-dihydroisobenzofuran



[0222] A solution of 5-chloro-1,3-dihydroisobenzofuran (110 g, 712 mmol) in H_2SO_4 (700 mL) at -10 °C was charged with a solution of KNO_3 (64.74 g, 640 mmol, 0.9 eq.) in H_2SO_4 (200 mL) dropwise at -5 °C – 0 °C. The resulting mixture was stirred for additional 30 min at 0 °C and then was slowly added to stirred ice-cooled H_2O. The precipitated solids were collected by filtration and washed with H_2O (3 x 1 L). The filter cake was dried *in vacuo* to afford the title compound (110 g, 77 %) as a light-brown solid which was used in a subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.05 (s, 1H), 7.75 (s, 1H), 5.07 – 5.02 (m, 4H).

Preparation 8

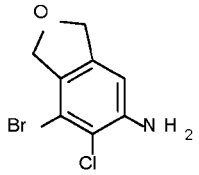
4-Bromo-5-chloro-6-nitro-1,3-dihydroisobenzofuran



[0223] To a stirred solution of 5-chloro-6-nitro-1,3-dihydroisobenzofuran (125 g, 626 mmol) in H_2SO_4 (700 mL) was added 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (179.1 g, 626.3 mmol, 1 eq.) in portions at -10 °C. The mixture was stirred for 1 h at -10 °C then slowly was added to stirred ice-cooled H_2O. The precipitated solids were collected by filtration and washed with H_2O (3 x 0.5 L). The filter cake was dried *in vacuo* and purified on silica (10:1 to 5:1 Hex/EtOAc) to obtain the title compound (83.5 g, 47.9%) as a white solid. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.07 (d, *J*=1.1 Hz,1H), 5.19 (dt, *J*=2.3, 1.1 Hz, 2H), 5.08 (t, 2H).

Preparation 9

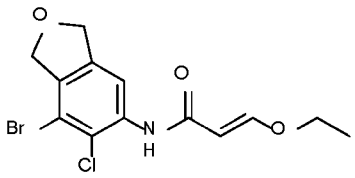
7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-amine



[0224] To a stirred mixture of 4-bromo-5-chloro-6-nitro-1,3-dihydroisobenzofuran (37.0 g, 133 mmol) and NH_4Cl (42.64 g, 797.2 mmol, 6 eq.) in EtOH (200 mL) and H_2O (40 mL) was added Fe (44.52 g, 797.2 mmol, 6 equiv.) in portions at RT. The resulting mixture was stirred for ~18 h at 80 °C. The resulting mixture was filtered hot and the filter cake was washed with EtOAc (3 x 500 mL). The filtrate was concentrated under reduced pressure and was purified on silica (15:1 to 10:1 Hex/EtOAc) to obtain the title compound (25 g, 76%) as a light-yellow solid. MS (ES) *m/z*=248 (M+1).

Preparation 10

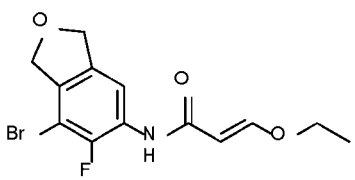
N-(7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxyacrylamide



[0225] To a stirred solution of 7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-amine (6.00 g, 24.1 mmol) and 3-ethoxyprop-2-enoyl chloride (4.06 g, 30.2 mmol) in THF (50 mL) was added pyridine (3.82 g, 48.3 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at RT. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (5:1) to afford the product (6.00 g, 66.0%) as a yellow solid. MS (ES) *m/z*=346 (M+1).

Preparation 11

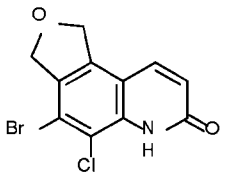
N-(7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxyacrylamide



[0226] 7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-amine was used in a manner analogous to the method of Preparation 10 to afford the title compound (1.4 g, 89%) as a pale-yellow solid. MS (ES) *m/z*=332 (M+1).

Preparation 12

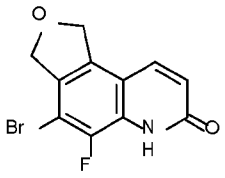
4-Bromo-5-chloro-3,6-dihydrofuro[3,4-f]quinolin-7(1H)-one



[0227] To a stirred solution of H_2SO_4 (20 mL) was added N-(7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxyacrylamide (6.10 g, 17.6 mmol) in portions at 0 °C. The resulting mixture was stirred for ~ 18 h at RT. The mixture was slowly added to stirred ice-cooled water (200 mL). The precipitated solids were collected by filtration and washed with H_2O (3 x 100 mL). The filter cake was dried under vacuum to afford the product (5.00 g, 87.0%) as a yellow solid. MS (ES) *m/z*=300 (M+1).

Preparation 13

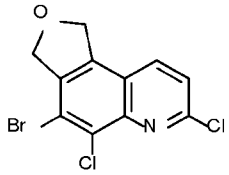
4-Bromo-5-fluoro-3,6-dihydrofuro[3,4-f]quinolin-7(1H)-one



[0228] N-(7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxyacrylamide was used in a manner analogous to that described for Preparation 12 to obtain the title compound (1.2 g, quantitative) as a tan solid. MS (ES) *m/z*=284 (M+1).

Preparation 14

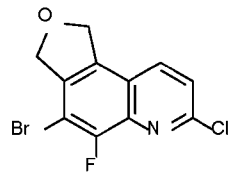
4-Bromo-5,7-dichloro-1,3-dihydrofuro[3,4-f]quinoline



[0229] To a stirred solution of 4-bromo-5-chloro-3,6-dihydrofuro[3,4-f]quinolin-7(1H)-one (5.00 g, 16.6 mmol) in DMF (20 mL) was added $POCl_3$ (9.30 mL, 99.8 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 90 °C. The mixture was slowly added to stirred ice-cooled water (200 mL). The precipitated solids were collected by filtration and washed with H_2O (3 x 100 mL). The filter cake was dried under vacuum to afford the product (3.50 g, 62.7%) as a yellow solid. MS (ES) *m/z*=318 (M+1).

Preparation 15

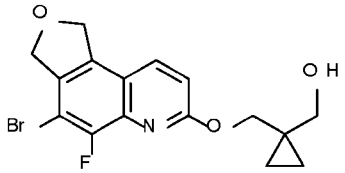
4-Bromo-7-chloro-5-fluoro-1,3-dihydrofuro[3,4-f]quinoline



[0230] A suspension of 4-bromo-5-fluoro-3,6-dihydrofuro[3,4-f]quinolin-7(1H)-one (1.2 g, 4.2 mmol) stirred in DCM (40 mL) was charged with (chloromethylene)dimethyliminium chloride (2.2 g, 17 mmol, 4 eq.) and stirred at RT for ~18 h. The reaction was diluted with DCM and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to a solid which was triturated with a small amount of DCM. The solids were filtered and washed with a small amount of DCM and air-dried to give Batch 1. The filtrate was concentrated and purified on silica gel, eluting with EtOAc/hexanes (0% to 80%) to give Batch 2. Both batches were combined to afford the title compound (1.0 g, 78%) as a tan solid. MS (ES) *m/z*=304 (M+1).

Preparation 16

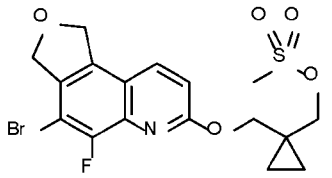
(1-(((4-Bromo-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxy)methyl)cyclopropyl)methanol



[0231] To a solution of (1-(hydroxymethyl)cyclopropyl)methanol (1.52 g, 14.9 mmol) in DMF (30 mL) was added lithium bis(trimethylsilyl)amide (1 M in THF, 15 mL, 15.0 mmol) at 0 °C under nitrogen. After 15 min, a solution of 4-bromo-7-chloro-5-fluoro-1,3-dihydrofuro[3,4-f]quinoline (1.50 g, 4.96 mmol) in DMF (8 mL) was added dropwise. The reaction mixture was heated to 50 °C. After 2 h, the reaction mixture was diluted with water (100 mL) and extracted with DCM (3 x 200 mL). The combined organics were washed with water (3 x 100 mL) and brine (3 x 100 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (1.35 g, crude). MS (ES) *m/z*=368 (M+1).

Preparation 17

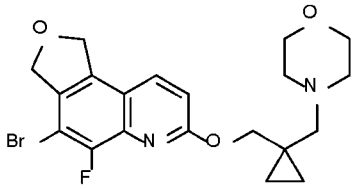
(1-(((4-Bromo-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxy)methyl)cyclopropyl)methyl methanesulfonate



[0232] A mixture of (1-(((4-bromo-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxy)methyl)cyclopropyl)methanol (1.35 g, 3.66 mmol) and THF (10 mL) was cooled to 0 °C under nitrogen. Diisopropylethylamine (4.74 g, 36.7 mmol) was added. The mixture was stirred for 20 min, then warmed to RT. Methanesulfonic anhydride (3.19 g, 18.4 mmol) was added dropwise. After 2 h, the reaction mixture was concentrated under reduced pressure to give crude title compound. MS (ES) *m/z*=446 (M+1).

Preparation 18

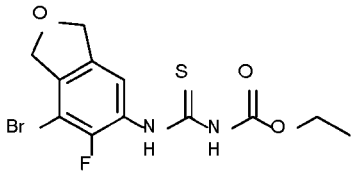
4-Bromo-5-fluoro-7-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,3-dihydrofuro[3,4-f]quinoline



[0233] To a mixture of (1-(((4-bromo-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxy)methyl)cyclopropyl)methyl methanesulfonate (2.22 g, crude, 4.93 mmol) and DMF (50 mL) was added diisopropylethylamine (4.76 g, 24.6 mmol) at RT under nitrogen. The mixture was stirred for 10 min, morpholine (1.29 g, 10.1 mmol) was added dropwise, then heated at 90 °C. After 3 h, the reaction mixture was diluted with EtOAc (200 mL) and washed with brine (3 x 50 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica eluting with 25-50% EtOAc in PE to obtain the title compound (0.40 g, 18%) as a yellow solid. MS (ES) *m/z*=437 (M+1).

Preparation 19

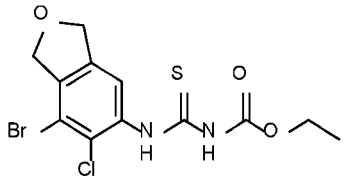
Ethyl N-[(7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)carbamothioyl]carbamate



[0234] A solution of 7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-amine (20.4 g, 87.9 mmol) in DCM (550 mL) was charged with ethoxycarbonyl isothiocyanate (9.7 mL, 82 mmol, 0.93 eq.) slowly via addition funnel and subsequently stirred at RT for ~ 4 h. The solids were filtered. The filtrate was concentrated, suspended in DCM (100 mL) and hexanes (350 mL) and stirred at RT. The resultant filtered solids and previous filtered solids were dried under vacuum at 50 °C for 2 h. The batches were combined to obtain the title compound (32.6 g, quantitative) as a white solid. MS (ES) *m/z*=363 (M+1).

Preparation 1A

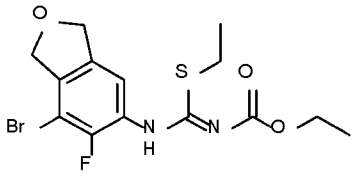
Ethyl N-[(7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)carbamothioyl]carbamate



7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-amine was used in a manner analogous to the method of Preparation 19 to afford the title compound (14 g, 92%) as a white solid. MS (ES) *m/z*=379 (M+1).

Preparation 20

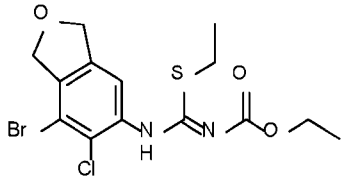
Ethyl (((7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)amino)(ethylthio)methylene)carbamate



[0235] A 2L 3-necked RBF, equipped with an overhead stirrer, dropping funnel and thermocouple was charged with a suspension of ethyl N-[(7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)carbamothioyl]carbamate (32.6 g, 89.8 mmol) and acetone (450 mL). To this was added solid K_2CO_3 (37.2 g, 269 mmol, 3.00 eq.) in several portions, followed by the dropwise addition of EtI (7.2 mL, 90 mmol, 1.0 eq.) over 20 min. The mixture was stirred at RT for ~18 h. The solids were filtered and the filtrate was concentrated and partitioned between DCM (500 mL) and H_2O (500 mL). The organics were further washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica (0 to 30% EtOAc/Hex) to obtain the title compound (30.9 g, 85.6%) as a white solid. MS (ES) *m/z*=391 (M+1).

Preparation 2A

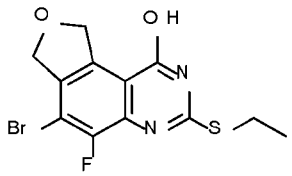
Ethyl (((7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)amino)(ethylthio)methylene)carbamate



[0236] Ethyl N-[(7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)carbamothioyl]carbamate was used in a manner analogous to the method of Preparation 20 to afford the title compound (15.4 g, crude) as a brown solid. MS (ES) *m/z*=407 (M+1).

Preparation 21

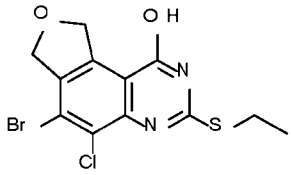
6-Bromo-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-ol



[0237] A 2L 4-necked RBF was equipped with an overhead stirrer, dropping funnel, N_2 inlet and thermocouple and was purged with N_2. NMP (anhydrous, 300 mL) was added. The mixture was heated to 175 °C. In a second flask, ethyl (((7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)amino)(ethylthio)methylene)carbamate (22.63 g, 57.83 mmol) and NMP (anhydrous, 100 mL) were combined and stirred under N_2 until a homogeneous solution was obtained. When the first flask had reached 175 °C, the contents of the second flask were poured into the dropping funnel and were added dropwise but rapidly to the hot NMP. After 30 min, the heat was turned off and the reaction cooled to 45 °C. H_2O (500 mL) was slowly added and the mixture was stirred at RT for 1 h. The solids were filtered, rinsed with H_2O (300 mL) and dried under vacuum at 50 °C for ~18 h to afford the title compound (15.2 g, 73%) as an off-white solid. MS (ES) *m/z*=363 (M+1).

Preparation 3A

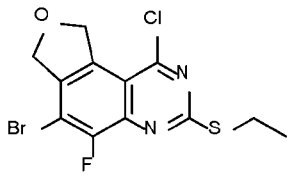
6-Bromo-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-1-ol



[0238] Ethyl (((7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)amino)(ethylthio)methylene)carbamate was used in a manner analogous to the method of Preparation 21 to afford the title compound (11.4 g, 86%) as a white solid. MS (ES) *m/z*=361 (M+1).

Preparation 22

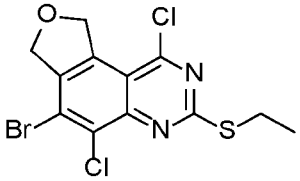
6-Bromo-1-chloro-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline



[0239] A 5L 3-necked RBF, equipped with a dropping funnel, thermocouple and an overhead stirrer was charged with a solution of DMF (50 mL, 646 mmol, 4 eq.) in DCM (1,000 mL) and was placed in an ice/water bath and cooled to ~4 °C. Oxalyl chloride (50.0 mL, 576 mmol, 4 eq.) was added dropwise via addition funnel over ~40 min. When the addition was complete, the reaction was stirred at ~4 °C for 15 min. Solid 6-bromo-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-ol (50.4 g, 140 mmol) was added in several portions to the reaction mixture and the resulting suspension was stirred at ~4 °C for 30 min. The ice bath was removed and the reaction was allowed to warm to RT and stir for 1 h. Then H_2O (1 L) was added and the mixture was stirred for 15 min. The mixture was partitioned and the organic layer was washed with brine (1 L) and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica, eluting with DCM/Hex (60% to 90%) to obtain the title compound (45.1g, 89%) as a white solid. MS (ES) *m/z*=363 (M+1).

Preparation 1B

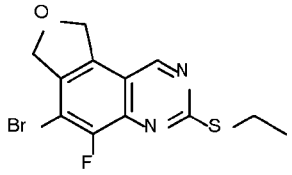
6-Bromo-1,5-dichloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazoline



[0240] 6-Bromo-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-1-ol was used in a manner analogous to the method of Preparation 22 to afford the title compound (7.5 g, 63%) as a yellow solid. MS (ES) *m/z*=379 (M+1).

Preparation 23

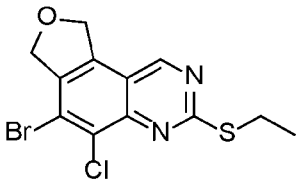
6-Bromo-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline



[0241] To a mixture of 6-bromo-1-chloro-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline (6.50 g, 17.9 mmol) and tetramethylethylenediamine (2.28 g, 19.7 mmol) in THF (100 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.73 g, 1.00 mmol) and sodium cyanoborohydride (in portions, 2.25 g, 35.8 mmol) at RT. The reaction mixture was stirred overnight under nitrogen, then diluted with water (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica, eluting with 16-20% EtOAc in PE to obtain the title compound (5.0 g, 75%) as a yellow solid. MS (ES) *m/z*=329 (M+1).

Preparation 2B

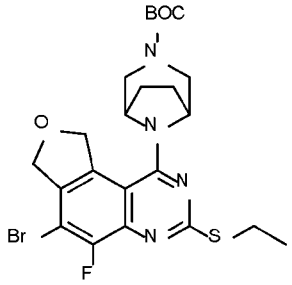
6-Bromo-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazoline



[0242] 6-Bromo-1,5-dichloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazoline was used in a manner analogous to the method of Preparation 23 to afford the title compound (1.2 g, 57%) as a yellow solid. MS (ES) *m/z*=345 (M+1).

Preparation 24

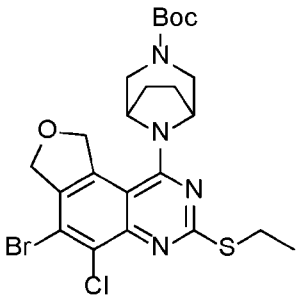
tert-Butyl 8-(6-bromo-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[0243] A suspension of 6-bromo-1-chloro-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline (21.0 g, 57.8 mmol) in ACN (580 mL) was charged with *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (15.2 g, 69.5 mmol, 1.20eq.) and DIPEA (40 mL, 229 mmol, 4 eq.) and was stirred at RT for 90 min. H_2O (1 L) was added slowly via addition funnel and the mixture was stirred at RT for 1 h. The solids were filtered, rinsed with H_2O (500 mL) and dried under vacuum at 50 °C to obtain the title compound (31 g, quantitative) as a white solid, MS (ES) *m/z*=539 (M+1).

Preparation 3B

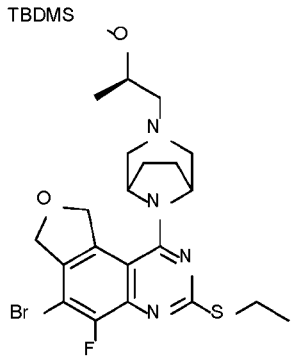
tert-Butyl 8-(6-bromo-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



6-Bromo-1,5-dichloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazoline was used in a manner analogous to the method of Preparation 24 to afford the title compound (6 g, 75%) as a yellow solid. MS (ES) *m/z*=555 (M+1).

Preparation 25

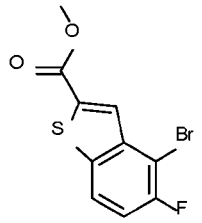
6-Bromo-1-(3-((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline



3-((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octane was used in a manner analogous to that described for Preparation 24 to obtain the title compound (4.7 g, 95%) as a tan solid.

Preparation 26

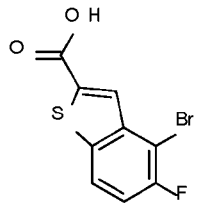
Methyl 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylate



[0244] A solution of methyl thioglycolate (0.18 mL, 2.0 mmol, 1 eq.) in THF (5 mL) was flushed with N_2 and charged with NaH (60 mass%) in mineral oil (0.101 g, 2.53 mmol, 1.24 eq.) at RT. Gas evolution was observed, and a precipitate formed in the flask. The reaction was stirred at RT for 20 min. A solution of 2-bromo-3,6-difluorobenzaldehyde (0.475 g, 2.04 mmol) in THF (5 mL) was added slowly via syringe over ~2 min. The reaction was stirred at RT for 9 h. Additional methyl thioglycolate (0.1 mL, 1 mmol, 0.5 eq.) and sodium hydride (60 mass%) in mineral oil (0.050 g, 1.3 mmol, 0.6 eq.) were added and stirring was continued at RT for ~18 h. The mixture was diluted with EtOAc and washed with sat. aq. NH_4Cl and brine. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica, eluting with 2% MTBE/Hex to obtain the title compound (0.346 g, 59%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 – 8.19 (dd, J= 4.49, 8.9 Hz, 1H), 8.05 (s, 1H), 7.62 (t, J= 9.0 Hz, 1H), 3.93 (s, 3H).

Preparation 27

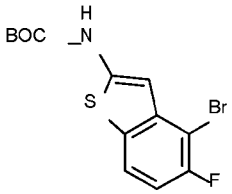
4-Bromo-5-fluorobenzo[b]thiophene-2-carboxylic acid



[0245] A solution of methyl 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylate (19.2 g, 66.4 mmol, 1 eq.) in MeOH (130 mL) and THF (130 mL) was charged with 5N NaOH (66 mL, 330 mmol, 5 eq.) and stirred at RT for 40 min. The mixture was concentrated and H_2O (500 mL) was added. The pH was adjusted to ~2 with 5N HCl. The mixture was extracted with EtOAc (2 x 500mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The solids were dried under vacuum at 50 °C to afford the title compound (17.6 g, 96%) as a white solid. MS (ES) *m/z*=229 (M-1-CO_2).

Preparation 28

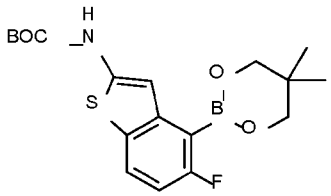
tert-Butyl (4-bromo-5-fluorobenzo[b]thiophen-2-yl)carbamate



[0246] A solution of 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylic acid (1.5 g, 5.5 mmol) in *t*-butanol (30 mL) was charged with TEA (1.5 mL, 11 mmol, 2.0 eq.) and diphenylphosphoryl azide (1.5 mL, 6.9 mmol, 1.3 eq.) and heated at 95 °C for 1 h. The mixture was cooled and concentrated. The residue was purified on silica, eluting with MTBE/Hex (4% to 20%) to obtain the title compound (0.987 g, 52%) as a white solid. MS (ES) *m/z*=290 (M+1).

Preparation 29

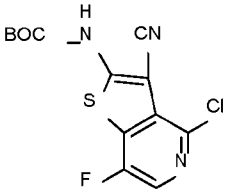
tert-Butyl (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate



[0247] A mixture of *tert*-butyl (4-bromo-5-fluorobenzo[b]thiophen-2-yl)carbamate (3.08 g, 8.90 mmol) and bis(neopentyl glycolato)diboron (4.02 g, 17.8 mmol, 2 eq.) and KOAc (2.62 g, 26.7 mmol, 3 eq.) in 1,4-dioxane (70 mL, 819.9 mmol) was sparged with N_2 for 20 min. To the mixture was added $Pd(ddpf)Cl_2$ (0.69 g, 0.90 mmol, 0.1eq.). The reaction was sonicated for 3 min, then put through a vacuum/N_2 refill cycle (3x) and was heated at 100 °C for 3 h. The mixture was cooled to RT, filtered through diatomaceous earth and was rinsed with 1:4 EtOAc/Hex. The filtrate was concentrated and the residue was purified on silica (0-40% MTBE/Hex) to obtain the title compound (2.95 g, 87%) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.81 – 10.79 (bs, 1H), 7.84 – 7.74 (dd, *J*=5.07, 8.59, 1H), 7.14 (s, 1H), 6.94 – 6.88 (m, 1H), 3.89 (bs, 4H), 1.49 (s, 10H), 1.03 (s, 6H).

Preparation 30

tert-Butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate



[0248] Ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate. A solution of 2-(4-chloro-5-fluoropyridin-3-yl)acetonitrile (11.8 g, 56.1 mmol) in DMF (112 mL) was cooled to 0 °C. Potassium *tert*-butoxide (7.00 g, 61.1 mmol) was added. After 15 min, ethoxycarbonyl isothiocyanate (7.45 mL, 61.8 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to RT overnight. The reaction mixture was poured into a mixture of ice/water (1.5 L), stirred until all ice had melted, and filtered through diatomaceous earth. The solids were dried in a vacuum oven (60 °C) overnight

and separated from the diatomaceous earth to give ethyl N-(3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate (11.9 g, 79%) as a solid. MS (ES) *m/z*=266 (M+1).

[0249] 2-Amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile. A suspension of ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (11.9 g, 44.4 mmol) in DMSO (90 mL) was cooled to 0 °C. NaOH (5 M in water, 90 mL) was added dropwise over 15 min. The reaction mixture was heated to 105 °C for 1 h, then cooled to RT. The reaction mixture was poured into a mixture of ice/water (1.8 L), stirred until all ice had melted, and filtered through diatomaceous earth. The solids were dried in a vacuum oven (50 °C) overnight and separated from the diatomaceous earth to give crude 2-amino-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile.

[0250] *tert*-Butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate. A mixture of crude 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (8.6 g, 44.4 mmol), DCM (90 mL), DMF (90 mL) and N,N-diisopropylethylamine (15.5 mL, 88.9 mmol) was cooled to 0 °C. 4-dimethylaminopyridine (0.54 g, 4.42 mmol) and di-*tert*-butyl dicarbonate (14.6 g, 66.7 mmol) were added. The reaction mixture was stirred at RT for 2 h. The solvents were removed under reduced pressure and the remaining material was diluted with DCM (400 mL) and 5% aq. citric acid (250 mL). The aqueous phase was washed twice with DCM. The combined organic phases were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give *tert*-butyl N-(3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate (7.5 g, 58%) as a brown solid. MS (ES) *m/z*=294 (M+1).

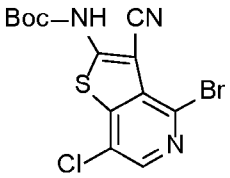
[0251] 2-((*tert*-Butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide. 3-Chloroperoxybenzoic acid (9.00 g, 40.2 mmol) was added to a solution of *tert*-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (7.85 g, 26.8 mmol) in DCM (180 mL). The reaction mixture was stirred at RT overnight, then cooled to 0 °C for ~15 min. Solids were collected by filtration and dried in a vacuum oven (60 °C). The filtrate was diluted with MeOH and silica gel, concentrated, and the residue was purified on silica, eluting with 0-6% MeOH in DCM. Fractions containing desired material were combined with the solids from the filtration and concentrated to give *tert*-butyl N-(3-cyano-7-fluoro-5-oxido-thieno[3,2-c]pyridin-5-ium-2-yl)carbamate (7.26 g, 88%) as an off-white solid. MS (ES) *m/z*=310 (M+1).

[0252] *tert*-Butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate. A suspension of 2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide (5.27 g, 17.0 mmol) in 1,2-dichloroethane (34 mL) was cooled to 0 °C. A solution of phosphoryl chloride (32 mL, 344 mmol)

in 1,2-dichloroethane (34 mL) was added dropwise. The reaction mixture was stirred at RT for 30 min, at 45 °C for 90 min, and cooled to RT. The reaction mixture was diluted with 1,2-dichloroethane (100 mL) and added to a mixture of sat. aq. $NaHCO_3$ (500 mL), NaOH (5 M in water, 40 mL), and ice. Solid $NaHCO_3$ was added to the stirred mixture to maintain pH ~6-7. Once bubbling ceased, the phases were separated. The aqueous phase was extracted 3x with DCM. The combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was diluted with MeOH and silica gel, concentrated, and the residue was purified on silica, eluting with 50-100% DCM in hexanes. Fractions containing desired material were concentrated to give the title compound (3.87 g, 69%) as a white solid. MS (ES) *m/z*=328 (M+1).

Preparation 1C

tert-Butyl (4-bromo-7-chloro-3-cyanothieno[3,2-c]pyridin-2-yl)carbamate



[0253] 3-Bromo-5-chloro-4-((4-methoxybenzyl)thio)pyridine. To a solution of 3-bromo-4,5-dichloropyridine (10.0 g, 44.1 mmol) in acetonitrile (90 mL) was added potassium carbonate (6.70 g, 48.5 mmol). The mixture was cooled to 0 °C and (4-methoxyphenyl)methanethiol (6.6 mL, 46.3 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to RT and stirred overnight. The mixture was diluted with water (200 mL) and EtOAc (300 mL), then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on silica, eluting with 0-60% EtOAc in heptane. Fractions containing desired material were concentrated to give 3-bromo-5-chloro-4-((4-methoxybenzyl)thio)pyridine (8.6 g, 57%) as a white solid. MS (ES) *m/z*=344 (M+1).

[0254] 2-(5-Chloro-4-((4-methoxybenzyl)thio)pyridin-3-yl)malononitrile. To a pressure vessel containing a solution of malonitrile (2.44 g, 37.0 mmol) in 1,4-dioxane (160 mL) was added a mixture of sodium *tert*-butoxide (7.11 g, 74.0 mmol) in THF (36 mL). The mixture was stirred for 15 min, then 3-bromo-5-chloro-4-((4-methoxybenzyl)thio)pyridine (8.50 g, 24.7 mmol) and

tetrakis(triphenylphosphine)palladium(0) (2.85 g, 2.47 mmol) were added. The pressure vessel was sealed and the reaction mixture was heated at 85 °C overnight. The reaction mixture was filtered and the solids were washed with EtOAc. The combined filtrates were concentrated under reduced pressure, then diluted with DCM. The mixture was filtered, and the solids were washed with DCM to obtain 2-(5-chloro-4-((4-methoxybenzyl)thio)pyridin-3-yl)malononitrile (7.5 g, 92%) as a yellow solid. MS (ES) *m/z*=330 (M+1).

[0255] 2-Amino-7-chlorothieno[3,2-c]pyridine-3-carbonitrile. Trifluoroacetic acid (5 mL) was added to a mixture of 2-(5-chloro-4-((4-methoxybenzyl)thio)pyridin-3-yl)malononitrile (0.740 g, 2.24 mmol) in DCM (25 mL). The reaction mixture was stirred at RT for 5 h, then concentrated under reduced pressure. The residue was diluted with DCM (5 mL) and trifluoroacetic acid (5 mL) was added. The reaction mixture was stirred at RT overnight, then concentrated under reduced pressure. The residue was diluted with 4:1 hexanes:EtOAc (30 mL) and stirred for 30 min. The mixture was filtered, and the solids were washed with minimal 4:1 hexanes:EtOAc to obtain 2-amino-7-chlorothieno[3,2-c]pyridine-3-carbonitrile (0.28 g, 60%) as a brown solid. MS (ES) *m/z*=210 (M+1).

[0256] *tert*-Butyl (7-chloro-3-cyanothieno[3,2-c]pyridin-2-yl)carbamate. 2-Amino-7-chlorothieno[3,2-c]pyridine-3-carbonitrile was used in an analogous manner to the method of Preparation 30 (Intermediate step *tert*-Butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate) to obtain *tert*-butyl (7-chloro-3-cyanothieno[3,2-c]pyridin-2-yl)carbamate (0.85 g, 52%) as a white solid. MS (ES) *m/z*=310 (M+1).

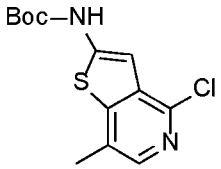
[0257] 2-((*tert*-Butoxycarbonyl)amino)-7-chloro-3-cyanothieno[3,2-c]pyridine 5-oxide. 3-Chloroperoxybenzoic acid (75 wt%; 4.0 g, 17 mmol) was added to a solution of *tert*-butyl (7-chloro-3-cyanothieno[3,2-c]pyridin-2-yl)carbamate (4.1 g, 13 mmol) in DCM (60 mL). The reaction mixture was stirred at RT overnight, then concentrated under reduced pressure. The material was purified on silica, eluting with 0-10% MeOH in DCM. Fractions containing desired material were concentrated to give 2-((*tert*-butoxycarbonyl)amino)-7-chloro-3-cyanothieno[3,2-c]pyridine 5-oxide (4.3 g, 90%) as a white solid. MS (ES) *m/z*=326 (M+1).

[0258] *tert*-Butyl (4-bromo-7-chloro-3-cyanothieno[3,2-c]pyridin-2-yl)carbamate. Molecular sieves (4A, 4 g) were added to a mixture of 2-((*tert*-butoxycarbonyl)amino)-7-chloro-3-cyanothieno[3,2-c]pyridine 5-oxide (4.4 g, 12 mmol), tetrabutylammonium bromide (5.9 g, 18 mmol), and p-toluenesulfonic anhydride (6.0 g, 18 mmol) in THF (300 mL). The reaction mixture was stirred at RT

overnight, then concentrated under reduced pressure. The material was purified on silica, eluting with 0-100% EtOAc in hexanes. Mixed fractions were purified on silica, eluting with MeOH in DCM. Fractions containing desired material from both silica purifications were combined and concentrated to give the title compound (3.0 g, 63%) as an off-white solid. MS (ES) *m/z*=388 (M+1).

Preparation 4B

tert-Butyl (4-chloro-7-methylthieno[3,2-c]pyridin-2-yl)carbamate



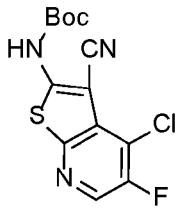
[0259] Methyl 4-chloro-7-methylthieno[3,2-c]pyridine-2-carboxylate. 2,4-Dichloro-5-methyl-pyridine-3-carbaldehyde (7.25 g, 38.2 mmol), potassium carbonate (10.5 g, 76.0 mmol), and DMF (127 mL) were combined, heated at 70 °C overnight, and cooled to RT. The reaction mixture was added to water (500 mL) and filtered. The solids were rinsed with water and dried to give methyl 4-chloro-7-methyl-thieno[3,2-c]pyridine-2-carboxylate (8.30 g, 90%) as a white solid. MS (ES) *m/z*=242 (M+1).

[0260] 4-Chloro-7-methylthieno[3,2-c]pyridine-2-carboxylic acid. Methyl 4-chloro-7-methylthieno[3,2-c]pyridine-2-carboxylate was used in an analogous manner to the method of Preparation 27 to obtain 4-chloro-7-methyl-thieno[3,2-c]pyridine-2-carboxylic acid (6.5 g, 84%) as a white solid. MS (ES) *m/z*=228 (M+1).

[0261] *tert*-Butyl (4-chloro-7-methylthieno[3,2-c]pyridin-2-yl)carbamate. 4-Chloro-7-methylthieno[3,2-c]pyridine-2-carboxylic acid was used in an analogous manner to the method of Preparation 28 to obtain the title compound (0.83 g, 63%). MS (ES) *m/z*=299 (M+1).

Preparation 1D

tert-Butyl (4-chloro-3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate



[0262] (2-Chloro-5-fluoropyridin-3-yl)methyl methanesulfonate. Methanesulfonicanhydride (11.0 g, 63.2 mmol) was added dropwise to a 0 °C solution of (2-chloro-5-fluoropyridin-3-yl)methanol (7.86 g, 48.7 mmol) and diisopropylethylamine (12.6 mL, 73.0 mmol) in THF (200 mL). The reaction mixture was allowed to warm to RT, then stirred overnight. The mixture was poured into water/ice and diluted with 1:1 MTBE:EtOAc. The layers were separated and the aqueous layer was extracted with 1:1 MTBE:EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give crude (2-chloro-5-fluoropyridin-3-yl)methyl methanesulfonate (11.9 g). MS (ES) *m/z*=240 (M+1).

[0263] 2-(2-Chloro-5-fluoropyridin-3-yl)acetonitrile. Trimethylsilylnitrile (7.80 mL, 59.6 mmol) was added dropwise to a 0 °C solution of (2-chloro-5-fluoropyridin-3-yl)methyl methanesulfonate (11.9 g, 49.7 mmol) in THF (125 mL) and acetonitrile (125 mL). Tetrabutylammonium fluoride (1M in THF; 59.6 mL, 59.6 mmol) was then added dropwise. The reaction mixture was allowed to warm to RT, stirred for 2 h, then concentrated under reduced pressure. The residue was dissolved in DCM (200 mL) and washed with a mixture of saturated aqueous sodium bicarbonate and brine. The aqueous layer was extracted with DCM (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on silica, eluting with 0-50% EtOAc in Hexanes. Mixed fractions were combined and purified on silica, eluting with 0-5% (10% MeOH in DCM) in DCM to give 2-(2-chloro-5-fluoropyridin-3-yl)acetonitrile (5.60 g, 66%) as a yellow oil that solidifies in the freezer.

[0264] Ethyl (3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate. 2-(2-Chloro-5-fluoropyridin-3-yl)acetonitrile was used in a manner analogous to the method of Preparation 30 (substep ethyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate) to afford ethyl (3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate (24.8 g, 80%) as a brown solid. MS (ES) *m/z*=266 (M+1).

[0265] 2-Amino-5-fluorothieno[2,3-b]pyridine-3-carbonitrile. Ethyl (3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate was used in a manner analogous to the method of Preparation 30 (substep 2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile) to afford 2-amino-5-fluorothieno[2,3-b]pyridine-3-carbonitrile (17.4 g, 100%) as a brown solid.

[0266] *tert*-Butyl (3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate. 2-amino-5-fluorothieno[2,3-b]pyridine-3-carbonitrile was used in a manner analogous to the method of Preparation 30 (substep *tert*-butyl (3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate) to afford

tert-butyl (3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate (19.6 g, 73%) as a brown solid. MS (ES) *m/z*=294 (M+1).

[0267] 2-((*tert*-Butoxycarbonyl)amino)-3-cyano-5-fluorothieno[2,3-b]pyridine 7-oxide. *tert*-Butyl (3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate was used in a manner analogous to the method of Preparation 30 (substep 2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridine 5-oxide) to afford 2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorothieno[2,3-b]pyridine 7-oxide (10.5 g, 94%) as a white solid. MS (ES) *m/z*=310 (M+1).

[0268] 6-Bromo-2-((tert-butoxycarbonyl)amino)-3-cyano-5-fluorothieno[2,3-b]pyridine 7-oxide. To a 0 °C suspension of 2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorothieno[2,3-b]pyridine 7-oxide (10.5 g, 31.4 mmol) in DCM (150 mL) and EtOAc (150 mL) was added N-bromosuccinimide (6.21 g, 31.4 mmol), then THF (30 mL). The reaction mixture was allowed to warm to RT, stirred for 72 h, then diluted with THF (10 mL). The mixture was treated with silica (10 g) and the solvent was removed under reduced pressure. The remaining solids were purified on silica, eluting with 0-50% (10% EtOAc in DCM) in DCM to give 6-bromo-2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorothieno[2,3-b]pyridine 7-oxide (8.50 g, 70%). MS (ES) *m/z*=388 (M+1).

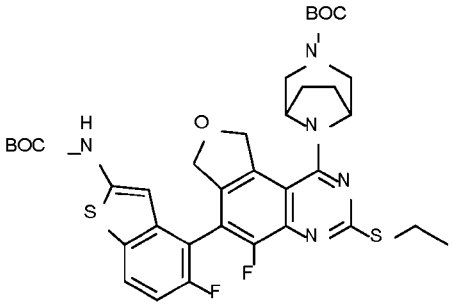
[0269] *tert*-Butyl (6-bromo-4-chloro-3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate. To a suspension of 6-bromo-2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorothieno[2,3-b]pyridine 7-oxide (8.35 g, 21.5 mmol) in THF (108 mL) was added bis(trimethylsilyl)amine (5.40 mL, 25.8 mmol) dropwise. The mixture was cooled to 0 °C and 2,2,2-trichloroacetyl chloride (24.0 mL, 215 mmol) was added dropwise. The reaction mixture was allowed to warm to RT, stirred for 30 min, then heated to 45 °C and stirred for 18 h. The mixture was diluted with aqueous NaOH (1N, 190 mL), DCM (500 mL), and saturated aqueous sodium bicarbonate. A precipitate formed that was removed by filtration. The solids were dissolved in THF/EtOAc. The solution was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give *tert*-butyl (6-bromo-4-chloro-3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate (5.60 g, 61%). MS (ES) *m/z*=406 (M+1).

[0270] *tert*-Butyl (4-chloro-3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate. A reaction vessel containing *tert*-butyl (6-bromo-4-chloro-3-cyano-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate (4.00 g, 9.74 mmol) and sodium formate (0.662 g, 9.74 mmol) in DMF (49 mL) was flushed with nitrogen for 30 min, then tetrakis(triphenylphosphine)palladium(0) (2.25 g, 1.95 mmol) was added. The reaction vessel was sealed and stirred at 80 °C for 18 h. Additional

tetrakis(triphenylphosphine)palladium(0) (1.1 g, 0.95 mmol) was added. The reaction vessel was sealed and stirred at 80 °C for 25 h, then poured into water/ice and diluted with 1:1 MTBE:EtOAc. The layers were separated and the aqueous layer was extracted with 1:1 MTBE:EtOAc twice more. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on silica, eluting with 0-30% EtOAc in Hexanes. Mixed fractions were combined and purified on silica, eluting with 0-10% (10% EtOAc in DCM) in DCM to give the title compound (0.80 g, 25%). MS (ES) *m/z*=328 (M+1).

Preparation 31

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-5-fluorobenzo[b]thiophen-4-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

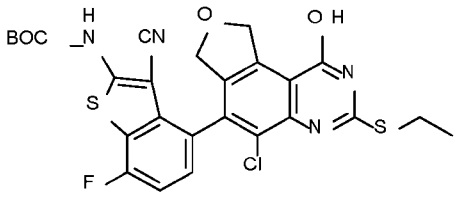
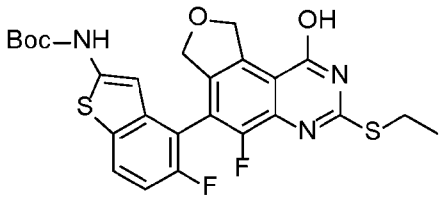
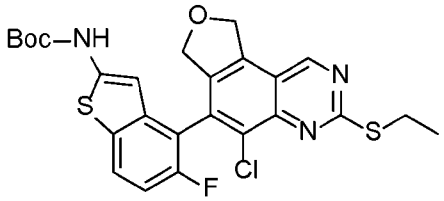


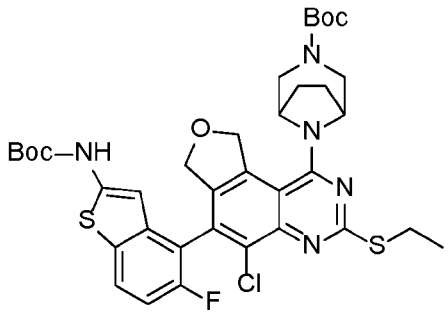
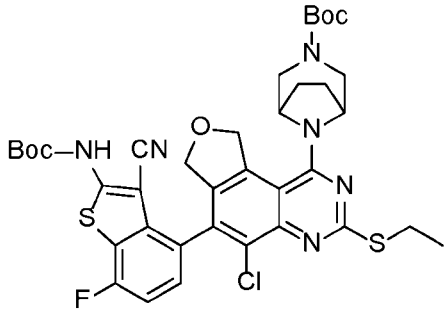
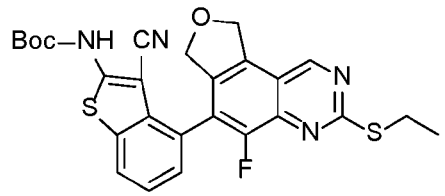
[0271] A 250 mL 3-necked RBF, equipped with a thermocouple, condenser and N_2 sparge line, was charged with a suspension of *tert*-butyl 8-(6-bromo-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (5.00 g, 9.27 mmol) and *tert*-butyl (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate (5.53 g, 13.9 mmol, 1.5 eq.) in 1,4-dioxane (100 mL) and H_2O (31 mL). The heat was set to 70 °C and started. At the same time, N_2 sparge was started. When the internal temperature had reached ~45 °C, the sparge line was removed and K_3PO_4 (2.95 g, 13.9 mmol, 1.5 eq.) and Pd-118 (0.620 g, 0.932 mmol, 0.10 eq.) were added. The reaction temperature was allowed to reach 70 °C and was stirred for 90 min. The reaction was cooled to RT, then the mixture was diluted with EtOAc, washed with H_2O and partitioned. The aqueous phase was extracted with EtOAc (100 mL), and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. MTBE (50 mL) was added and the mixture was sonicated for 20 min. Solids were filtered to obtain product as batch 1. The filtrate was concentrated and the residue was purified on silica, eluting with EtOAc/Hexanes (0-30%).

Product-containing fractions were concentrated to a tan foam which was dissolved in DCM (20 mL) and treated dropwise with hexanes (60 mL) while stirring rapidly for 1 h. The resulting solids were filtered and rinsed with hexanes (50 mL) to obtain product as batch 2. The two batches were combined to give the title compound (6.4 g, 88%) as a white solid. MS (ES) *m/z*=726 (M+1).

[0272] The following compounds in Table 1 were prepared in similar manner as described in Preparation 31. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 1:

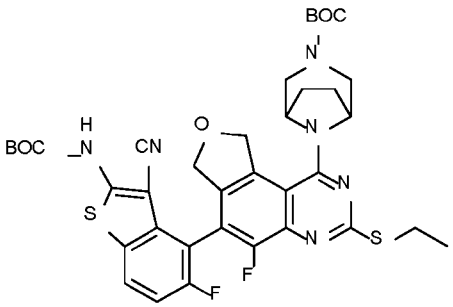
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
4A	*tert*-Butyl (4-(5-chloro-3-(ethylthio)-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		573
5A	*tert*-Butyl (4-(3-(ethylthio)-5-fluoro-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		532
5B	*tert*-Butyl (4-(5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		532

6B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-5-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		742
7B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		767
2C	*tert*-Butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		523

Preparation 32

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-

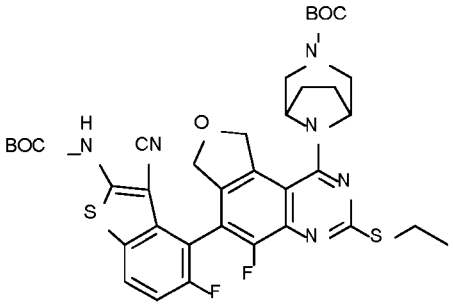
carboxylate



[0273] *tert*-Butyl 8-(6-(2-((tert-butoxycarbonyl)amino)-5-fluorobenzo[b]thiophen-4-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (9.00 g, 12.4 mmol) and THF (180 mL) were combined in a flask. The flask was placed in a -45 °C bath under nitrogen. ((Chlorosulfonyl)imino)methanone (7.90 g, 55.8 mmol) was added. After 4 h, the cold reaction mixture was poured into DMF (270 mL) and stirred at 0 °C for 1 h. The mixture was diluted with EtOAc (1 L), then washed with water (2 x 300 mL) and brine (2 x 200 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica, eluting with 20-30% EtOAc in PE to obtain the title compound (6.5 g, 70%) as a white solid. MS (ES) *m/z*=751 (M+1).

Preparations 8B and 9B

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, Atropisomer 1 and Atropisomer 2

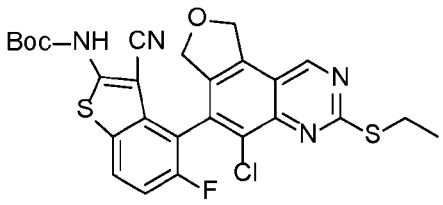


[0274] Chiral separation of *tert*-butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-

diazabicyclo[3.2.1]octane-3-carboxylate (supercritical fluid chromatography; CHIRALPAK AD-H, 50 x 250 mm, 30% EtOH : 70% CO_2, 180 mL/min) was performed, to afford the title compounds (Atropisomer 1 3.20 g; Atropisomer 2 3.25 g). MS (ES) *m/z*=751 (M+1), for both.

Preparation 10B

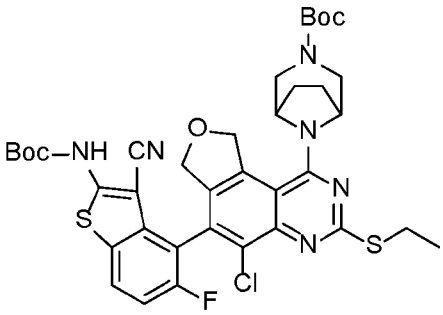
tert-Butyl (4-(5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate



tert-Butyl (4-(5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate was used in a manner analogous to the method of Preparation 32 to afford the title compound (0.69 g, 82%) as a yellow solid. MS (ES) *m/z*=557 (M+1).

Preparation 11B

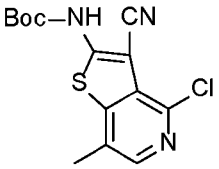
tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[0275] *tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-5-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate was used in a manner analogous to the method of Preparation 32 to afford the title compound (0.72 g, 50%) as a yellow solid. MS (ES) *m/z*=767 (M+1).

Preparation 12B

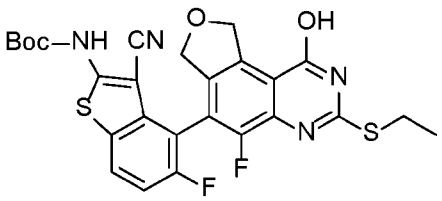
tert-Butyl (4-chloro-3-cyano-7-methylthieno[3,2-c]pyridin-2-yl)carbamate



[0276] *tert*-Butyl (4-chloro-7-methylthieno[3,2-c]pyridin-2-yl)carbamate was used in a manner analogous to the method of Preparation 32 to afford the title compound (0.54 g, 31%). MS (ES) *m/z*=324 (M+1).

Preparation 6A

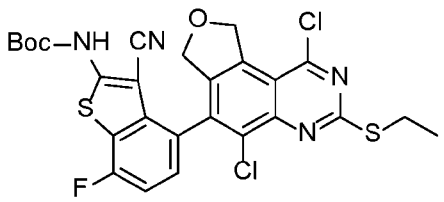
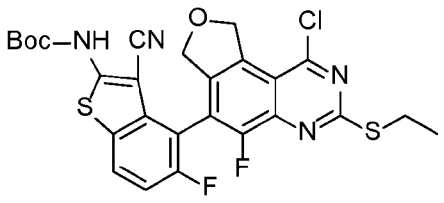
tert-Butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate



[0277] A mixture of *tert*-butyl (4-(3-(ethylthio)-5-fluoro-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate (0.750 g, 1.41 mmol) and acetonitrile (10 mL) was stirred at -40 °C. Sulfurisocyanatidic chloride (0.184 mL, 2.12 mmol) was slowly added and the mixture was allowed to warm to 0 °C. After consumption of the starting material (monitored by LCMS), the mixture was cooled to 0 °C. DMF (4 mL) was slowly added. Upon reaction completion (monitored by LCMS), the mixture was diluted with DCM (20 mL) and saturated aq. ammonium chloride (20 mL). The layers were separated and the aqueous layer was extracted with DCM (3x 30 mL). The combined organics were passed through a hydrophobic frit and concentrated under reduced pressure to obtain the crude title compound. MS (ES) m/z=557 (M+1).

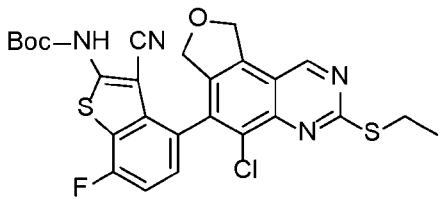
[0278] The following compounds in Table 2 were prepared in similar manner as described in Preparation 22. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

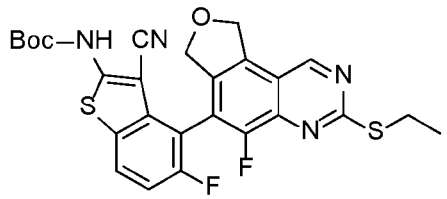
Table 2:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
7A	*tert*-Butyl (3-cyano-4-(1,5-dichloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate		591
8A	*tert*-Butyl (4-(1-chloro-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate		575

[0279] The following compounds in Table 3 were prepared in similar manner as described in Preparation 23. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

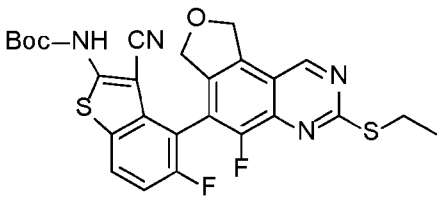
Table 3:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
9A	*tert*-Butyl (4-(5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		557

10A	*tert*-Butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		541

Preparations 13B and 14B

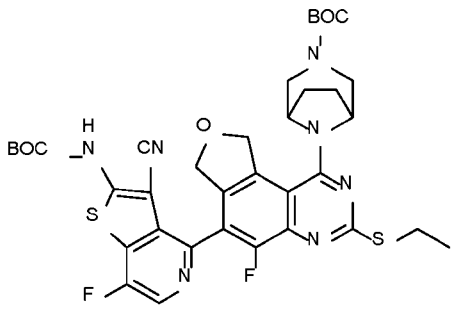
tert-Butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate, Atropisomer 1 and Atropisomer 2



[0280] Chiral separation of *tert*-butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate (supercritical fluid chromatography; CHIRALPAK IG, 20 x 250 mm, 35% Isopropanol (with 0.5% dimethylethylamine) : 65% CO_2, 80 mL/min) was performed, to afford the title compounds (Atropisomer 1 0.995 g; Atropisomer 2 0.990 g). MS (ES) *m/z*=541 (M+1), for both.

Preparation 33

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



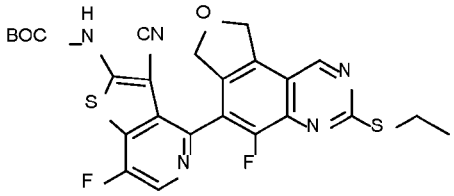
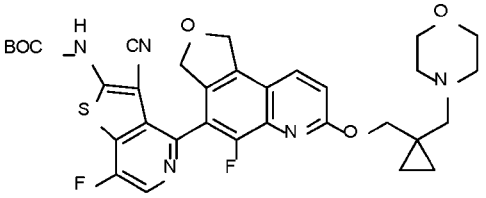
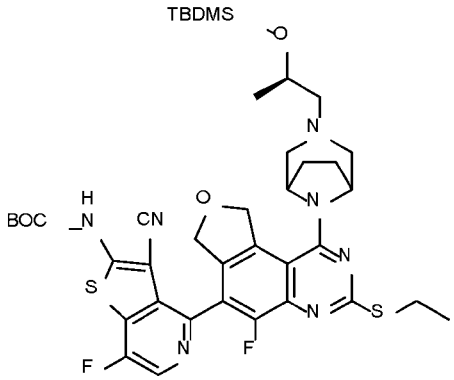
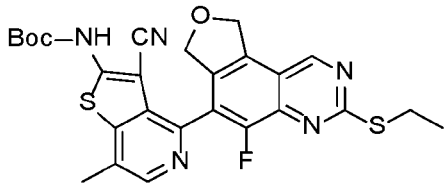
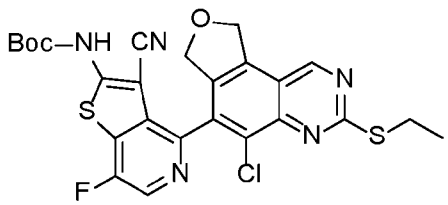
[0281] To a solution of *tert*-butyl 8-(6-bromo-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (25.0 g, 46.3 mmol) and 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (20.9 g, 92.7 mmol) in 1,4-dioxane (300 mL) was added potassium acetate (13.6 g, 139 mmol) and dichloropalladium; {2-[2-(diphenylphosphanyl)phenoxy]phenyl}diphenylphosphane (4.98 g, 6.95 mmol) at RT under nitrogen. The mixture was stirred overnight at 85 °C, then filtered. The filter cake was washed with 1,4-dioxane (2 x 100 mL). The filtrate was concentrated under reduced pressure and purified on silica, eluting with 0-20% EtOAc in PE to obtain *tert*-butyl 8-(6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (23 g, 87%) as a yellow solid.

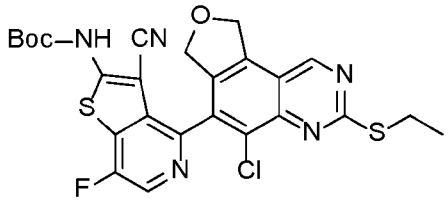
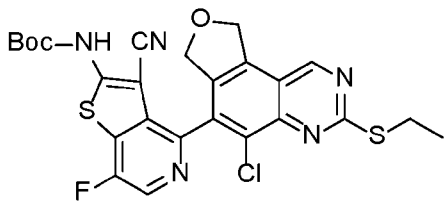
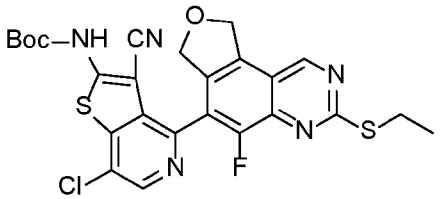
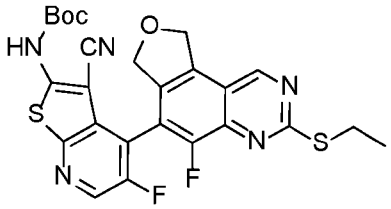
[0282] To a stirred mixture of *tert*-butyl 8-(6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (6.99 g, 12.2 mmol) and *tert*-butyl (4-chloro-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (4.00 g, 12.2 mmol) in toluene (150 mL) was added potassium phosphate (7.77 g, 36.6 mmol), [2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl] (1.75 g, 3.66 mmol), and XPhos Palladacycle Gen 4 (CAS 1599466-81-5; 0.026 g, 0.031 mmol) at RT under nitrogen. The mixture was stirred for 4 h at 80 °C, then diluted with water (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica, eluting with 0-45% EtOAc in PE to obtain the title compound (6.0 g, 65%) as a yellow solid. MS (ES) *m/z*=752 (M+1).

[0283] The following compounds in Table 4 were prepared in similar manner as described in Preparation 33. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 4:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)

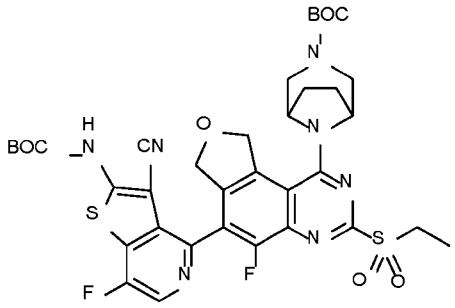
34	*tert*-Butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		542
35	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-7-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
36	*tert*-Butyl (4-(1-(3-((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		824
15B	*tert*-Butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-methylthieno[3,2-c]pyridin-2-yl)carbamate		538
16B	*tert*-Butyl (4-(5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		558

17B [1]	*tert*-Butyl (4-(5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Atropisomer 1		558
18B [1]	*tert*-Butyl (4-(5-chloro-3-(ethylthio)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Atropisomer 2		558
3C	*tert*-Butyl (7-chloro-3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		558
2D	*tert*-Butyl (3-cyano-4-(3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate		542

[1] Prep-Chiral-HPLC; Phenomenex Lux i-Cellulose-5, 30 x 150 mm, 10-65% EtOH in Heptane, 42.5 mL/min

Preparation 37

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

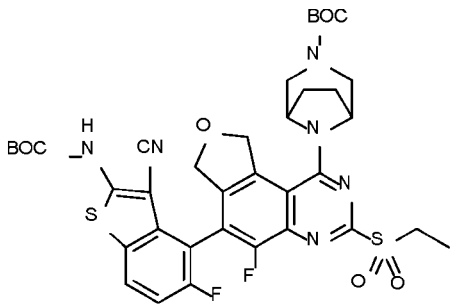
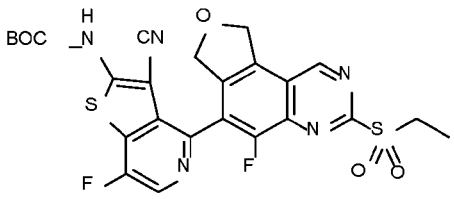
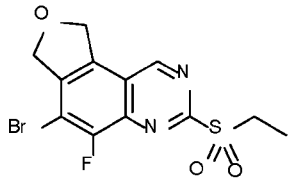
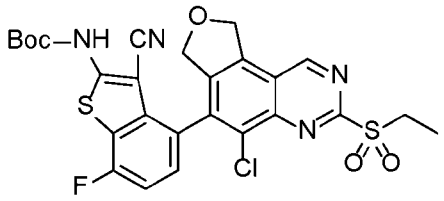
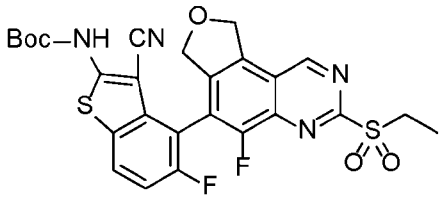


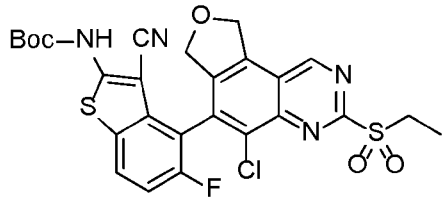
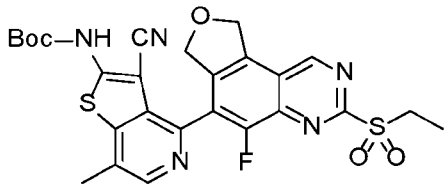
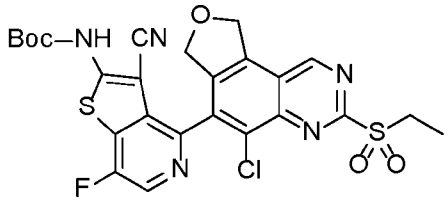
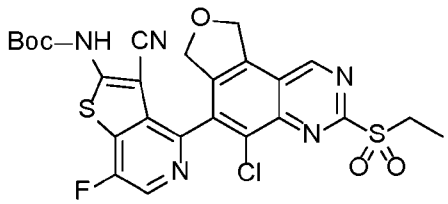
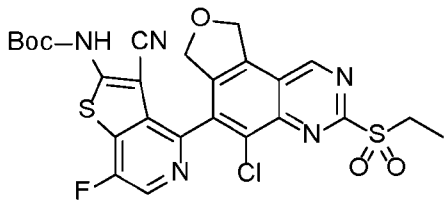
[0284] To a solution of *tert*-butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (8.4 g, 11.2 mmol) in DCM (100 mL) was added *m*CPBA (4.05 g, 23.5 mmol) in portions at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. The mixture was diluted with DCM (800 mL) and washed with sat. aq. $NaHCO_3$ (3 x 400 mL) and brine (2 x 300 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica, eluting with 0-10% MeOH in DCM to obtain the title compound (8.3 g, 95%) as an off-white solid. MS (ES) *m/z*=784 (M+1).

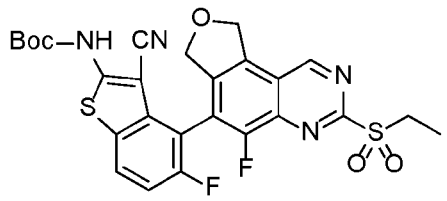
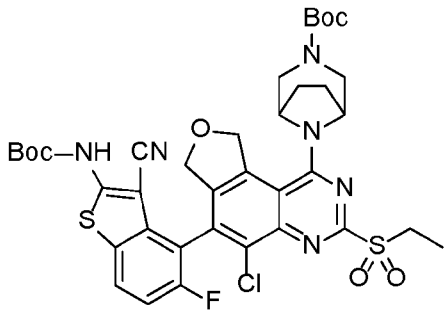
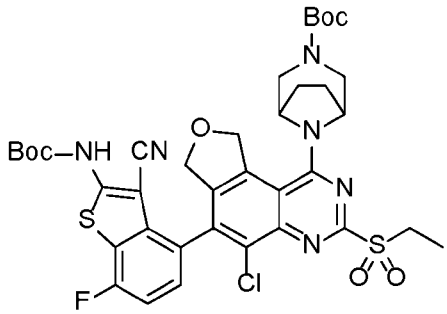
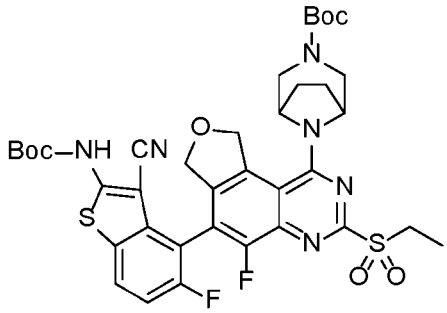
[0285] The following compounds in Table 5 were prepared in similar manner as described in Preparation 37. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

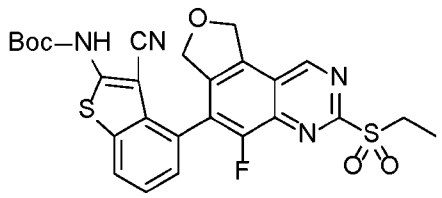
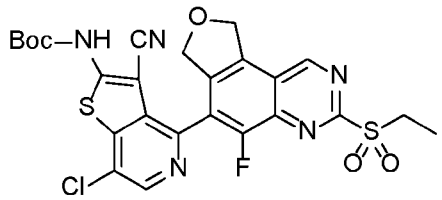
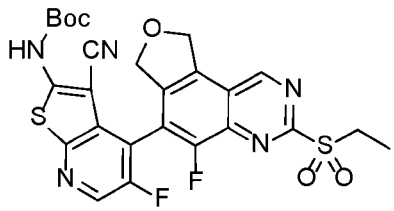
Table 5:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)

38	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		783
39	*tert*-Butyl (3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		574
40	6-Bromo-3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline		360
11A	*tert*-Butyl (4-(5-chloro-3-(ethylsulfonyl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		589
12A	*tert*-Butyl (3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		573

19B	*tert*-Butyl (4-(5-chloro-3-(ethylsulfonyl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate		589
20B	*tert*-Butyl (3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-methylthieno[3,2-c]pyridin-2-yl)carbamate		570
21B	*tert*-Butyl (4-(5-chloro-3-(ethylsulfonyl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		590
22B [1]	*tert*-Butyl (4-(5-chloro-3-(ethylsulfonyl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate. Atropisomer 1		590
23B [2]	*tert*-Butyl (4-(5-chloro-3-(ethylsulfonyl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate. Atropisomer 2		590

24B [3]	*tert*-Butyl (3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		573
25B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-(ethylsulfonyl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		799
26B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-(ethylsulfonyl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		799
27B [4]	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		783

4C	*tert*-Butyl (3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		555
5C	*tert*-Butyl (7-chloro-3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		590
3D	*tert*-Butyl (3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate		574

[1] Single atropisomer (from precursor in Preparation 17B)

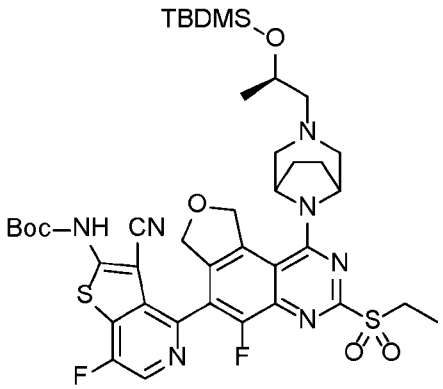
[2] Single atropisomer (from precursor in Preparation 18B)

[3] Single atropisomer (from precursor in Preparation 14B)

[4] Single atropisomer (from precursor in Preparation 9B)

Preparation 41

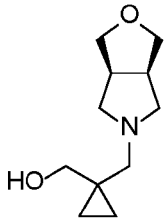
tert-Butyl (4-(1-(3-((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate



[0286] *tert*-Butyl (4-(1-(3-((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(ethylthio)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (4 g, 5 mmol), hexaammonium heptamolybdate tetrahydrate (1 g, 1 mmol), and hydrogen peroxide (8 mL, 35 wt% in water, 100 mmol) were combined in DCM (30 mL) and EtOH (30 mL). The mixture was stirred at RT for 1 h, then concentrated under reduced pressure. Diluted with water (100 mL) and stirred 30 min. Filtered and dried the resulting solids in a vacuum oven (45 °C) to give the title compound (2 g, 50%) as a white solid. MS (ES) *m/z*=856 (M+1).

Preparation 28B

(1-(((3aR,6aS)-Tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)methyl)cyclopropyl)methanol

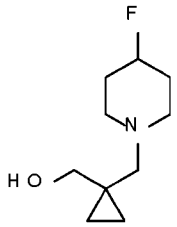


[0287] To a stirred solution of ethyl 1-(bromomethyl)cyclopropane-1-carboxylate (1.5 g, 7.2 mmol) and (3aR,6aS)-hexahydro-1H-furo[3,4-c]pyrrole hydrochloride (0.82 g, 7.2 mmol) in acetonitrile (15 mL) was added potassium carbonate (2.00 g, 14.5 mmol) at RT under nitrogen. The mixture was stirred at RT for 3 h, then filtered. The filter cake was washed with acetonitrile (2 x 20 mL). The combined filtrates were concentrated under reduced pressure to give crude ethyl 1-(((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)methyl)cyclopropane-1-carboxylate (1.2 g, 69%) as a colorless oil. MS (ES) *m/z*=240 (M+1).

[0288] The crude ethyl ester (1.2 g, 5.0 mmol) was mixed with THF (10 mL) and cooled to 0 °C under nitrogen. Lithium aluminum hydride (2.5M in THF, 10 mL, 25 mmol) was added dropwise and the mixture was allowed to stir at RT. After 1 h, the reaction mixture was cooled to 0 °C and quenched with water (0.95 g), aqueous NaOH (0.95 g), and water (3 x 0.95 g). The resulting mixture was filtered. The filter cake was washed with THF (3 x 100 mL). The combined filtrates were concentrated under reduced pressure to give crude (1-(((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)methyl)cyclopropyl)methanol (0.75 g, 76%) as a colorless oil. MS (ES) *m/z*=198 (M+1).

Preparation 42

(1-((4-Fluoropiperidin-1-yl)methyl)cyclopropyl)methanol



[0289] 1-(Methoxycarbonyl)cyclopropane-1-carboxylic acid (0.800 g, 5.55 mmol), oxalyl chloride (0.54 mL, 6.11 mmol), DCM (13.9 mL) and DMF (0.022 mL) were combined, stirred at RT for 1 h, and concentrated under reduced pressure to give crude methyl 1-(chlorocarbonyl)cyclopropane-1-carboxylate.

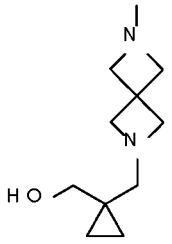
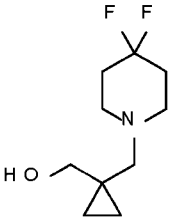
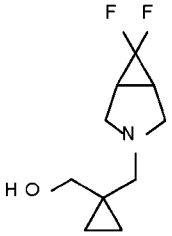
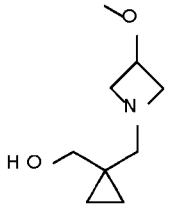
[0290] The crude acid chloride was combined with 4-fluoropiperidine (0.59 mL, 5.55 mmol) and triethylamine (3.87 mL, 27.8 mmol) in DCM (13.9 mL). The mixture was stirred at RT for 2 h, then concentrated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and washed with aqueous $KHSO_4$ (1M, 30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The organics were dried over magnesium sulfate and concentrated under reduced pressure to give crude methyl 1-(4-fluoropiperidine-1-carbonyl)cyclopropane-1-carboxylate (0.93 g, 73%).

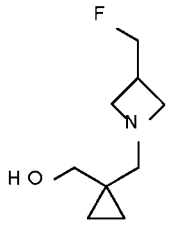
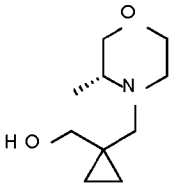
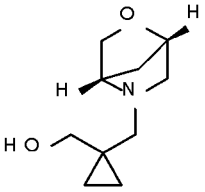
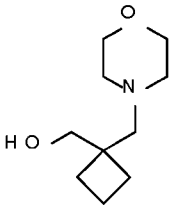
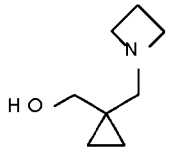
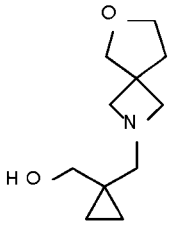
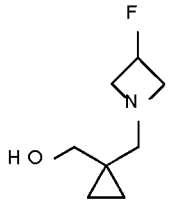
[0291] The crude methyl ester was mixed with THF (20 mL) and cooled to 0 °C. Lithium aluminum hydride (2M in THF, 4.05 mL, 8.10 mmol) was added dropwise and the mixture was allowed to stir at RT. After 1 h, the reaction mixture was diluted with EtOAc (20 mL). Water (0.31 mL), aqueous NaOH (2M, 0.31 mL), and water (0.62 mL) were added in succession. The mixture was stirred at RT. After 30 min, the mixture was filtered through diatomaceous earth. The filtrate was concentrated under

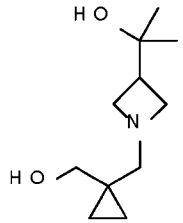
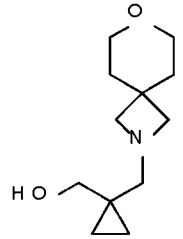
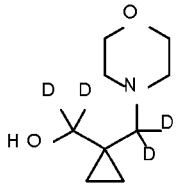
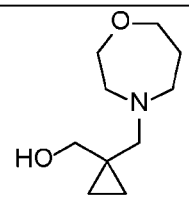
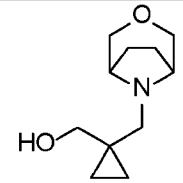
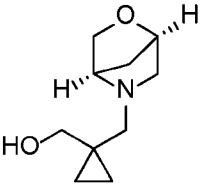
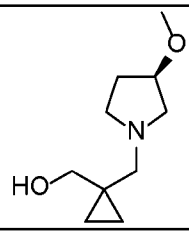
reduced pressure to give the title compound (0.60 g, 79%) as a colorless oil, with no further purification. MS (ES) *m/z*=188 (M+1).

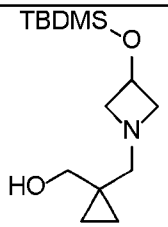
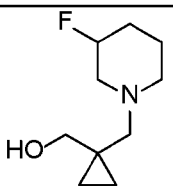
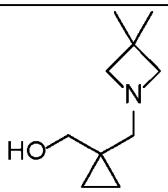
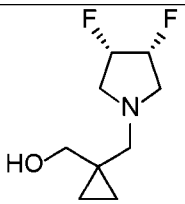
[0292] The following compounds in Table 6 were prepared in similar manner as described in Preparation 42. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 6:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
43[1]	(1-((6-Methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)cyclopropyl)methanol		
44	(1-((4,4-Difluoropiperidin-1-yl)methyl)cyclopropyl)methanol		
45	(1-((6,6-Difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)cyclopropyl)methanol		
46	(1-((3-Methoxyazetidin-1-yl)methyl)cyclopropyl)methanol		172

47	(1-((3-(Fluoromethyl)azetidin-1-yl)methyl)cyclopropyl)methanol		174
48	(R)-(1-((3-Methylmorpholino)methyl)cyclopropyl)methanol		
49	(1-(((1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methanol		184
50	(1-(Morpholinomethyl)cyclobutyl)methanol		186
51	(1-(Azetidin-1-ylmethyl)cyclopropyl)methanol		
52	(1-((6-Oxa-2-azaspiro[3.4]octan-2-yl)methyl)cyclopropyl)methanol		
53	(1-((3-Fluoroazetidin-1-yl)methyl)cyclopropyl)methanol		160

54	2-(1-((1-(Hydroxymethyl)cyclopropyl)methyl)azetidin-3-yl)propan-2-ol		200
55	(1-((7-Oxa-2-azaspiro[3.5]nonan-2-yl)methyl)cyclopropyl)methanol		
56[2]	(1-(Morpholinomethyl-d2)cyclopropyl)methan-d2-ol		
13A	(1-((1,4-Oxazepan-4-yl)methyl)cyclopropyl)methanol		186
14A	(1-((-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropyl)methanol		198
15A	(1-(((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methanol		184
16A	(R)-(1-((3-Methoxypyrrolidin-1-yl)methyl)cyclopropyl)methanol		186

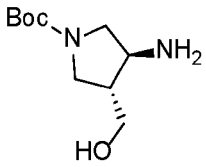
17A	1-((1-(Hydroxymethyl)cyclopropyl)methyl)azetidin-3-ol		272
18A	(1-((3-Fluoropiperidin-1-yl)methyl)cyclopropyl)methanol		188
19A	(1-((3,3-Dimethylazetidin-1-yl)methyl)cyclopropyl)methanol		
20A	(1-(((3R,4S)-3,4-Difluoropyrrolidin-1-yl)methyl)cyclopropyl)methanol		

[1] using *tert*-butyl 2-(2,6-diazaspiro[3.3]heptan-2-yl)acetate

[2] using deuterated lithium aluminum hydride

Preparation 29B

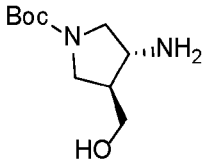
tert-Butyl (3S,4R)-3-amino-4-(hydroxymethyl)pyrrolidine-1-carboxylate



[0293] To a solution of 1-(*tert*-butyl) 3-ethyl (3R,4S)-4-aminopyrrolidine-1,3-dicarboxylate (0.100 g, 0.387 mmol) in THF (3 mL) was added lithium aluminum hydride (1M in diethyl ether, 0.465 mL, 0.465 mmol). The reaction mixture was stirred for 3 h at 0 °C, then diluted with MTBE (5 mL), water (5 drops, at which point fizzing ceased), and aqueous NaOH (15%, 5 drops). The mixture was stirred at RT. After 15 min, the mixture was dried with magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the crude title compound (0.084 g, 100%) with no further purification.

Preparation 30B

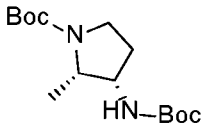
tert-Butyl (3R,4S)-3-amino-4-(hydroxymethyl)pyrrolidine-1-carboxylate



[0294] 1-(*tert*-Butyl) 3-ethyl (3S,4R)-4-aminopyrrolidine-1,3-dicarboxylate was used in a manner analogous to the method of Preparation 29B to afford the crude title compound (0.100 g, 100%).

Preparation 31B

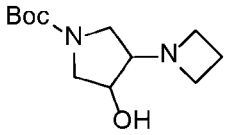
tert-Butyl (2S,3S)-3-((*tert*-butoxycarbonyl)amino)-2-methylpyrrolidine-1-carboxylate



[0295] *tert*-Butyl (2S,3S)-3-amino-2-methylpyrrolidine-1-carboxylate (0.450 g, 2.25 mmol), Boc-anhydride (0.687 g, 3.15 mmol) and diisopropylethylamine (1.96 mL, 11.2 mmol) were combined in chloroform (10 mL). The reaction mixture was stirred overnight at RT, then diluted with saturated aqueous ammonium chloride (20 mL). The mixture was extracted with DCM (3 x 20 mL). The combined organic layers were passed through a hydrophobic frit and the filtrate was concentrated under reduced pressure to give the crude title compound (0.60 g, 90%) with no further purification. MS (ES) *m/z*=323 (M+Na).

Preparation 4D

tert-Butyl 3-(azetidin-1-yl)-4-hydroxypyrrolidine-1-carboxylate

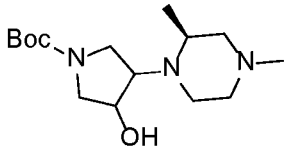
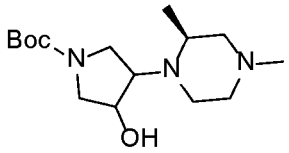
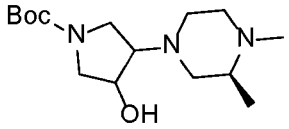
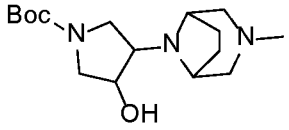
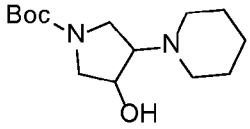


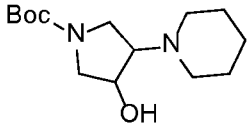
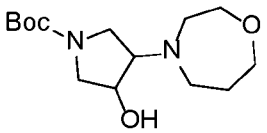
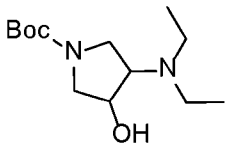
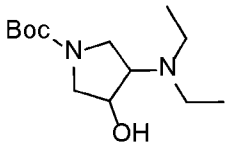
[0296] A mixture of *tert*-butyl 6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (3 g, 20 mmol) and azetidine (1 mL, 20 mmol) in water (20 mL) was heated at 80 °C for 4.5 h, then cooled to RT. The mixture was extracted with EtOAc. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase purification, eluting

with 20% ACN in aq. NH_4HCO_3 with pH 9 buffer, to give the title compound (2.4 g, 60%) as a white solid. MS (ES) *m/z*=243 (M+1). The title compound is a mix of Trans Isomers.

[0297] The following compounds in Table 7 were prepared in similar manner as described in Preparation 4D. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 7:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
5D [1]	*tert*-Butyl 3-((S)-2,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidine-1-carboxylate, Isomer 2		300
6D [1]	*tert*-Butyl 3-((S)-2,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidine-1-carboxylate, Isomer 1		300
7D [2]	*tert*-Butyl 3-((S)-3,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidine-1-carboxylate		300
8D [3]	*tert*-Butyl 3-hydroxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidine-1-carboxylate		312
9D [4]	*tert*-Butyl 3-hydroxy-4-(piperidin-1-yl)pyrrolidine-1-carboxylate, Isomer 1		271

10D [4]	*tert*-Butyl 3-hydroxy-4-(piperidin-1-yl)pyrrolidine-1-carboxylate, Isomer 2		271
11D [5]	*tert*-Butyl 3-hydroxy-4-(1,4-oxazepan-4-yl)pyrrolidine-1-carboxylate		287
12D [6]	*tert*-Butyl 3-(diethylamino)-4-hydroxypyrrolidine-1-carboxylate, Isomer 1		259
13D [6]	*tert*-Butyl 3-(diethylamino)-4-hydroxypyrrolidine-1-carboxylate, Isomer 2		259

[1] Clean Trans Isomers, Analysis of Preparations 5D and 6D with Analytical-Chiral-SFC; Chiralpak-IC, 25-50% Isopropanol (w/ 0.2% isopropylamine) in CO_2 shows Preparation 6D to elute first and Preparation 5D to elute second

[2] Clean Trans Isomer, Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 20% MeOH (w/ 0.5% dimethylethylamine) in CO_2, 65 g/min shows Preparation 7D to elute second

[3] Mix of Trans Isomers

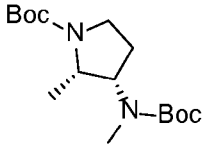
[4] Clean Trans Isomers, Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 25% MeOH (w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[5] Mix of Trans Isomers

[6] Clean Trans Isomers, Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 10% MeOH (w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

Preparation 32B

tert-Butyl (2S,3S)-3-((tert-butoxycarbonyl)(methyl)amino)-2-methylpyrrolidine-1-carboxylate

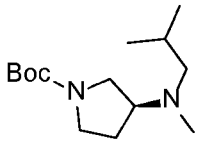
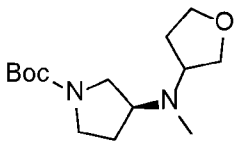
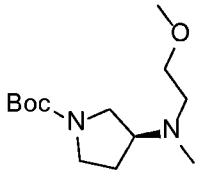
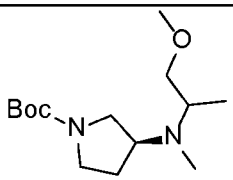
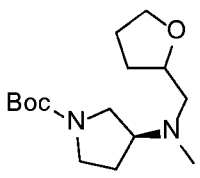


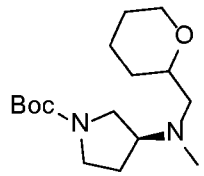
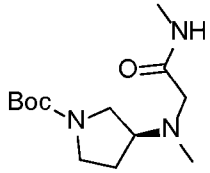
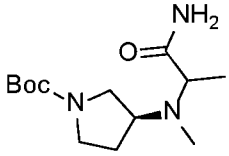
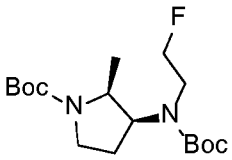
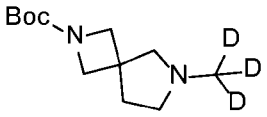
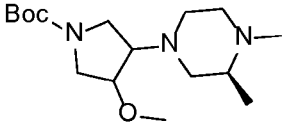
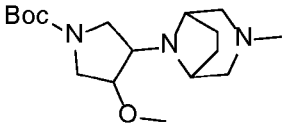
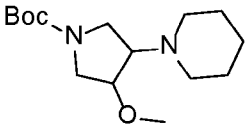
[0298] To a 0 °C solution of *tert*-butyl (2S,3S)-3-((*tert*-butoxycarbonyl)amino)-2-methylpyrrolidine-1-carboxylate (0.300 g, 1.00 mmol) in DMF (4.5 mL) was added sodium hydride (0.044 g, 1.10 mmol). The reaction mixture was stirred for 30 min at RT, then cooled to 0 °C. Iodomethane (0.068 mL, 1.10

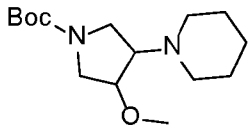
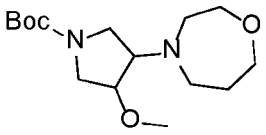
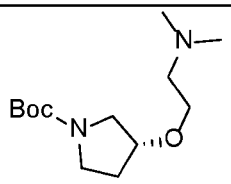
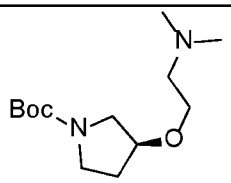
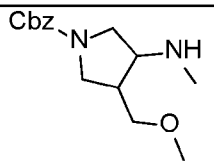
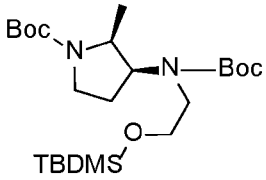
mmol) was added. The reaction mixture was stirred for 2 h at RT then diluted with saturated aqueous ammonium chloride (20 mL). The mixture was extracted with DCM (3 x 20 mL). The combined organic layers were passed through a hydrophobic frit and the filtrate was concentrated under reduced pressure to give the crude title compound with no further purification.

[0299] The following compounds in Table 8 were prepared in similar manner as described in Preparation 32B. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 8:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
6C	*tert*-Butyl (S)-3-(isobutyl(methyl)amino)pyrrolidine-1-carboxylate		257
7C	*tert*-Butyl (3S)-3-(methyl(tetrahydrofuran-3-yl)amino)pyrrolidine-1-carboxylate		271
8C	*tert*-Butyl (S)-3-((2-methoxyethyl)(methyl)amino)pyrrolidine-1-carboxylate		259
9C	*tert*-Butyl (3S)-3-((1-methoxypropan-2-yl)(methyl)amino)pyrrolidine-1-carboxylate		273
10C	*tert*-Butyl (3S)-3-(methyl((tetrahydrofuran-2-yl)methyl)amino)pyrrolidine-1-carboxylate		285

11C	*tert*-Butyl (3S)-3-(methyl((tetrahydro-2H-pyran-2-yl)methyl)amino)pyrrolidine-1-carboxylate		299
12C	*tert*-Butyl (S)-3-(methyl(2-(methylamino)-2-oxoethyl)amino)pyrrolidine-1-carboxylate		272
13C	*tert*-Butyl (3S)-3-((1-amino-1-oxopropan-2-yl)(methyl)amino)pyrrolidine-1-carboxylate		272
14C	*tert*-Butyl (2S,3S)-3-((*tert*-butoxycarbonyl)(2-fluoroethyl)amino)-2-methylpyrrolidine-1-carboxylate		347
14D	*tert*-Butyl 6-(methyl-d3)-2,6-diazaspiro[3.4]octane-2-carboxylate		230
15D [1]	*tert*-Butyl 3-((S)-3,4-dimethylpiperazin-1-yl)-4-methoxypyrrolidine-1-carboxylate		314
16D [2]	*tert*-Butyl 3-methoxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidine-1-carboxylate		326
17D [3]	*tert*-Butyl 3-methoxy-4-(piperidin-1-yl)pyrrolidine-1-carboxylate, Isomer 1		285

18D [3]	*tert*-Butyl 3-methoxy-4-(piperidin-1-yl)pyrrolidine-1-carboxylate, Isomer 2		285
19D [4]	*tert*-Butyl 3-methoxy-4-(1,4-oxazepan-4-yl)pyrrolidine-1-carboxylate		301
20D	*tert*-Butyl (R)-3-(2-(dimethylamino)ethoxy)pyrrolidine-1-carboxylate		259
21D	*tert*-Butyl (S)-3-(2-(dimethylamino)ethoxy)pyrrolidine-1-carboxylate		259
22D [5]	Benzyl 3-(methoxymethyl)-4-(methylamino)pyrrolidine-1-carboxylate		279
23D	*tert*-Butyl (2S,3S)-3-((*tert*-butoxycarbonyl)(2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-2-methylpyrrolidine-1-carboxylate		459

[1] Clean Trans Isomer, Separated in Preparation 7D

[2] Mix of Trans Isomers

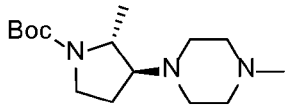
[3] Clean Trans Isomers, Separated in Preparations 9D and 10D

[4] Mix of Trans Isomers

[5] Mix of Cis Isomers

Preparation 24D

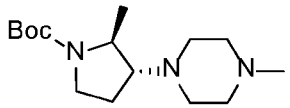
tert-Butyl (2R,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate



[0300] 2-Chloro-N-(2-chloroethyl)-N-methylethan-1-amine hydrochloride (0.481 g, 2.50 mmol) was added to a mixture of *tert*-butyl (2R,3S)-3-amino-2-methylpyrrolidine-1-carboxylate (0.50 g, 2.50 mmol), potassium carbonate (1.73 g, 12.5 mmol), and potassium iodide (0.0104 g, 0.062 mmol) in acetonitrile (5 mL). The reaction mixture was stirred for 16 h at 82 °C overnight at RT, then cooled, diluted with DCM, and filtered to remove solids. The filtrate was concentrated under reduced pressure. The residue was purified by reversed phase purification, eluting with a gradient of ACN in water (with 0.1% formic acid), to give the title compound (0.319 g, 45%) as a yellow solid. MS (ES) *m/z*=284 (M+1).

Preparation 25D

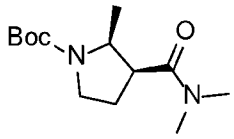
tert-Butyl (2S,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate



[0301] *tert*-Butyl (2S,3R)-3-amino-2-methylpyrrolidine-1-carboxylate was used in a manner analogous to the method of Preparation 24D to afford the title compound (0.298 g, 42%). MS (ES) *m/z*=284 (M+1).

Preparation 15C

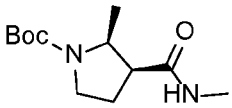
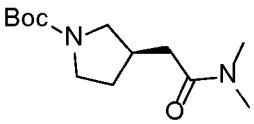
tert-Butyl (2S,3S)-3-(dimethylcarbamoyl)-2-methylpyrrolidine-1-carboxylate



[0302] A mixture of (2S,3S)-1-(*tert*-butoxycarbonyl)-2-methylpyrrolidine-3-carboxylic acid (1.00 g, 4.36 mmol), hexafluorophosphate azabenzotriazole tetramethyl uranium (2.49 g, 6.54 mmol), and dimethylamine (2M in THF; 4.36 mL, 8.72 mmol) in DCM (30 mL) was treated with diisopropylethylamine (2.28 mL, 13.1 mmol). The reaction mixture was stirred overnight at RT, then concentrated under reduced pressure. The residue was purified on silica, eluting with 0-100% EtOAc in heptane to obtain the title compound (1.08 g, 97%). MS (ES) *m/z*=201 (M+1, -tBu).

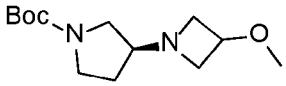
[0303] The following compounds in Table 9 were prepared in similar manner as described in Preparation 15C. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 9:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
26D	*tert*-Butyl (2S,3S)-2-methyl-3-(methylcarbamoyl)pyrrolidine-1-carboxylate		187 -tBu
27D	*tert*-Butyl (R)-3-(2-(dimethylamino)-2-oxoethyl)pyrrolidine-1-carboxylate		201 -tBu

Preparation 16C

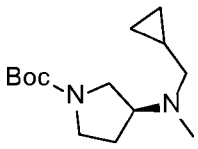
tert-Butyl (S)-3-(3-methoxyazetidin-1-yl)pyrrolidine-1-carboxylate



[0304] 3-methoxyazetidine (0.0985 g, 1.13 mmol) and diisopropylethylamine (0.433 mL, 2.49 mmol) were added to *tert*-butyl (R)-3-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate (0.300 g, 1.13 mmol). The reaction mixture was stirred for 17 h at 80 °C. The mixture was diluted with MeOH (1 mL). The material was purified on strong cation exchange media (25 g), eluting first with MeOH, then with 2M ammoniated MeOH. The basic fraction was concentrated under reduced pressure to obtain the crude title compound, which was used as-is.

Preparation 17C

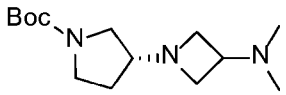
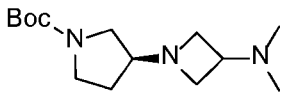
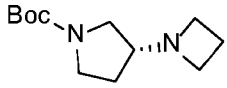
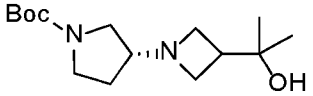
tert-Butyl (S)-3-((cyclopropylmethyl)(methyl)amino)pyrrolidine-1-carboxylate

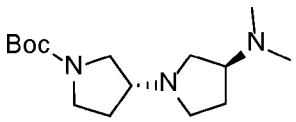
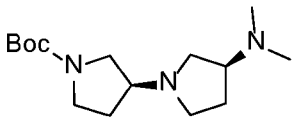
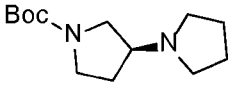
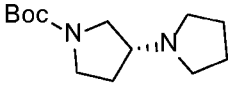
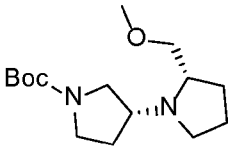
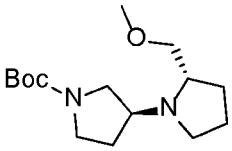
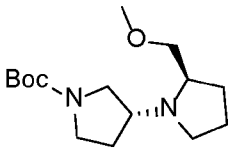
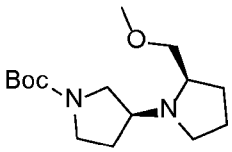
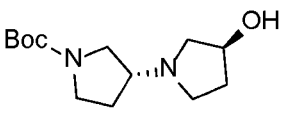


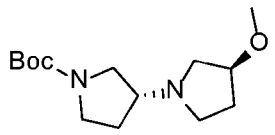
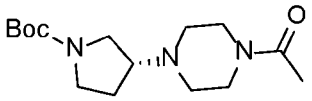
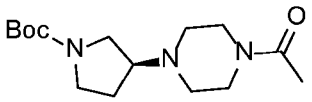
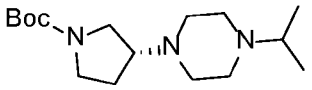
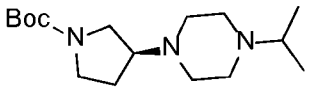
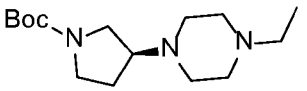
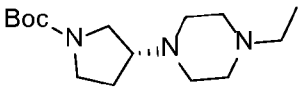
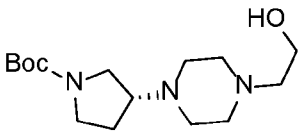
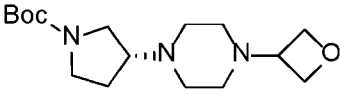
[0305] 1-Cyclopropyl-N-methylmethanamine was used in a manner analogous to the method of Preparation 16C to afford the crude title compound, which was used as-is.

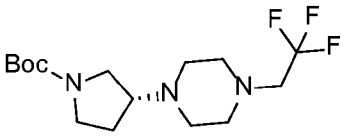
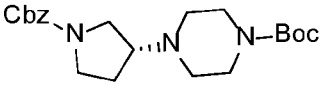
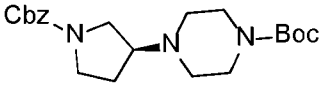
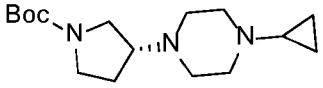
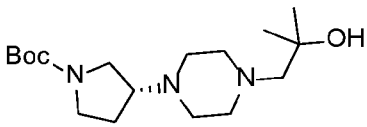
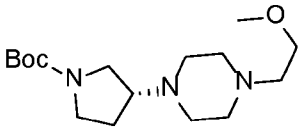
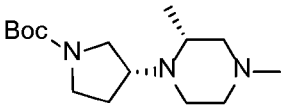
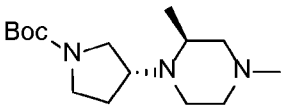
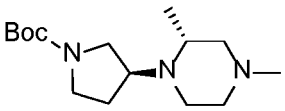
[0306] The following compounds in Table 10 were prepared in similar manner as described in Preparation 16C. In some cases, tosylates were used in replacement of mesylates. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

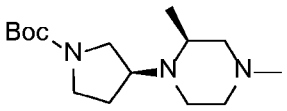
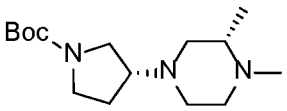
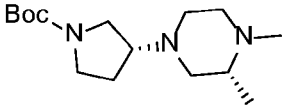
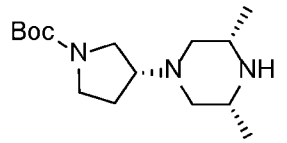
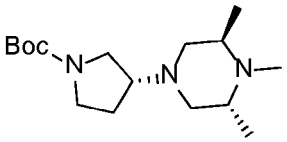
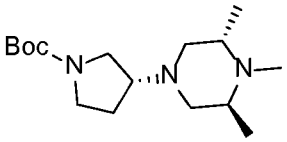
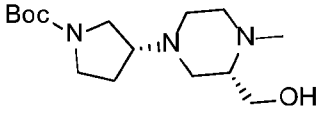
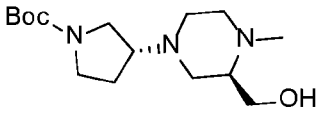
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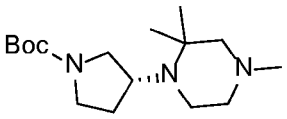
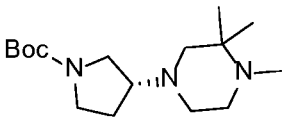
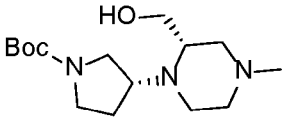
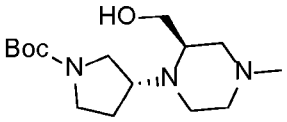
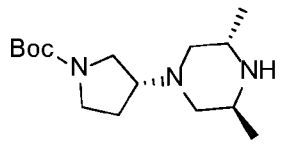
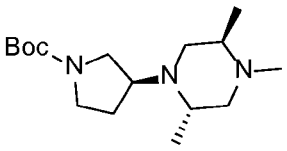
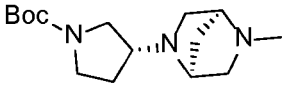
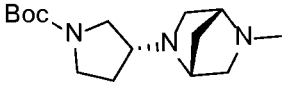
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
28D	*tert*-Butyl (R)-3-(3-(dimethylamino)azetidin-1-yl)pyrrolidine-1-carboxylate		270
29D	*tert*-Butyl (S)-3-(3-(dimethylamino)azetidin-1-yl)pyrrolidine-1-carboxylate		270
30D	*tert*-Butyl (R)-3-(azetidin-1-yl)pyrrolidine-1-carboxylate		227
31D	*tert*-Butyl (R)-3-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyrrolidine-1-carboxylate		285

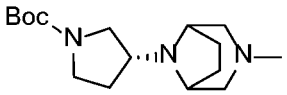
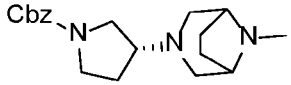
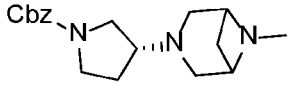
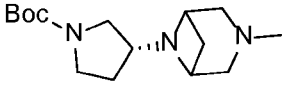
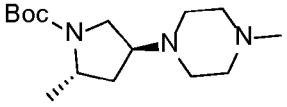
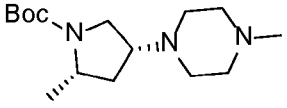
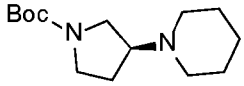
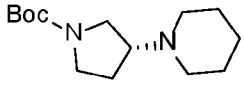
32D	*tert*-Butyl (3S,3'R)-3-(dimethylamino)-[1,3'-bipyrrolidine]-1'-carboxylate		284
33D	*tert*-Butyl (3S,3'S)-3-(dimethylamino)-[1,3'-bipyrrolidine]-1'-carboxylate		284
34D	*tert*-Butyl (S)-[1,3'-bipyrrolidine]-1'-carboxylate		241
35D	*tert*-Butyl (R)-[1,3'-bipyrrolidine]-1'-carboxylate		241
36D	*tert*-Butyl (2S,3'R)-2-(methoxymethyl)-[1,3'-bipyrrolidine]-1'-carboxylate		285
37D	*tert*-Butyl (2S,3'S)-2-(methoxymethyl)-[1,3'-bipyrrolidine]-1'-carboxylate		285
38D	*tert*-Butyl (2R,3'R)-2-(methoxymethyl)-[1,3'-bipyrrolidine]-1'-carboxylate		285
39D	*tert*-Butyl (2R,3'S)-2-(methoxymethyl)-[1,3'-bipyrrolidine]-1'-carboxylate		285
40D	*tert*-Butyl (3S,3'R)-3-hydroxy-[1,3'-bipyrrolidine]-1'-carboxylate		257

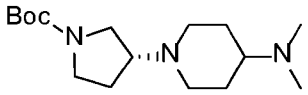
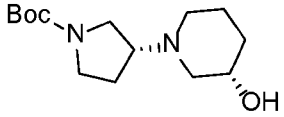
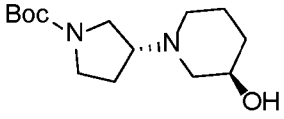
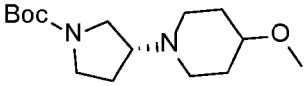
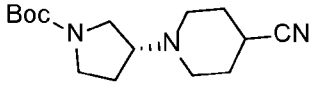
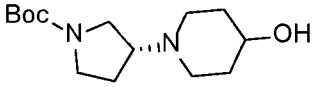
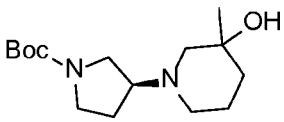
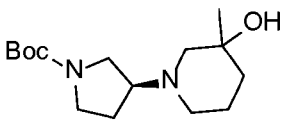
41D	*tert*-Butyl (3S,3'R)-3-methoxy-[1,3'-bipyrrolidine]-1'-carboxylate		271
42D	*tert*-Butyl (R)-3-(4-acetylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
43D	*tert*-Butyl (S)-3-(4-acetylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
44D	*tert*-Butyl (R)-3-(4-isopropylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
45D	*tert*-Butyl (S)-3-(4-isopropylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
46D	*tert*-Butyl (S)-3-(4-ethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
47D	*tert*-Butyl (R)-3-(4-ethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
48D	*tert*-Butyl (R)-3-(4-(2-hydroxyethyl)piperazin-1-yl)pyrrolidine-1-carboxylate		300
49D	*tert*-Butyl (R)-3-(4-(oxetan-3-yl)piperazin-1-yl)pyrrolidine-1-carboxylate		312

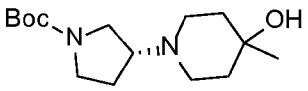
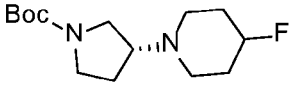
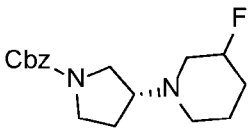
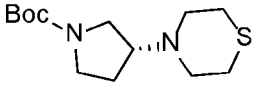
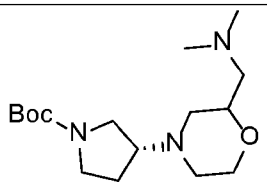
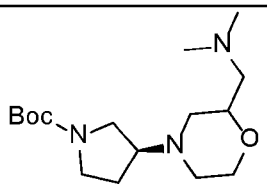
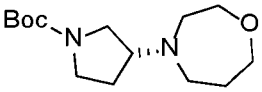
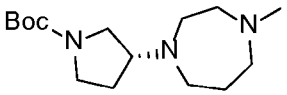
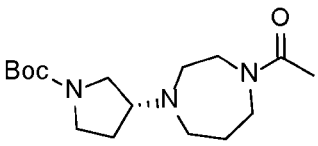
50D	*tert*-Butyl (R)-3-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyrrolidine-1-carboxylate		338
51D	*tert*-Butyl (R)-4-(1-((benzyloxy)carbonyl)pyrrolidin-3-yl)piperazine-1-carboxylate		390
52D	*tert*-Butyl (S)-4-(1-((benzyloxy)carbonyl)pyrrolidin-3-yl)piperazine-1-carboxylate		390
53D	*tert*-Butyl (R)-3-(4-cyclopropylpiperazin-1-yl)pyrrolidine-1-carboxylate		296
54D	*tert*-Butyl (R)-3-(4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)pyrrolidine-1-carboxylate		328
55D	*tert*-Butyl (R)-3-(4-(2-methoxyethyl)piperazin-1-yl)pyrrolidine-1-carboxylate		314
56D	*tert*-Butyl (R)-3-((R)-2,4-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
57D	*tert*-Butyl (R)-3-((S)-2,4-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
58D	*tert*-Butyl (S)-3-((R)-2,4-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284

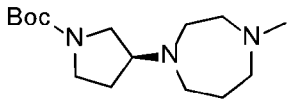
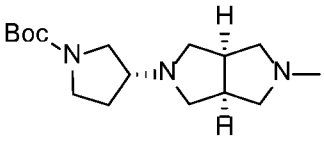
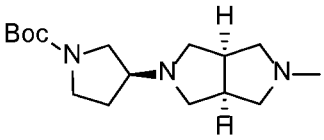
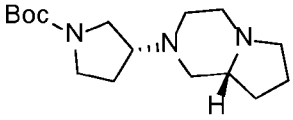
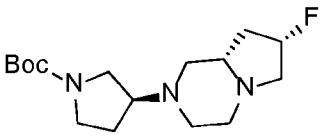
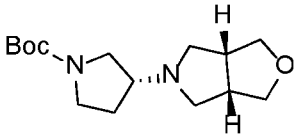
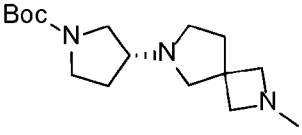
59D	*tert*-Butyl (S)-3-((S)-2,4-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
60D	*tert*-Butyl (R)-3-((S)-3,4-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
61D	*tert*-Butyl (R)-3-((R)-3,4-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
62D	*tert*-Butyl (R)-3-((3R,5S)-3,5-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
63D	*tert*-Butyl (R)-3-((3R,5R)-3,4,5-trimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
64D	*tert*-Butyl (R)-3-((3S,5S)-3,4,5-trimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
65D	*tert*-Butyl (R)-3-((S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		300
66D	*tert*-Butyl (R)-3-((R)-3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		300

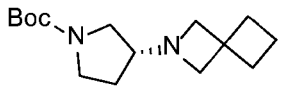
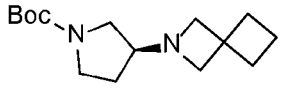
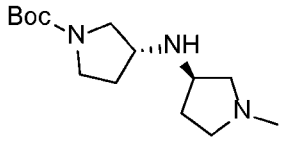
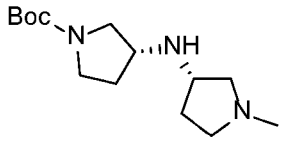
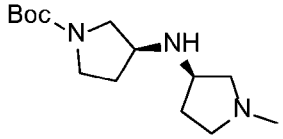
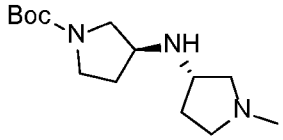
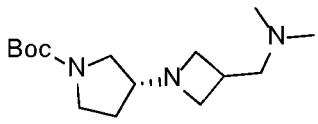
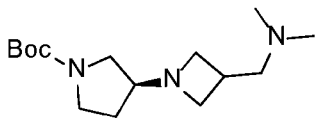
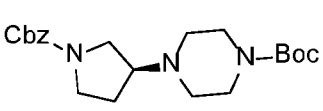
67D	*tert*-Butyl (R)-3-(2,2,4-trimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
68D	*tert*-Butyl (R)-3-(3,3,4-trimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
69D	*tert*-Butyl (R)-3-((S)-2-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		300
70D	*tert*-Butyl (R)-3-((R)-2-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		300
71D	*tert*-Butyl (R)-3-((3S,5S)-3,5-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
72D	*tert*-Butyl (S)-3-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
73D	*tert*-Butyl (R)-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrrolidine-1-carboxylate		282
74D	*tert*-Butyl (R)-3-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrrolidine-1-carboxylate		282

75D	*tert*-Butyl (3R)-3-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidine-1-carboxylate		296
76D	Benzyl (3R)-3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrrolidine-1-carboxylate		330
77D	Benzyl (3R)-3-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrrolidine-1-carboxylate		316
78D	*tert*-Butyl (3R)-3-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrrolidine-1-carboxylate		282
79D	*tert*-Butyl (2S,4S)-2-methyl-4-(4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
80D	*tert*-Butyl (2S,4R)-2-methyl-4-(4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
81D	*tert*-Butyl (S)-3-(piperidin-1-yl)pyrrolidine-1-carboxylate		255
82D	*tert*-Butyl (S)-3-(piperidin-1-yl)pyrrolidine-1-carboxylate		255

83D	*tert*-Butyl (R)-3-(4-(dimethylamino)piperidin-1-yl)pyrrolidine-1-carboxylate		298
84D	*tert*-Butyl (R)-3-((S)-3-hydroxypiperidin-1-yl)pyrrolidine-1-carboxylate		271
85D	*tert*-Butyl (R)-3-((R)-3-hydroxypiperidin-1-yl)pyrrolidine-1-carboxylate		271
86D	*tert*-Butyl (R)-3-(4-methoxypiperidin-1-yl)pyrrolidine-1-carboxylate		285
87D	*tert*-Butyl (R)-3-(4-cyanopiperidin-1-yl)pyrrolidine-1-carboxylate		280
88D	*tert*-Butyl (R)-3-(4-hydroxypiperidin-1-yl)pyrrolidine-1-carboxylate		271
89D [1]	*tert*-Butyl (3S)-3-(3-hydroxy-3-methylpiperidin-1-yl)pyrrolidine-1-carboxylate, Isomer 1		285
90D [1]	*tert*-Butyl (3S)-3-(3-hydroxy-3-methylpiperidin-1-yl)pyrrolidine-1-carboxylate, Isomer 2		285

91D	*tert*-Butyl (R)-3-(4-hydroxy-4-methylpiperidin-1-yl)pyrrolidine-1-carboxylate		285
92D	*tert*-Butyl (R)-3-(4-fluoropiperidin-1-yl)pyrrolidine-1-carboxylate		273
93D	Benzyl (3R)-3-(3-fluoropiperidin-1-yl)pyrrolidine-1-carboxylate		307
94D	*tert*-Butyl (R)-3-thiomorpholinopyrrolidine-1-carboxylate		273
95D	*tert*-Butyl (3R)-3-(2-((dimethylamino)methyl)morpholino)pyrrolidine-1-carboxylate		314
96D	*tert*-Butyl (3S)-3-(2-((dimethylamino)methyl)morpholino)pyrrolidine-1-carboxylate		314
97D	*tert*-Butyl (R)-3-(1,4-oxazepan-4-yl)pyrrolidine-1-carboxylate		271
98D	*tert*-Butyl (R)-3-(4-methyl-1,4-diazepan-1-yl)pyrrolidine-1-carboxylate		284
99D	*tert*-Butyl (R)-3-(4-acetyl-1,4-diazepan-1-yl)pyrrolidine-1-carboxylate		312

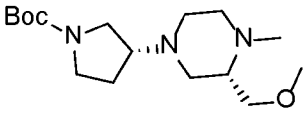
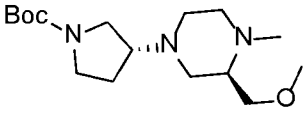
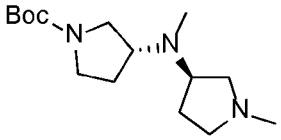
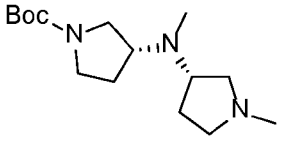
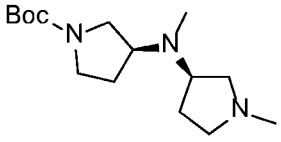
100D	*tert*-Butyl (S)-3-(4-methyl-1,4-diazepan-1-yl)pyrrolidine-1-carboxylate		284
101D	*tert*-Butyl (R)-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrrolidine-1-carboxylate		296
102D	*tert*-Butyl (S)-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrrolidine-1-carboxylate		296
103D	*tert*-Butyl (R)-3-((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrrolidine-1-carboxylate		296
104D	*tert*-Butyl (S)-3-((7S,8aS)-7-fluorohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrrolidine-1-carboxylate		314
105D	*tert*-Butyl (R)-3-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrrolidine-1-carboxylate		283
106D	*tert*-Butyl (R)-3-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)pyrrolidine-1-carboxylate		296

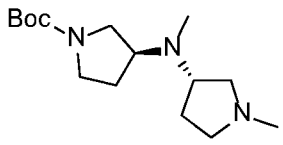
107D	*tert*-Butyl (R)-3-(2-azaspiro[3.3]heptan-2-yl)pyrrolidine-1-carboxylate		267
108D	*tert*-Butyl (S)-3-(2-azaspiro[3.3]heptan-2-yl)pyrrolidine-1-carboxylate		267
109D	*tert*-Butyl (R)-3-(((R)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		270
110D	*tert*-Butyl (R)-3-(((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		270
111D	*tert*-Butyl (S)-3-(((R)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		270
112D	*tert*-Butyl (S)-3-(((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		270
113D	*tert*-Butyl (R)-3-(3-((dimethylamino)methyl)azetidin-1-yl)pyrrolidine-1-carboxylate		284
114D	*tert*-Butyl (S)-3-(3-((dimethylamino)methyl)azetidin-1-yl)pyrrolidine-1-carboxylate		284
115D	*tert*-Butyl (S)-4-(1-((benzyloxy)carbonyl)pyrrolidin-3-yl)piperazine-1-carboxylate		390

[1] Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 20% MeOH (w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[0307] The following compounds in Table 11 were prepared in similar manner as described in Preparation 32B. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

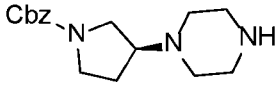
Table 11:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
116D	*tert*-Butyl (R)-3-((S)-3-(methoxymethyl)-4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		314
117D	*tert*-Butyl (R)-3-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		314
118D	*tert*-Butyl (R)-3-(methyl((R)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		284
119D	*tert*-Butyl (R)-3-(methyl((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		284
120D	*tert*-Butyl (S)-3-(methyl((R)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		284

121D	*tert*-Butyl (S)-3-(methyl((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidine-1-carboxylate		284

Preparation 122D

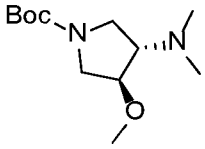
Benzyl (S)-3-(piperazin-1-yl)pyrrolidine-1-carboxylate



[0308] To a solution of *tert*-butyl (S)-4-(1-((benzyloxy)carbonyl)pyrrolidin-3-yl)piperazine-1-carboxylate (0.562 g, 1.30 mmol) in DCM (4 mL) was added TFA (3 mL). The reaction mixture was stirred for 4.5 h at RT. The mixture was concentrated. The residue was purified on strong cation exchange media (10 g), eluting first with MeOH, then with 2M ammoniated MeOH. The basic fraction was concentrated under reduced pressure to obtain the title compound (0.306 g, 79%) as a brown oil. MS (ES) *m/z*=290 (M+1).

Preparation 33B

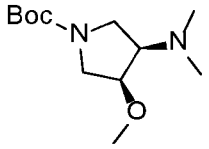
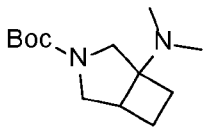
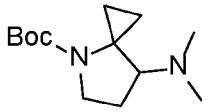
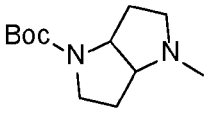
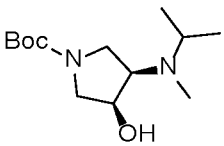
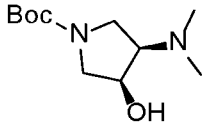
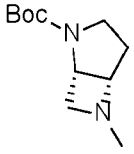
tert-Butyl (3S,4S)-3-(dimethylamino)-4-methoxypyrrolidine-1-carboxylate

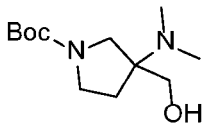
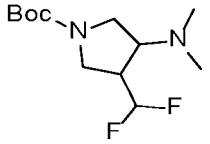
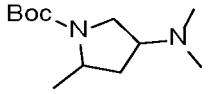
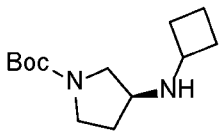
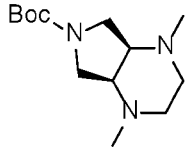
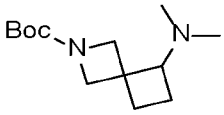
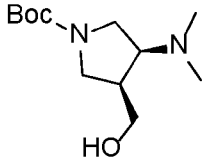
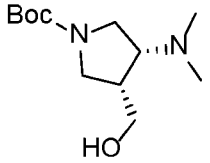
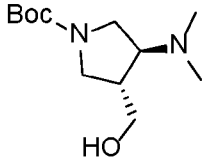


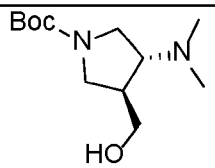
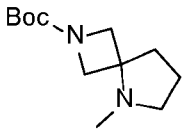
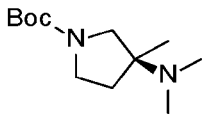
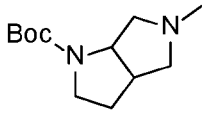
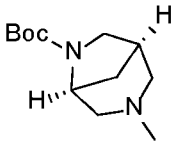
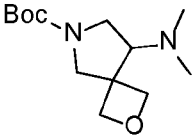
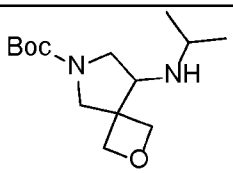
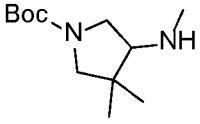
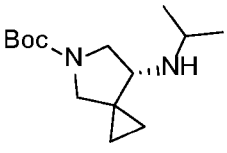
[0309] *tert*-Butyl (3S,4S)-3-methoxy-4-(methylamino)pyrrolidine-1-carboxylate (0.500 g, 2.17 mmol), formaldehyde (37 wt% in water; 0.97 mL, 13.0 mmol) and sodium triacetoxyborohydride (2.76 g, 13.0 mmol) were dissolved in MeOH (6 mL). The reaction mixture was stirred for 18 h at 50 °C. The mixture was concentrated under reduced pressure, poured into sat. aq. $NaHCO_3$ (20 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude title compound (0.53 g) as a waxy solid. MS (ES) *m/z*=245 (M+1).

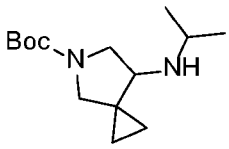
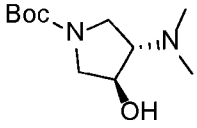
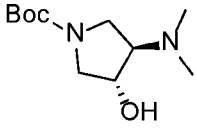
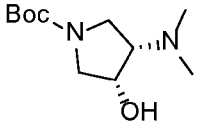
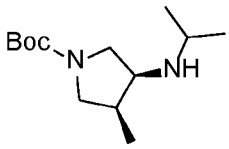
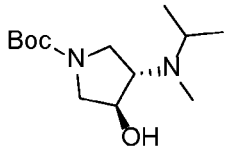
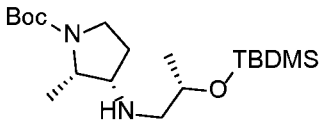
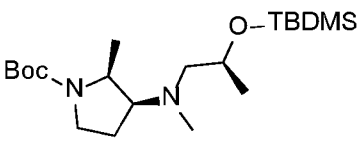
[0310] The following compounds in Table 12 were prepared in similar manner as described in Preparation 33B. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

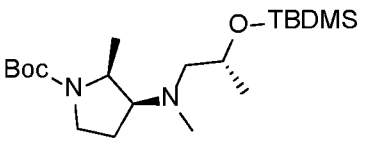
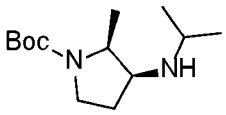
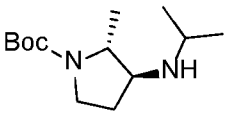
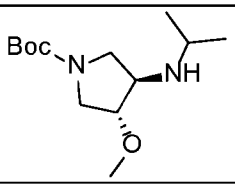
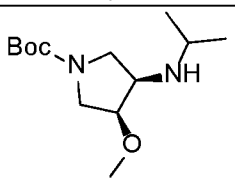
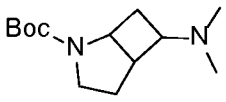
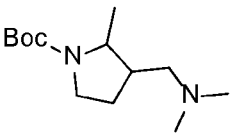
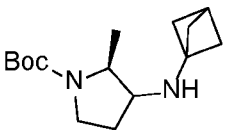
Table 12:

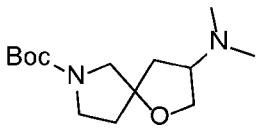
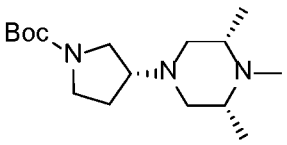
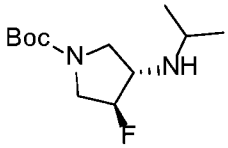
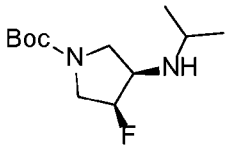
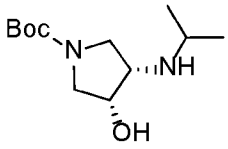
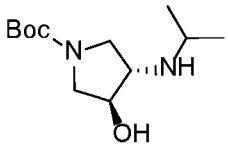
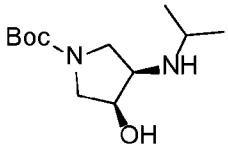
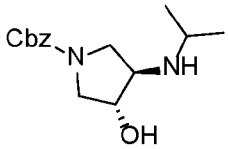
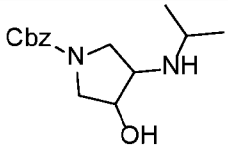
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
34B	*tert*-Butyl (3R,4S)-3-(dimethylamino)-4-methoxypyrrolidine-1-carboxylate		245
35B	*tert*-Butyl 1-(dimethylamino)-3-azabicyclo[3.2.0]heptane-3-carboxylate		
36B	*tert*-Butyl 7-(dimethylamino)-4-azaspiro[2.4]heptane-4-carboxylate		241
37B	*tert*-Butyl 4-methylhexahydropyrrolo[3,2-b]pyrrole-1(2H)-carboxylate		227
38B	*tert*-Butyl (3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidine-1-carboxylate		259
39B	*tert*-Butyl (3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidine-1-carboxylate		231
40B	*tert*-Butyl (1S,5S)-6-methyl-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate		213

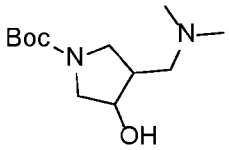
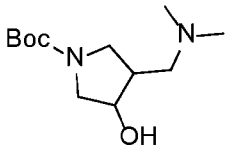
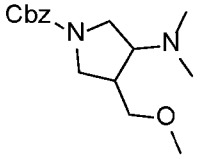
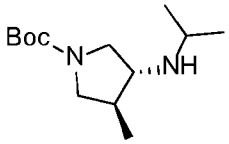
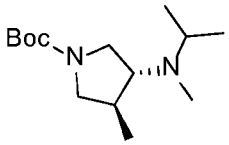
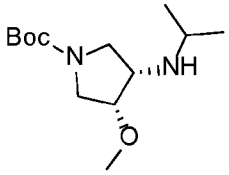
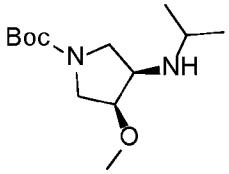
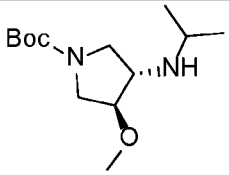
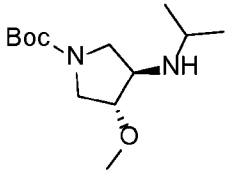
41B	*tert*-Butyl 3-(dimethylamino)-3-(hydroxymethyl)pyrrolidine-1-carboxylate		
42B	*tert*-Butyl 3-(difluoromethyl)-4-(dimethylamino)pyrrolidine-1-carboxylate, Mix of Trans Isomers		265
43B	*tert*-Butyl 4-(dimethylamino)-2-methylpyrrolidine-1-carboxylate		229
44B	*tert*-Butyl (S)-3-(cyclobutylamino)pyrrolidine-1-carboxylate		241
45B	*tert*-Butyl (4aR,7aS)-1,4-dimethyloctahydro-6H-pyrrolo[3,4-b]pyrazine-6-carboxylate		256
46B	*tert*-Butyl 5-(dimethylamino)-2-azaspiro[3.3]heptane-2-carboxylate		
47B	*tert*-Butyl (3S,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidine-1-carboxylate		
48B	*tert*-Butyl (3R,4R)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidine-1-carboxylate		
49B	*tert*-Butyl (3S,4R)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidine-1-carboxylate		

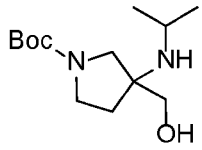
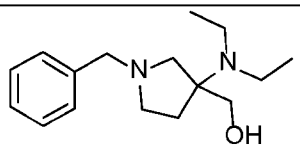
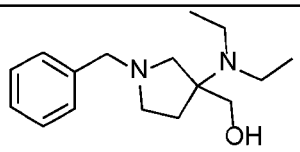
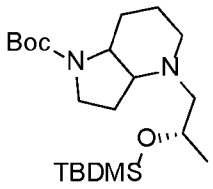
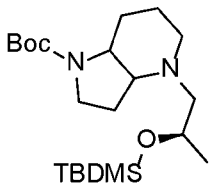
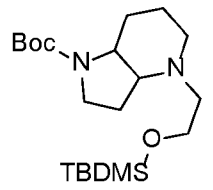
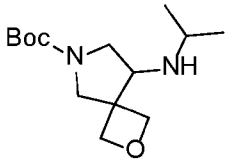
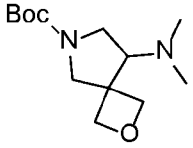
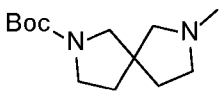
50B	*tert*-butyl (3R,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidine-1-carboxylate		
51B	*tert*-Butyl 5-methyl-2,5-diazaspiro[3.4]octane-2-carboxylate		227
52B	*tert*-Butyl (S)-3-(dimethylamino)-3-methylpyrrolidine-1-carboxylate		229
53B	*tert*-Butyl 5-methylhexahydropyrrolo[3,4-b]pyrrole-1(2H)-carboxylate, Mix of Cis Isomers		
18C	*tert*-Butyl (1R,5S)-3-methyl-3,6-diazabicyclo[3.2.1]octane-6-carboxylate		227
19C	*tert*-Butyl 8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octane-6-carboxylate		257
20C	*tert*-Butyl 8-(isopropylamino)-2-oxa-6-azaspiro[3.4]octane-6-carboxylate		271
21C	*tert*-Butyl 3,3-dimethyl-4-(methylamino)pyrrolidine-1-carboxylate		229
22C	*tert*-Butyl (R)-7-(isopropylamino)-5-azaspiro[2.4]heptane-5-carboxylate		255

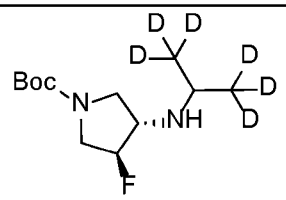
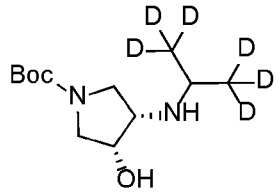
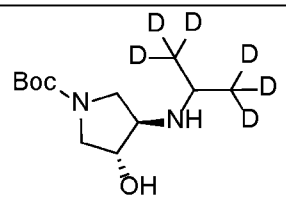
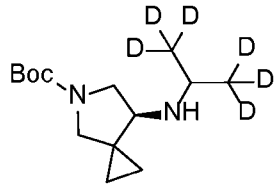
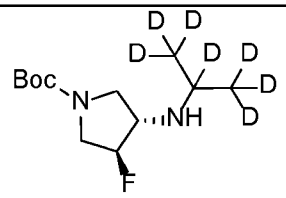
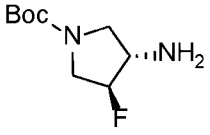
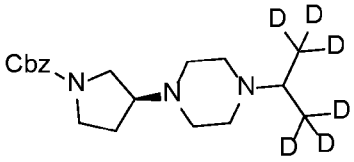
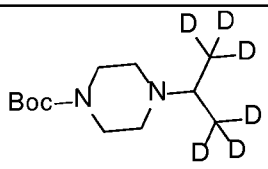
23C	*tert*-Butyl 7-(isopropylamino)-5-azaspiro[2.4]heptane-5-carboxylate		255
24C	*tert*-Butyl (3S,4S)-3-(dimethylamino)-4-hydroxypyrrolidine-1-carboxylate		231
25C	*tert*-Butyl (3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidine-1-carboxylate		231
26C	*tert*-Butyl (3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidine-1-carboxylate		231
27C	*tert*-Butyl (3S,4S)-3-(isopropylamino)-4-methylpyrrolidine-1-carboxylate		243
28C	*tert*-Butyl (3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidine-1-carboxylate		259
29C	*tert*-Butyl (2S,3S)-3-(((S)-2-((*tert*-butyldimethylsilyl)oxy)propyl)amino)-2-methylpyrrolidine-1-carboxylate		373
30C	*tert*-Butyl (2S,3S)-3-(((S)-2-((*tert*-butyldimethylsilyl)oxy)propyl)(methyl)amino)-2-methylpyrrolidine-1-carboxylate		387

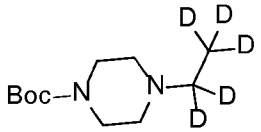
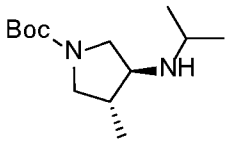
31C	*tert*-Butyl (2S,3S)-3-(((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)(methyl)amino)-2-methylpyrrolidine-1-carboxylate		387
32C	*tert*-Butyl (2S,3S)-3-(isopropylamino)-2-methylpyrrolidine-1-carboxylate		243
33C	*tert*-Butyl (2R,3S)-3-(isopropylamino)-2-methylpyrrolidine-1-carboxylate		
34C	*tert*-Butyl (3R,4R)-3-(isopropylamino)-4-methoxypyrrolidine-1-carboxylate		
35C	*tert*-Butyl (3R,4S)-3-(isopropylamino)-4-methoxypyrrolidine-1-carboxylate		
36C	*tert*-Butyl 6-(dimethylamino)-2-azabicyclo[3.2.0]heptane-2-carboxylate		241
37C	*tert*-Butyl 3-((dimethylamino)methyl)-2-methylpyrrolidine-1-carboxylate, Mix of Cis Isomers		243
38C	*tert*-Butyl (2S)-3-(bicyclo[1.1.1]pentan-1-ylamino)-2-methylpyrrolidine-1-carboxylate		267

123D	*tert*-Butyl 3-(dimethylamino)-1-oxa-7-azaspiro[4.4]nonane-7-carboxylate		271
124D	*tert*-Butyl (R)-3-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		298
125D	*tert*-Butyl (3S,4S)-3-fluoro-4-(isopropylamino)pyrrolidine-1-carboxylate		247
126D	*tert*-Butyl (3S,4R)-3-fluoro-4-(isopropylamino)pyrrolidine-1-carboxylate		247
127D	*tert*-Butyl (3R,4S)-3-hydroxy-4-(isopropylamino)pyrrolidine-1-carboxylate		245
128D	*tert*-Butyl (3S,4S)-3-hydroxy-4-(isopropylamino)pyrrolidine-1-carboxylate		245
129D	*tert*-Butyl (3S,4R)-3-hydroxy-4-(isopropylamino)pyrrolidine-1-carboxylate		245
130D	Benzyl (3R,4R)-3-hydroxy-4-(isopropylamino)pyrrolidine-1-carboxylate		279
131D [1]	Benzyl 3-hydroxy-4-(isopropylamino)pyrrolidine-1-carboxylate		279

132D [2]	*tert*-Butyl 3-((dimethylamino)methyl)-4-hydroxypyrrolidine-1-carboxylate		245
133D [3]	*tert*-Butyl 3-((dimethylamino)methyl)-4-hydroxypyrrolidine-1-carboxylate		245
134D [4]	Benzyl 3-(dimethylamino)-4-(methoxymethyl)pyrrolidine-1-carboxylate		293
135D	*tert*-Butyl (3R,4S)-3-(isopropylamino)-4-methylpyrrolidine-1-carboxylate		243
136D	*tert*-Butyl (3R,4S)-3-(isopropyl(methyl)amino)-4-methylpyrrolidine-1-carboxylate		257
137D	*tert*-Butyl (3S,4R)-3-(isopropylamino)-4-methoxypyrrolidine-1-carboxylate		259
138D	*tert*-Butyl (3R,4S)-3-(isopropylamino)-4-methoxypyrrolidine-1-carboxylate		259
139D	*tert*-Butyl (3S,4S)-3-(isopropylamino)-4-methoxypyrrolidine-1-carboxylate		259
140D	*tert*-Butyl (3R,4R)-3-(isopropylamino)-4-methoxypyrrolidine-1-carboxylate		259

141D	*tert*-Butyl 3-(hydroxymethyl)-3-(isopropylamino)pyrrolidine-1-carboxylate		259
142D [5]	(1-Benzyl-3-(diethylamino)pyrrolidin-3-yl)methanol, Isomer 1		263
143D [5]	(1-Benzyl-3-(diethylamino)pyrrolidin-3-yl)methanol, Isomer 2		263
144D	*tert*-Butyl 4-((S)-2-((*tert*-butyldimethylsilyl)oxy)propyl)octahydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate		399
145D	*tert*-Butyl 4-((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)octahydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate		399
146D	*tert*-Butyl 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)octahydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate		385
147D	*tert*-Butyl 8-(isopropylamino)-2-oxa-6-azaspiro[3.4]octane-6-carboxylate		271
148D	*tert*-Butyl 8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octane-6-carboxylate		257
149D	*tert*-Butyl 7-methyl-2,7-diazaspiro[4.4]nonane-2-carboxylate		241

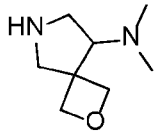
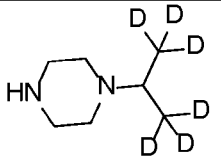
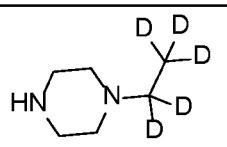
150D	*tert*-Butyl (3S,4S)-3-fluoro-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidine-1-carboxylate		253
151D	*tert*-Butyl (3R,4S)-3-hydroxy-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidine-1-carboxylate		251
152D	*tert*-Butyl (3R,4R)-3-hydroxy-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidine-1-carboxylate		251
153D	*tert*-Butyl (S)-7-((propan-2-yl-1,1,1,3,3,3-d6)amino)-5-azaspiro[2.4]heptane-5-carboxylate		261
154D [6]	*tert*-Butyl (3S,4S)-3-fluoro-4-((propan-2-yl-d7)amino)pyrrolidine-1-carboxylate		254
155D [7]	*tert*-Butyl (3S,4S)-3-amino-4-fluoropyrrolidine-1-carboxylate		205
156D	Benzyl (S)-3-(4-(propan-2-yl-1,1,1,3,3,3-d6)piperazin-1-yl)pyrrolidine-1-carboxylate		338
157D	*tert*-Butyl 4-(propan-2-yl-1,1,1,3,3,3-d6)piperazine-1-carboxylate		235

158D	*tert*-Butyl 4-(ethyl-d5)piperazine-1-carboxylate		220
159D	*tert*-Butyl (3S,4R)-3-(isopropylamino)-4-methylpyrrolidine-1-carboxylate		243

[1] Mix of Trans Isomers
[2] Mix of Cis Isomers
[3] Mix of Trans Isomers
[4] Mix of Cis Isomers
[5] Prep-Chiral-HPLC; Chiralpak-IF, 20 x 250 mm, 5% Hexanes (with 10 mM ammoniated methanol) : 95% EtOH, 20 mL/min
[6] Sodium borodeuteride was used
[7] Impurity contained in Preparation 154D

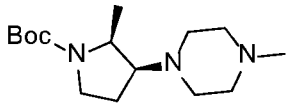
[0311] The following compounds in Table 13 were prepared in similar manner as described in Preparation 122D. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 13:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
160D	N,N-Dimethyl-2-oxa-6-azaspiro[3.4]octan-8-amine		157
161D	1-(Propan-2-yl-1,1,1,3,3,3-d6)piperazine		135
162D	1-(Ethyl-d5)piperazine		120

Preparation 163D

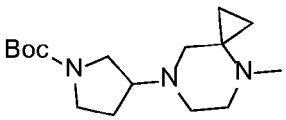
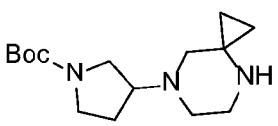
tert-Butyl (2S,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate

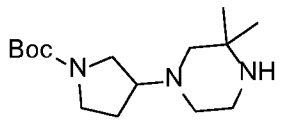
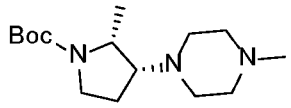
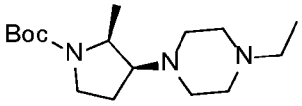
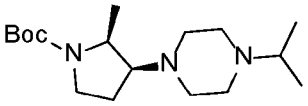
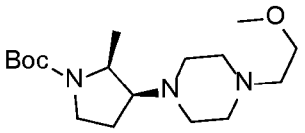
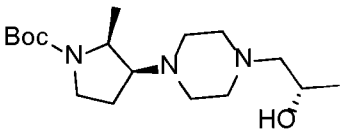
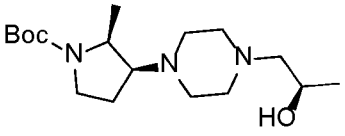


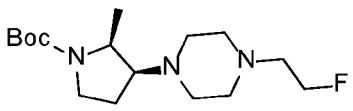
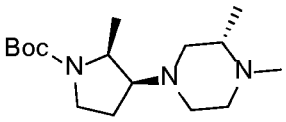
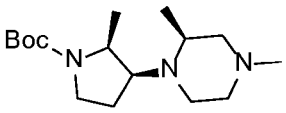
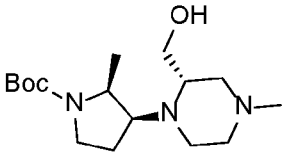
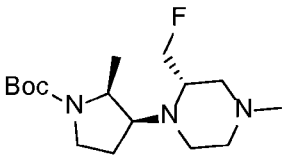
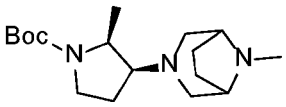
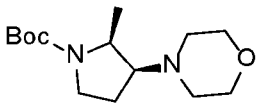
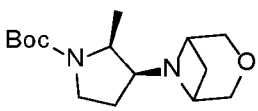
[0312] To a solution of tert-butyl (S)-2-methyl-3-oxopyrrolidine-1-carboxylate (2.20 g, 11.0 mmol), 1-methylpiperazine (1.66 g, 16.6 mmol), and acetic acid (0.63 mL, 11.0 mmol) in DCM (15 mL) was added sodium triacetoxyborohydride (3.74 g, 17.7 mmol) in portions. The mixture was stirred at room temperature. After 28 h, the mixture was cooled to 0 °C and diluted with saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude title compound (3.18 g) as a yellow oil. MS (ES) *m/z*=284 (M+1).

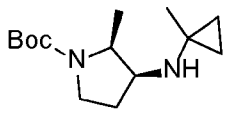
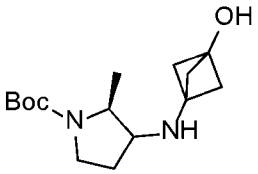
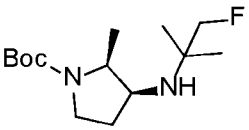
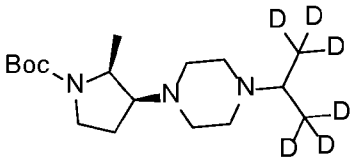
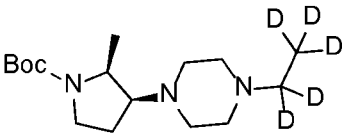
[0313] The following compounds in Table 14 were prepared in similar manner as described in Preparation 163D. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 14:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
164D	tert-Butyl 3-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)pyrrolidine-1-carboxylate		296
165D	tert-Butyl 3-(4,7-diazaspiro[2.5]octan-7-yl)pyrrolidine-1-carboxylate		282

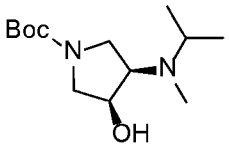
166D	tert-Butyl 3-(3,3-dimethylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
167D	tert-Butyl (2R,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidine-1-carboxylate		284
168D	tert-Butyl (2S,3S)-3-(4-ethylpiperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		298
169D	tert-Butyl (2S,3S)-3-(4-isopropylpiperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		312
170D	tert-Butyl (2S,3S)-3-(4-(2-methoxyethyl)piperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		328
171D	tert-Butyl (2S,3S)-3-(4-((S)-2-hydroxypropyl)piperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		328
172D	tert-Butyl (2S,3S)-3-(4-((R)-2-hydroxypropyl)piperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		328

173D	tert-Butyl (2S,3S)-3-(4-(2-fluoroethyl)piperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		316
174D	tert-Butyl (2S,3S)-3-((S)-3,4-dimethylpiperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		298
175D	tert-Butyl (2S,3S)-3-((S)-2,4-dimethylpiperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		298
176D	tert-Butyl (2S,3S)-3-((S)-2-(hydroxymethyl)-4-methylpiperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		314
177D	tert-Butyl (2S,3S)-3-((S)-2-(fluoromethyl)-4-methylpiperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		316
178D	tert-Butyl (2S,3S)-2-methyl-3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrrolidine-1-carboxylate		310
179D	tert-Butyl (2S,3S)-2-methyl-3-morpholinopyrrolidine-1-carboxylate		271
180D	tert-Butyl (2S,3S)-3-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)-2-methylpyrrolidine-1-carboxylate		283

181D	tert-Butyl (2S,3S)-2-methyl-3-((1-methylcyclopropyl)amino)pyrrolidine-1-carboxylate		255
182D	tert-Butyl (2S)-3-((3-hydroxybicyclo[1.1.1]pentan-1-yl)amino)-2-methylpyrrolidine-1-carboxylate		283
183D	tert-Butyl (2S,3S)-3-((1-fluoro-2-methylpropan-2-yl)amino)-2-methylpyrrolidine-1-carboxylate		275
184D	tert-Butyl (2S,3S)-2-methyl-3-(4-(propan-2-yl-1,1,1,3,3,3-d6)piperazin-1-yl)pyrrolidine-1-carboxylate		318
185D	tert-Butyl (2S,3S)-3-(4-(ethyl-d5)piperazin-1-yl)-2-methylpyrrolidine-1-carboxylate		303

Preparation 186D

tert-Butyl (3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidine-1-carboxylate



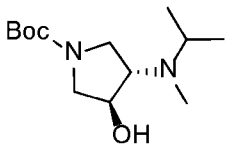
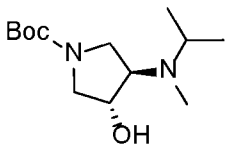
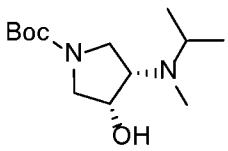
[0314] To a solution of *tert*-butyl (3R,4S)-3-amino-4-hydroxypyrrolidine-1-carboxylate (1.00 g, 4.94 mmol) in acetone (20 mL) was added 20% palladium hydroxide on carbon (0.50 g). The mixture was hydrogenated for 2 h at RT under a hydrogen atmosphere (balloon), then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure to give crude (1.3 g) *tert*-

butyl (3S,4R)-3-hydroxy-4-(isopropylamino)pyrrolidine-1-carboxylate as a gray solid. MS (ES) *m/z*=245 (M+1).

[0315] To a solution of *tert*-butyl (3S,4R)-3-hydroxy-4-(isopropylamino)pyrrolidine-1-carboxylate (1.30 g, 5.32 mmol) and $(HCHO)_n$ (0.32 g, 10.6 mmol) in methanol (20 mL) was added 20% palladium hydroxide on carbon (0.75 g). The mixture was hydrogenated for 2 h at RT under a hydrogen atmosphere (balloon), then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure and the residue was diluted with EtOAc (100 mL). The resulting mixture was washed with saturated aqueous sodium carbonate (50 mL), water (2 x 50 mL), and brine (50 mL). The organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (1.1 g) as a yellow oil. MS (ES) *m/z*=259 (M+1).

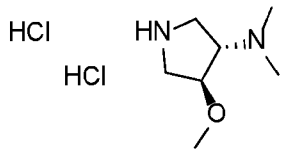
[0316] The following compounds in Table 15 were prepared in similar manner as described in Preparation 186D. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 15:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
187D	*tert*-Butyl (3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidine-1-carboxylate		259
188D	*tert*-Butyl (3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidine-1-carboxylate		259
189D	*tert*-Butyl (3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidine-1-carboxylate		259

Preparation 54B

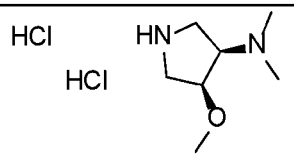
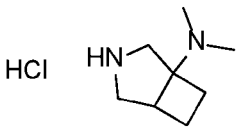
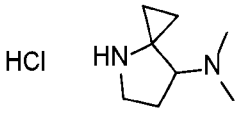
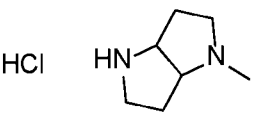
(3S,4S)-4-Methoxy-N,N-dimethylpyrrolidin-3-amine dihydrochloride

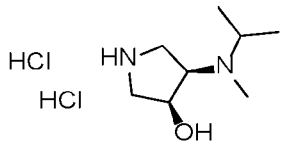
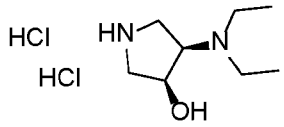
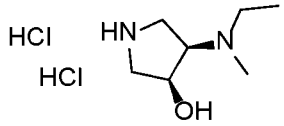
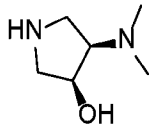
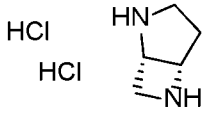
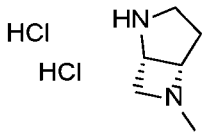
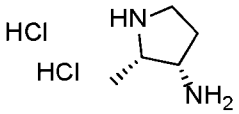
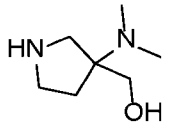
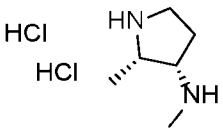
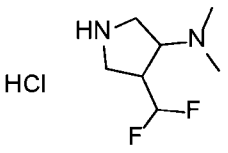


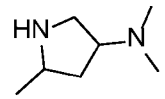
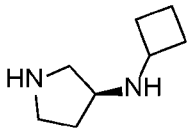
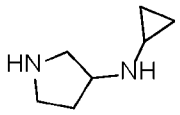
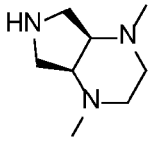
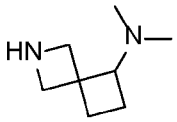
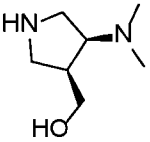
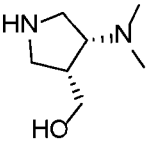
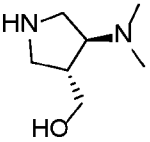
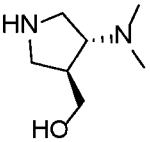
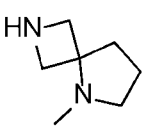
[0317] To a solution of *tert*-butyl (3S,4S)-3-(dimethylamino)-4-methoxypyrrolidine-1-carboxylate (0.53 g, 2.17 mmol) in DCM (6 mL) was added HCl (4M in 1,4-dioxane; 4 mL, 16.0 mmol). The reaction mixture was stirred for 18 h at RT, then concentrated under reduced pressure. The residue was diluted with DCM and concentrated under reduced pressure (3 cycles) to obtain the crude title compound (0.48 g, quant) as a yellow solid. MS (ES) *m/z*=145 (M+1).

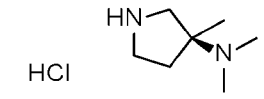
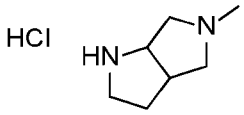
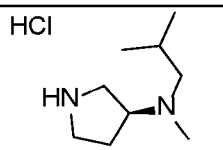
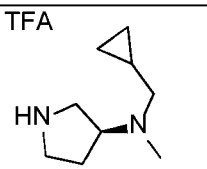
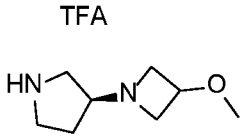
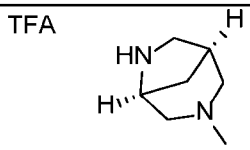
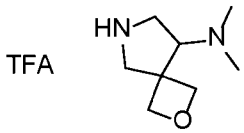
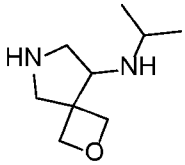
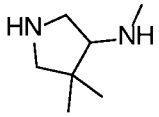
[0318] The following compounds in Table 16 were prepared in similar manner as described in Preparation 54B. In some instances, TFA was substituted for HCl. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

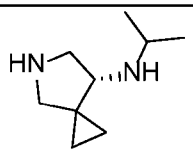
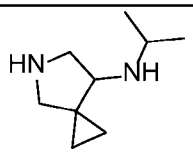
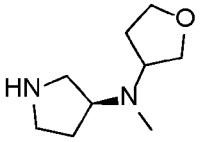
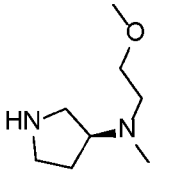
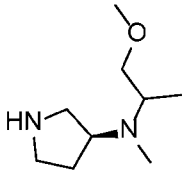
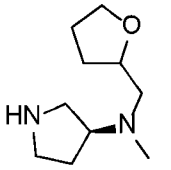
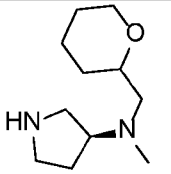
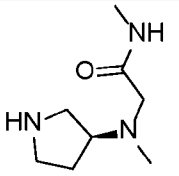
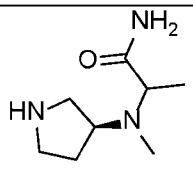
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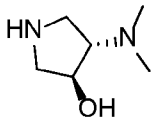
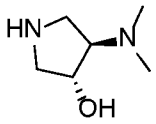
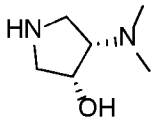
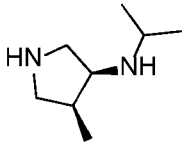
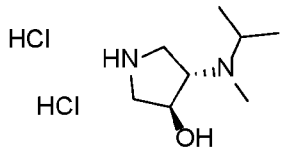
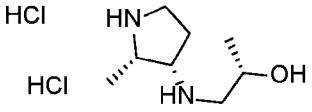
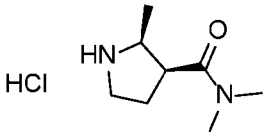
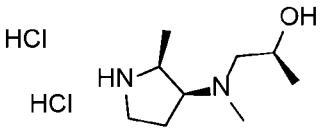
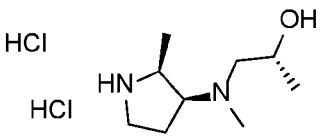
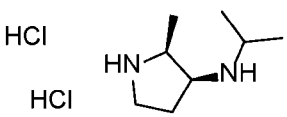
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
55B	(3R,4S)-4-Methoxy-N,N-dimethylpyrrolidin-3-amine dihydrochloride		145
56B	N,N-Dimethyl-3-azabicyclo[3.2.0]heptan-1-amine hydrochloride		
57B	N,N-Dimethyl-4-azaspiro[2.4]heptan-7-amine hydrochloride		141
58B	1-Methyloctahydropyrrolo[3,2-b]pyrrole hydrochloride		127

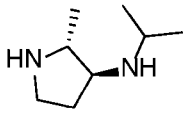
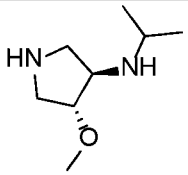
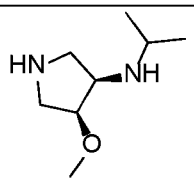
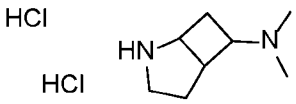
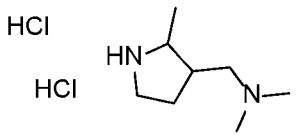
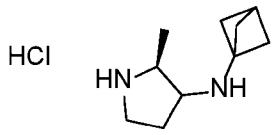
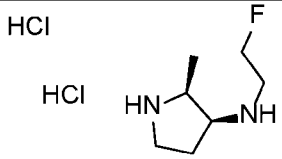
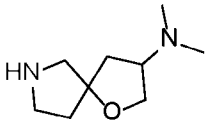
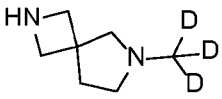
59B	(3S,4R)-4-(Isopropyl(methyl)amino)pyrrolidin-3-ol dihyrdrochloride		
60B	(3S,4R)-4-(Diethylamino)pyrrolidin-3-ol dihydrochloride		159
61B	(3S,4R)-4-(Ethyl(methyl)amino)pyrrolidin-3-ol dihydrochoride		145
62B	(3S,4R)-4-(Dimethylamino)pyrrolidin-3-ol		131
63B	(1S,5S)-2,6-Diazabicyclo[3.2.0]heptane dihydrochloride		
64B	(1S,5S)-6-Methyl-2,6-diazabicyclo[3.2.0]heptane dihydrochloride		113
65B	(2S,3S)-2-Methylpyrrolidin-3-amine dihydrochloride		101
66B	(3-(Dimethylamino)pyrrolidin-3-yl)methanol		
67B	(2S,3S)-N,2-Dimethylpyrrolidin-3-amine dihydrochloride		115
68B	4-(Difluoromethyl)-N,N-dimethylpyrrolidin-3-amine hydrochloride, Mix of Trans Isomers		165

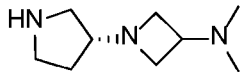
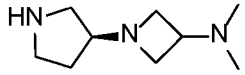
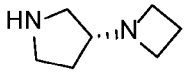
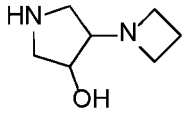
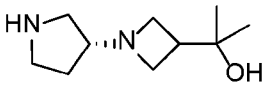
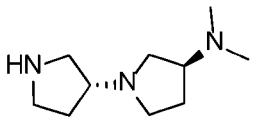
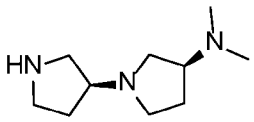
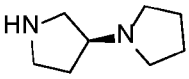
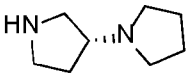
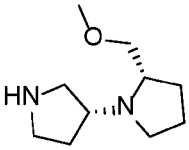
69B	N,N,5-trimethylpyrrolidin-3-amine trifluoroacetic acid	TFA 	129
70B	(S)-N-Cyclobutylpyrrolidin-3-amine dihydrochloride	HCl HCl 	141
71B	N-Cyclopropylpyrrolidin-3-amine dihydrochloride	HCl HCl 	127
72B	(4aR,7aS)-1,4-Dimethyloctahydro-1H-pyrrolo[3,4-b]pyrazine dihydrochloride	HCl HCl 	156
73B	N,N-Dimethyl-2-azaspiro[3.3]heptan-5-amine dihydrochloride	HCl HCl 	141
74B	((3S,4S)-4-(Dimethylamino)pyrrolidin-3-yl)methanol hydrochloride	HCl 	
75B	((3R,4R)-4-(Dimethylamino)pyrrolidin-3-yl)methanol hydrochloride	HCl 	
76B	((3R,4S)-4-(Dimethylamino)pyrrolidin-3-yl)methanol hydrochloride	HCl 	
77B	((3S,4R)-4-(Dimethylamino)pyrrolidin-3-yl)methanol hydrochloride	HCl 	
78B	5-Methyl-2,5-diazaspiro[3.4]octane dihydrochloride	HCl HCl 	127

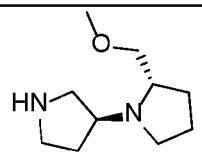
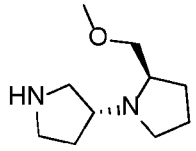
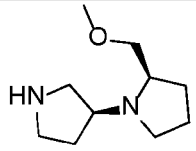
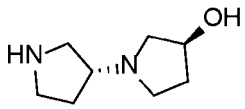
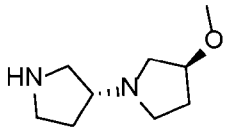
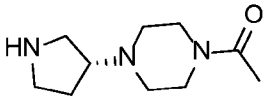
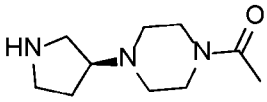
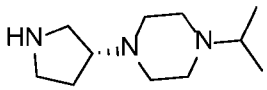
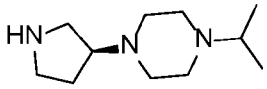
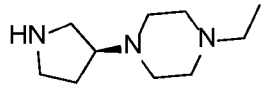
79B	(S)-N,N,3-Trimethylpyrrolidin-3-amine hydrochloride		129
80B	5-Methyloctahydropyrrolo[3,4-b]pyrrole hydrochloride, Mix of Cis Isomers		
39C	(S)-N-Isobutyl-N-methylpyrrolidin-3-amine hydrochloride		157
40C	(S)-N-(Cyclopropylmethyl)-N-methylpyrrolidin-3-amine trifluoroacetic acid		155
41C	(S)-3-(3-Methoxyazetidin-1-yl)pyrrolidine trifluoroacetic acid		157
42C	(1S,5S)-3-Methyl-3,6-diazabicyclo[3.2.1]octane trifluoroacetic acid		127
43C	N,N-Dimethyl-2-oxa-6-azaspiro[3.4]octan-8-amine trifluoroacetic acid		157
44C	N-Isopropyl-2-oxa-6-azaspiro[3.4]octan-8-amine		171
45C	N,4,4-Trimethylpyrrolidin-3-amine		129

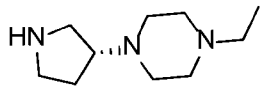
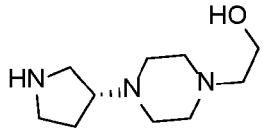
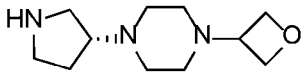
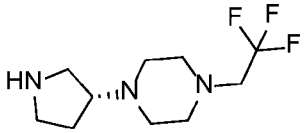
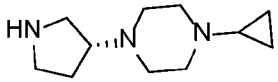
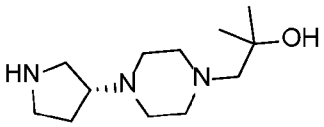
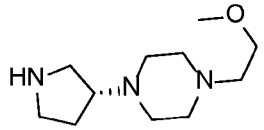
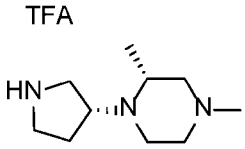
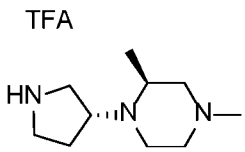
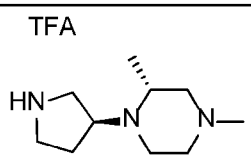
46C	(R)-N-Isopropyl-5-azaspiro[2.4]heptan-7-amine		155
47C	N-Isopropyl-5-azaspiro[2.4]heptan-7-amine		155
48C	(3S)-N-Methyl-N-(tetrahydrofuran-3-yl)pyrrolidin-3-amine		171
49C	(S)-N-(2-Methoxyethyl)-N-methylpyrrolidin-3-amine		159
50C	(3S)-N-(1-Methoxypropan-2-yl)-N-methylpyrrolidin-3-amine		173
51C	(3S)-N-Methyl-N-((tetrahydrofuran-2-yl)methyl)pyrrolidin-3-amine		185
52C	(3S)-N-Methyl-N-((tetrahydro-2H-pyran-2-yl)methyl)pyrrolidin-3-amine		199
53C	(S)-N-Methyl-2-(methyl(pyrrolidin-3-yl)amino)acetamide		172
54C	2-(Methyl((S)-pyrrolidin-3-yl)amino)propanamide		172

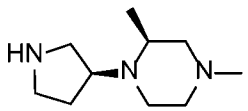
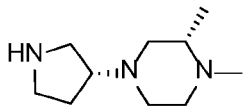
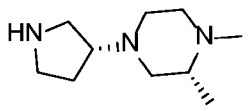
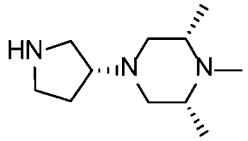
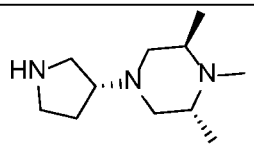
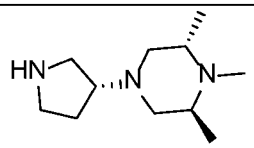
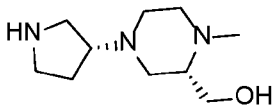
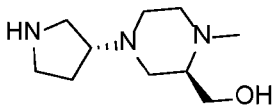
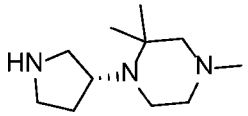
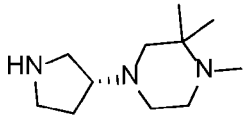
55C	(3S,4S)-4-(Dimethylamino)pyrrolidin-3-ol		131
56C	(3R,4R)-4-(Dimethylamino)pyrrolidin-3-ol		131
57C	(3R,4S)-4-(Dimethylamino)pyrrolidin-3-ol		131
58C	(3S,4S)-N-Isopropyl-4-methylpyrrolidin-3-amine		143
59C	(3S,4S)-4-(Isopropyl(methyl)amino)pyrrolidin-3-ol dihydrochloride		159
60C	(S)-1-(((2S,3S)-2-Methylpyrrolidin-3-yl)amino)propan-2-ol dihydrochloride		159
61C	(2S,3S)-N,N,2-Trimethylpyrrolidine-3-carboxamide hydrochloride		157
62C	(S)-1-(Methyl((2S,3S)-2-methylpyrrolidin-3-yl)amino)propan-2-ol dihydrochloride		173
63C	(R)-1-(Methyl((2S,3S)-2-methylpyrrolidin-3-yl)amino)propan-2-ol dihydrochloride		173
64C	(2S,3S)-N-Isopropyl-2-methylpyrrolidin-3-amine dihydrochloride		143

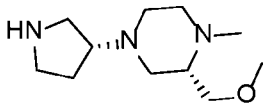
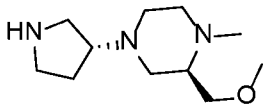
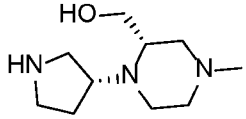
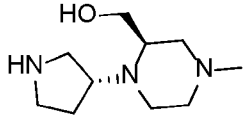
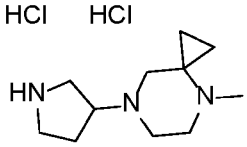
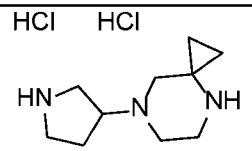
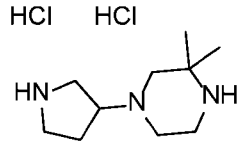
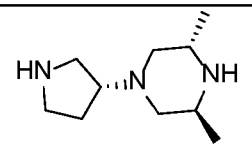
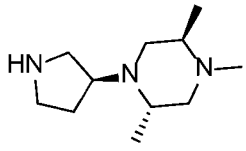
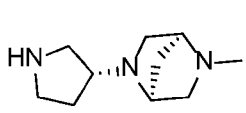
65C	(2R,3S)-N-Isopropyl-2-methylpyrrolidin-3-amine		
66C	(3R,4R)-N-Isopropyl-4-methoxypyrrolidin-3-amine		
67C	(3R,4S)-N-Isopropyl-4-methoxypyrrolidin-3-amine		
68C	N,N-Dimethyl-2-azabicyclo[3.2.0]heptan-6-amine dihydrochloride		141
69C	N,N-Dimethyl-1-(2-methylpyrrolidin-3-yl)methanamine dihydrochloride, Mix of Cis Isomers		143
70C	(2S)-N-(Bicyclo[1.1.1]pentan-1-yl)-2-methylpyrrolidin-3-amine hydrochloride		167
71C	(2S,3S)-N-(2-Fluoroethyl)-2-methylpyrrolidin-3-amine dihydrochloride		147
190D	N,N-Dimethyl-1-oxa-7-azaspiro[4.4]nonan-3-amine		171
191D	6-(Methyl-d3)-2,6-diazaspiro[3.4]octane		130

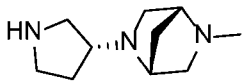
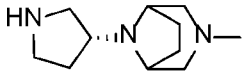
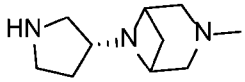
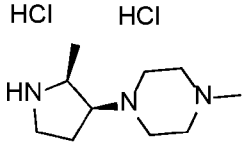
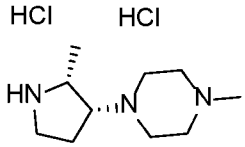
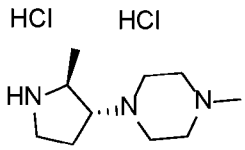
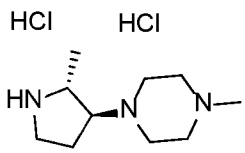
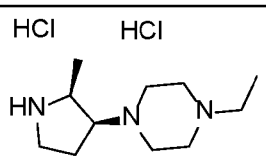
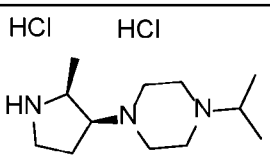
192D	(R)-N,N-Dimethyl-1-(pyrrolidin-3-yl)azetidin-3-amine		170
193D	(S)-N,N-Dimethyl-1-(pyrrolidin-3-yl)azetidin-3-amine		170
194D	(R)-3-(Azetidin-1-yl)pyrrolidine		127
195D [1]	4-(Azetidin-1-yl)pyrrolidin-3-ol		143
196D	(R)-2-(1-(Pyrrolidin-3-yl)azetidin-3-yl)propan-2-ol		185
197D	(3S,3'R)-N,N-Dimethyl-[1,3'-bipyrrolidin]-3-amine		184
198D	(3S,3'S)-N,N-Dimethyl-[1,3'-bipyrrolidin]-3-amine		184
199D	(S)-1,3'-Bipyrrolidine		141
200D	(R)-1,3'-Bipyrrolidine		141
201D	(2S,3'R)-2-(Methoxymethyl)-1,3'-bipyrrolidine		185

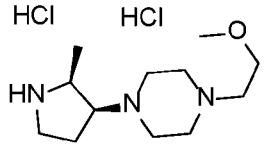
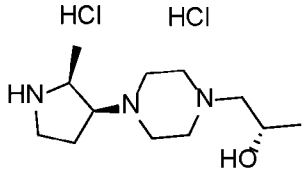
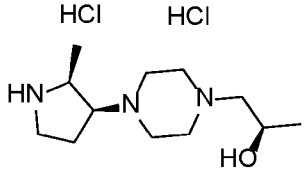
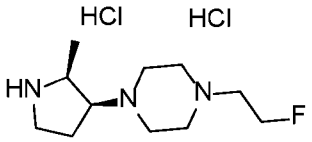
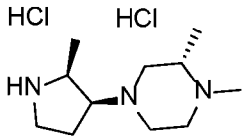
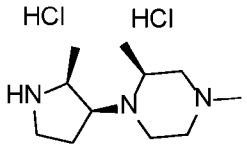
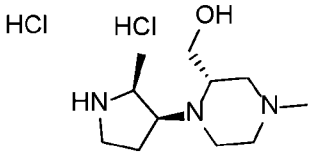
202D	(2S,3'S)-2-(Methoxymethyl)-1,3'-bipyrrolidine		185
203D	(2R,3'R)-2-(Methoxymethyl)-1,3'-bipyrrolidine		185
204D	(2R,3'S)-2-(Methoxymethyl)-1,3'-bipyrrolidine		185
205D	(3S,3'R)-[1,3'-Bipyrrolidin]-3-ol		157
206D	(3S,3'R)-3-Methoxy-1,3'-bipyrrolidine		171
207D	(R)-1-(4-(Pyrrolidin-3-yl)piperazin-1-yl)ethan-1-one bistrifluoroacetic acid	TFA TFA 	198
208D	(S)-1-(4-(Pyrrolidin-3-yl)piperazin-1-yl)ethan-1-one		198
209D	(R)-1-Isopropyl-4-(pyrrolidin-3-yl)piperazine		198
210D	(S)-1-Isopropyl-4-(pyrrolidin-3-yl)piperazine		198
211D	(S)-1-ethyl-4-(Pyrrolidin-3-yl)piperazine		184

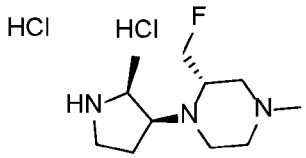
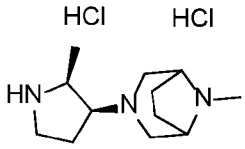
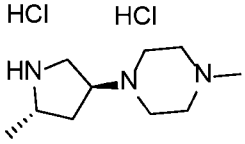
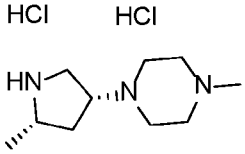
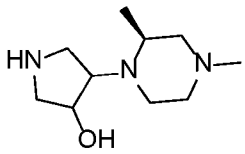
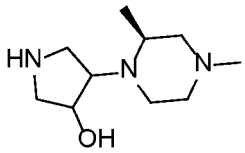
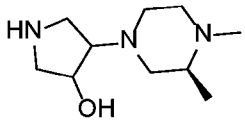
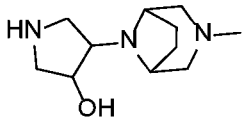
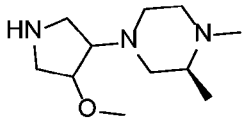
212D	(R)-1-ethyl-4-(Pyrrolidin-3-yl)piperazine		184
213D	(R)-2-(4-(Pyrrolidin-3-yl)piperazin-1-yl)ethan-1-ol		200
214D	(R)-1-(Oxetan-3-yl)-4-(pyrrolidin-3-yl)piperazine		212
215D	(R)-1-(Pyrrolidin-3-yl)-4-(2,2,2-trifluoroethyl)piperazine		238
216D	(R)-1-Cyclopropyl-4-(pyrrolidin-3-yl)piperazine		196
217D	(R)-2-Methyl-1-(4-(pyrrolidin-3-yl)piperazin-1-yl)propan-2-ol		228
218D	(R)-1-(2-Methoxyethyl)-4-(pyrrolidin-3-yl)piperazine		214
219D	(R)-2,4-Dimethyl-1-((R)-pyrrolidin-3-yl)piperazine trifluoroacetic acid		184
220D	(S)-2,4-Dimethyl-1-((R)-pyrrolidin-3-yl)piperazine trifluoroacetic acid		184
221D	(R)-2,4-Dimethyl-1-((S)-pyrrolidin-3-yl)piperazine trifluoroacetic acid		184

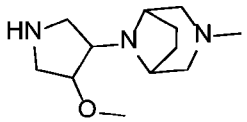
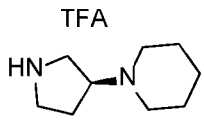
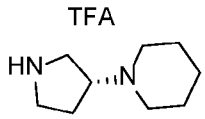
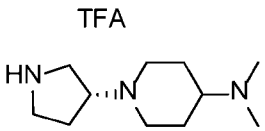
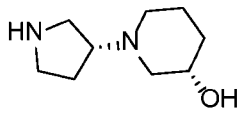
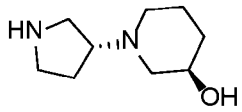
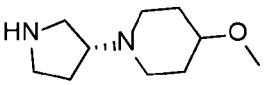
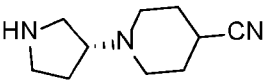
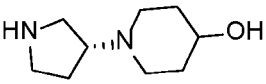
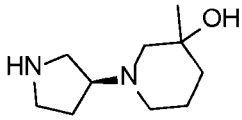
222D	(S)-2,4-Dimethyl-1-((S)-pyrrolidin-3-yl)piperazine		184
223D	(S)-1,2-Dimethyl-4-((R)-pyrrolidin-3-yl)piperazine		184
224D	(R)-1,2-Dimethyl-4-((R)-pyrrolidin-3-yl)piperazine		184
225D	(2R,6S)-1,2,6-Trimethyl-4-((R)-pyrrolidin-3-yl)piperazine		198
226D	(2R,6R)-1,2,6-Trimethyl-4-((R)-pyrrolidin-3-yl)piperazine		198
227D	(2S,6S)-1,2,6-Trimethyl-4-((R)-pyrrolidin-3-yl)piperazine		198
228D	((S)-1-Methyl-4-((R)-pyrrolidin-3-yl)piperazin-2-yl)methanol		200
229D	((R)-1-Methyl-4-((R)-pyrrolidin-3-yl)piperazin-2-yl)methanol		200
230D	(R)-2,2,4-Trimethyl-1-(pyrrolidin-3-yl)piperazine		198
231D	(R)-1,2,2-Trimethyl-4-(pyrrolidin-3-yl)piperazine		198

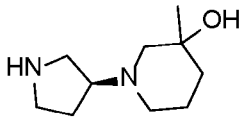
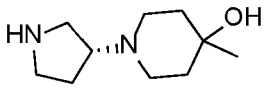
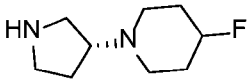
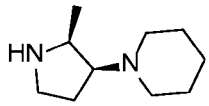
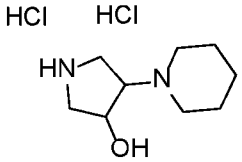
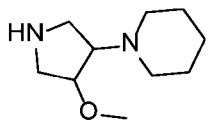
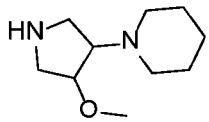
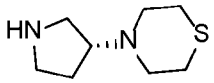
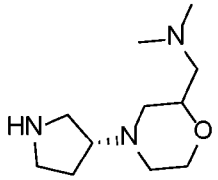
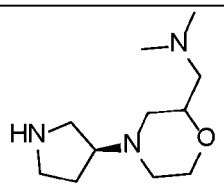
232D	(S)-2-(Methoxymethyl)-1-methyl-4-((R)-pyrrolidin-3-yl)piperazine		214
233D	(R)-2-(Methoxymethyl)-1-methyl-4-((R)-pyrrolidin-3-yl)piperazine		214
234D	((S)-4-Methyl-1-((R)-pyrrolidin-3-yl)piperazin-2-yl)methanol		200
235D	((R)-4-Methyl-1-((R)-pyrrolidin-3-yl)piperazin-2-yl)methanol		200
236D	4-Methyl-7-(pyrrolidin-3-yl)-4,7-diazaspiro[2.5]octane dihydrochloride		196
237D	7-(Pyrrolidin-3-yl)-4,7-diazaspiro[2.5]octane dihydrochloride		182
238D	3,3-Dimethyl-1-(pyrrolidin-3-yl)piperazine dihydrochloride		184
239D	(3S,5S)-3,5-Dimethyl-1-((R)-pyrrolidin-3-yl)piperazine		184
240D	(2R,5S)-1,2,5-Trimethyl-4-((S)-pyrrolidin-3-yl)piperazine		198
241D	(1S,4S)-2-Methyl-5-((R)-pyrrolidin-3-yl)-2,5-diazabicyclo[2.2.1]heptane		182

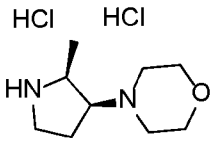
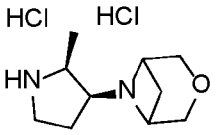
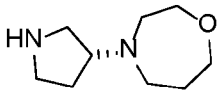
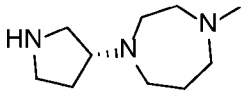
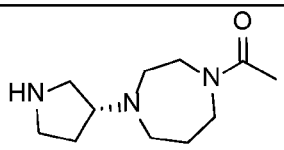
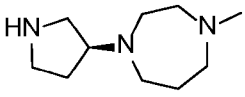
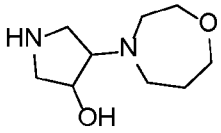
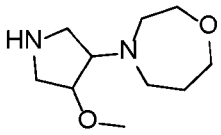
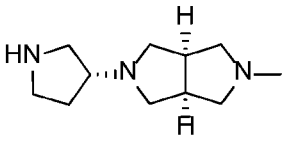
242D	(1R,4R)-2-Methyl-5-((R)-pyrrolidin-3-yl)-2,5-diazabicyclo[2.2.1]heptane		182
243D	3-Methyl-8-((R)-pyrrolidin-3-yl)-3,8-diazabicyclo[3.2.1]octane		196
244D	3-Methyl-6-((R)-pyrrolidin-3-yl)-3,6-diazabicyclo[3.1.1]heptane		182
245D	1-Methyl-4-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		184
246D	1-Methyl-4-((2R,3R)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		184
247D	1-Methyl-4-((2S,3R)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		184
248D	1-Methyl-4-((2R,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		184
249D	1-Ethyl-4-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		198
250D	1-Isopropyl-4-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		212

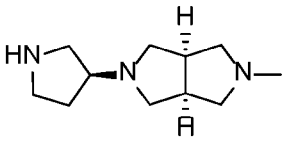
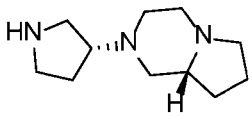
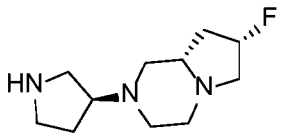
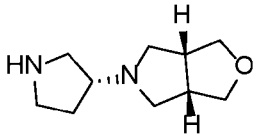
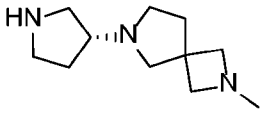
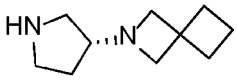
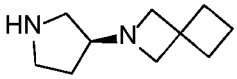
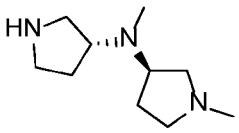
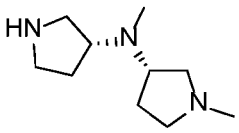
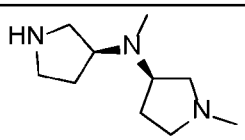
251D	1-(2-Methoxyethyl)-4-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		228
252D	(S)-1-(4-((2S,3S)-2-Methylpyrrolidin-3-yl)piperazin-1-yl)propan-2-ol dihydrochloride		228
253D	(R)-1-(4-((2S,3S)-2-Methylpyrrolidin-3-yl)piperazin-1-yl)propan-2-ol dihydrochloride		228
254D	1-(2-Fluoroethyl)-4-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		216
255D	(S)-1,2-Dimethyl-4-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		198
256D	(S)-2,4-Dimethyl-1-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		198
257D	((S)-4-Methyl-1-((2S,3S)-2-methylpyrrolidin-3-yl)piperazin-2-yl)methanol dihydrochloride		214

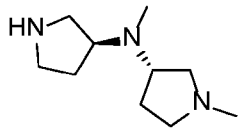
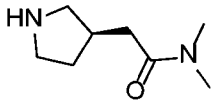
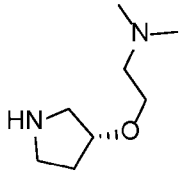
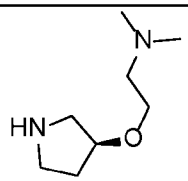
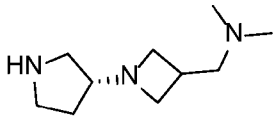
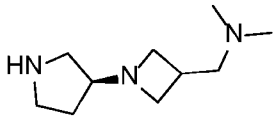
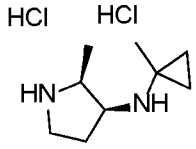
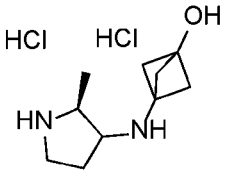
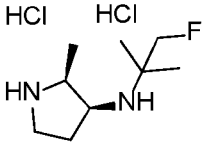
258D	(S)-2-(Fluoromethyl)-4-methyl-1-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		216
259D	8-methyl-3-((2S,3S)-2-Methylpyrrolidin-3-yl)-3,8-diazabicyclo[3.2.1]octane dihydrochloride		210
260D	1-methyl-4-((3S,5S)-5-Methylpyrrolidin-3-yl)piperazine dihydrochloride		184
261D	1-methyl-4-((3R,5S)-5-Methylpyrrolidin-3-yl)piperazine dihydrochloride		184
262D [2]	4-((S)-2,4-Dimethylpiperazin-1-yl)pyrrolidin-3-ol, Isomer 2		200
263D [2]	4-((S)-2,4-Dimethylpiperazin-1-yl)pyrrolidin-3-ol, Isomer 1		200
264D [3]	4-((S)-3,4-Dimethylpiperazin-1-yl)pyrrolidin-3-ol		200
265D [4]	4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-3-ol		212
266D [5]	(2S)-4-(4-Methoxypyrrolidin-3-yl)-1,2-dimethylpiperazine		214

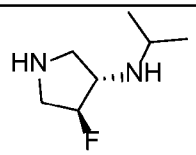
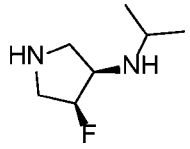
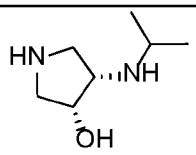
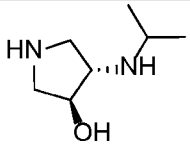
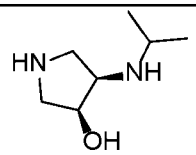
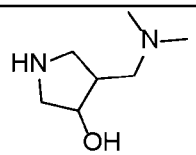
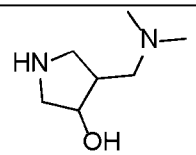
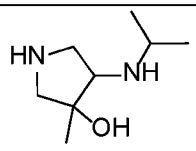
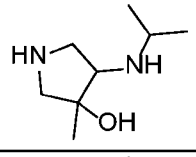
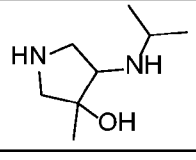
267D [6]	8-(4-Methoxypyrrolidin-3-yl)-3-methyl-3,8-diazabicyclo[3.2.1]octane		226
268D	(S)-1-(Pyrrolidin-3-yl)piperidine trifluoroacetic acid		155
269D	(R)-1-(Pyrrolidin-3-yl)piperidine trifluoroacetic acid		155
270D	(R)-N,N-Dimethyl-1-(pyrrolidin-3-yl)piperidin-4-amine trifluoroacetic acid		198
271D	(S)-1-((R)-Pyrrolidin-3-yl)piperidin-3-ol		171
272D	(R)-1-((R)-Pyrrolidin-3-yl)piperidin-3-ol		171
273D	(R)-4-Methoxy-1-(pyrrolidin-3-yl)piperidine		185
274D	(R)-1-(Pyrrolidin-3-yl)piperidine-4-carbonitrile		180
275D	(R)-1-(Pyrrolidin-3-yl)piperidin-4-ol		171
276D [7]	3-Methyl-1-((S)-pyrrolidin-3-yl)piperidin-3-ol, Isomer 1		185

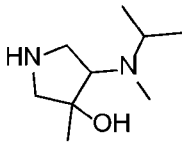
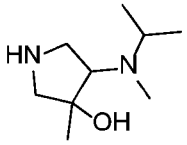
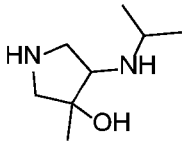
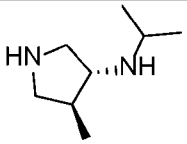
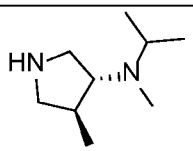
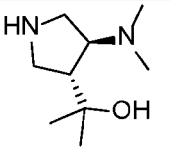
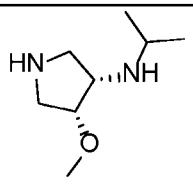
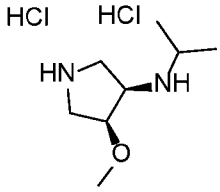
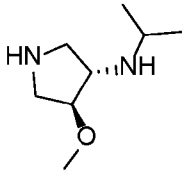
277D [7]	3-Methyl-1-((S)-pyrrolidin-3-yl)piperidin-3-ol, Isomer 2		185
278D	(R)-4-Methyl-1-(pyrrolidin-3-yl)piperidin-4-ol		185
279D	(R)-4-Fluoro-1-(pyrrolidin-3-yl)piperidine		173
280D	1-((2S,3S)-2-Methylpyrrolidin-3-yl)piperidine		169
281D [8]	4-(Piperidin-1-yl)pyrrolidin-3-ol dihydrochloride		171
282D [9]	1-(4-Methoxypyrrolidin-3-yl)piperidine, Isomer 1		185
283D [9]	1-(4-Methoxypyrrolidin-3-yl)piperidine, Isomer 2		185
284D	(R)-4-(Pyrrolidin-3-yl)thiomorpholine		173
285D	N,N-Dimethyl-1-(4-((R)-pyrrolidin-3-yl)morpholin-2-yl)methanamine		214
286D	N,N-Dimethyl-1-(4-((S)-pyrrolidin-3-yl)morpholin-2-yl)methanamine		214

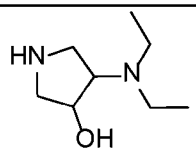
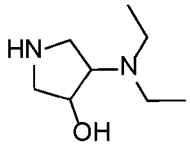
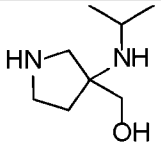
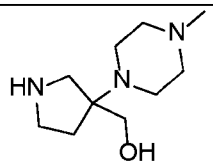
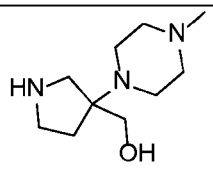
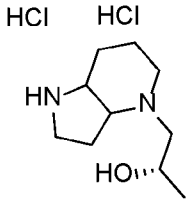
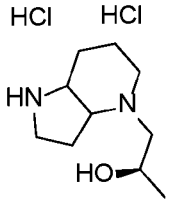
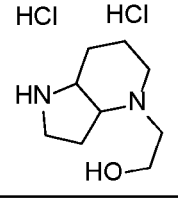
287D	4-((2S,3S)-2-Methylpyrrolidin-3-yl)morpholine dihydrochloride		171
288D	6-((2S,3S)-2-Methylpyrrolidin-3-yl)-3-oxa-6-azabicyclo[3.1.1]heptane dihydrochloride		183
289D	(R)-4-(Pyrrolidin-3-yl)-1,4-oxazepane		171
290D	(R)-1-Methyl-4-(pyrrolidin-3-yl)-1,4-diazepane		184
291D	(R)-1-(4-(Pyrrolidin-3-yl)-1,4-diazepan-1-yl)ethan-1-one		212
292D	(S)-1-Methyl-4-(pyrrolidin-3-yl)-1,4-diazepane		184
293D [10]	4-(1,4-Oxazepan-4-yl)pyrrolidin-3-ol		187
294D [11]	4-(4-Methoxypyrrolidin-3-yl)-1,4-oxazepane		201
295D	(3aR,6aS)-2-Methyl-5-((R)-pyrrolidin-3-yl)octahydropyrrolo[3,4-c]pyrrole		196

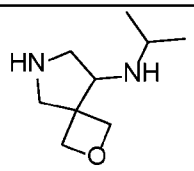
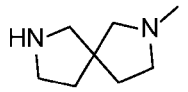
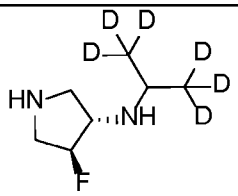
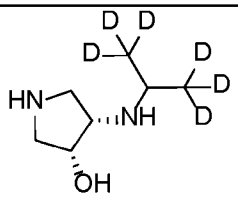
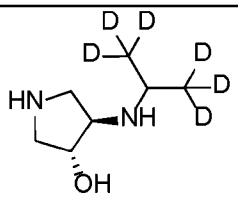
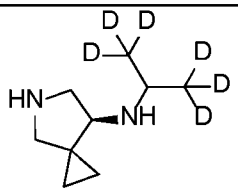
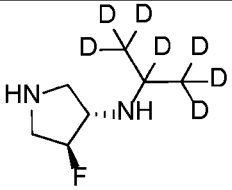
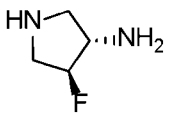
296D	(3aR,6aS)-2-Methyl-5-((S)-pyrrolidin-3-yl)octahydropyrrolo[3,4-c]pyrrole		196
297D	(R)-2-((R)-Pyrrolidin-3-yl)octahydropyrrolo[1,2-a]pyrazine		196
298D	(7S,8aS)-7-Fluoro-2-((S)-pyrrolidin-3-yl)octahydropyrrolo[1,2-a]pyrazine		214
299D	(3aR,6aS)-5-((R)-Pyrrolidin-3-yl)hexahydro-1H-furo[3,4-c]pyrrole		183
300D	(R)-2-Methyl-6-(pyrrolidin-3-yl)-2,6-diazaspiro[3.4]octane		196
301D	(R)-2-(Pyrrolidin-3-yl)-2-azaspiro[3.3]heptane		167
302D	(S)-2-(Pyrrolidin-3-yl)-2-azaspiro[3.3]heptane		167
303D	(R)-N,1-Dimethyl-N-((R)-pyrrolidin-3-yl)pyrrolidin-3-amine		184
304D	(S)-N,1-Dimethyl-N-((R)-pyrrolidin-3-yl)pyrrolidin-3-amine		184
305D	(R)-N,1-Dimethyl-N-((S)-pyrrolidin-3-yl)pyrrolidin-3-amine		184

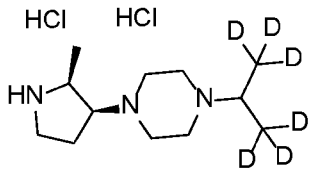
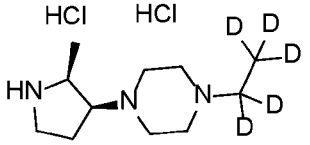
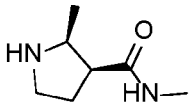
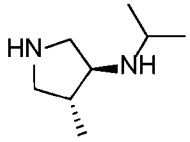
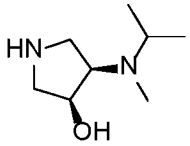
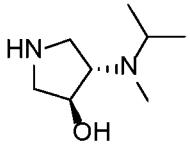
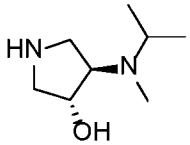
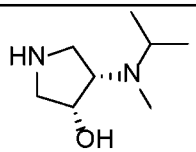
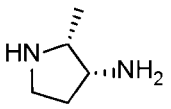
306D	(S)-N,1-Dimethyl-N-((S)-pyrrolidin-3-yl)pyrrolidin-3-amine		184
307D	(R)-N,N-Dimethyl-2-(pyrrolidin-3-yl)acetamide		157
308D	(R)-N,N-Dimethyl-2-(pyrrolidin-3-yloxy)ethan-1-amine		159
309D	(S)-N,N-Dimethyl-2-(pyrrolidin-3-yloxy)ethan-1-amine		159
310D	(R)-N,N-Dimethyl-1-(1-(pyrrolidin-3-yl)azetidin-3-yl)methanamine		184
311D	(S)-N,N-Dimethyl-1-(1-(pyrrolidin-3-yl)azetidin-3-yl)methanamine		184
312D	(2S,3S)-2-Methyl-N-(1-methylcyclopropyl)pyrrolidin-3-amine dihydrochloride		155
313D	3-(((2S)-2-Methylpyrrolidin-3-yl)amino)bicyclo[1.1.1]pentan-1-ol dihydrochloride		183
314D	(2S,3S)-N-(1-Fluoro-2-methylpropan-2-yl)-2-methylpyrrolidin-3-amine dihydrochloride		175

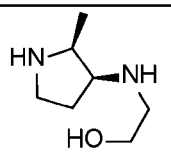
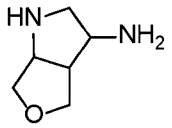
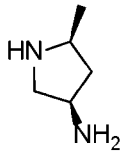
315D	(3S,4S)-4-Fluoro-N-isopropylpyrrolidin-3-amine		147
316D	(3R,4S)-4-Fluoro-N-isopropylpyrrolidin-3-amine		147
317D	(3R,4S)-4-(Isopropylamino)pyrrolidin-3-ol		145
318D	(3S,4S)-4-(Isopropylamino)pyrrolidin-3-ol		145
319D	(3S,4R)-4-(Isopropylamino)pyrrolidin-3-ol		145
320D [12]	4-((Dimethylamino)methyl)pyrrolidin-3-ol		145
321D [13]	4-((Dimethylamino)methyl)pyrrolidin-3-ol		145
322D [14]	4-(Isopropylamino)-3-methylpyrrolidin-3-ol		159
323D [15]	4-(Isopropylamino)-3-methylpyrrolidin-3-ol, Isomer 1		159
324D [15]	4-(Isopropylamino)-3-methylpyrrolidin-3-ol, Isomer 2		159

325D [16]	4-(Isopropyl(methyl)amino)-3-methylpyrrolidin-3-ol, Isomer 1		173
326D [16]	4-(Isopropyl(methyl)amino)-3-methylpyrrolidin-3-ol, Isomer 2		173
327D [17]	4-(Isopropylamino)-3-methylpyrrolidin-3-ol		173
328D	(3R,4S)-N-Isopropyl-4-methylpyrrolidin-3-amine		143
329D	(3R,4S)-N-Isopropyl-N,4-dimethylpyrrolidin-3-amine		157
330D	2-((3R,4S)-4-(Dimethylamino)pyrrolidin-3-yl)propan-2-ol		173
331D	(3S,4R)-N-Isopropyl-4-methoxypyrrolidin-3-amine		159
332D	(3R,4S)-N-Isopropyl-4-methoxypyrrolidin-3-amine dihydrochloride		159
333D	(3S,4S)-N-Isopropyl-4-methoxypyrrolidin-3-amine		159

334D [18]	4-(Diethylamino)pyrrolidin-3-ol, Isomer 1		159
335D [18]	4-(Diethylamino)pyrrolidin-3-ol, Isomer 2		159
336D	(3-(Isopropylamino)pyrrolidin-3-yl)methanol		159
337D	(3-(4-Methylpiperazin-1-yl)pyrrolidin-3-yl)methanol, Isomer 1		200
338D	(3-(4-Methylpiperazin-1-yl)pyrrolidin-3-yl)methanol, Isomer 2		200
339D	(2S)-1-(Octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)propan-2-ol dihydrochloride		185
340D	(2R)-1-(Octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)propan-2-ol dihydrochloride		185
341D	2-(Octahydro-4H-pyrrolo[3,2-b]pyridin-4-yl)ethan-1-ol dihydrochloride		171

342D	N-Isopropyl-2-oxa-6-azaspiro[3.4]octan-8-amine		171
343D	2-Methyl-2,7-diazaspiro[4.4]nonane		141
344D	(3S,4S)-4-Fluoro-N-(propan-2-yl-1,1,1,3,3,3-d6)pyrrolidin-3-amine		153
345D	(3R,4S)-4-((Propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-3-ol		151
346D	(3R,4R)-4-((Propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-3-ol		151
347D	(S)-N-(Propan-2-yl-1,1,1,3,3,3-d6)-5-azaspiro[2.4]heptan-7-amine		161
348D	(3S,4S)-4-Fluoro-N-(propan-2-yl-d7)pyrrolidin-3-amine		154
349D [19]	(3S,4S)-4-Fluoropyrrolidin-3-amine		

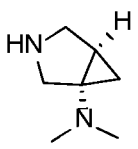
350D	1-((2S,3S)-2-Methylpyrrolidin-3-yl)-4-(propan-2-yl-1,1,1,3,3,3-d6)piperazine dihydrochloride		218
351D	1-(Ethyl-d5)-4-((2S,3S)-2-methylpyrrolidin-3-yl)piperazine dihydrochloride		203
352D	(2S,3S)-N,2-Dimethylpyrrolidine-3-carboxamide		143
353D	(3S,4R)-N-Isopropyl-4-methylpyrrolidin-3-amine		143
354D	(3S,4R)-4-(Isopropyl(methyl)amino)pyrrolidin-3-ol		159
355D	(3S,4S)-4-(Isopropyl(methyl)amino)pyrrolidin-3-ol		159
356D	(3R,4R)-4-(Isopropyl(methyl)amino)pyrrolidin-3-ol		159
357D	(3R,4S)-4-(Isopropyl(methyl)amino)pyrrolidin-3-ol		159
358D	(2R,3R)-2-Methylpyrrolidin-3-amine		101

359D	2-(((2S,3S)-2-Methylpyrrolidin-3-yl)amino)ethan-1-ol		145
360D	Hexahydro-1H-furo[3,4-b]pyrrol-3-amine		129
361D	(3R,5S)-5-Methylpyrrolidin-3-amine		101

[1] Mix of Trans Isomers
[2] Clean Trans Isomers, Separated in Preparations 5D and 6D
[3] Clean Trans Isomer, Separated in Preparation 7D
[4] Mix of Trans Isomers
[5] Clean Trans Isomer, Separated in Preparation 7D
[6] Mix of Trans Isomers
[7] Clean Isomers, Separated in Preparations 89D and 90D
[8] Mix of Trans Isomers
[9] Clean Trans Isomers, Separated in Preparations 9D and 10D
[10] Mix of Trans Isomers
[11] Mix of Trans Isomers
[12] Mix of Cis Isomers
[13] Mix of Trans Isomers
[14] Mix of Trans Isomers (nitrogen and oxygen substituents)
[15] Clean Trans Isomers (nitrogen and oxygen substituents)
[16] Clean Trans Isomers (nitrogen and oxygen substituents)
[17] Clean Cis Isomer (nitrogen and oxygen substituents)
[18] Clean Trans Isomers, Separated in Preparations 12D and 13D
[19] Byproduct from impurity in Preparation 348D

Preparation 81B

(1S,5R)-N,N-Dimethyl-3-azabicyclo[3.1.0]hexan-1-amine



[0319] Benzyl (1S,5R)-1-((*tert*-butoxycarbonyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate. A mixture of *tert*-butyl ((1S,5R)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate (0.250 g, 1.26 mmol) and triethylamine (0.47 mL, 3.28 mmol) in DCM (2.5 mL) was cooled to -78 °C. A solution of benzyl chloroformate (0.195 mL, 1.32 mmol) in DCM (1.1 mL) was added slowly over 5 min. The reaction mixture was allowed to warm to RT and stirred for 16 h. The mixture was quenched with slow addition of 1M aqueous HCl (2.5 mL), stirred for a few minutes, and passed through a hydrophobic filter. The aqueous material trapped by the filter was extracted with DCM (2 x 10 mL). The organic layers, including the original filtrate, were combined and concentrated under reduced pressure. The crude material was purified on silica eluting 0-50% acetone in cyclohexane to obtain benzyl (1S,5R)-1-((*tert*-butoxycarbonyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.395 g, 88%) as a white solid. MS (ES) *m/z*=277 (M+1-tButyl).

[0320] Benzyl (1S,5R)-1-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate. Trifluoroacetic acid (1.69 mL) was added to a solution of benzyl (1S,5R)-1-((*tert*-butoxycarbonyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.392 g, 1.10 mmol) in DCM (6 mL). The reaction mixture was stirred for 3 h at RT, then concentrated under reduced pressure. The residue was purified on strong cation exchange media (10 g), eluting first with MeOH, then with 2M ammoniated MeOH. The basic fraction was concentrated under reduced pressure to obtain benzyl (1S,5R)-1-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.246 g, 95%) as a colorless oil. MS (ES) *m/z*=233 (M+1).

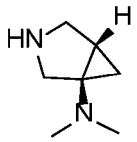
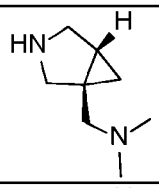
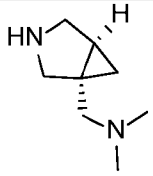
[0321] Benzyl (1S,5R)-1-(dimethylamino)-3-azabicyclo[3.1.0]hexane-3-carboxylate. Paraformaldehyde (1.62 g, 51.3 mmol) was added portionwise to a solution of benzyl (1S,5R)-1-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.243 g, 1.03 mmol) in formic acid (2.0 mL). The reaction mixture was stirred for 2 h at 100 °C, then cooled to RT. The mixture was diluted with water, pH adjusted to ~14 with 4N aqueous NaOH, and diluted with MTBE (50 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain benzyl (1S,5R)-1-(dimethylamino)-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.279 g, quant) as a yellow oil. MS (ES) *m/z*=261 (M+1).

[0322] (1S,5R)-N,N-Dimethyl-3-azabicyclo[3.1.0]hexan-1-amine. Benzyl (1S,5R)-1-(dimethylamino)-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.279 g, 1.05 mmol) and palladium(II) hydroxide (20 wt% on carbon; 0.111 g) were combined in MeOH (3 mL). The mixture was cycled

between vacuum and nitrogen three times, then exposed to hydrogen (1 atm) and stirred overnight. The mixture was filtered through diatomaceous earth and the solids were washed with MeOH. The combined filtrates were concentrated under reduced pressure to obtain the title compound (0.120 g, 72%) as an orange oil. MS (ES) *m/z*=127 (M+1).

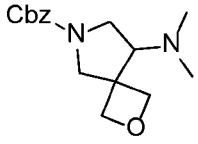
[0323] The following compounds in Table 17 were prepared in similar manner as described in Preparation 81B. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 17:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
82B	(1R,5S)-N,N-Dimethyl-3-azabicyclo[3.1.0]hexan-1-amine		127
83B	1-((1R,5R)-3-Azabicyclo[3.1.0]hexan-1-yl)-N,N-dimethylmethanamine		141
84B	1-((1S,5S)-3-Azabicyclo[3.1.0]hexan-1-yl)-N,N-dimethylmethanamine		141

Preparations 362D and 363D

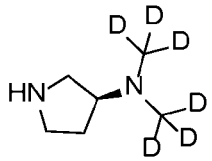
Benzyl 8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octane-6-carboxylate, Isomers 1 and 2



[0324] N,N-dimethyl-2-oxa-6-azaspiro[3.4]octan-8-amine was used in a manner analogous to the method of Preparation 81B (substep benzyl (1S,5R)-1-((*tert*-butoxycarbonyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate) to afford the racemic compound (0.50 g, 53%). MS (ES) *m/z*=291 (M+1). Title compound Isomers 1 and 2 were separated with Prep-Chiral-SFC; Chiralpak-IG, 20 x 250 mm, 30% (MeOH w/ 0.5% dimethylethylamine) in CO2, 80 mL/min.

Preparation 85B

(S)-N,N-Bis(methyl-d3)pyrrolidin-3-amine



[0325] Benzyl (S)-3-((*tert*-butoxycarbonyl)(methyl-d3)amino)pyrrolidine-1-carboxylate. To a 0 °C suspension of sodium hydride (60 wt%; 0.15 g, 3.7 mmol) in DMF (2 mL) was slowly added a solution of benzyl (S)-3-((*tert*-butoxycarbonyl)amino)pyrrolidine-1-carboxylate (1.0 g, 3.1 mmol) in DMF (5 mL). The reaction mixture was stirred for 30 min at 0 °C, then warmed to RT. The reaction mixture was stirred for 30 min at RT, then cooled to 0 °C. Iodomethane-d3 (0.22 mL, 3.4 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C, then warmed to RT and stirred for 2 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified on silica eluting 0-100% EtOAc in heptane to obtain benzyl (S)-3-((*tert*-butoxycarbonyl)(methyl-d3)amino)pyrrolidine-1-carboxylate (0.98 g, 93%) as a colorless oil.

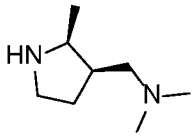
[0326] *tert*-Butyl (S)-(methyl-d3)(pyrrolidin-3-yl)carbamate. Pd/C (10 wt%; 0.28 g) was added to a solution of benzyl (S)-3-((*tert*-butoxycarbonyl)(methyl-d3)amino)pyrrolidine-1-carboxylate (0.900 g, 2.67 mmol) in MeOH (10 mL). The reaction mixture was exposed to hydrogen (1 atm) and stirred. After reaction completion (monitored by LC-MS), the mixture was filtered through diatomaceous earth and the solids were washed with MeOH. The combined filtrates were concentrated under reduced pressure to obtain *tert*-butyl (S)-(methyl-d3)(pyrrolidin-3-yl)carbamate (0.516 g, 95%) as a waxy solid.

[0327] (S)-N,N-Bis(methyl-d3)pyrrolidin-3-amine. Lithium aluminum deuteride (0.160 g, 3.81 mmol) was added to a solution of *tert*-butyl (S)-(methyl-d3)(pyrrolidin-3-yl)carbamate (0.516 g, 2.54

mmol). The reaction mixture was stirred for 30 min at RT, then 6 h at 70 °C. The Fieser workup for aluminum hydride reactions was carried out. The filtrate was concentrated under reduced pressure to give the crude title compound which was used without further purification.

Preparation 72C

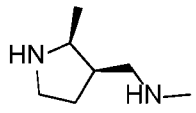
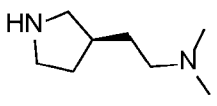
N,N-Dimethyl-1-((2S,3R)-2-methylpyrrolidin-3-yl)methanamine



[0328] Lithium aluminum hydride (1M in ether, 13.7 mL, 13.7 mmol) was added to a solution of (2S,3S)-N,N,2-trimethylpyrrolidine-3-carboxamide hydrochloride (0.660 g, 3.43 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, then 18 h at RT. The Fieser workup for aluminum hydride reactions was carried out. The filtrate was concentrated under reduced pressure to give the crude title compound (0.405 g, 83%) which was used without further purification. MS (ES) *m/z*=143 (M+1).

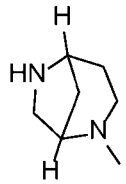
[0329] The following compounds in Table 18 were prepared in similar manner as described in Preparation 72C. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 18:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
364D	N-Methyl-1-((2S,3R)-2-methylpyrrolidin-3-yl)methanamine		129
365D	(R)-N,N-Dimethyl-2-(pyrrolidin-3-yl)ethan-1-amine		143

Preparation 73C

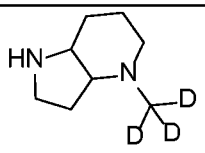
2-Methyl-2,6-diazabicyclo[3.2.1]octane, Mix of Cis Isomers

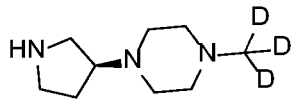
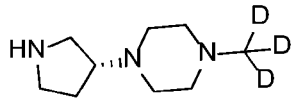


[0330] Lithium aluminum hydride (2M in THF; 1.7 mL, 3.4 mmol) was added to THF (3.4 mL) under nitrogen at 0 °C. A solution of *tert*-butyl 2,6-diazabicyclo[3.2.1]octane-2-carboxylate (Mix of Cis Isomers; 0.330 g, 1.49 mmol) in THF (1.7 mL) was added dropwise over 1-2 min. The reaction mixture was warmed to RT and stirred for 18 h. Additional lithium aluminum hydride (2M in THF; 1.7 mL, 3.4 mmol) was added at RT and the reaction mixture was stirred for a total of 6 days. The mixture was diluted with THF (10 mL) and cooled to 0 °C. Distilled water (0.32 mL), 1M aqueous NaOH (0.32 mL), and distilled water (1.0 mL) were added dropwise. The mixture was warmed to RT and stirred for 15 min. Magnesium sulfate was added, the mixture was filtered, and the solids were washed with DCM. The combined filtrates were concentrated under reduced pressure to obtain the crude title compound (0.143 g) as a yellow oil. MS (ES) *m/z*=127 (M+1).

[0331] The following compounds in Table 19 were prepared in similar manner as described in Preparation 73C. Lithium aluminum deuteride may have been used in place of lithium aluminum hydride. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

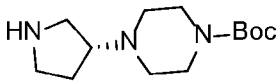
Table 19:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
366D	4-(Methyl-d3)octahydro-1H-pyrrolo[3,2-b]pyridine		6

367D	(S)-1-(Methyl-d3)-4-(pyrrolidin-3-yl)piperazine		6
368D	(R)-1-(Methyl-d3)-4-(pyrrolidin-3-yl)piperazine		6

Preparation 369D

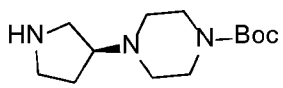
tert-Butyl (R)-4-(pyrrolidin-3-yl)piperazine-1-carboxylate

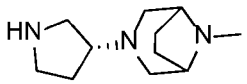
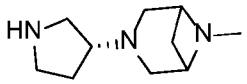
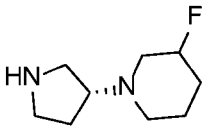
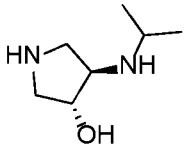
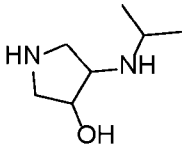
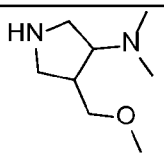
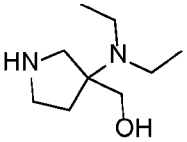
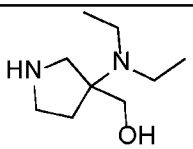
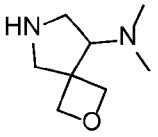
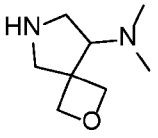


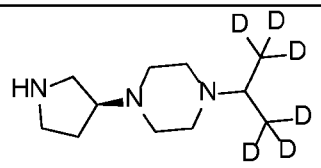
[0332] *tert*-Butyl (R)-4-(1-((benzyloxy)carbonyl)pyrrolidin-3-yl)piperazine-1-carboxylate (1.44g, 3.70 mmol) and palladium hydroxide on carbon (0.104 g) were placed in a flask. The flask was cycled through vacuum and nitrogen three times. EtOH (10 mL) was added. The flask was placed under hydrogen (balloon) and the reaction mixture was stirred at RT for 16 h. The mixture was filtered through diatomaceous earth and the filter cake was washed with EtOH. The combined filtrates were concentrated under reduced pressure to give the title compound (0.89 g, 94%). MS (ES) *m/z*=256 (M+1).

[0333] The following compounds in Table 20 were prepared in similar manner as described in Preparation NEW. In some cases, a benzyl protecting groups was removed. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 20:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
370D	*tert*-Butyl (S)-4-(pyrrolidin-3-yl)piperazine-1-carboxylate		256

371D	8-Methyl-3-((R)-pyrrolidin-3-yl)-3,8-diazabicyclo[3.2.1]octane		196
372D	6-Methyl-3-((R)-pyrrolidin-3-yl)-3,6-diazabicyclo[3.1.1]heptane		182
373D	3-Fluoro-1-((R)-pyrrolidin-3-yl)piperidine		173
374D	(3R,4R)-4-(Isopropylamino)pyrrolidin-3-ol		145
375D [1]	4-(Isopropylamino)pyrrolidin-3-ol		145
376D [2]	4-(Methoxymethyl)-N,N-dimethylpyrrolidin-3-amine		159
377D [3]	(3-(Diethylamino)pyrrolidin-3-yl)methanol, Isomer 1		173
378D [3]	(3-(Diethylamino)pyrrolidin-3-yl)methanol, Isomer 2		173
379D [4]	N,N-Dimethyl-2-oxa-6-azaspiro[3.4]octan-8-amine, Isomer 1		157
380D [4]	N,N-Dimethyl-2-oxa-6-azaspiro[3.4]octan-8-amine, Isomer 2		157

381D	(S)-1-(Propan-2-yl-1,1,1,3,3,3-d6)-4-(pyrrolidin-3-yl)piperazine		204

[1] Mix of Trans Isomers

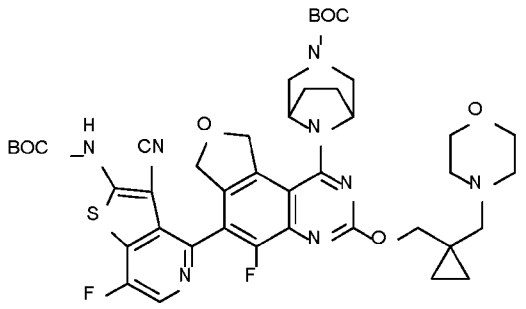
[2] Mix of Cis Isomers

[3] Clean Isomers, Separated in Preparations 142D and 143D

[4] Clean Isomers, Separated in Preparations 362D and 363D

Preparation 57

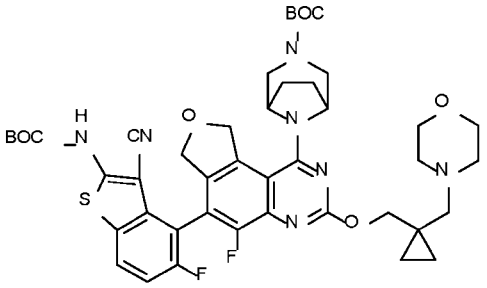
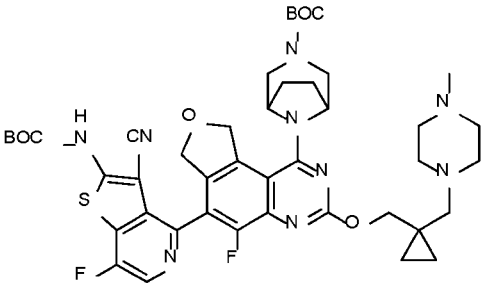
tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

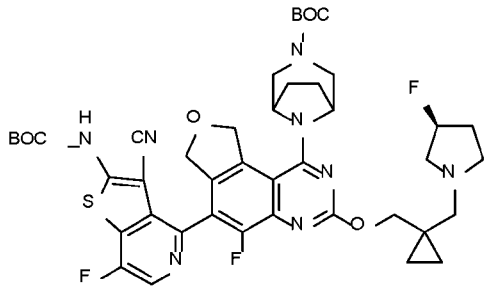
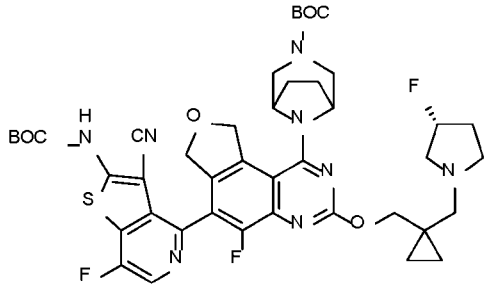


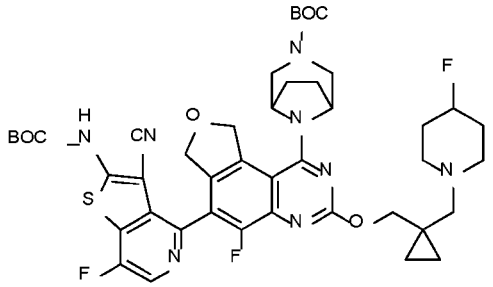
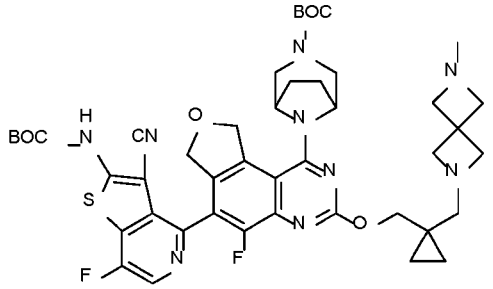
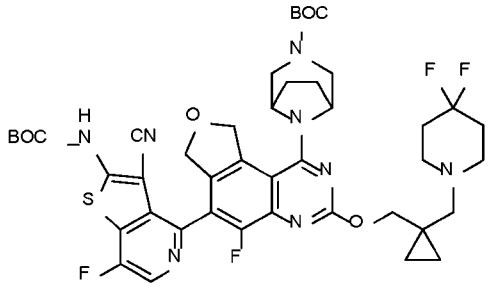
[0334] To a solution of (1-(morpholinomethyl)cyclopropyl)methanol (0.980 g, 5.74 mmol) in THF (10 mL) was added lithium bis(trimethylsilyl)amide (1 M in THF, 3.44 mL, 3.44 mmol) at RT. After 10 min, a solution of *tert*-butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.900 g, 1.15 mmol) in THF (10 mL) was added dropwise. After 2 h, the reaction mixture was diluted with EtOAc (200 mL) and washed with water (2 x 200 mL) and brine (100 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica eluting with PE / EtOAc (1:1) to obtain the title compound (0.720 g, 73%) as an off-white solid. MS (ES) *m/z*=861 (M+1).

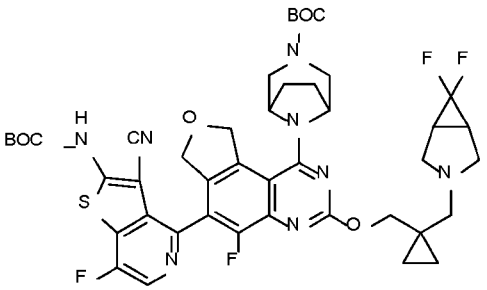
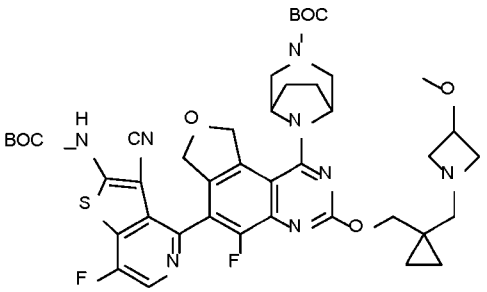
[0335] The following compounds in Table 21 were prepared in similar manner as described in Preparation 57. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

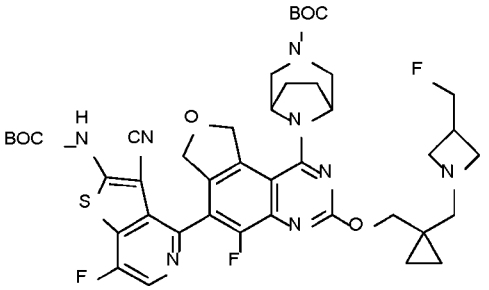
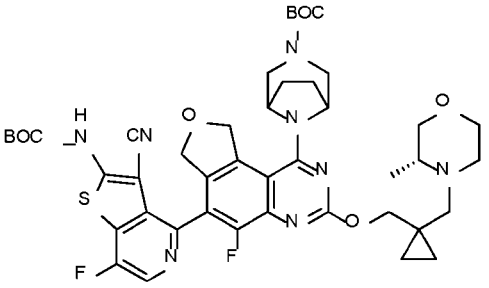
Table 21:

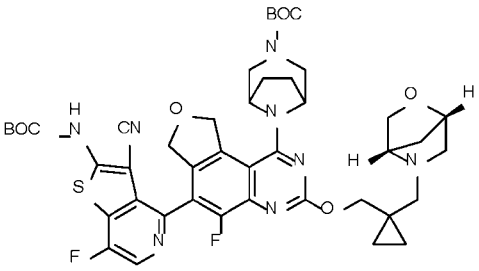
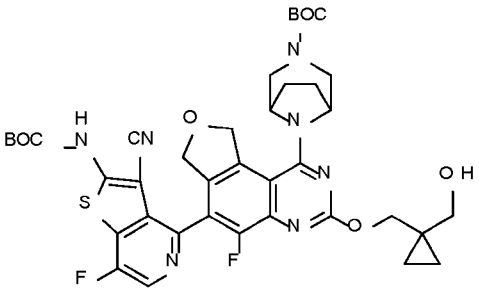
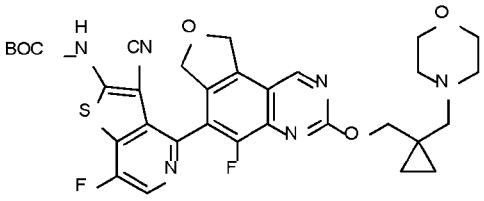
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
58	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		860
59	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		874

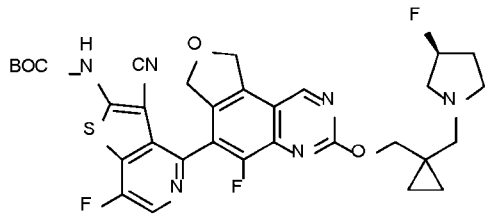
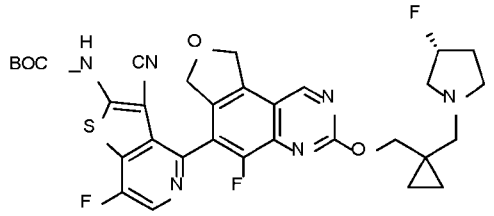
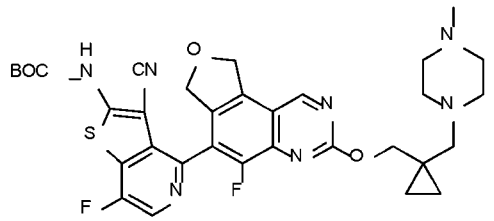
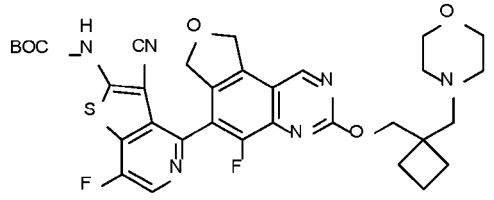
60	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((S)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		863
61	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		863

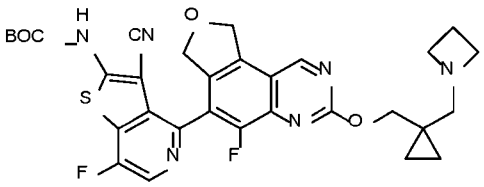
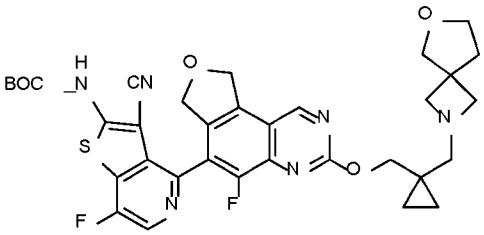
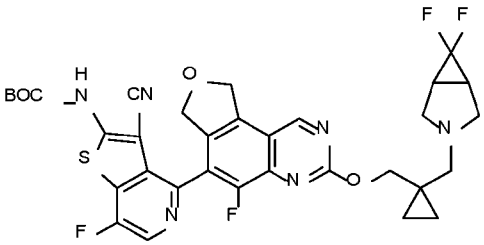
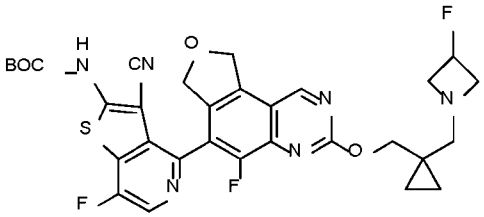
62	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((S)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		878
63	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		886
64	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-((4,4-difluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		895

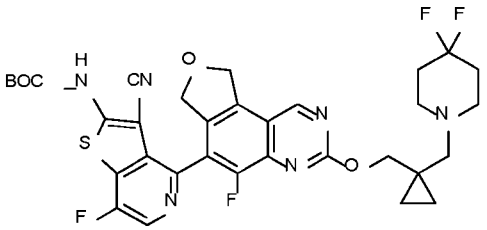
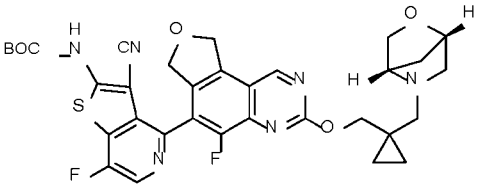
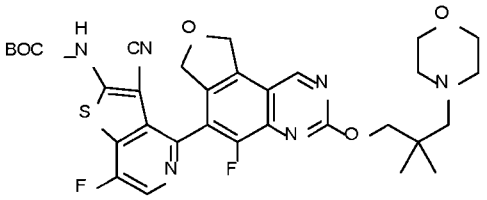
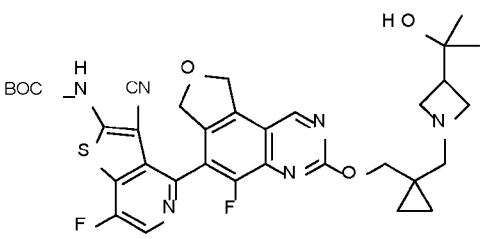
65	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		893
66	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((3-methoxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		861

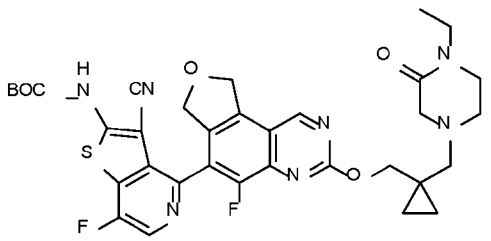
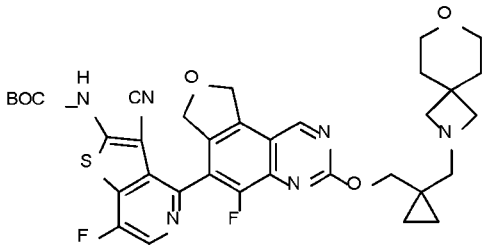
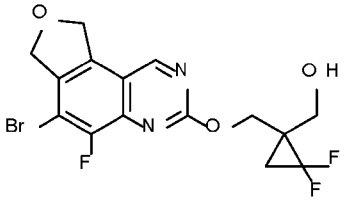
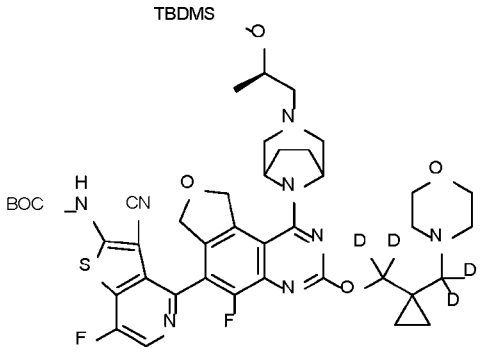
67	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((3-(fluoromethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		863
68	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		876

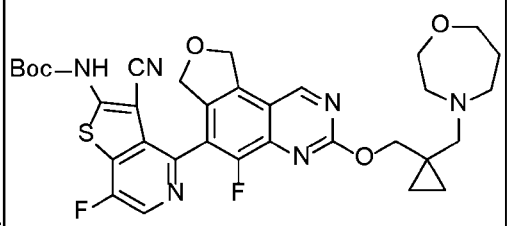
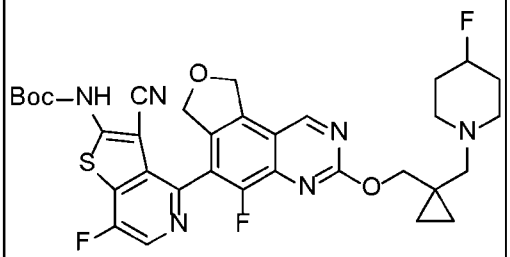
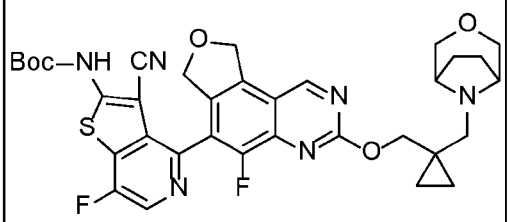
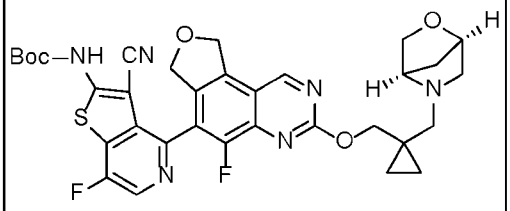
69	*tert*-Butyl 8-(3-((1-(((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		873
70	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(hydroxymethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		792
71	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		651

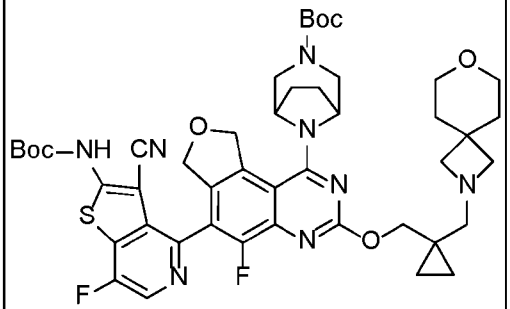
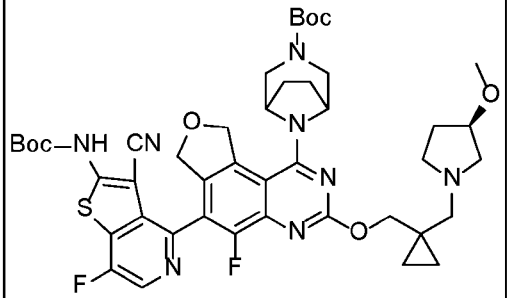
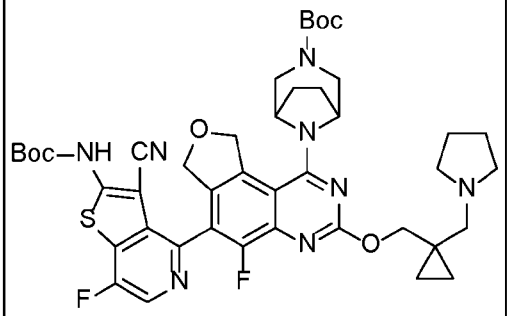
72	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-(((S)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		653
73	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		653
74	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664
75	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-(morpholinomethyl)cyclobutyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		665

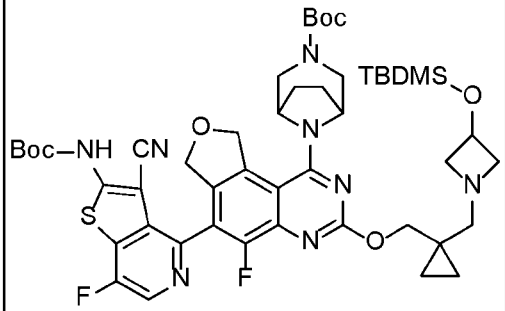
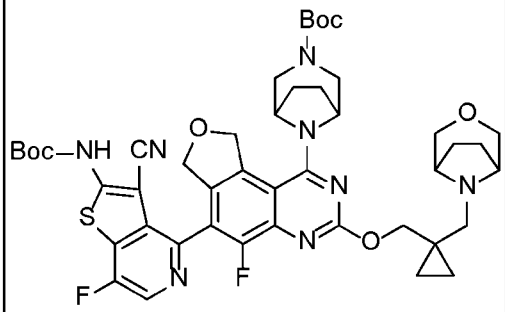
76	*tert*-Butyl (4-(3-((1-(azetidin-1-ylmethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		621
77	*tert*-Butyl (4-(3-((1-((6-oxa-2-azaspiro[3.4]octan-2-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		677
78	*tert*-Butyl (3-cyano-4-(3-((1-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		683
79	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-((3-fluoroazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		639

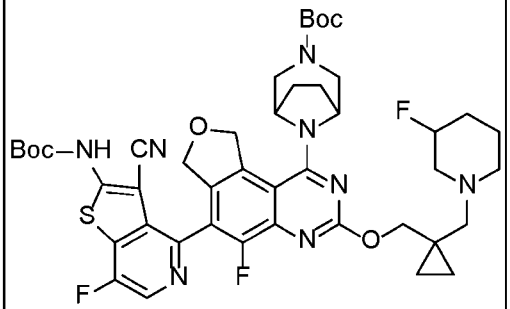
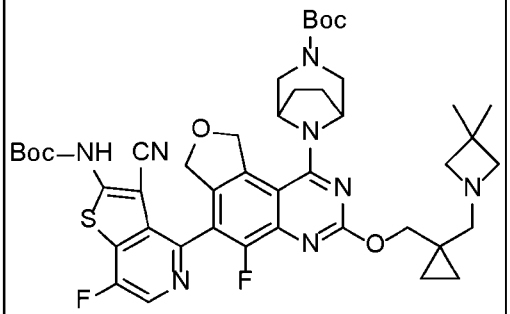
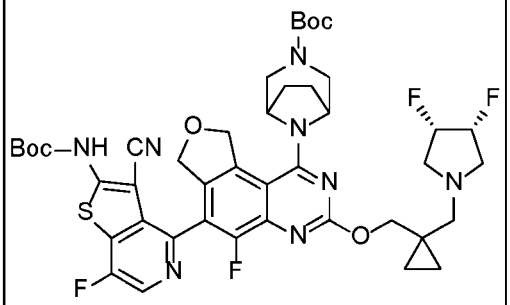
80	*tert*-Butyl (3-cyano-4-(3-((1-((4,4-difluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		685
81	*tert*-Butyl (4-(3-((1-(((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
82	*tert*-Butyl (3-cyano-4-(3-(2,2-dimethyl-3-morpholinopropoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		653
83	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-((3-(2-hydroxypropan-2-yl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		679

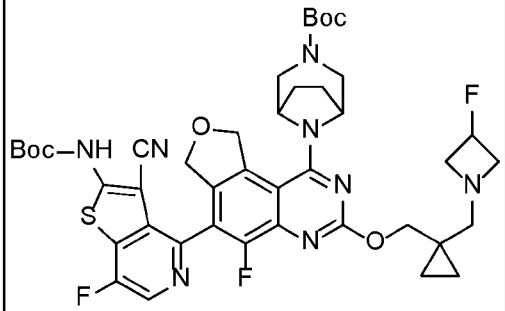
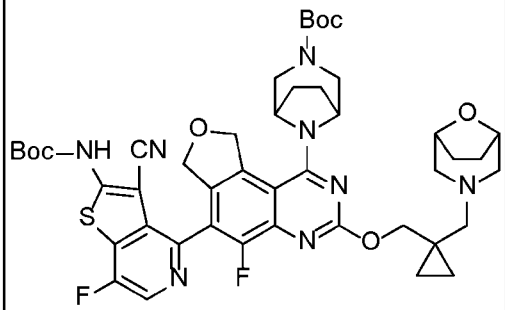
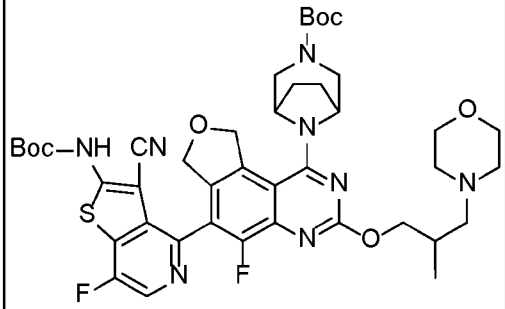
84	*tert*-Butyl (3-cyano-4-(3-((1-((4-ethyl-3-oxopiperazin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		692
85	*tert*-Butyl (4-(3-((1-((7-oxa-2-azaspiro[3.5]nonan-2-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		691
86	(1-(((6-Bromo-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol		404
87	*tert*-Butyl (4-(1-(3-((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(morpholinomethyl-d2)cyclopropyl)methoxy-d2)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		937

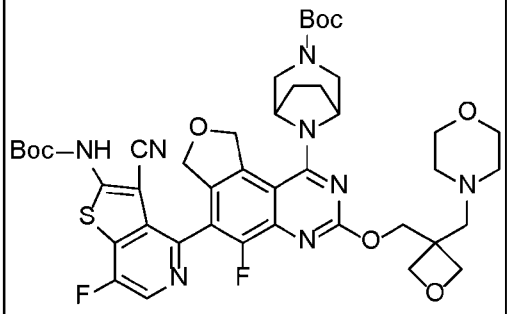
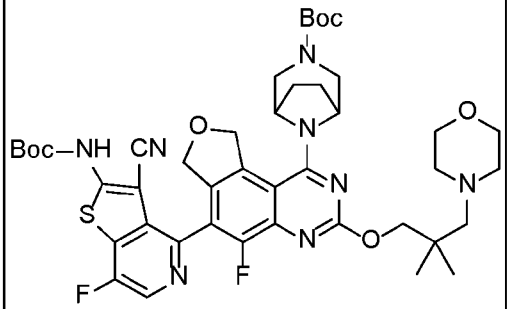
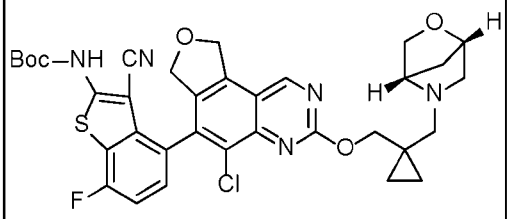
21A	*tert*-Butyl (4-(3-((1-((1,4-oxazepan-4-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		665
22A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		667
23A	*tert*-Butyl (4-(3-((1-((-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		677
24A	*tert*-Butyl (4-(3-((1-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663

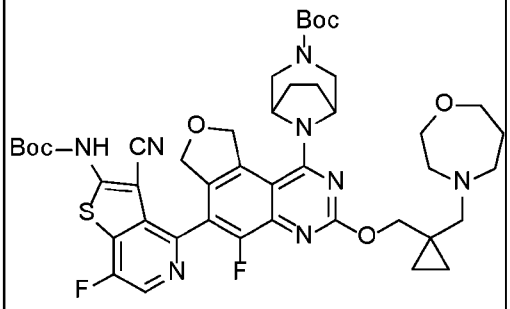
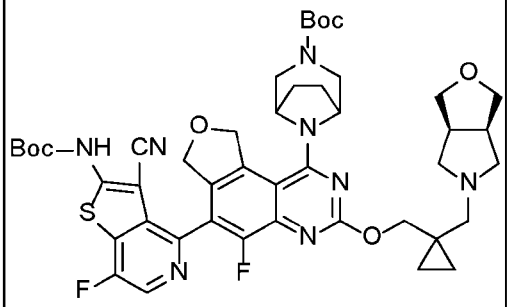
25A	*tert*-Butyl 8-(3-((1-((7-oxa-2-azaspiro[3.5]nonan-2-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		902
26A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((R)-3-methoxypyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		875
27A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		845

28A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((3-hydroxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylatec		961
29A	*tert*-Butyl 8-(3-((1-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		887

30A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((3-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		877
31A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-((3,3-dimethylazetidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		859
32A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-(((3R,4S)-3,4-difluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		881

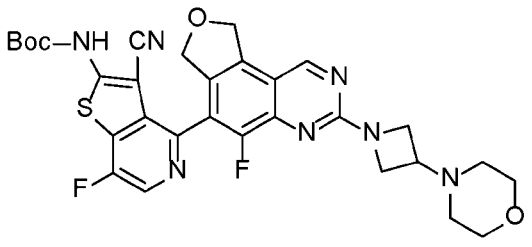
33A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((3-fluoroazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		849
34A	*tert*-Butyl 8-(3-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		887
35A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(2-methyl-3-morpholinopropoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		849

36A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((3-(morpholinomethyl)oxetan-3-yl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		877
37A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-(2,2-dimethyl-3-morpholinopropoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		863
86B	*tert*-Butyl (4-(3-((1-(((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		678

87B	*tert*-Butyl 8-(3-((1-((1,4-oxazepan-4-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		875
88B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		887

Preparation 38A

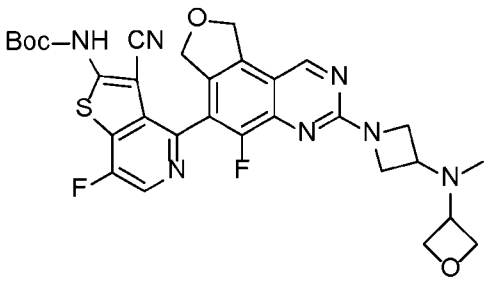
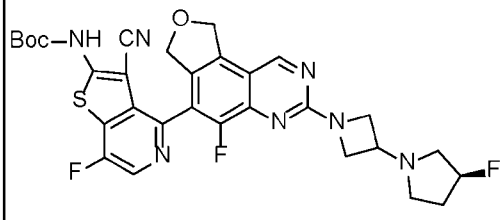
tert-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-morpholinoazetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate

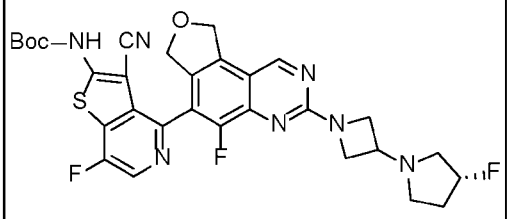
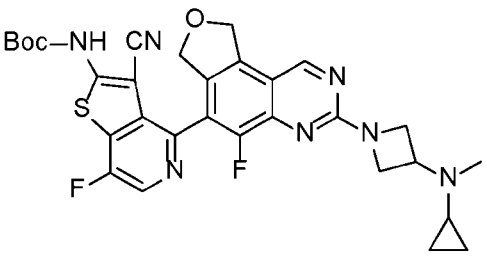
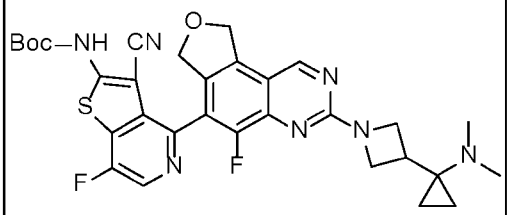
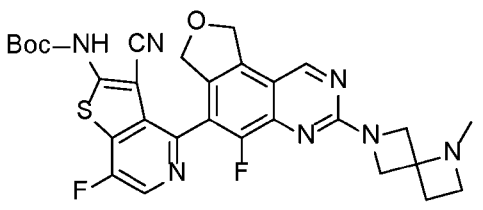


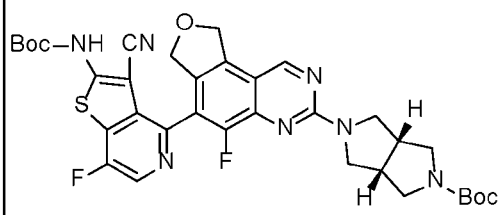
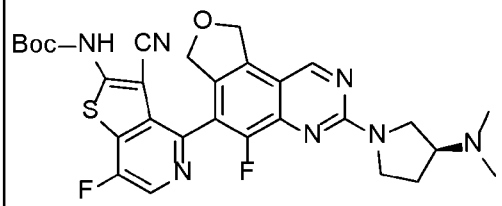
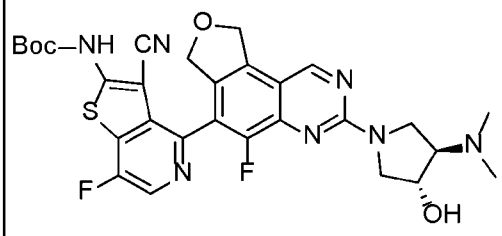
[0336] To *tert*-butyl (3-cyano-4-(3-(ethylsulfonyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (0.200 g, 0.349 mmol) was added diisopropylethylamine (0.180 g, 1.39 mmol), 4-(azetidin-3-yl)morpholine (0.099 g, 0.70 mmol), and THF (3 mL). The reaction mixture was heated at 70 °C. After 1 h, the mixture was concentrated under reduced pressure. The residue was purified on strong cation exchange media (10 g), eluting first with MeOH, then with 2M ammoniated MeOH. The basic fraction was concentrated under reduced pressure to obtain the title compound (0.170 g, 78%) as a brown solid. MS (ES) *m/z*=622 (M+1).

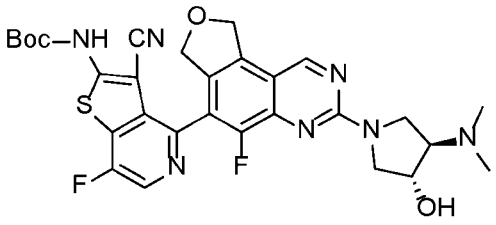
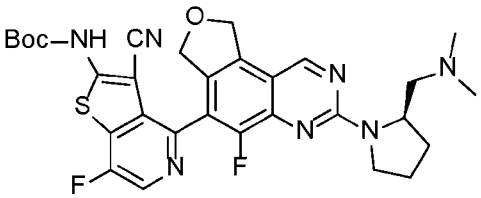
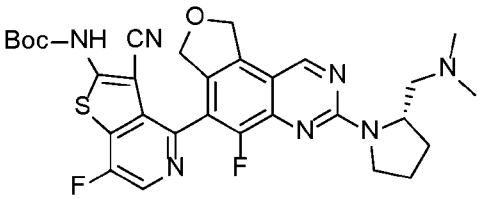
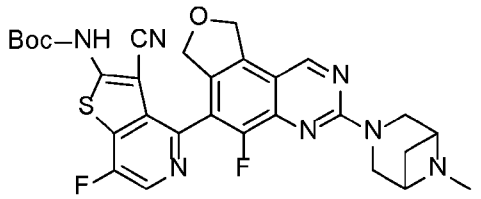
[0337] The following compounds in Table 22 were prepared in similar manner as described in Preparation 38A. Various bases, such as sodium hydride or lithium bis(trimethylsilyl)amide, were used in place of diisopropylethylamine. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

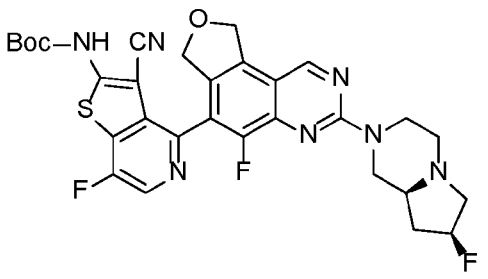
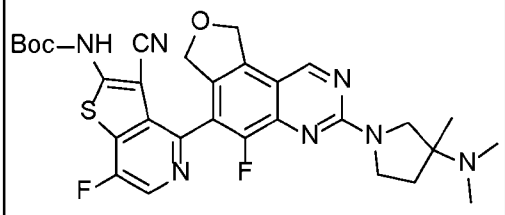
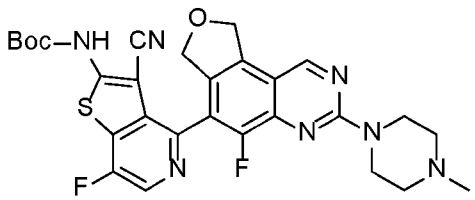
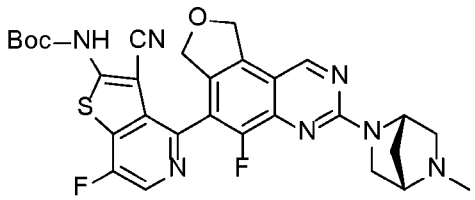
Table 22:

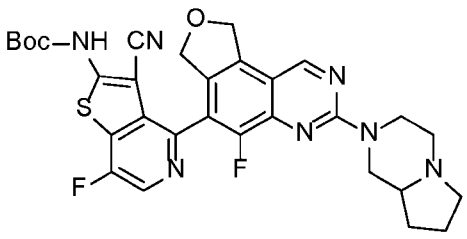
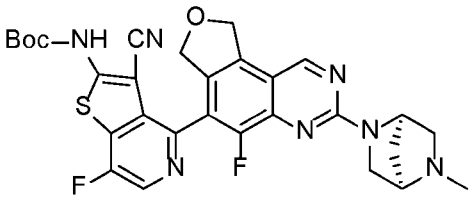
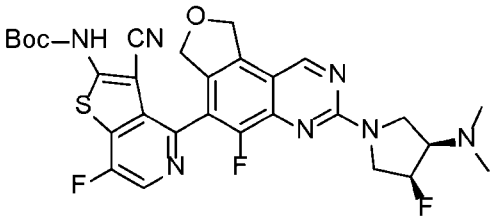
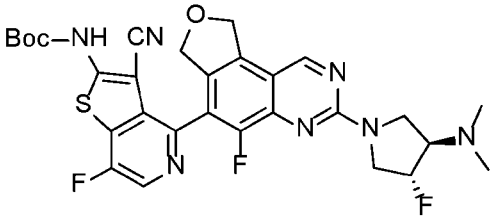
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
39A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(methyl(oxetan-3-yl)amino)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		622
40A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-((S)-3-fluoropyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624

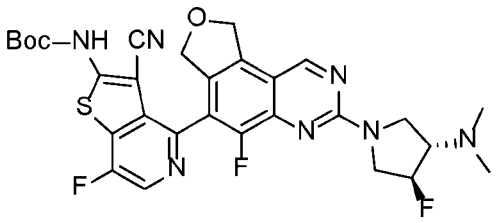
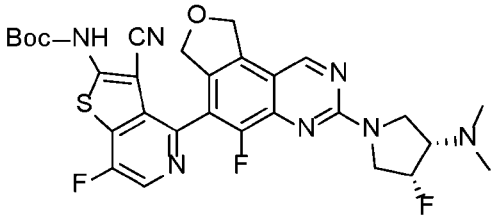
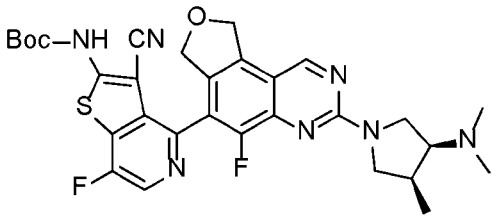
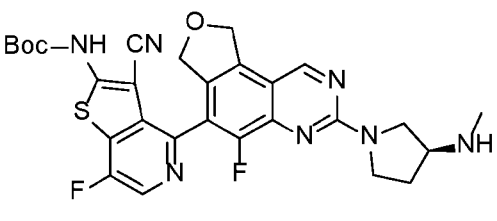
41A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-((R)-3-fluoropyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624
42A	*tert*-Butyl (3-cyano-4-(3-(3-(cyclopropyl(methyl)amino)azetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606
43A	*tert*-Butyl (3-cyano-4-(3-(3-(1-(dimethylamino)cyclopropyl)azetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
44A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592

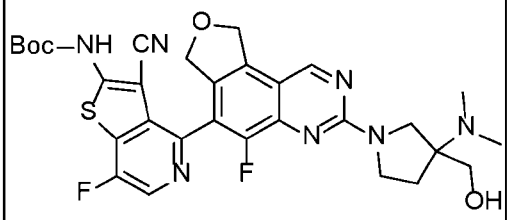
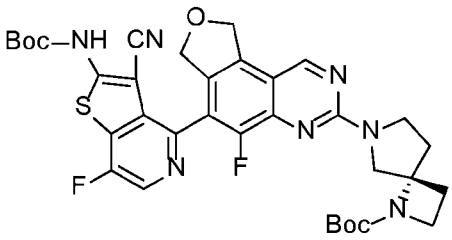
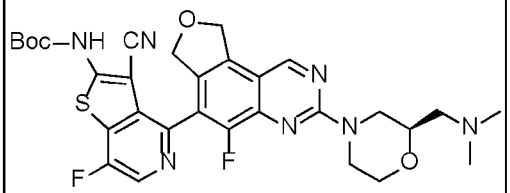
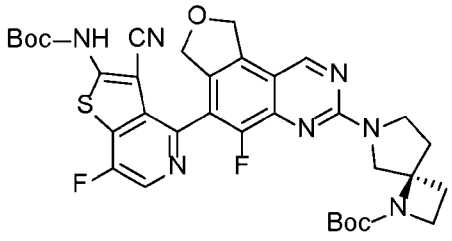
45A	*tert*-Butyl (3aR,6aS)-5-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate		692
46A	*tert*-Butyl (3-cyano-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		594
47A [1]	rel-*tert*-Butyl (3-cyano-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Trans Isomer 1		610

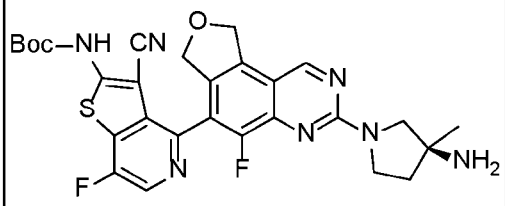
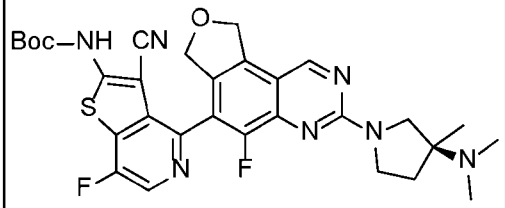
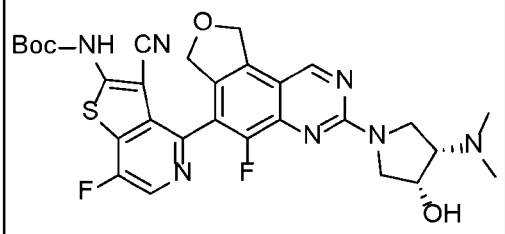
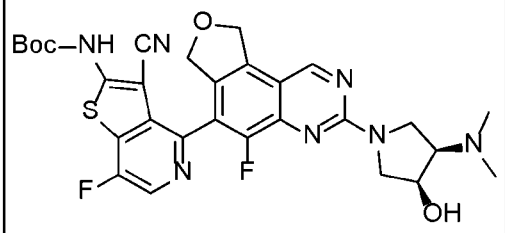
48A [1]	rel-*tert*-Butyl (3-cyano-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Trans Isomer 2		610
49A	*tert*-Butyl (3-cyano-4-(3-((R)-2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
50A	*tert*-Butyl (3-cyano-4-(3-((S)-2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
51A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592

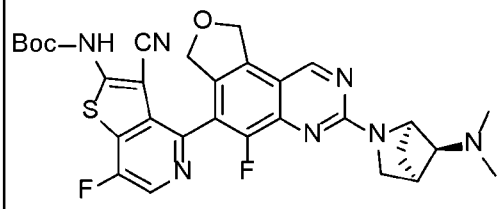
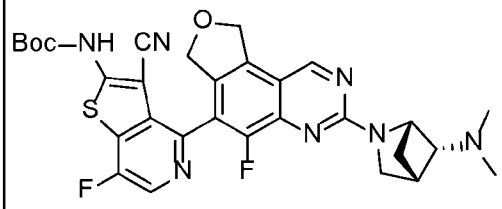
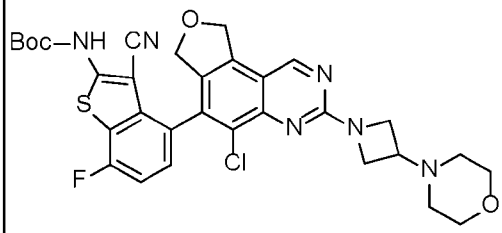
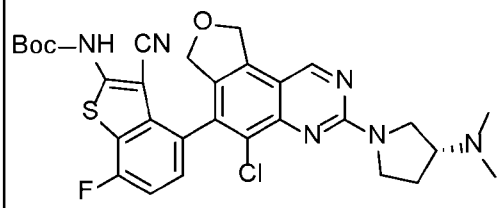
52A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((7S,8aS)-7-fluorohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624
53A	*tert*-Butyl (3-cyano-4-(3-(3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
54A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-methylpiperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		580
55A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592

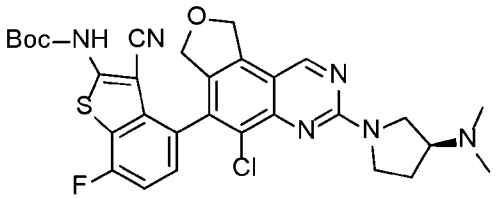
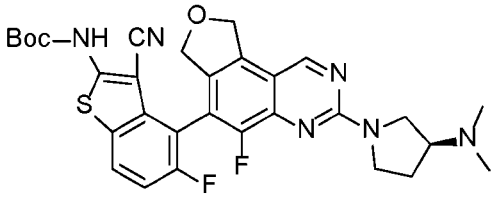
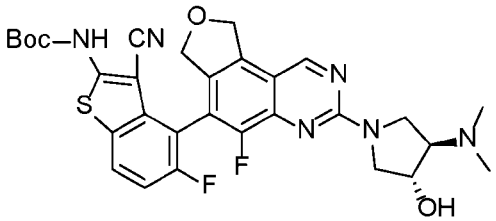
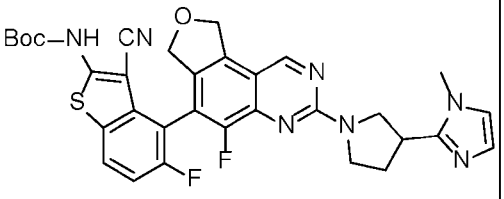
56A	tert-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606
57A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592
58A	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		612
59A	*tert*-Butyl (3-cyano-4-(3-((3R,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		612

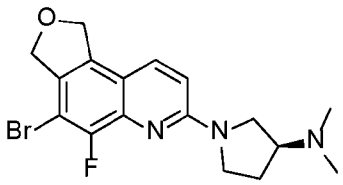
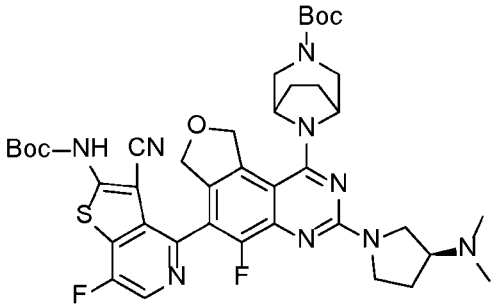
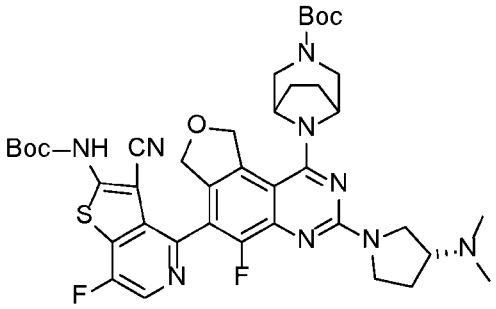
60A	*tert*-Butyl (3-cyano-4-(3-((3S,4S)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		612
61A	*tert*-Butyl (3-cyano-4-(3-((3S,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		612
62A	*tert*-Butyl (3-cyano-4-(3-((3S,4S)-3-(dimethylamino)-4-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
63A	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(methylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		580

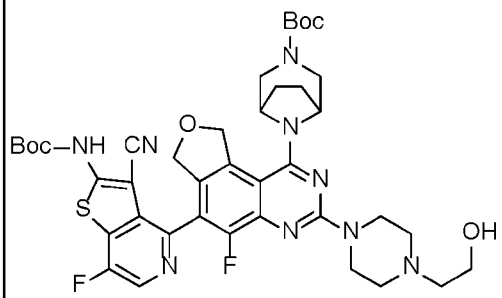
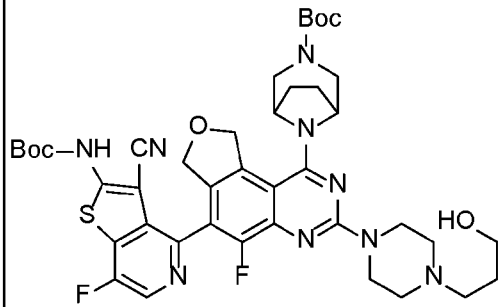
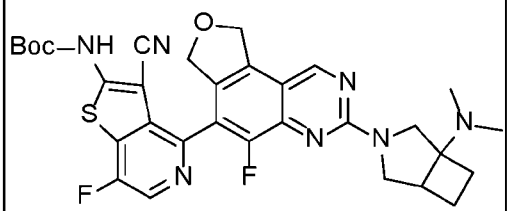
64A	*tert*-Butyl (3-cyano-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
65A	*tert*-Butyl (4R)-6-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate		692
66A	*tert*-Butyl (3-cyano-4-(3-((R)-2-((dimethylamino)methyl)morpholino)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
67A	*tert*-Butyl (4S)-6-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate		692

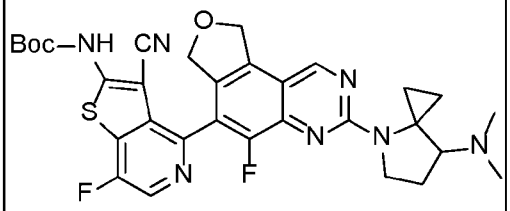
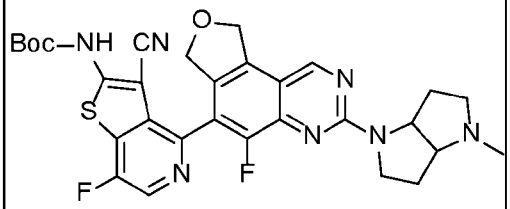
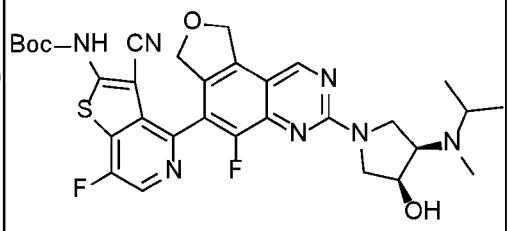
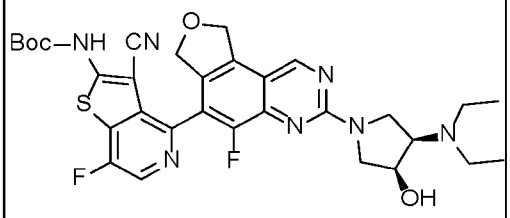
68A	*tert*-Butyl (4-(3-((S)-3-amino-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		580
69A	*tert*-Butyl (3-cyano-4-(3-((S)-3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
70A	*tert*-Butyl (3-cyano-4-(3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		610
71A	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		610

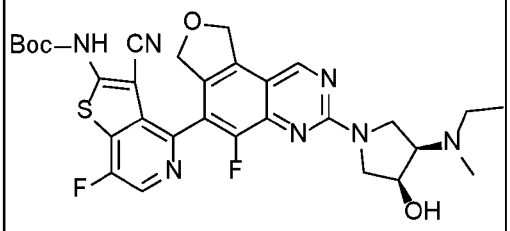
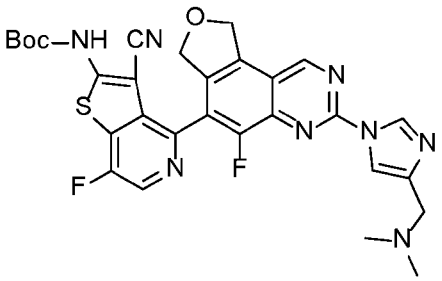
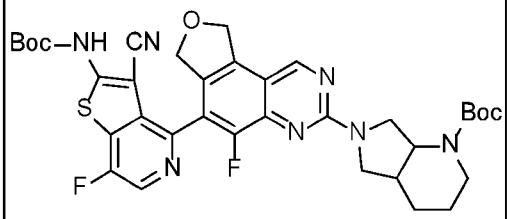
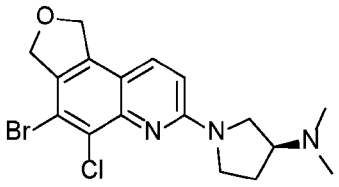
72A	*tert*-Butyl (3-cyano-4-(3-((1R,4R,5S)-5-(dimethylamino)-2-azabicyclo[2.1.1]hexan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606
73A	*tert*-Butyl (3-cyano-4-(3-((1S,4S,5R)-5-(dimethylamino)-2-azabicyclo[2.1.1]hexan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606
74A	*tert*-Butyl (4-(5-chloro-3-(3-morpholinoazetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		637
75A	*tert*-Butyl (4-(5-chloro-3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		609

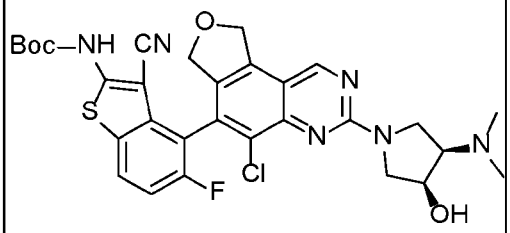
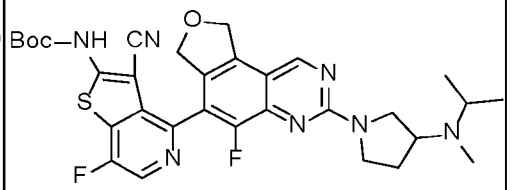
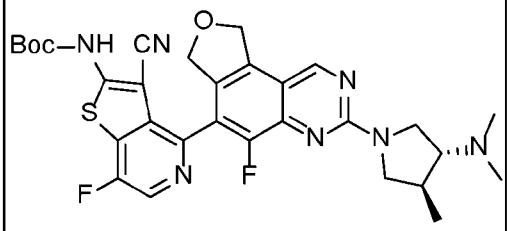
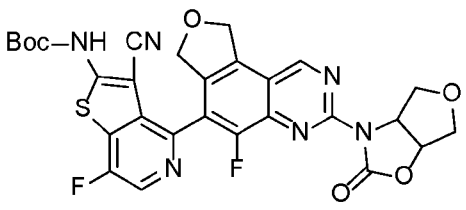
76A	*tert*-Butyl (4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		609
77A	*tert*-Butyl (3-cyano-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		593
78A [2]	rel-*tert*-Butyl (3-cyano-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		609
79A	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-(3-(1-methyl-1H-imidazol-2-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		630

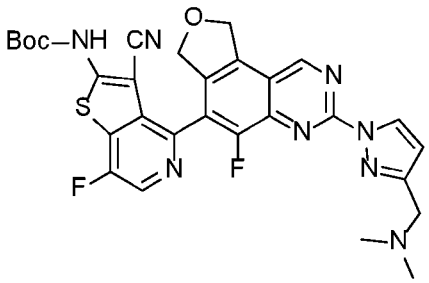
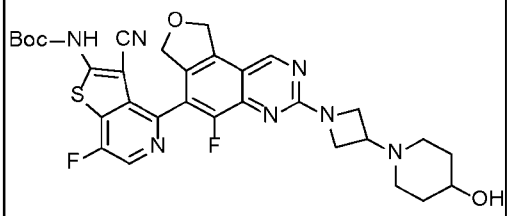
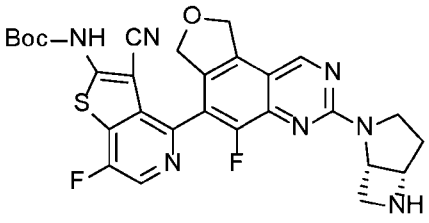
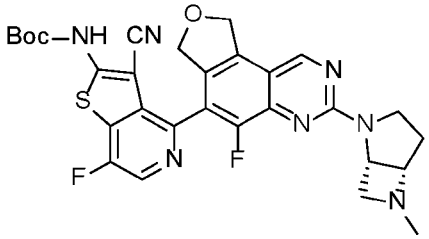
80A [3]	(S)-1-(4-Bromo-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-N,N-dimethylpyrrolidin-3-amine		380, 382
81A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		804
82A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		804

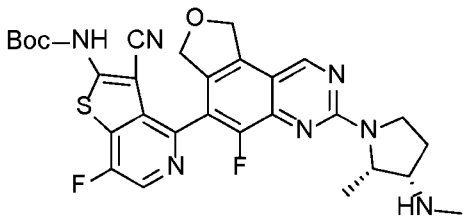
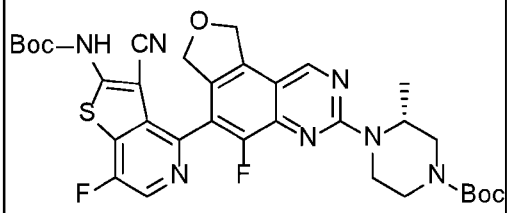
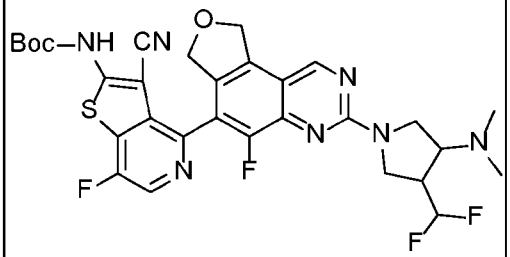
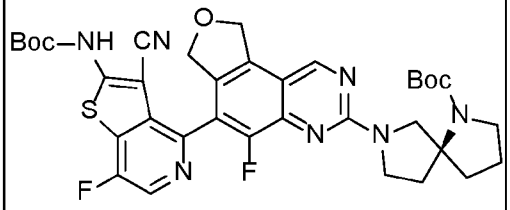
83A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(4-(2-hydroxyethyl)piperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820
84A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(4-(3-hydroxypropyl)piperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		834
89B	*tert*-Butyl (3-cyano-4-(3-(1-(dimethylamino)-3-azabicyclo[3.2.0]heptan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620

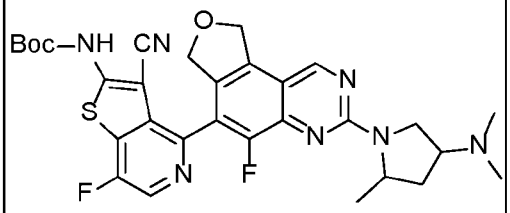
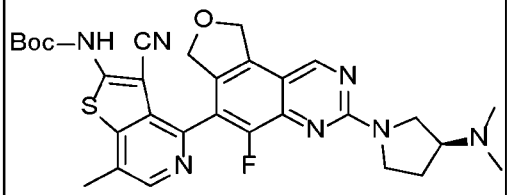
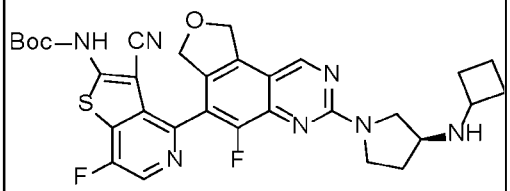
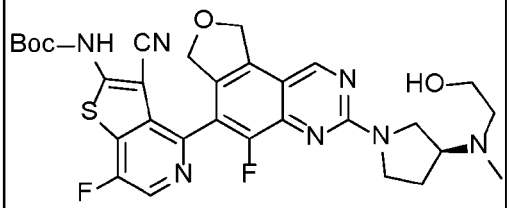
90B	*tert*-Butyl (3-cyano-4-(3-(7-(dimethylamino)-4-azaspiro[2.4]heptan-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
91B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-methylhexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606
92B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
93B	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		638

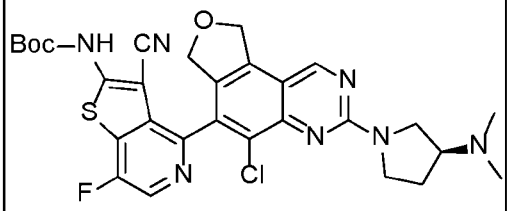
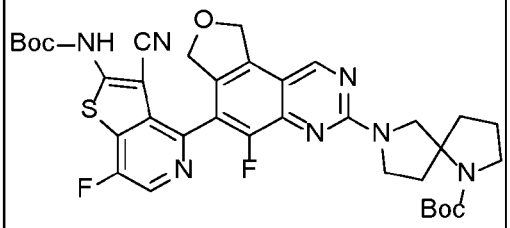
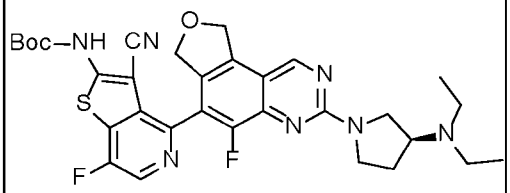
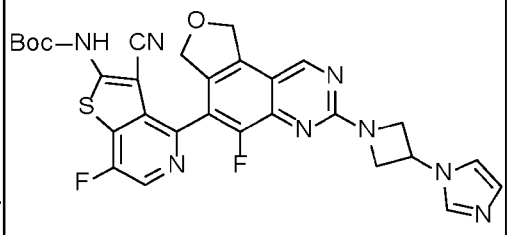
94B	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(ethyl(methyl)amino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
95B	*tert*-Butyl (3-cyano-4-(3-(4-((dimethylamino)methyl)-1H-imidazol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		605
96B	*tert*-Butyl 6-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate		706
97B [4]	(S)-1-(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-N,N-dimethylpyrrolidin-3-amine		396, 398

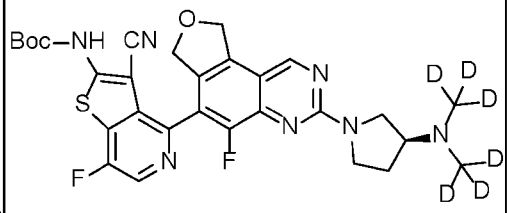
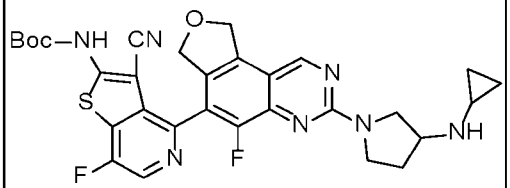
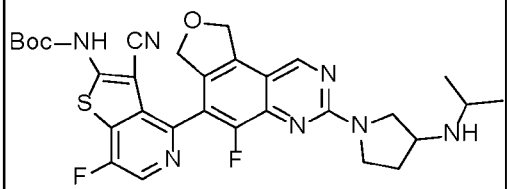
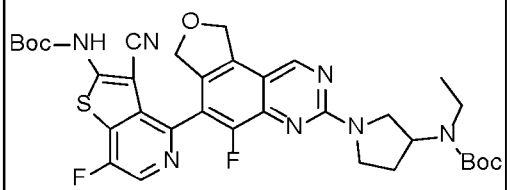
98B	*tert*-Butyl (4-(5-chloro-3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate		625
99B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		622
100B	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(dimethylamino)-4-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
101B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(2-oxotetrahydrofuro[3,4-d]oxazol-3(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		

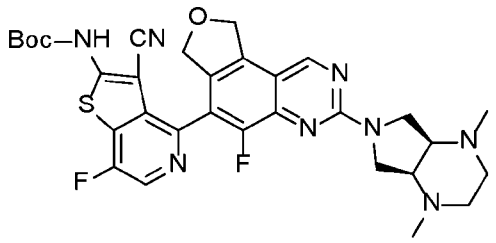
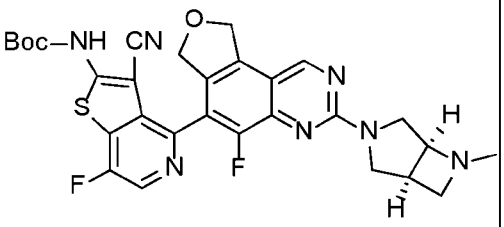
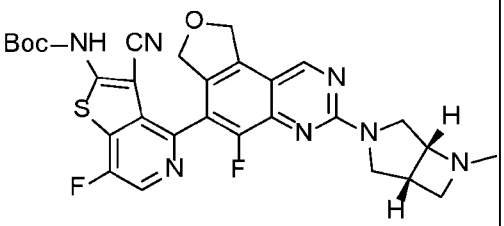
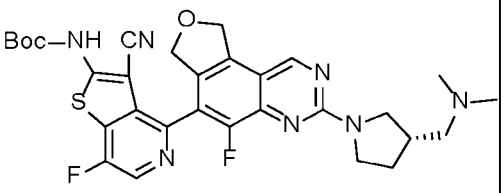
102B	*tert*-Butyl (3-cyano-4-(3-(3-((dimethylamino)methyl)-1H-pyrazol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		605
103B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(4-hydroxypiperidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		636
104B	*tert*-Butyl (4-(3-((1S,5S)-2,6-diazabicyclo[3.2.0]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		578
105B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1S,5S)-6-methyl-2,6-diazabicyclo[3.2.0]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592

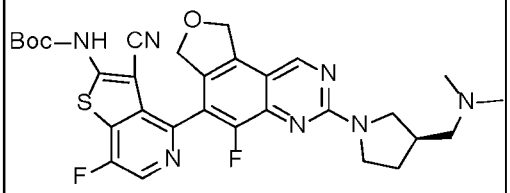
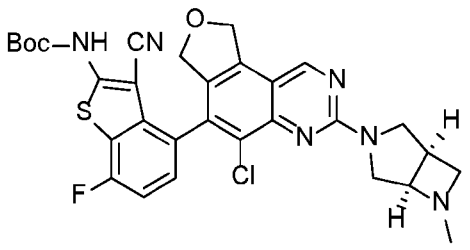
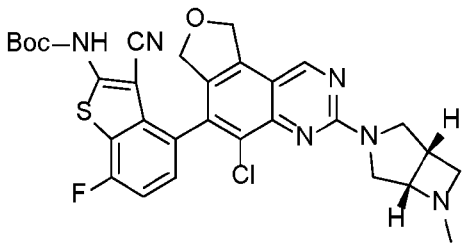
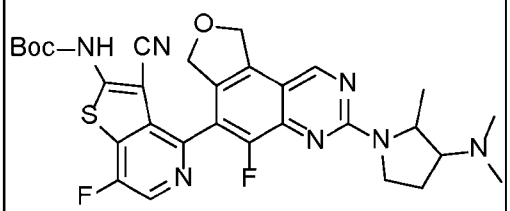
106B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(methylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		594
107B	*tert*-Butyl (3R)-4-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-3-methylpiperazine-1-carboxylate		680
108B	*tert*-butyl (3-cyano-4-(3-(3-(difluoromethyl)-4-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Mix of Trans Isomers		644
109B	*tert*-Butyl (5S)-7-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate		706

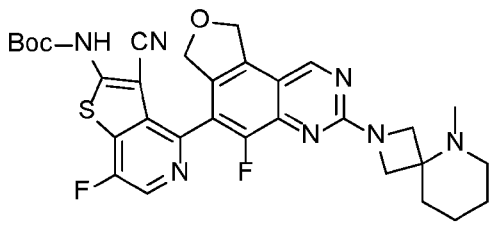
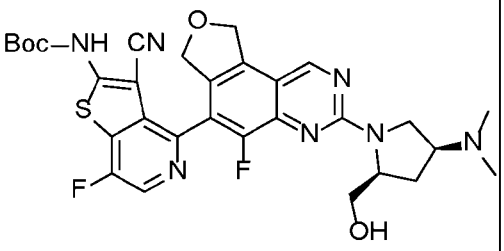
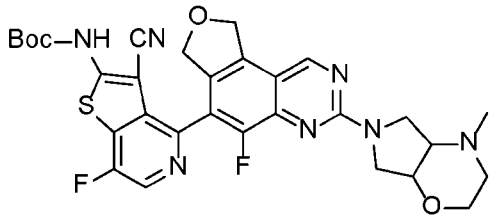
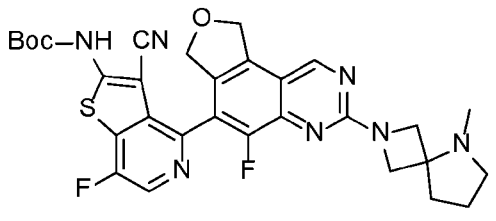
110B	*tert*-Butyl (3-cyano-4-(3-(4-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
111B	*tert*-Butyl (3-cyano-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-methylthieno[3,2-c]pyridin-2-yl)carbamate		590
112B	*tert*-Butyl (3-cyano-4-(3-((S)-3-(cyclobutylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
113B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-((2-hydroxyethyl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624

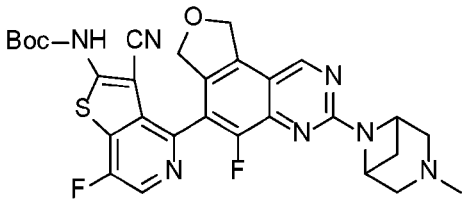
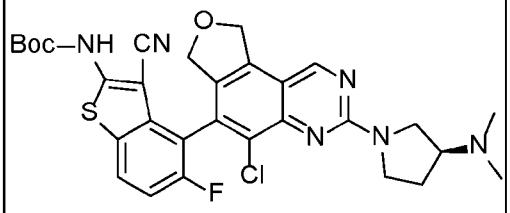
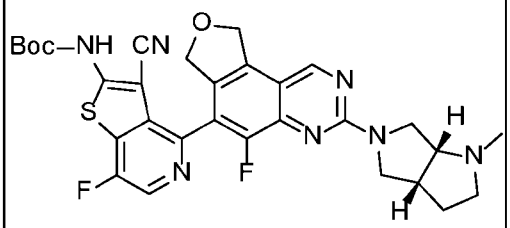
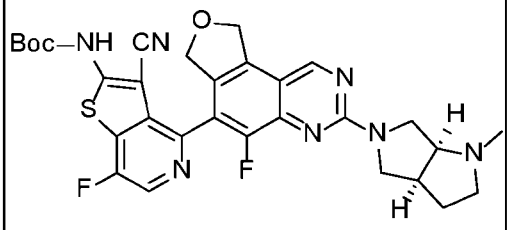
114B	*tert*-Butyl (4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		610
115B	*tert*-Butyl 7-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-1,7-diazaspiro[4.4]nonane-1-carboxylate		706
116B	*tert*-Butyl (3-cyano-4-(3-((S)-3-(diethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		622
117B	*tert*-Butyl (4-(3-(3-(1H-imidazol-1-yl)azetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		603

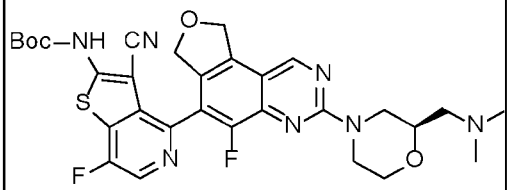
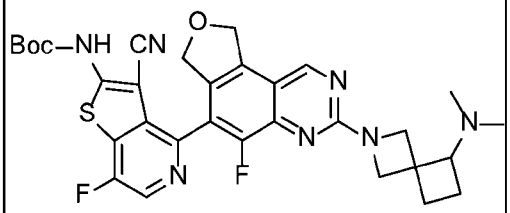
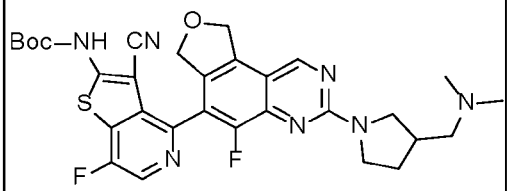
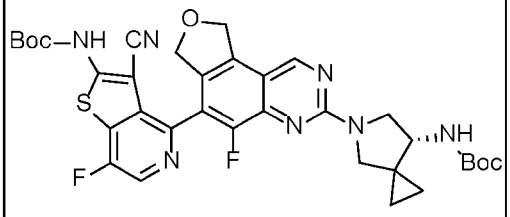
118B	*tert*-Butyl (4-(3-((S)-3-(bis(methyl-d3)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		600
119B	*tert*-Butyl (3-cyano-4-(3-(3-(cyclopropylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606
120B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		608
121B	*tert*-Butyl (1-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)pyrrolidin-3-yl)(ethyl)carbamate		694

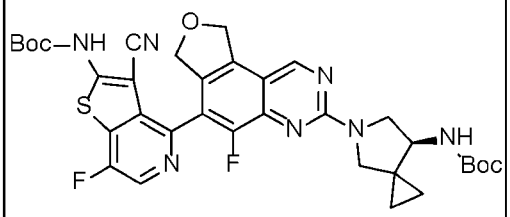
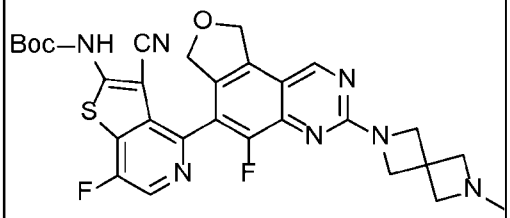
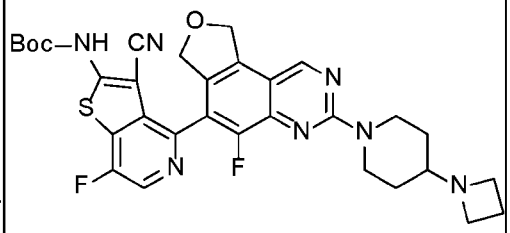
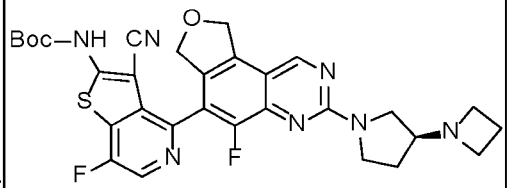
122B	*tert*-Butyl (3-cyano-4-(3-((4aR,7aS)-1,4-dimethyloctahydro-6H-pyrrolo[3,4-b]pyrazin-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		635
123B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1S,5S)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592
124B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1R,5R)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592
125B	*tert*-Butyl (3-cyano-4-(3-((S)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608

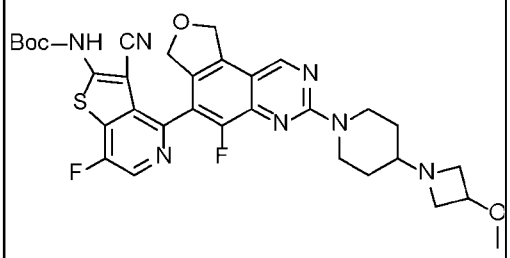
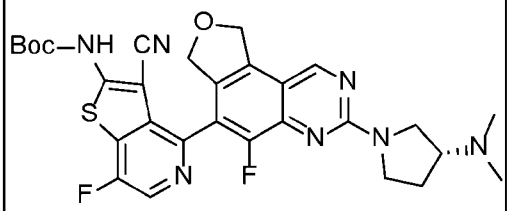
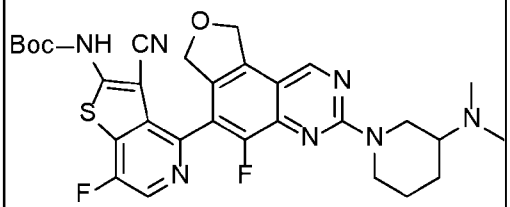
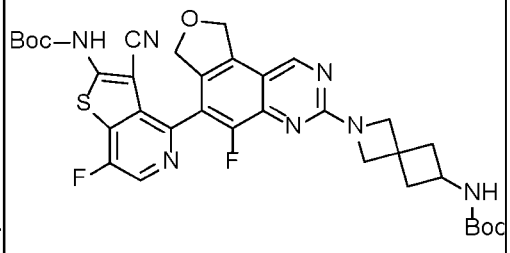
126B	*tert*-Butyl (3-cyano-4-(3-((R)-3-((dimethylamino)methyl) pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
127B	*tert*-Butyl (4-(5-chloro-3-((1R,5R)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		607
128B	*tert*-Butyl (4-(5-chloro-3-((1S,5S)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate		607
129B	*tert*-Butyl (3-cyano-4-(3-(3-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608

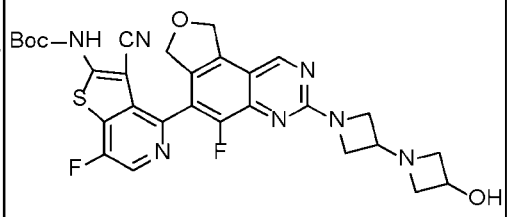
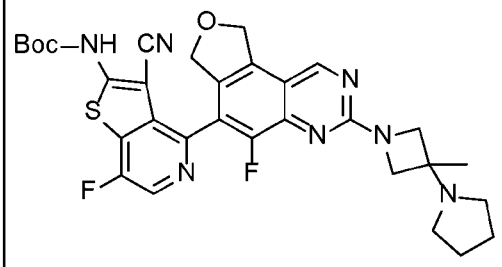
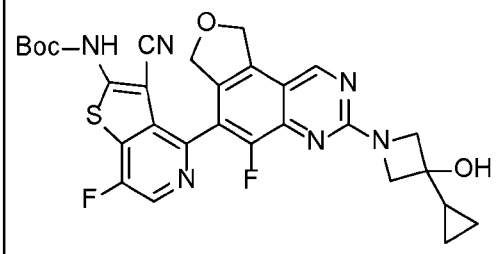
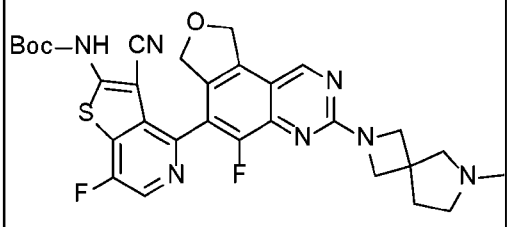
130B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(5-methyl-2,5-diazaspiro[3.5]nonan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		619
131B	*tert*-Butyl (3-cyano-4-(3-((2S,4S)-4-(dimethylamino)-2-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
132B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-methylhexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Mix of Cis Isomers		622
133B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(5-methyl-2,5-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606

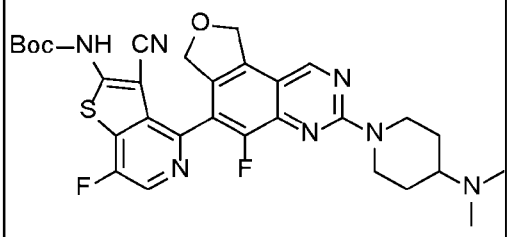
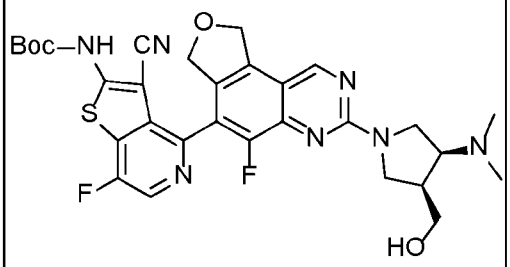
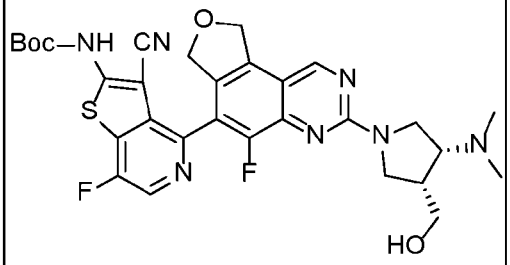
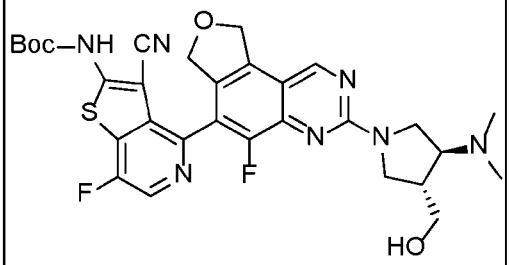
134B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592
135B	*tert*-Butyl (4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate		609
136B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606
137B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606

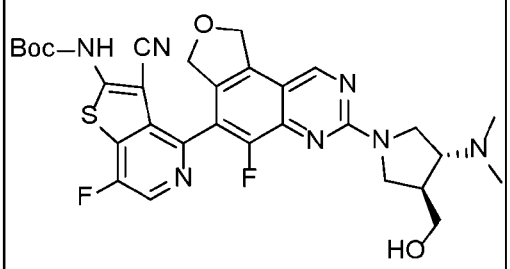
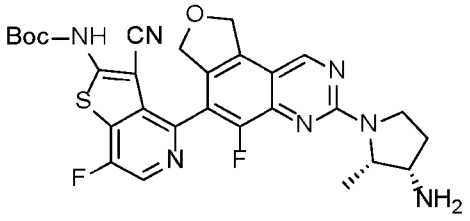
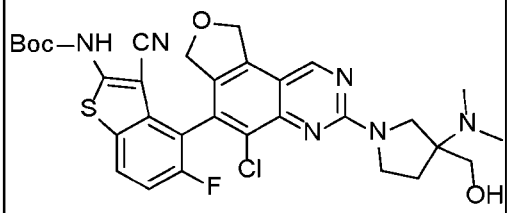
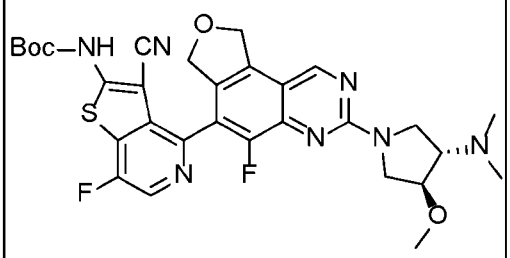
138B	*tert*-Butyl (3-cyano-4-(3-((R)-2-((dimethylamino)methyl)morpholino)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
139B	*tert*-Butyl (3-cyano-4-(3-(5-(dimethylamino)-2-azaspiro[3.3]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
140B	*tert*-Butyl (3-cyano-4-(3-(3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
141B	*tert*-Butyl (4-(3-((R)-7-((*tert*-butoxycarbonyl)amino)-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		692

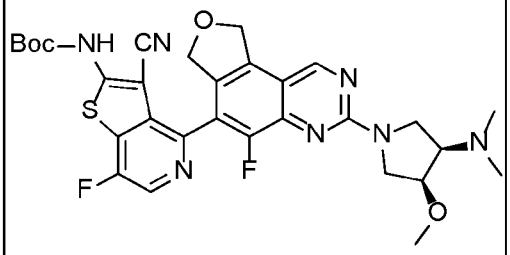
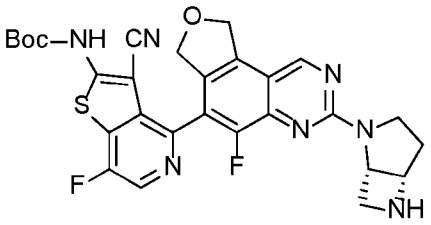
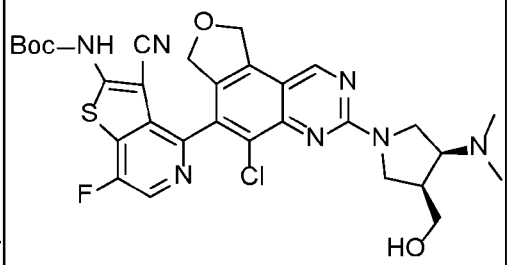
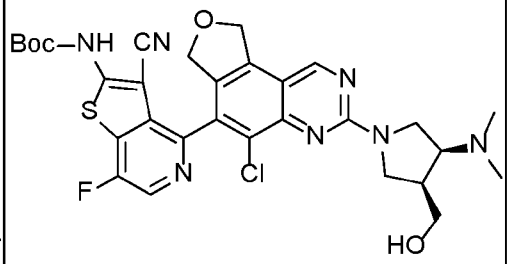
142B	*tert*-Butyl (4-(3-((S)-7-((*tert*-butoxycarbonyl)amino)-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		692
143B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		592
144B	*tert*-Butyl (4-(3-(4-(azetidin-1-yl)piperidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
145B	*tert*-Butyl (4-(3-((S)-3-(azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606

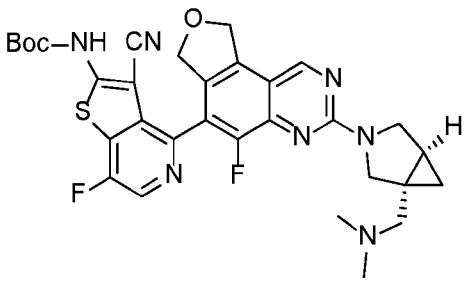
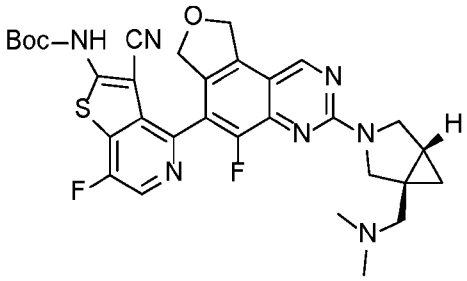
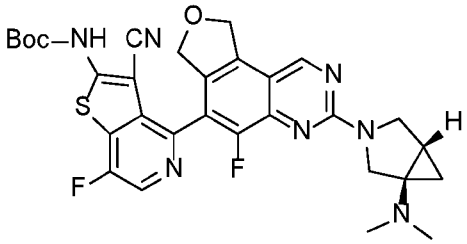
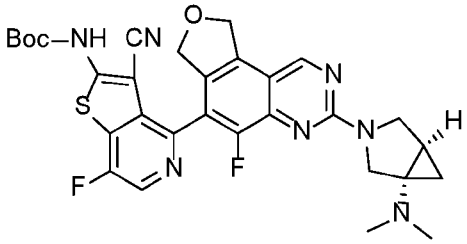
146B	*tert*-butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-(3-methoxyazetidin-1-yl)piperidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
147B	*tert*-Butyl (3-cyano-4-(3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		594
148B	*tert*-Butyl (3-cyano-4-(3-(3-(dimethylamino)piperidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
149B	*tert*-Butyl (4-(3-(6-((*tert*-butoxycarbonyl)amino)-2-azaspiro[3.3]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		692

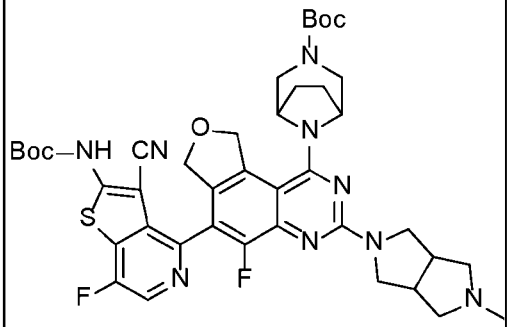
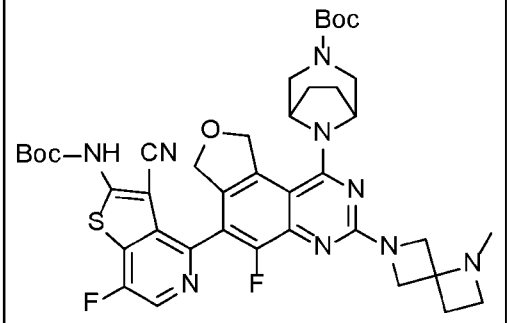
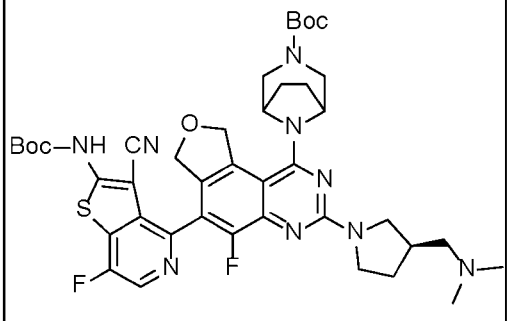
150B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-[1,3'-biazetidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		608
151B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-methyl-3-(pyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		620
152B	*tert*-Butyl (3-cyano-4-(3-(3-cyclopropyl-3-hydroxyazetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		593
153B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(6-methyl-2,6-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606

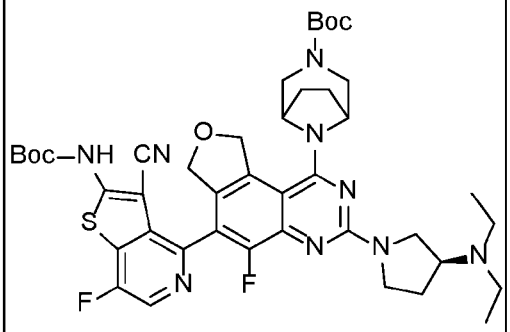
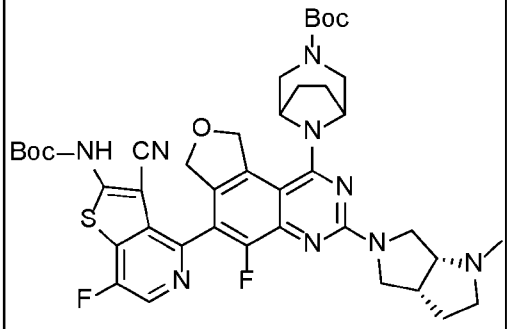
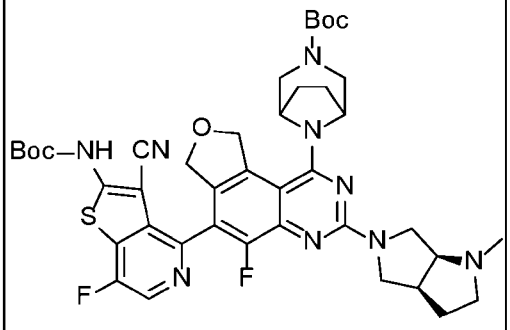
154B	*tert*-Butyl (3-cyano-4-(3-(4-(dimethylamino)piperidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
155B	*tert*-Butyl (3-cyano-4-(3-((3S,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		
156B	*tert*-Butyl (3-cyano-4-(3-((3R,4R)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		
157B	*tert*-Butyl (3-cyano-4-(3-((3S,4R)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		

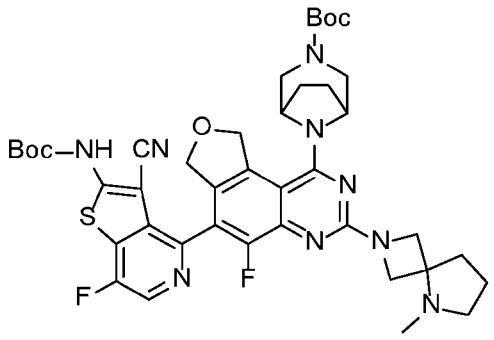
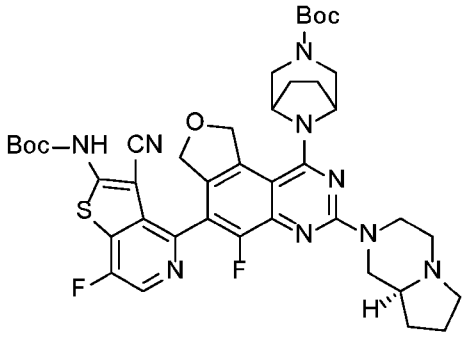
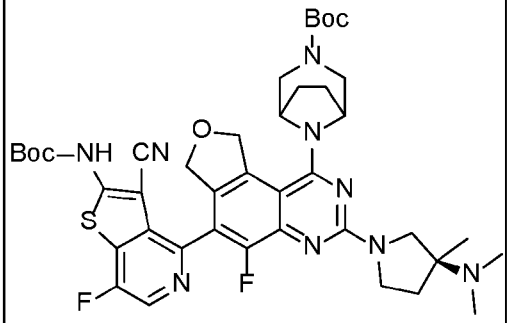
158B	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		
159B	*tert*-Butyl (4-(3-((2S,3S)-3-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		580
160B	*tert*-Butyl (4-(5-chloro-3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate		639
161B	*tert*-Butyl (3-cyano-4-(3-((3S,4S)-3-(dimethylamino)-4-methoxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624

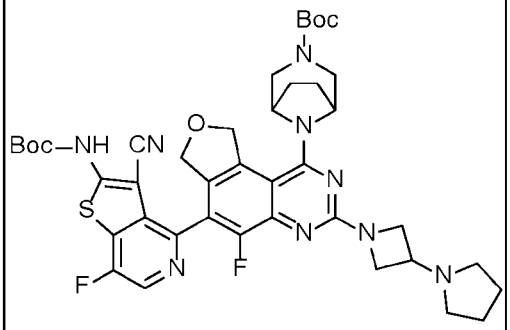
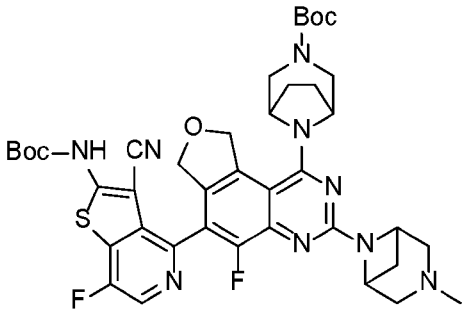
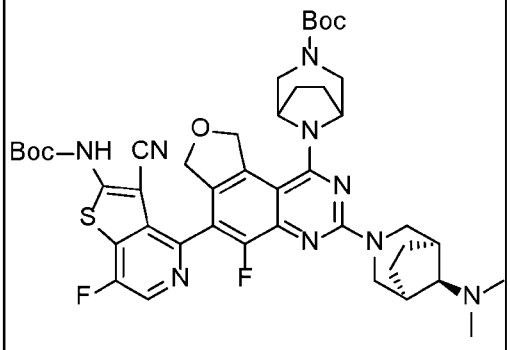
162B	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(dimethylamino)-4-methoxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
163B	*tert*-Butyl (4-(3-((1S,5S)-2,6-diazabicyclo[3.2.0]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		578
164B [5]	*tert*-Butyl (4-(5-chloro-3-((3S,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Atropisomer 1		640
165B [6]	*tert*-Butyl (4-(5-chloro-3-((3S,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Atropisomer 2		640

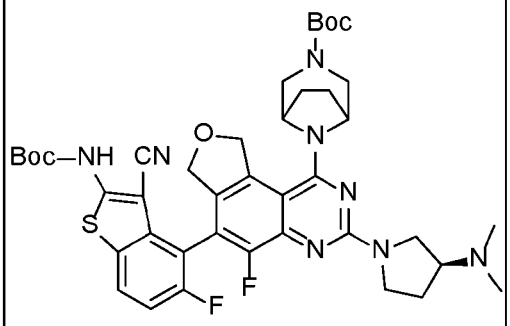
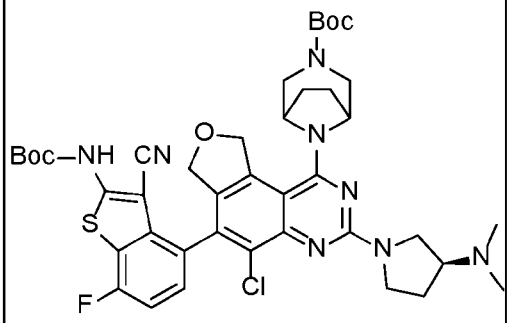
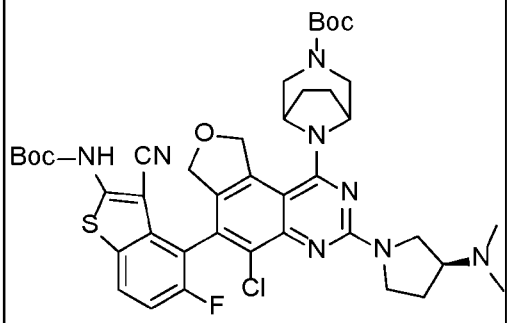
166B	*tert*-Butyl (3-cyano-4-(3-((1R,5S)-1-((dimethylamino)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
167B	*tert*-Butyl (3-cyano-4-(3-((1S,5R)-1-((dimethylamino)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
168B	*tert*-Butyl (3-cyano-4-(3-((1R,5S)-1-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606
169B	*tert*-Butyl (3-cyano-4-(3-((1S,5R)-1-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606

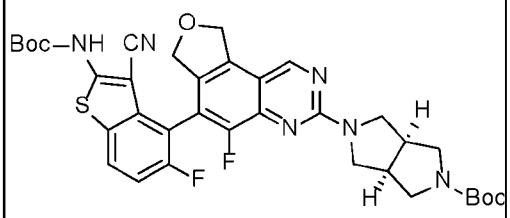
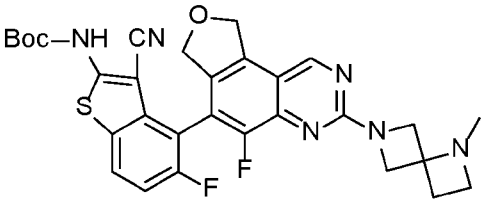
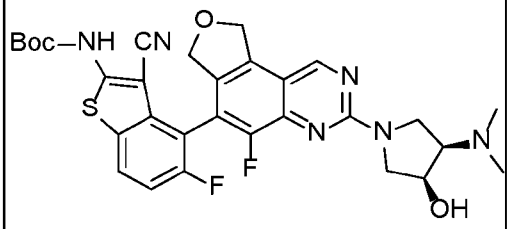
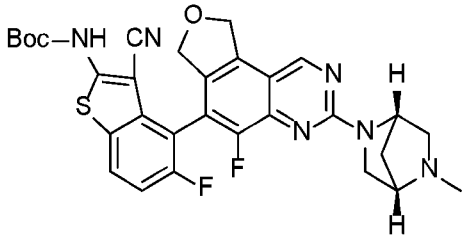
170B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		816
171B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		802
172B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((R)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		818

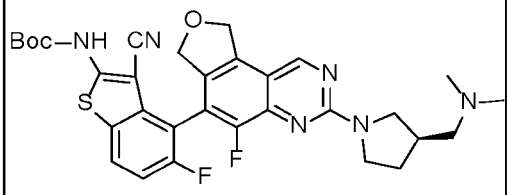
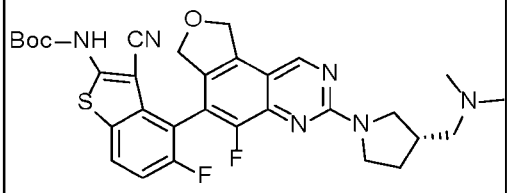
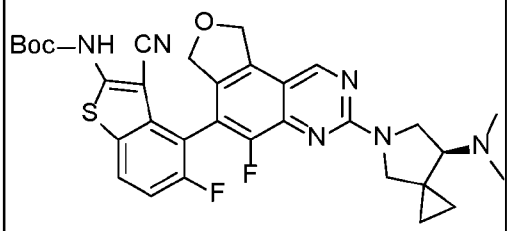
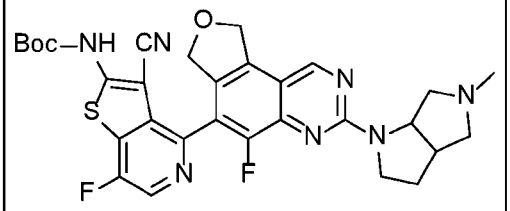
173B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((S)-3-(diethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		832
174B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		816
175B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		816

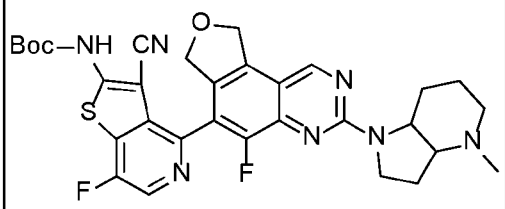
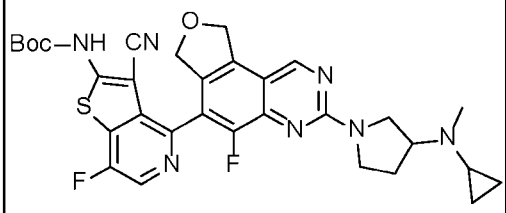
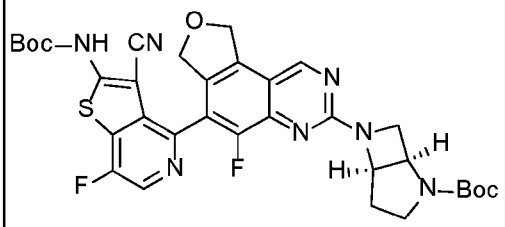
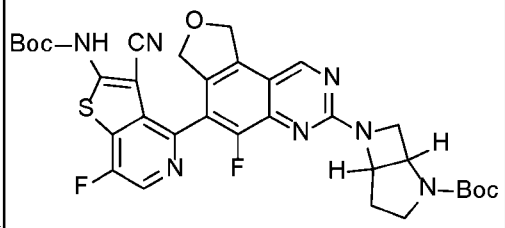
176B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(5-methyl-2,5-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		816
177B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		816
178B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((S)-3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		818

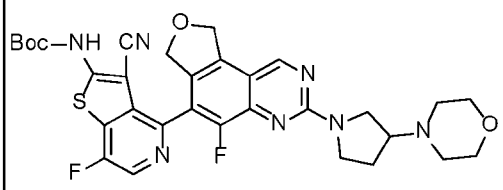
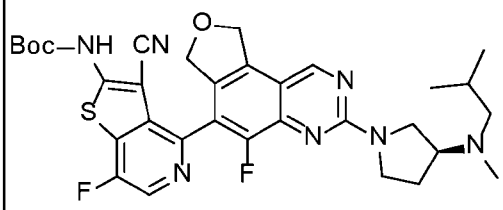
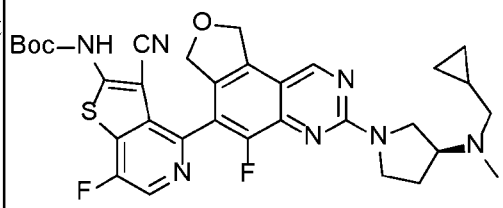
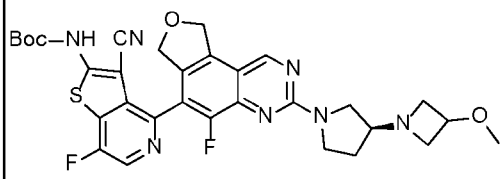
179B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(3-(pyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		816
180B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		802
181B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1R,5S,8R)-8-(dimethylamino)-3-azabicyclo[3.2.1]octan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		844

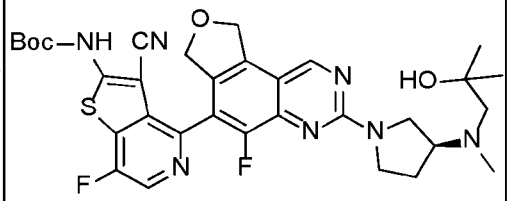
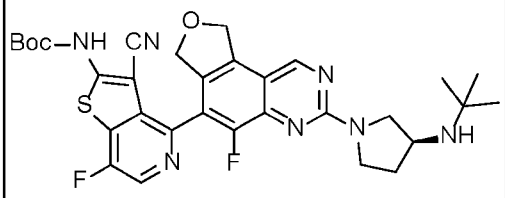
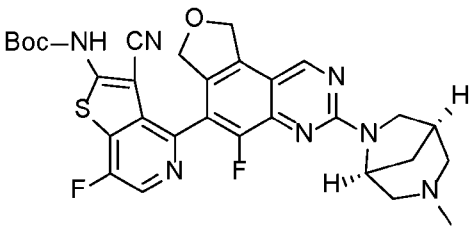
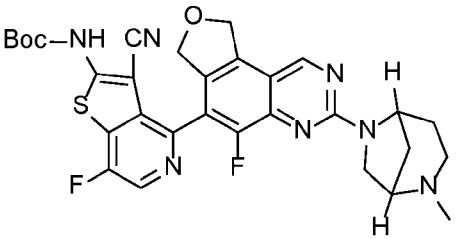
182B [7]	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		803
183B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		819
184B	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		819

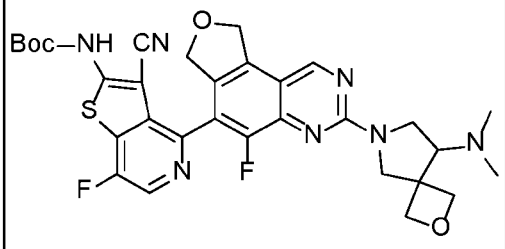
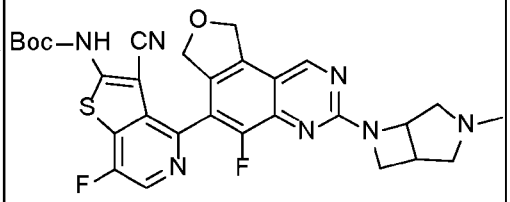
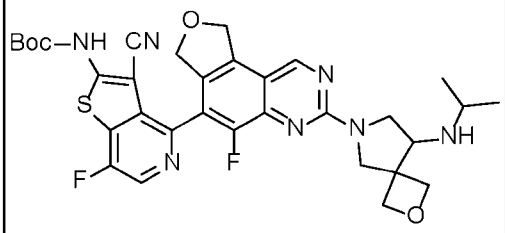
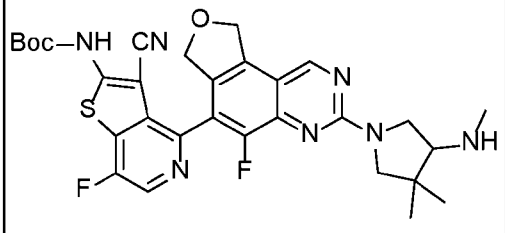
185B [8]	*tert*-Butyl (3aR,6aS)-5-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate		691
186B [8]	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		591
187B [8]	*tert*-Butyl (3-cyano-4-(3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		609
188B [8]	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		591

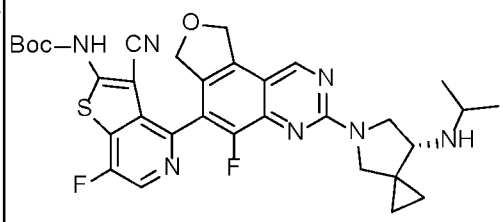
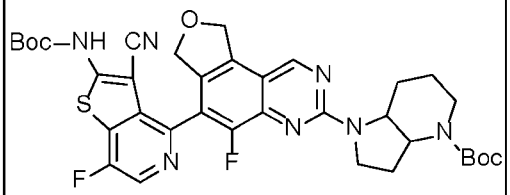
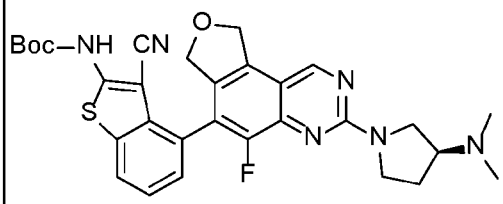
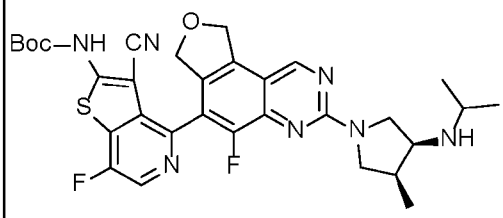
189B [8]	*tert*-Butyl (3-cyano-4-(3-((R)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		607
190B [8]	*tert*-Butyl (3-cyano-4-(3-((S)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		607
191B [8]	*tert*-Butyl (3-cyano-4-(3-((S)-7-(dimethylamino)-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		619
192B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Mix of Cis Isomers		

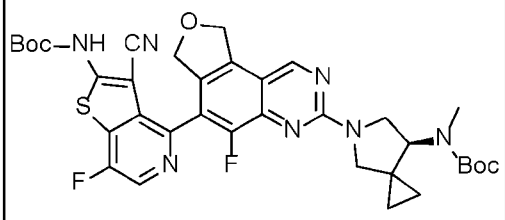
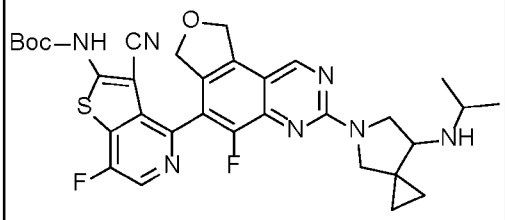
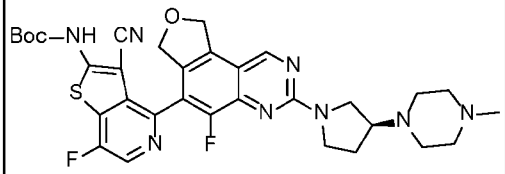
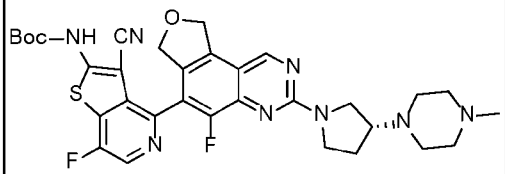
74C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-methyloctahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Mix of Cis Isomers		620
75C	*tert*-Butyl (3-cyano-4-(3-(3-(cyclopropyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
76C	*tert*-Butyl (1R,5R)-6-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate		678
77C	*tert*-Butyl 6-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate, Mix of Cis Isomers		678

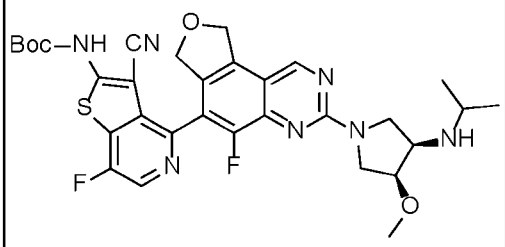
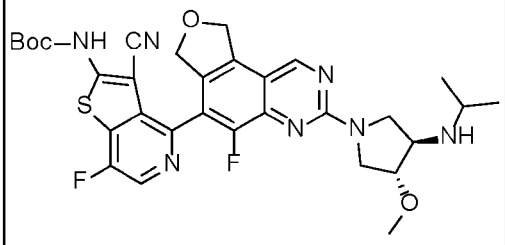
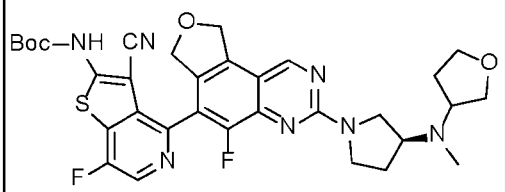
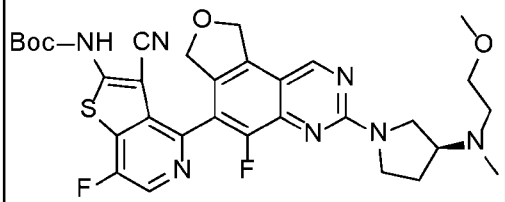
78C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-morpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		636
79C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(isobutyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		636
80C	*tert*-Butyl (3-cyano-4-(3-((S)-3-((cyclopropylmethyl)(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		634
81C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(3-methoxyazetidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		636

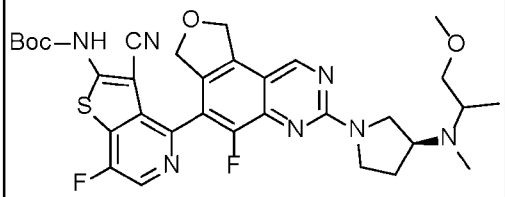
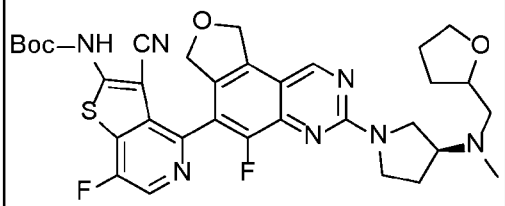
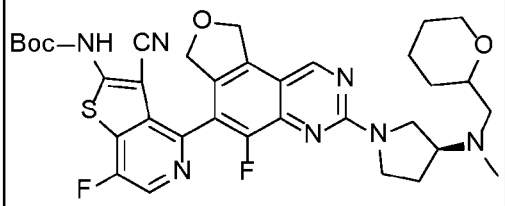
82C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-((2-hydroxy-2-methylpropyl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		652
83C	*tert*-Butyl (4-(3-((S)-3-(tert-butylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		622
84C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1R,5S)-3-methyl-3,6-diazabicyclo[3.2.1]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606
85C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(2-methyl-2,6-diazabicyclo[3.2.1]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Mix of Cis Isomers		606

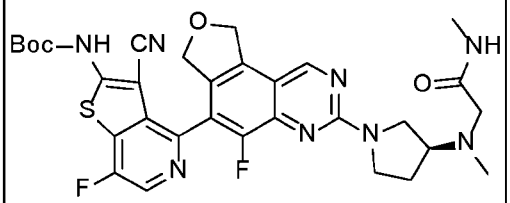
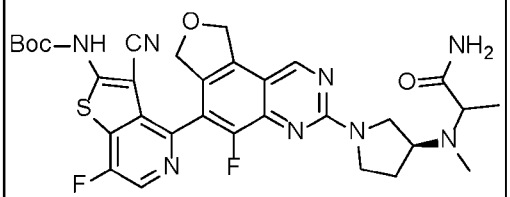
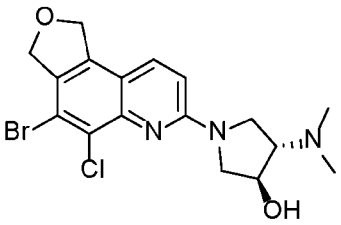
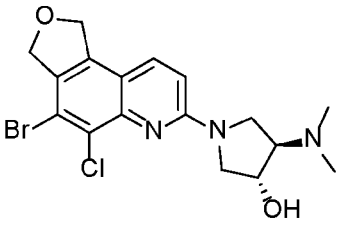
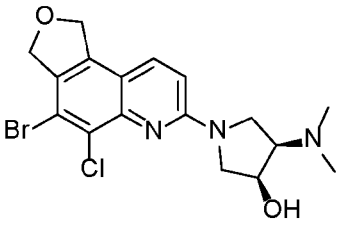
86C	*tert*-Butyl (3-cyano-4-(3-(8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		636
87C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-methyl-3,6-diazabicyclo[3.2.0]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Mix of Cis Isomers		592
88C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(8-(isopropylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
89C	*tert*-Butyl (3-cyano-4-(3-(3,3-dimethyl-4-(methylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608

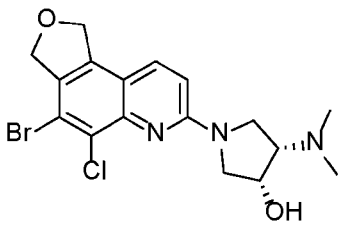
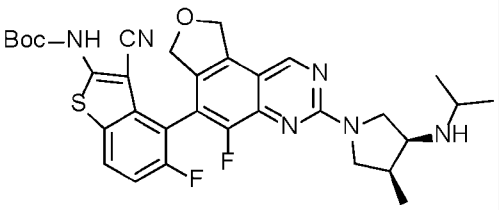
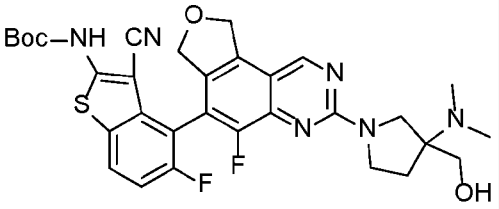
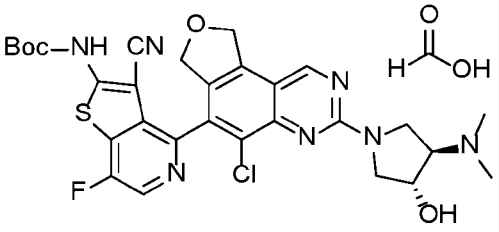
90C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-7-(isopropylamino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		634
91C	*tert*-Butyl 1-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)octahydro-4H-pyrrolo[3,2-b]pyridine-4-carboxylate, Mix of Cis Isomers		706
92C	*tert*-Butyl (3-cyano-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		575
93C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		622

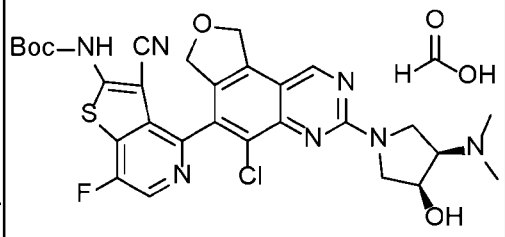
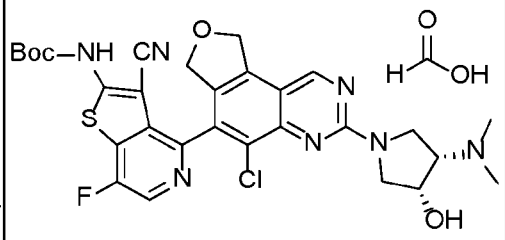
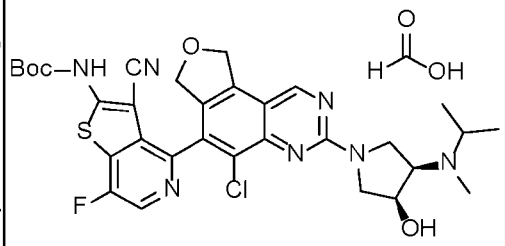
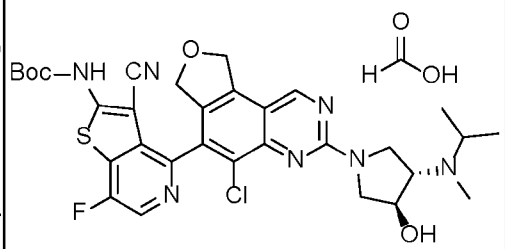
94C	*tert*-Butyl ((7S)-5-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-5-azaspiro[2.4]heptan-7-yl)(methyl)carbamate		706
95C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(7-(isopropylamino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		634
96C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		649
97C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		649

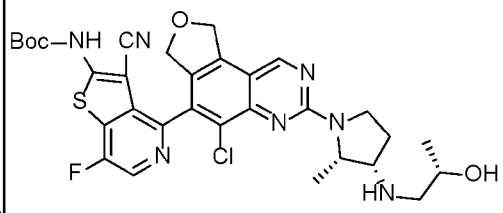
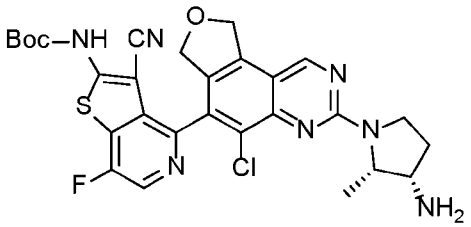
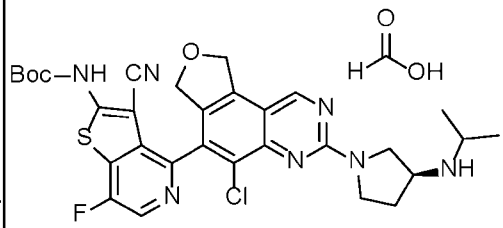
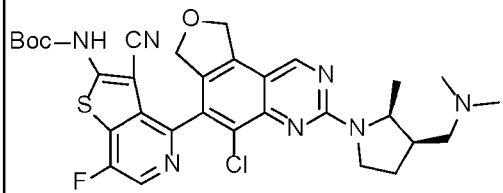
98C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
99C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
100C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl(tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
101C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-((2-methoxyethyl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638

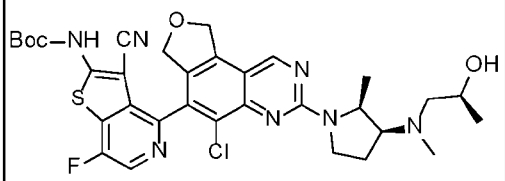
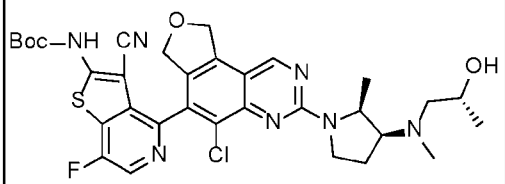
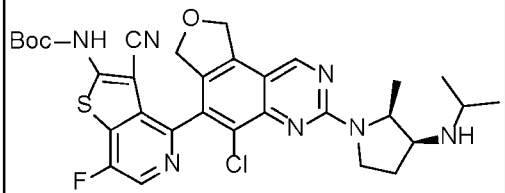
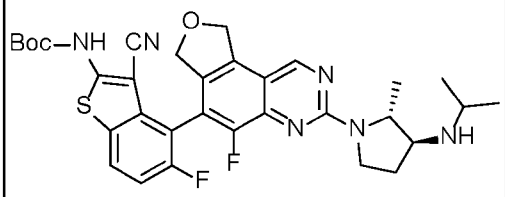
102C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-((1-methoxypropan-2-yl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		652
103C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl((tetrahydrofuran-2-yl)methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664
104C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl((tetrahydro-2H-pyran-2-yl)methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		678

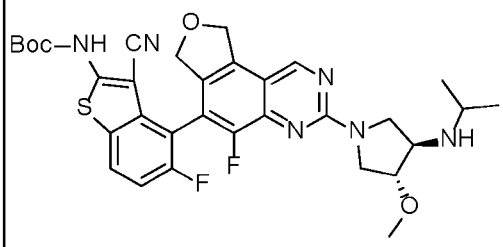
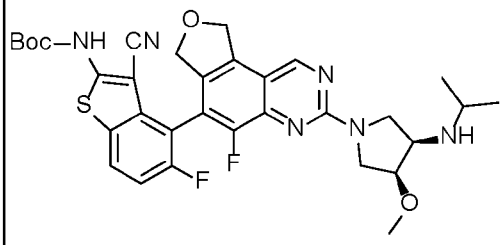
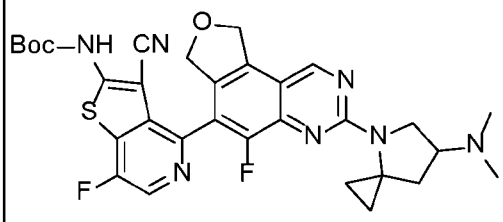
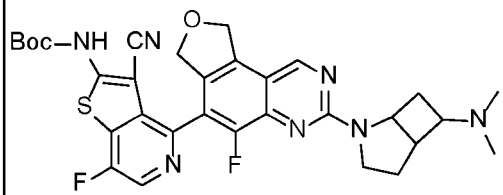
105C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(methyl(2-(methylamino)-2-oxoethyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		651
106C	*tert*-Butyl (4-(3-((3S)-3-((1-amino-1-oxopropan-2-yl)(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		651
107C [4]	(3S,4S)-1-(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-4-(dimethylamino)pyrrolidin-3-ol		412
108C [4]	(3R,4R)-1-(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-4-(dimethylamino)pyrrolidin-3-ol		412
109C [4]	(3S,4R)-1-(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-4-(dimethylamino)pyrrolidin-3-ol		412

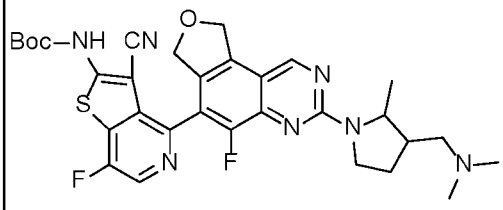
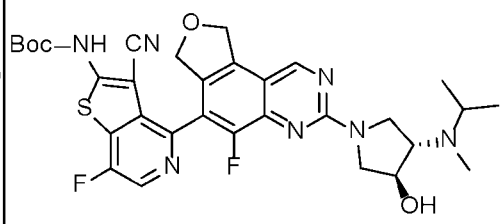
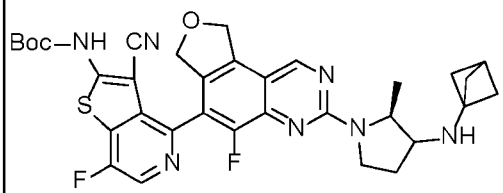
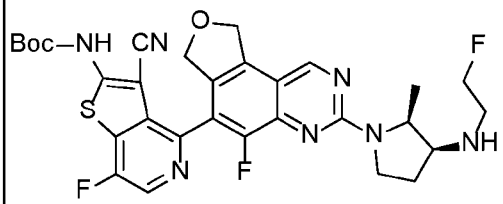
110C [4]	(3R,4S)-1-(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-4-(dimethylamino)pyrrolidin-3-ol		412
111C	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3S,4S)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		621
112C	*tert*-Butyl (3-cyano-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		623
113C	*tert*-Butyl (4-(5-chloro-3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate formic acid		626

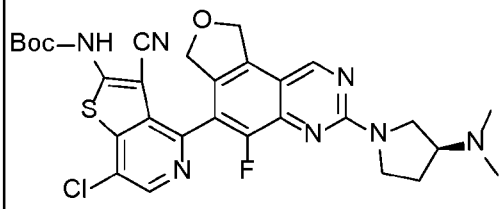
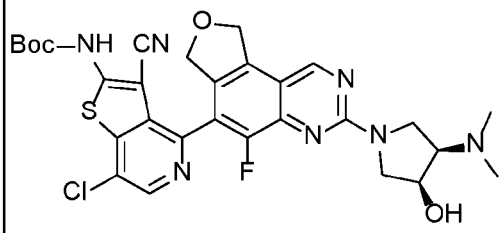
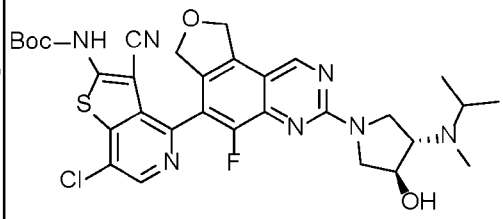
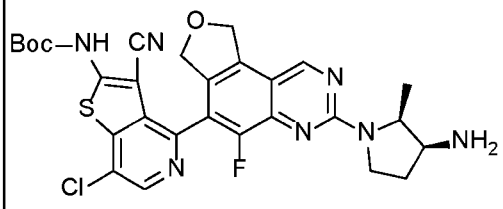
114C	*tert*-Butyl (4-(5-chloro-3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate formic acid		626
115C	*tert*-Butyl (4-(5-chloro-3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate formic acid		626
116C	*tert*-Butyl (4-(5-chloro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate formic acid		654
117C	*tert*-Butyl (4-(5-chloro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate formic acid		654

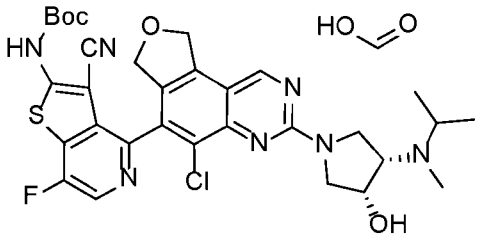
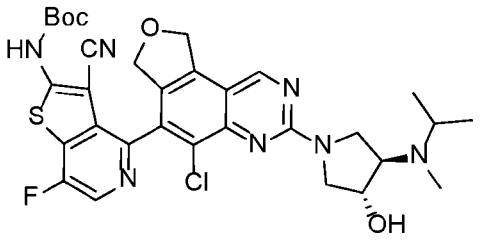
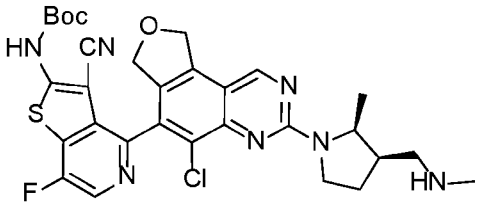
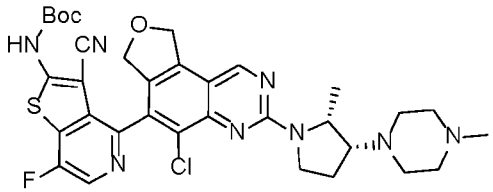
118C	*tert*-Butyl (4-(5-chloro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		654
119C	*tert*-Butyl (4-(3-((2S,3S)-3-amino-2-methylpyrrolidin-1-yl)-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		596
120C	*tert*-Butyl (4-(5-chloro-3-((S)-3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate formic acid		624
121C	*tert*-Butyl (4-(5-chloro-3-((2S,3R)-3-((dimethylamino)methyl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		638

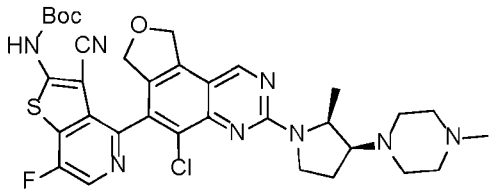
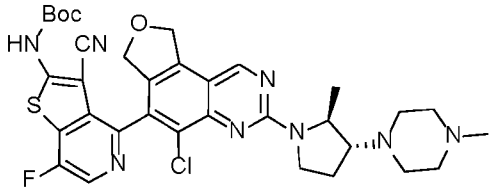
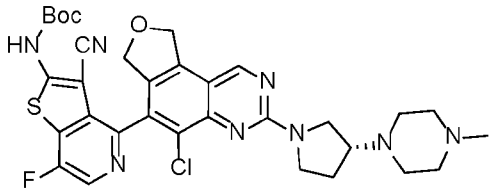
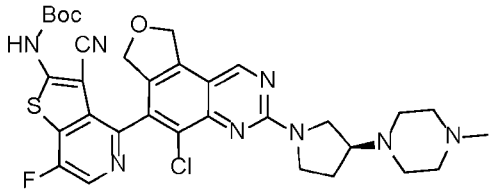
122C	*tert*-Butyl (4-(5-chloro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		668
123C	*tert*-Butyl (4-(5-chloro-3-((2S,3S)-3-(((R)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		668
124C	*tert*-Butyl (4-(5-chloro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		638
125C	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((2R,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		621

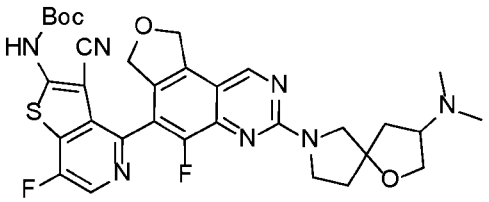
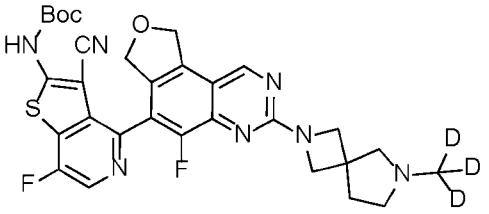
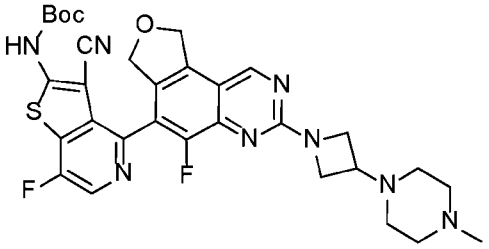
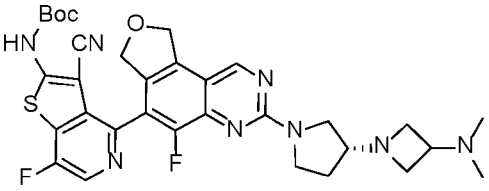
126C	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3R,4R)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		637
127C	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		637
128C	*tert*-Butyl (3-cyano-4-(3-(6-(dimethylamino)-4-azaspiro[2.4]heptan-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
129C	*tert*-Butyl (3-cyano-4-(3-(6-(dimethylamino)-2-azabicyclo[3.2.0]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620

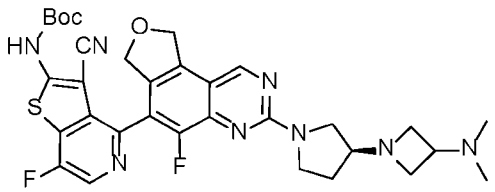
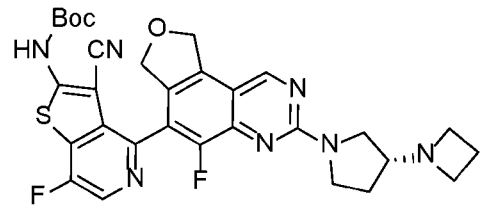
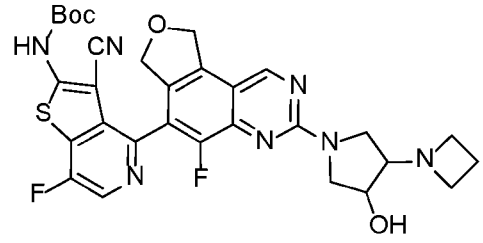
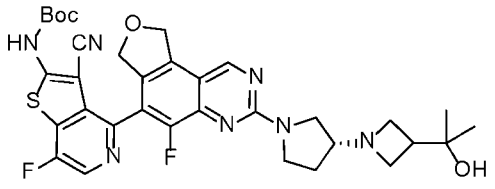
130C	*tert*-Butyl (3-cyano-4-(3-(3-((dimethylamino)methyl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Mix of Cis Isomers		622
131C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
132C	*tert*-Butyl (4-(3-((2S)-3-(bicyclo[1.1.1]pentan-1-ylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		646
133C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((2-fluoroethyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		626

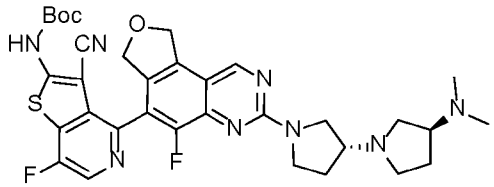
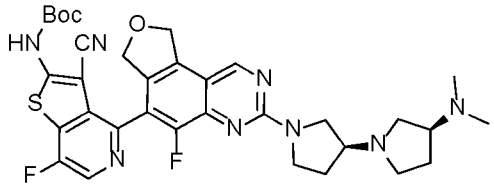
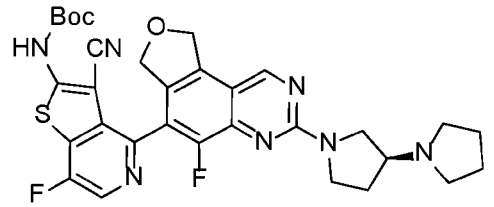
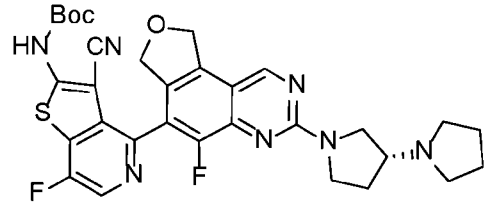
134C	*tert*-Butyl (7-chloro-3-cyano-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		610
135C	*tert*-Butyl (7-chloro-3-cyano-4-(3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		626
136C	*tert*-Butyl (7-chloro-3-cyano-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		654
137C	*tert*-Butyl (4-(3-((2S,3S)-3-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-chloro-3-cyanothieno[3,2-c]pyridin-2-yl)carbamate		596

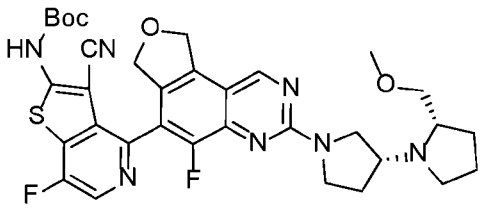
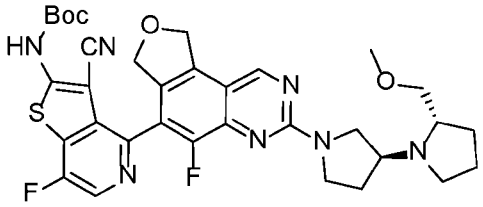
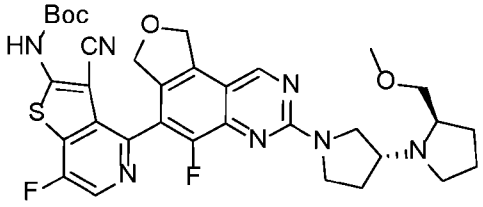
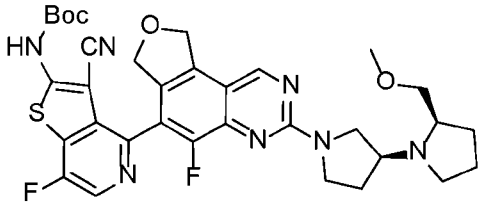
382D	*tert*-Butyl (4-(5-chloro-3-((3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate formic acid		654
383D	*tert*-Butyl (4-(5-chloro-3-((3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		654
384D	*tert*-Butyl (4-(5-chloro-3-((2S,3R)-2-methyl-3-((methylamino)methyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
385D	*tert*-Butyl (4-(5-chloro-3-((2R,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		679

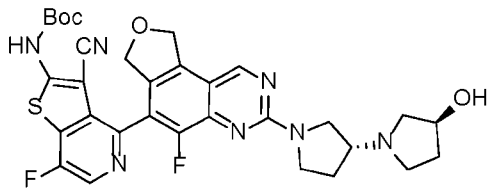
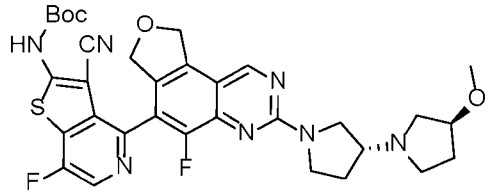
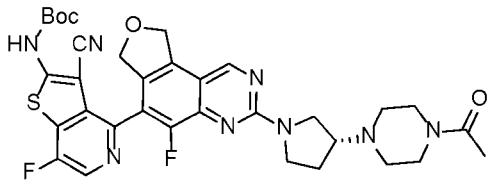
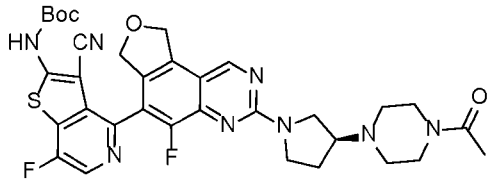
386D	*tert*-Butyl (4-(5-chloro-3-((2S,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		679
387D	*tert*-Butyl (4-(5-chloro-3-((2S,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		679
388D	*tert*-Butyl (4-(5-chloro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		665
389D	*tert*-Butyl (4-(5-chloro-3-((S)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		665

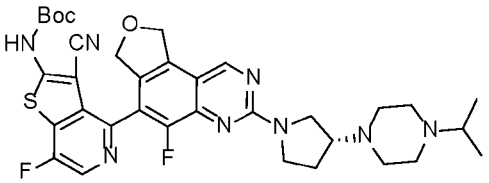
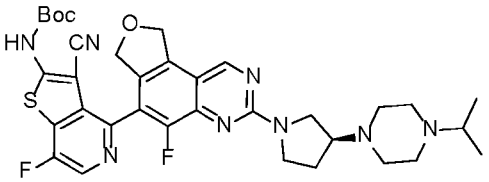
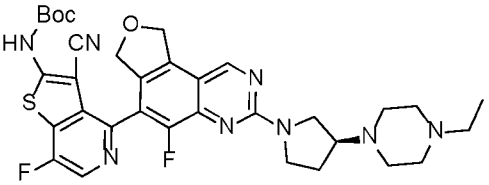
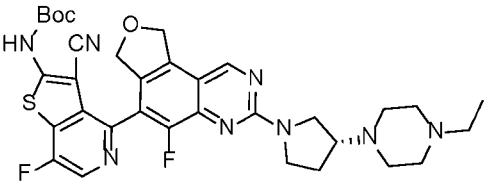
390D	*tert*-Butyl (3-cyano-4-(3-(3-(dimethylamino)-1-oxa-7-azaspiro[4.4]nonan-7-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		650
391D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(6-(methyl-d3)-2,6-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		609
392D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		635
393D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		649

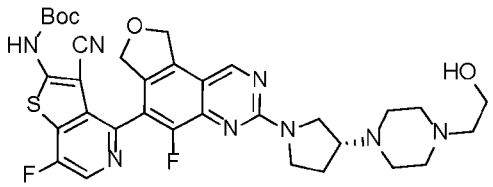
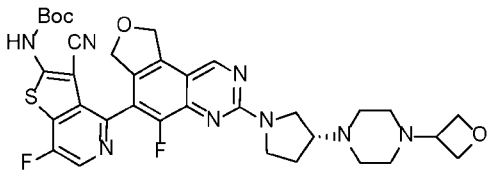
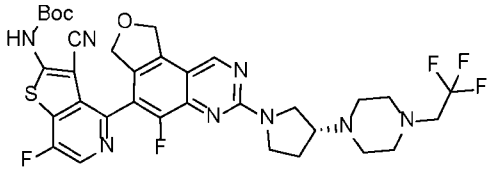
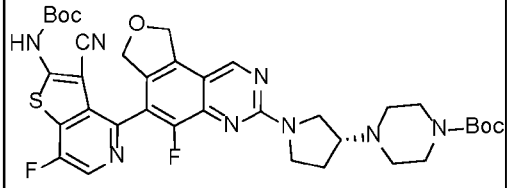
394D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		649
395D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		606
396D [9]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		622
397D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664

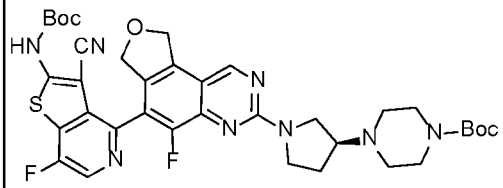
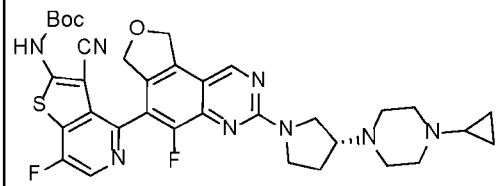
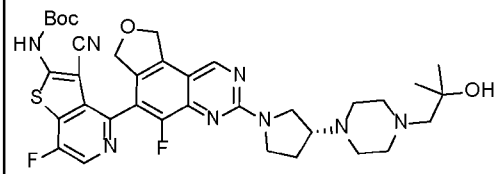
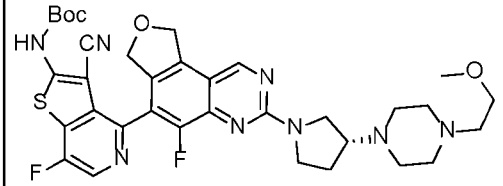
398D	*tert*-Butyl (3-cyano-4-(3-((3S,3'R)-3-(dimethylamino)-[1,3'-bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
399D	*tert*-Butyl (3-cyano-4-(3-((3S,3'S)-3-(dimethylamino)-[1,3'-bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
400D	*tert*-Butyl (4-(3-((S)-[1,3'-bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620
401D	*tert*-Butyl (4-(3-((R)-[1,3'-bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		620

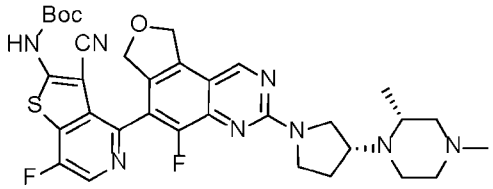
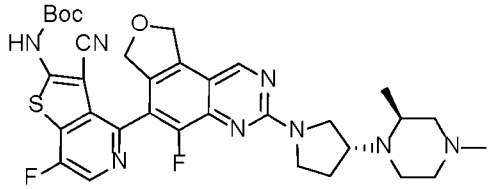
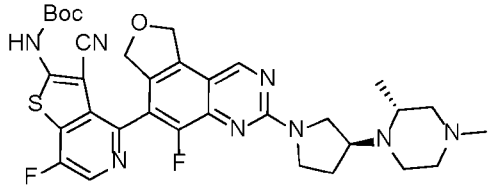
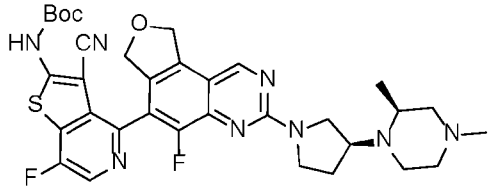
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403D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3'S)-2-(methoxymethyl)-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664
404D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2R,3'R)-2-(methoxymethyl)-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664
405D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2R,3'S)-2-(methoxymethyl)-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664

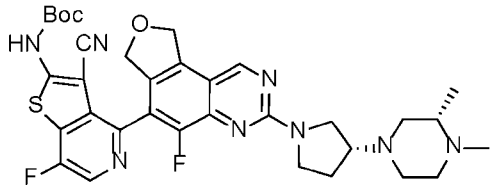
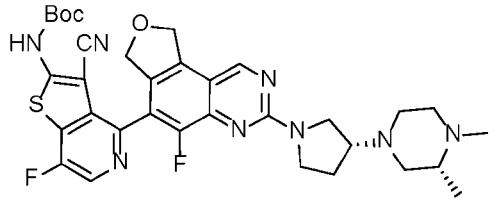
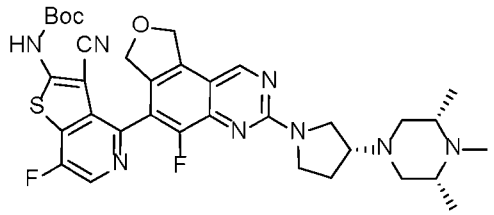
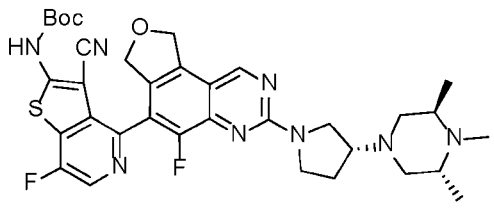
406D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,3'R)-3-hydroxy-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		636
407D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,3'R)-3-methoxy-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
408D	*tert*-Butyl (4-(3-((R)-3-(4-acetylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		677
409D	*tert*-Butyl (4-(3-((S)-3-(4-acetylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		677

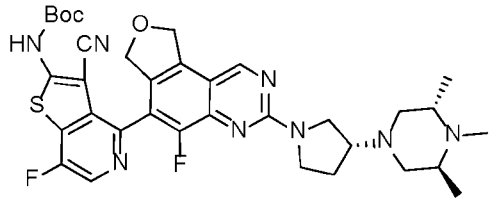
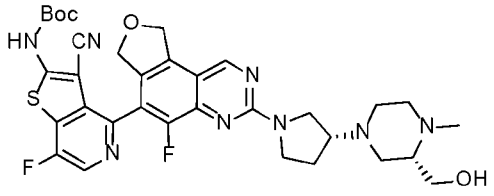
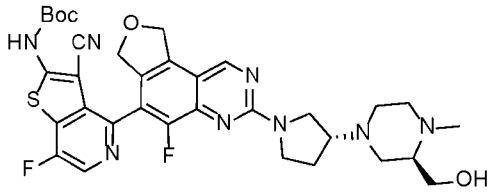
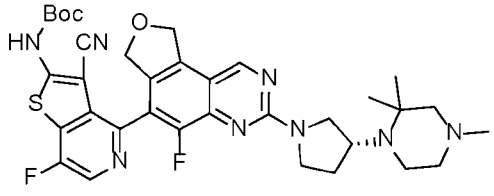
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411D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(4-isopropylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		677
412D	*tert*-Butyl (3-cyano-4-(3-((S)-3-(4-ethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
413D	*tert*-Butyl (3-cyano-4-(3-((R)-3-(4-ethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663

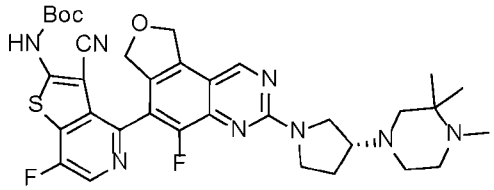
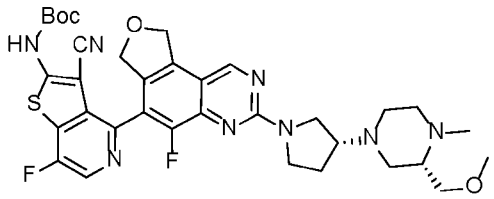
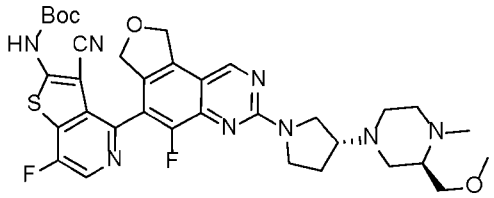
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415D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(oxetan-3-yl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		691
416D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		717
417D	*tert*-Butyl 4-((3R)-1-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)pyrrolidin-3-yl)piperazine-1-carboxylate		735

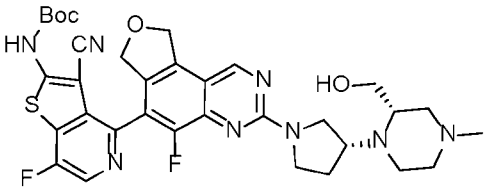
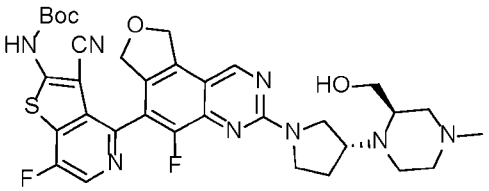
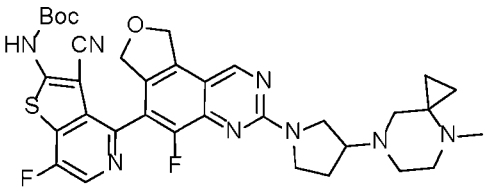
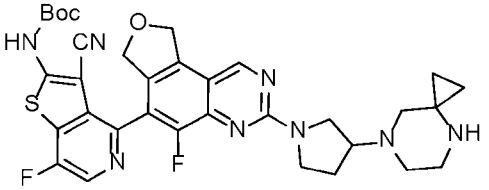
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419D	*tert*-Butyl (3-cyano-4-(3-((R)-3-(4-cyclopropylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		675
420D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		707
421D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(2-methoxyethyl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		693

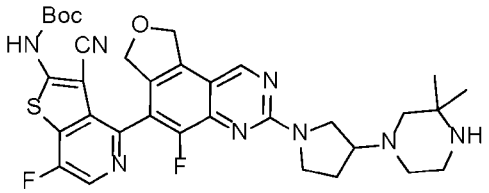
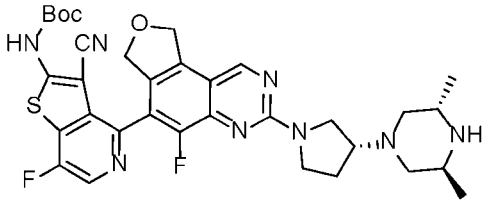
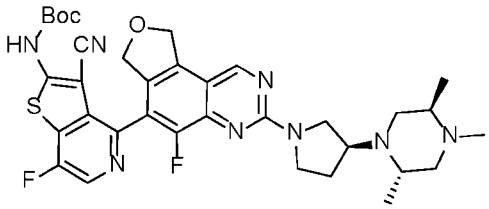
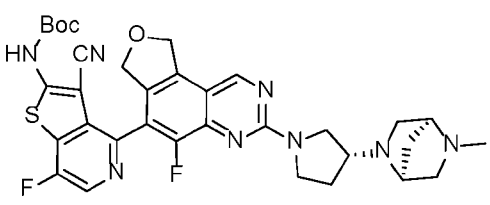
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423D	*tert*-Butyl (3-cyano-4-(3-((R)-3-((S)-2,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
424D	*tert*-Butyl (3-cyano-4-(3-((S)-3-((R)-2,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
425D	*tert*-Butyl (3-cyano-4-(3-((S)-3-((S)-2,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663

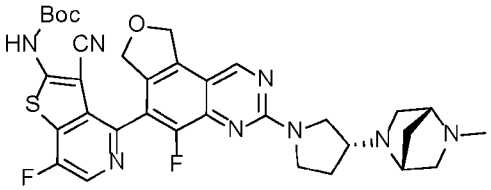
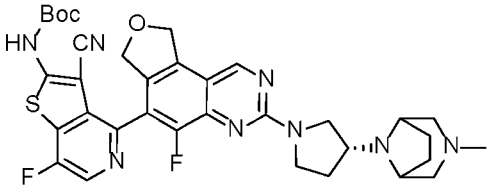
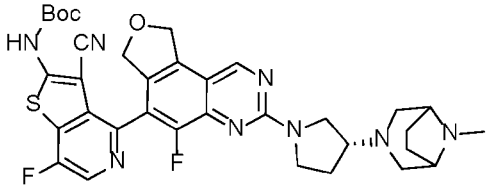
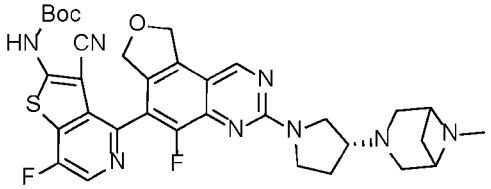
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427D	*tert*-Butyl (3-cyano-4-(3-((R)-3-((R)-3,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
428D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		677
429D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((3R,5R)-3,4,5-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		677

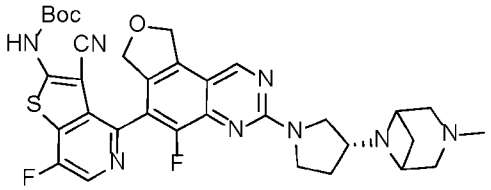
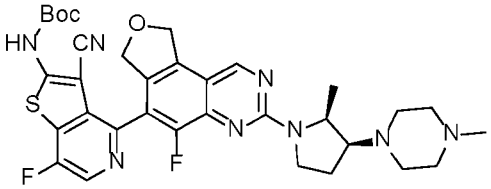
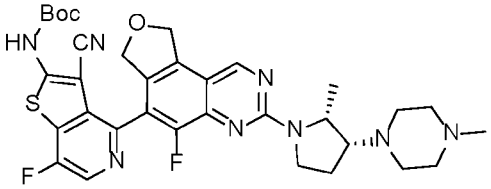
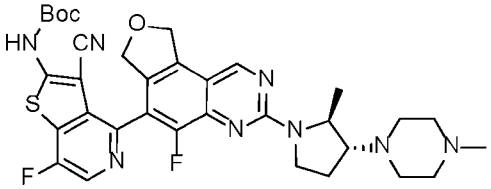
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431D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		679
432D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((R)-3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		679
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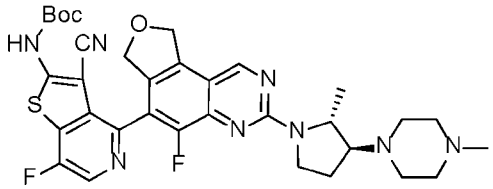
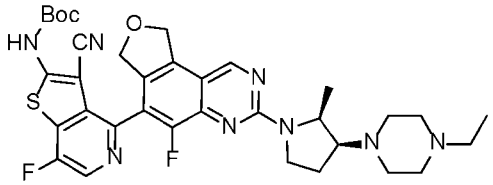
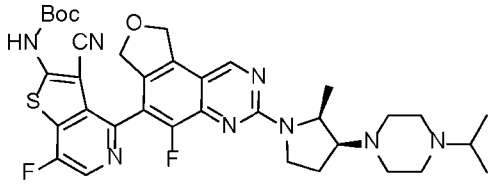
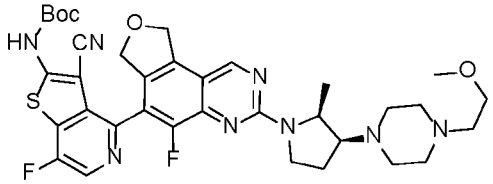
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435D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((S)-3-(methoxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		693
436D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		693

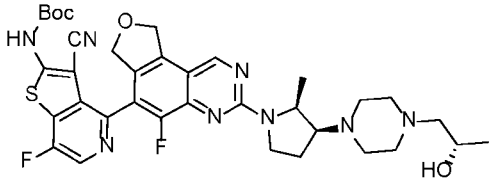
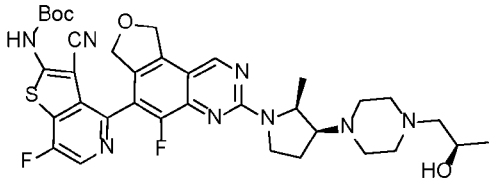
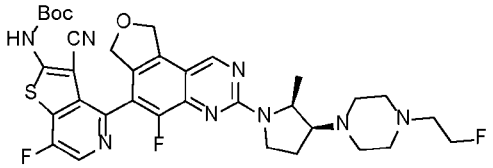
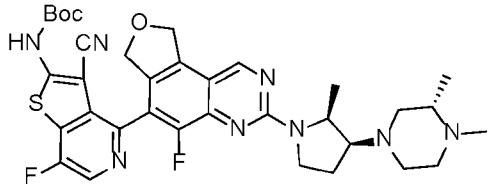
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438D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((R)-2-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		679
439D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		675
440D	*tert*-Butyl (4-(3-(3-(4,7-diazaspiro[2.5]octan-7-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		661

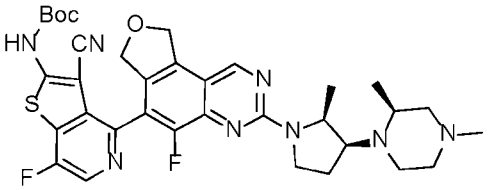
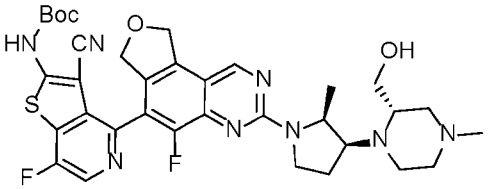
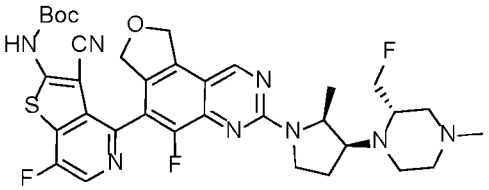
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442D	*tert*-Butyl (3-cyano-4-(3-((R)-3-((3S,5S)-3,5-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
443D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		677
444D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		661

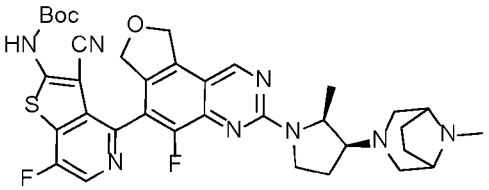
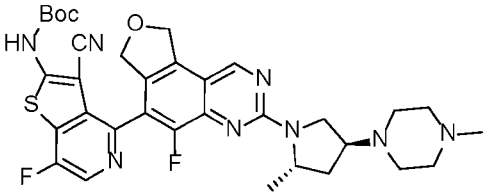
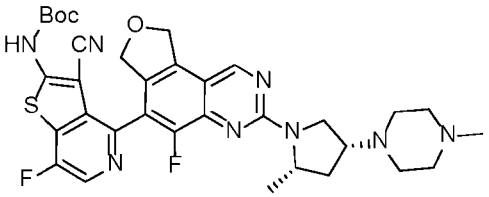
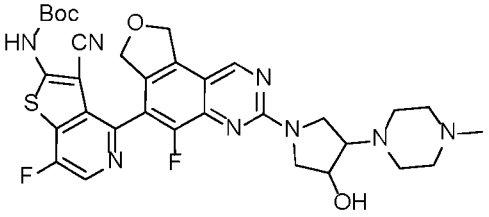
445D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		661
446D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R)-3-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		675
447D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R)-3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		675
448D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R)-3-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		661

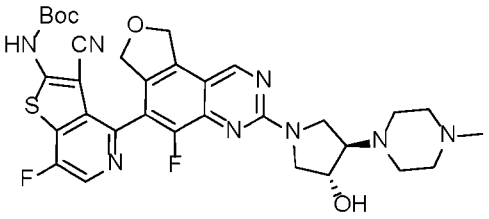
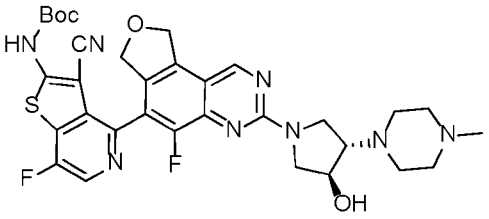
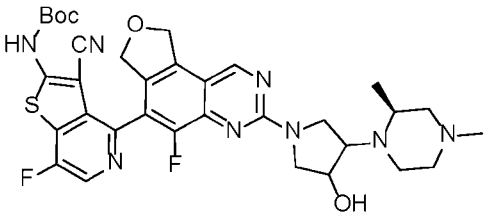
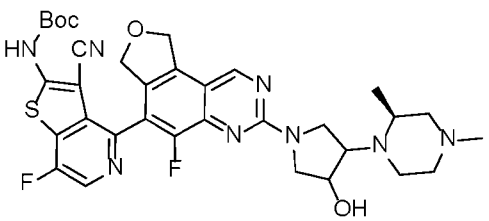
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450D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663
451D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2R,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663
452D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663

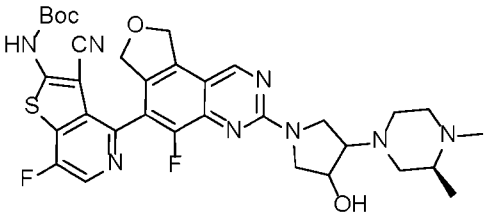
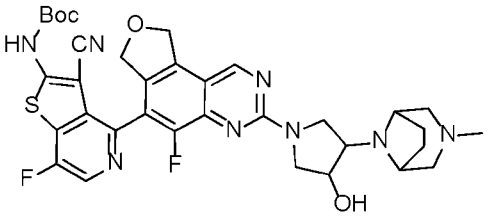
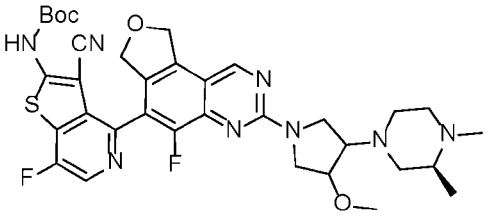
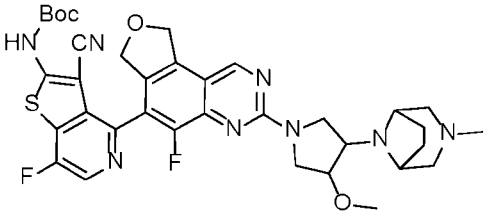
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454D	*tert*-Butyl (3-cyano-4-(3-((2S,3S)-3-(4-ethylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		677
455D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-isopropylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		691
456D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-(2-methoxyethyl)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		707

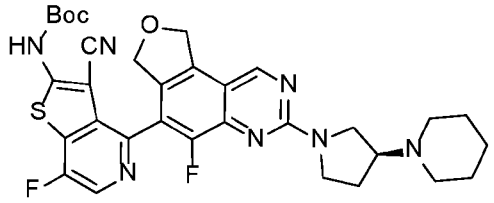
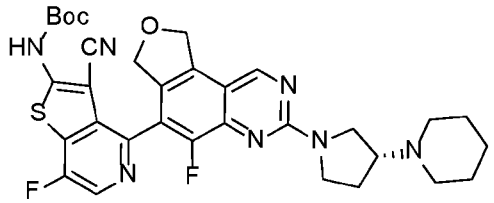
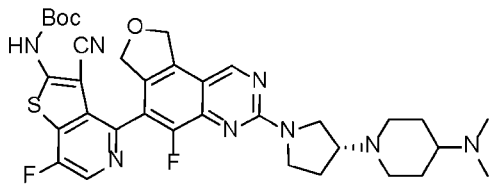
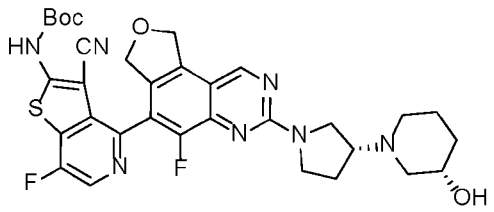
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458D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-((R)-2-hydroxypropyl)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		707
459D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-(2-fluoroethyl)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		695
460D	*tert*-Butyl (3-cyano-4-(3-((2S,3S)-3-((S)-3,4-dimethylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		677

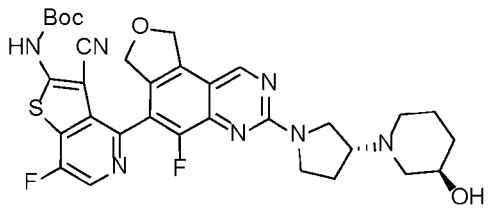
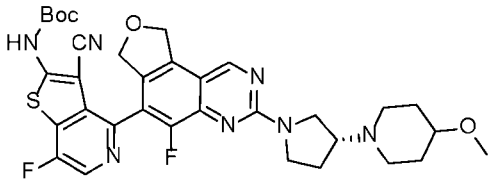
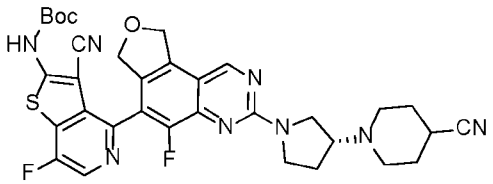
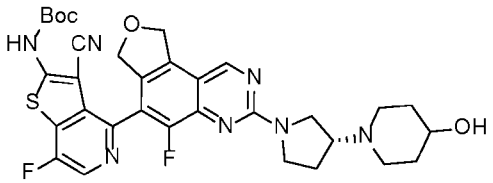
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462D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((S)-2-(hydroxymethyl)-4-methylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		693
463D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((S)-2-(fluoromethyl)-4-methylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		695

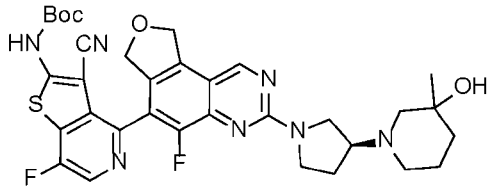
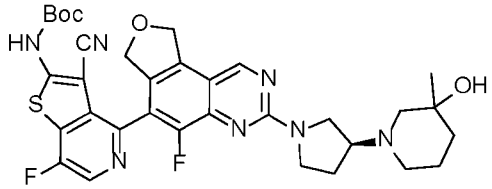
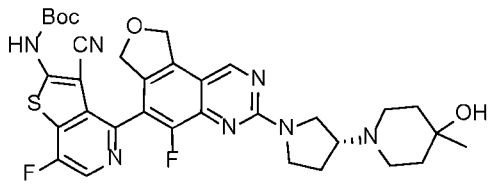
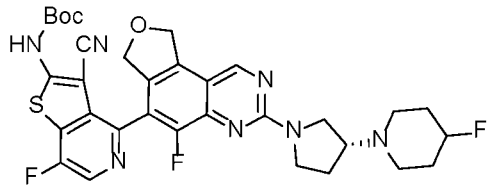
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465D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,4S)-2-methyl-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663
466D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,4R)-2-methyl-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663
467D [10]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		665

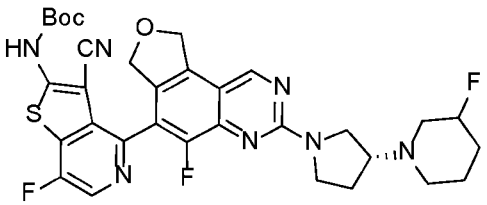
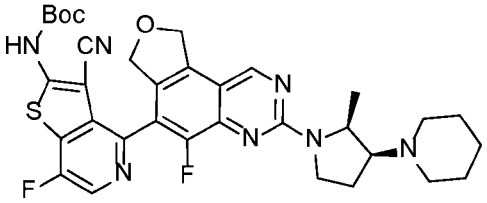
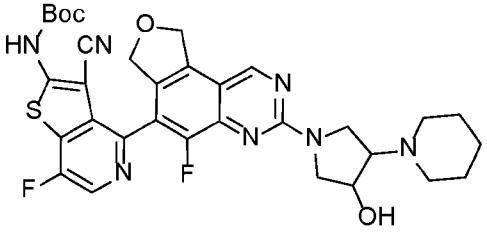
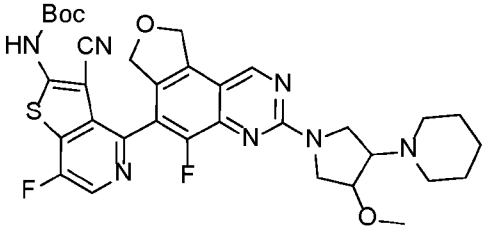
468D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		665
469D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		665
470D [11]	*tert*-Butyl (3-cyano-4-(3-(3-((S)-2,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2		679
471D [11]	*tert*-Butyl (3-cyano-4-(3-(3-((S)-2,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate. Isomer 1		679

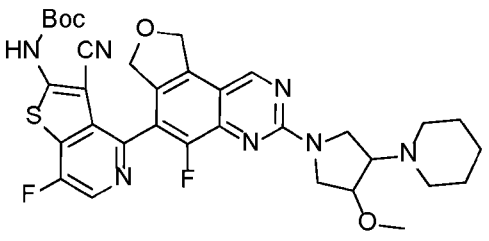
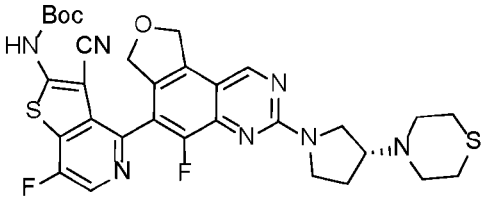
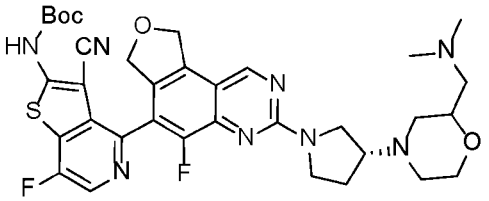
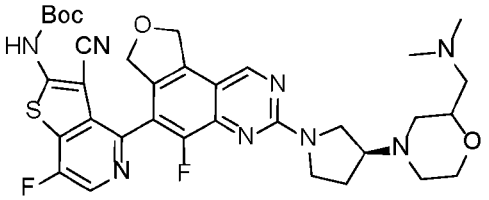
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473D [13]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		691
474D [14]	*tert*-Butyl (3-cyano-4-(3-(3-((S)-3,4-dimethylpiperazin-1-yl)-4-methoxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		693
475D [15]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		705

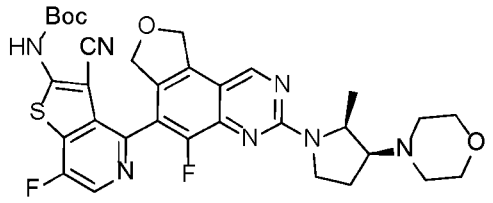
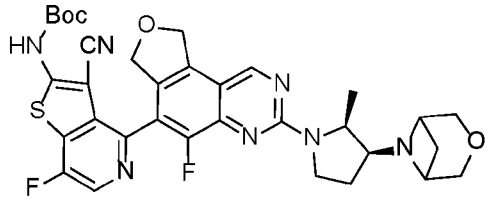
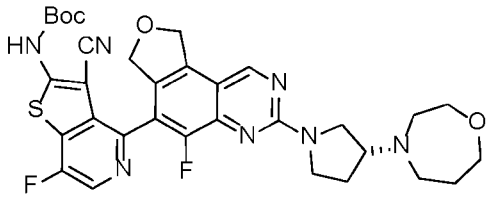
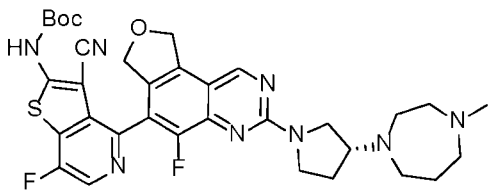
476D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		634
477D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		634
478D	*tert*-Butyl (3-cyano-4-(3-((R)-3-(4-(dimethylamino)piperidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		677
479D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((S)-3-hydroxypiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650

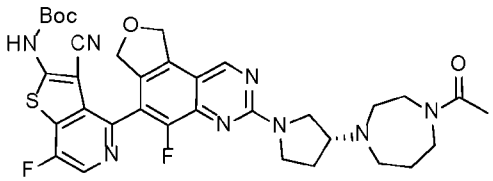
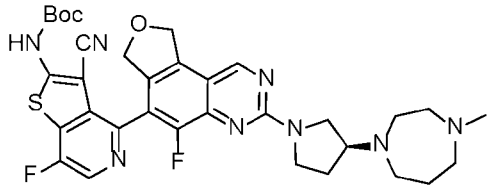
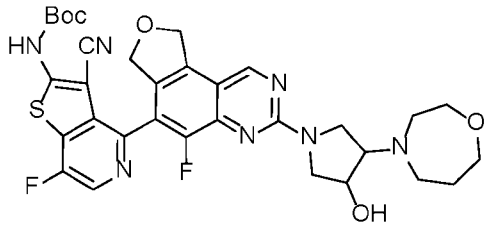
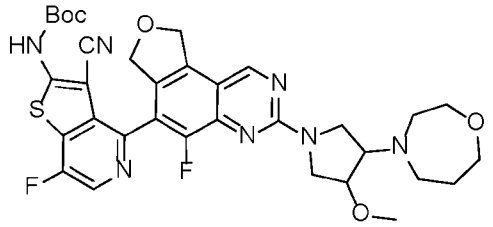
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481D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-methoxypiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664
482D	*tert*-Butyl (3-cyano-4-(3-((R)-3-(4-cyanopiperidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		659
483D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-hydroxypiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650

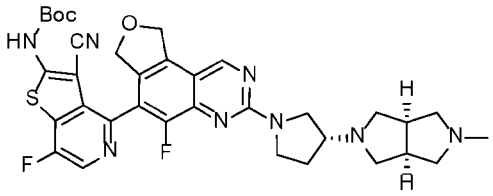
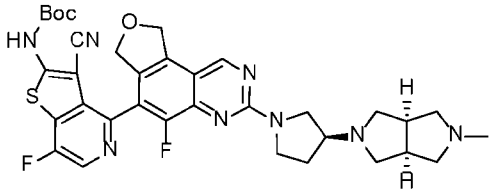
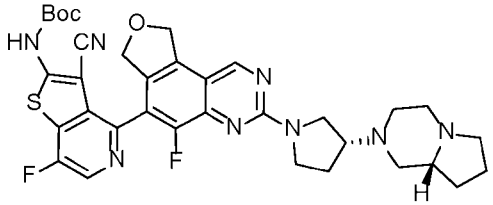
484D [16]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-(3-hydroxy-3-methylpiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Isomer 1		664
485D [16]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-(3-hydroxy-3-methylpiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2		664
486D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-hydroxy-4-methylpiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664
487D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-fluoropiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		652

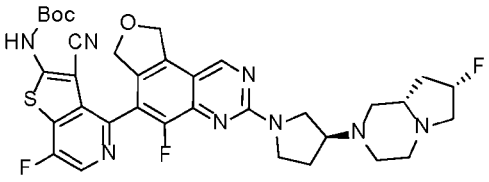
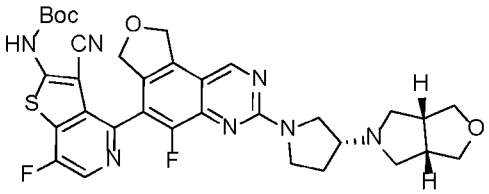
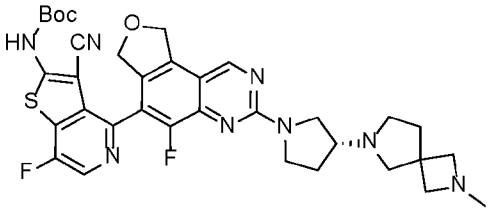
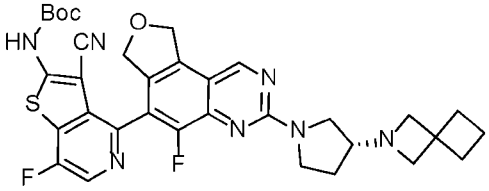
488D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R)-3-(3-fluoropiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		652
489D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		648
490D [17]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
491D [18]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Isomer 1		664

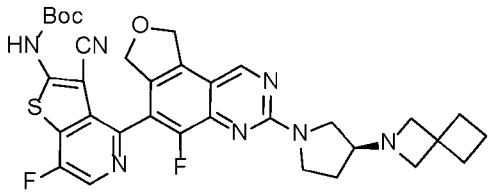
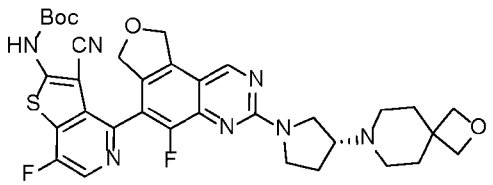
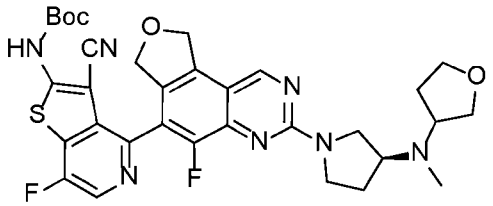
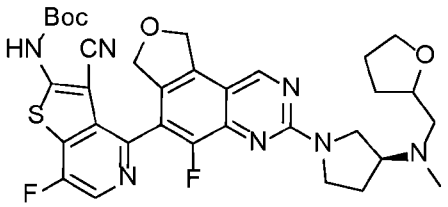
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493D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-thiomorpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		652
494D	*tert*-Butyl (3-cyano-4-(3-((3R)-3-(2-((dimethylamino)methyl)morpholino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		693
495D	*tert*-Butyl (3-cyano-4-(3-((3S)-3-(2-((dimethylamino)methyl)morpholino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		693

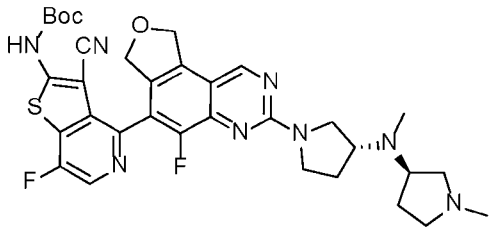
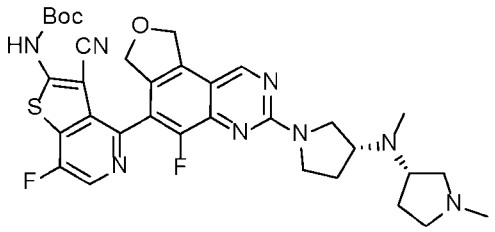
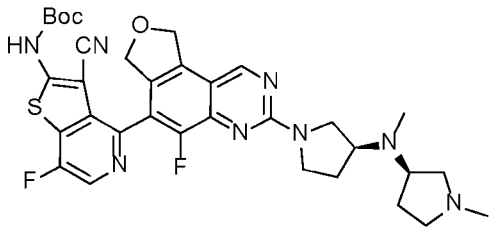
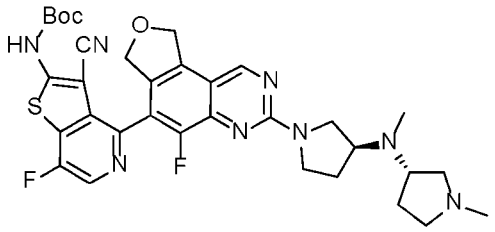
496D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-morpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
497D	*tert*-Butyl (4-(3-((2S,3S)-3-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		662
498D	*tert*-Butyl (4-(3-((R)-3-(1,4-oxazepan-4-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		650
499D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-methyl-1,4-diazepan-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663

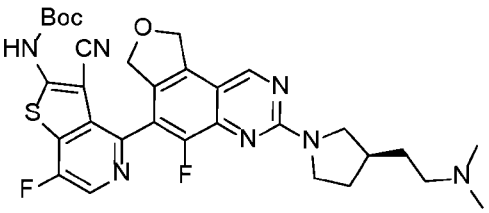
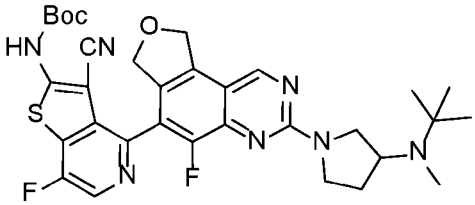
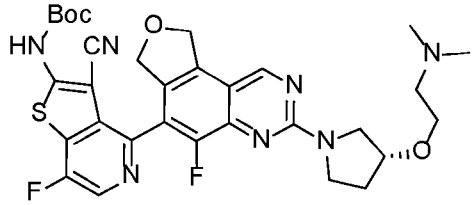
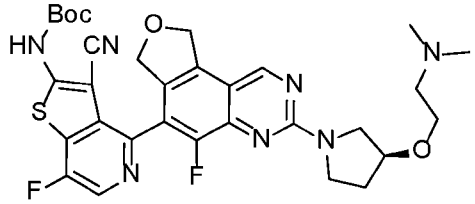
500D	*tert*-Butyl (4-(3-((R)-3-(4-acetyl-1,4-diazepan-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		691
501D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(4-methyl-1,4-diazepan-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663
502D [19]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(1,4-oxazepan-4-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		666
503D [20]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(1,4-oxazepan-4-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		680

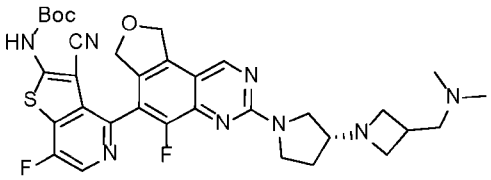
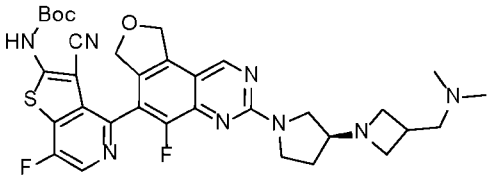
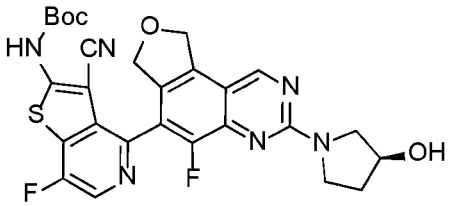
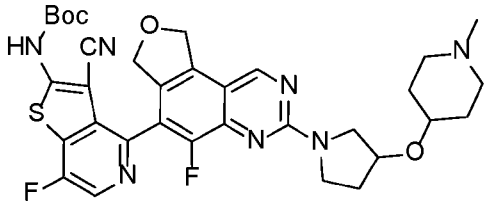
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505D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		675
506D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		675

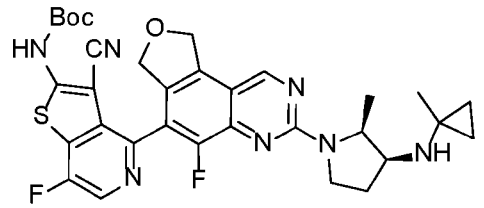
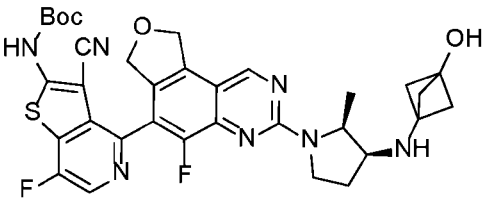
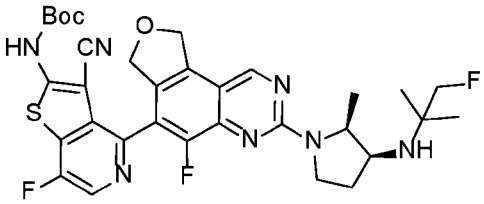
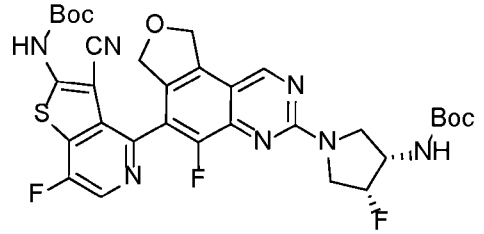
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508D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		662
509D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		675
510D	*tert*-Butyl (4-(3-((R)-3-(2-azaspiro[3.3]heptan-2-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		646

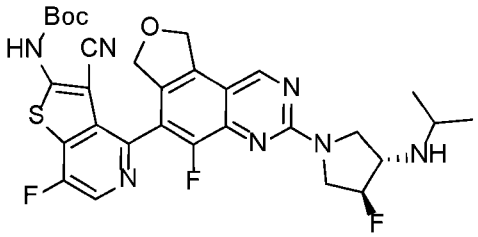
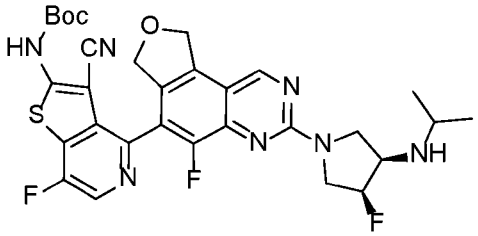
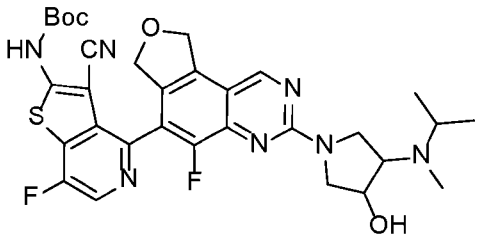
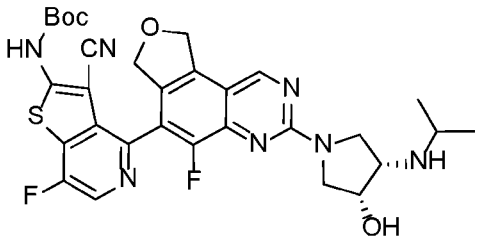
511D	*tert*-Butyl (4-(3-((S)-3-(2-azaspiro[3.3]heptan-2-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		646
512D	*tert*-Butyl (4-(3-((R)-3-(2-oxa-7-azaspiro[3.5]nonan-7-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		676
513D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl(tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
514D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl((tetrahydrofuran-2-yl)methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664

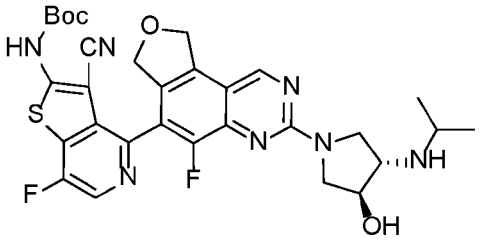
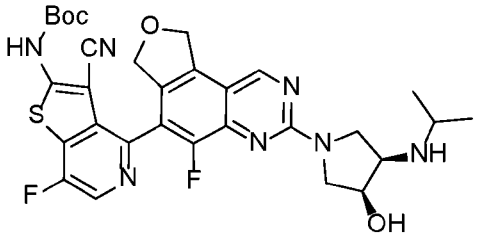
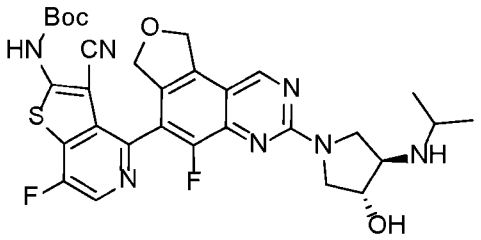
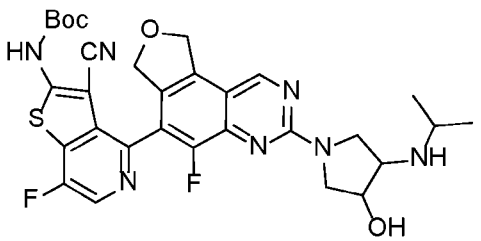
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516D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(methyl((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663
517D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(methyl((R)-1-methylpyrrolidin-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663
518D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(methyl((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		663

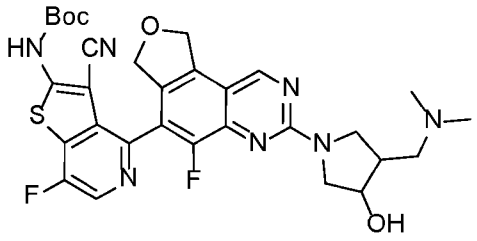
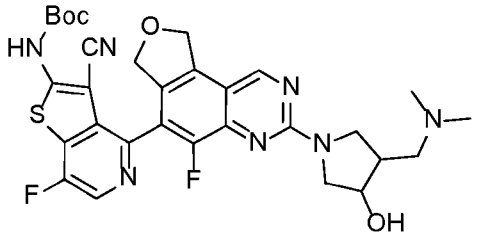
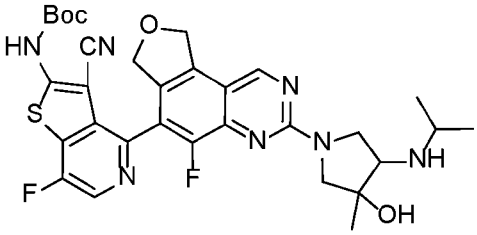
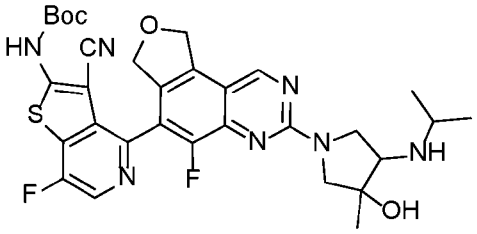
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520D	*tert*-Butyl (4-(3-(3-(*tert*-Butyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		636
521D	*tert*-Butyl (3-cyano-4-(3-((R)-3-(2-(dimethylamino)ethoxy)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		638
522D	*tert*-Butyl (3-cyano-4-(3-((S)-3-(2-(dimethylamino)ethoxy)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		638

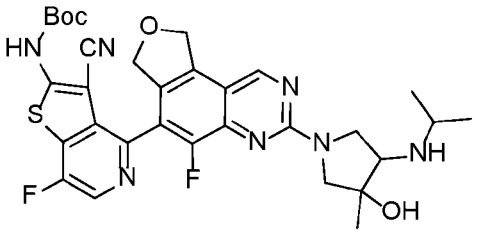
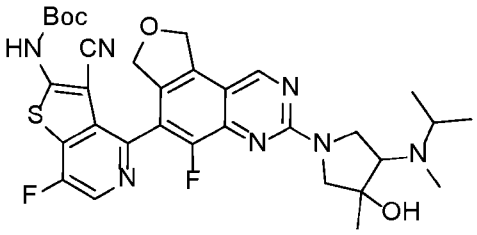
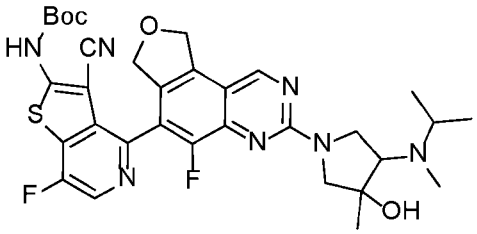
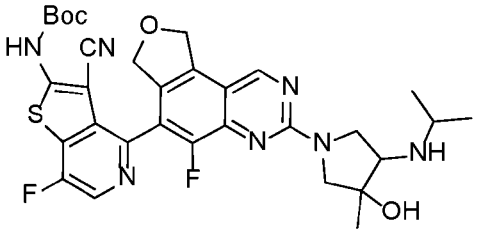
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524D	*tert*-Butyl (3-cyano-4-(3-((S)-3-(3-((dimethylamino)methyl)azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		663
525D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		567
526D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-((1-methylpiperidin-4-yl)oxy)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664

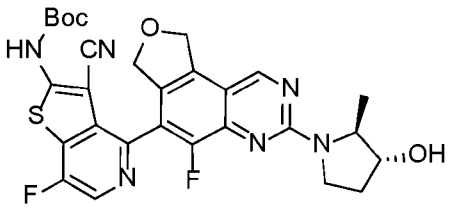
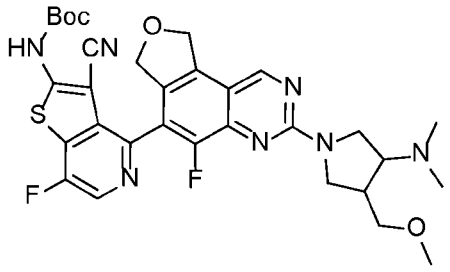
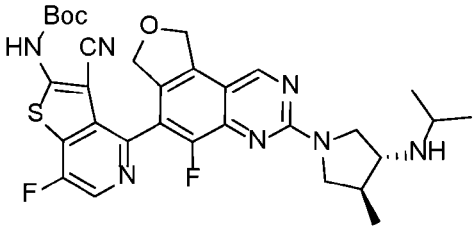
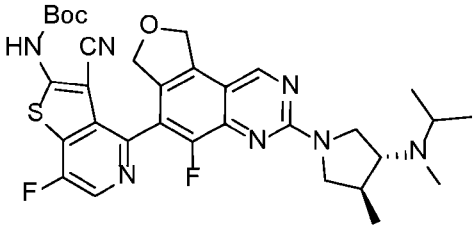
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528D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((3-hydroxybicyclo[1.1.1]pentan-1-yl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		
529D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((1-fluoro-2-methylpropan-2-yl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		654
530D	*tert*-Butyl (4-(3-((3S,4R)-3-((*tert*-butoxycarbonyl)amino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		684

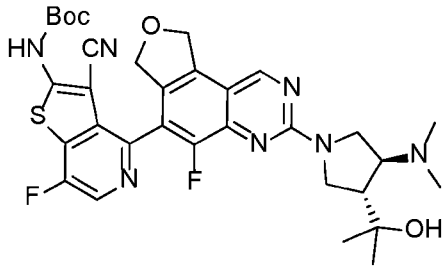
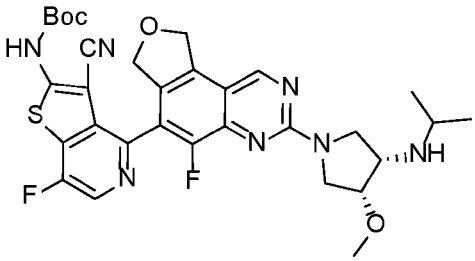
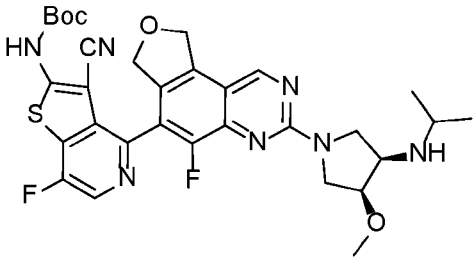
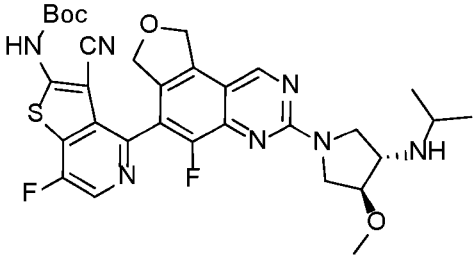
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532D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4R)-3-fluoro-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		626
533D [21]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
534D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624

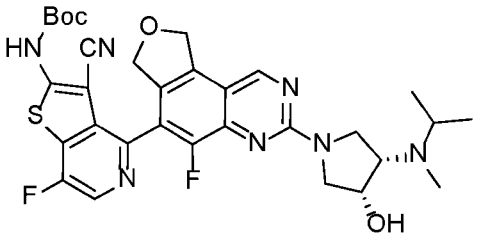
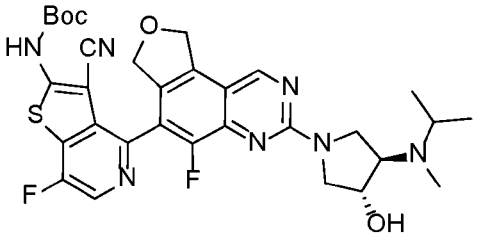
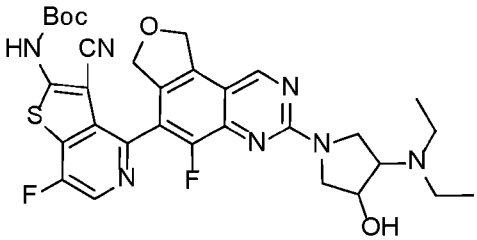
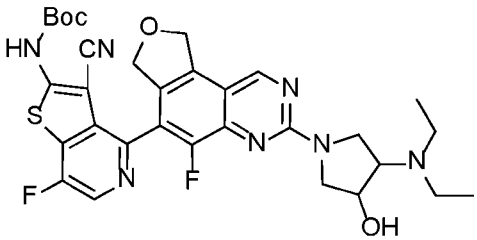
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536D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4R)-3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624
537D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624
538D [22]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624

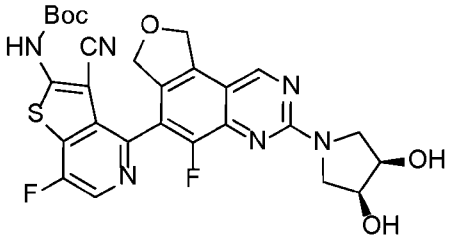
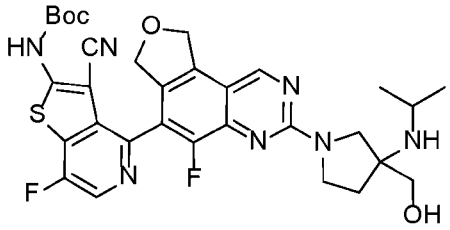
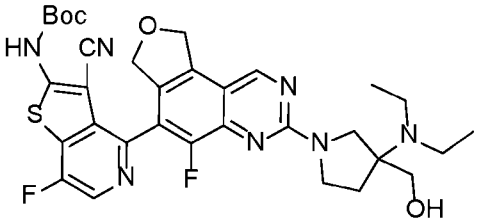
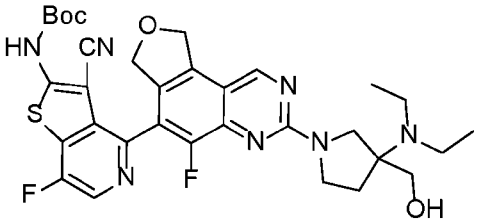
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540D [24]	*tert*-Butyl (3-cyano-4-(3-(3-((dimethylamino)methyl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
541D [25]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
542D [26]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Isomer 1		638

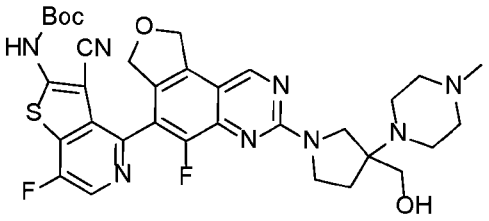
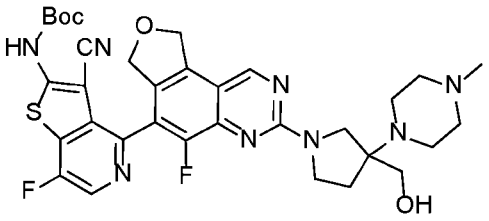
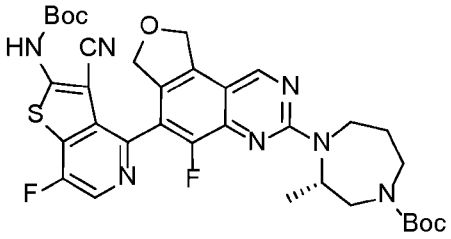
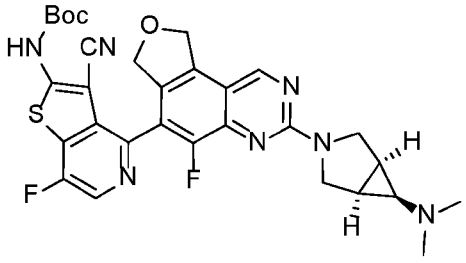
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544D [27]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropyl(methyl)amino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Isomer 1		652
545D [27]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropyl(methyl)amino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2		652
546D [28]	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638

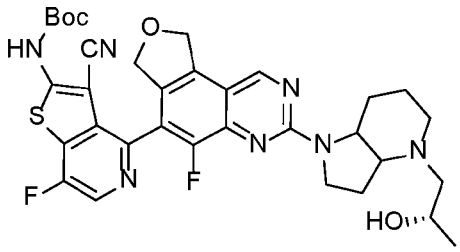
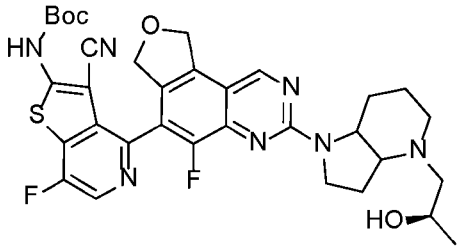
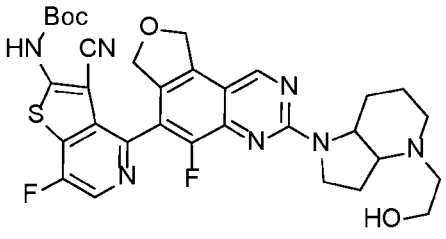
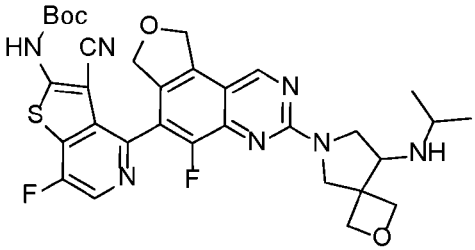
549D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3R)-3-hydroxy-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		581
550D [29]	*tert*-Butyl (3-cyano-4-(3-(3-(dimethylamino)-4-(methoxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		638
551D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		622
552D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropyl(methyl)amino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		636

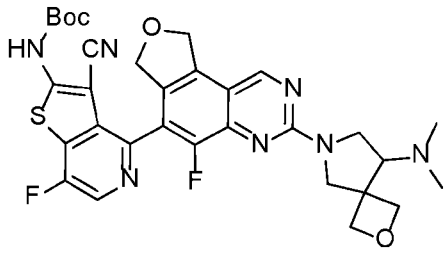
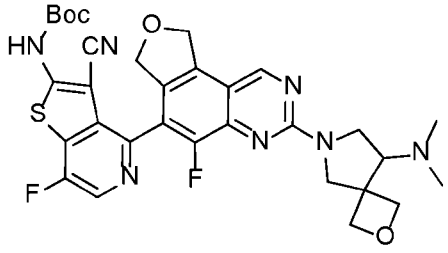
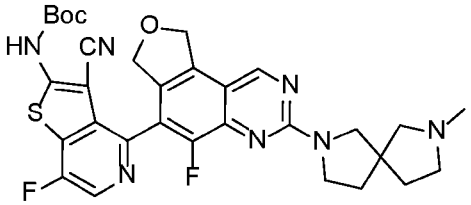
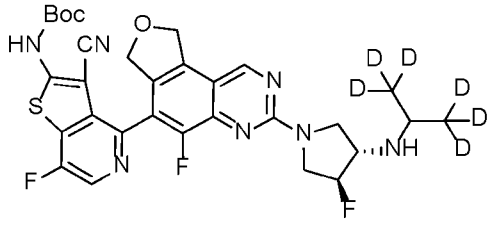
553D	*tert*-Butyl (3-cyano-4-(3-((3S,4R)-3-(dimethylamino)-4-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		652
554D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4R)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
555D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
556D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638

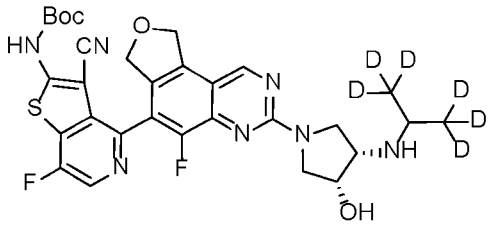
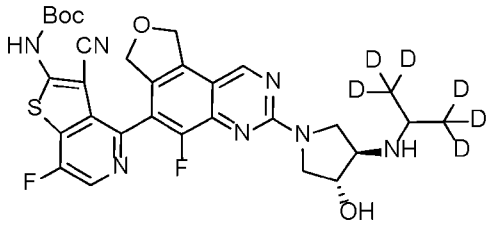
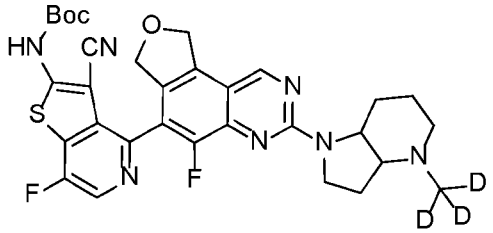
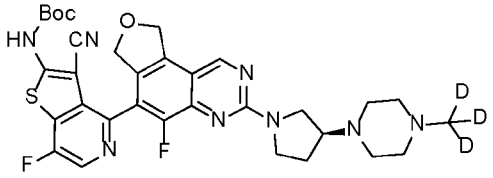
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558D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
559D [30]	*tert*-Butyl (3-cyano-4-(3-(3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 1		638
560D [30]	*tert*-Butyl (3-cyano-4-(3-(3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2		638

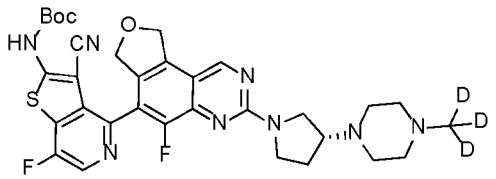
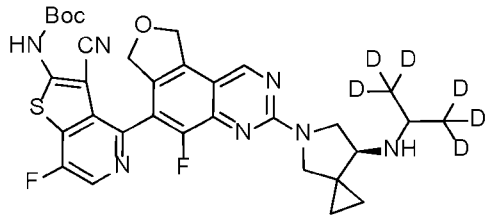
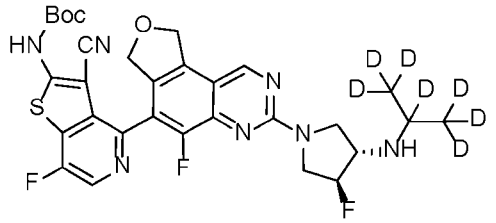
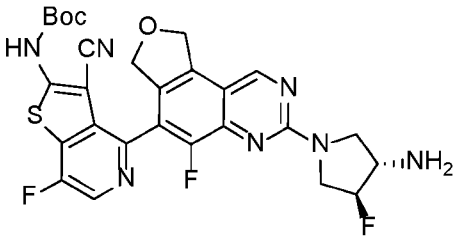
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562D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(hydroxymethyl)-3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638
563D [31]	*tert*-Butyl (3-cyano-4-(3-(3-(diethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 1		652
564D [31]	*tert*-Butyl (3-cyano-4-(3-(3-(diethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2		652

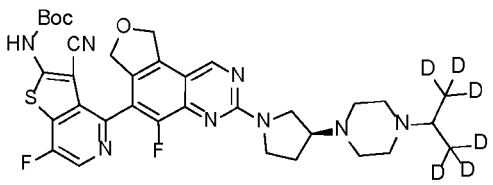
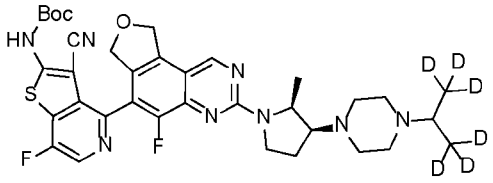
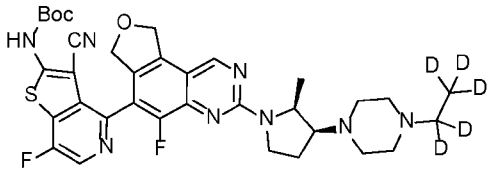
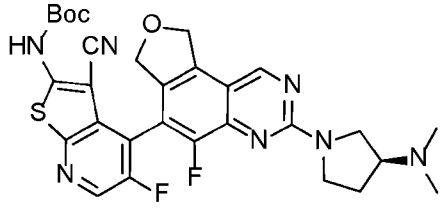
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566D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(3-(hydroxymethyl)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2		679
567D	*tert*-Butyl (3S)-4-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-3-methyl-1,4-diazepane-1-carboxylate		694
568D	*tert*-Butyl (3-cyano-4-(3-((1R,5S,6r)-6-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		606

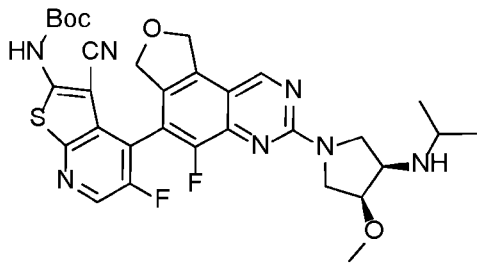
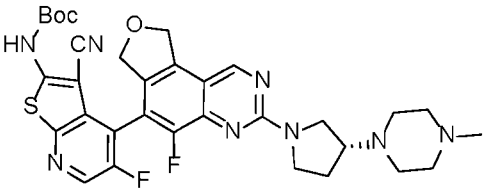
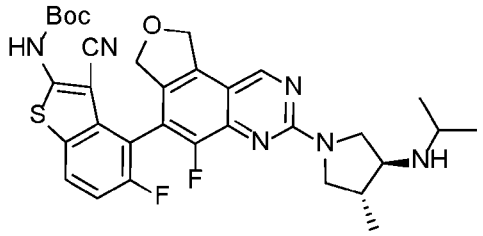
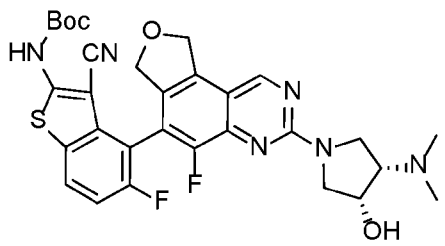
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570D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-((R)-2-hydroxypropyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		664
571D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-(2-hydroxyethyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650
572D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(8-(isopropylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		650

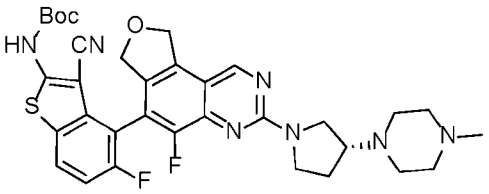
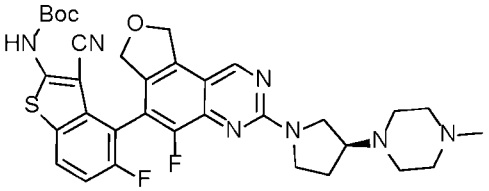
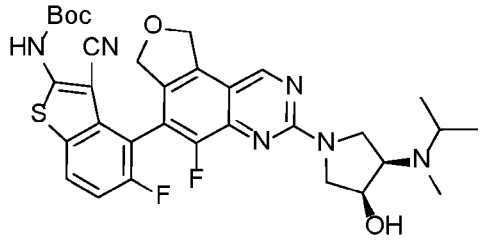
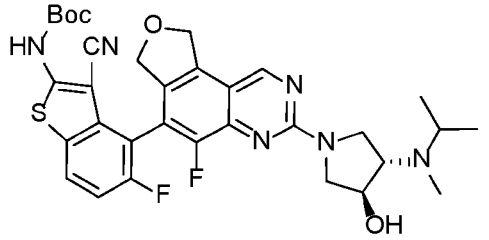
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574D	*tert*-Butyl (3-cyano-4-(3-(8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2		636
575D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		620
576D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-fluoro-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		632

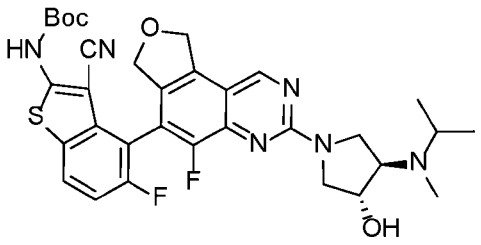
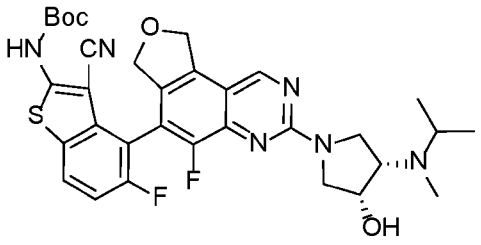
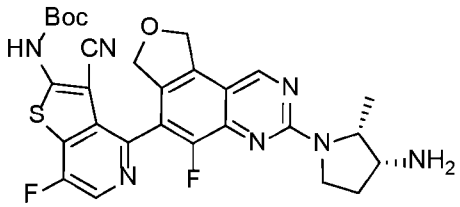
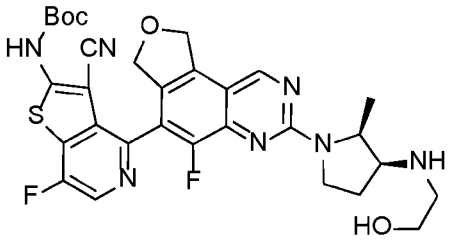
577D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		630
578D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		630
579D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-(4-(methyl-d3)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		623
580D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(4-(methyl-d3)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		652

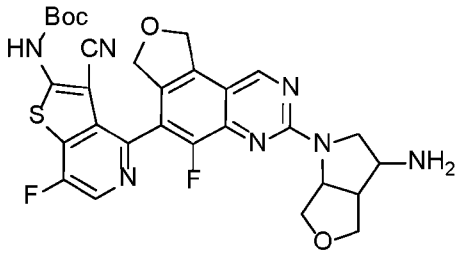
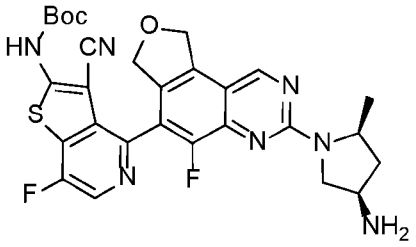
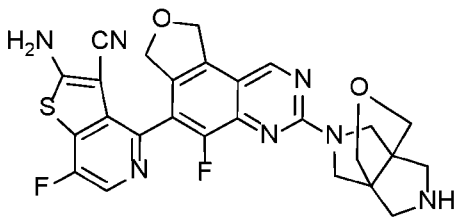
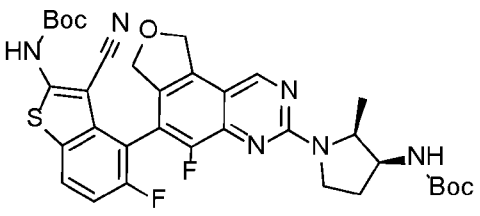
581D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(methyl-d3)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		652
582D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-7-((propan-2-yl-1,1,1,3,3,3-d6)amino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		640
583D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-fluoro-4-((propan-2-yl-d7)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		633
584D [32]	*tert*-Butyl (4-(3-((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		584

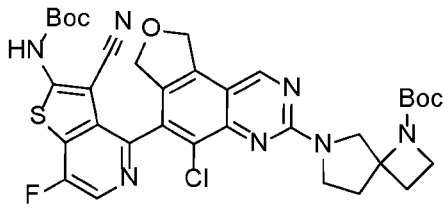
585D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((S)-3-(4-(propan-2-yl-1,1,1,3,3,3-d6)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		683
586D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(4-(propan-2-yl-1,1,1,3,3,3-d6)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		697
587D	*tert*-Butyl (3-cyano-4-(3-((2S,3S)-3-(4-(ethyl-d5)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		682
588D	*tert*-Butyl (3-cyano-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorothieno[2,3-b]pyridin-2-yl)carbamate		594

589D	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[2,3-b]pyridin-2-yl)carbamate		638
590D	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[2,3-b]pyridin-2-yl)carbamate		649
591D	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3S,4R)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		621
592D	*tert*-Butyl (3-cyano-4-(3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate		609

593D [8]	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		648
594D [8]	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((S)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		648
595D	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		637
596D	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		637

597D	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		637
598D	*tert*-Butyl (3-cyano-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophen-2-yl)carbamate		637
599D	*tert*-Butyl (4-(3-((2R,3R)-3-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		580
600D	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((2-hydroxyethyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		624

601D	*tert*-Butyl (4-(3-(3-aminohexahydro-1H-furo[3,4-b]pyrrol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
602D	*tert*-Butyl (4-(3-((2S,4R)-4-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		580
603D [33]	2-Amino-4-(3-(dihydro-1H,4H-3a,6a-(methanooxymethano)pyrrolo[3,4-c]pyrrol-2(3H)-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		534
604D	*tert*-Butyl (4-(3-((2S,3S)-3-((*tert*-butoxycarbonyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate		679

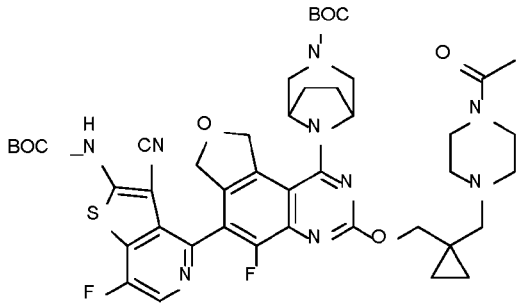
605D	*tert*-Butyl 6-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)-1,6-diazaspiro[3.4]octane-1-carboxylate		708

[1] Preparations 47A and 48A represent separated trans isomer pairs
[2] Preparation 78A – both trans isomers present
[3] Starting material – 4-bromo-7-chloro-5-fluoro-1,3-dihydrofuro[3,4-f]quinoline
[4] Starting material – 4-bromo-5,7-dichloro-1,3-dihydrofuro[3,4-f]quinoline
[5] Single atropisomer (from precursor in Preparation 17B)
[6] Single atropisomer (from precursor in Preparation 18B)
[7] Single atropisomer (from precursor in Preparation 9B)
[8] Single atropisomer (from precursor in Preparation 14B)
[9] Mix of Trans Isomers
[10] Mix of Trans Isomers
[11] Clean Trans Isomers, Separated in Preparations 5D and 6D
[12] Clean Trans Isomer, Separated in Preparation 7D
[13] Mix of Trans Isomers
[14] Clean Trans Isomer, Separated in Preparation 7D
[15] Mix of Trans Isomers
[16] Clean Isomers, Separated in Preparations 89D and 90D
[17] Mix of Trans Isomers
[18] Clean Trans Isomers, Separated in Preparations 9D and 10D
[19] Mix of Trans Isomers
[20] Mix of Trans Isomers
[21] Mix of Trans Isomers
[22] Mix of Trans Isomers
[23] Mix of Cis Isomers
[24] Mix of Trans Isomers
[25] Mix of Trans Isomers (nitrogen and oxygen substituents)
[26] Clean Trans Isomers (nitrogen and oxygen substituents)
[27] Clean Trans Isomers (nitrogen and oxygen substituents)
[28] Clean Cis Isomer (nitrogen and oxygen substituents)
[29] Mix of Cis Isomers

[30] Clean Trans Isomers, Separated in Preparations 12D and 13D
[31] Clean Isomers, Separated in Preparations 142D and 143D
[32] Byproduct from impurity in Preparation 583D
[33] After completion, reaction was concentrated and material was deprotected with TFA in DCM

Preparation 88

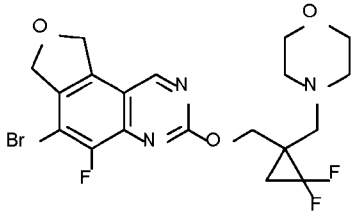
tert-Butyl 8-(3-((1-((4-acetylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[0338] *tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(hydroxymethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, ethanesulfonyl chloride, and 1-(piperazin-1-yl)ethan-1-one were used in a manner analogous to the methods of Preparations 17 and 18 to afford the title compound (0.064 g, 62%) as a yellow solid. MS (ES) *m/z*=902 (M+1).

Preparation 89

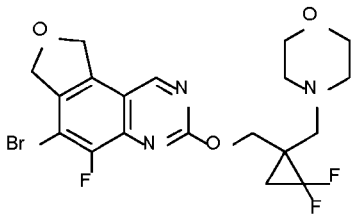
6-Bromo-3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline



[0339] (1-(((6-Bromo-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)oxy)methyl)-2,2-difluorocyclopropyl)methanol, methanesulfonic anhydride, and morpholine were used in a manner analogous to the methods of Preparations 17 and 18 to afford the title compound (1.5 g, 61%) as a yellow solid. MS (ES) *m/z*=474 (M+1).

Preparations 90 and 91

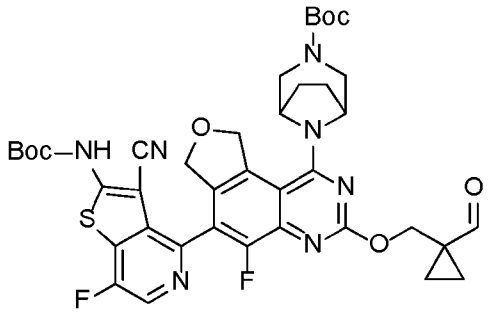
6-Bromo-3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline, Isomer 1 and Isomer 2



[0340] Chiral separation of 6-bromo-3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline (supercritical fluid chromatography; CHIRALPAK IG, 30 x 250 mm, 45% 1:1 DCM:MeOH (with 0.1% 2M ammoniated methanol) : 55% CO_2, 100 mL/min) was performed, to afford the title compounds (Isomer 1 0.63 g; Isomer 2 0.52 g) as yellow solids. MS (ES) *m/z*=474 (M+1), for both.

Preparation 193B

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-formylcyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

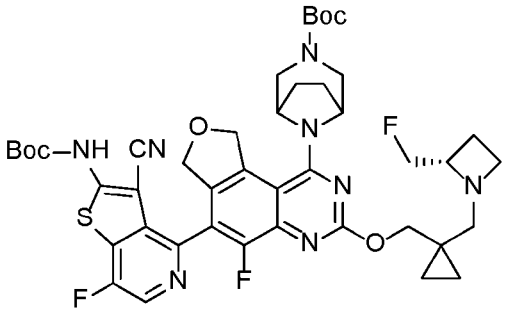


[0341] Combined *tert*-butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(hydroxymethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-

f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.37 g, 0.47 mmol), DCM (4.7 mL), and Dess-Martin periodinane (0.24 g, 0.56 mmol). The reaction mixture was stirred for 3 h. A small amount of Dess-Martin periodinane was added. After an additional 1 h, the mixture was diluted with DCM and aqueous sodium bicarbonate, then stirred vigorously for 10 min. The layers were separated. The organic layer was washed with water and brine, dried over magnesium sulfate, filatered, and concentrated under reduced pressure to give the title compound (0.34 g, 91%). MS (ES) *m/z*=790 (M+1).

Preparation 194B

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((S)-2-(fluoromethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

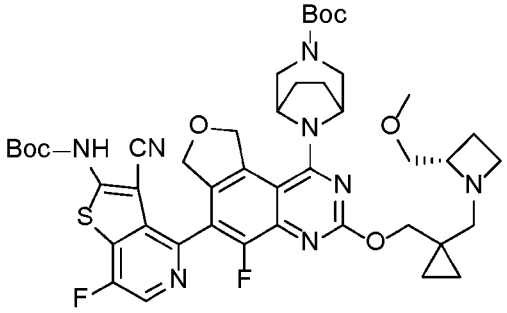


[0342] *Combined* tert-butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-formylcyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.165 g, 0.209 mmol), DCM (0.81 mL), and MeOH (0.25 mL). Added (S)-2-(fluoromethyl)azetidine 2,2,2-trifluoroacetate (79 wt%, 0.107 g, 0.418 mmol) as a solution in DCM (0.5 mL). The reaction mixture was stirred for 5 min, then sodium triacetoxyborohydride (0.155 g, 0.731 mmol) was added. The reaction mixture was stirred overnight, then loaded onto a strong cation exchange cartridge. The cartridge was eluted with MeOH (75 mL), then ammoniated methanol. The latter fraction was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with a gradient of 0-20% ammoniated MeOH in DCM, to give the title compound (0.15 g, 84%). MS (ES) *m/z*=863 (M+1).

Preparation 195B

tert-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-

fluoro-3-((1-(((S)-2-(methoxymethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

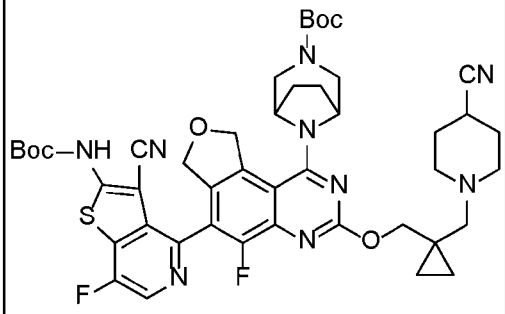
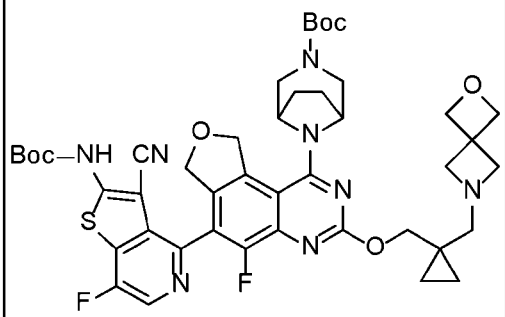


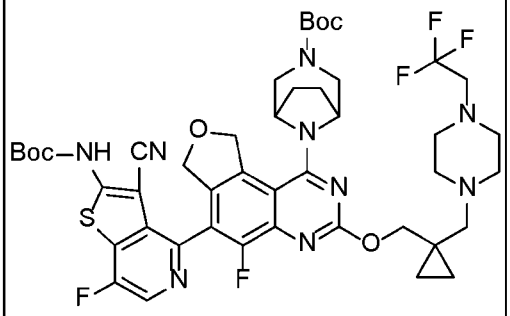
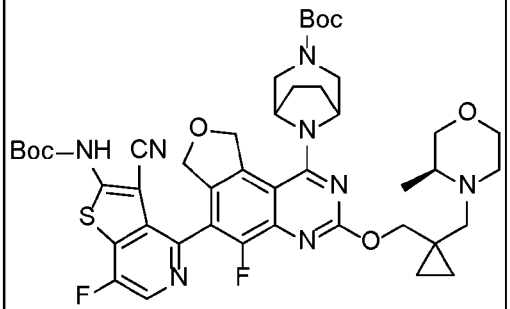
[0343] (S)-2-(Methoxymethyl)azetidine 2,2,2-trifluoroacetate was used in a manner analogous to the method of Preparation 194B to afford the title compound (0.080 g, 48%). MS (ES) *m/z*=875 (M+1).

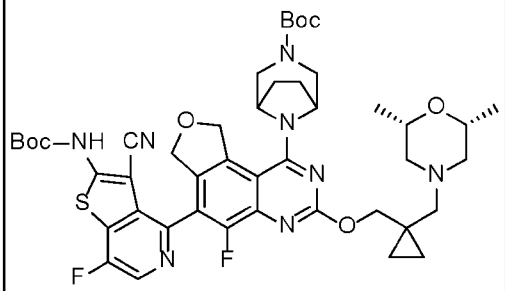
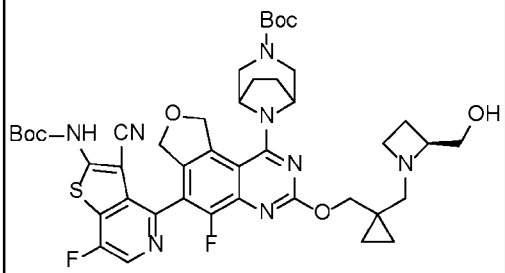
[0344] The following compounds in Table 23 were prepared in similar manner as described in Preparations 17 and 18, using *tert*-butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(hydroxymethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

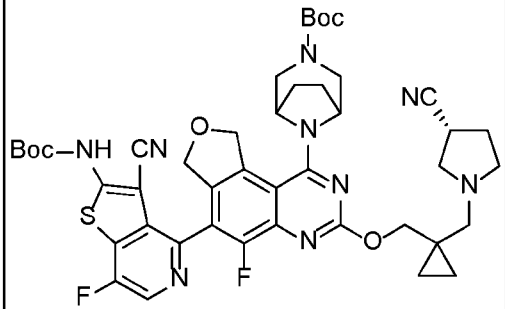
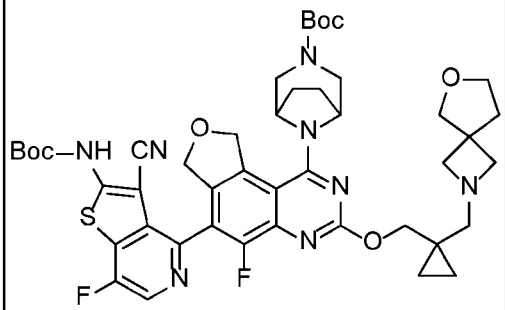
Table 23:

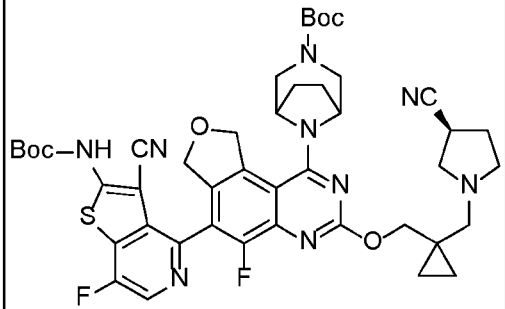
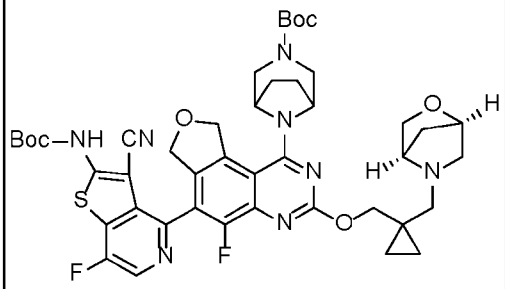
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)

85A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-((4-cyanopiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		885
86A	*tert*-Butyl 8-(3-((1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		873

87A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		942
88A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((S)-3-methylmorpholino)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		875

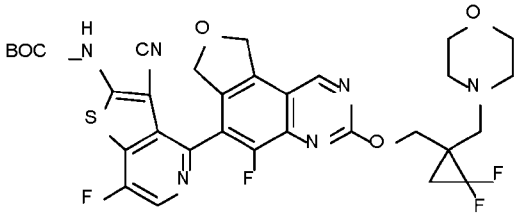
89A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-(((2R,6S)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		889
90A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(((S)-2-(hydroxymethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		861

91A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-(((R)-3-cyanopyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		870
92A	*tert*-Butyl 8-(3-((1-((6-oxa-2-azaspiro[3.4]octan-2-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		887

93A	*tert*-Butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-3-((1-(((S)-3-cyanopyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		870
94A	*tert*-Butyl 8-(3-((1-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		873

Preparation 92

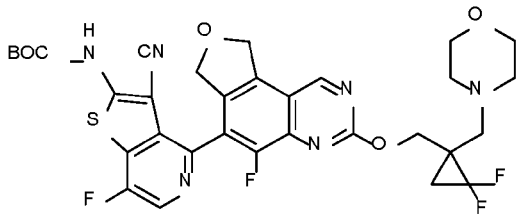
tert-Butyl (3-cyano-4-(3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 1



[0345] 6-Bromo-3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline, Isomer 1 was used in a manner analogous to the method of Preparation 33 to afford the title compound (0.36 g, 59%) as a yellow solid. MS (ES) *m/z*=687 (M+1).

Preparation 93

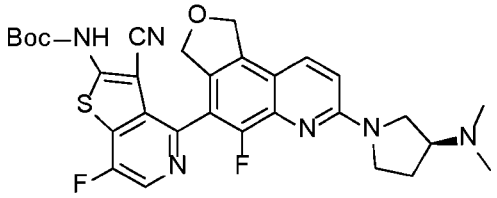
tert-Butyl (3-cyano-4-(3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate, Isomer 2



[0346] 6-Bromo-3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline, Isomer 2 was used in a manner analogous to the method of Preparation 33 to afford the title compound (0.50 g, 63%) as a yellow solid. MS (ES) *m/z*=687 (M+1).

Preparation 95A

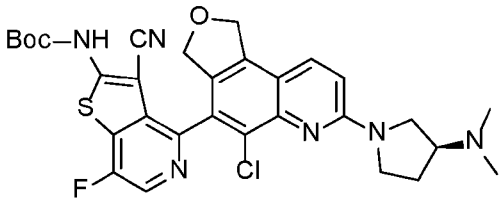
tert-Butyl (3-cyano-4-(7-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate



[0347] (S)-1-(4-Bromo-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-N,N-dimethylpyrrolidin-3-amine was used in a manner analogous to the method of Preparation 33 to afford the title compound (0.32 g, 21%). MS (ES) *m/z*=593 (M+1).

Preparation 196B

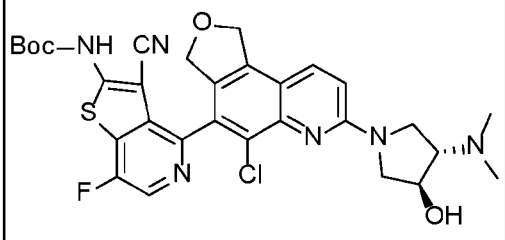
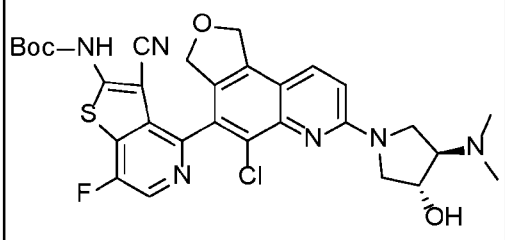
tert-Butyl (3-cyano-4-(7-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate

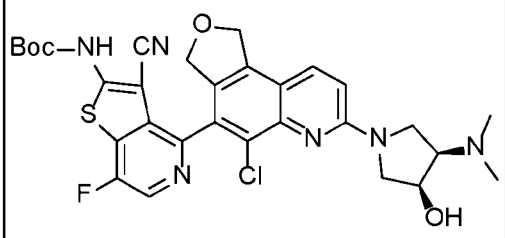
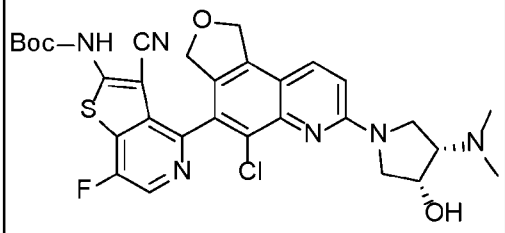


[0348] *(S)-1-(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)-N,N-dimethylpyrrolidin-3-*amine was used in a manner analogous to the method of Preparation 33 to afford the title compound (0.060 g, 8%). MS (ES) *m/z*=609 (M+1).

[0349] The following compounds in Table 24 were prepared in similar manner as described in Preparation 33. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

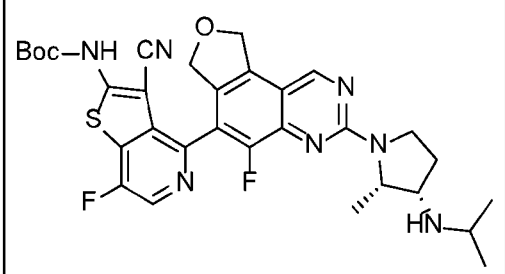
Table 24:

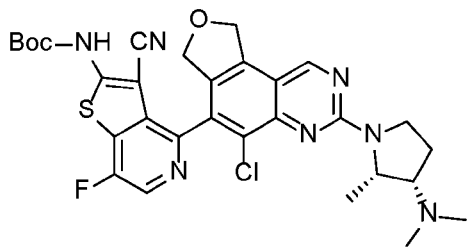
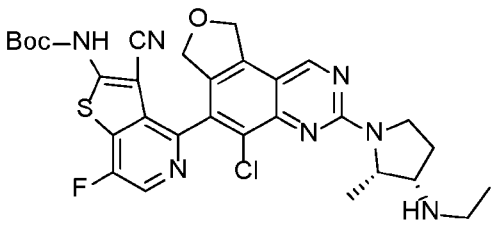
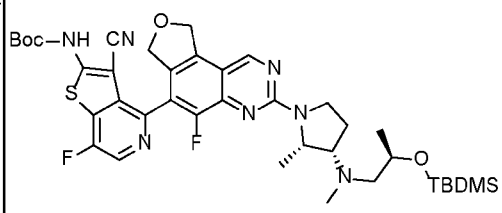
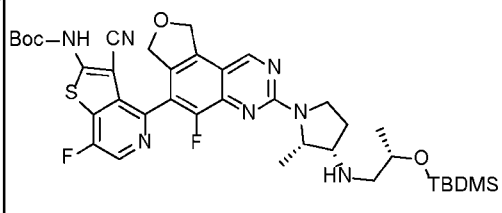
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
138C	*tert*-Butyl (4-(5-chloro-7-((3S,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		625
139C	*tert*-Butyl (4-(5-chloro-7-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		625

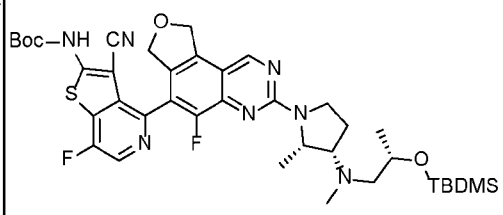
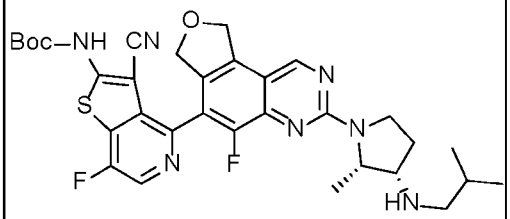
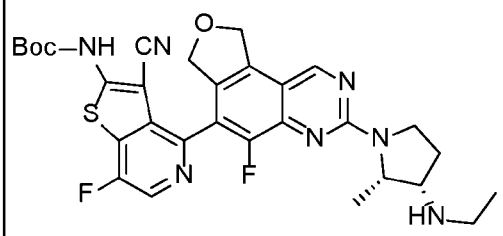
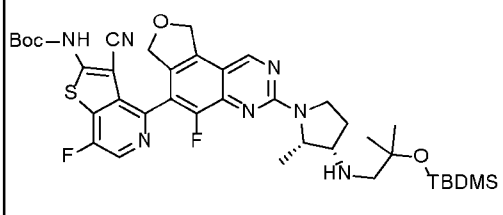
140C	*tert*-Butyl (4-(5-chloro-7-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		625
141C	*tert*-Butyl (4-(5-chloro-7-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		625

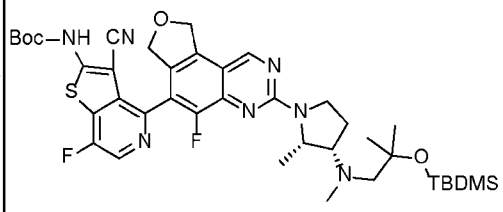
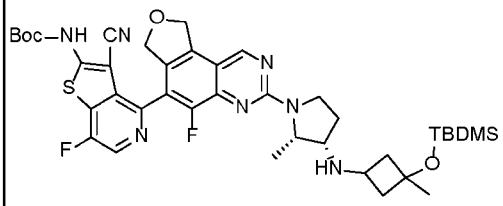
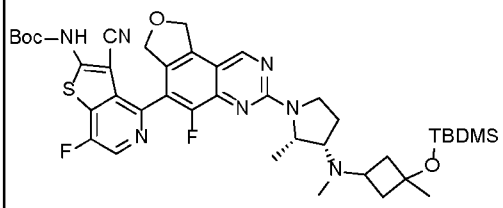
[0350] The following compounds in Table 25 were prepared in similar manner as described in Preparation 33B. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

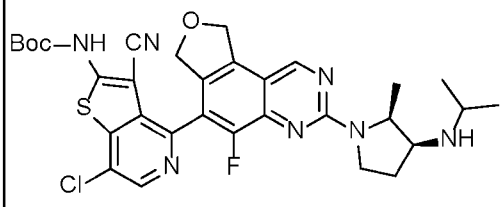
Table 25:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
197B	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		622

142C	*tert*-Butyl (4-(5-chloro-3-((2S,3S)-3-(dimethylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
143C	*tert*-Butyl (4-(5-chloro-3-((2S,3S)-3-(ethylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		624
144C	*tert*-Butyl (4-(3-((2S,3S)-3-(((R)-2-((*tert*-butyldimethylsilyl)oxy)propyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		766
145C	*tert*-Butyl (4-(3-((2S,3S)-3-(((S)-2-((*tert*-butyldimethylsilyl)oxy)propyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		752

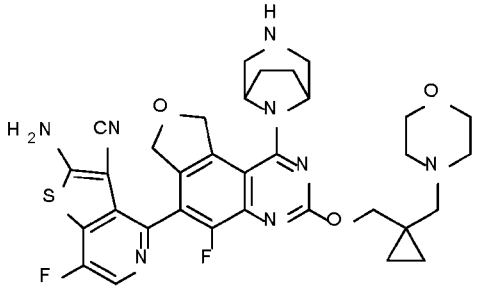
146C	*tert*-Butyl (4-(3-((2S,3S)-3-(((S)-2-((*tert*-butyldimethylsilyl)oxy)propyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		766
147C	*tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(isobutylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		636
148C	*tert*-Butyl (3-cyano-4-(3-((2S,3S)-3-(ethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		608
149C	*tert*-Butyl (4-(3-((2S,3S)-3-((2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		766

150C	*tert*-Butyl (4-(3-((2S,3S)-3-((2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		780
151C	*tert*-Butyl (4-(3-((2S,3S)-3-((3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		778
152C	*tert*-Butyl (4-(3-((2S,3S)-3-((3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate		792

153C	*tert*-Butyl (7-chloro-3-cyano-4-(5-fluoro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate		638

Preparation 94

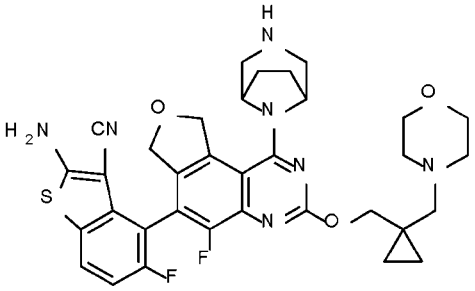
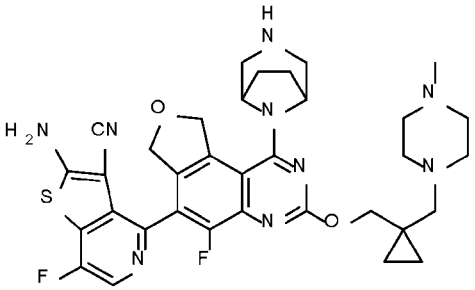
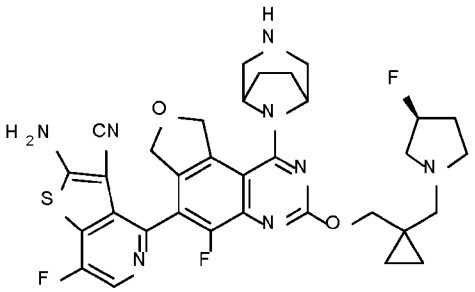
4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile

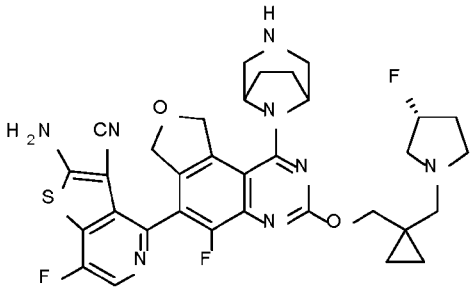
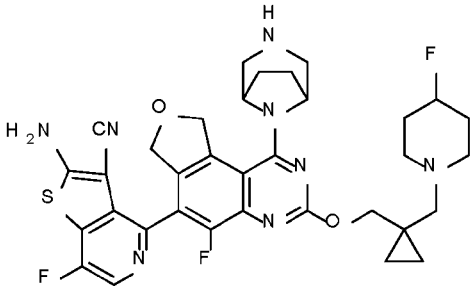
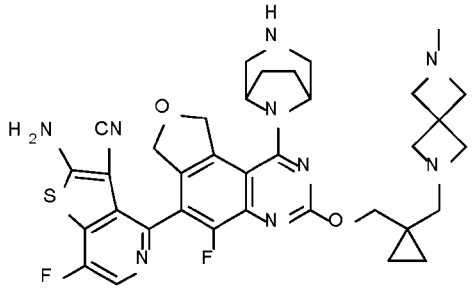


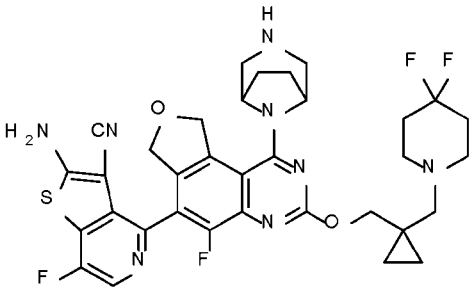
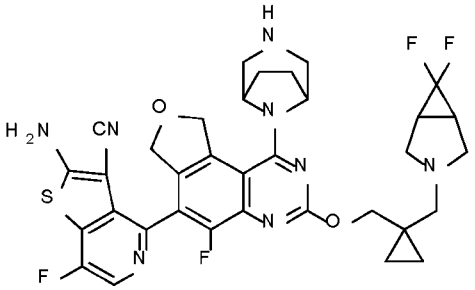
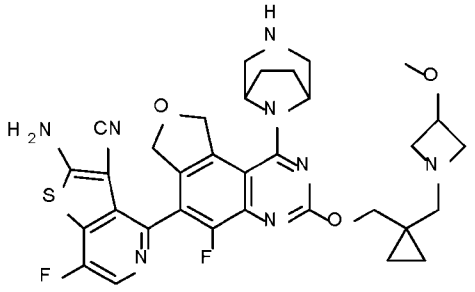
[0351] To a stirred mixture of *tert*-butyl 8-(6-(2-((*tert*-butoxycarbonyl)amino)-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.720 g, 0.836 mmol) in DCM (10 mL) was added TFA (10 mL) at RT. After 2 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (200 mL) and washed with saturated aq. $NaHCO_3$ (200 mL), water (200 mL), and brine (100 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude title compound as a light brown solid. MS (ES) *m/z*=661 (M+1).

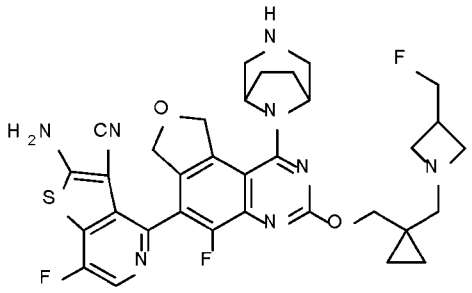
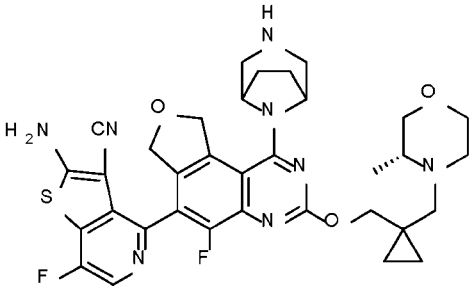
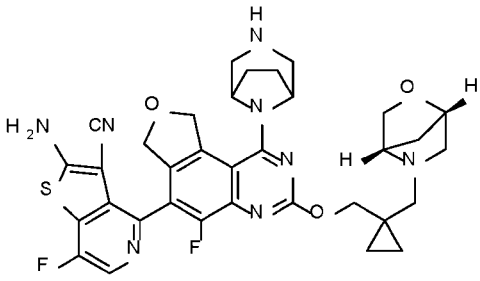
[0352] The following compounds in Table 26 were prepared in similar manner as described in Preparation 94. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

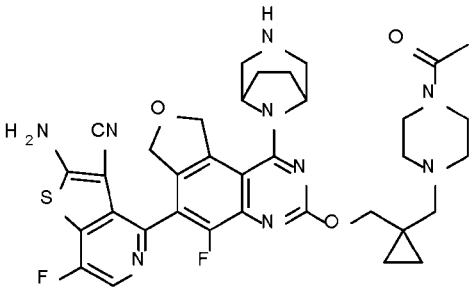
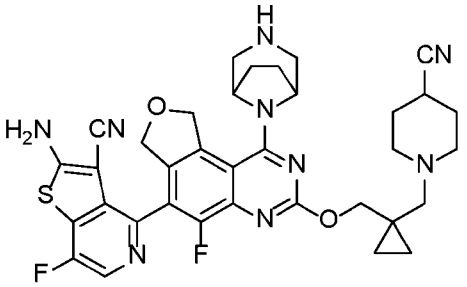
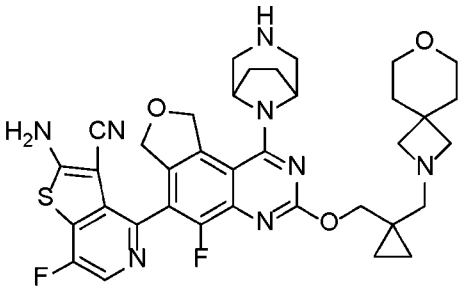
Table 26:

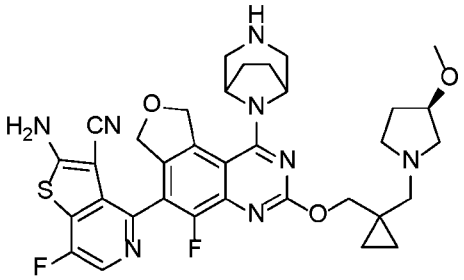
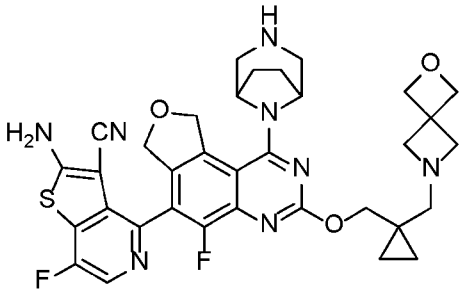
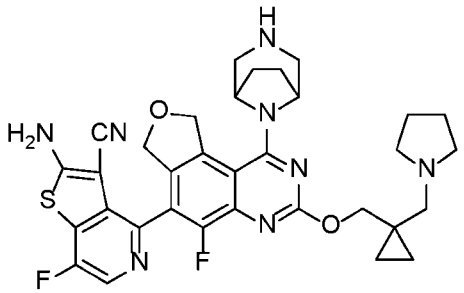
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
95	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-5-fluorobenzo[b]thiophene-3-carbonitrile		660
96	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		674
97	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((S)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		663

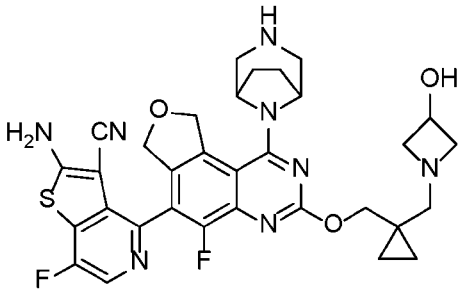
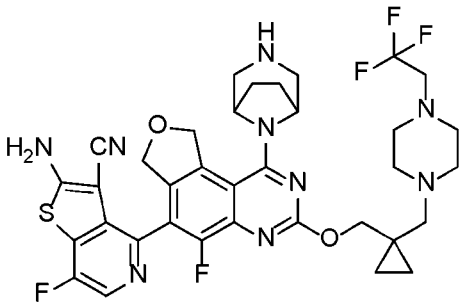
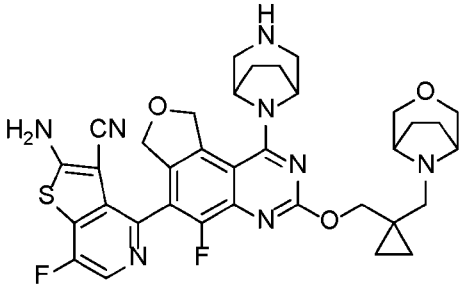
98	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		663
99	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		677
100	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		686

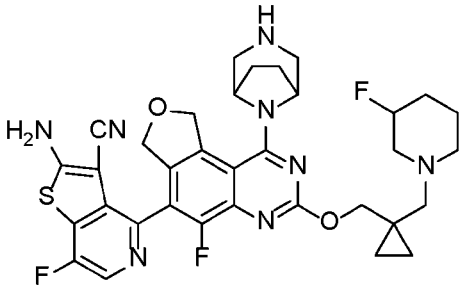
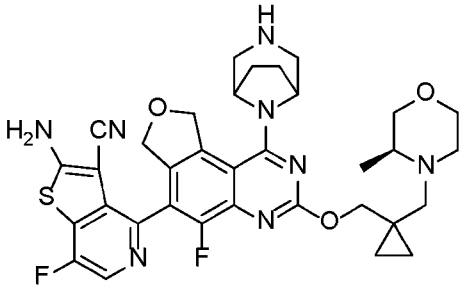
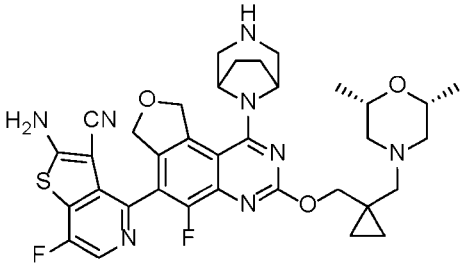
101	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-((4,4-difluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		695
102	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		693
103	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((3-methoxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		661

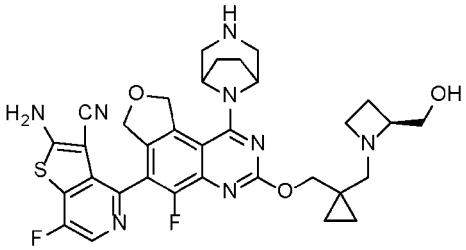
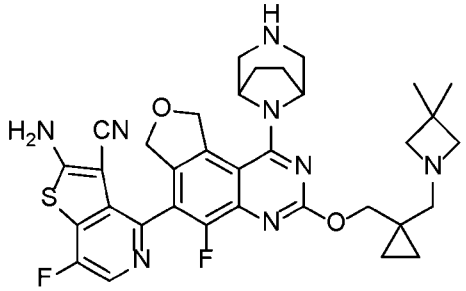
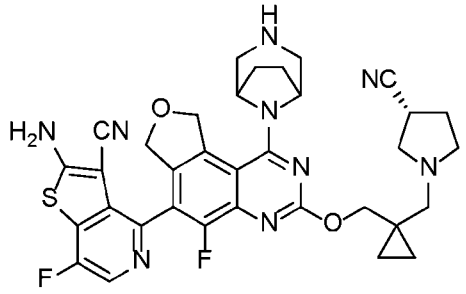
104	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((3-(fluoromethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		663
105	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		675
106	4-(3-((1-(((1S,4S)-2-oxa-5-Azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		673

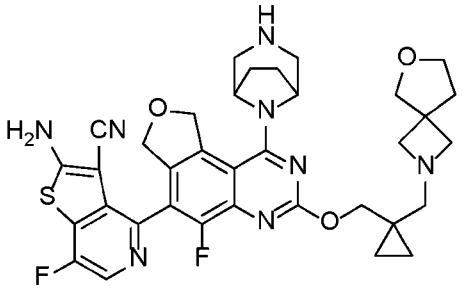
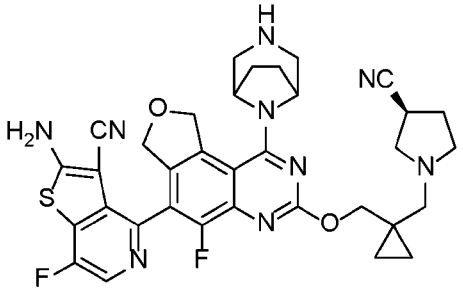
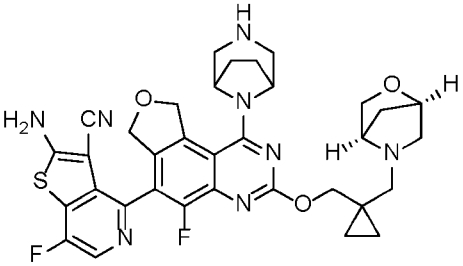
107	4-(3-((1-((4-Acetylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		702
96A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-((4-cyanopiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		684
97A	4-(3-((1-((7-Oxa-2-azaspiro[3.5]nonan-2-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		701

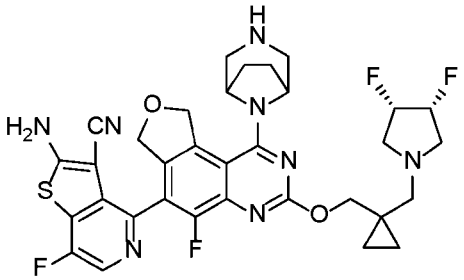
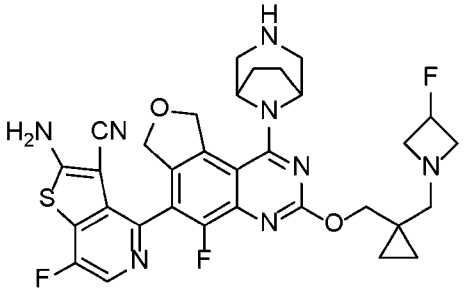
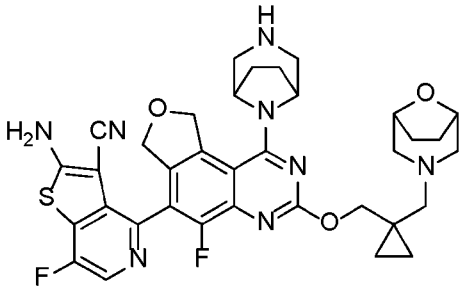
98A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((R)-3-methoxypyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		675
99A	4-(3-((1-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		673
100A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		645

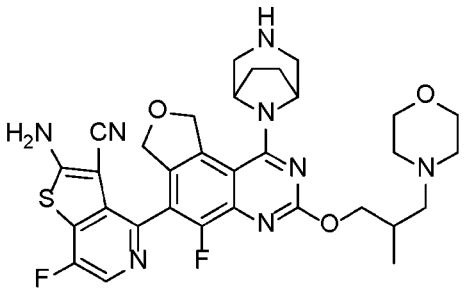
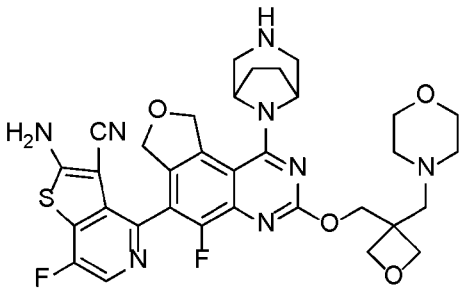
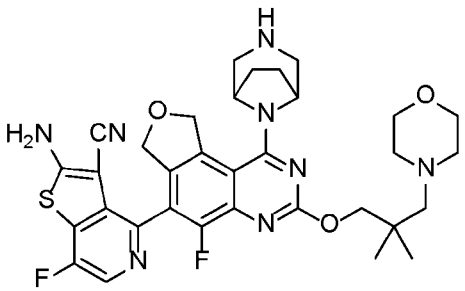
101A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((3-hydroxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		647
102A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		742
103A	4-(3-((1-((3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		687

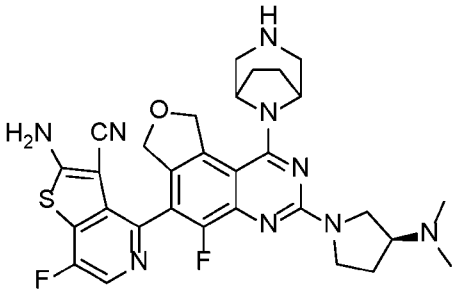
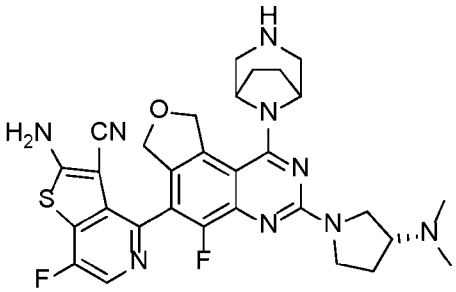
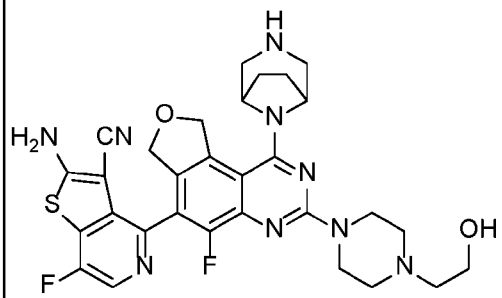
104A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((3-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		677
105A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((S)-3-methylmorpholino)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		675
106A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((2R,6S)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		689

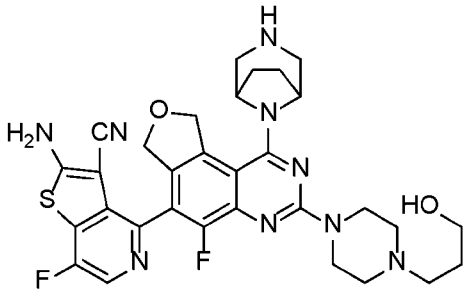
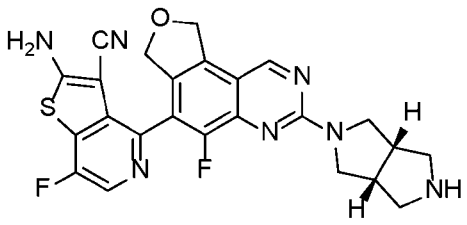
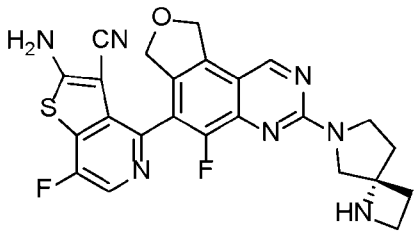
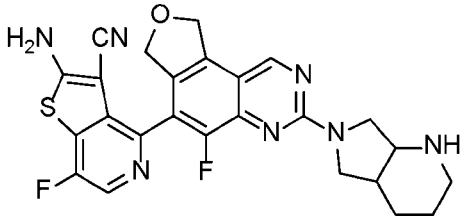
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108A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-((3,3-dimethylazetidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		659
109A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((R)-3-cyanopyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		670

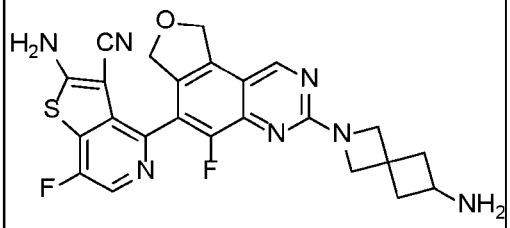
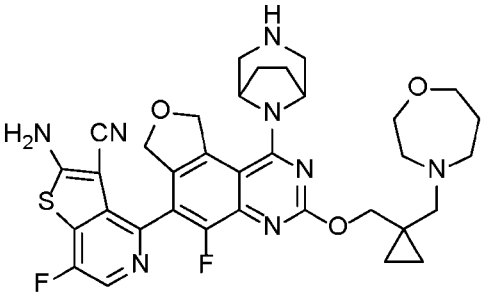
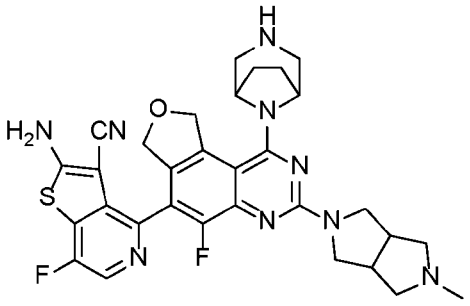
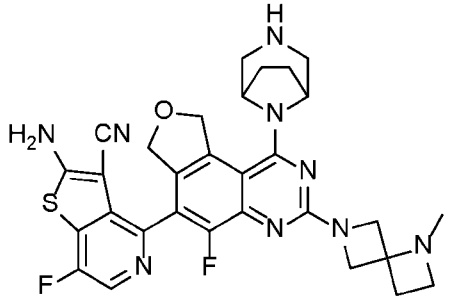
110A	4-(3-((1-((6-Oxa-2-azaspiro[3.4]octan-2-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		687
111A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((S)-3-cyanopyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		670
112A	4-(3-((1-(((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		673

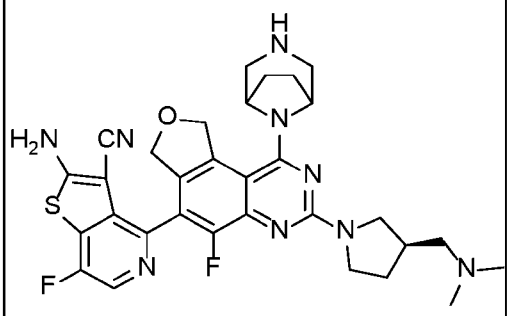
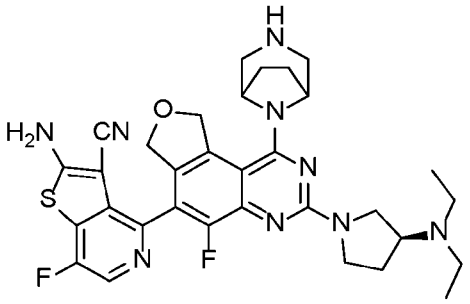
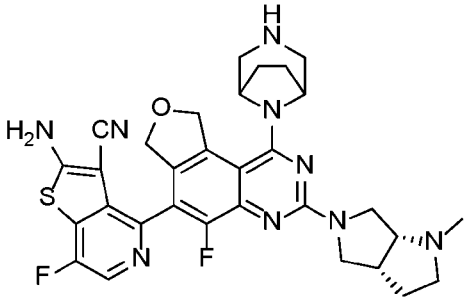
113A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((3R,4S)-3,4-difluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		681
114A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-((3-fluoroazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		649
115A	4-(3-((1-((8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		687

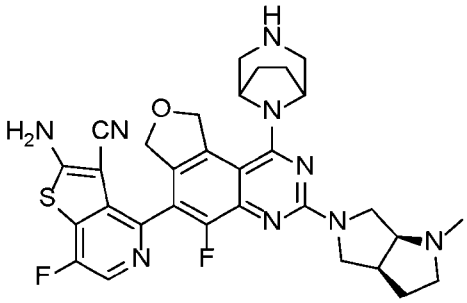
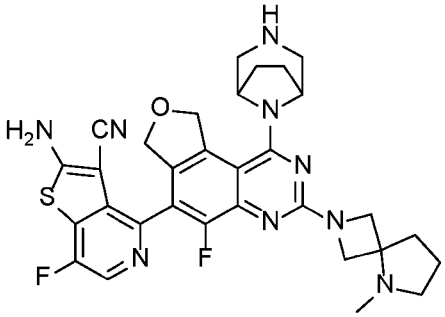
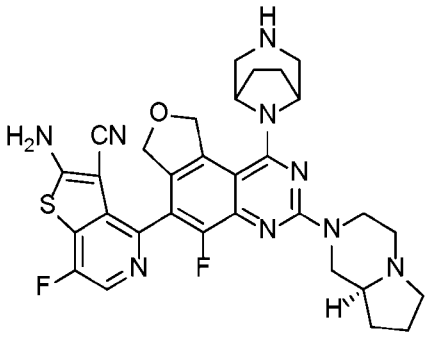
116A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(2-methyl-3-morpholinopropoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		649
117A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((3-(morpholinomethyl)oxetan-3-yl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		677
118A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-(2,2-dimethyl-3-morpholinopropoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		663

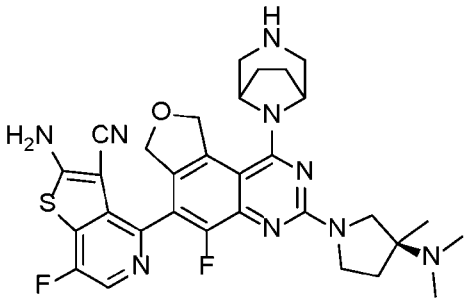
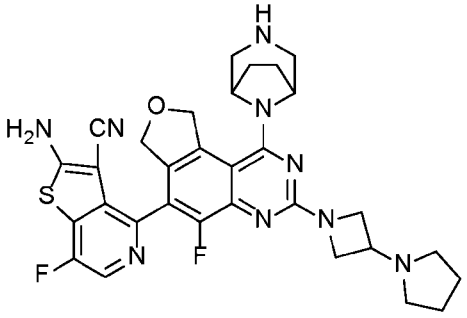
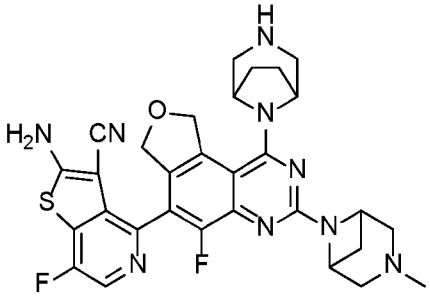
119A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		604
120A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		604
121A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(4-(2-hydroxyethyl)piperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		

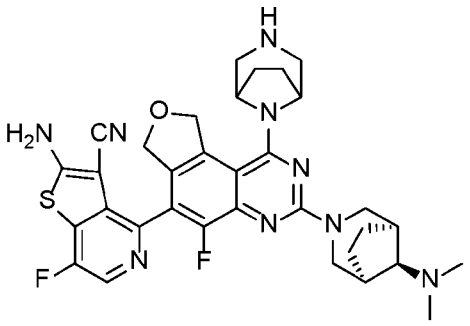
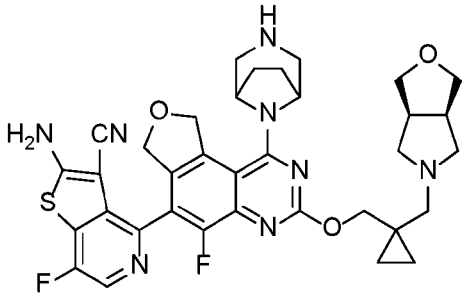
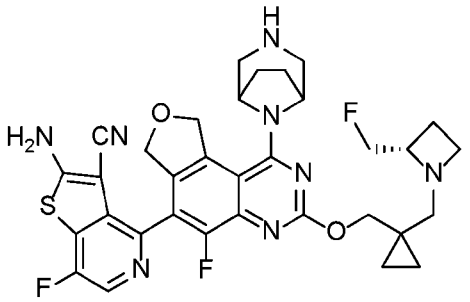
122A	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(4-(3-hydroxypropyl)piperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		
123A	2-Amino-7-fluoro-4-(5-fluoro-3-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
124A	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
198B	2-Amino-7-fluoro-4-(5-fluoro-3-(octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506

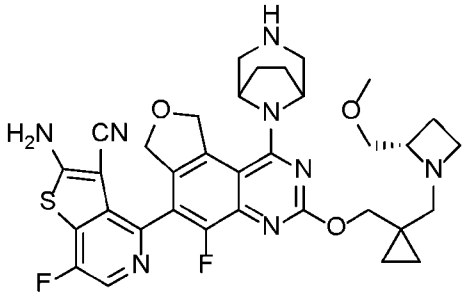
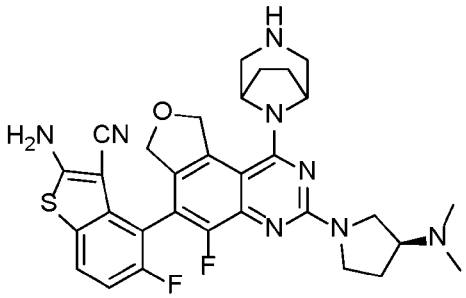
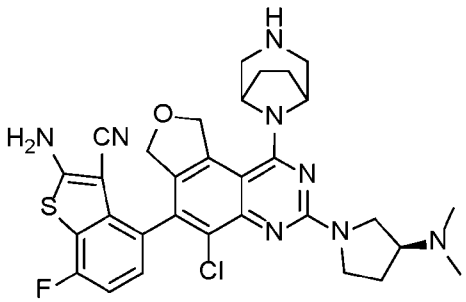
199B	2-Amino-4-(3-(6-amino-2-azaspiro[3.3]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		492
200B	4-(3-((1-((1,4-Oxazepan-4-yl)methyl)cyclopropyl)methoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		675
201B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		616
202B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		602

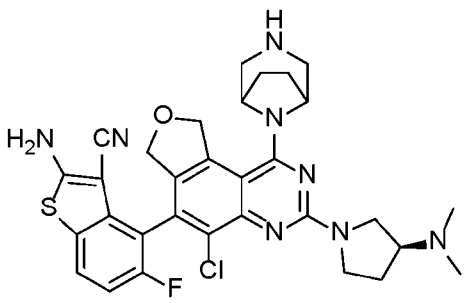
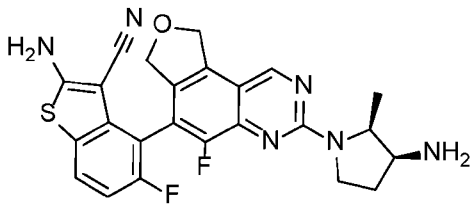
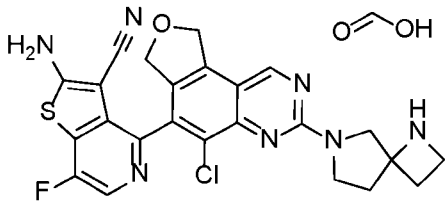
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204B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((S)-3-(diethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		632
205B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		616

206B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		616
207B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(5-methyl-2,5-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		616
208B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		616

209B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((S)-3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		618
210B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(3-(pyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		616
211B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		602

212B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((1R,5S,8R)-8-(dimethylamino)-3-azabicyclo[3.2.1]octan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		644
213B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		687
214B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((S)-2-(fluoromethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		663

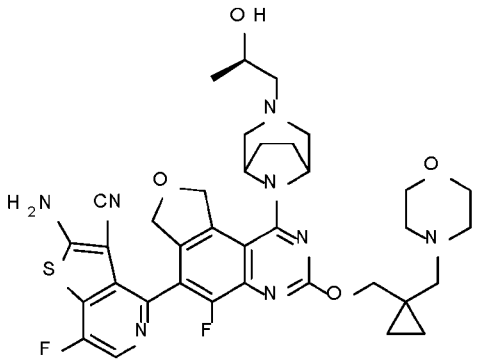
215B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(((S)-2-(methoxymethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		675
216B [1]	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-5-fluorobenzo[b]thiophene-3-carbonitrile		603
217B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile		619

218B	4-(1-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-5-fluorobenzo[b]thiophene-3-carbonitrile		619
606D	2-Amino-4-(3-((2S,3S)-3-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile		479
607D	2-Amino-4-(5-chloro-3-(1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formic acid		508

[1] Single atropisomer (from precursor in Preparation 9B)

Example 1

2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile

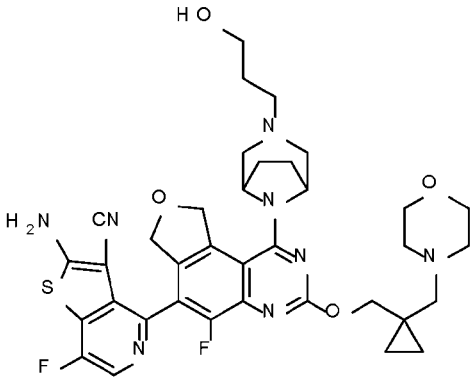
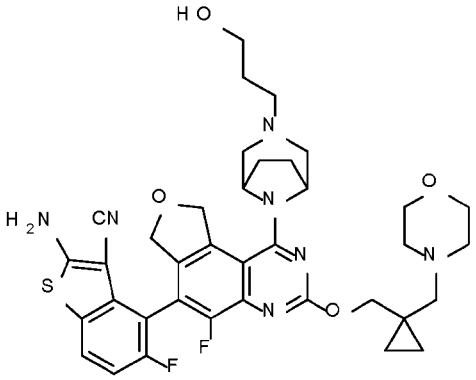
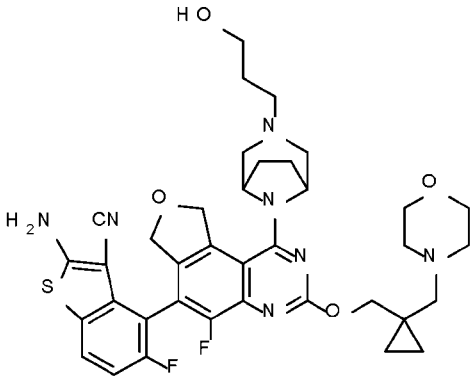


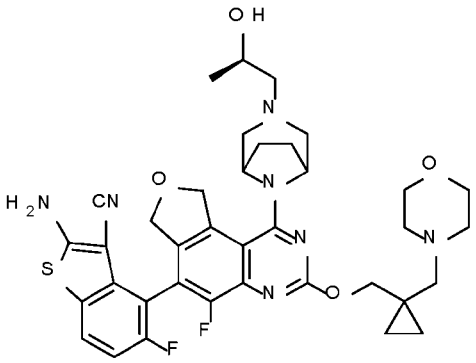
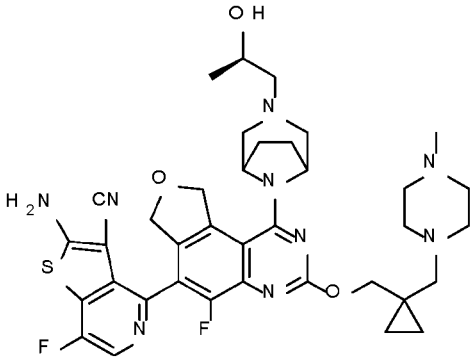
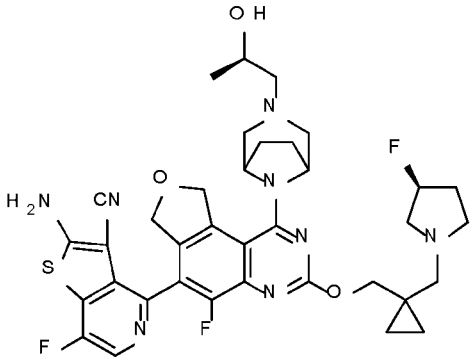
[0353] To a solution of 4-(1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile (0.150 g, 0.227 mmol) in DCM (2 mL) and MeOH (2 mL) was added (R)-2-hydroxypropanal (0.042 g, 0.568 mmol). After 5 min, sodium cyanoborohydride (0.043 g, 0.681 mmol) was added in portions. The reaction mixture was stirred for 1 h at RT, then diluted with water. The mixture was extracted with 10:1 DCM:MeOH (2 x 150 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by reversed phase purification, eluting with 45% to 55% ACN in 10 mM aq. NH_4HCO_3 with 0.05% NH_4OH, to give the title compound (0.079 g, 48%) as a white solid. MS (ES) *m/z*=719 (M+1).

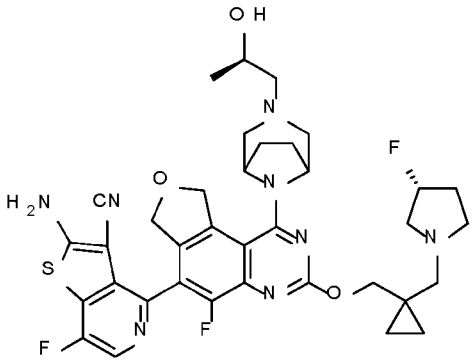
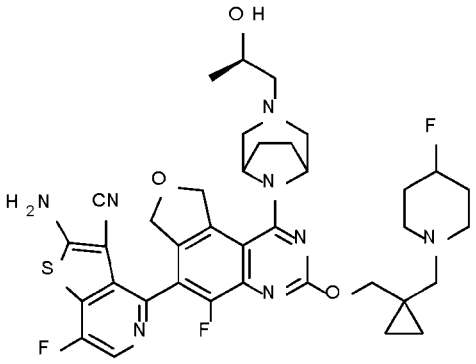
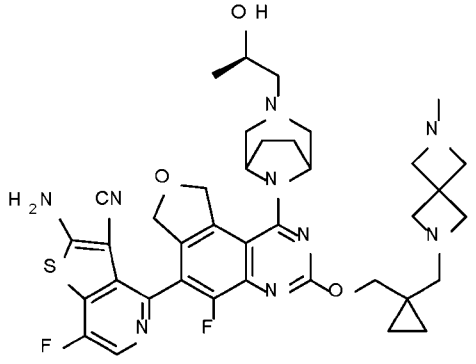
[0354] The following compounds in Table 27 were prepared in similar manner as described in Example 1. (2R)-2-((Tetrahydro-2H-pyran-2-yl)oxy)propanal was substituted for (R)-2-hydroxypropanal in some cases. Various methods (including, but not limited to, strong cation exchange chromatography with ammoniated methanol) were used to purify the compounds, which would be apparent to one skilled in the art.

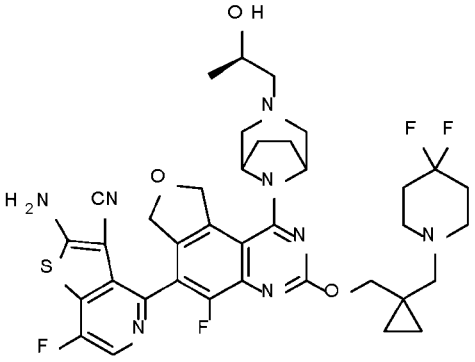
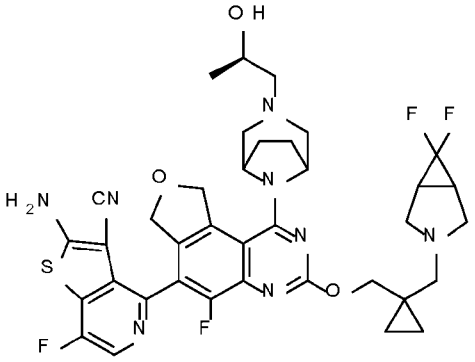
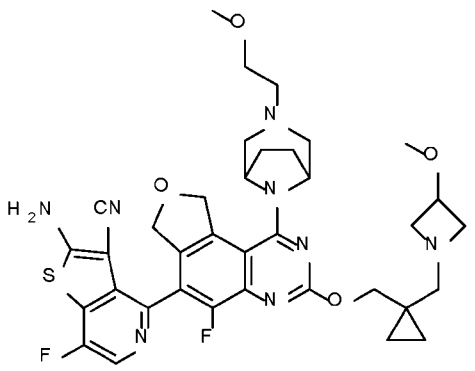
Table 27:

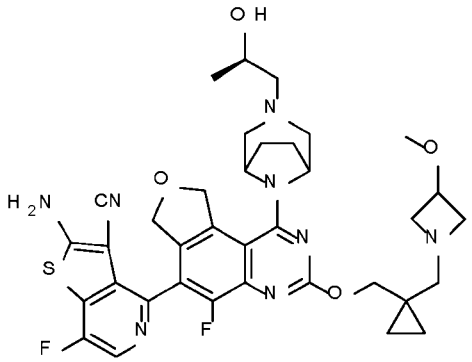
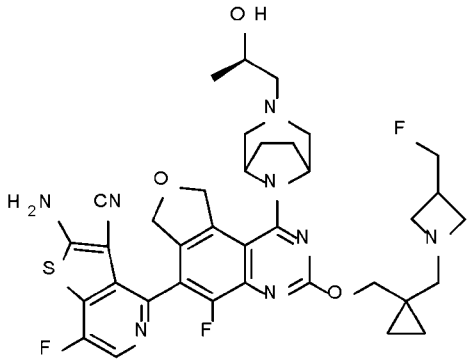
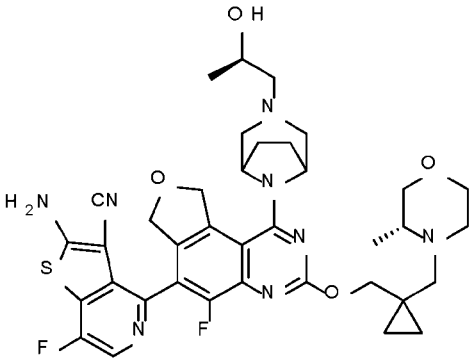
Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)

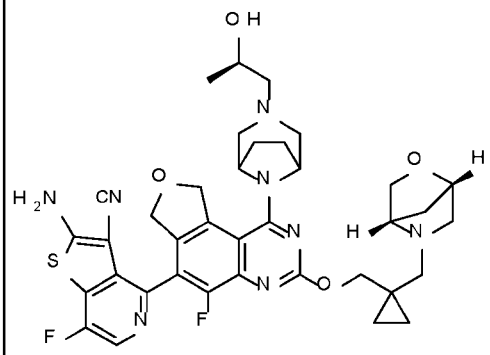
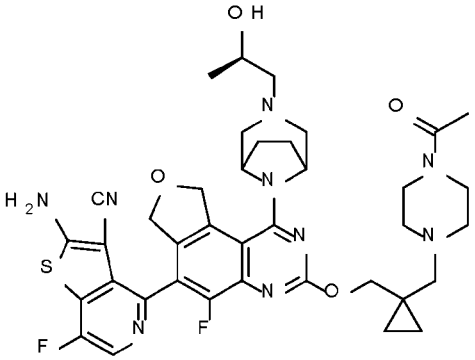
2	2-Amino-7-fluoro-4-(5-fluoro-1-(3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		719
3 [1]	2-Amino-5-fluoro-4-(5-fluoro-1-(3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Isomer 1		718
4 [1]	2-Amino-5-fluoro-4-(5-fluoro-1-(3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Isomer 2		718

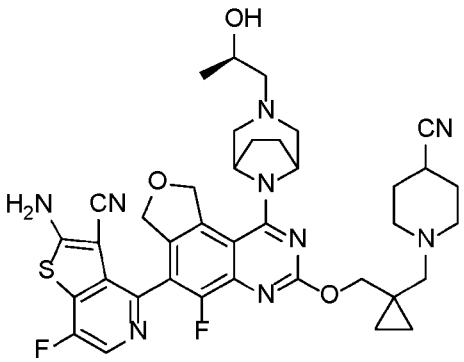
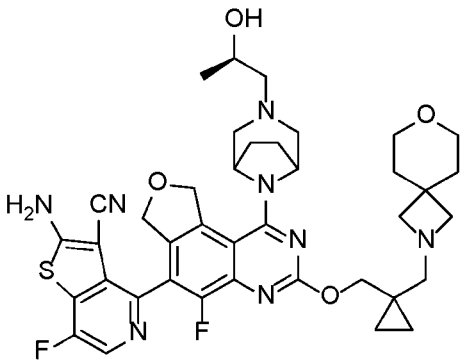
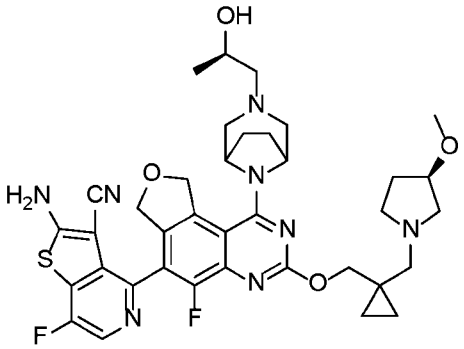
5	2-Amino-5-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile		718
6	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		732
7	2-Amino-7-fluoro-4-(5-fluoro-3-((1-(((S)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		721

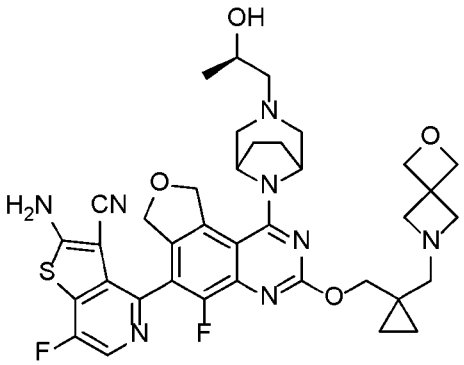
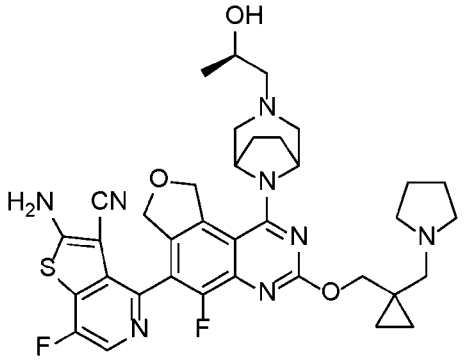
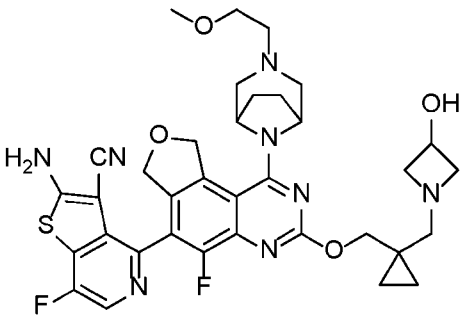
8	2-Amino-7-fluoro-4-(5-fluoro-3-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		721
9	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		735
10	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		744

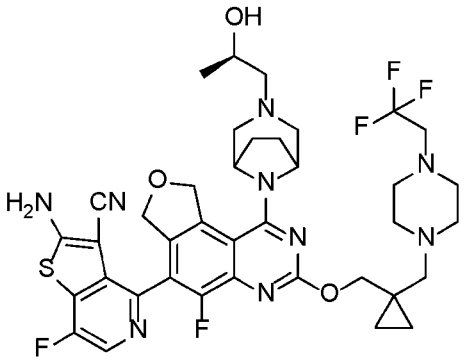
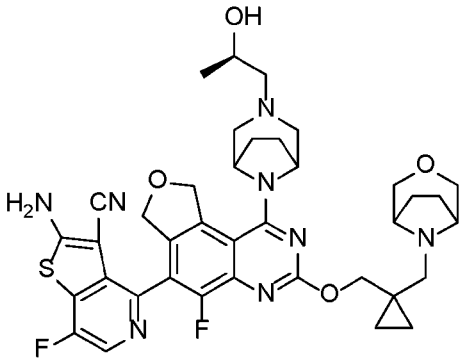
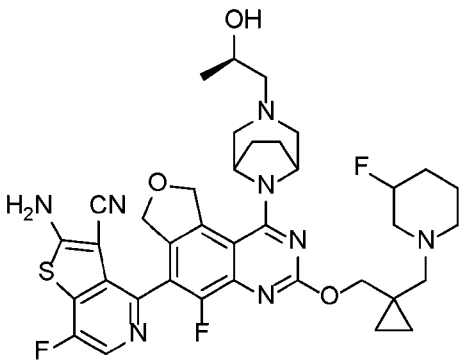
11	2-Amino-4-(3-((1-((4,4-difluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		753
12	2-Amino-4-(3-((1-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		751
13	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-methoxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		719

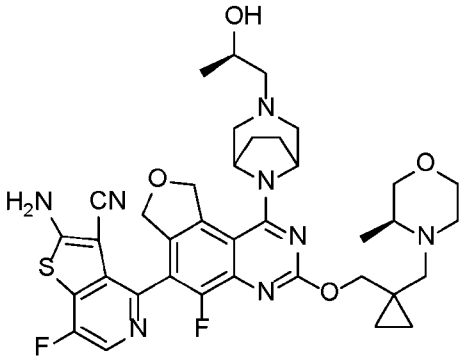
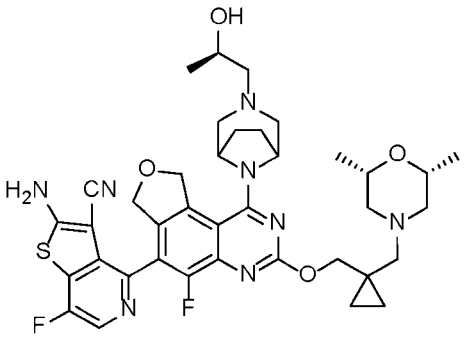
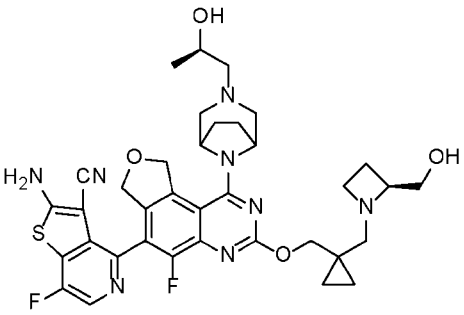
14	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-((3-methoxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		719
15	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-(fluoromethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		721
16	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((R)-3-methylmorpholino)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		733

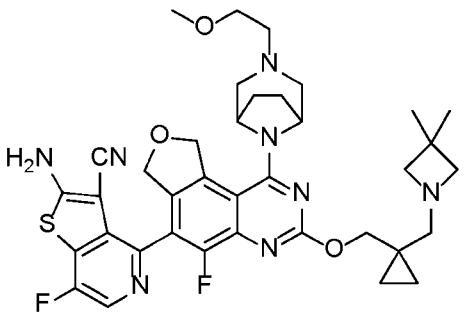
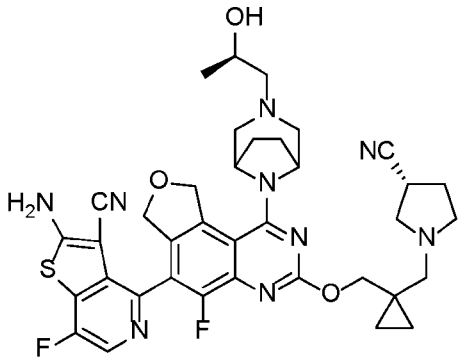
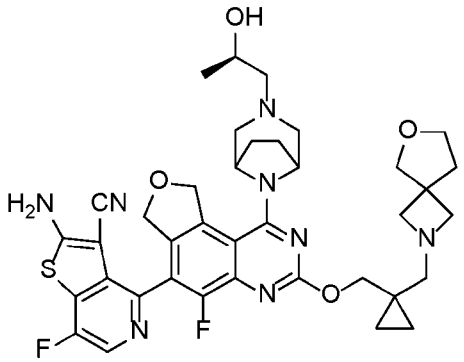
17	4-(3-((1-(((1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		731
18	4-(3-((1-((4-Acetylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		760

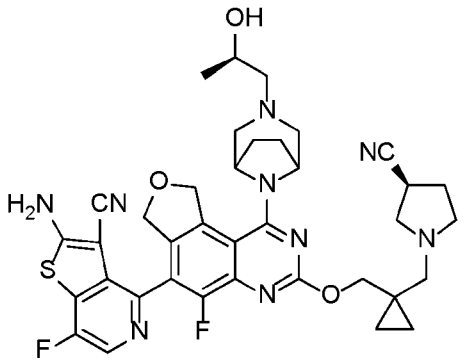
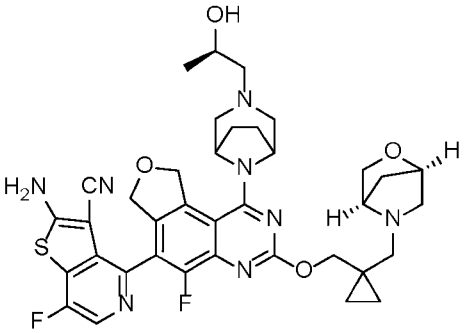
1A	2-Amino-4-(3-((1-((4-cyanopiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		742
2A	4-(3-((1-((7-Oxa-2-azaspiro[3.5]nonan-2-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		759
3A	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((R)-3-methoxypyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		733

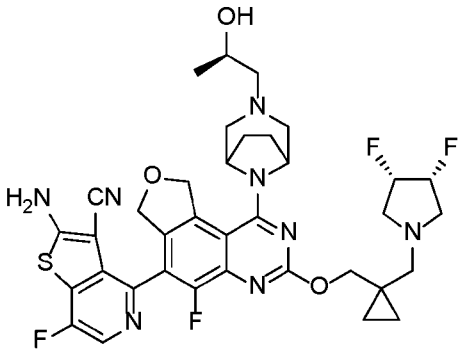
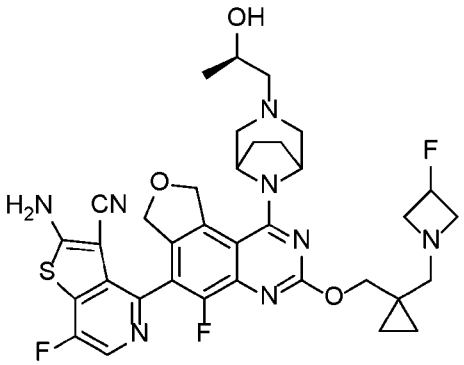
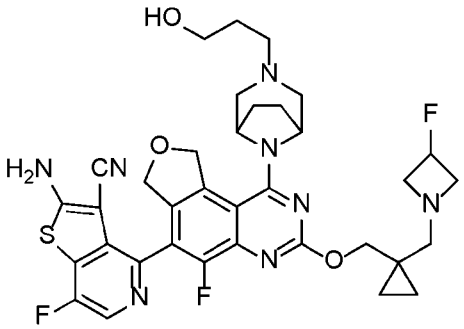
4A	4-(3-((1-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		731
5A	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		703
6A	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-hydroxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		705

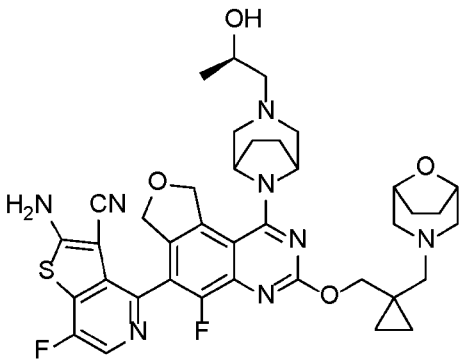
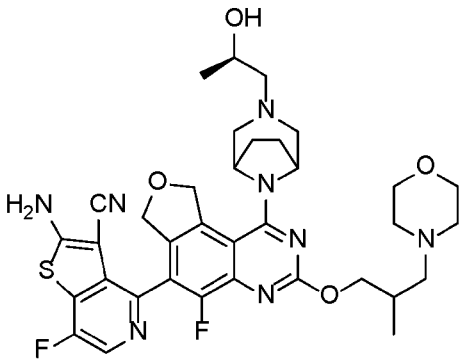
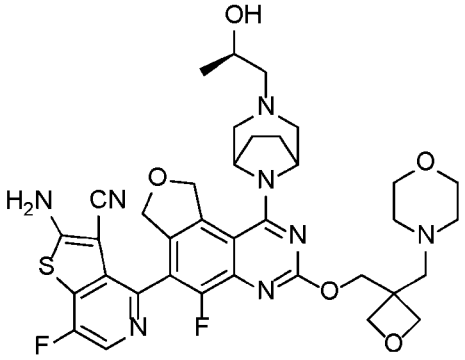
7A	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		801
8A	4-(3-((1-((3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		745
9A	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		735

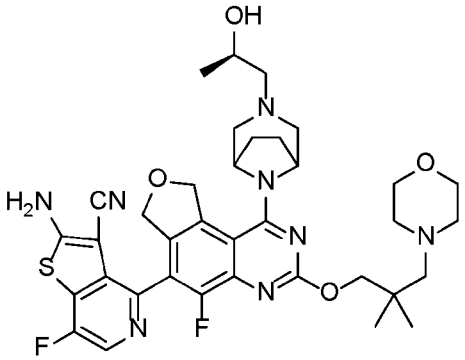
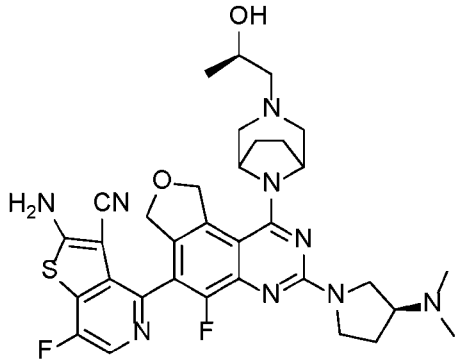
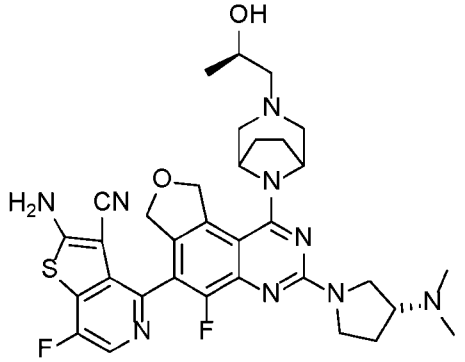
10A	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((S)-3-methylmorpholino)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		733
11A	2-Amino-4-(3-((1-(((2R,6S)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		747
12A	2-Amino-7-fluoro-4-(5-fluoro-3-((1-(((S)-2-(hydroxymethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		719

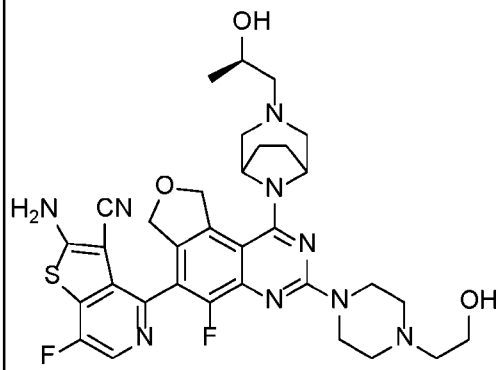
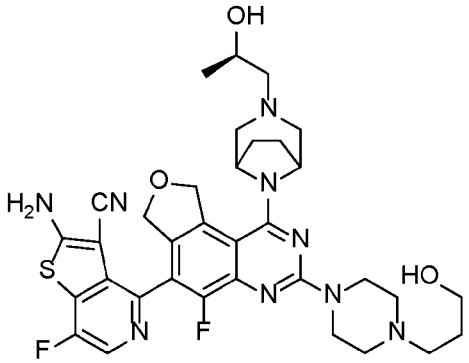
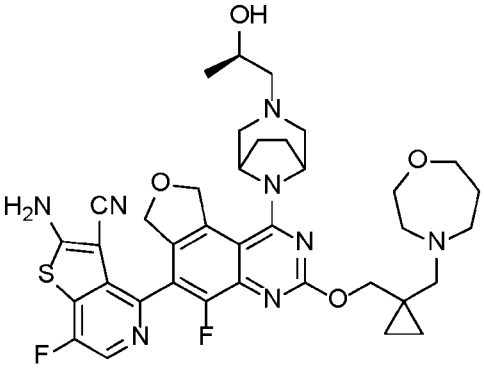
13A	2-Amino-4-(3-((1-((3,3-dimethylazetidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		717
14A	2-Amino-4-(3-((1-(((R)-3-cyanopyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		728
15A	4-(3-((1-((6-Oxa-2-azaspiro[3.4]octan-2-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		745

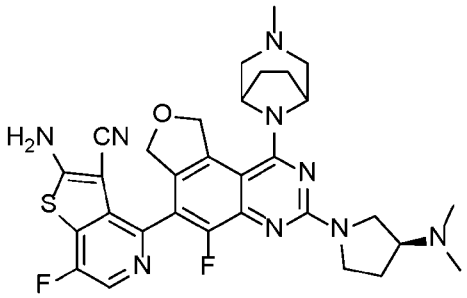
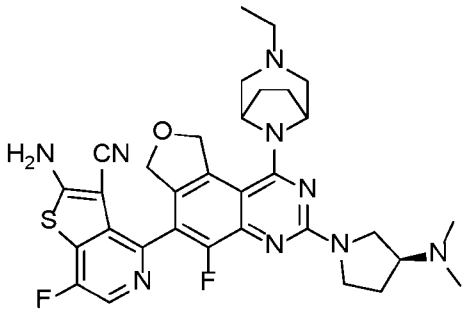
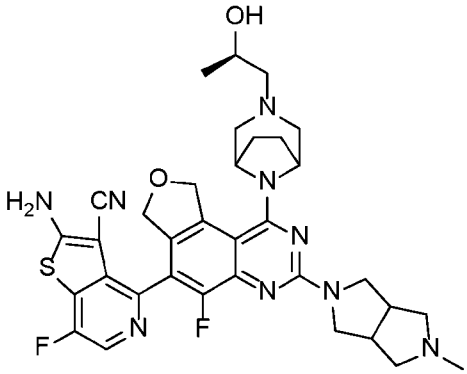
16A	2-Amino-4-(3-((1-(((S)-3-cyanopyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		728
17A	4-(3-((1-(((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		731

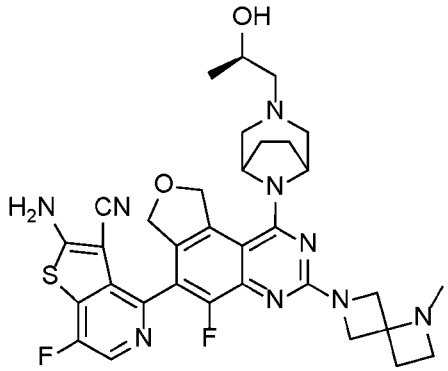
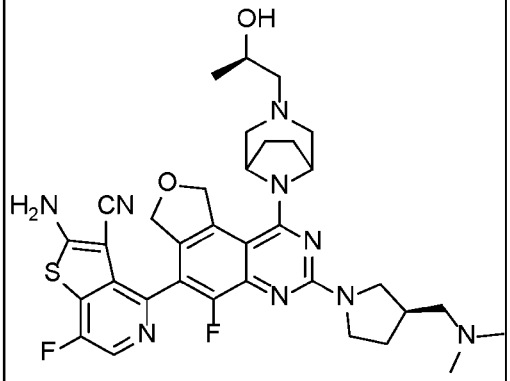
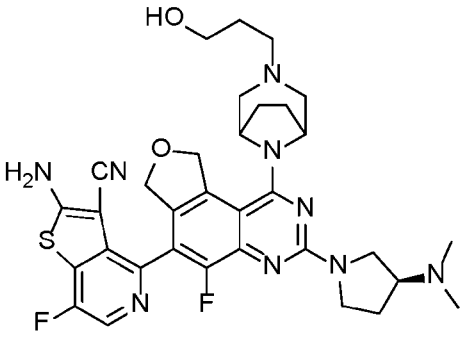
18A	2-Amino-4-(3-((1-(((3R,4S)-3,4-difluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		739
19A	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-fluoroazetidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		707
20A	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-fluoroazetidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		707

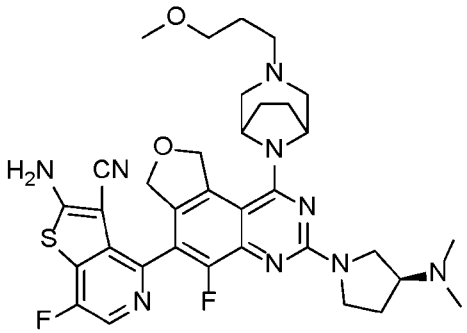
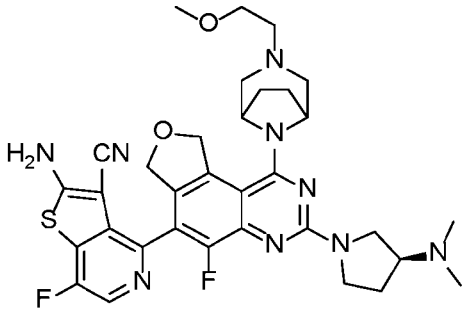
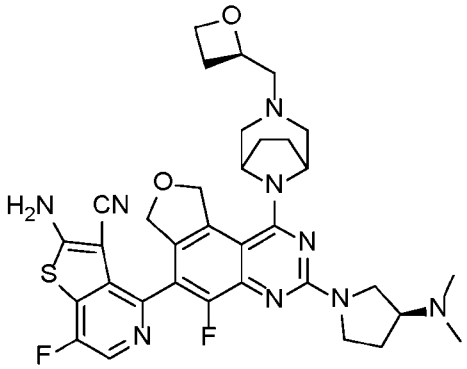
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22A	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(2-methyl-3-morpholinopropoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		707
23A	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((3-(morpholinomethyl)oxetan-3-yl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		735

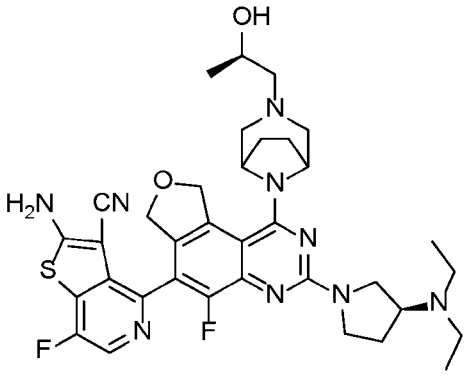
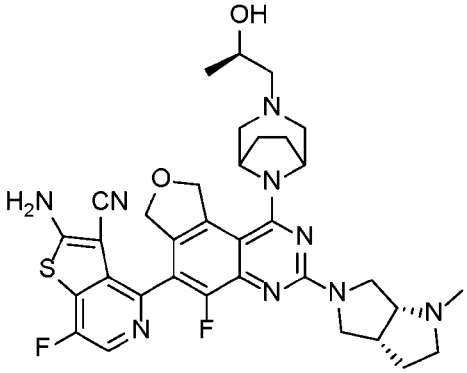
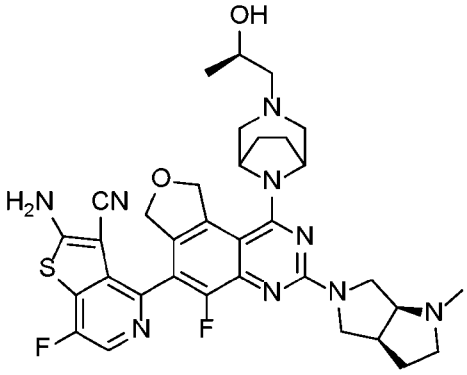
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25A	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		662
26A	2-Amino-4-(3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		662

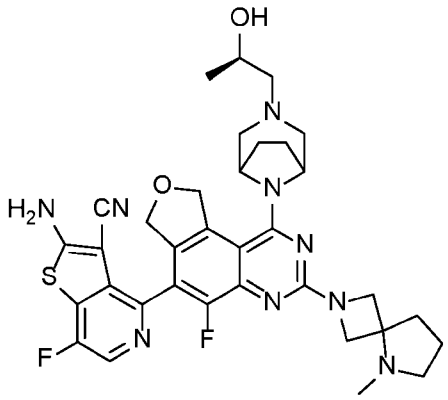
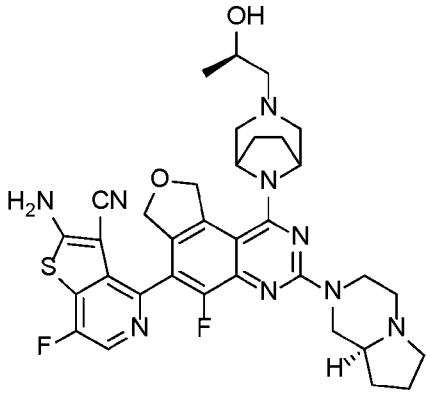
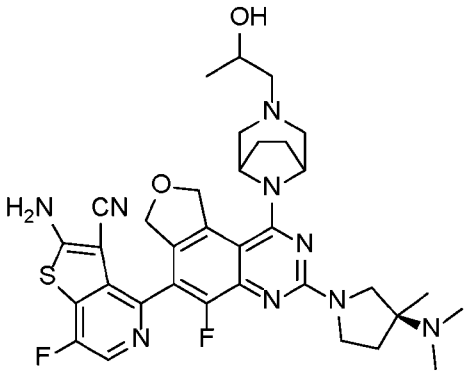
27A	2-Amino-7-fluoro-4-(5-fluoro-3-(4-(2-hydroxyethyl)piperazin-1-yl)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		678
28A	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(4-(3-hydroxypropyl)piperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		692
1B	4-(3-((1-((1,4-Oxazepan-4-yl)methyl)cyclopropyl)methoxy)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		733

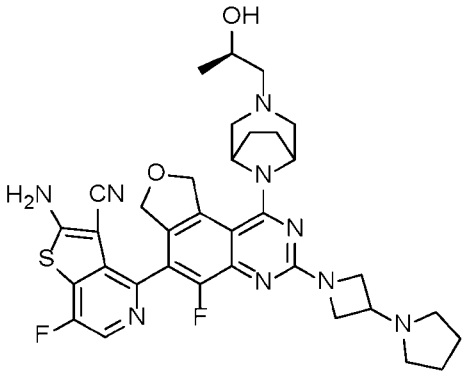
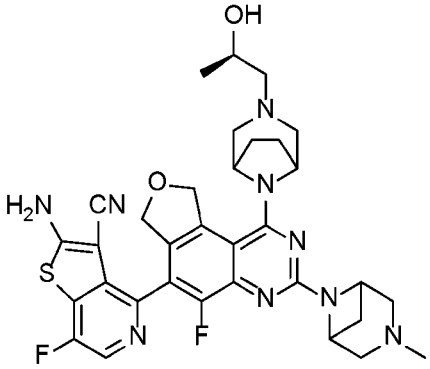
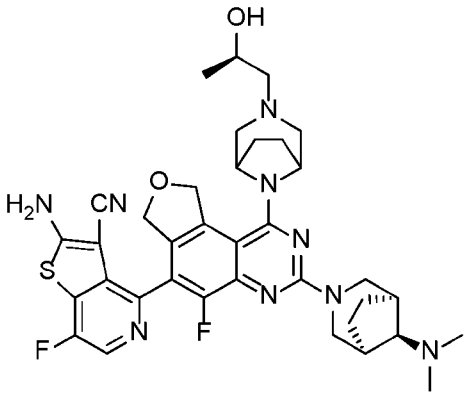
2B	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		618
3B	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-1-(3-ethyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		632
4B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		674

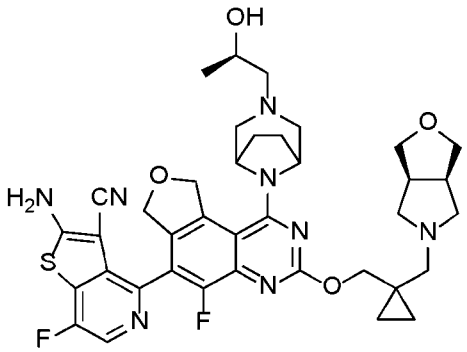
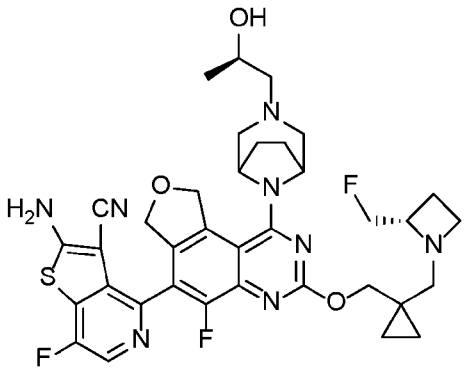
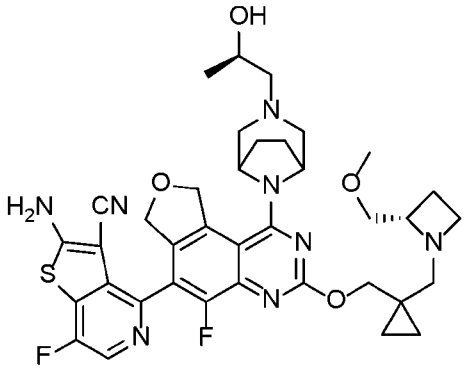
5B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		660
6B	2-Amino-4-(3-((R)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		676
7B	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		662

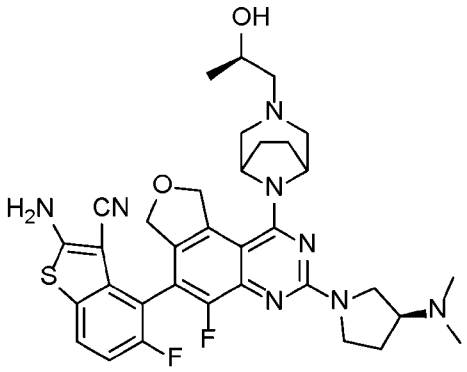
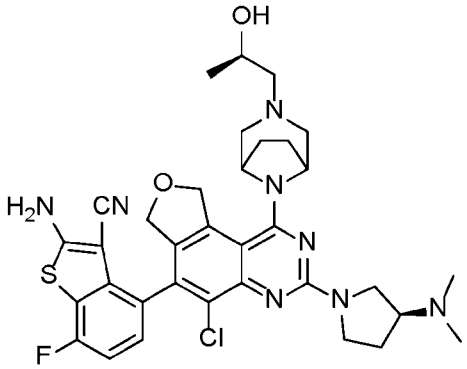
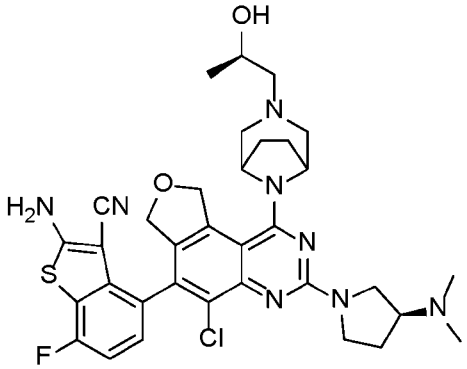
8B	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		676
9B	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		662
10B	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-(((R)-oxetan-2-yl)methyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		674

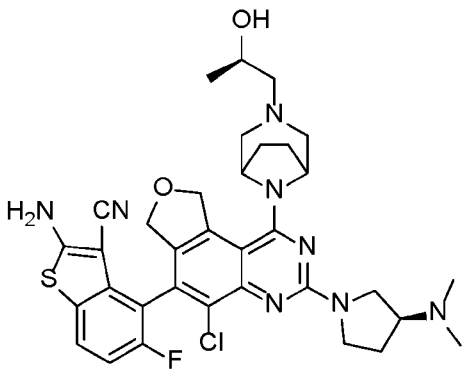
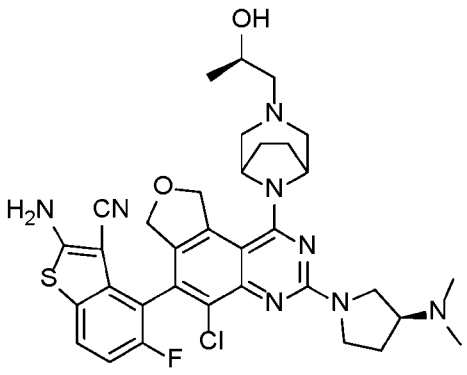
11B	2-Amino-4-(3-((S)-3-(diethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		690
12B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		674
13B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		674

14B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(5-methyl-2,5-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		674
15B	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		674
16B	2-Amino-4-(3-((S)-3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-1-(3-(2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		676

17B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(3-(pyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		674
18B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		660
19B	2-Amino-4-(3-((1R,5S,8R)-8-(dimethylamino)-3-azabicyclo[3.2.1]octan-3-yl)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		702

20B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		745
21B	2-Amino-7-fluoro-4-(5-fluoro-3-((1-(((S)-2-(fluoromethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		721
22B	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(((S)-2-(methoxymethyl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		733

23B [2]	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile		661
24B [3]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile. Atropisomer 1		677
25B [3]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile. Atropisomer 2		677

26B [4]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		677
27B [4]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 2		677

[1] Prep-Chiral-HPLC; CHIRAL ART Cellulose-SZ, 20 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 20 mL/min

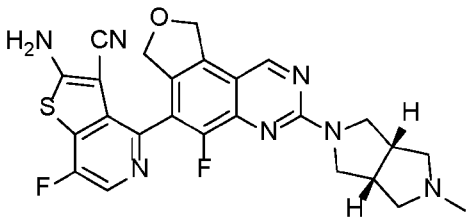
[2] Single atropisomer (from precursor in Preparation 9B)

[3] Prep-Chiral-HPLC; CHIRAL ART Cellulose-SZ, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 40 mL/min

[4] Prep-Chiral-HPLC; Chiralpak-IG, 30 x 250 mm, 10% MeOH in (1:1 Hexanes:MTBE w/ 0.5% 2M ammoniated methanol), 40 mL/min

Example 29A

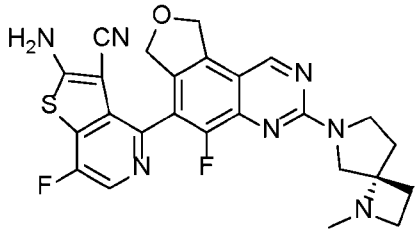
2-Amino-7-fluoro-4-(5-fluoro-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile



[0355] 2-Amino-7-fluoro-4-(5-fluoro-3-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile and formaldehyde (with acetic acid as the solvent) were used in a manner analogous to the method of Example 1 to afford the title compound (0.014 g, 48%). MS (ES) *m/z*=506 (M+1).

Example 30A

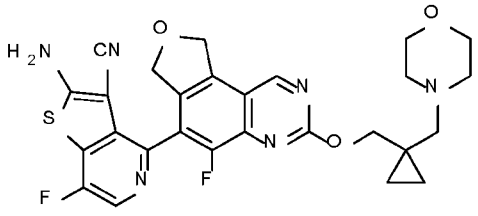
2-Amino-7-fluoro-4-(5-fluoro-3-((S)-1-methyl-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile



[0356] 2-Amino-7-fluoro-4-(5-fluoro-3-((S)-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile and formaldehyde (with acetic acid as the solvent) were used in a manner analogous to the method of Example 1 to afford the title compound (0.028 g, 51%). MS (ES) *m/z*=506 (M+1).

Example 19

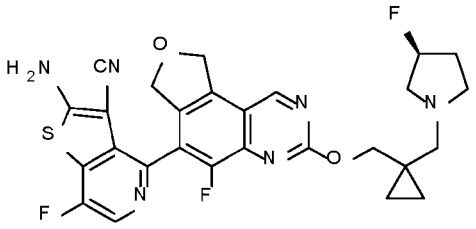
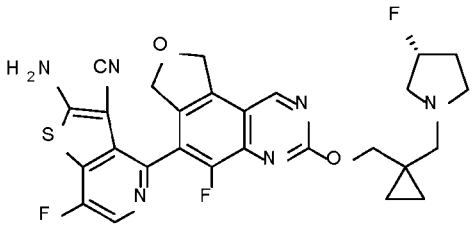
2-Amino-7-fluoro-4-(5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile

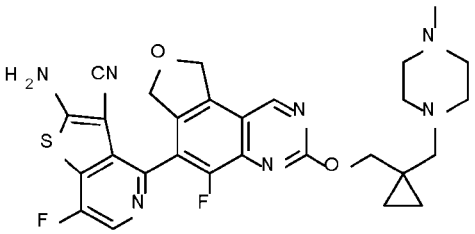
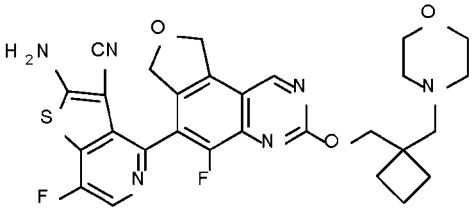
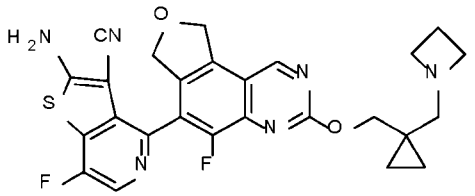
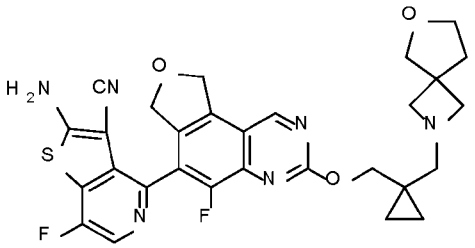


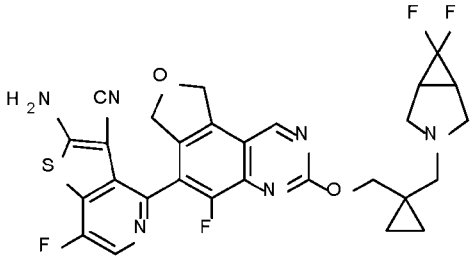
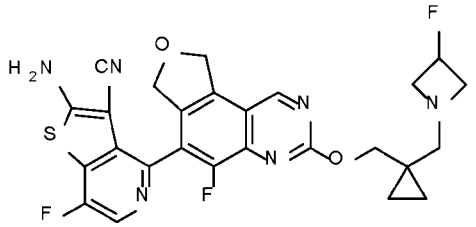
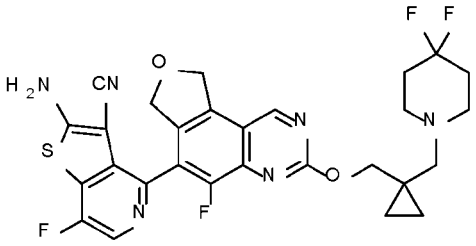
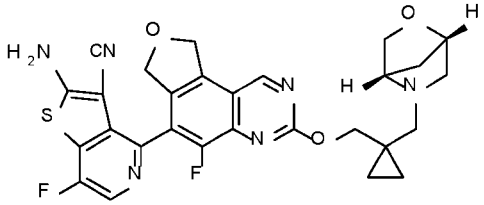
[0357] *tert*-Butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((1-(morpholinomethyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate (0.33 g, 0.51 mmol) and 1,1,1,3,3,3-hexafluoropropan-2-ol (4 mL) were combined. The mixture was stirred for 1 h at 100 °C, then concentrated under reduced pressure. The residue was purified by reversed phase purification, eluting with 31% to 48% ACN in 10 mM aq. NH_4HCO_3, followed by lyophilization, to give the title compound (0.070 g, 29%) as a white solid. MS (ES) *m/z*=551 (M+1).

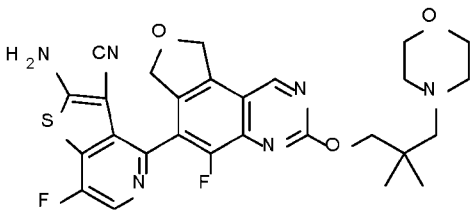
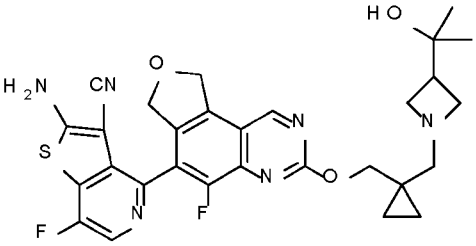
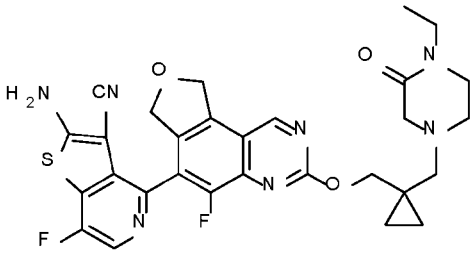
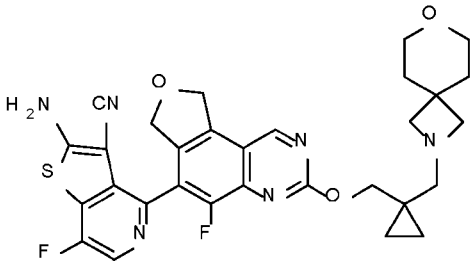
[0358] The following compounds in Table 28 were prepared in similar manner as described in Preparation 94 or Example 19. Various deprotecting reagents, such as HCl, TFA, or TBAF, were used. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

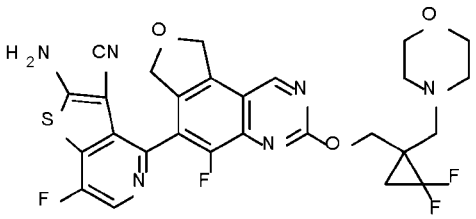
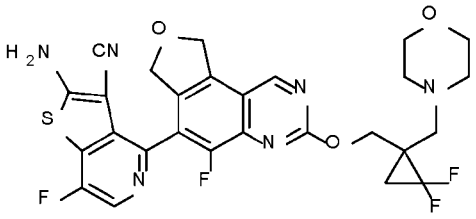
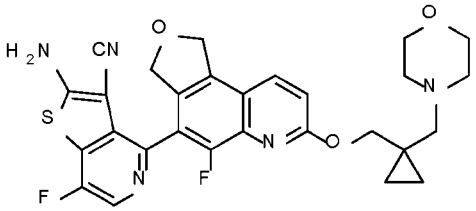
Table 28:

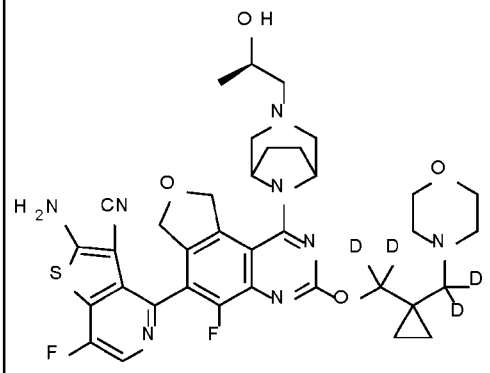
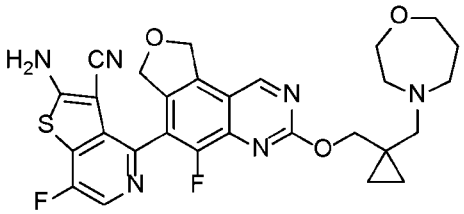
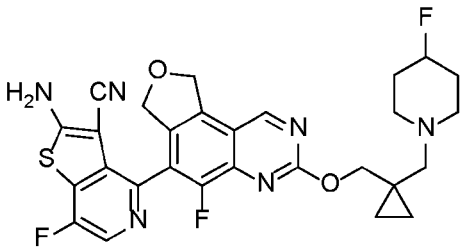
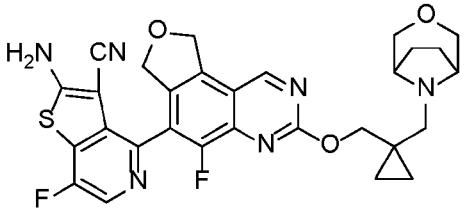
Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)
20	2-Amino-7-fluoro-4-(5-fluoro-3-((1-(((S)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		553
21	2-Amino-7-fluoro-4-(5-fluoro-3-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		553

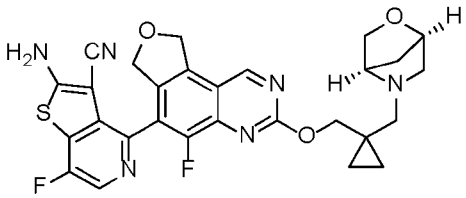
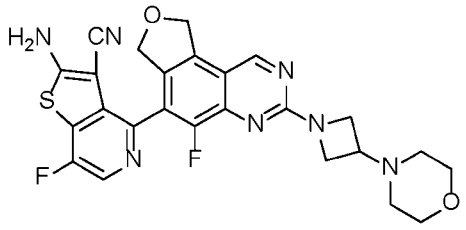
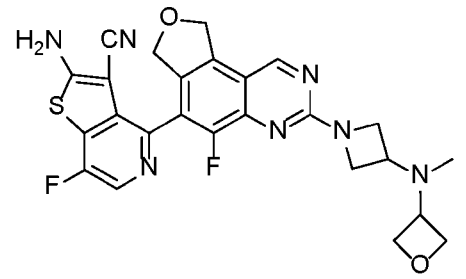
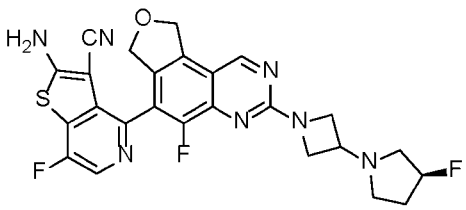
22	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
23	2-Amino-7-fluoro-4-(5-fluoro-3-((1-(morpholinomethyl)cyclobutyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		565
24	2-Amino-4-(3-((1-(azetidin-1-ylmethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		521
25	4-(3-((1-((6-Oxa-2-azaspiro[3.4]octan-2-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		577

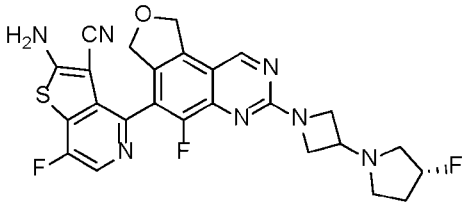
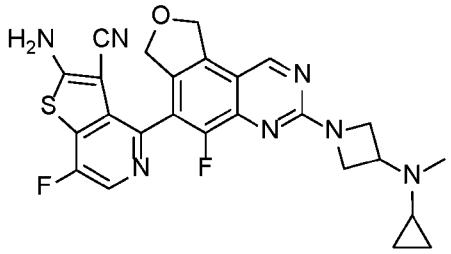
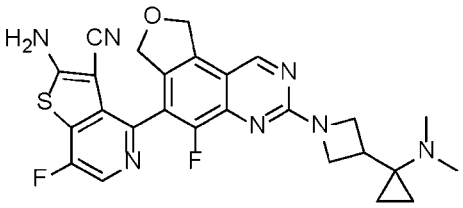
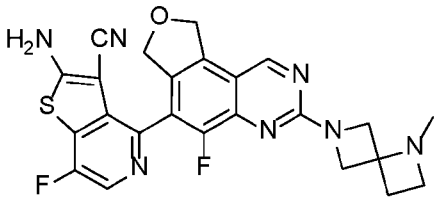
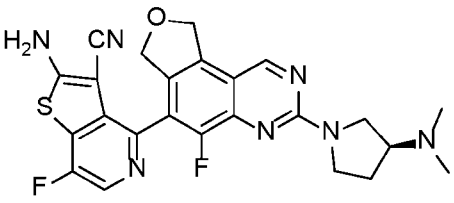
26	2-Amino-4-(3-((1-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		583
27	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-fluoroazetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		539
28	2-Amino-4-(3-((1-((4,4-difluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		585
29	4-(3-((1-(((1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563

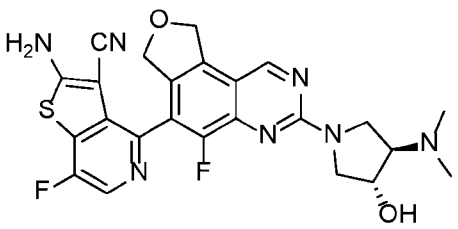
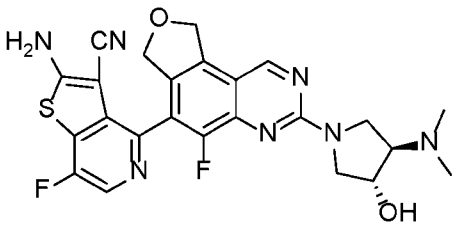
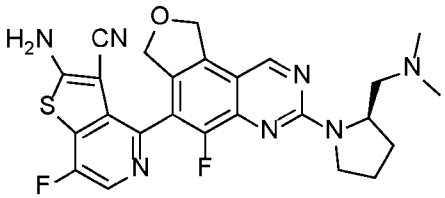
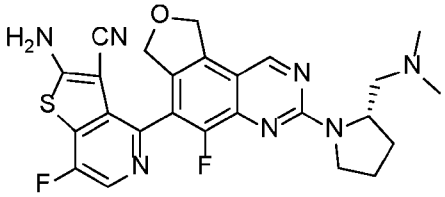
30	2-Amino-4-(3-(2,2-dimethyl-3-morpholinopropoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		553
31	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((3-(2-hydroxypropan-2-yl)azetidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		579
32	2-Amino-4-(3-((1-((4-ethyl-3-oxopiperazin-1-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		592
33	4-(3-((1-((7-Oxa-2-azaspiro[3.5]nonan-2-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		591

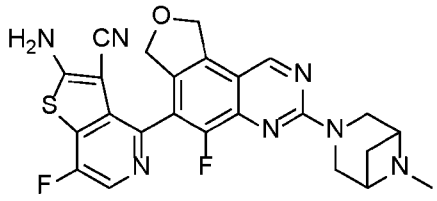
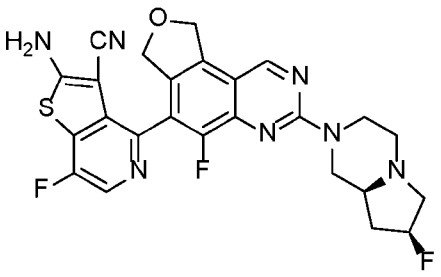
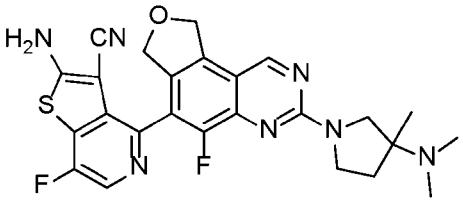
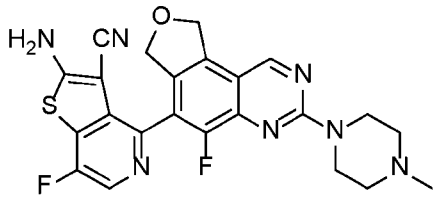
34	2-Amino-4-(3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		587
35	2-Amino-4-(3-((2,2-difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		587
36	2-Amino-7-fluoro-4-(5-fluoro-7-((1-(morpholinomethyl)cyclopropyl)methoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)thieno[3,2-c]pyridine-3-carbonitrile		550

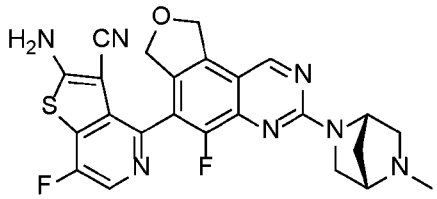
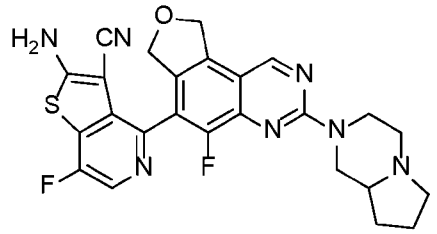
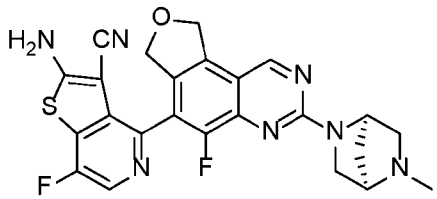
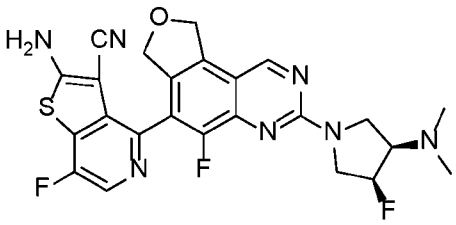
37	2-Amino-7-fluoro-4-(5-fluoro-1-(3-((R)-2-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-((1-(morpholinomethyl-d2)cyclopropyl)methoxy-d2)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		723
31A	4-(3-((1-((1,4-Oxazepan-4-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		565
32A	2-Amino-7-fluoro-4-(5-fluoro-3-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		567
33A	4-(3-((1-((3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropyl)methoxy)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		577

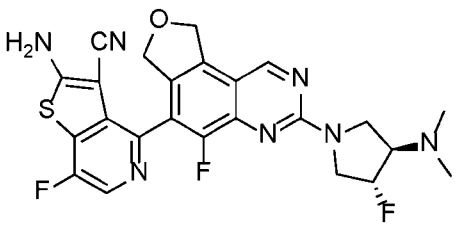
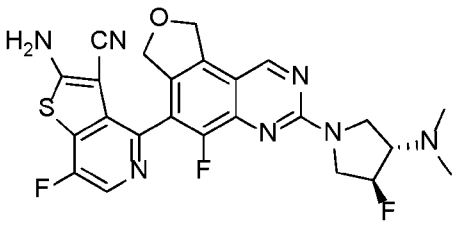
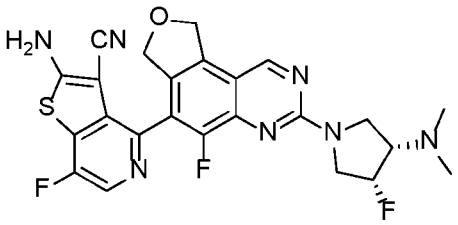
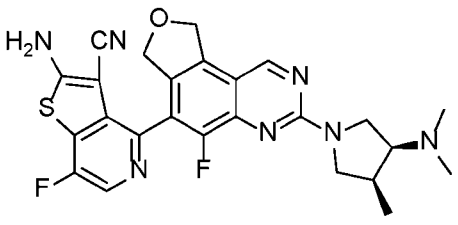
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35A	2-Amino-7-fluoro-4-(5-fluoro-3-(3-morpholinoazetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
36A	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(methyl(oxetan-3-yl)amino)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
37A	2-Amino-7-fluoro-4-(5-fluoro-3-(3-((S)-3-fluoropyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524

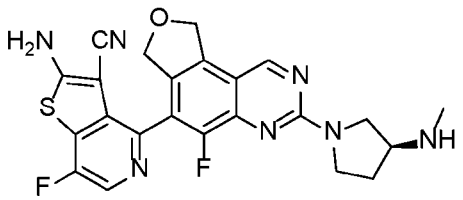
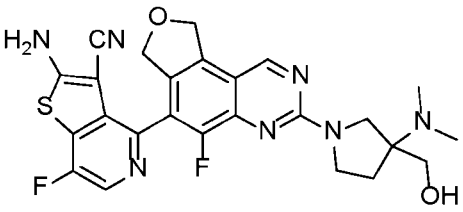
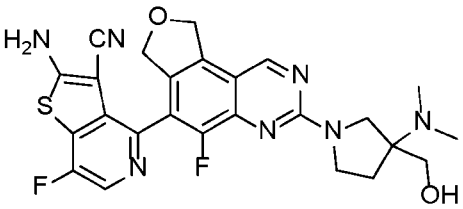
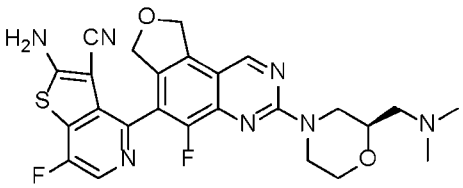
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39A	2-Amino-4-(3-(3-(cyclopropyl(methyl)amino)azetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
40A	2-Amino-4-(3-(3-(1-(dimethylamino)cyclopropyl)azetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
41A	2-Amino-7-fluoro-4-(5-fluoro-3-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
42A	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		494

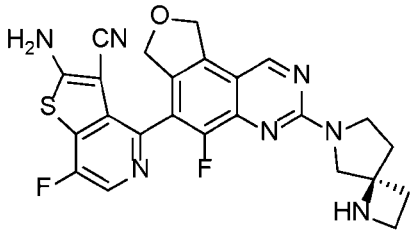
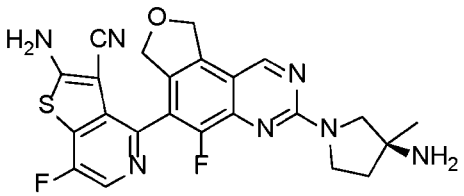
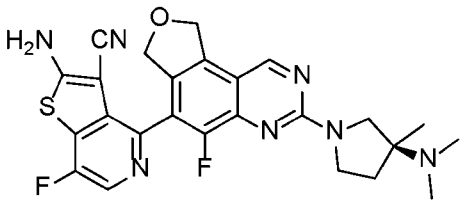
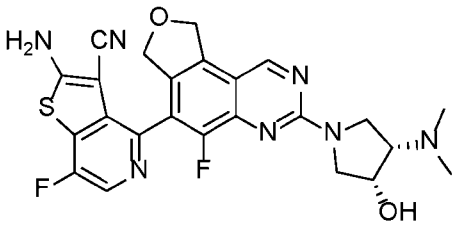
43A [1]	rel-2-Amino-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Trans Isomer 1		510
44A [1]	rel-2-Amino-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Trans Isomer 2		510
45A	2-Amino-4-(3-((R)-2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
46A	2-Amino-4-(3-((S)-2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508

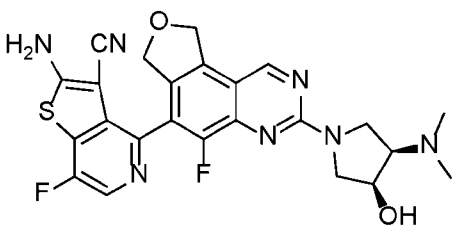
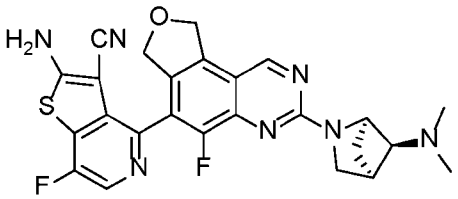
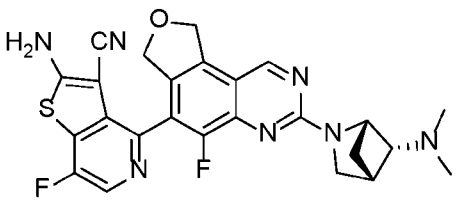
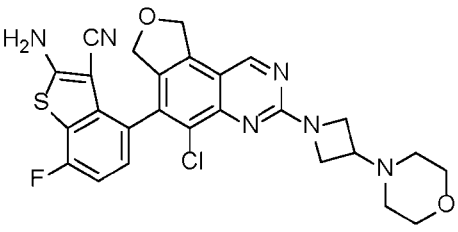
47A	2-Amino-7-fluoro-4-(5-fluoro-3-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
48A	2-Amino-7-fluoro-4-(5-fluoro-3-((7S,8aS)-7-fluorohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524
49A	2-Amino-4-(3-(3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
50A	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methylpiperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		480

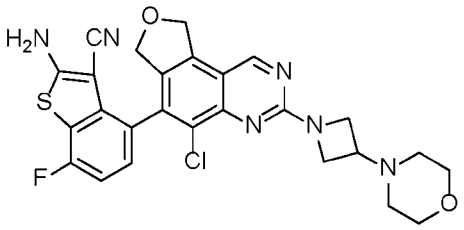
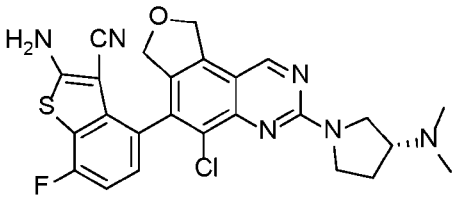
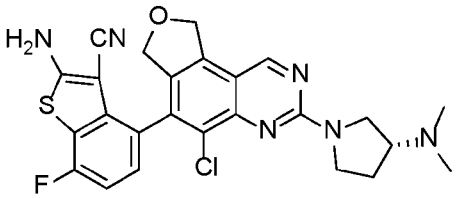
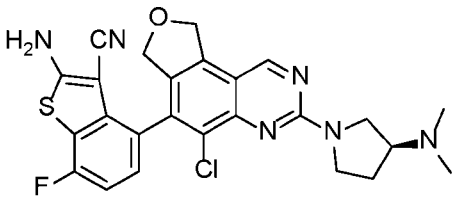
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52A	2-Amino-7-fluoro-4-(5-fluoro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
53A	2-Amino-7-fluoro-4-(5-fluoro-3-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
54A	2-Amino-4-(3-((3R,4S)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		512

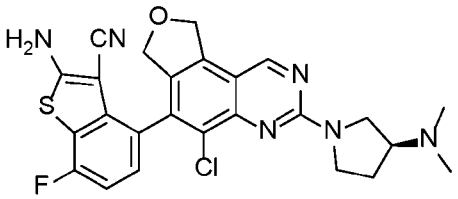
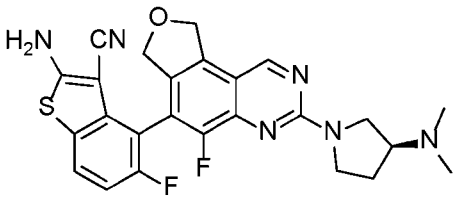
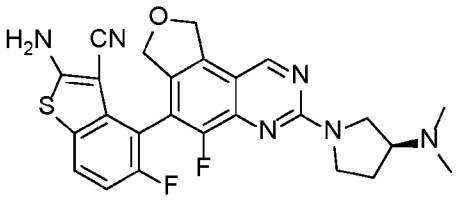
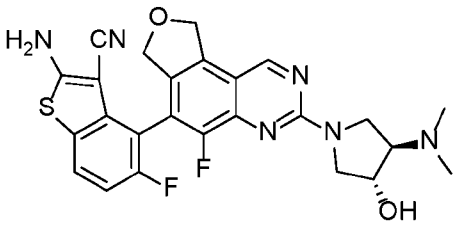
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56A	2-Amino-4-(3-((3S,4S)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		512
57A	2-Amino-4-(3-((3S,4R)-3-(dimethylamino)-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		512
58A	2-Amino-4-(3-((3S,4S)-3-(dimethylamino)-4-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508

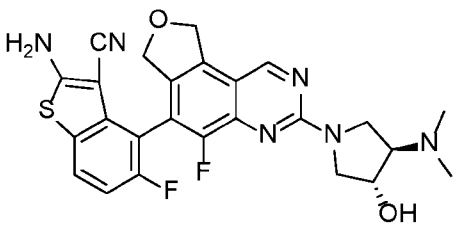
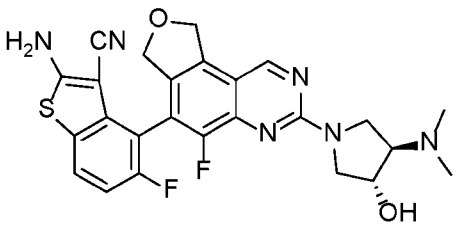
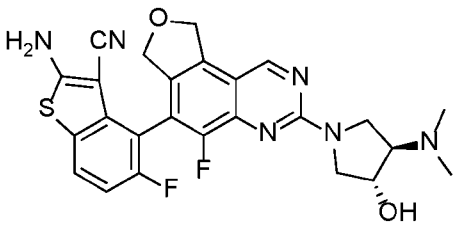
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60A [2]	2-Amino-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Enantiomer 1		524
61A [2]	2-Amino-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Enantiomer 2		524
62A	2-Amino-4-(3-((R)-2-((dimethylamino)methyl)morpholino)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524

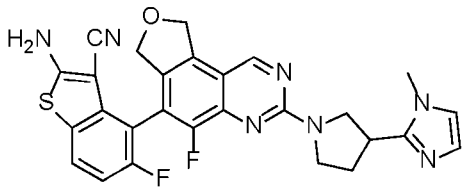
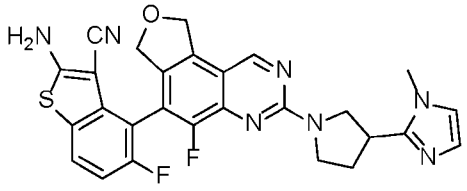
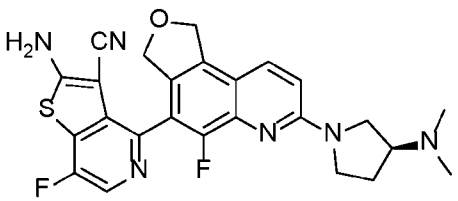
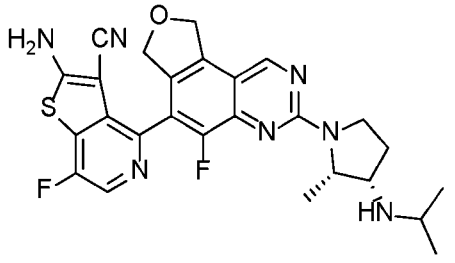
63A	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
64A	2-Amino-4-(3-((S)-3-amino-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		480
65A	2-Amino-4-(3-((S)-3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
66A	2-Amino-4-(3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		510

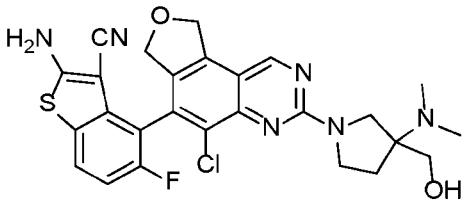
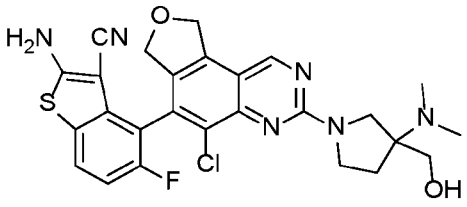
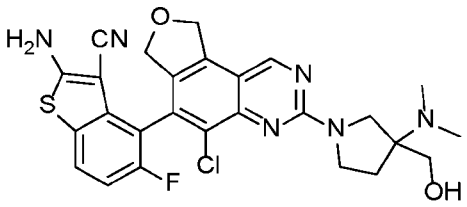
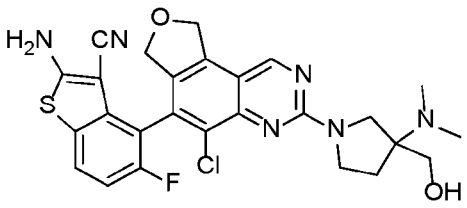
67A	2-Amino-4-(3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		510
68A	2-Amino-4-(3-((1R,4R,5S)-5-(dimethylamino)-2-azabicyclo[2.1.1]hexan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
69A	2-Amino-4-(3-((1S,4S,5R)-5-(dimethylamino)-2-azabicyclo[2.1.1]hexan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
70A [3]	2-Amino-4-(5-chloro-3-(3-morpholinoazetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		537

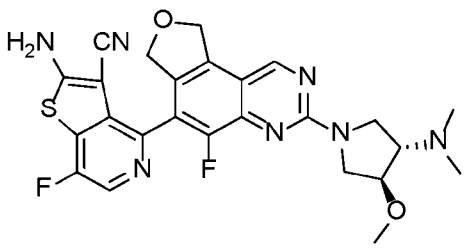
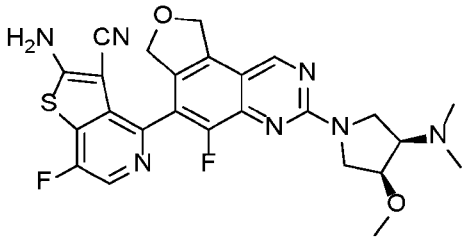
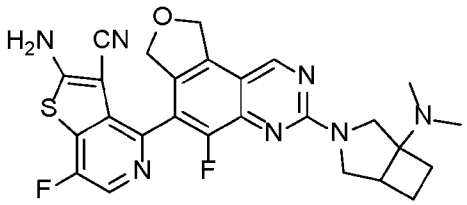
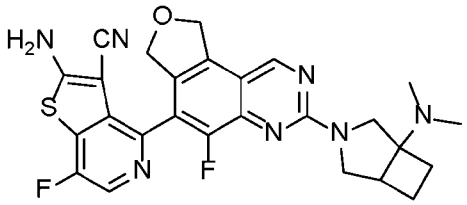
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72A [4]	2-Amino-4-(5-chloro-3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		509
73A [4]	2-Amino-4-(5-chloro-3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 2		509
74A [5]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile, Atropsiomer 1		509

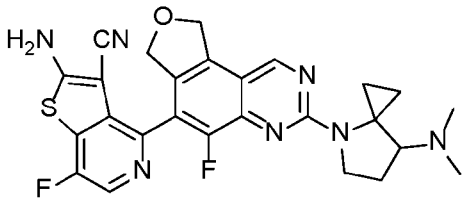
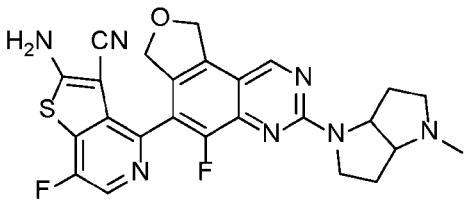
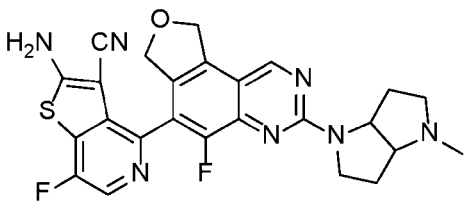
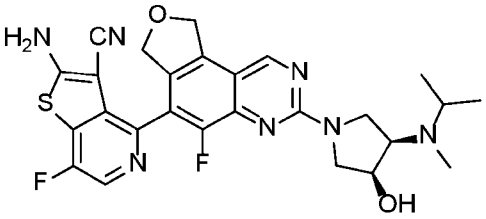
75A [5]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile, Atropsiomer 2		509
76A [6]	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		493
77A [6]	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 2		493
78A [7]	rel-2-Amino-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 1		509

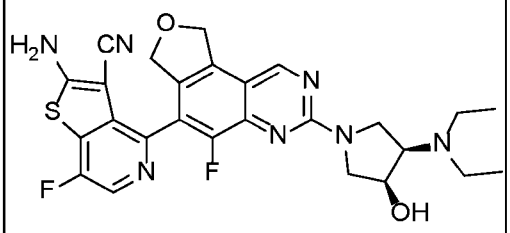
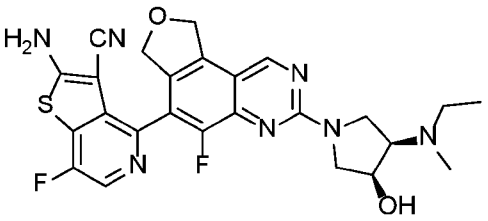
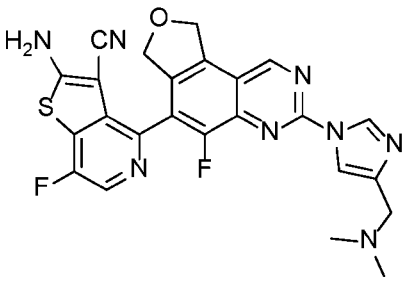
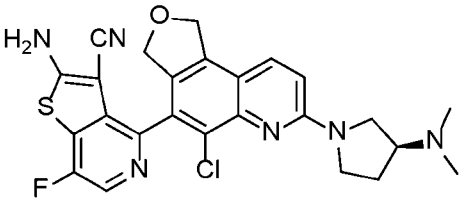
79A [7]	rel-2-Amino-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 2		509
80A [7]	rel-2-Amino-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 3		509
81A [7]	rel-2-Amino-4-(3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 4		509

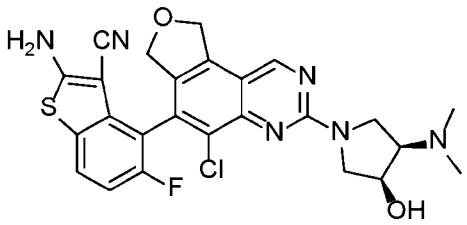
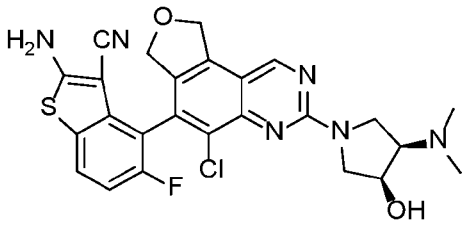
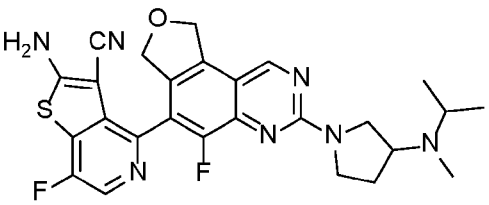
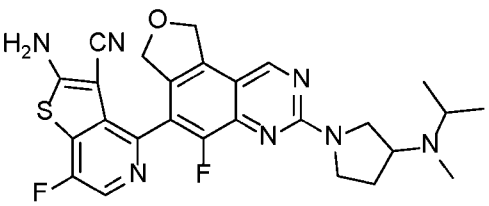
82A [8]	2-Amino-5-fluoro-4-(5-fluoro-3-(3-(1-methyl-1H-imidazol-2-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Diastereomer Mix 1		530
83A [8]	2-Amino-5-fluoro-4-(5-fluoro-3-(3-(1-methyl-1H-imidazol-2-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Diastereomer Mix 2		530
84A	2-Amino-4-(7-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		493
28B	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522

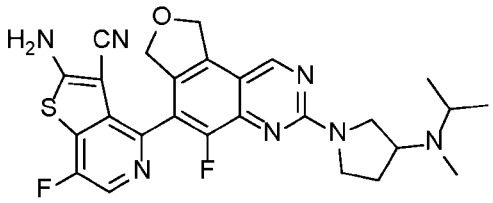
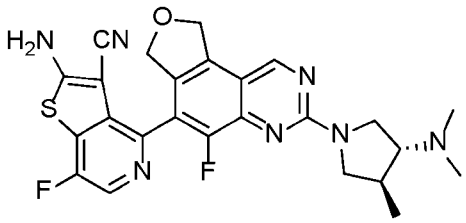
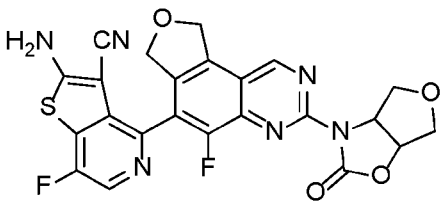
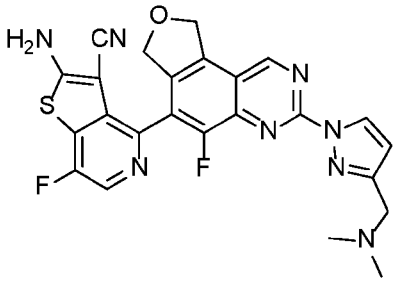
29B [9]	2-Amino-4-(5-chloro-3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 1		539
30B [9]	2-Amino-4-(5-chloro-3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 2		539
31B [9]	2-Amino-4-(5-chloro-3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 3		539
32B [9]	2-Amino-4-(5-chloro-3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 4		539

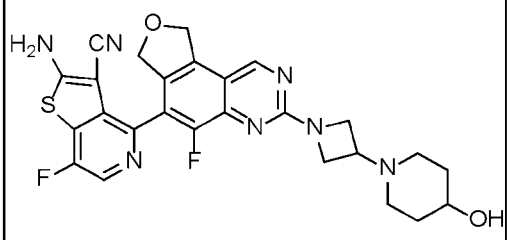
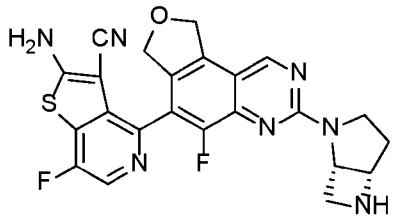
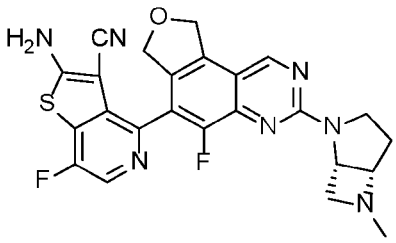
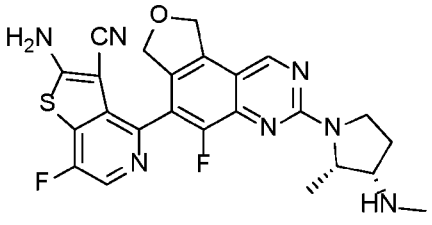
33B	2-Amino-4-(3-((3S,4S)-3-(dimethylamino)-4-methoxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
34B	2-Amino-4-(3-((3R,4S)-3-(dimethylamino)-4-methoxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
35B [10]	2-Amino-4-(3-(1-(dimethylamino)-3-azabicyclo[3.2.0]heptan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		520
36B [10]	2-Amino-4-(3-(1-(dimethylamino)-3-azabicyclo[3.2.0]heptan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		520

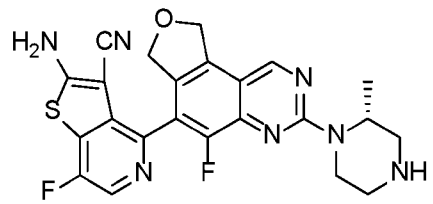
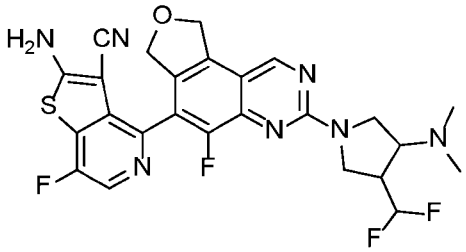
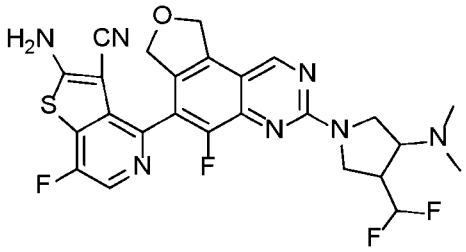
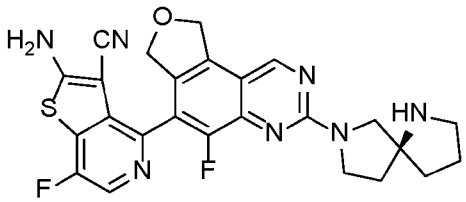
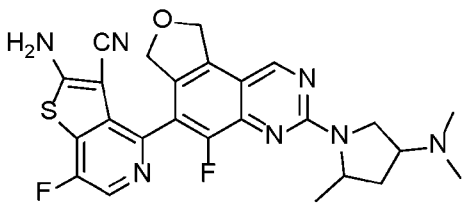
37B	2-Amino-4-(3-(7-(dimethylamino)-4-azaspiro[2.4]heptan-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
38B [11]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methylhexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		506
39B [11]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methylhexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		506
40B	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538

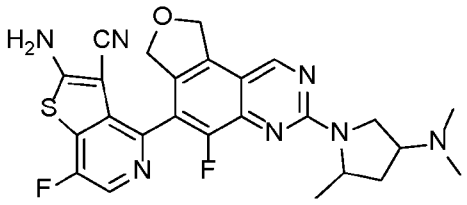
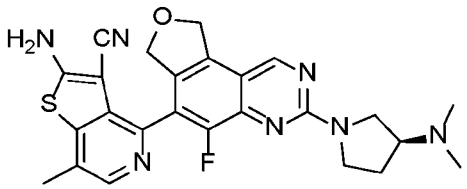
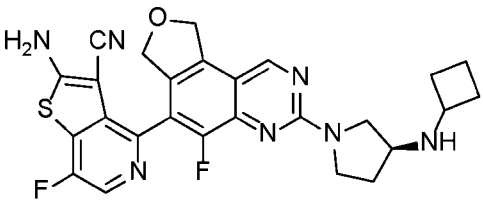
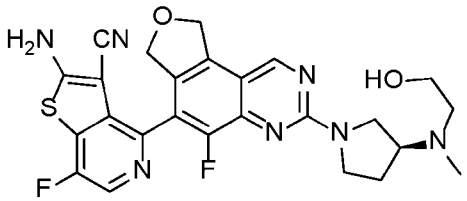
41B	2-Amino-4-(3-((3R,4S)-3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		538
42B	2-Amino-4-(3-((3R,4S)-3-(ethyl(methyl)amino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
43B	2-Amino-4-(3-(4-((dimethylamino)methyl)-1H-imidazol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		505
44B	2-Amino-4-(5-chloro-7-((S)-3-(dimethylamino)pyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		509

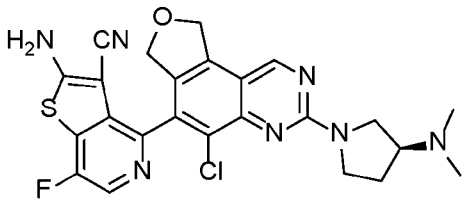
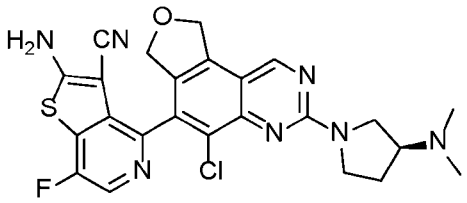
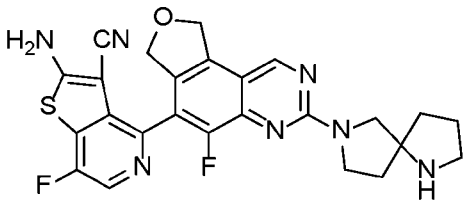
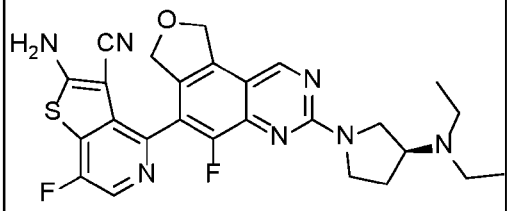
45B [12]	2-Amino-4-(5-chloro-3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		525
46B [12]	2-Amino-4-(5-chloro-3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 2		525
47B	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
48B [13]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		522

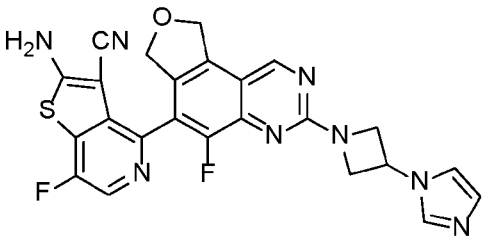
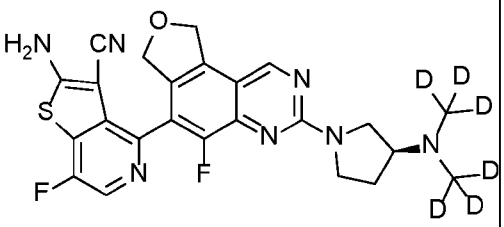
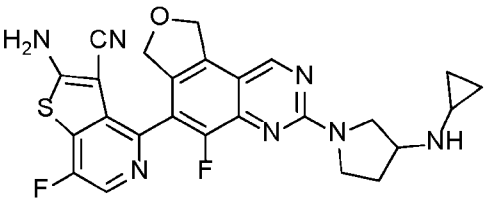
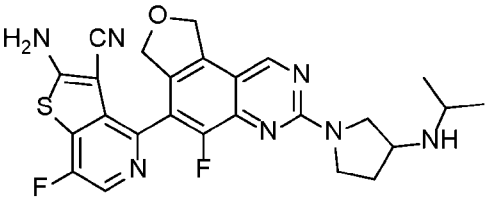
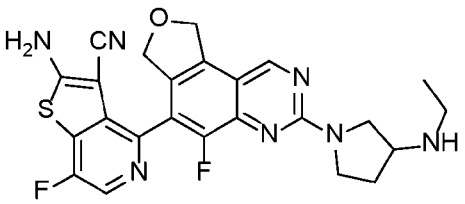
49B [13]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		522
50B	2-Amino-4-(3-((3R,4S)-3-(dimethylamino)-4-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
51B	2-Amino-7-fluoro-4-(5-fluoro-3-(2-oxotetrahydrofuro[3,4-d]oxazol-3(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		509
52B	2-Amino-4-(3-(3-((dimethylamino)methyl)-1H-pyrazol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		505

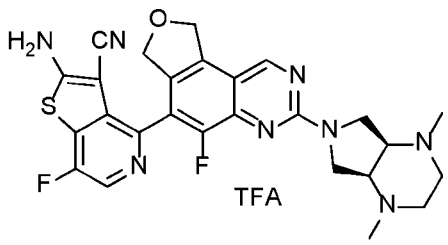
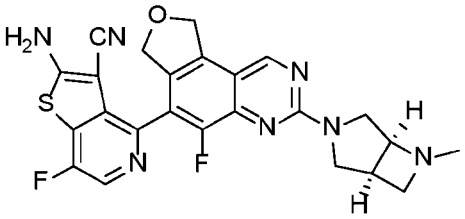
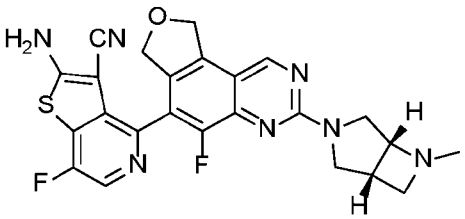
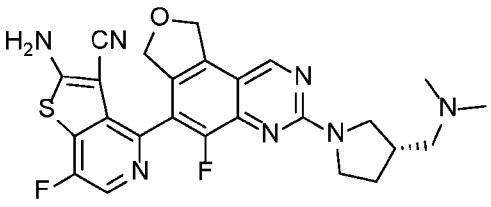
53B	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(4-hydroxypiperidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		536
54B	4-(3-((1S,5S)-2,6-Diazabicyclo[3.2.0]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		478
55B	2-Amino-7-fluoro-4-(5-fluoro-3-((1S,5S)-6-methyl-2,6-diazabicyclo[3.2.0]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
56B	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(methylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		494

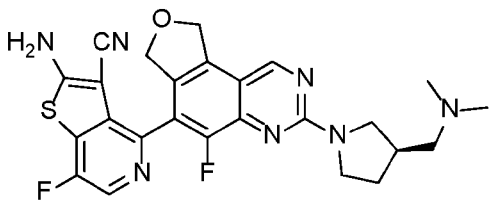
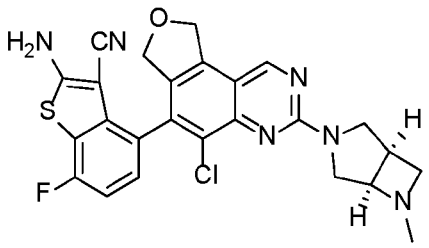
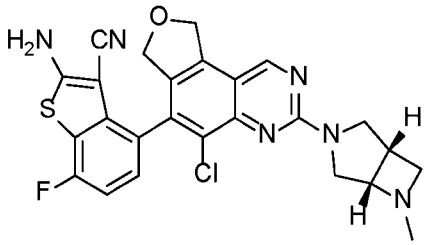
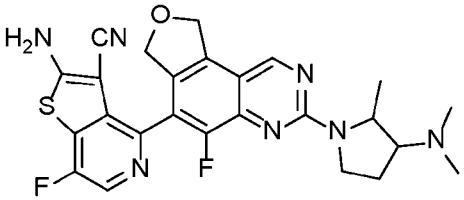
57B	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-2-methylpiperazin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		480
58B [14]	2-Amino-4-(3-(3-(difluoromethyl)-4-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		544
59B [14]	2-Amino-4-(3-(3-(difluoromethyl)-4-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		544
60B	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-1,7-diazaspiro[4.4]nonan-7-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
61B [15]	2-Amino-4-(3-(4-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508

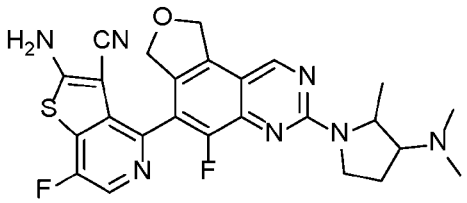
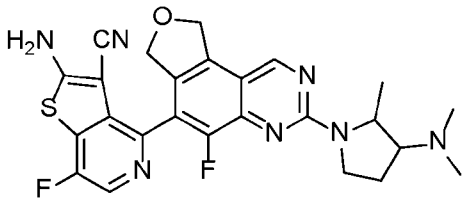
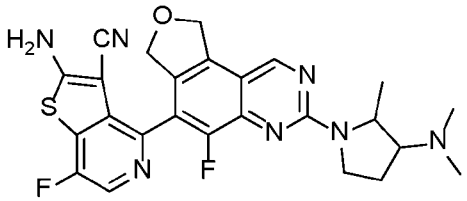
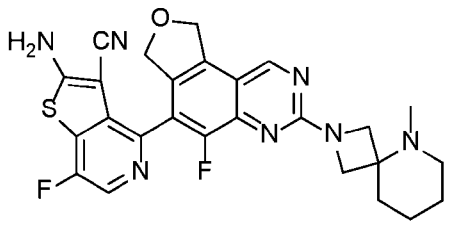
62B [15]	2-Amino-4-(3-(4-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
63B	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-methylthieno[3,2-c]pyridine-3-carbonitrile		490
64B	2-Amino-4-(3-((S)-3-(cyclobutylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
65B	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-((2-hydroxyethyl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524

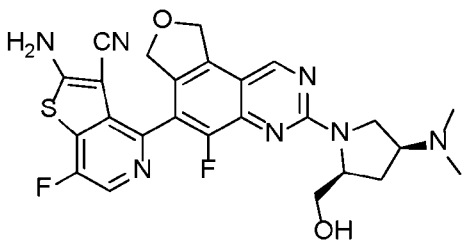
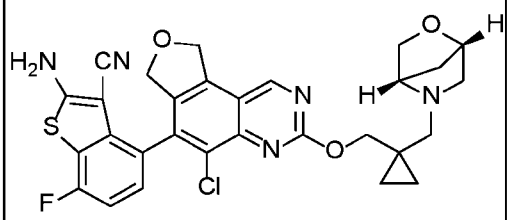
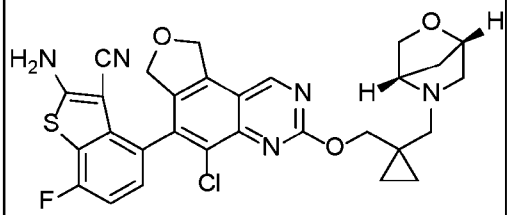
66B [16]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		511
67B [16]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		511
68B	2-Amino-7-fluoro-4-(5-fluoro-3-(1,7-diazaspiro[4.4]nonan-7-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
69B	2-Amino-4-(3-((S)-3-(diethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		522

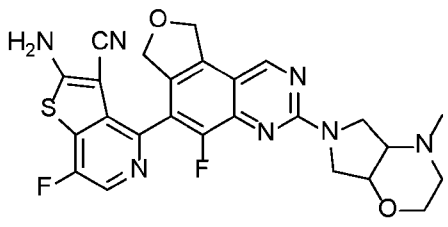
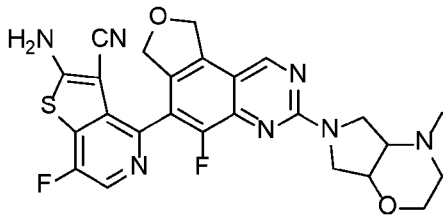
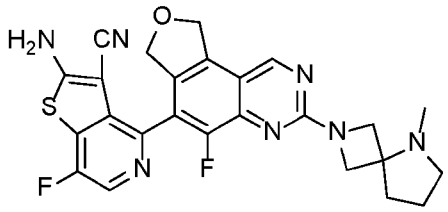
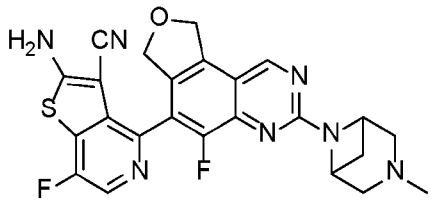
70B	4-(3-(3-(1H-Imidazol-1-yl)azetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		503
71B	2-Amino-4-(3-((S)-3-(bis(methyl-d3)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		500
72B	2-Amino-4-(3-(3-(cyclopropylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
73B	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		508
74B	2-Amino-4-(3-(3-(ethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		494

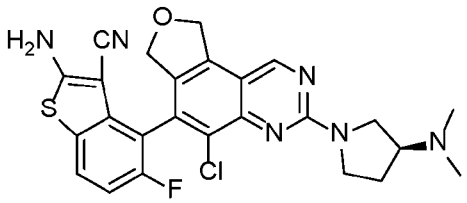
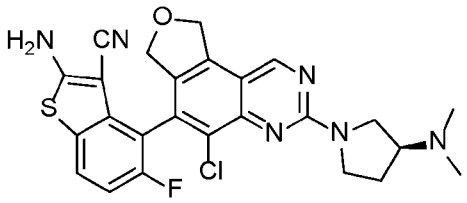
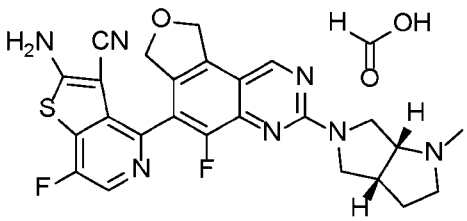
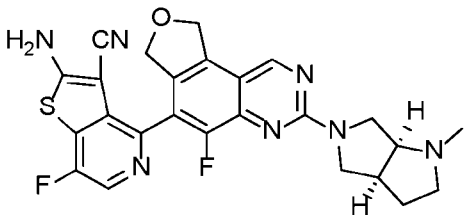
75B	2-Amino-4-(3-((4aR,7aS)-1,4-dimethyloctahydro-6H-pyrrolo[3,4-b]pyrazin-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		535
76B	2-Amino-7-fluoro-4-(5-fluoro-3-((1S,5S)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
77B	2-Amino-7-fluoro-4-(5-fluoro-3-((1R,5R)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
78B	2-Amino-4-(3-((S)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508

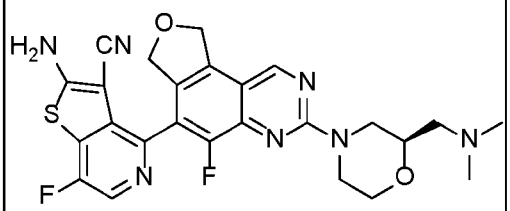
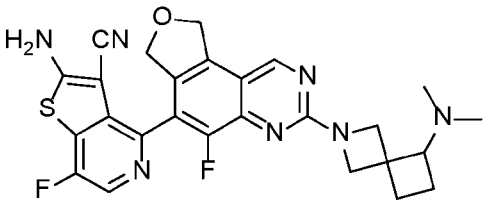
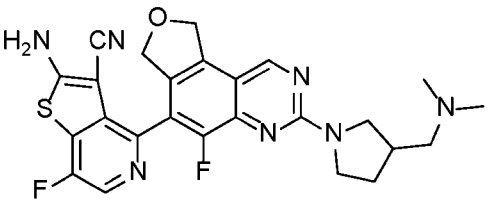
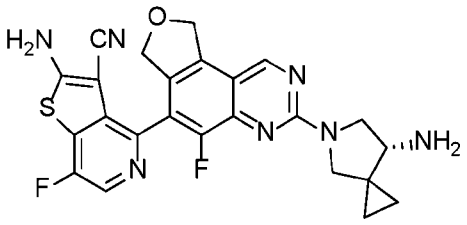
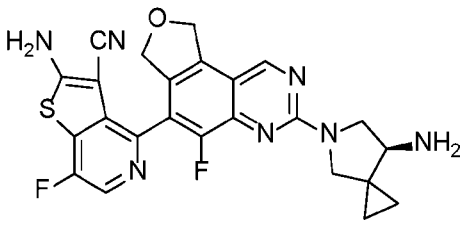
79B	2-Amino-4-(3-((R)-3-((dimethylamino)methyl) pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
80B	2-Amino-4-(5-chloro-3-((1R,5R)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile		507
81B	2-Amino-4-(5-chloro-3-((1S,5S)-6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile		507
82B [17]	2-Amino-4-(3-(3-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Diastereomer 1		508

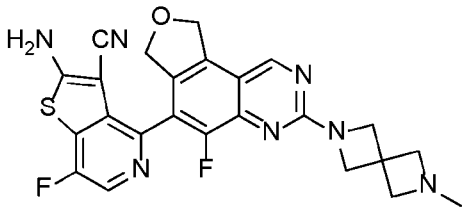
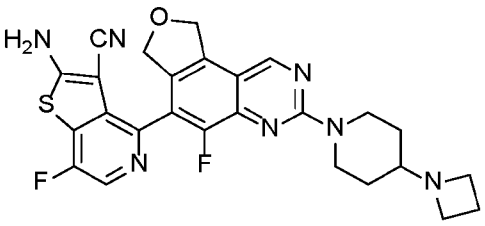
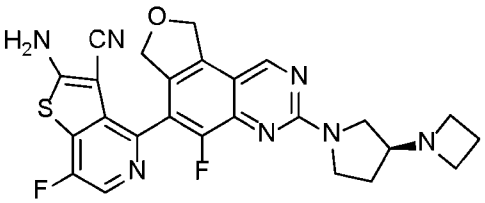
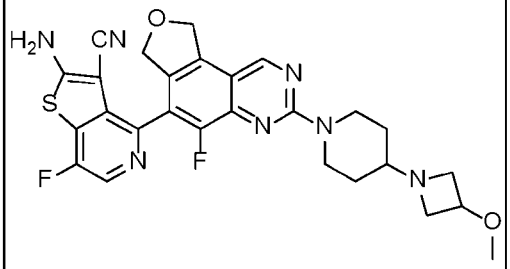
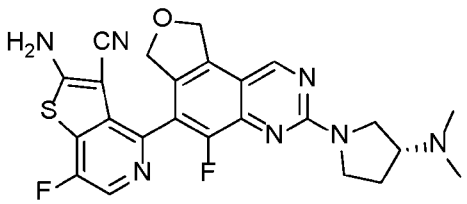
83B [17]	2-Amino-4-(3-(3-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Diastereomer 2		508
84B [17]	2-Amino-4-(3-(3-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Diastereomer 3		508
85B [17]	2-Amino-4-(3-(3-(dimethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Diastereomer 4		508
86B	2-Amino-7-fluoro-4-(5-fluoro-3-(5-methyl-2,5-diazaspiro[3.5]nonan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520

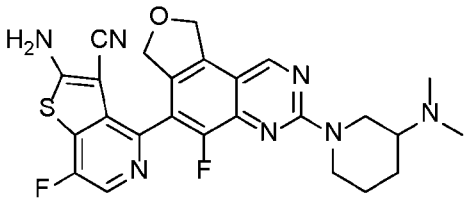
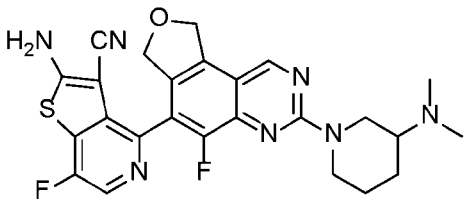
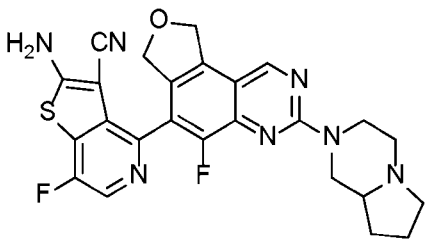
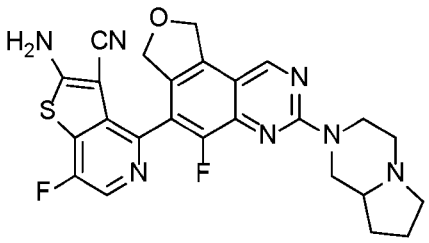
87B	2-Amino-4-(3-((2S,4S)-4-(dimethylamino)-2-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
88B [18]	4-(3-((1-(((1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		578
89B [18]	4-(3-((1-(((1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 2		578

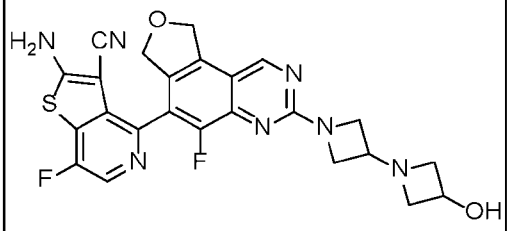
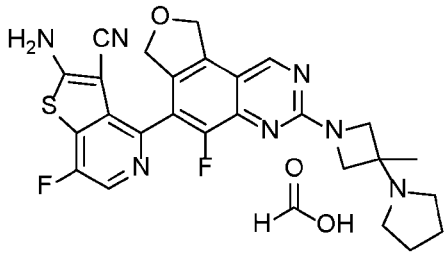
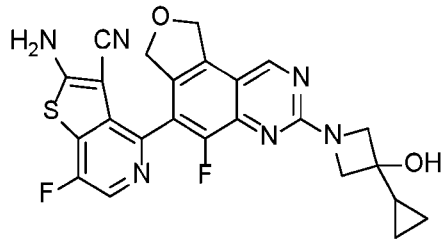
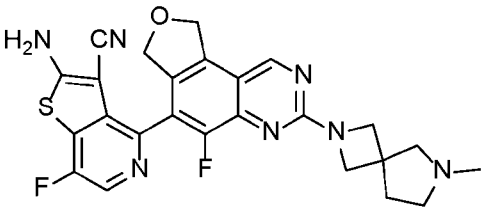
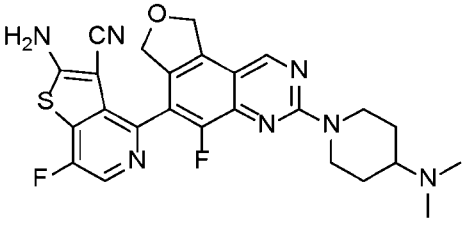
90B [19]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methylhexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
91B [19]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methylhexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
92B	2-Amino-7-fluoro-4-(5-fluoro-3-(5-methyl-2,5-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
93B	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492

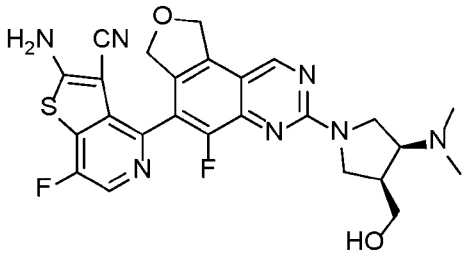
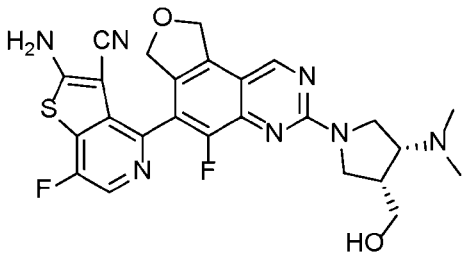
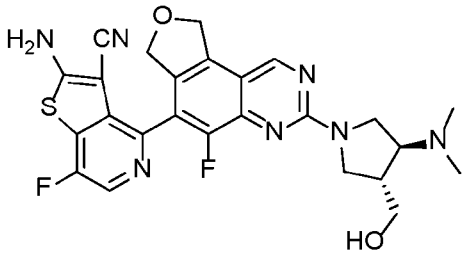
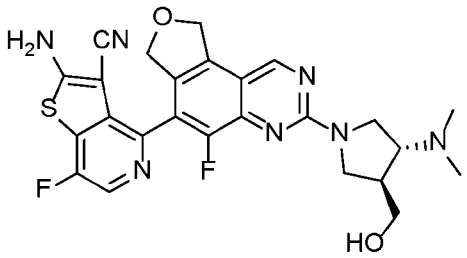
94B [20]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		509
95B [20]	2-Amino-4-(5-chloro-3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 2		509
96B	2-Amino-7-fluoro-4-(5-fluoro-3-((3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		506
97B	2-Amino-7-fluoro-4-(5-fluoro-3-((3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506

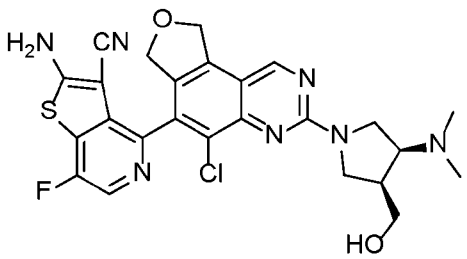
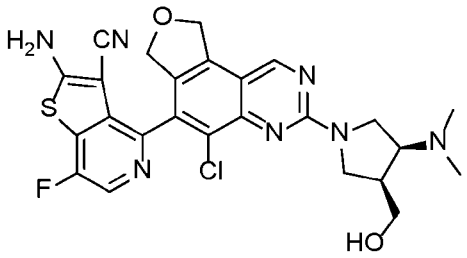
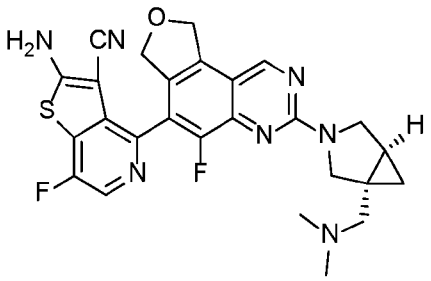
98B	2-Amino-4-(3-((R)-2-((dimethylamino)methyl) morpholino)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
99B	2-Amino-4-(3-(5-(dimethylamino)-2-azaspiro[3.3]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
100B	2-Amino-4-(3-(3-((dimethylamino)methyl) pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
101B	2-Amino-4-(3-((R)-7-amino-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		492
102B	2-Amino-4-(3-((S)-7-amino-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		492

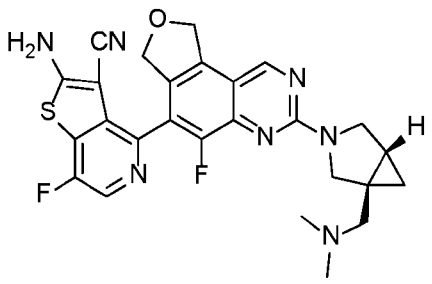
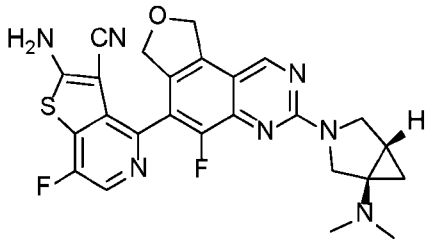
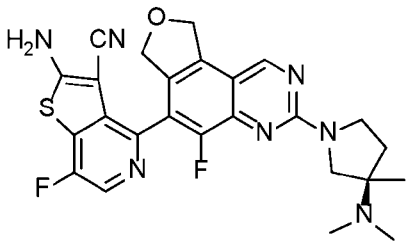
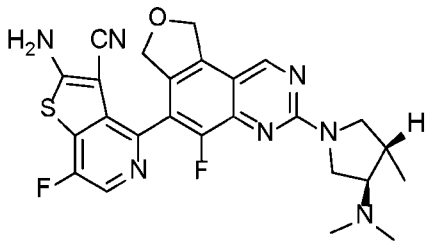
103B	2-Amino-7-fluoro-4-(5-fluoro-3-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
104B	2-Amino-4-(3-(4-(azetidin-1-yl)piperidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
105B	2-Amino-4-(3-((S)-3-(azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
106B	2-Amino-7-fluoro-4-(5-fluoro-3-(4-(3-methoxyazetidin-1-yl)piperidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
107B	2-Amino-4-(3-((R)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		494

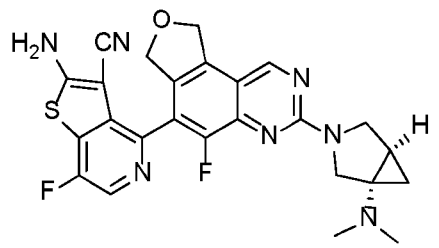
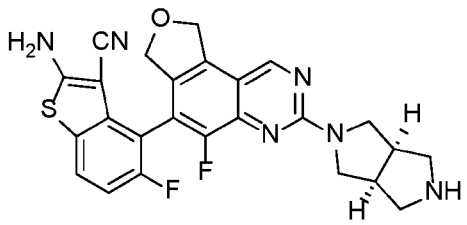
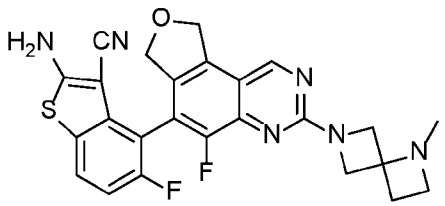
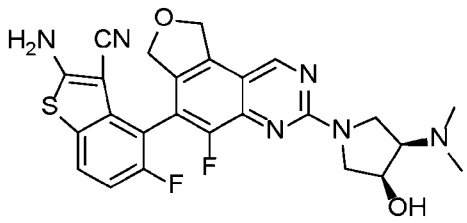
108B [21]	2-Amino-4-(3-(3-(dimethylamino)piperidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		508
109B [21]	2-Amino-4-(3-(3-(dimethylamino)piperidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		508
110B [22]	2-Amino-7-fluoro-4-(5-fluoro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		506
111B [22]	2-Amino-7-fluoro-4-(5-fluoro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		506

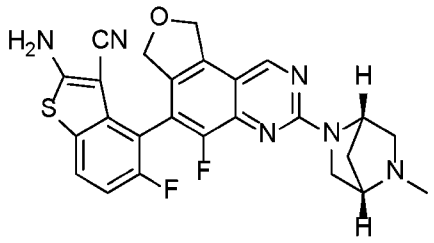
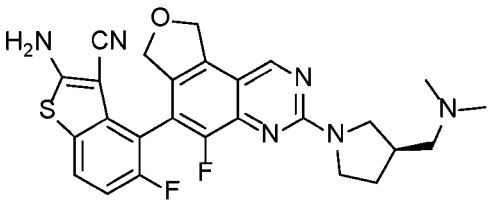
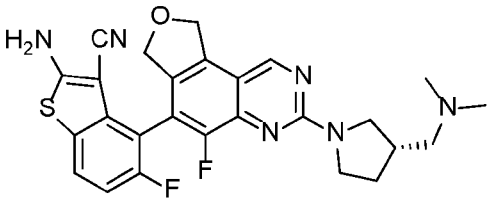
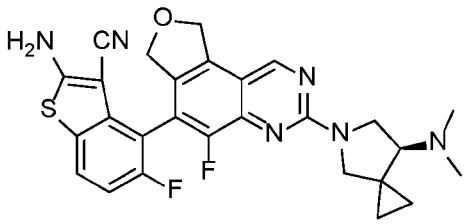
112B	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-[1,3'-biazetidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		508
113B	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methyl-3-(pyrrolidin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		520
114B	2-Amino-4-(3-(3-cyclopropyl-3-hydroxyazetidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		493
115B	2-Amino-7-fluoro-4-(5-fluoro-3-(6-methyl-2,6-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
116B	2-Amino-4-(3-(4-(dimethylamino)piperidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508

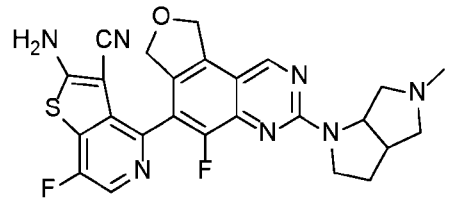
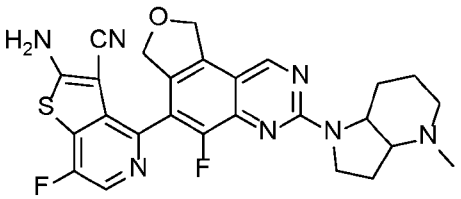
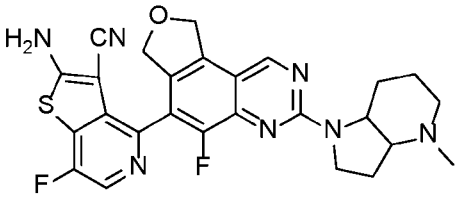
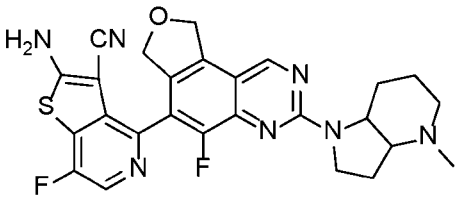
117B	2-Amino-4-(3-((3S,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
118B	2-Amino-4-(3-((3R,4R)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
119B	2-Amino-4-(3-((3S,4R)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
120B	2-Amino-4-(3-((3R,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524

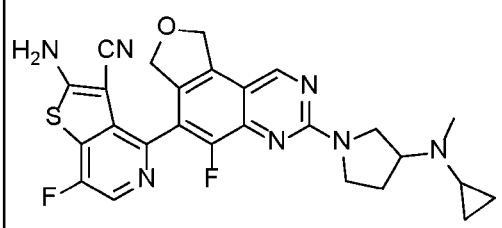
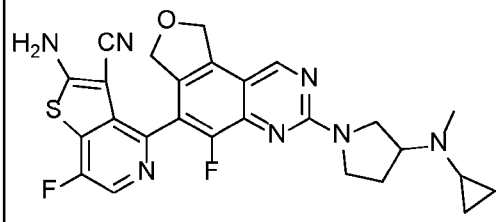
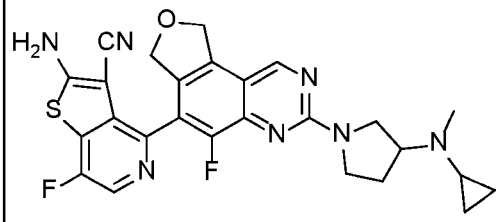
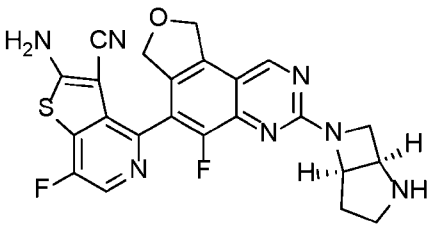
121B [23]	2-Amino-4-(5-chloro-3-((3S,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		540
122B [24]	2-Amino-4-(5-chloro-3-((3S,4S)-3-(dimethylamino)-4-(hydroxymethyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		540
123B	2-Amino-4-(3-((1R,5S)-1-((dimethylamino)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520

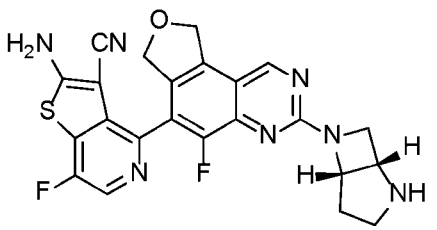
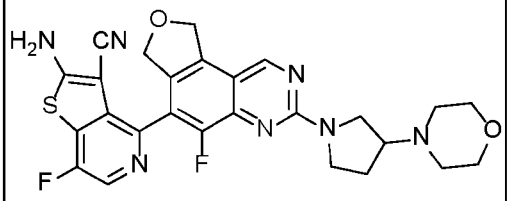
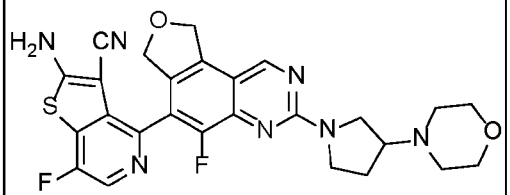
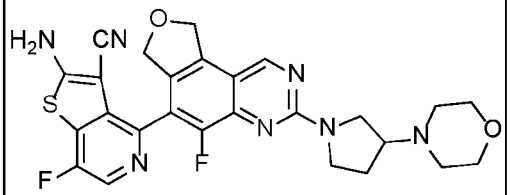
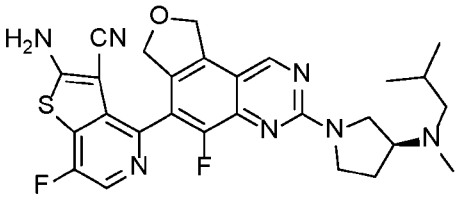
124B	2-Amino-4-(3-((1S,5R)-1-((dimethylamino)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
125B	2-Amino-4-(3-((1R,5S)-1-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
126B [25]	2-Amino-4-(3-((R)-3-(dimethylamino)-3-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
127B [25]	2-Amino-4-(3-((3R,4S)-3-(dimethylamino)-4-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508

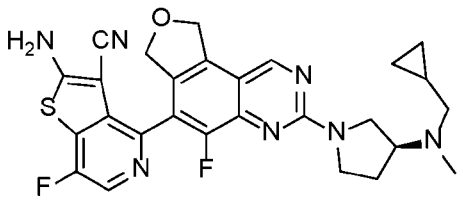
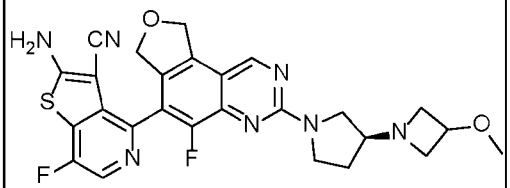
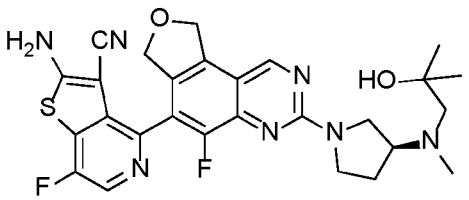
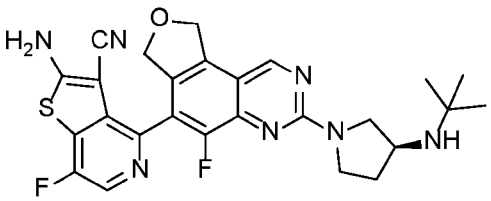
128B	2-Amino-4-(3-((1S,5R)-1-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
129B [26]	2-Amino-5-fluoro-4-(5-fluoro-3-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile		491
130B [26]	2-Amino-5-fluoro-4-(5-fluoro-3-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile		491
131B [26]	2-Amino-4-(3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile		509

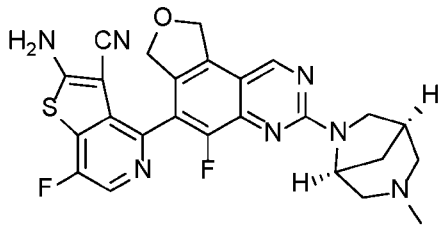
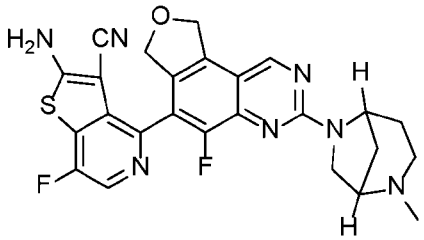
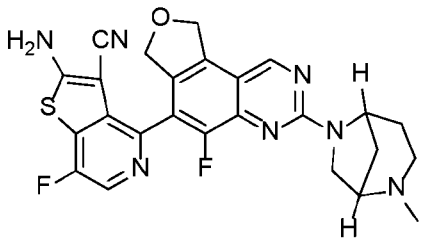
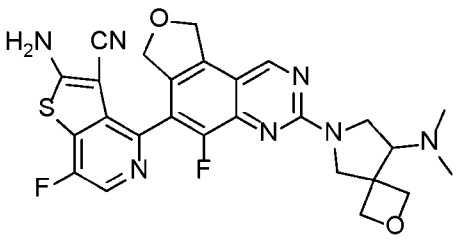
132B [26]	2-Amino-5-fluoro-4-(5-fluoro-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile		491
133B [26]	2-Amino-4-(3-((R)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile		507
134B [26]	2-Amino-4-(3-((S)-3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile		507
135B [26]	2-Amino-4-(3-((S)-7-(dimethylamino)-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile		519

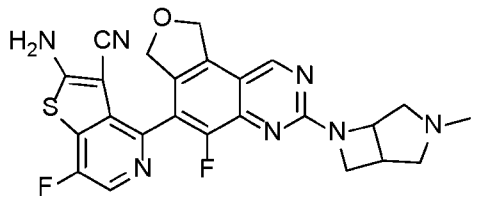
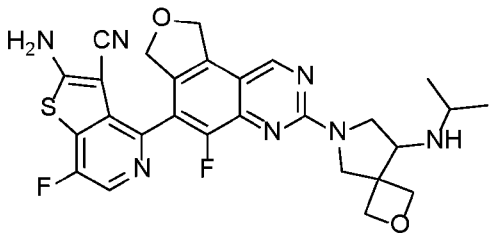
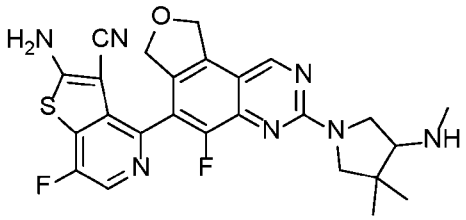
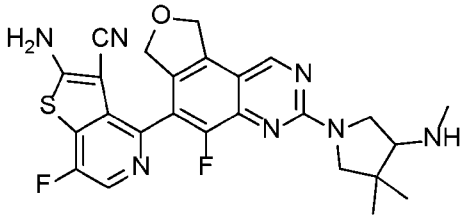
136B	2-Amino-7-fluoro-4-(5-fluoro-3-(5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
1C [27]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methyloctahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520
2C [28]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methyloctahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520
3C [28]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-methyloctahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520

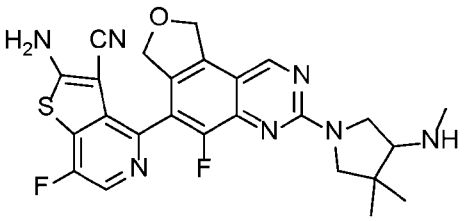
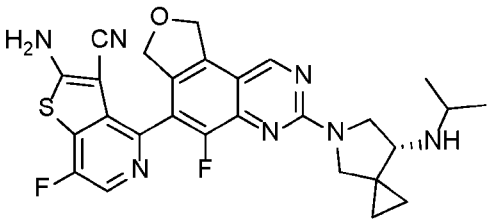
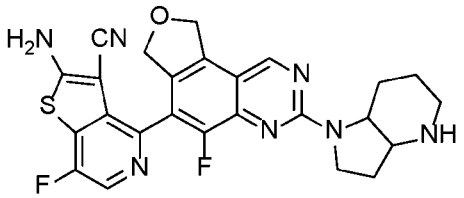
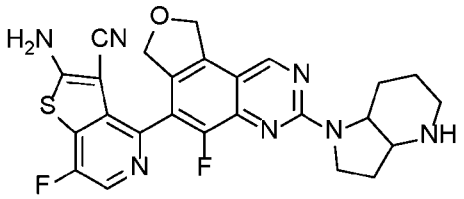
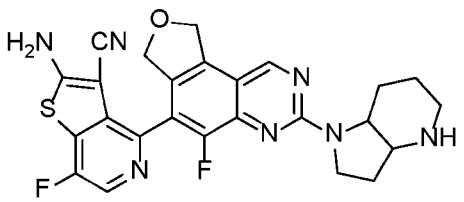
4C	2-Amino-4-(3-(3-(cyclopropyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
5C [29]	2-Amino-4-(3-(3-(cyclopropyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		520
6C [29]	2-Amino-4-(3-(3-(cyclopropyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		520
7C	4-(3-((1R,5R)-2,6-Diazabicyclo[3.2.0]heptan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		478

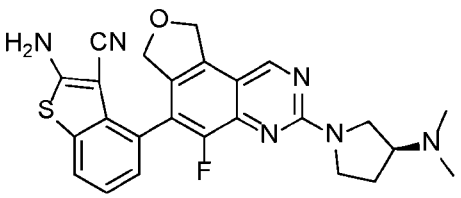
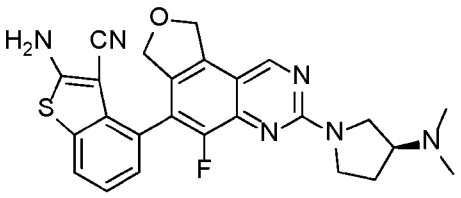
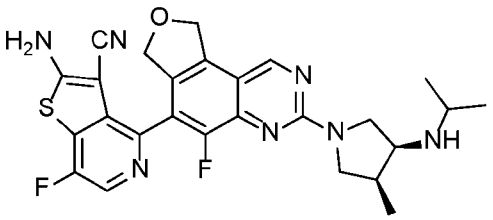
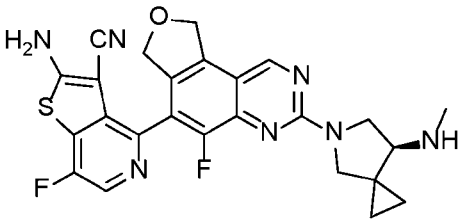
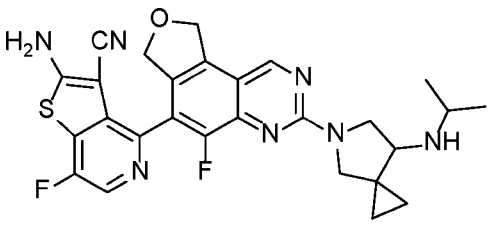
8C [30]	4-(3-((1S,5S)-2,6-Diazabicyclo[3.2.0]heptan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		478
9C	2-Amino-7-fluoro-4-(5-fluoro-3-(3-morpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		536
10C [31]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-morpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		536
11C [31]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-morpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		536
12C	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(isobutyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		536

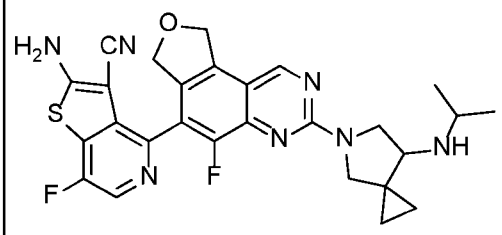
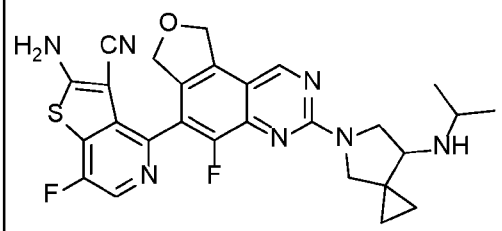
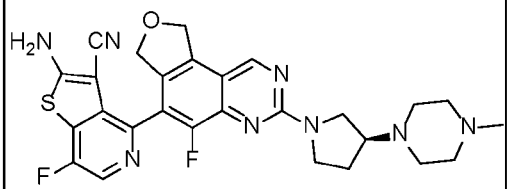
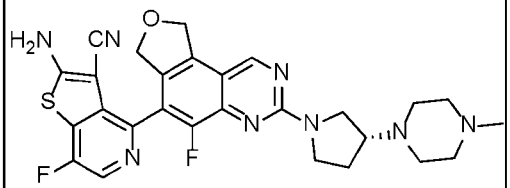
13C	2-Amino-4-(3-((S)-3-((cyclopropylmethyl)(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		534
14C	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(3-methoxyazetidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		536
15C	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-((2-hydroxy-2-methylpropyl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552
16C	2-Amino-4-(3-((S)-3-(tert-butylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		522

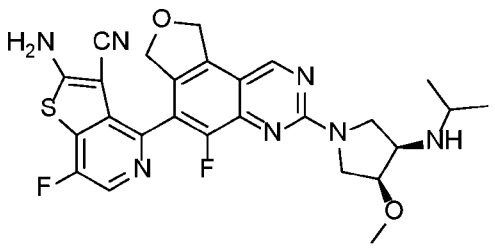
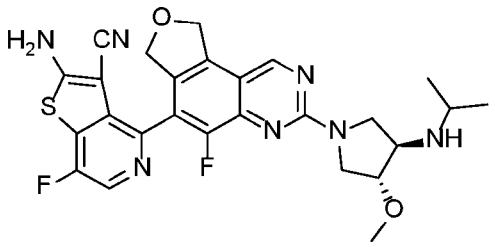
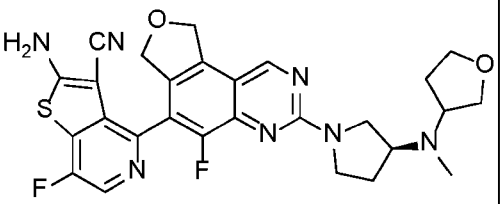
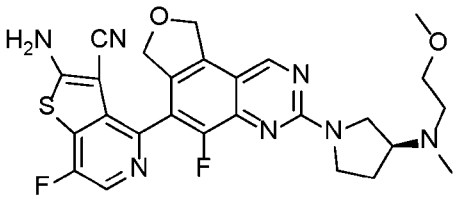
17C	2-Amino-7-fluoro-4-(5-fluoro-3-((1R,5S)-3-methyl-3,6-diazabicyclo[3.2.1]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
18C [32]	2-Amino-7-fluoro-4-(5-fluoro-3-(2-methyl-2,6-diazabicyclo[3.2.1]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
19C [32]	2-Amino-7-fluoro-4-(5-fluoro-3-(2-methyl-2,6-diazabicyclo[3.2.1]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
20C	2-Amino-4-(3-(8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		536

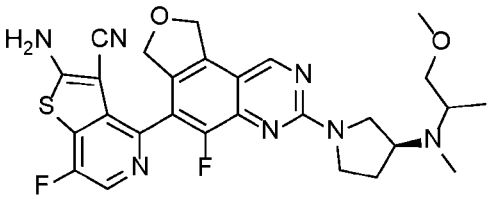
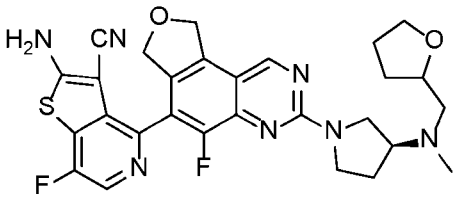
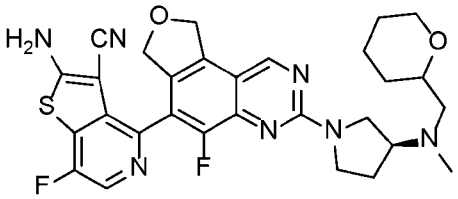
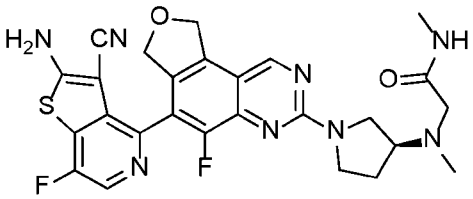
21C [33]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methyl-3,6-diazabicyclo[3.2.0]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
22C	2-Amino-7-fluoro-4-(5-fluoro-3-(8-(isopropylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
23C	2-Amino-4-(3-(3,3-dimethyl-4-(methylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
24C [34]	2-Amino-4-(3-(3,3-dimethyl-4-(methylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		508

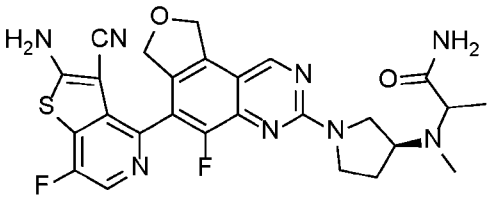
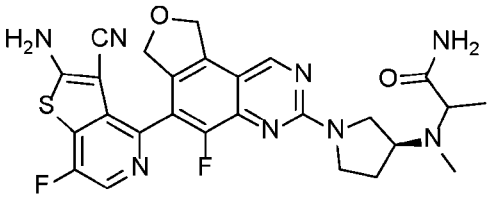
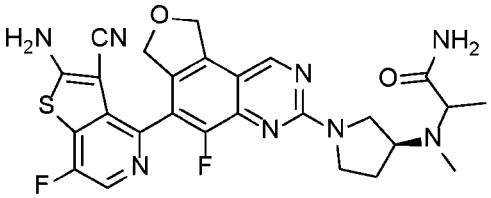
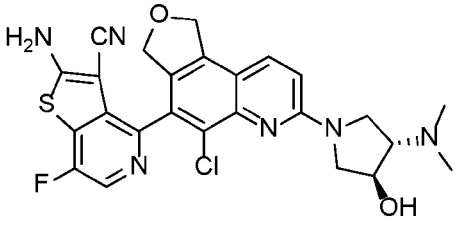
25C [34]	2-Amino-4-(3-(3,3-dimethyl-4-(methylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		508
26C	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-7-(isopropylamino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		534
27C [35]	2-Amino-7-fluoro-4-(5-fluoro-3-(octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
28C [36]	2-Amino-7-fluoro-4-(5-fluoro-3-(octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
29C [36]	2-Amino-7-fluoro-4-(5-fluoro-3-(octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506

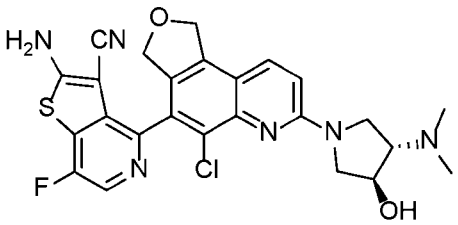
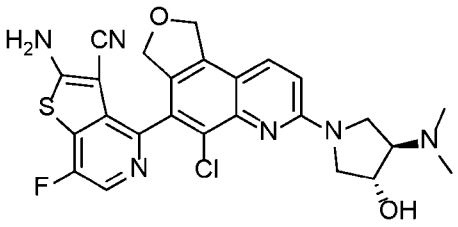
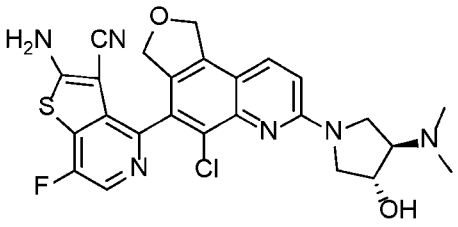
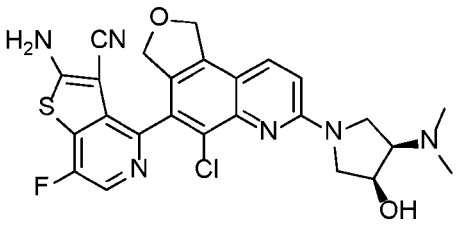
30C [37]	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Isomer 1		475
31C [37]	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Isomer 2		475
32C	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
33C	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-7-(methylamino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
34C	2-Amino-7-fluoro-4-(5-fluoro-3-(7-(isopropylamino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		534

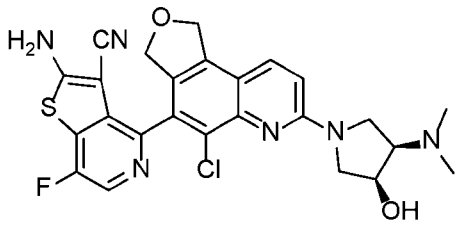
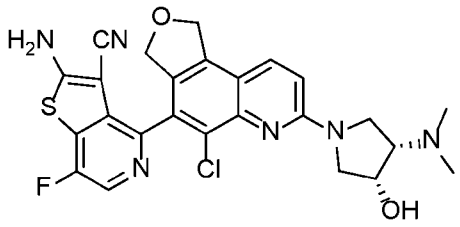
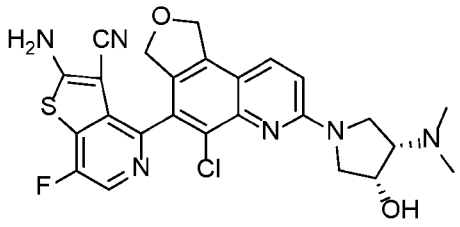
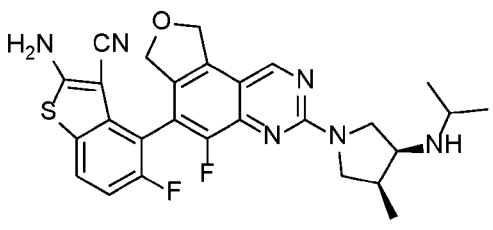
35C [38]	2-Amino-7-fluoro-4-(5-fluoro-3-(7-(isopropylamino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		534
36C [38]	2-Amino-7-fluoro-4-(5-fluoro-3-(7-(isopropylamino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		534
37C	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		549
38C	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		549

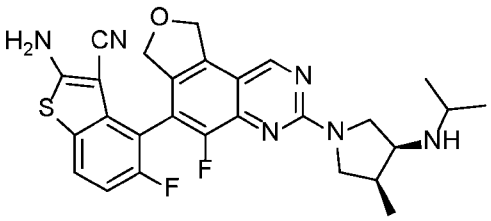
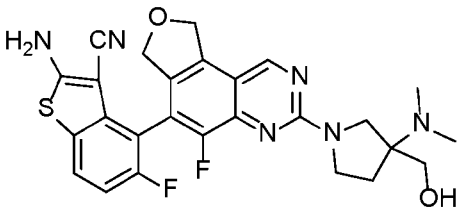
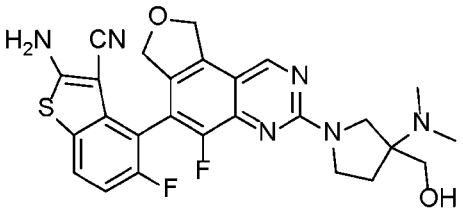
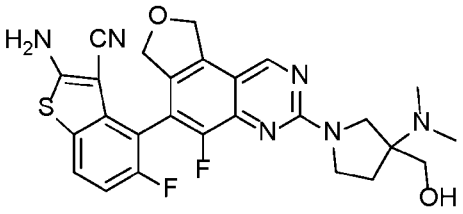
39C	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
40C	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
41C	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl(tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
42C	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-((2-methoxyethyl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538

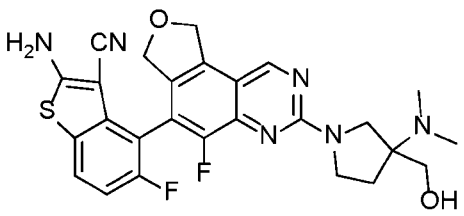
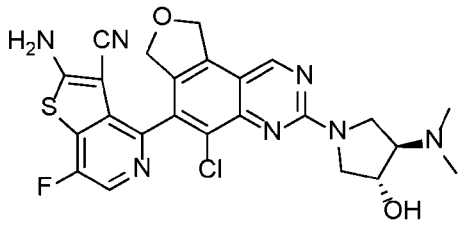
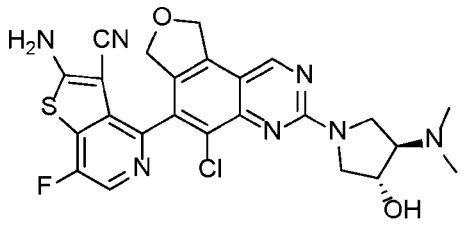
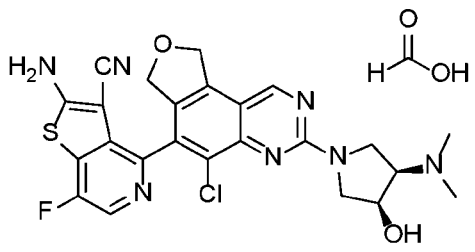
43C	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-((1-methoxypropan-2-yl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552
44C	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl((tetrahydrofuran-2-yl)methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
45C	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl((tetrahydro-2H-pyran-2-yl)methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		578
46C	2-(((3S)-1-(6-(2-Amino-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)pyrrolidin-3-yl)(methyl)amino)-N-methylacetamide		551

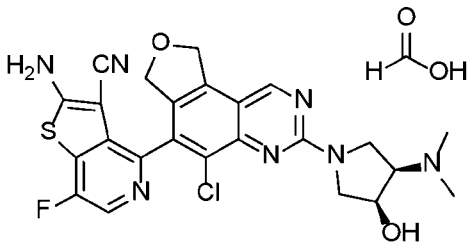
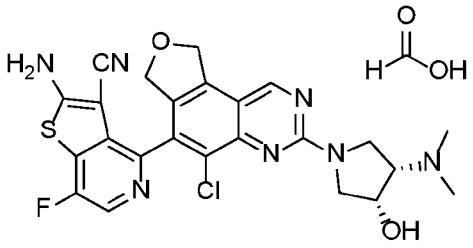
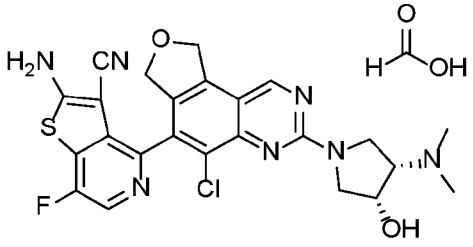
47C	2-(((3S)-1-(6-(2-Amino-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)pyrrolidin-3-yl)(methyl)amino)propanamide		551
48C [39]	2-(((3S)-1-(6-(2-Amino-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)pyrrolidin-3-yl)(methyl)amino)propanamide, Isomer 1		551
49C [39]	2-(((3S)-1-(6-(2-Amino-3-cyano-7-fluorothieno[3,2-c]pyridin-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl)pyrrolidin-3-yl)(methyl)amino)propanamide, Isomer 2		551
50C [40]	2-Amino-4-(5-chloro-7-((3S,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		525

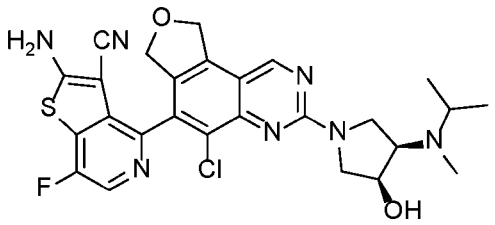
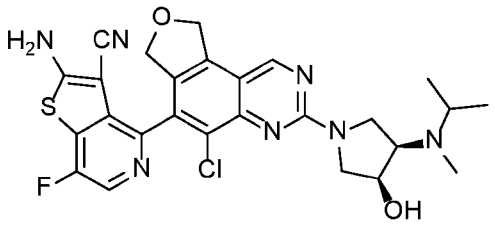
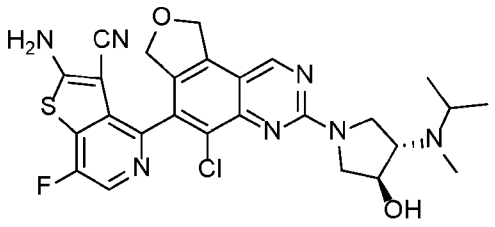
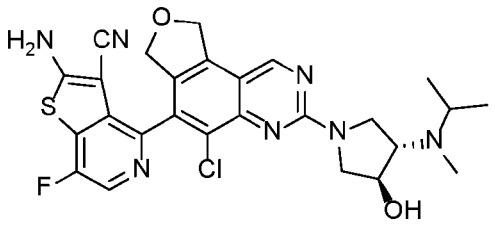
51C [40]	2-Amino-4-(5-chloro-7-((3S,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		525
52C [41]	2-Amino-4-(5-chloro-7-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		525
53C [41]	2-Amino-4-(5-chloro-7-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		525
54C [42]	2-Amino-4-(5-chloro-7-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		525

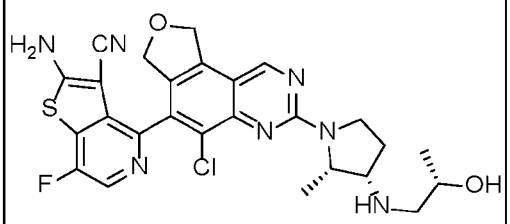
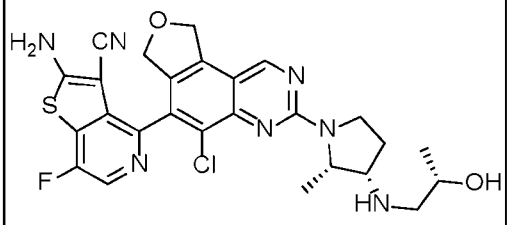
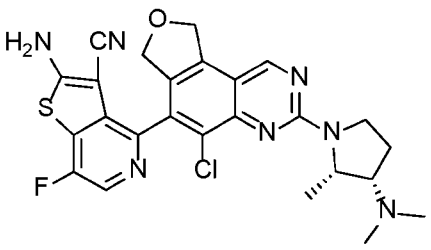
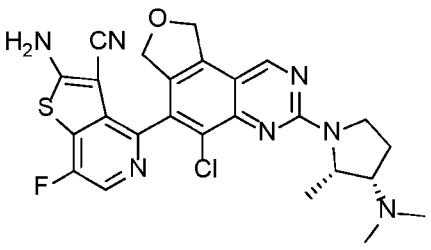
55C [42]	2-Amino-4-(5-chloro-7-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		525
56C [43]	2-Amino-4-(5-chloro-7-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		525
57C [43]	2-Amino-4-(5-chloro-7-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		525
58C [44]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4S)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		521

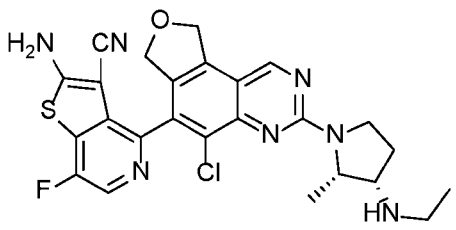
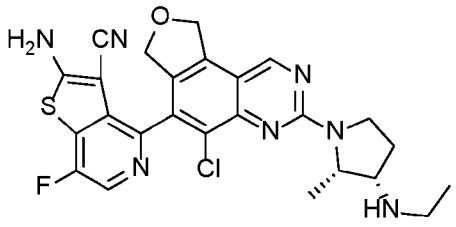
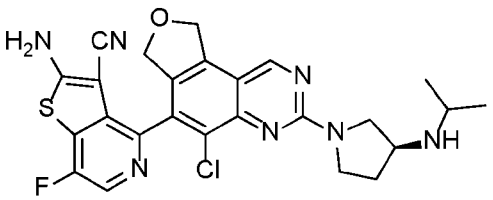
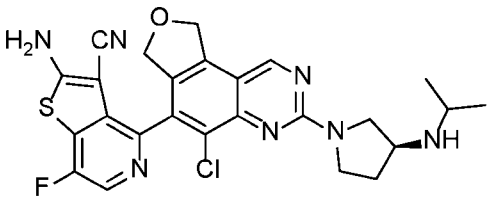
59C [44]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4S)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		521
60C [45]	2-Amino-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 1		523
61C [45]	2-Amino-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 2		523
62C [45]	2-Amino-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 3		523

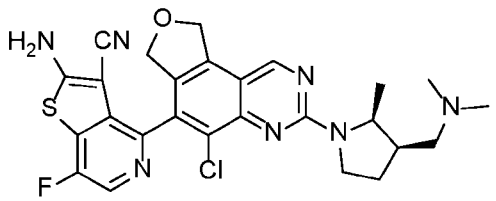
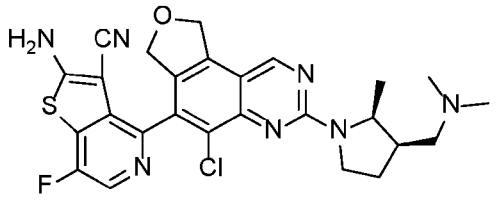
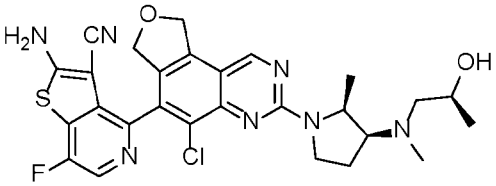
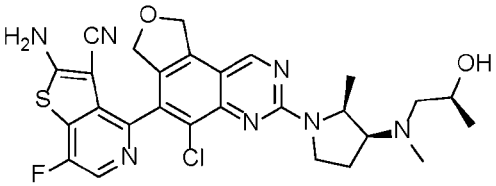
63C [45]	2-Amino-4-(3-(3-(dimethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Diastereomer 4		523
64C [46]	2-Amino-4-(5-chloro-3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		526
65C [46]	2-Amino-4-(5-chloro-3-((3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		526
66C [47]	2-Amino-4-(5-chloro-3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1 formic acid		526

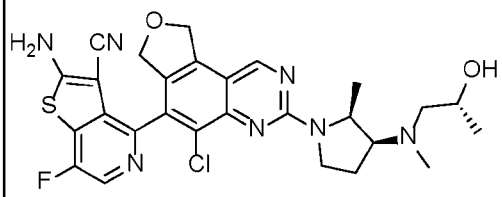
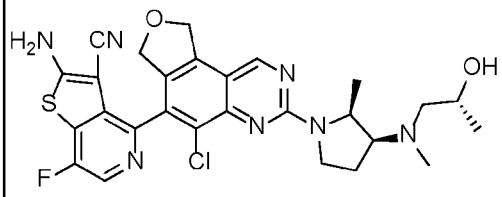
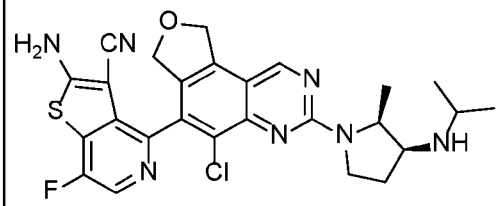
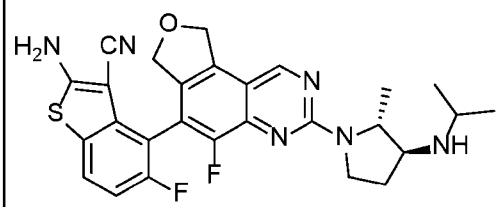
67C [47]	2-Amino-4-(5-chloro-3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2 formic acid		526
68C [48]	2-Amino-4-(5-chloro-3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropsiomer 1 formic acid		526
69C [48]	2-Amino-4-(5-chloro-3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropsiomer 2 formic acid		526

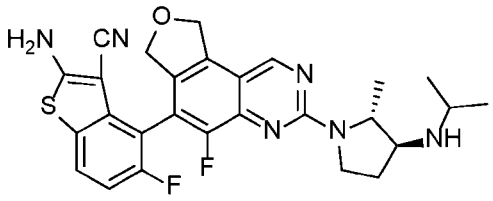
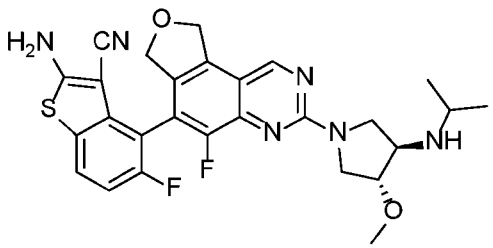
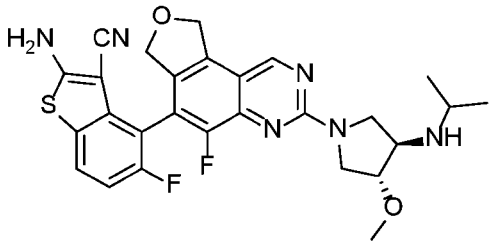
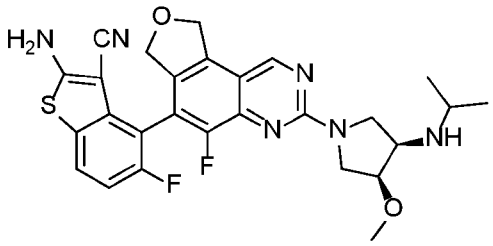
70C [49]	2-Amino-4-(5-chloro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		554
71C [49]	2-Amino-4-(5-chloro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		554
72C [50]	2-Amino-4-(5-chloro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		554
73C [50]	2-Amino-4-(5-chloro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		554

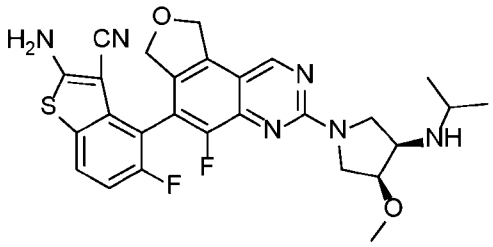
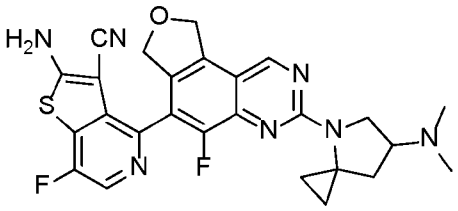
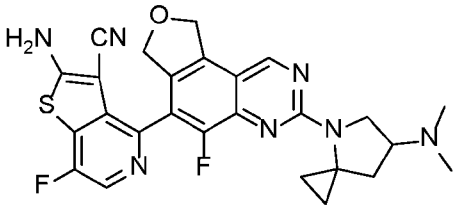
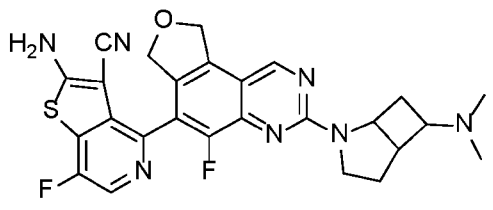
74C [51]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		554
75C [51]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		554
76C [52]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(dimethylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		524
77C [52]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(dimethylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		524

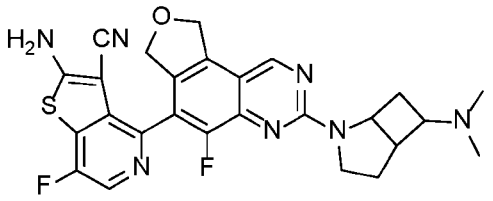
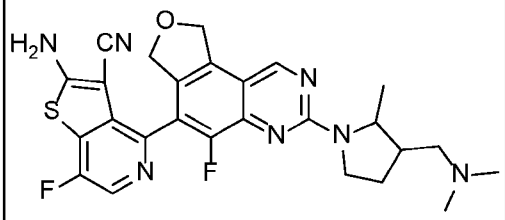
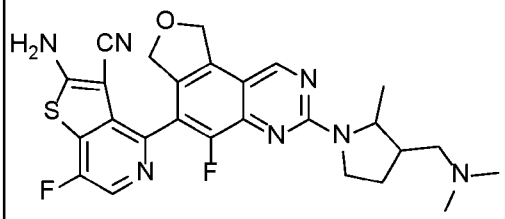
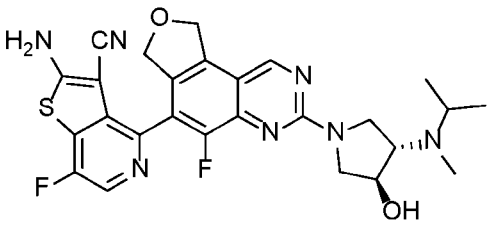
78C [53]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(ethylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		524
79C [53]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(ethylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		524
80C [54]	2-Amino-4-(5-chloro-3-((S)-3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		524
81C [54]	2-Amino-4-(5-chloro-3-((S)-3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		524

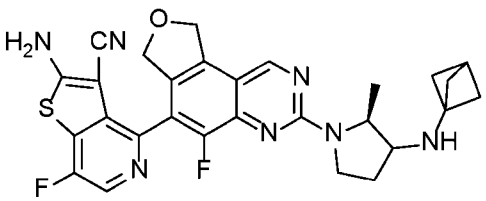
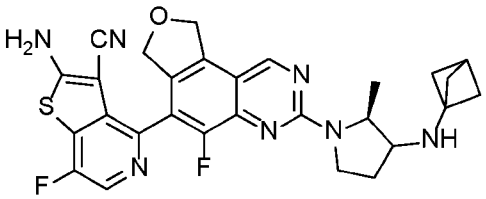
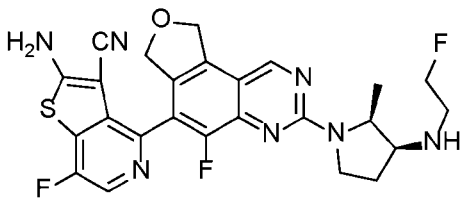
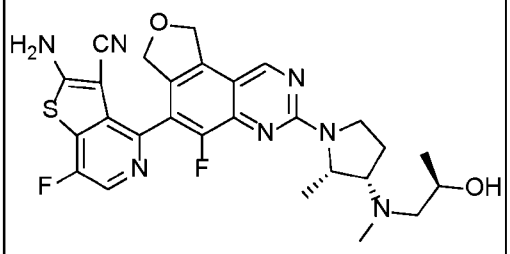
82C [55]	2-Amino-4-(5-chloro-3-((2S,3R)-3-((dimethylamino)methyl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		538
83C [55]	2-Amino-4-(5-chloro-3-((2S,3R)-3-((dimethylamino)methyl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		538
84C [56]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		568
85C [56]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		568

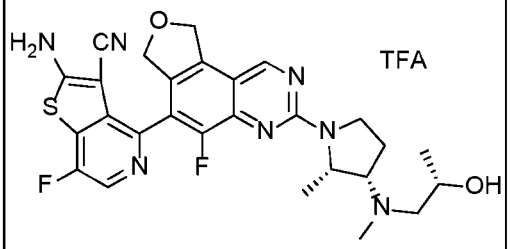
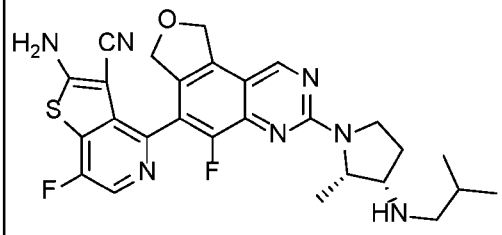
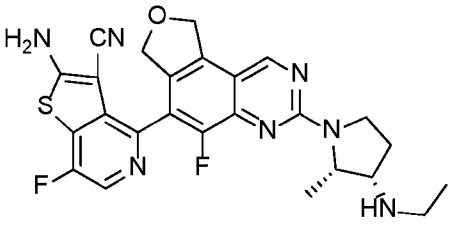
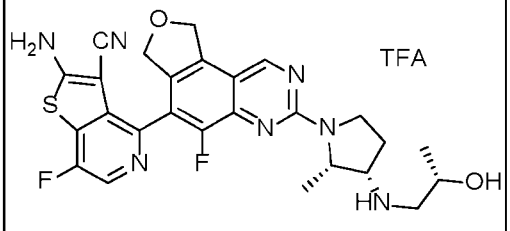
86C [57]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(((R)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		568
87C [57]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(((R)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		568
88C [58]	2-Amino-4-(5-chloro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		538
89C [59]	2-Amino-5-fluoro-4-(5-fluoro-3-((2R,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		521

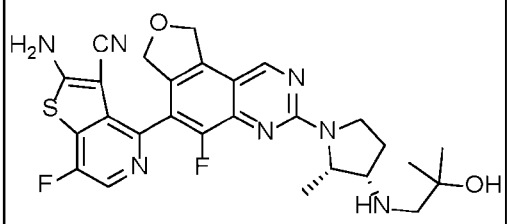
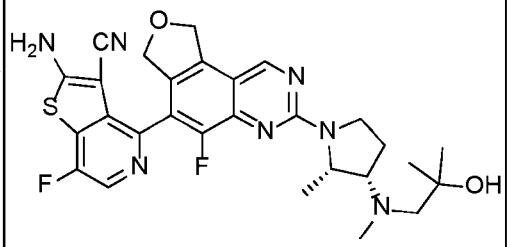
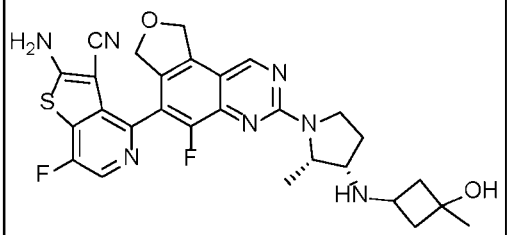
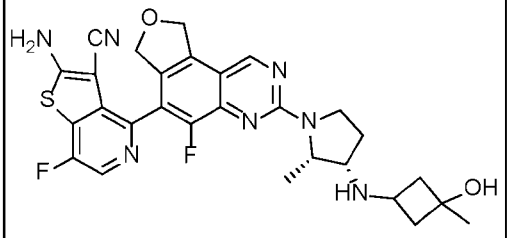
90C [59]	2-Amino-5-fluoro-4-(5-fluoro-3-((2R,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		521
91C [60]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4R)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		537
92C [60]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4R)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		537
93C [61]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		537

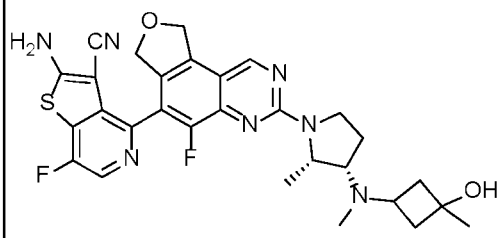
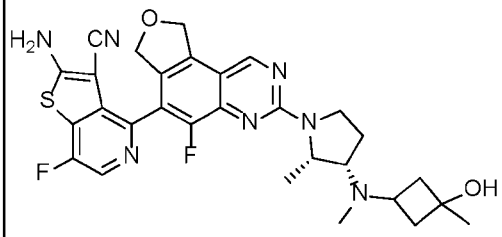
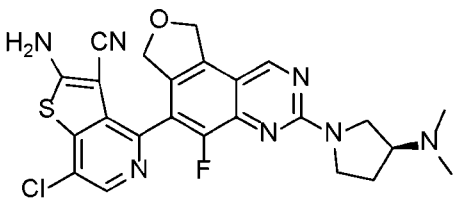
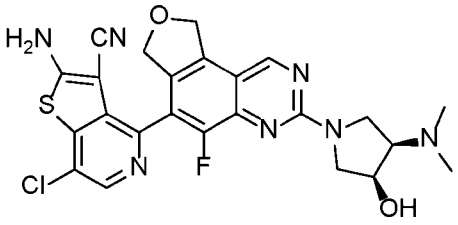
94C [61]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		537
95C [62]	2-Amino-4-(3-(6-(dimethylamino)-4-azaspiro[2.4]heptan-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		520
96C [62]	2-Amino-4-(3-(6-(dimethylamino)-4-azaspiro[2.4]heptan-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		520
97C [63]	2-Amino-4-(3-(6-(dimethylamino)-2-azabicyclo[3.2.0]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		520

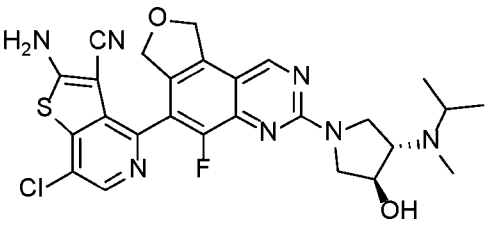
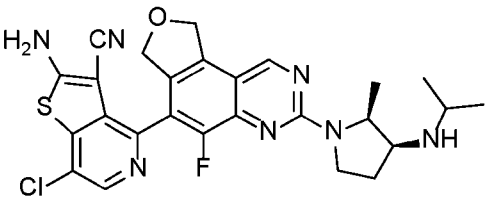
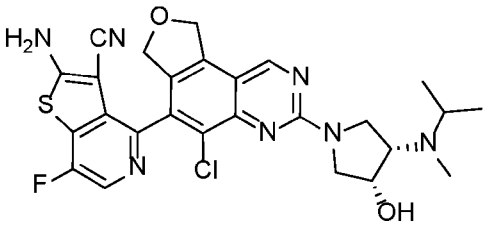
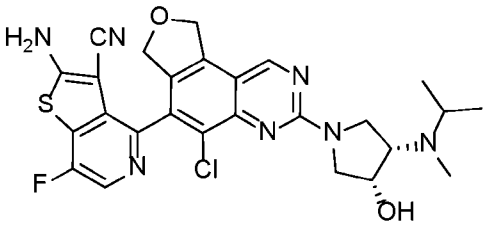
98C [63]	2-Amino-4-(3-(6-(dimethylamino)-2-azabicyclo[3.2.0]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		520
99C [64]	2-Amino-4-(3-(3-((dimethylamino)methyl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		522
100C [64]	2-Amino-4-(3-(3-((dimethylamino)methyl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		522
101C	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538

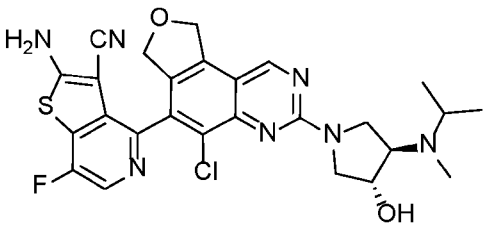
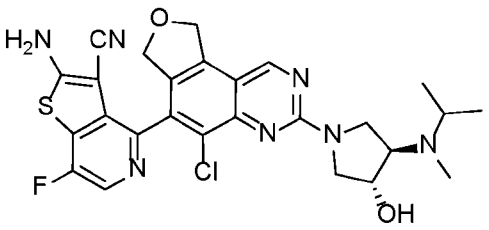
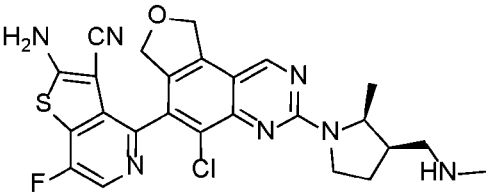
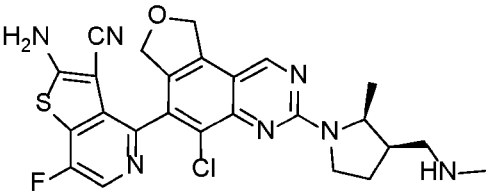
102C [65]	2-Amino-4-(3-((2S)-3-(bicyclo[1.1.1]pentan-1-ylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		546
103C [65]	2-Amino-4-(3-((2S)-3-(bicyclo[1.1.1]pentan-1-ylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		546
104C	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((2-fluoroethyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		526
105C	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(((R)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552

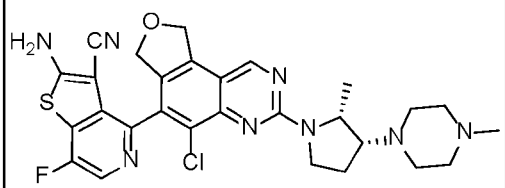
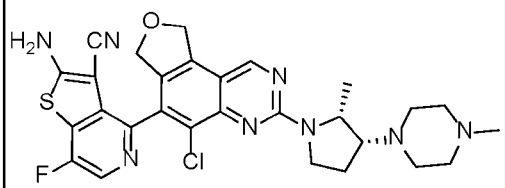
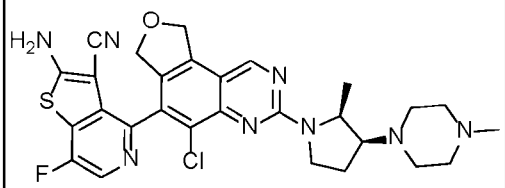
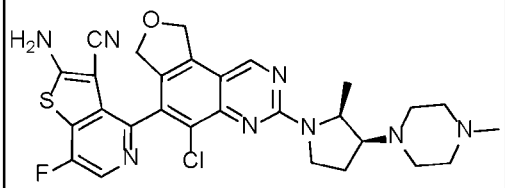
106C	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile trifluoroacetic acid		552
107C	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(isobutylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		536
108C	2-Amino-4-(3-((2S,3S)-3-(ethylamino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		508
109C	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(((S)-2-hydroxypropyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile trifluoroacetic acid		538

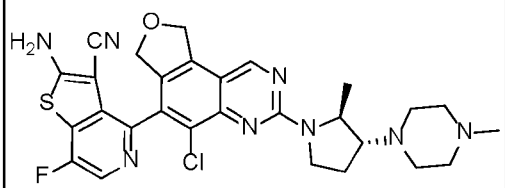
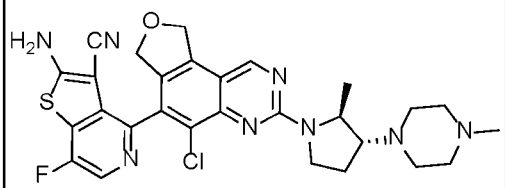
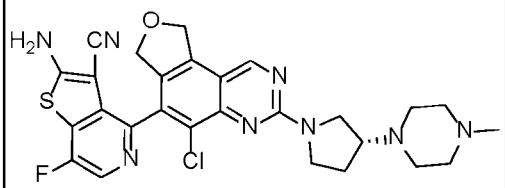
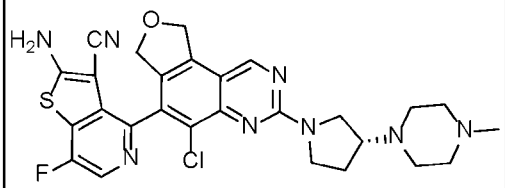
110C	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((2-hydroxy-2-methylpropyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552
111C	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((2-hydroxy-2-methylpropyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		566
112C [66]	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((3-hydroxy-3-methylcyclobutyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		564
113C [66]	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((3-hydroxy-3-methylcyclobutyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		564

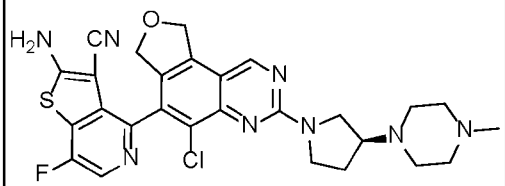
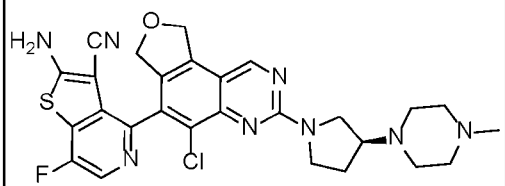
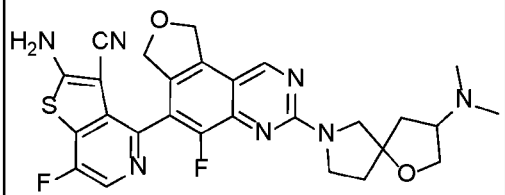
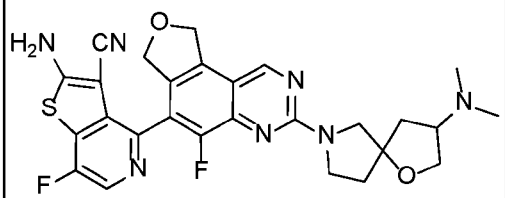
114C [67]	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((3-hydroxy-3-methylcyclobutyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		578
115C [67]	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((3-hydroxy-3-methylcyclobutyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		578
116C	2-Amino-7-chloro-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		510
117C	2-Amino-7-chloro-4-(3-((3R,4S)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		526

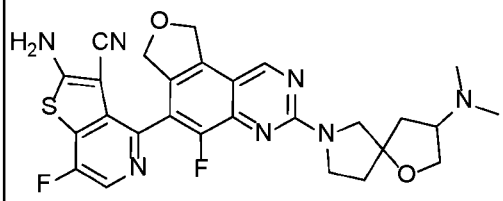
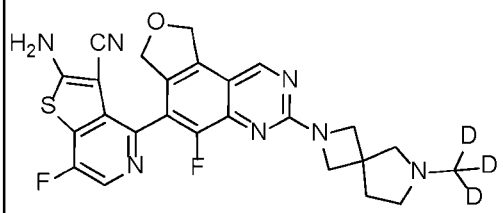
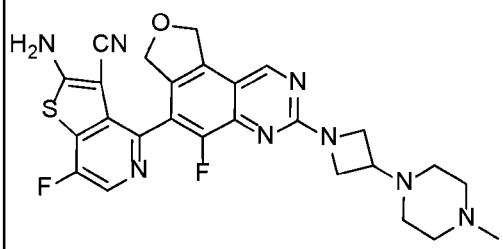
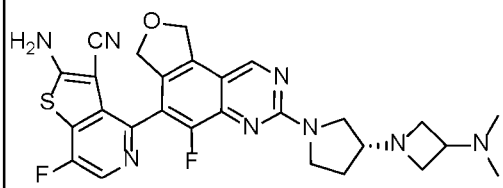
118C	2-Amino-7-chloro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		554
119C	2-Amino-7-chloro-4-(5-fluoro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
1D [68]	2-Amino-4-(5-chloro-3-((3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		554
2D [68]	2-Amino-4-(5-chloro-3-((3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		554

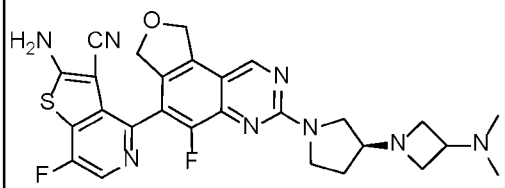
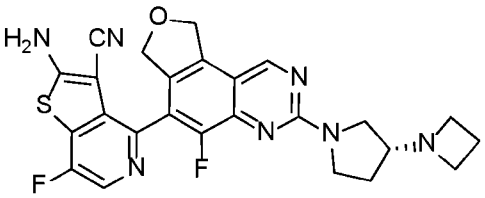
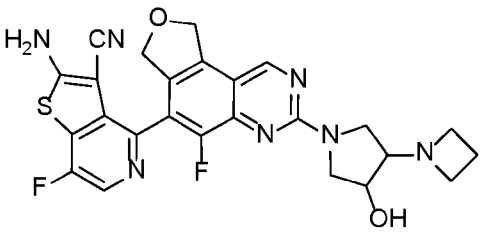
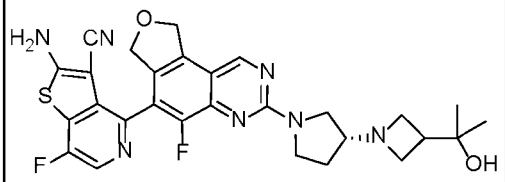
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4D [69]	2-Amino-4-(5-chloro-3-((3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		554
5D [70]	2-Amino-4-(5-chloro-3-((2S,3R)-2-methyl-3-((methylamino)methyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		524
6D [70]	2-Amino-4-(5-chloro-3-((2S,3R)-2-methyl-3-((methylamino)methyl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		524

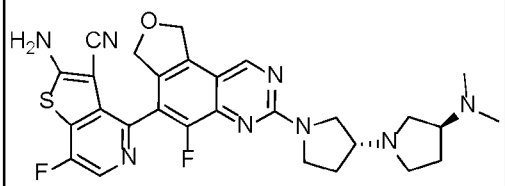
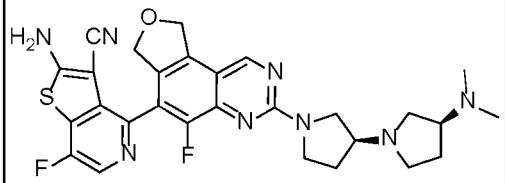
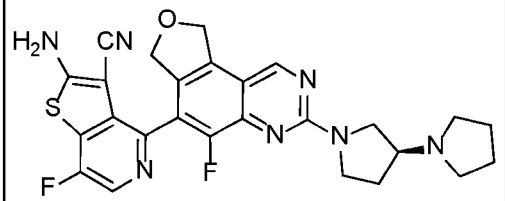
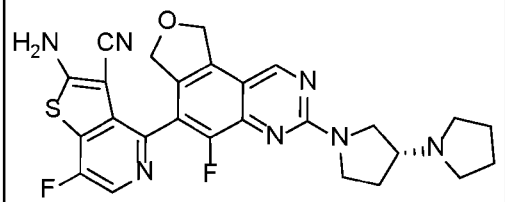
7D [71]	2-Amino-4-(5-chloro-3-((2R,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		579
8D [71]	2-Amino-4-(5-chloro-3-((2R,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		579
9D [72]	2-Amino-4-(5-chloro-3-((2S,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		579
10D [72]	2-Amino-4-(5-chloro-3-((2S,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		579

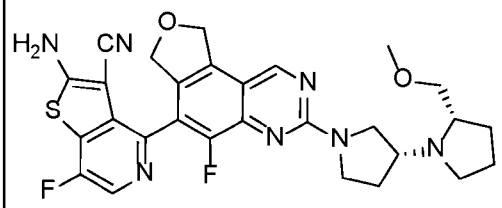
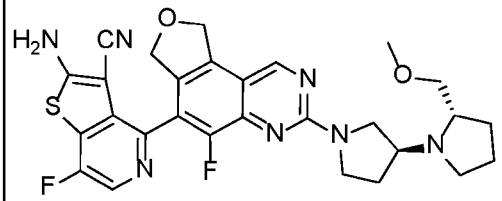
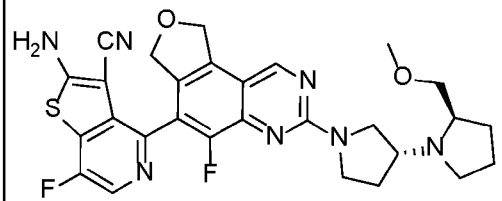
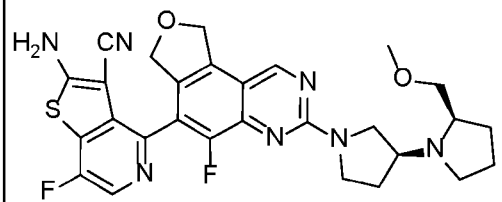
11D [73]	2-Amino-4-(5-chloro-3-((2S,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		579
12D [73]	2-Amino-4-(5-chloro-3-((2S,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		579
13D [74]	2-Amino-4-(5-chloro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		565
14D [74]	2-Amino-4-(5-chloro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		565

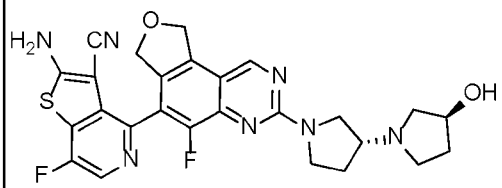
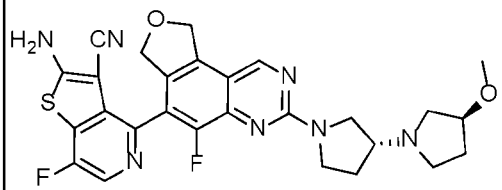
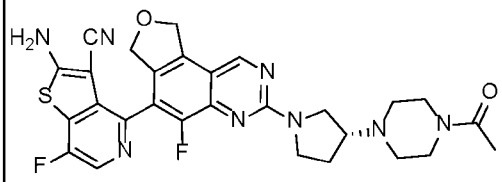
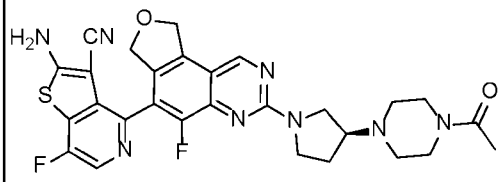
15D [75]	2-Amino-4-(5-chloro-3-((S)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 1		565
16D [75]	2-Amino-4-(5-chloro-3-((S)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Atropisomer 2		565
17D	2-Amino-4-(3-(3-(dimethylamino)-1-oxa-7-azaspiro[4.4]nonan-7-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		550
18D [76]	2-Amino-4-(3-(3-(dimethylamino)-1-oxa-7-azaspiro[4.4]nonan-7-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		550

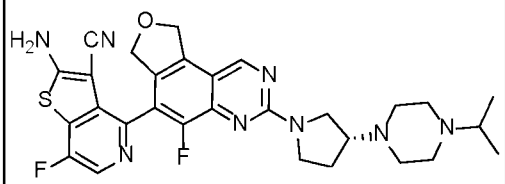
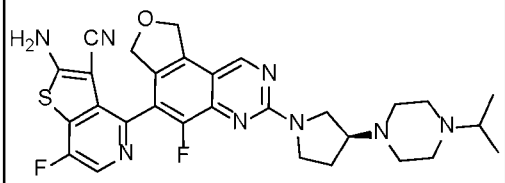
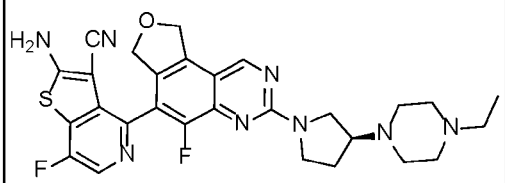
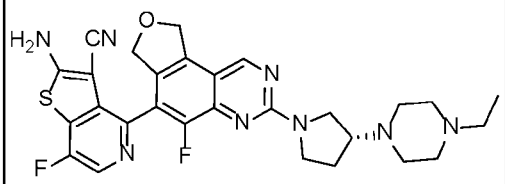
19D [76]	2-Amino-4-(3-(3-(dimethylamino)-1-oxa-7-azaspiro[4.4]nonan-7-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		550
20D	2-Amino-7-fluoro-4-(5-fluoro-3-(6-(methyl-d3)-2,6-diazaspiro[3.4]octan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		509
21D	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		535
22D	2-Amino-4-(3-((R)-3-(3-(dimethylamino)azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		549

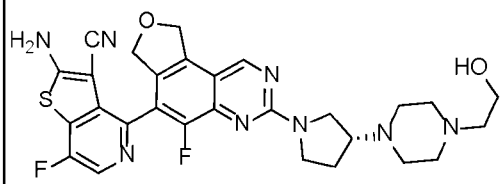
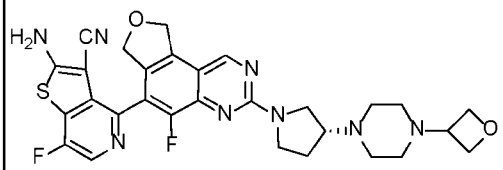
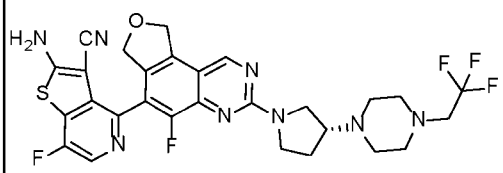
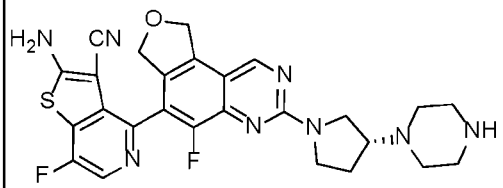
23D	2-Amino-4-(3-((S)-3-(3-(dimethylamino)azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		549
24D	2-Amino-4-(3-((R)-3-(azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506
25D [77]	2-Amino-4-(3-(3-(azetidin-1-yl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		522
26D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564

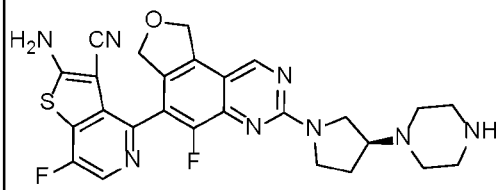
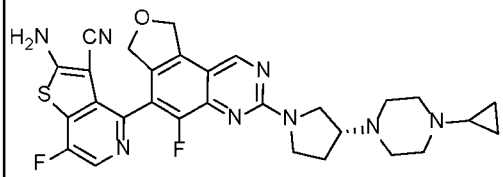
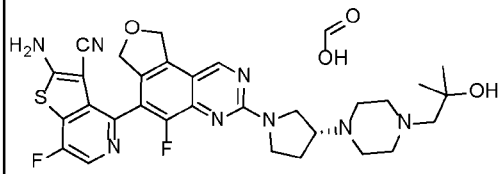
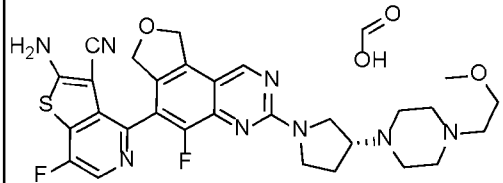
27D	2-Amino-4-(3-((3S,3'R)-3-(dimethylamino)-[1,3'-bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
28D	2-Amino-4-(3-((3S,3'S)-3-(dimethylamino)-[1,3'-bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
29D	4-(3-((S)-[1,3'-Bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
30D	4-(3-((R)-[1,3'-Bipyrrolidin]-1'-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520

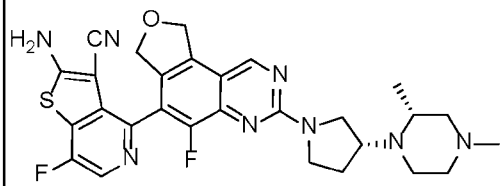
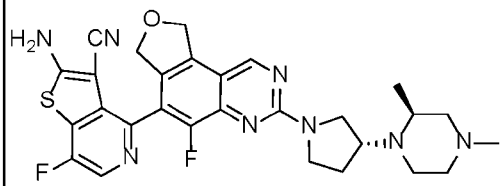
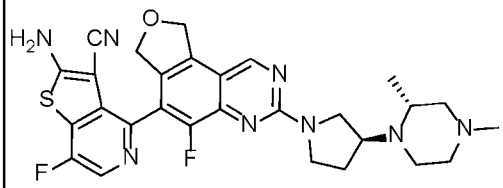
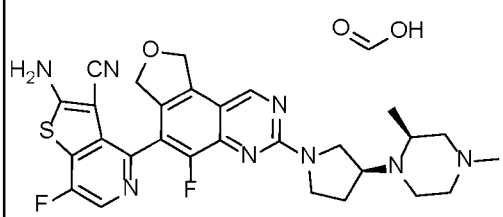
31D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3'R)-2-(methoxymethyl)-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
32D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3'S)-2-(methoxymethyl)-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
33D	2-Amino-7-fluoro-4-(5-fluoro-3-((2R,3'R)-2-(methoxymethyl)-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
34D	2-Amino-7-fluoro-4-(5-fluoro-3-((2R,3'S)-2-(methoxymethyl)-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564

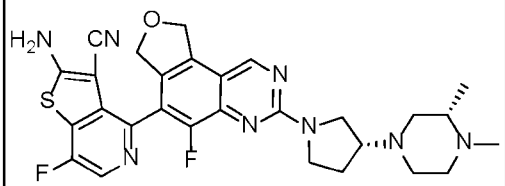
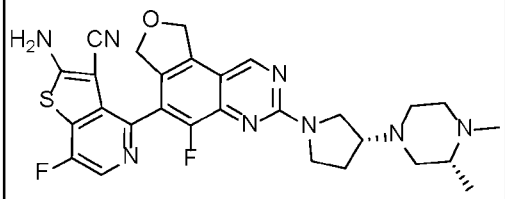
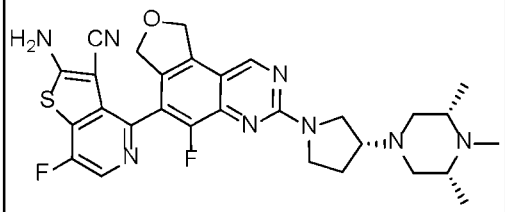
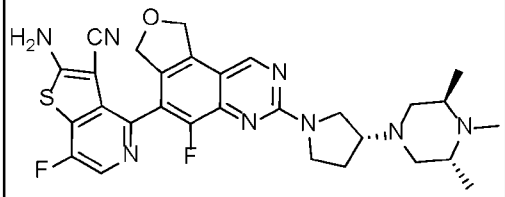
35D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,3'R)-3-hydroxy-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		536
36D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,3'R)-3-methoxy-[1,3'-bipyrrolidin]-1'-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
37D	4-(3-((R)-3-(4-Acetylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		577
38D	4-(3-((S)-3-(4-Acetylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		577

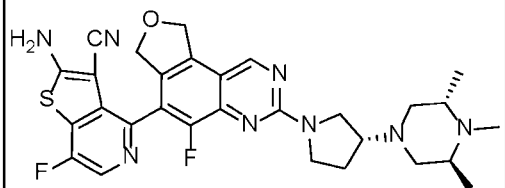
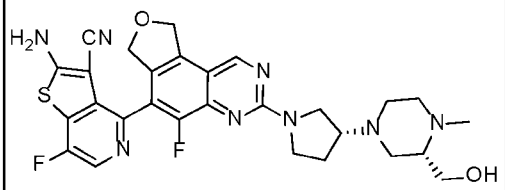
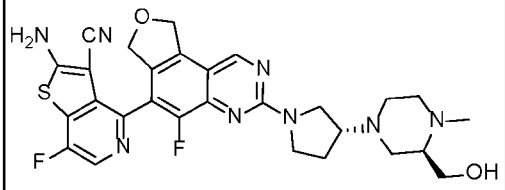
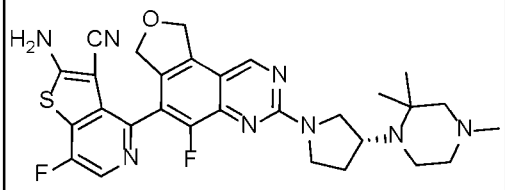
39D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-isopropylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577
40D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(4-isopropylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577
41D	2-Amino-4-(3-((S)-3-(4-ethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
42D	2-Amino-4-(3-((R)-3-(4-ethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563

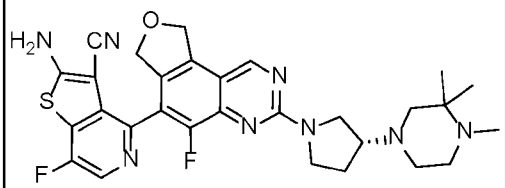
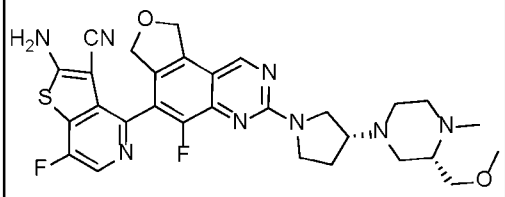
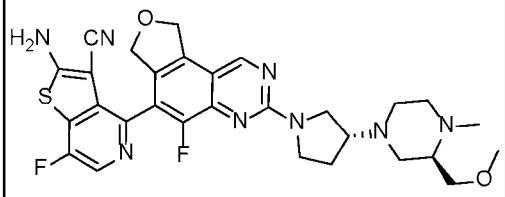
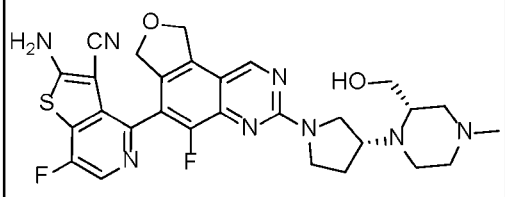
43D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(2-hydroxyethyl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		579
44D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(oxetan-3-yl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		591
45D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		617
46D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		535

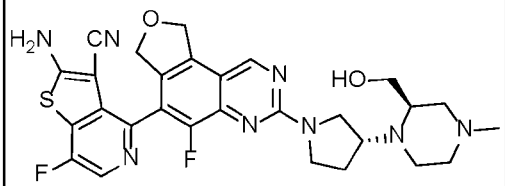
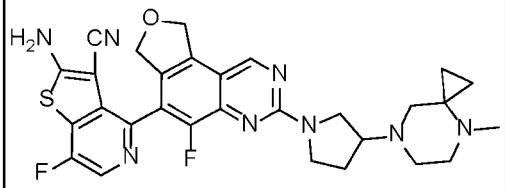
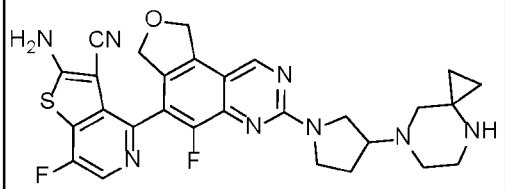
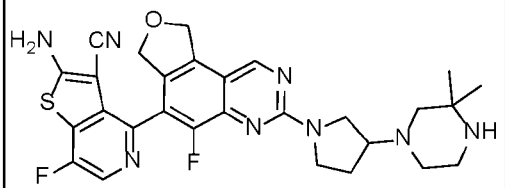
47D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		535
48D	2-Amino-4-(3-((R)-3-(4-cyclopropylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		575
49D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		607
50D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(2-methoxyethyl)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		593

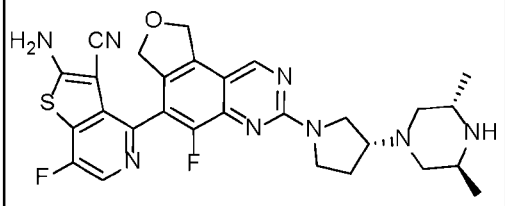
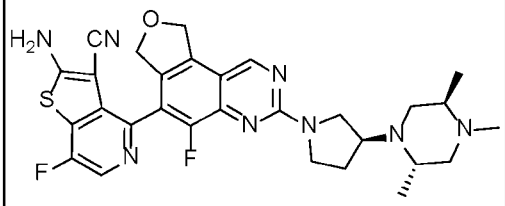
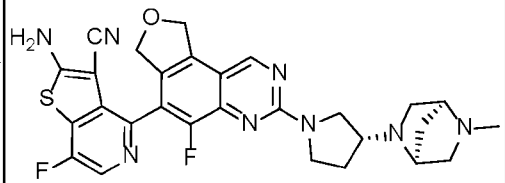
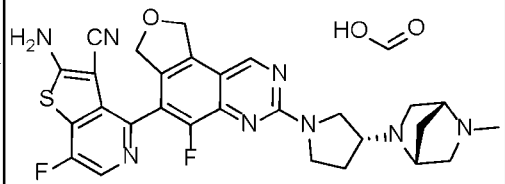
51D	2-Amino-4-(3-((R)-3-((R)-2,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
52D	2-Amino-4-(3-((R)-3-((S)-2,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
53D	2-Amino-4-(3-((S)-3-((R)-2,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
54D	2-Amino-4-(3-((S)-3-((S)-2,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formic acid		563

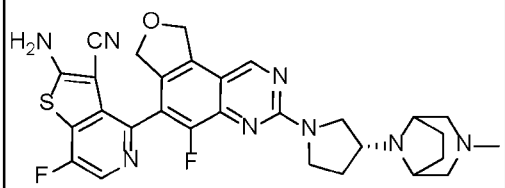
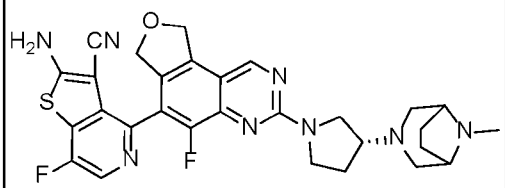
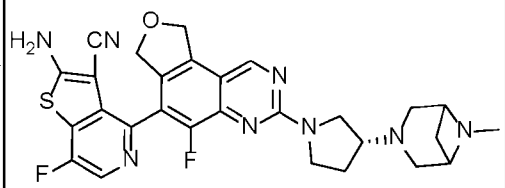
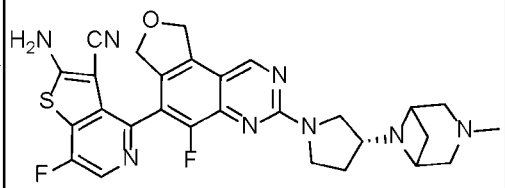
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56D	2-Amino-4-(3-((R)-3-((R)-3,4-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
57D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577
58D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((3R,5R)-3,4,5-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577

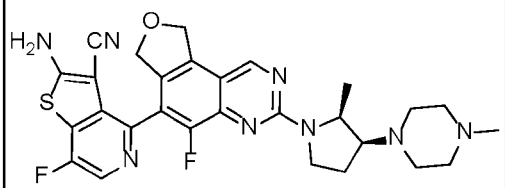
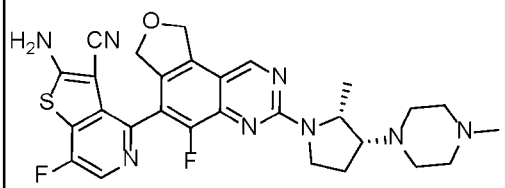
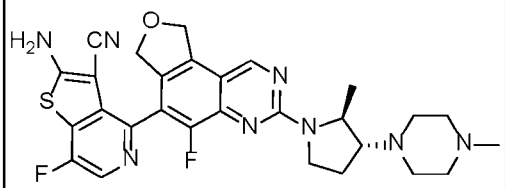
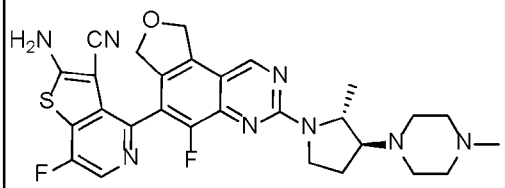
59D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((3S,5S)-3,4,5-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577
60D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		579
61D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((R)-3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		579
62D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(2,2,4-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577

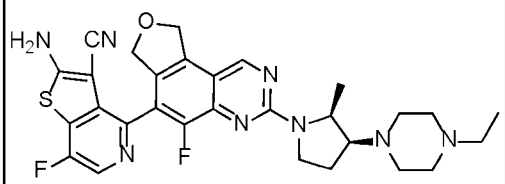
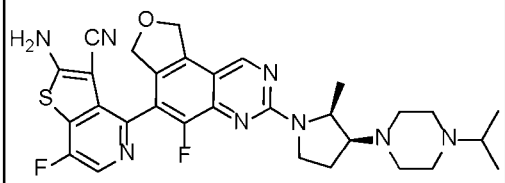
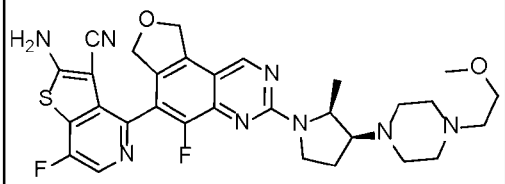
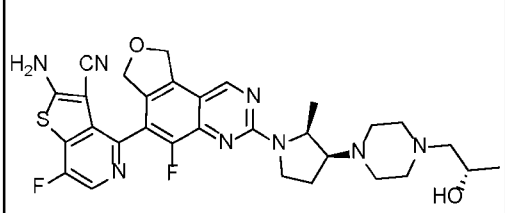
63D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(3,3,4-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577
64D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((S)-3-(methoxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		593
65D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((R)-3-(methoxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		593
66D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((S)-2-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		579

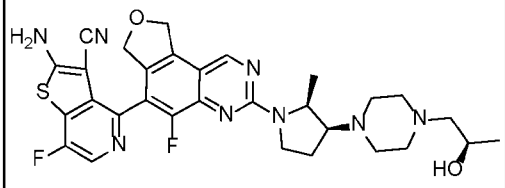
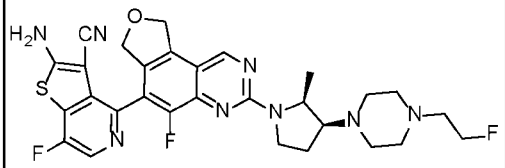
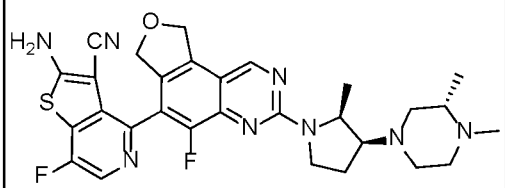
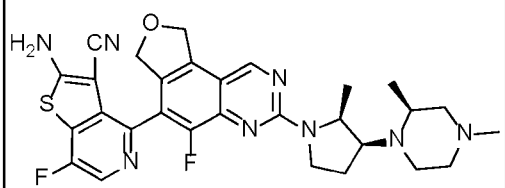
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68D	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		575
69D	4-(3-(3-(4,7-Diazaspiro[2.5]octan-7-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		561
70D	2-Amino-4-(3-(3-(3,3-dimethylpiperazin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563

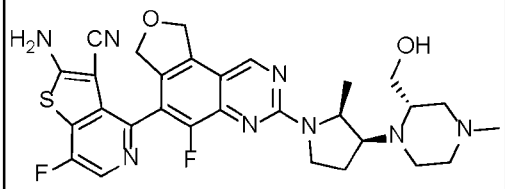
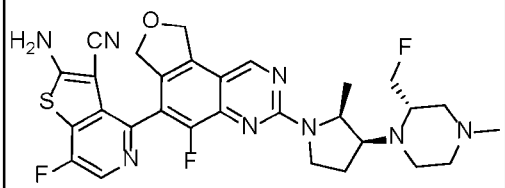
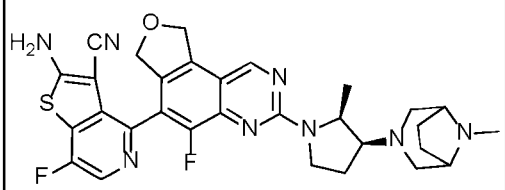
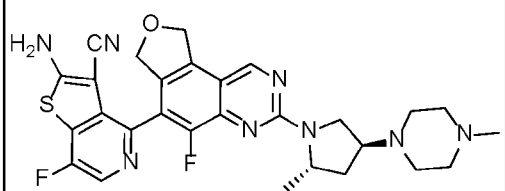
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72D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-((2S,5R)-2,4,5-trimethylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		577
73D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		561
74D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		561

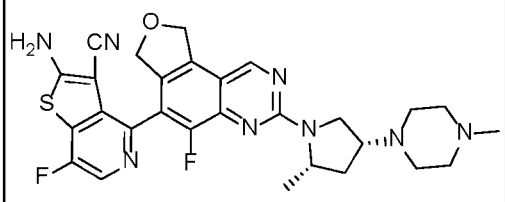
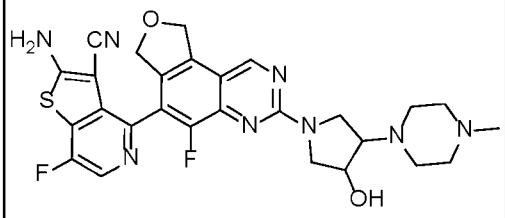
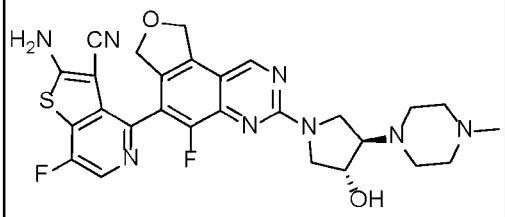
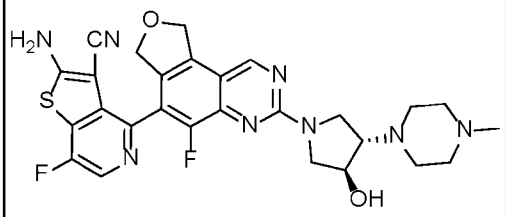
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76D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R)-3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		575
77D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R)-3-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		561
78D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R)-3-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		561

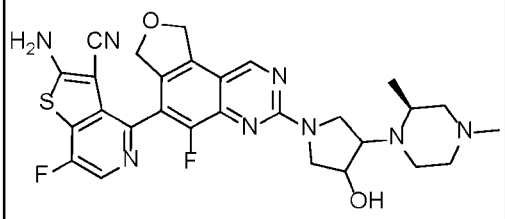
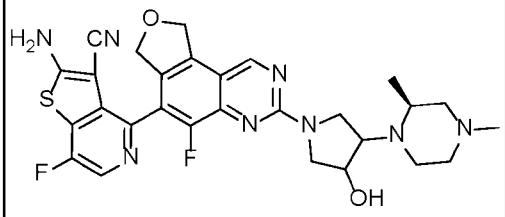
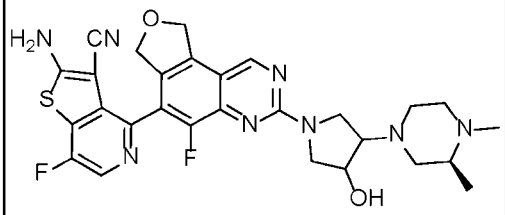
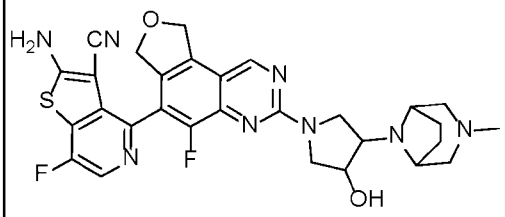
79D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		563
80D	2-Amino-7-fluoro-4-(5-fluoro-3-((2R,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		563
81D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3R)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		563
82D	2-Amino-7-fluoro-4-(5-fluoro-3-((2R,3S)-2-methyl-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		563

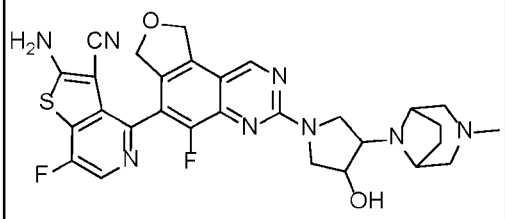
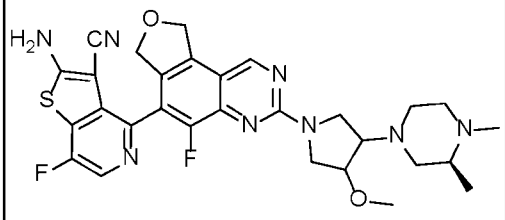
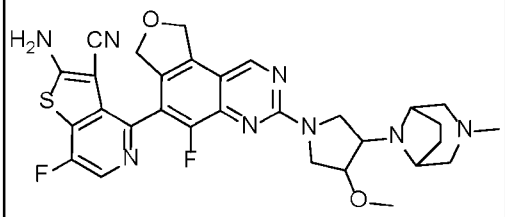
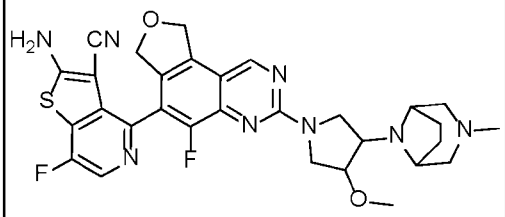
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84D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-isopropylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		591
85D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-(2-methoxyethyl)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		607
86D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-((S)-2-hydroxypropyl)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		607

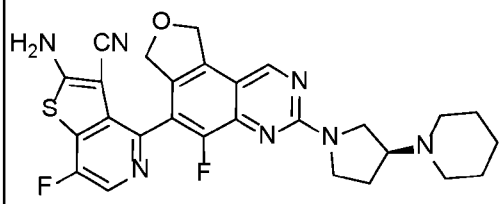
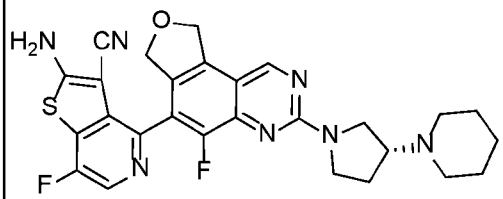
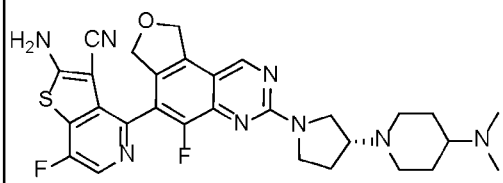
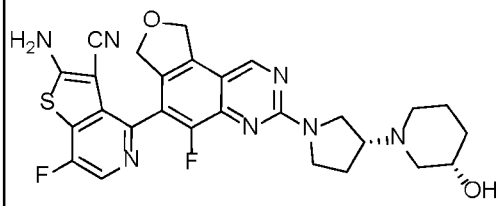
87D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-((R)-2-hydroxypropyl)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		607
88D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(4-(2-fluoroethyl)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		595
89D	2-Amino-4-(3-((2S,3S)-3-((S)-3,4-dimethylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		577
90D	2-Amino-4-(3-((2S,3S)-3-((S)-2,4-dimethylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		577

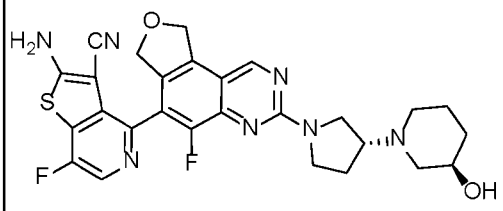
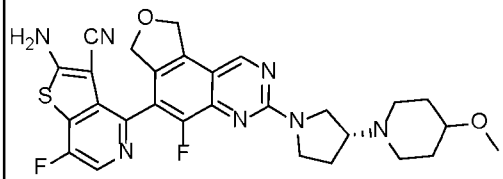
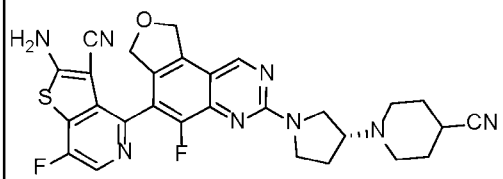
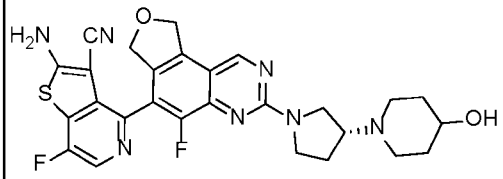
91D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((S)-2-(hydroxymethyl)-4-methylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		593
92D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((S)-2-(fluoromethyl)-4-methylpiperazin-1-yl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		595
93D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		589
94D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,4S)-2-methyl-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		563

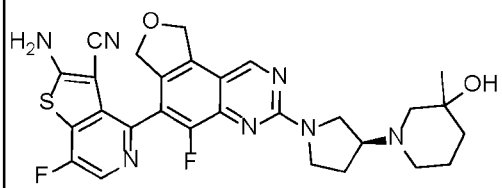
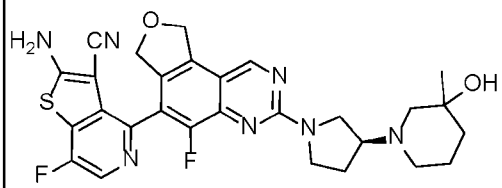
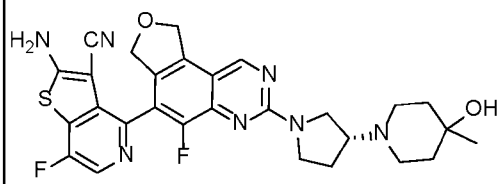
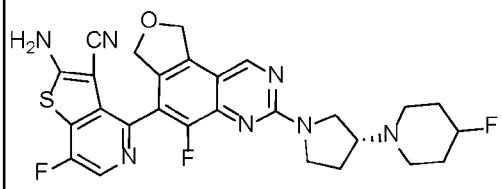
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96D [78]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		565
97D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		565
98D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		565

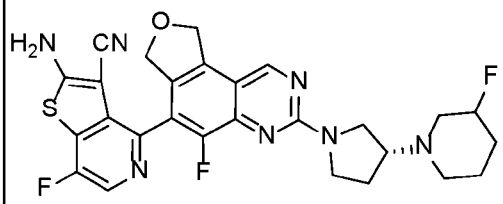
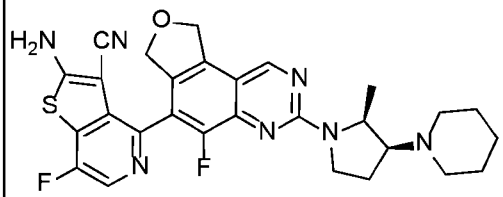
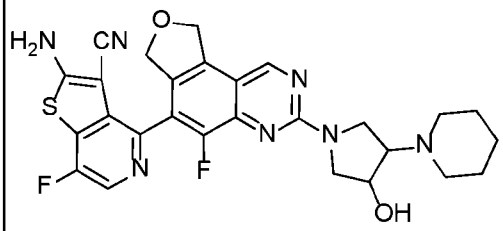
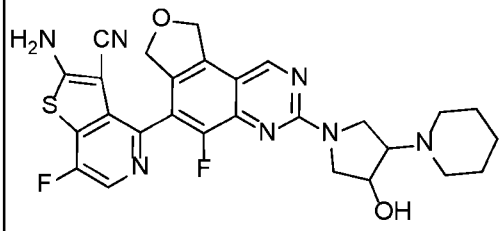
99D [79]	2-Amino-4-(3-(3-((S)-2,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile. Isomer 2		579
100D [79]	2-Amino-4-(3-(3-((S)-2,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile. Isomer 1		579
101D [80]	2-Amino-4-(3-(3-((S)-3,4-dimethylpiperazin-1-yl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		579
102D [81]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		591

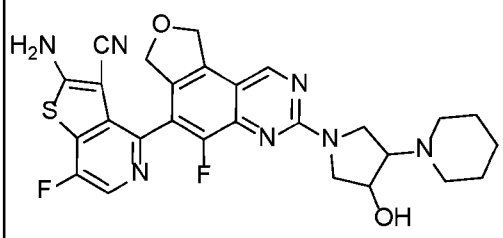
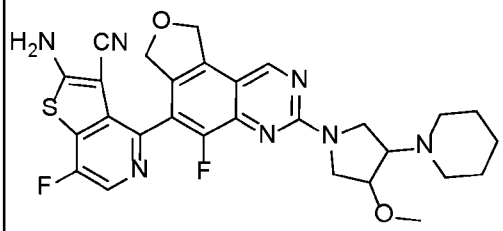
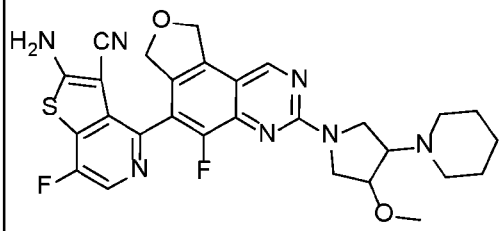
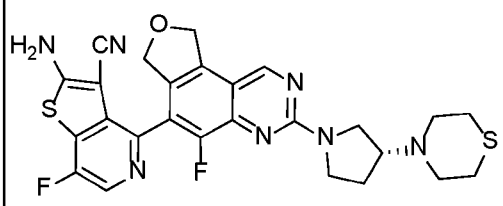
103D [81]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		591
104D [82]	2-Amino-4-(3-(3-((S)-3,4-dimethylpiperazin-1-yl)-4-methoxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		593
105D [83]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		605
106D [83]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		605

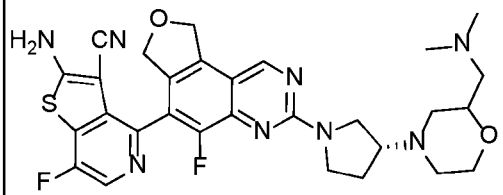
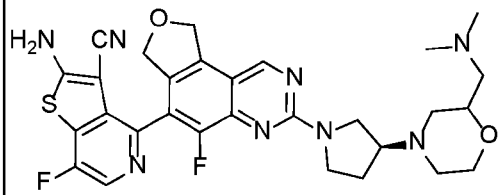
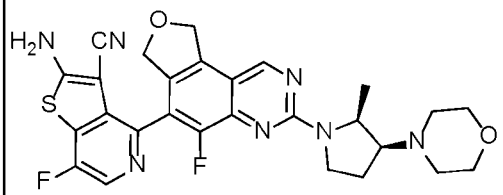
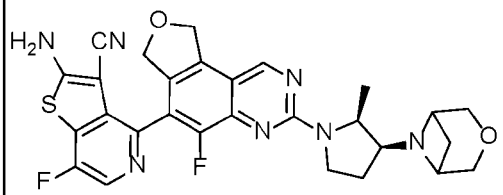
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108D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		534
109D	2-Amino-4-(3-((R)-3-(4-(dimethylamino)piperidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		577
110D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((S)-3-hydroxypiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550

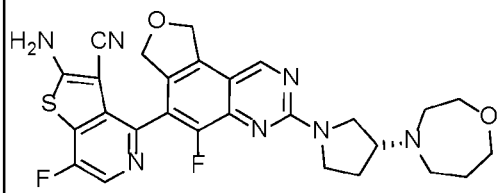
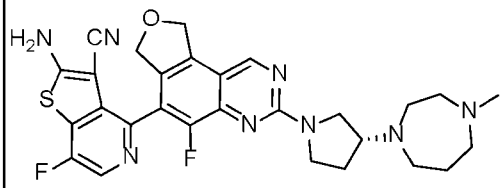
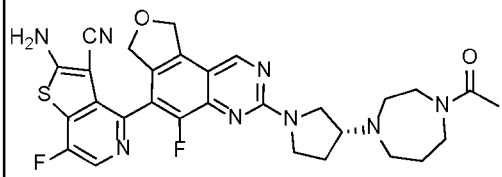
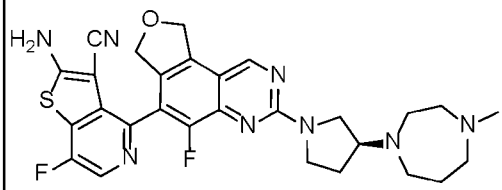
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112D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-methoxypiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
113D	2-Amino-4-(3-((R)-3-(4-cyanopiperidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		559
114D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-hydroxypiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550

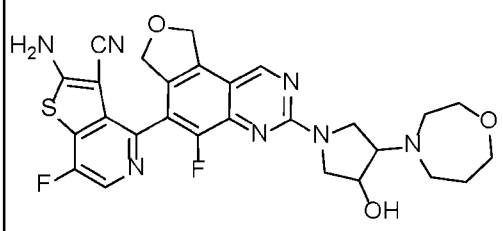
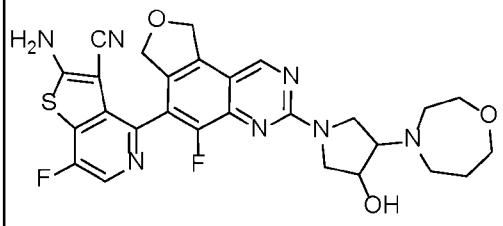
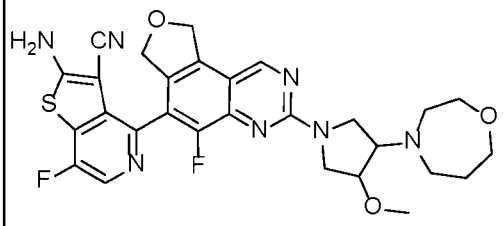
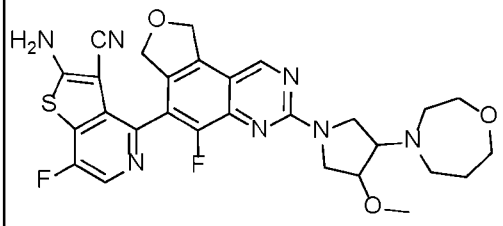
115D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(3-hydroxy-3-methylpiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		564
116D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(3-hydroxy-3-methylpiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		564
117D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-hydroxy-4-methylpiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
118D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-fluoropiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552

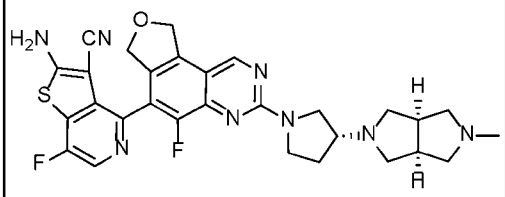
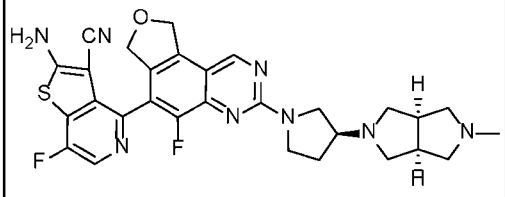
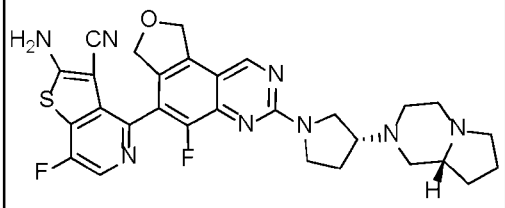
119D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R)-3-(3-fluoropiperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552
120D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		548
121D [84]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
122D [85]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		550

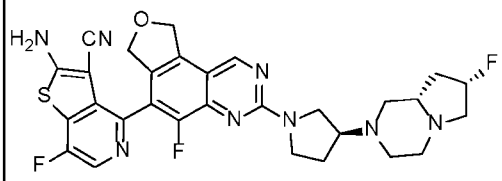
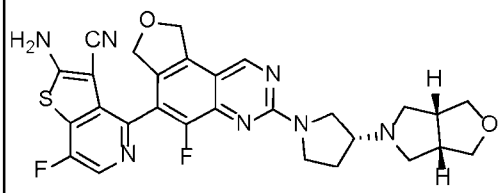
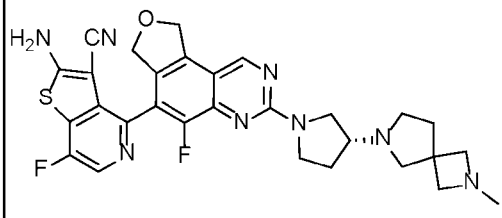
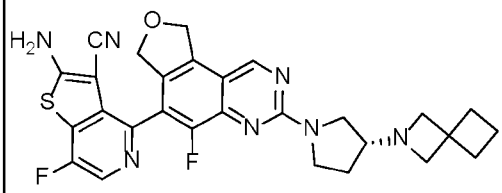
123D [85]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		550
124D [86]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		564
125D [86]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(piperidin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		564
126D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-thiomorpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552

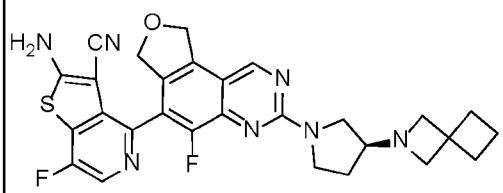
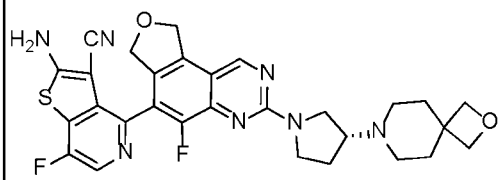
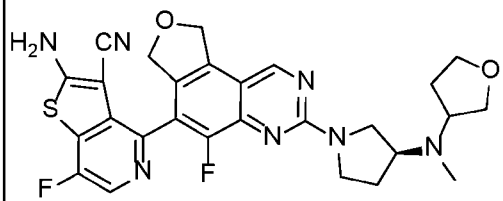
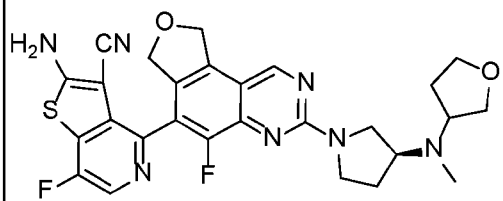
127D	2-Amino-4-(3-((3R)-3-(2-((dimethylamino)methyl)morpholino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		593
128D	2-Amino-4-(3-((3S)-3-(2-((dimethylamino)methyl)morpholino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		593
129D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-morpholinopyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
130D	4-(3-((2S,3S)-3-(3-Oxa-6-azabicyclo[3.1.1]heptan-6-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		562

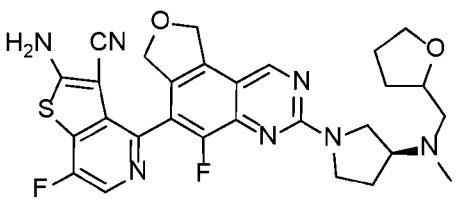
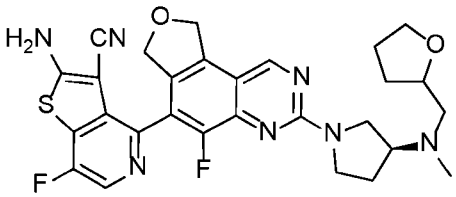
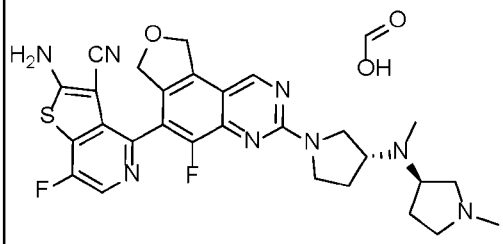
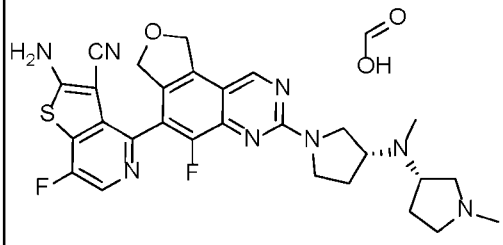
131D	4-(3-((R)-3-(1,4-Oxazepan-4-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		550
132D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-methyl-1,4-diazepan-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		563
133D	4-(3-((R)-3-(4-Acetyl-1,4-diazepan-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		591
134D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(4-methyl-1,4-diazepan-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		563

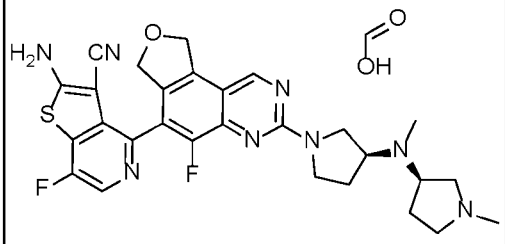
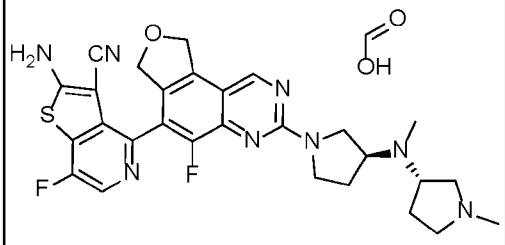
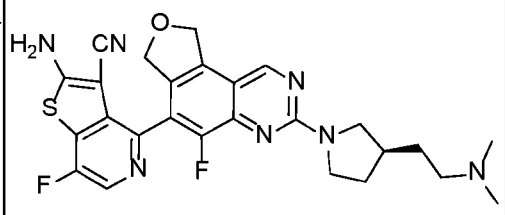
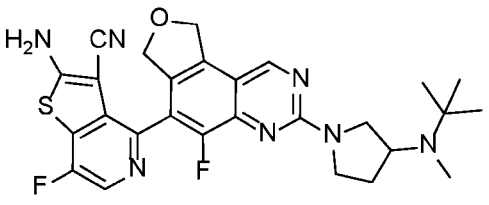
135D [87]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(1,4-oxazepan-4-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		566
136D [87]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(1,4-oxazepan-4-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		566
137D [88]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(1,4-oxazepan-4-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		580
138D [88]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-methoxy-4-(1,4-oxazepan-4-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		580

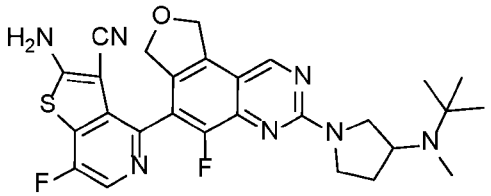
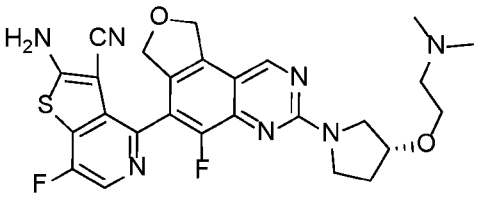
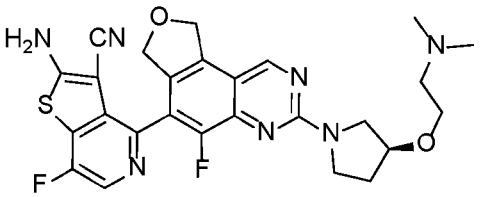
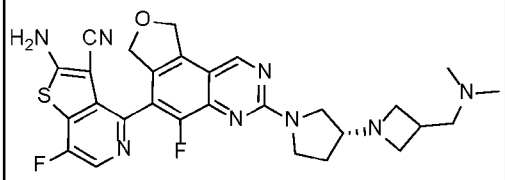
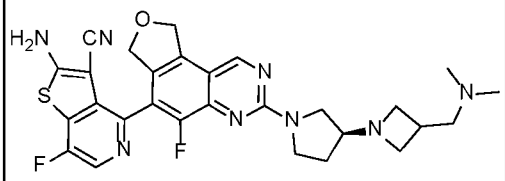
139D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		575
140D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		575
141D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((R)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		575

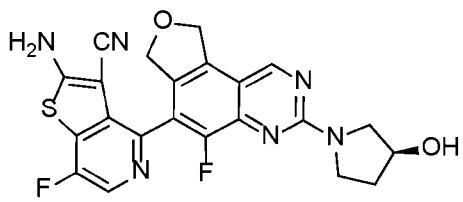
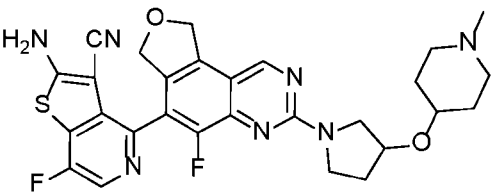
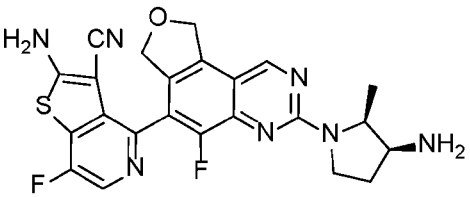
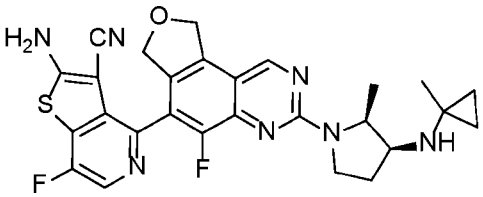
142D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-((7S,8aS)-7-fluorohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		593
143D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		562
144D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		575
145D	4-(3-((R)-3-(2-Azaspiro[3.3]heptan-2-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		546

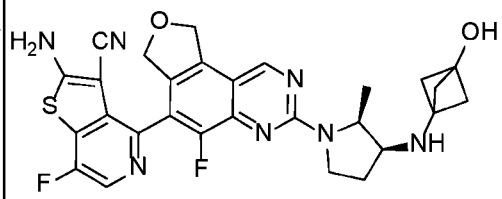
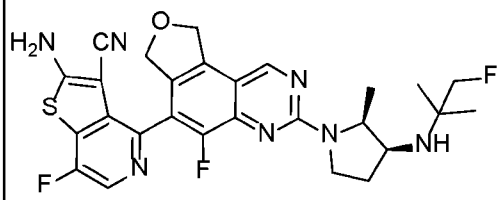
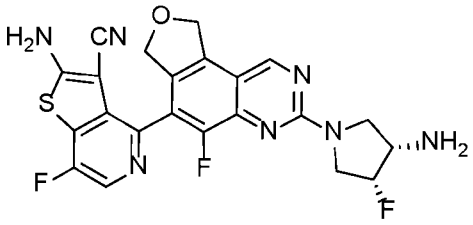
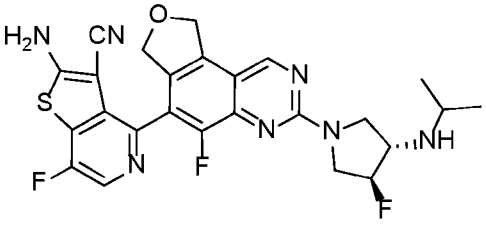
146D	4-(3-((S)-3-(2-Azaspiro[3.3]heptan-2-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		546
147D	4-(3-((R)-3-(2-Oxa-7-azaspiro[3.5]nonan-7-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-2-amino-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		576
148D [89]	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl(tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		550
149D [89]	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl(tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		550

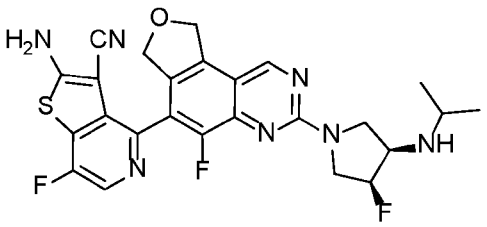
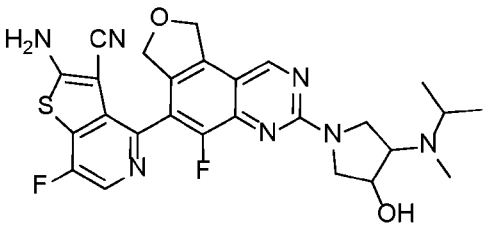
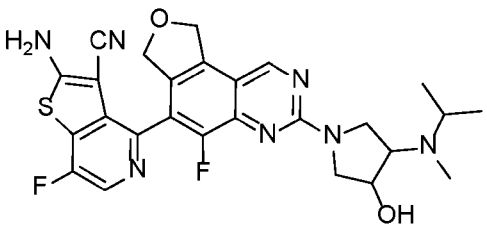
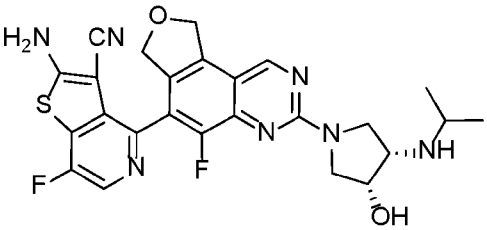
150D [90]	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl((tetrahydrofuran-2-yl)methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		564
151D [90]	2-Amino-7-fluoro-4-(5-fluoro-3-((3S)-3-(methyl((tetrahydrofuran-2-yl)methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		564
152D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(methyl((R)-1-methylpyrrolidin-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		563
153D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(methyl((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		563

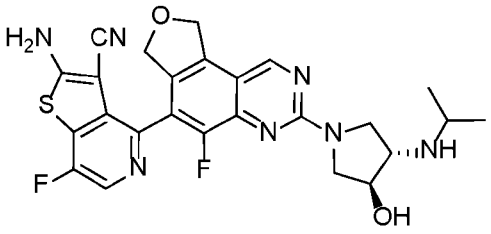
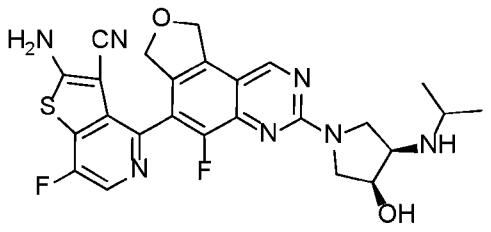
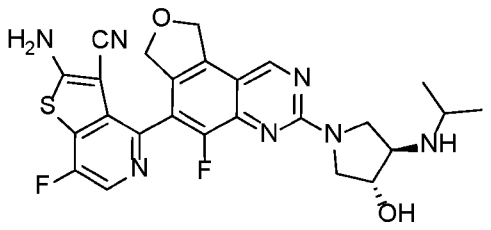
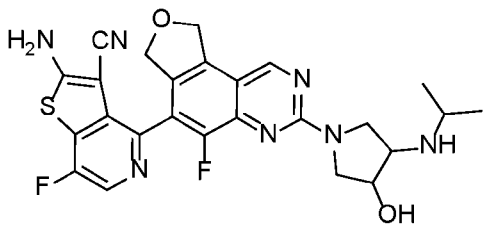
154D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(methyl((R)-1-methylpyrrolidin-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		563
155D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(methyl((S)-1-methylpyrrolidin-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid		563
156D	2-Amino-4-(3-((S)-3-(2-(dimethylamino)ethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		522
157D [91]	2-Amino-4-(3-(3-(*tert*-butyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		536

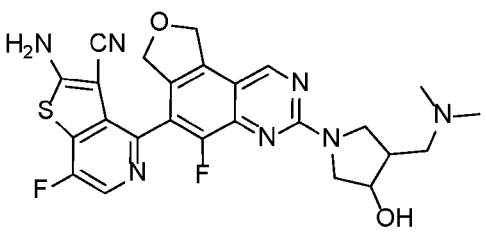
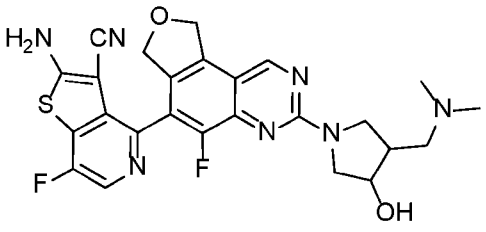
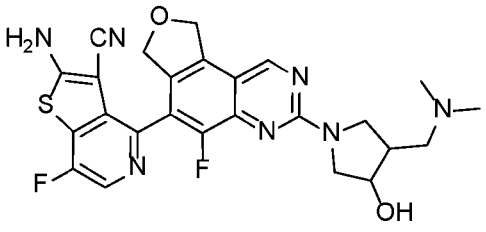
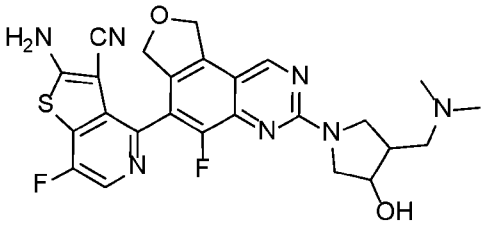
158D [91]	2-Amino-4-(3-(3-(*tert*-butyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		536
159D	2-Amino-4-(3-((R)-3-(2-(dimethylamino)ethoxy)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		538
160D	2-Amino-4-(3-((S)-3-(2-(dimethylamino)ethoxy)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		538
161D	2-Amino-4-(3-((R)-3-(3-((dimethylamino)methyl)azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563
162D	2-Amino-4-(3-((S)-3-(3-((dimethylamino)methyl)azetidin-1-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		563

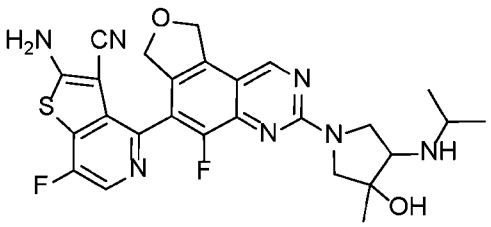
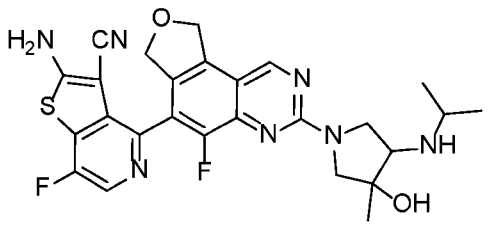
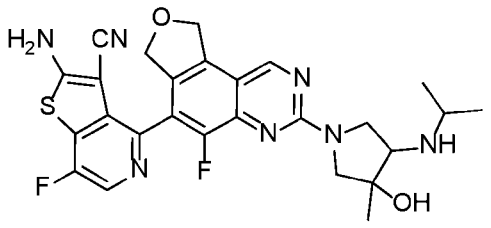
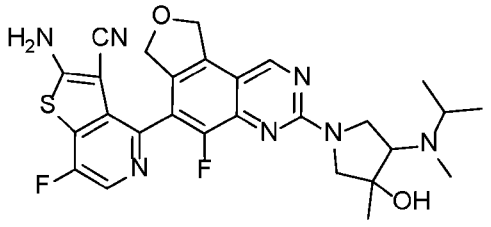
163D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-hydroxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		467
164D	2-Amino-7-fluoro-4-(5-fluoro-3-(3-((1-methylpiperidin-4-yl)oxy)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		564
165D	2-Amino-4-(3-((2S,3S)-3-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		480
166D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-((1-methylcyclopropyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		534

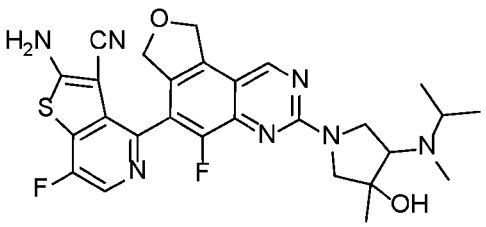
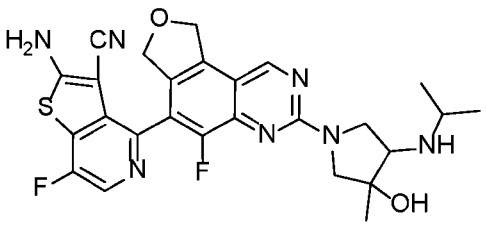
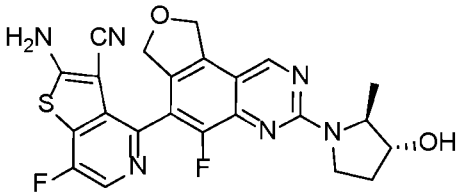
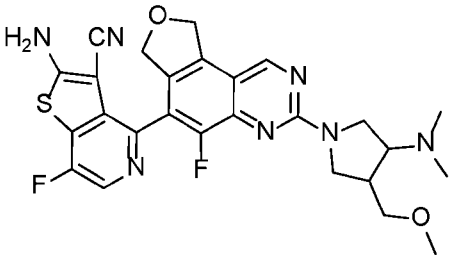
167D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((3-hydroxybicyclo[1.1.1]pentan-1-yl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		562
168D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-(3-fluoro-2,2-dimethylpropyl)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		554
169D	2-Amino-4-(3-((3S,4R)-3-amino-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		484
170D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-fluoro-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		526

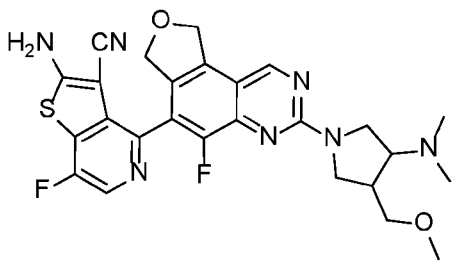
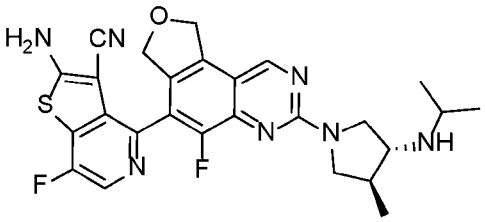
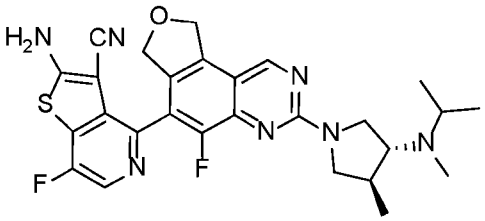
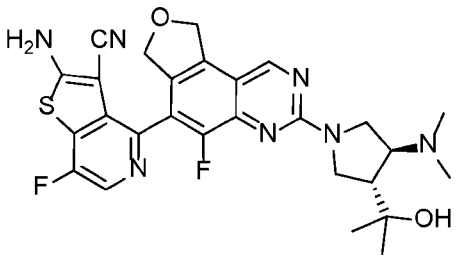
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172D [92]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		538
173D [92]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		538
174D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524

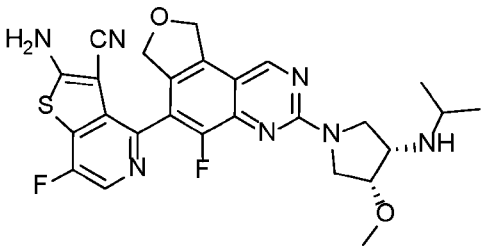
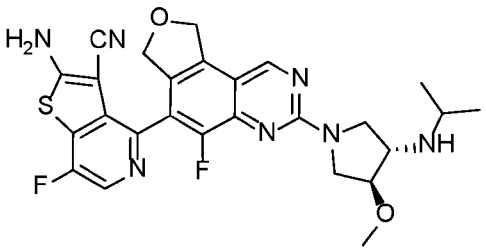
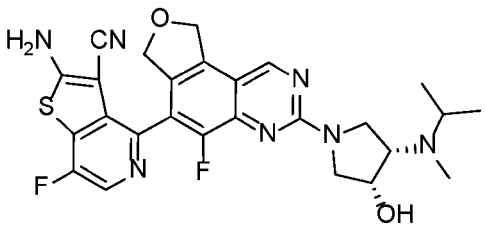
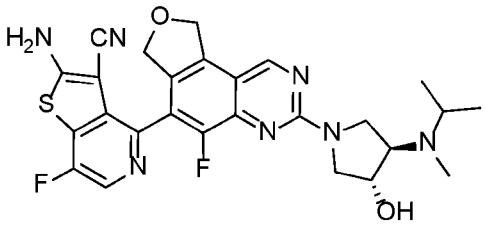
175D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524
176D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4R)-3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524
177D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524
178D [93]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		524

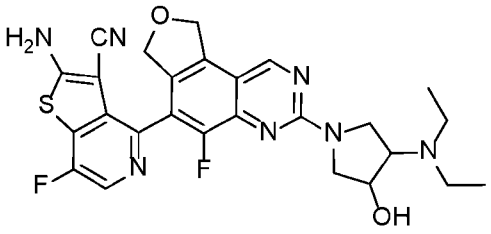
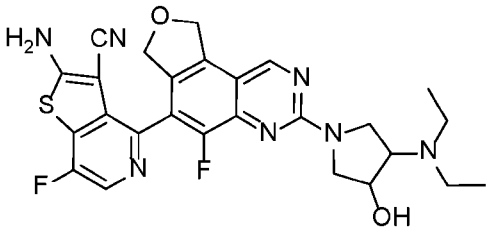
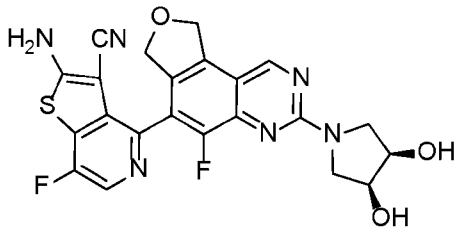
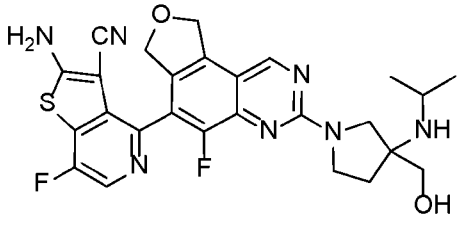
179D [94]	2-Amino-4-(3-(3-((dimethylamino)methyl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
180D [95]	2-Amino-4-(3-(3-((dimethylamino)methyl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		524
181D [96]	2-Amino-4-(3-(3-((dimethylamino)methyl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		524
182D [96]	2-Amino-4-(3-(3-((dimethylamino)methyl)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		524

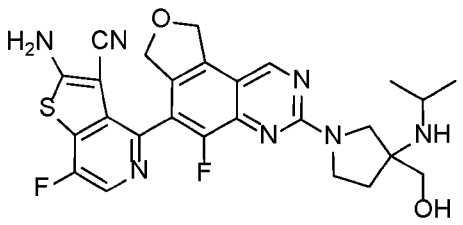
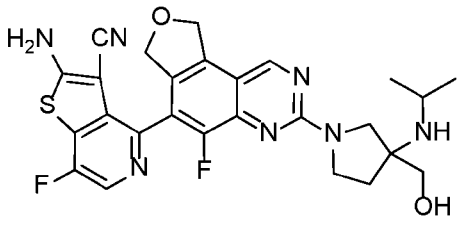
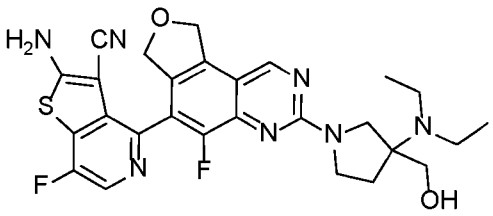
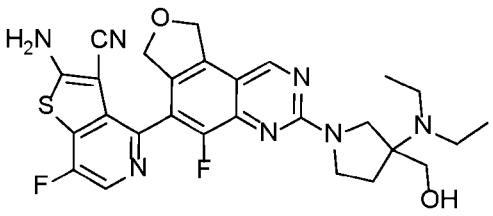
183D [97]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
184D [98]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		538
185D [98]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		538
186D [99]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropyl(methyl)amino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		552

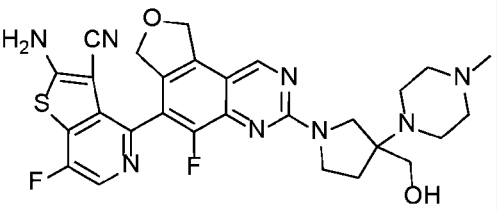
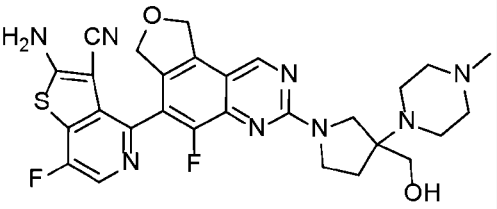
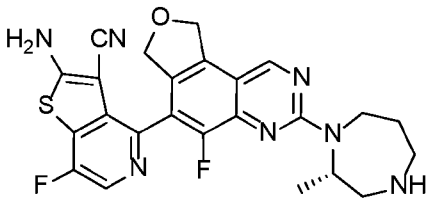
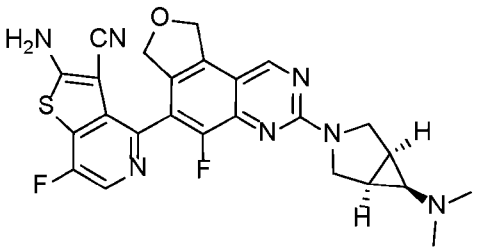
187D [99]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropyl(methyl)amino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		552
188D [100]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-hydroxy-4-(isopropylamino)-3-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
189D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3R)-3-hydroxy-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		481
190D [101]	2-Amino-4-(3-(3-(dimethylamino)-4-(methoxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		538

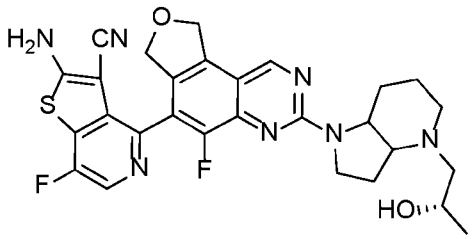
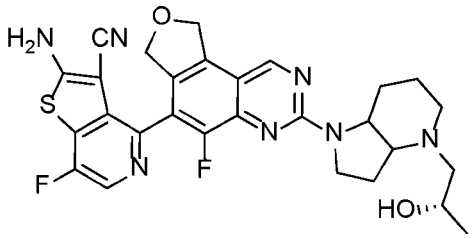
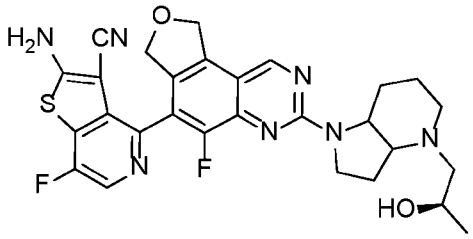
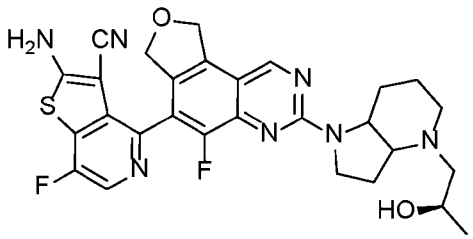
191D [101]	2-Amino-4-(3-(3-(dimethylamino)-4-(methoxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		538
192D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
193D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropyl(methyl)amino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		536
194D	2-Amino-4-(3-((3S,4R)-3-(dimethylamino)-4-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		552

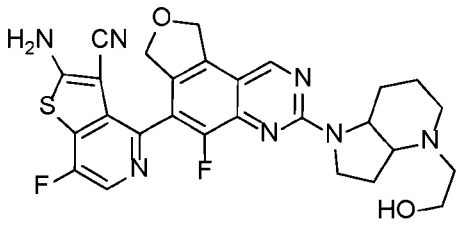
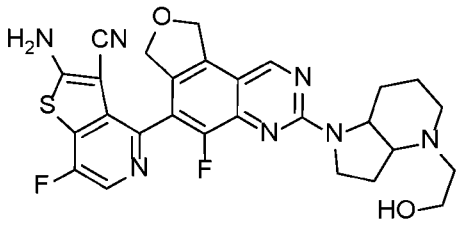
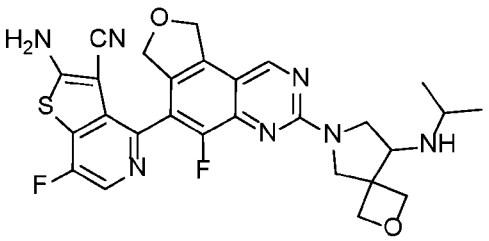
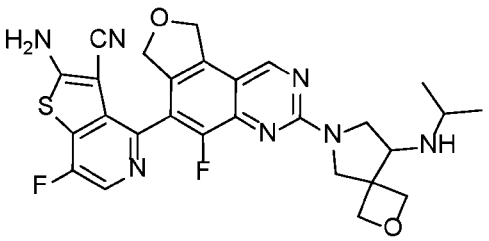
195D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4R)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
197D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
198D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
199D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538

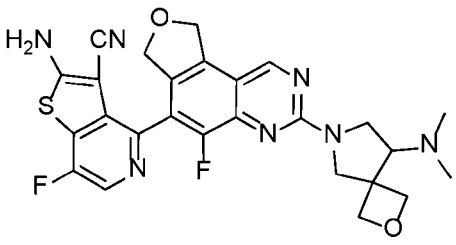
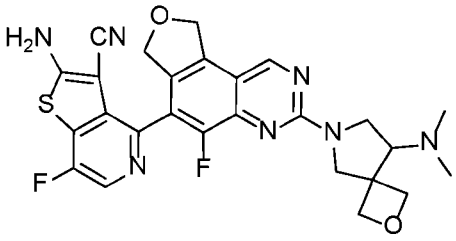
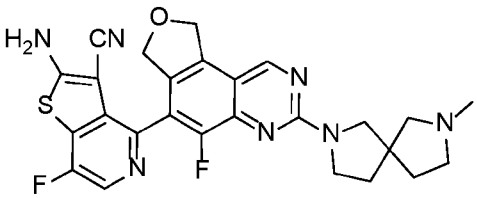
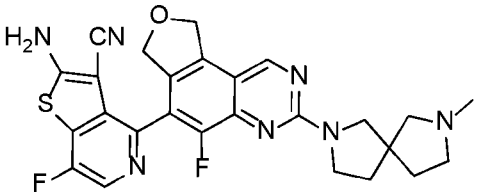
200D [102]	2-Amino-4-(3-(3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile. Isomer 1		538
201D [102]	2-Amino-4-(3-(3-(diethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile. Isomer 2		538
202D	2-Amino-4-(3-((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		483
203D	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(hydroxymethyl)-3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538

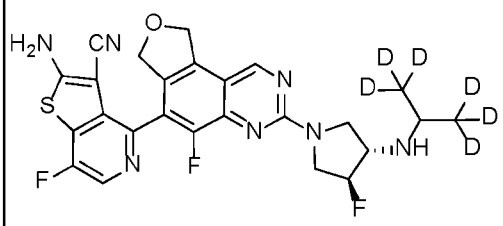
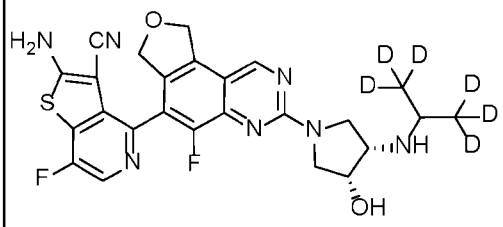
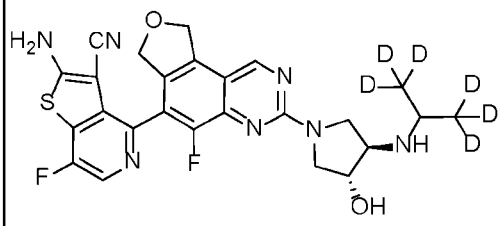
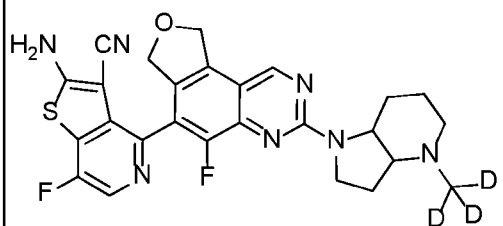
204D [103]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(hydroxymethyl)-3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		538
205D [103]	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(hydroxymethyl)-3-(isopropylamino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		538
206D	2-Amino-4-(3-(3-(diethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		552
207D	2-Amino-4-(3-(3-(diethylamino)-3-(hydroxymethyl)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		552

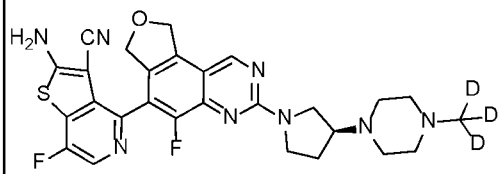
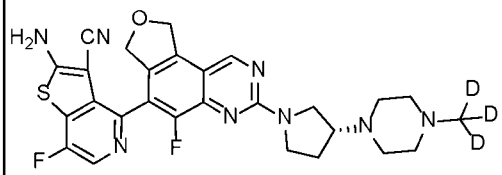
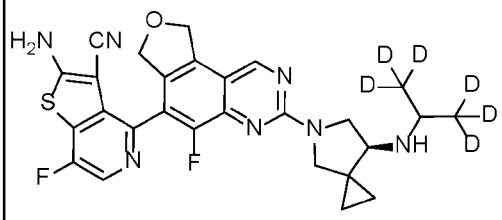
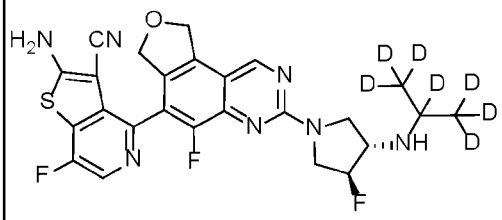
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209D	2-Amino-7-fluoro-4-(5-fluoro-3-(3-(hydroxymethyl)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		579
210D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-2-methyl-1,4-diazepan-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		494
211D	2-Amino-4-(3-((1R,5S,6r)-6-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		506

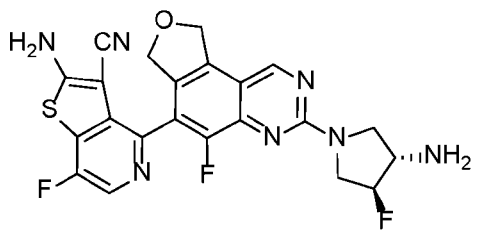
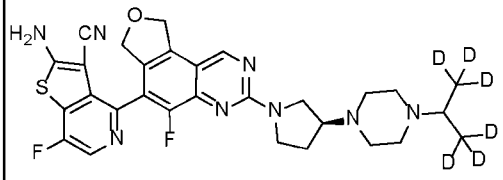
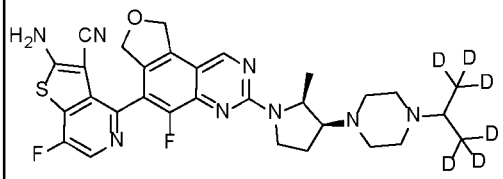
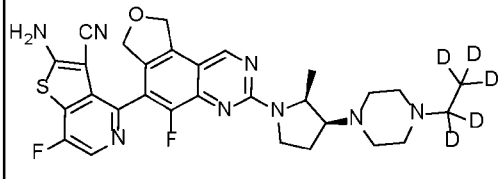
212D [104]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-((S)-2-hydroxypropyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		564
213D [104]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-((S)-2-hydroxypropyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		564
214D [105]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-((R)-2-hydroxypropyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		564
215D [105]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-((R)-2-hydroxypropyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		564

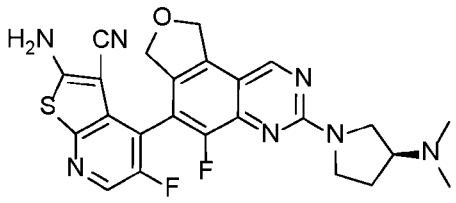
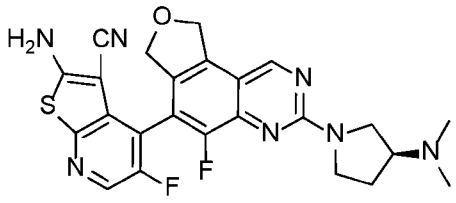
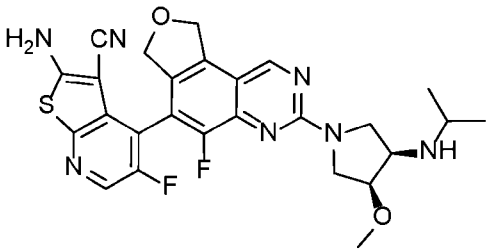
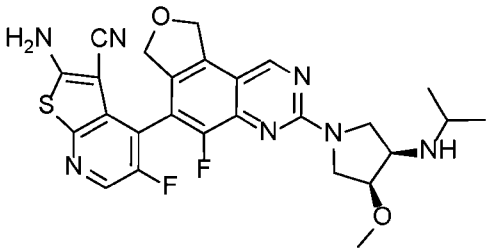
216D [106]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-(2-hydroxyethyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		550
217D [106]	2-Amino-7-fluoro-4-(5-fluoro-3-(4-(2-hydroxyethyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		550
218D [107]	2-Amino-7-fluoro-4-(5-fluoro-3-(8-(isopropylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		550
219D [107]	2-Amino-7-fluoro-4-(5-fluoro-3-(8-(isopropylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		550

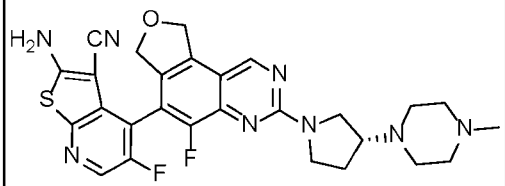
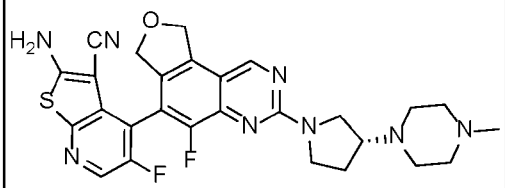
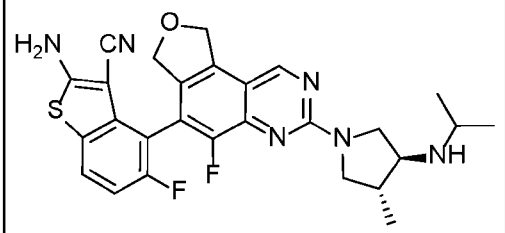
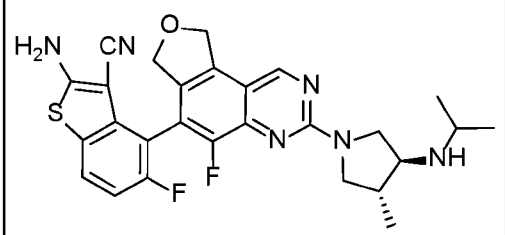
220D [108]	2-Amino-4-(3-(8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		536
221D [108]	2-Amino-4-(3-(8-(dimethylamino)-2-oxa-6-azaspiro[3.4]octan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		536
222D [109]	2-Amino-7-fluoro-4-(5-fluoro-3-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		520
223D [109]	2-Amino-7-fluoro-4-(5-fluoro-3-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		520

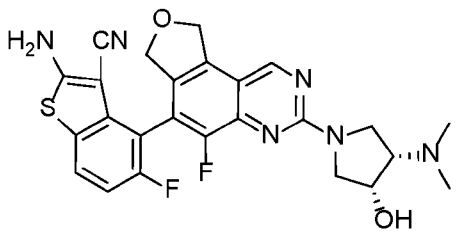
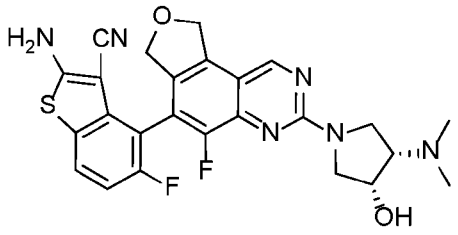
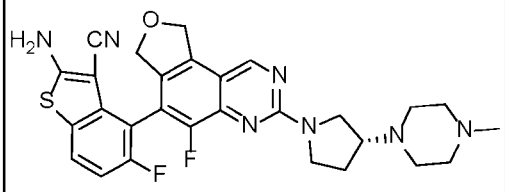
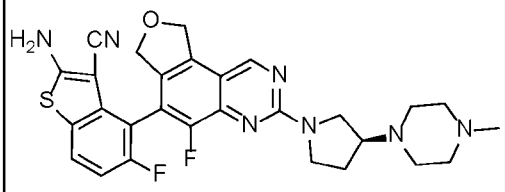
224D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-fluoro-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		532
225D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		530
226D	2-Amino-7-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		530
227D	2-Amino-7-fluoro-4-(5-fluoro-3-(4-(methyl-d3)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		523

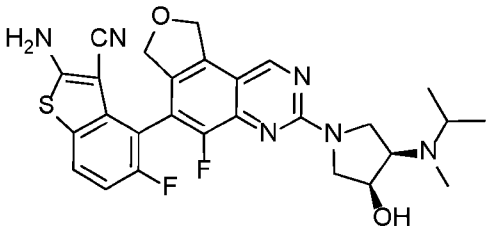
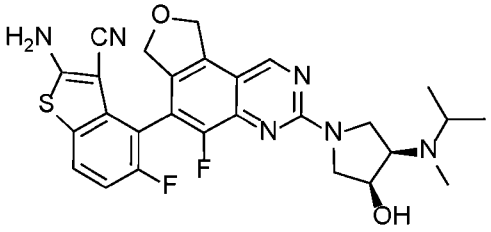
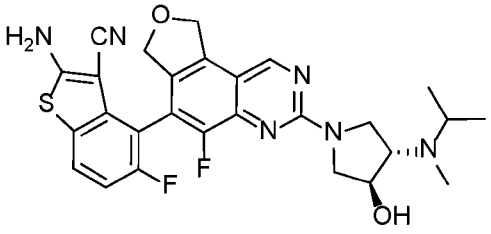
228D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(4-(methyl-d3)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552
229D	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-3-(4-(methyl-d3)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		552
230D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-7-((propan-2-yl-1,1,1,3,3,3-d6)amino)-5-azaspiro[2.4]heptan-5-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		540
231D	2-Amino-7-fluoro-4-(5-fluoro-3-((3S,4S)-3-fluoro-4-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		533

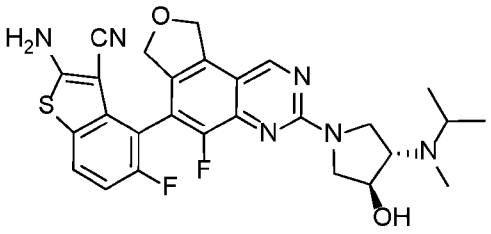
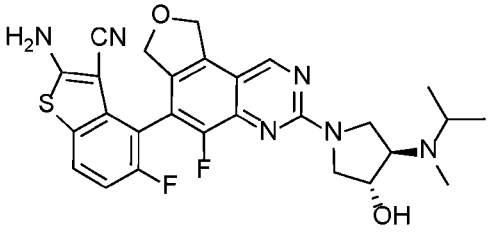
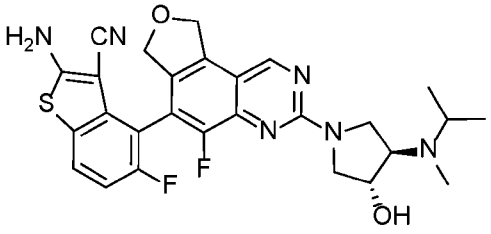
232D [110]	2-Amino-4-(3-((3S,4S)-3-amino-4-fluoropyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		484
233D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(4-(propan-2-yl-1,1,1,3,3,3-d6)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		583
234D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(4-(propan-2-yl-1,1,1,3,3,3-d6)piperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		597
235D	2-Amino-4-(3-((2S,3S)-3-(4-(ethyl-d5)piperazin-1-yl)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		582

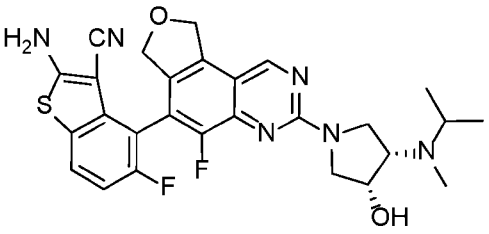
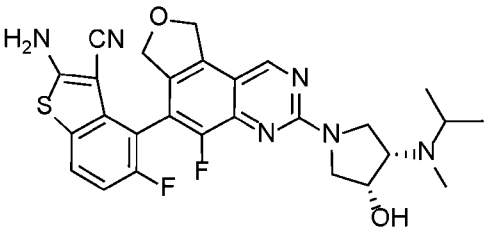
236D [111]	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorothieno[2,3-b]pyridine-3-carbonitrile, Atropisomer 1		494
237D [111]	2-Amino-4-(3-((S)-3-(dimethylamino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorothieno[2,3-b]pyridine-3-carbonitrile, Atropisomer 2		494
238D [112]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[2,3-b]pyridine-3-carbonitrile, Atropisomer 1		538
239D [112]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-(isopropylamino)-4-methoxypyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[2,3-b]pyridine-3-carbonitrile, Atropisomer 2		538

240D [113]	2-Amino-5-fluoro-4-(5-fluoro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[2,3-b]pyridine-3-carbonitrile, Atropisomer 1		549
241D [113]	2-Amino-5-fluoro-4-(5-fluoro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[2,3-b]pyridine-3-carbonitrile, Atropisomer 2		549
242D [114]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4R)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		521
243D [114]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4R)-3-(isopropylamino)-4-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		521

244D [115]	2-Amino-4-(3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 1		509
245D [115]	2-Amino-4-(3-((3S,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluorobenzo[b]thiophene-3-carbonitrile, Atropisomer 2		509
246D [26]	2-Amino-5-fluoro-4-(5-fluoro-3-((R)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		548
247D [26]	2-Amino-5-fluoro-4-(5-fluoro-3-((S)-3-(4-methylpiperazin-1-yl)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		548

248D [116]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		537
249D [116]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4R)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		537
250D [117]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		537

251D [117]	2-Amino-5-fluoro-4-(5-fluoro-3-((3S,4S)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		537
252D [118]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropsiomer 1		537
253D [118]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4R)-3-hydroxy-4-(isopropyl(methyl)amino) pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropsiomer 2		537

254D [119]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		537
255D [119]	2-Amino-5-fluoro-4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-(isopropyl(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		537

[1] Clean Trans Isomers; separation of Trans Isomer Pairs occurred in Preparations 47A and 48A

[2] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 10-53% (EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min

[3] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-90% (1:1 MeOH:EtOH) in Heptane, 50 mL/min

[4] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 10-70% EtOH in Heptane, 42.5 mL/min

[5] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-55% (1:1 MeOH:EtOH) in Heptane, 50 mL/min

[6] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-3, 30 x 150 mm, 13-100% (EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min

[7] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-3, 30 x 150 mm, 5-100% (1:1 MeOH:EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min; diastereomers 78A-81A each consist of a single atropisomer and a single trans isomer.

[8] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-1, 30 x 150 mm, 50-100% (Isopropanol w/ 0.1% isopropylamine) in Heptane, 40.0 mL/min

[9] Prep-Chiral-HPLC; Chiralpak-IK, 3 x 25 cm, 50% EtOH in (Hexanes w/ 10mM

ammoniated methanol), the pure fraction afforded Diastereomer 4. Mixed fractions further separated with Prep-Chiral-HPLC; Chiralpak-IF, 3 x 25 cm, 30% EtOH in (Hexanes w/ 10mM ammoniated methanol), the pure fraction afforded Diastereomer 3. Mixed fractions further separated with Prep-Chiral-HPLC; Chiralpak-IH, 3 x 25 mm, 30% EtOH in (Hexanes w/ 10mM ammoniated methanol), the first pure fraction afforded Diastereomer 1 and the second pure fraction afforded Diastereomer 2.

[10] Prep-Chiral-HPLC; Phenomenex Lux i-Cellulose-5, 30 x 150 mm, 10-100% (Isopropanol w/ 0.1% isopropylamine) in Heptane, 36 mL/min

[11] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 5-45% (1:1 MeOH:EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min

[12] Prep-Chiral-HPLC; Chiralpak-ID, 30 x 250 mm, 50% EtOH in (Hexanes w/ 10mM ammoniated methanol), 40 mL/min

[13] Prep-Chiral-SFC; S,S Whelk-O, 20 x 250 mm, 30% (EtOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[14] Clean Trans Isomers; Prep-Chiral-SFC; Phenomenex Lux i-Cellulose-5, 30 x 150 mm, 15% (MeOH w/ 0.1% isopropylamine) in CO_2

[15] Example 61B is a mix of Cis Isomers, Example 62B is a mix of Trans Isomers; Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-3, 30 x 150 mm, 5-70% EtOH in Heptane, 42.5 mL/min

[16] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 10-65% EtOH in Heptane, 42.5 mL/min

[17] Prep-HPLC; C18, 5-98% Acetonitrile in (10 mM ammonium acetate in 95:5 Water:MeOH), the first eluting peak contained Examples 82B and 83B, the second eluting peak contained Examples 84B and 85B. Examples 82B and 83B were further separated with Prep-Chiral-HPLC; Phenomenex Lux i-Cellulose-5, 30 x 150 mm, 6-80% (Isopropanol w/ 0.2% isopropylamine) in Heptane, 40 mL/min, Example 82B was the first eluting peak. Examples 84B and 85B were further separated with Prep-Chiral-HPLC; Phenomenex Lux i-Cellulose-5, 30 x 150 mm, 4-45% (1:1 MeOH:EtOH) in Heptane, 42.5 mL/min, Example 84B was the first eluting peak.

[18] Prep-Chiral-HPLC; Chiralpak-IK, 3 x 25 cm, 50% EtOH in (Hexanes w/ 10mM ammoniated methanol), 40 mL/min

[19] Clean Cis Isomers; Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 10-70% (EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min

[20] Prep-Chiral-HPLC; Chiralpak-ID, 3 x 25 cm, 50% EtOH in (Hexanes w/ 10mM ammoniated methanol), 40 mL/min

[21] Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 45% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[22] Prep-Chiral-SFC; Chiralpak-IC, 20 x 250 mm, 45% (EtOH w/ 0.5% dimethylethylamine)

in CO_2, 80 mL/min

[23] Single atropisomer (from precursor in Preparation 17B)

[24] Single atropisomer (from precursor in Preparation 18B)

[25] Ring-opened byproducts from Example 125B

[26] Single atropisomer (from precursor in Preparation 14B)

[27] Mix of Cis Isomers

[28] Clean Cis Isomers; Prep-Chiral-SFC; S,S Whelk-O, 20 x 250 mm, 40% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[29] Prep-Chiral-HPLC; Chiralpak-IG, 19 x 150 mm, 70-100% Acetonitrile in 20 mM ammonium bicarbonate, 40 mL/min

[30] Prep-Chiral-SFC; Chiralpak-IC, 20 x 250 mm, 30% (EtOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min. Example 8C was the second isomer to elute, and was assigned (S,S) stereochemistry after analysis of Example 7C (known (R,R) stereochemistry) matched the first isomer to elute.

[31] Prep-Chiral-HPLC; Chiralpak-IC, 20 x 150 mm, 70-100% Acetonitrile in 20 mM ammonium bicarbonate, 40 mL/min

[32] Clean Cis Isomers; Prep-Chiral-SFC; Chiralpak-IG, 20 x 250 mm, 45% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[33] Mix of Cis Isomers

[34] Prep-Chiral-HPLC; Chiralpak-AD, 20 x 150 mm, 100% EtOH w/ 0.2% dimethylethylamine, 10 mL/min

[35] Mix of Cis Isomers

[36] Clean Cis Isomers; Prep-Chiral-SFC; Chiralpak-IH, 20 x 250 mm, 30% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[37] Prep-Chiral-SFC; Chiralpak-IH, 20 x 250 mm, 30% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[38] Prep-Chiral-SFC; Chiralpak-IC, 20 x 250 mm, 40% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[39] Prep-Chiral-SFC; Chiralpak-IH, 20 x 250 mm, 30% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min

[40] Prep-Chiral-HPLC; CHIRAL ART Cellulose-SB, 20 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 20 mL/min

[41] Prep-Chiral-HPLC; CHIRAL ART Cellulose-SB, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 40 mL/min

[42] Prep-Chiral-SFC; Chiralpak-IG, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 40 mL/min

[43] Prep-Chiral-HPLC; Chiralpak-IK, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 40 mL/min

[44] Prep-Chiral-HPLC; Chiralpak-ID, 30 x 250 mm, 50% 1:1 Hexanes:MTBE (with 0.5% 2M ammoniated methanol) : 50% MeOH, 40 mL/min

[45] Diastereomer refers to each compound being a single atropisomer and a single quaternary center. Prep-Chiral-HPLC; Chiralpak-IE, 30 x 250 mm, 80% 1:1 Hexanes:MTBE (with 0.5% 2M ammoniated methanol) : 20% EtOH, 40 mL/min, the first eluting peak contained Examples 60C and 61C, the second eluting peak contained Example 62C, the third eluting peak contained Example 63C. Examples 60C and 61C were further separated with Prep-Chiral-SFC; Chiralpak-IH, 30 x 250 mm, 50% (MeOH with 20 mM ammoniated methanol) in CO_2, 90 mL/min, Example 60C was the first eluting peak.

[46] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 5-85% EtOH in Heptane, 42.5 mL/min

[47] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-100% EtOH in Heptane, 42.5 mL/min

[48] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-1, 30 x 150 mm, 10-75% EtOH in Heptane, 42.5 mL/min

[49] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 10-55% (EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min

[50] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 10-75% (EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min

[51] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-63% EtOH in Heptane, 42.5 mL/min

[52] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 10-40% EtOH in Heptane, 42.5 mL/min

[53] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 10-40% (EtOH w/ 0.1% isopropylamine) in Heptane, 37.5 mL/min

[54] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 15-60% EtOH in Heptane, 40 mL/min

[55] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 15-45% 1:1 MeOH:EtOH in Heptane, 42.5 mL/min

[56] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-60% EtOH in Heptane, 37.5 mL/min

[57] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-55% EtOH in Heptane, 37.5 mL/min

[58] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 15-45% 1:1 MeOH:EtOH in Heptane, 37.5 mL/min

[59] Prep-Chiral-HPLC; Chiralpak-IG, 30 x 250 mm, 70% Hexanes (with 10 mM ammoniated methanol) : 30% Isopropanol, 40 mL/min

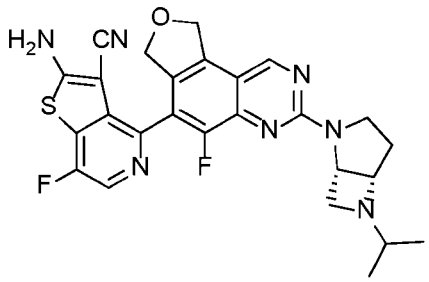
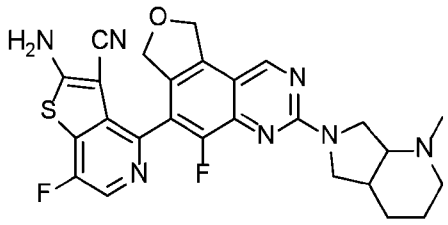
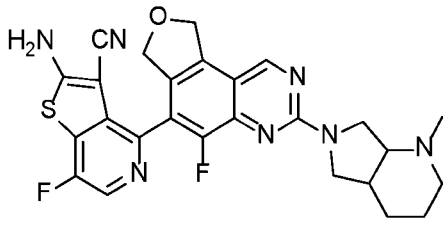
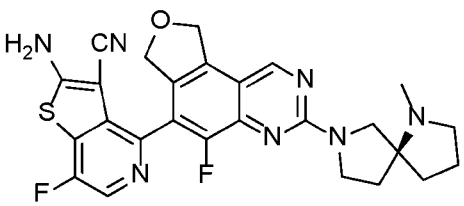
[60] Prep-Chiral-HPLC; Chiral NQ(2)5u, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% Isopropanol, 40 mL/min
[61] Prep-Chiral-HPLC; Chiral NQ(2)5u, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% Isopropanol, 40 mL/min
[62] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 5-60% (EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min
[63] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-90% Isopropanol in Heptane, 37.5 mL/min
[64] Clean Cis Isomers; Prep-Chiral-HPLC; Phenomenex Lux i-Cellulose-5, 30 x 150 mm, 5-45% (1:1 MeOH:EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min
[65] Prep-HPLC; C18, Acetonitrile in Water
[66] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 10-100% (EtOH w/ 0.1% isopropylamine) in Heptane, 40 mL/min
[67] Prep-Chiral-SFC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 25% MeOH in CO_2, 37.5 mL/min
[68] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 18-60% 1:1 MeOH:EtOH in Heptane, 50 mL/min
[69] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 15-100% 1:1 MeOH:EtOH in Heptane, 40 mL/min
[70] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 15-60% (1:1 MeOH:EtOH w/ 0.1% isopropylamine) in Heptane, 42.5 mL/min
[71] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 5-60% EtOH in Heptane, 42.5 mL/min
[72] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-1, 30 x 150 mm, 10-100% Isopropanol in Heptane, 30 mL/min
[73] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 20-50% 1:1 MeOH:EtOH in Heptane, 42.5 mL/min
[74] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 10-100% 1:1 MeOH:EtOH in Heptane, 37.5 mL/min
[75] Prep-Chiral-HPLC; Phenomenex Lux Cellulose-2, 30 x 150 mm, 10-70% 1:1 MeOH:EtOH in Heptane, 37.5 mL/min
[76] Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 45% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min
[77] Mix of Trans Isomers
[78] Mix of Trans Isomers
[79] Clean Trans Isomers, Separated in Preparations 5D and 6D
[80] Clean Trans Isomer, Separated in Preparation 7D

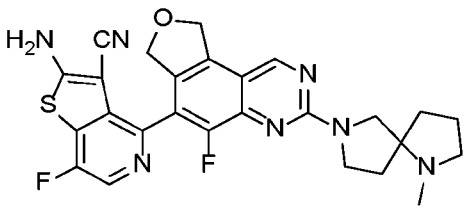
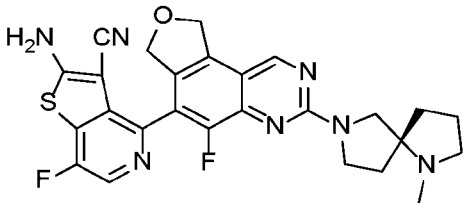
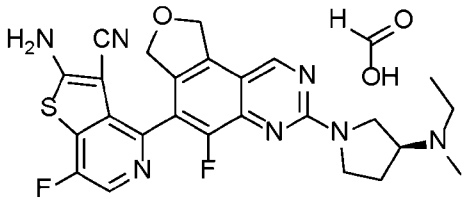
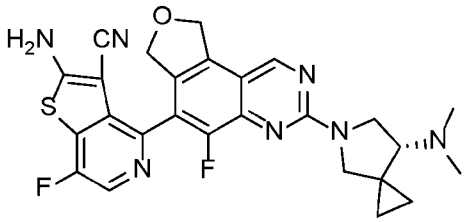
[81] Clean Trans Isomers; Prep-Chiral-HPLC; Chiralpak-IG, 20 x 150 mm, 50-100% Acetonitrile in (20 mM ammonium bicarbonate in pH 9 buffer), 40 mL/min
[82] Clean Trans Isomer, Separated in Preparation 7D
[83] Clean Trans Isomers; Prep-Chiral-HPLC; Chiralpak-IG, 20 x 150 mm, 50-100% Acetonitrile in (20 mM ammonium bicarbonate in pH 9 buffer), 40 mL/min
[84] Mix of Trans Isomers
[85] Clean Trans Isomers; Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 45% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min
[86] Clean Trans Isomers, Separated in Preparations 9D and 10D
[87] Clean Trans Isomers; Prep-Chiral-HPLC; Chiralpak-IC, 20 x 150 mm, 70-100% Acetonitrile in (20 mM ammonium bicarbonate in pH 9 buffer), 40 mL/min
[88] Clean Trans Isomers; Prep-Chiral-HPLC; Chiralpak-IC, 20 x 150 mm, 70-100% Acetonitrile in (20 mM ammonium bicarbonate in pH 9 buffer), 40 mL/min
[89] Prep-Chiral-SFC; S,S Whelk-O, 20 x 150 mm, 30% (Isopropanol w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min
[90] Prep-Chiral-SFC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 20% (EtOH w/ 0.1% isopropylamine) in CO_2
[91] Prep-Chiral-SFC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 18% (EtOH w/ 0.1% isopropylamine) in CO_2
[92] Clean Trans Isomers; Prep-Chiral-SFC; Chiralpak-IC, 20 x 250 mm, 40% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 65 g/min
[93] Mix of Trans Isomers
[94] Mix of Cis Isomers
[95] Mix of Trans Isomers
[96] Clean Trans Isomers; Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 45% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min
[97] Mix of Trans Isomers (nitrogen and oxygen substituents)
[98] Clean Trans Isomers (nitrogen and oxygen substituents)
[99] Clean Trans Isomers (nitrogen and oxygen substituents)
[100] Clean Cis Isomer (nitrogen and oxygen substituents)
[101] Clean Cis Isomers; Prep-HPLC; C18, 35-70% Acetonitrile in (20 mM ammonium bicarbonate in pH 9 buffer), 40 mL/min
[102] Clean Trans Isomers, Separated in Preparations 12D and 13D
[103] Prep-Chiral-SFC; Chiralpak-AD, 20 x 250 mm, 40% (EtOH w/ 0.5% dimethylethylamine) in CO_2, 65 g/min
[104] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 20-100% (EtOH w/ 0.1% isopropylamine) in Heptane, 45 mL/min

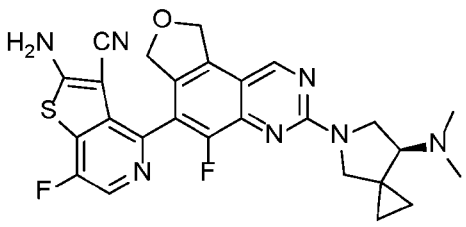
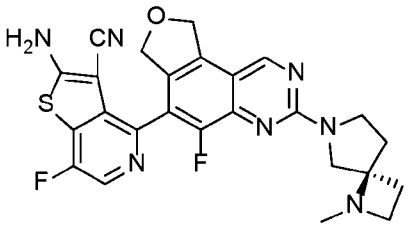
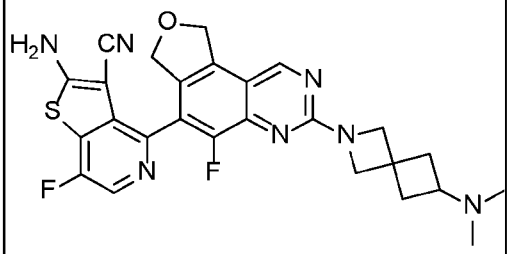
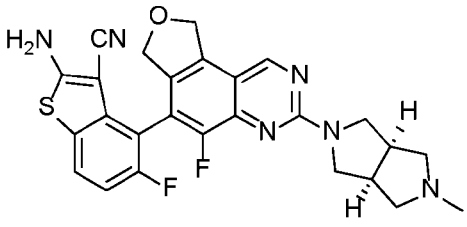
[105] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-3, 30 x 150 mm, 20-100% (1:1 MeOH:EtOH w/ 0.1% isopropylamine) in Heptane, 50 mL/min
[106] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 10-60% (1:1 MeOH:EtOH w/ 0.1% isopropylamine) in Heptane, 34.5 mL/min
[107] Prep-Chiral-HPLC; Chiralpak-IG, 20 x 150 mm, 70-100% Acetonitrile in (20 mM ammonium bicarbonate in pH 9 buffer), 40 mL/min
[108] Clean Isomers, from **********
[109] Prep-Chiral-SFC; Chiralpak-IC, 20 x 250 mm, 45% (MeOH w/ 0.5% dimethylethylamine) in CO_2, 80 mL/min
[110] Separated byproduct from impurity in Example 231D
[111] Prep-Chiral-HPLC; Chiralpak-IG, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 40 mL/min
[112] Prep-Chiral-HPLC; Chiral Art Cellulose-SC, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% Isopropanol, 40 mL/min
[113] Prep-Chiral-HPLC; Chiralpak-IE, 30 x 250 mm, 70% 1:1 Hexanes:MTBE (with 0.5% 2M ammoniated methanol) : 30% EtOH, 35 mL/min
[114] Prep-Chiral-HPLC; Chiralpak-IG, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 40 mL/min
[115] Prep-Chiral-HPLC; Chiralpak-IK, 30 x 250 mm, 80% Hexanes (with 10 mM ammoniated methanol) : 20% EtOH, 40 mL/min
[116] Prep-Chiral-HPLC; Chiralpak-ID, 30 x 250 mm, 50% Hexanes (with 10 mM ammoniated methanol) : 50% EtOH, 40 mL/min
[117] Prep-Chiral-HPLC; Chiralpak-IG, 30 x 250 mm, 60% Hexanes (with 10 mM ammoniated methanol) : 40% EtOH, 40 mL/min
[118] Prep-Chiral-HPLC; Chiral Art Cellulose-SZ, 30 x 250 mm, 70% Hexanes (with 10 mM ammoniated methanol) : 30% EtOH, 40 mL/min
[119] Prep-Chiral-HPLC; Chiralpak-IE, 30 x 250 mm, 75% 1:1 Hexanes:MTBE (with 0.5% 2M ammoniated methanol) : 25% MeOH, 40 mL/min

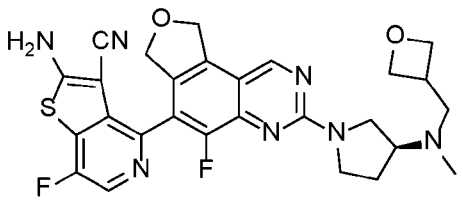
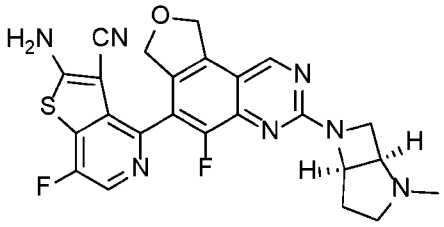
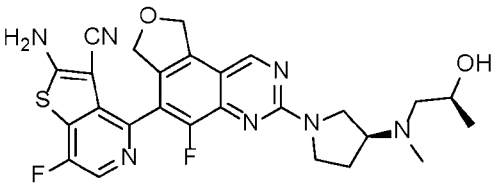
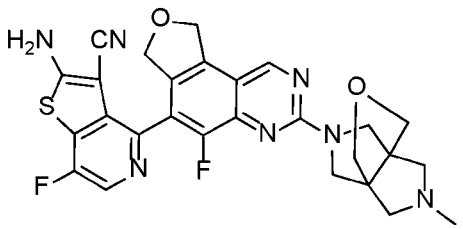
[0359] The following compounds in Table 29 were prepared in similar manner as described in Preparation 33B or Example 1. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

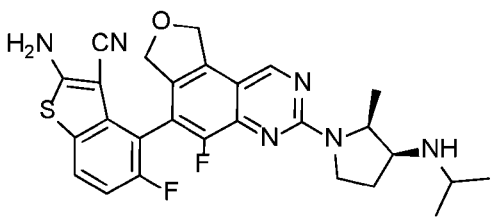
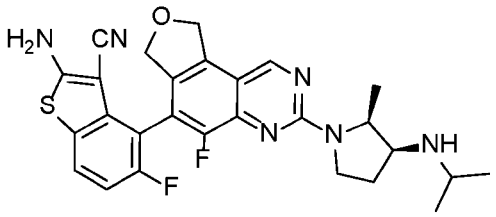
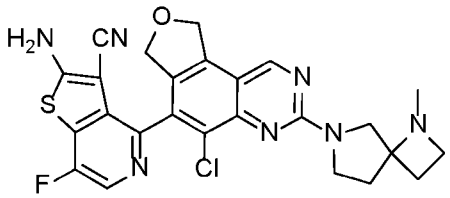
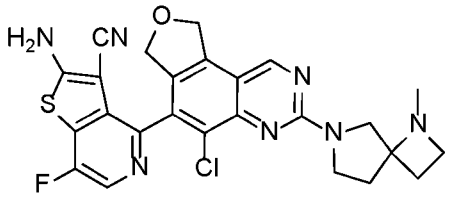
Table 29:

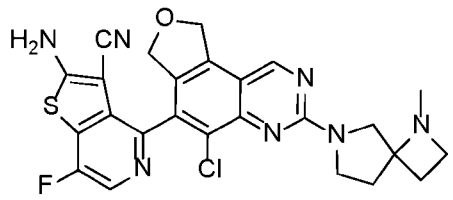
Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)
137B	2-Amino-7-fluoro-4-(5-fluoro-3-((1S,5S)-6-isopropyl-2,6-diazabicyclo[3.2.0]heptan-2-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520
138B [1]	2-Amino-7-fluoro-4-(5-fluoro-3-(1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		520
139B [1]	2-Amino-7-fluoro-4-(5-fluoro-3-(1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		520
140B	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520

141B	2-Amino-7-fluoro-4-(5-fluoro-3-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520
142B [2]	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		520
143B	2-Amino-4-(3-((S)-3-(ethyl(methyl)amino)pyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile formic acid		508
144B	2-Amino-4-(3-((R)-7-(dimethylamino)-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520

145B	2-Amino-4-(3-((S)-7-(dimethylamino)-5-azaspiro[2.4]heptan-5-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
146B	2-Amino-7-fluoro-4-(5-fluoro-3-((R)-1-methyl-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		506
147B	2-Amino-4-(3-(6-(dimethylamino)-2-azaspiro[3.3]heptan-2-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		520
148B [3]	2-Amino-5-fluoro-4-(5-fluoro-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile		505

120C	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(methyl(oxetan-3-ylmethyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
121C	2-Amino-7-fluoro-4-(5-fluoro-3-((1R,5R)-2-methyl-2,6-diazabicyclo[3.2.0]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		492
256D	2-Amino-7-fluoro-4-(5-fluoro-3-((S)-3-(((S)-2-hydroxypropyl)(methyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
257D	2-Amino-7-fluoro-4-(5-fluoro-3-(5-methyldihydro-1H,4H-3a,6a-(methanooxymethano)pyrrolo[3,4-c]pyrrol-2(3H)-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		548

258D [4]	2-Amino-5-fluoro-4-(5-fluoro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 1		521
259D [4]	2-Amino-5-fluoro-4-(5-fluoro-3-((2S,3S)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)benzo[b]thiophene-3-carbonitrile, Atropisomer 2		521
260D [5]	2-Amino-4-(5-chloro-3-(1-methyl-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Diastereomer 1		522
261D [5]	2-Amino-4-(5-chloro-3-(1-methyl-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Diastereomer 2		522

262D [5]	2-Amino-4-(5-chloro-3-(1-methyl-1,6-diazaspiro[3.4]octan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Diastereomer 3		522

[1] Prep-HPLC; C18, 35-70% Acetonitrile in (20 mM ammonium bicarbonate in pH 9 buffer), 40 mL/min

[2] Prep-Chiral-SFC; Phenomenex Lux Cellulose-4, 30 x 100 mm, 40% MeOH in CO_2; the chiral purification was performed on Example 141B. Example 142B was the second isomer to elute, and was assigned (R) stereochemistry after analysis of Example 140B (known (S) stereochemistry) matched the first isomer to elute.

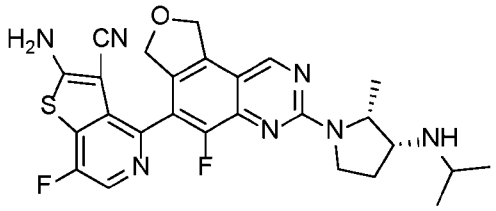
[3] Single atropisomer (from precursor in Preparation 14B)

[4] Prep-Chiral-HPLC; Chiralpak-ID, 30 x 250 mm, 70% Hexanes (with 10 mM ammoniated methanol) : 30% EtOH, 40 mL/min

[5] Diastereomer refers to each compound being a single atropisomer and a single spiro center. Prep-Chiral-HPLC; Phenomenex Lux Cellulose-4, 30 x 150 mm, 10-60% 1:1 MeOH:EtOH in Heptane, 37.5 mL/min, the first eluting peak contained Examples 260D and 261D, the second eluting peak contained Example 262D and the fourth diastereomer. Examples 260D and 261D were further separated with Prep-Chiral-SFC; Phenomenex Lux Cellulose-3, 30 x 100 mm, 15% (MeOH w/ 0.1% isopropylamine) in CO_2, Example 260D was the first eluting peak. Example 262D and the fourth diastereomer were further separated with Prep-Chiral-HPLC; Phenomenex Lux i-Cellulose-5, 30 x 150 mm, 10-100% (Isopropanol w/ 0.1% isopropylamine) in Heptane, 34.5 mL/min, Example 262D was the first eluting peak.

Example 263D

2-Amino-7-fluoro-4-(5-fluoro-3-((2R,3R)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile



[0360] *tert*-Butyl (4-(3-((2R,3R)-3-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (0.150 g, 0.259 mmol),

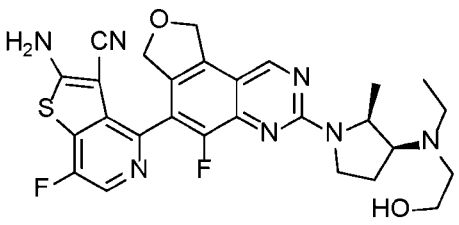
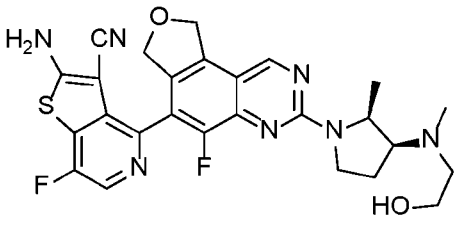
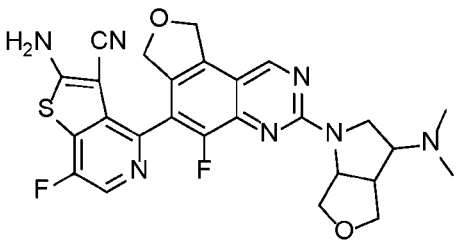
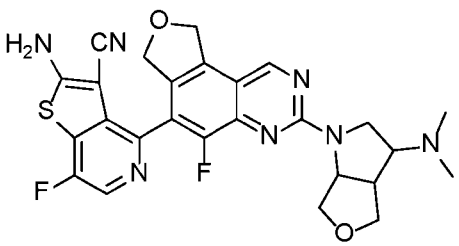
acetone (0.038 mL, 0.518 mmol), and soidum triacetoxyborohydride (0.110 g, 0.518 mmol) were dissolved in MeOH (8 mL) and acetic acid (2 mL). The reaction mixture was heated at 50 °C for 18 h. Additional acetone (0.038 mL, 0.518 mmol), and soidum ttriacetoxyborohydride (0.110 g, 0.518 mmol) were added. The reaction mixture was heated at 50 °C for 18 h, then concentrated under reduced pressure and diluted with saturated aqueous sodium bicarbonate (20 mL). The mixture was extracted with EtOAc (3 x 40 mL). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on silica, eluting with 0-20% MeOH in DCM to obtain the BOC-protected intermediate, *tert*-butyl (3-cyano-7-fluoro-4-(5-fluoro-3-((2R,3R)-3-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridin-2-yl)carbamate.

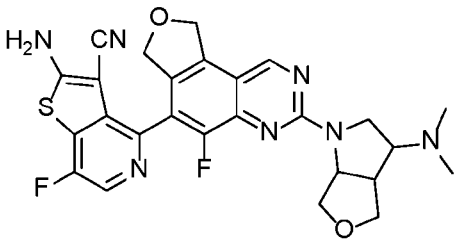
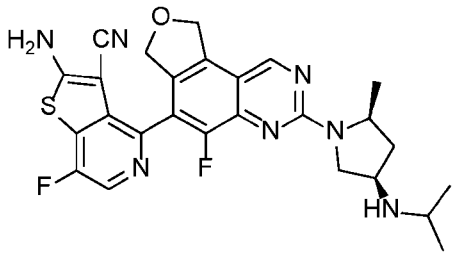
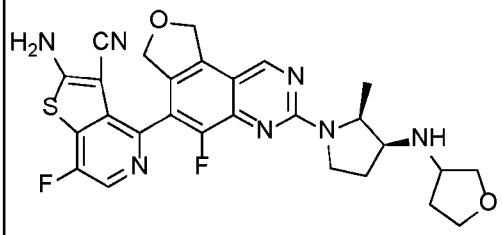
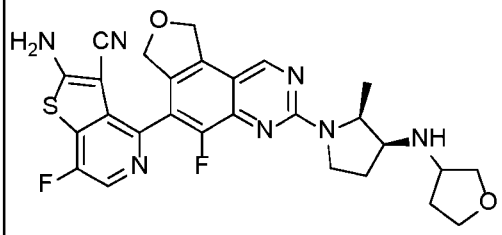
[0361] The intermediate was dissolved in DCM (5 mL) and treated with TFA (3 mL). The reaction mixture was heated at 38 °C for 1 h, then concentrated under reduced pressure. The residue was purified by reversed phase purification, eluting with 0-100% acetonitrile in 10 mM aqueous ammonium (with 5% MeOH), to give the title compound (0.022 g, 15%) as a yellow solid. MS (ES) *m/z*=522 (M+1).

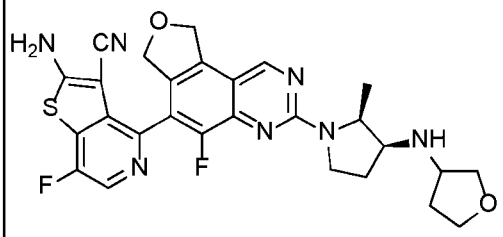
[0362] The following compounds in Table 30 were prepared in similar manner as described in Example 263D. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 30:

Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)

264D	2-Amino-4-(3-((2S,3S)-3-(ethyl(2-hydroxyethyl)amino)-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		552
265D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-3-((2-hydroxyethyl)(methyl)amino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		538
266D	2-Amino-4-(3-(3-(dimethylamino)hexahydro-1H-furo[3,4-b]pyrrol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile		536
267D [1]	2-Amino-4-(3-(3-(dimethylamino)hexahydro-1H-furo[3,4-b]pyrrol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		536

268D [1]	2-Amino-4-(3-(3-(dimethylamino)hexahydro-1H-furo[3,4-b]pyrrol-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		536
269D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,4R)-4-(isopropylamino)-2-methylpyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		522
270D	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-((tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile		550
271D [2]	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-((tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		550

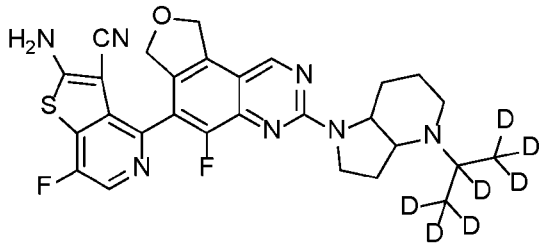
272D [2]	2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-((tetrahydrofuran-3-yl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		550

[1] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-3, 30 x 150 mm, 20-100% 1:1 MeOH:EtOH in Heptane, 40 mL/min

[2] Prep-Chiral-HPLC; Phenomenex Lux i-Amylose-1, 30 x 150 mm, 18-90% (1:1 MeOH:EtOH w/ 0.1% isopropylamine) in Heptane, 60 mL/min

Example 273D

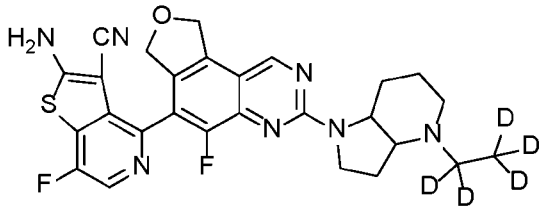
2-Amino-7-fluoro-4-(5-fluoro-3-(4-(propan-2-yl-d7)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile



[0363] A solution of 2-amino-7-fluoro-4-(5-fluoro-3-(octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile (50wt%, 0.045 g, 0.045 mmol) in acetonitrile was treated with diisopropylethylamine (0.039 mL, 0.22 mmol) and 2-iodopropane-1,1,1,2,3,3,3-d7 (0.0045 mL, 0.045 mmol). The reaction mixture was heated at 60 °C for 1 h, 70 °C for 3 days, then concentrated under reduced pressure. The residue was purified by reversed phase purification, eluting with acetonitrile in aqueous ammonium bicarbonate buffer, to give the title compound (0.018 g, 66%) as a yellow solid. MS (ES) *m/z*=555 (M+1).

Example 274D

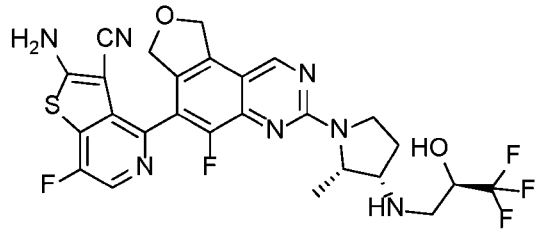
2-Amino-4-(3-(4-(ethyl-d5)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluorothieno[3,2-c]pyridine-3-carbonitrile



[0364] 1-Iodoethane-1,1,2,2,2-d5 was used in a manner analogous to the method of Example 273D to afford the title compound (0.034 g, 77%) as a yellow solid. MS (ES) *m/z*=539 (M+1).

Example 122C

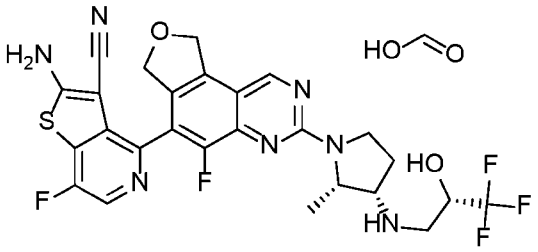
2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(((R)-3,3,3-trifluoro-2-hydroxypropyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile



[0365] A solution of *tert*-butyl (4-(3-((2S,3S)-3-amino-2-methylpyrrolidin-1-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluorothieno[3,2-c]pyridin-2-yl)carbamate (0.150 g, 0.259 mmol) and (R)-2-(trifluoromethyl)oxirane (0.029 g, 0.259 mmol) in isopropanol (4 mL) was heated to 75 °C for 8 h, then cooled to RT. The material was purified by reversed phase purification, eluting with 10% to 100% ACN in water (both with 0.1% formic acid), to give the title compound (0.0054 g, 3.4%) as a yellow solid. MS (ES) *m/z*=592 (M+1).

Example 275D

2-Amino-7-fluoro-4-(5-fluoro-3-((2S,3S)-2-methyl-3-(((S)-3,3,3-trifluoro-2-hydroxypropyl)amino)pyrrolidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)thieno[3,2-c]pyridine-3-carbonitrile formic acid



[0366] (S)-2-(Trifluoromethyl)oxirane was used in a manner analogous to the method of Example 122C to afford the title compound (0.0086 g, 5%). MS (ES) *m/z*=592 (M+1).

Biological Assays

[0367] The following assays demonstrate that the exemplified compounds are potent inhibitors of Kras G12C, G12D, and/or G12V and inhibit growth of certain tumors *in vitro* and/or *in vivo*.

PANC-1 Cellular Active RAS GTPase ELISA (KRas G12D Mutation)

[0368] The purpose of this assay is to measure the ability of test compounds to inhibit constitutive RAS GTPase activity in human PANC-1 (RRID:CVCL_0480) pancreatic ductal adenocarcinoma cells (Supplier: ATCC#CRL-1469). The RAS GTPase ELISA kit (Active Motif Cat# 52097) contains a 96-well glutathione-coated capture plate and kit-supplied Glutathione-S-Transferase (GST)-fused to Raf-Ras Binding Domain (RBD) protein. Activated pan-RAS (GTP-bound) in cell extracts specifically bind to the Raf-RBD. Bound RAS is detected with a primary Ras antibody that recognizes human K-Ras (and H-Ras). An HRP-conjugated anti-rat IgG secondary antibody recognizes the primary antibody, and a development substrate solution facilitates a chemiluminescent readout.

[0369] PANC-1 cells are plated at a concentration of 75,000 cells/well in 80 µL complete media (DMEM, high-glucose, L-glutamine, GIBCO; 10% heat-inactivated fetal bovine serum, GIBCO) and incubated overnight at 37 °C/5% CO_2. Approximately 24 hours later, 20 µL of (1:3) serially-diluted (in complete media) test compound (1-50 µM top concentration) and 20 µL of serially-diluted (in complete media) controls (Maximum signal wells: 0.5 % DMSO and Minimum signal wells: 10 µM reference positive control compound) are added to the cell plate and incubated for 2 hours at 37 °C/5 % CO_2. Complete Lysis/Binding Buffer is prepared containing Protease Inhibitor cocktail (PIC) and stored on ice. One hour before cell plate incubation is completed, GST-Raf-RBD is diluted in

lysis/binding buffer, and 50 µL of mixed buffer per well is added to the supplied opaque white ELISA assay plate and is incubated for a minimum of 1 hour at 4 °C, with gently rocking. After 2 hours, the cells are washed with 100 µL ice-cold Ca2+/Mg2+-free PBS and lysed with 100 µL of kit supplied lysis/binding buffer (AM11). After 30-50 minutes of vigorous plate shaking at ambient temperature, cell plate is centrifuged at 410xg (approx. 1500 rpm) for 10 minutes. Wash buffer diluted to 1X with ultrapure H_2O and 0.2µm filtered is prepared at ambient temperature during the centrifugation step and then used to wash (3 x 100 µL) the GST-Raf-RBD coated assay plate. Next, 50 µL of cell lysate is added to the GST-Raf-RBD coated assay plate and incubated for 1 hour at ambient temperature with gentle shaking. During this incubation period, 1X Antibody Binding Buffer is prepared from thawed concentrate. The assay plate is washed 3 x 100 µL with 1X Wash Buffer, and then 50 µL of Primary RAS Antibody (kit supplied #101678), diluted 1:500 in 1x Antibody Binding buffer, is added. After a one hour of ambient incubation with gentle shaking, the assay plate is washed 3 x 100 µL with 1X Wash Buffer. Subsequently, 50 µL of Anti-rat HRP-conjugated IgG secondary antibody (0.25 µg/ µL) (diluted 1:5000 in 1X Antibody Binding buffer) is added to each well of the assay plate and incubated an additional hour at ambient temperature with gentle shaking. Finally, the assay plate is washed 4 x 100 µL with 1X Wash buffer, followed by addition of 50 µL of mixed ambient temperature chemiluminescent working solution (combination of Reaction buffer with a chemiluminescence substrate). Data from each well's luminescent emission is recorded with a 2104 EnVision™ Plate Reader (Perkin Elmer) using a luminescence program optimized for the assay plate dimensions.

[0370] The signal is converted to percent inhibition using the following equation: % Inhibition = 100 – [(Test Compound Signal – Median Minimum Signal) / (Median Maximum Signal – Median Minimum Signal) x 100]. The Maximum signal is a control well without inhibitor (DMSO). The Minimum signal is a control well containing a reference inhibitor sufficient to fully inhibit activity. The IC_{50} is determined by fitting the percent inhibition at each inhibitor concentration to the four parameter nonlinear logistic equation using Genedata Screener®, v17: y = (A+((B-A)/(1+((x/C)^D)))) where, y = % inhibition, A = minimum asymptote, B = maximum asymptote, C = relative IC_{50} or the inhibitor concentration producing 50% inhibition within the fitted range of both asymptotes, and D = Hill Slope.

[0371] In the above assay, compounds of Examples 1-3, 5-9, 11-18, 37, 1A-5A, 7A-11A, 13A-22A, 25A, 30A, 42A, 52A, 55A, 58A, 65A, 76A, 1B, 20B, 21B, and 105B were tested and all exhibited an

ability to inhibit constitutive RAS GTPase activity indicating inhibition of KRas G12D mutant enzyme with a relative IC_{50} of <100 nM. This data shows that compounds of Formula I as described herein are potent inhibitors of KRAS-GTP activity in this human pancreatic cancer cell culture demonstrating the ability to inhibit KRas G12D mutants.

MKN-45 Cellular Active RAS GTPase ELISA (KRas Wild-type)

[0372] The purpose of this assay is to measure the ability of test compounds to inhibit constitutive RAS GTPase activity in human MKN-45 gastric adenocarcinoma cell (Supplier: JCRB, SupplierID: JCRB 0254, Lot:05222009). The RAS GTPase ELISA kit (Active Motif Cat# 52097) contains a 96-well glutathione-coated capture plate and kit-supplied Glutathione-S-Transferase (GST)-fused to Raf-Ras Binding Domain (RBD) protein. Activated pan-RAS (GTP-bound) in cell extracts specifically bind to the Raf-RBD. Bound RAS is detected with a primary Ras antibody that recognizes human K-Ras (and H-Ras). An HRP-conjugated anti-rat IgG secondary antibody recognizes the primary antibody, and a development substrate solution facilitates a chemiluminescent readout.

[0373] MKN-45 cells are plated at a concentration of 75,000 cells/well in 80 µL complete media (DMEM, high- glucose, L-glutamine, GIBCO; 10% heat-inactivated fetal bovine serum, GIBCO) and incubated overnight at 37 °C/5% CO_2. Approximately 24 hours later, 20 µL of (1:3) serially-diluted (in complete media) test compound (1-10 µM top concentration) and 20 µL of serially-diluted (in complete media) controls (Maximum signal wells: 0.1 % DMSO and Minimum signal wells: 10 µM reference positive control compound) are added to the cell plate and incubated for 2 hours at 37 °C/5 % CO_2. Complete Lysis/Binding Buffer is prepared containing Protease Inhibitor cocktail (PIC) and stored on ice. One hour before cell plate incubation is completed, GST-Raf-RBD is diluted in lysis/binding buffer, and 50 µL of mixed buffer per well is added to the supplied opaque white ELISA assay plate and is incubated for a minimum of 1 hour at 4 °C, with gently rocking. After 2 hours, the cells are washed with 100 µL ice-cold Ca2+/Mg2+-free PBS and lysed with 100 µL of kit supplied lysis/binding buffer (AM11). After 30-50 minutes of vigorous plate shaking at ambient temperature, cell plate is centrifuged at 410xg (approx. 1500 rpm) for 10 minutes. Wash buffer diluted to 1X with ultrapure H_2O during the centrifugation step and then used to wash (3 x 100 µL) the GST-Raf-RBD coated assay plate. Next, 50 µL of cell lysate is added to the GST-Raf-RBD coated assay plate and incubated for 1 hour at ambient temperature with gentle shaking. During this incubation period, 1X

Antibody Binding Buffer is prepared from thawed concentrate. The assay plate is washed 3 x 100 µL with 1X Wash Buffer, and then 50 µL of Primary RAS Antibody (kit supplied #101678), diluted 1:500 in 1x Antibody Binding buffer, is added. After a one hour of ambient incubation with gentle shaking, the assay plate is washed 3 x 100 µL with 1X Wash Buffer. Subsequently, 50 µL of Anti-rat HRP-conjugated IgG secondary antibody (0.25 µg/ µL) (diluted 1:5000 in 1X Antibody Binding buffer) is added to each well of the assay plate and incubated an additional hour at ambient temperature with gentle shaking. Finally, the assay plate is washed 4 x 100 µL with 1X Wash buffer, followed by addition of 50 µL of mixed ambient temperature chemiluminescent working solution (combination of Reaction buffer with a chemiluminescence substrate). Data from each well's luminescent emission is recorded with a 2104 EnVision™ Plate Reader (Perkin Elmer) using a luminescence program optimized for the assay plate dimensions.

[0374] The signal is converted to percent inhibition using the following equation: % Inhibition = 100 – [(Test Compound Signal – Median Minimum Signal) / (Median Maximum Signal – Median Minimum Signal) x 100]. The Maximum signal is a control well without inhibitor (DMSO). The Minimum signal is a control well containing a reference inhibitor sufficient to fully inhibit activity. The IC_{50} is determined by fitting the percent inhibition at each inhibitor concentration to the four parameter nonlinear logistic equation using Genedata Screener®, v17: y = (A+((B-A)/(1+((x/C)^ D)))) where, y = % inhibition, A = minimum asymptote, B = maximum asymptote, C = relative IC_{50} or the inhibitor concentration producing 50% inhibition within the fitted range of both asymptotes, and D = Hill Slope.

[0375] Compounds of Examples 1-3, 5-9, 11-18, 37, 1A, 3A, 4A, 6A, 7A, 9A, 10A, 13A-17A, 19A, 20A, 22A-25A, 1B-5B, 7B-11B, 13B, 14B, 17B, and 20B-23B were tested in both assays above (PANC-1 Cellular Active RAS GTPase ELISA and MKN-45 Cellular Active RAS GTPase ELISA) and all showed a significant (i.e., greater than 10-fold) selective inhibition preference for KRas G12D mutant over KRas wild-type.

Cellular Phospho-ERK AlphaLISA® Assay for KRAS Inhibition

[0376] The purpose of these assays is to quantify the ability of test compounds to selectively inhibit KRAS signaling in cells with amplified KRAS and expressing activating KRAS G12 mutations (Table 31). Cancer cell lines used in this study were selected based on the presence of homozygous activating

KRAS G12 mutations, or amplification of the KRAS gene. In addition, these assays were performed in a set of RAS-less mouse embryonic fibroblast (MEF) cells which were engineered to only express KRAS wild type, HRAS, and NRAS, respectively (Table 31). MEF cells were used to confirm KRAS selectivity of the test compounds.

Table 31: Cell Line Information

Cell Line Name	RAS Mutation/Features	Assay Seeding Density (Cells/Well)
MKN45	WT KRAS Amplification / Human Gastric Cancer	20,000
SW620	KRAS G12V/ Human Colorectal Cancer	20,000
HPAC	KRAS G12D/ Human Pancreatic Cancer	2,500
NCI-1373	KRAS G12C/ Human Lung Cancer	5,000
MEF-NRAS	RAS-less MEFs Expressing NRAS only	20,000
MEF-HRAS	RAS-less MEFs Expressing HRAS only	10,000
MEF-KRAS	RAS-less MEFs Expressing KRAS only	2,500

[0377] The compounds' activity is determined by measuring changes in the phosphorylation levels of the downstream effector Extracellular Signal-regulated Kinase-1 and 2 (ERK1/2) in the compound treated cells. Phosphorylation levels of ERK-1/2 are measured using the AlphaLISA® SureFire® Ultra™ p-ERK 1/2 (Thr202/Tyr204) Assay Kit (#ALSU-PERK-A50K, PerkinElmer® Waltham, MA). The AlphaLISA® assay is a quantitative sandwich immunoassay that can be used to detect phosphorylation of target proteins from cellular lysates using bead-based Alpha technology. The assay kit contains two antibodies, one that binds the phospho-Thr202/Tyr204 epitope on ERK-1/2, and another one that recognizes a separate site on the protein. One of these antibodies is biotinylated and associated with streptavidin-coated Alpha Donor beads, the other antibody is conjugated to AlphaLISA® Acceptor beads. When ERK-1/2 is phosphorylated in cellular lysate, the Donor and

Acceptor beads are brought into proximity with each other. When the Donor bead is excited by 600 nm wavelength light, a photosensitizer inside the bead converts ambient oxygen to an excited singlet state. When the Acceptor bead is within 200 nm of this reaction, the singlet oxygen reacts with the Acceptor leading to a chemiluminescent emission. The amount of light measured is proportional to the amount of phosphorylated ERK-1/2 in the lysate. The AlphaLISA® SureFire® Ultra™ p-ERK 1/2 (Thr202/Tyr204) Assay Kit contains AlphaLISA® antibody-conjugated Donor and Acceptor Beads, Lysis buffer concentrate, and a set of proprietary buffers (Activation Buffer, Reaction Buffer 1, Reaction Buffer 2, and Dilution Buffer).

[0378] To perform the assays, test compounds and controls are acoustically dispensed (Labcyte ECHO®, San Jose, CA) into a white 384-well assay plate (Proxiplate-384, PerkinElmer #6008280) in a 10-point 3-fold dilution series in 30 nL DMSO. Cells are then added to the assay plate in 8 µL per well assay medium (HBSS, Sigma #55021C, 10% FBS, GIBCO # 10082-147) at a cell line specific density (Table 31). The final compound concentrations range from 0.5 to 10,000 nM and the final DMSO concentration is 0.375% in each well. Maximum signal control wells contain 0.375% DMSO only (negative control), and minimum signal control wells contain 10,000 nM control compound (positive control). Cells in suspension are incubated with the test and reference compounds for 2 h at 37°C/5 % CO_2. Following the 2 h incubation, cells are lysed by adding 2 µL of the AlphaLISA® Lysis buffer concentrate (5X) supplemented with protease/phosphatase inhibitor cocktail (Thermo Scientific # 78442). The assay plate is covered with an opaque lid and shaken at 750 rpm on a multi-plate shaker (Heidolph, Schwabach, Germany) for 30 min at room temperature to induce cell lysis. During the lysis, the AlphaLISA® Acceptor beads are diluted 1:50 in a prepared buffer mixture (1:1 AlphaLISA® Reaction Buffers 1 and 2 with a 1:25 dilution of AlphaLISA® Activation Buffer). Following cell lysis, plates are centrifuged briefly, and 5 µL per well prepared Acceptor beads are added. The plate is then covered and incubated in the dark for 2 h at room temperature. During the Acceptor bead incubation, Donor beads are prepared by diluting the Alpha streptavidin Donor beads 1:50 in AlphaLISA® Dilution buffer. Following the Acceptor bead incubation, 5 µL per well of Donor bead mixture is added to the plates. Plates are then covered and allowed to incubate in the dark at room temperature for 2 h. After this incubation period, the AlphaLISA signal is read using a PHERAstar® FSX multimode plate reader (BMG Labtech, Ortenberg, Germany) equipped with an AlphaLISA® compatible optics cube.

[0379] Raw signal obtained from the AlphaLISA® assay is analyzed using Genedata Screener® 17.0.3. Within the program, data is normalized to 32 wells treated with inhibition control (max inhibition/positive control) and 32 wells treated with 0.375% DMSO only (minimum inhibition/negative control) to calculate the % Activity of the compound:

$$\%\ Activity = 100x\ (1 - \frac{(treated\ value - positive\ control)}{(negative\ control - positive\ control)})\ \ eq.\ 1$$

% Activity values are fit to a four-parameter non-linear logistic equation using Genedata Screener® 17.0.3. to -determine IC_{50} values:

$$y = Bottom + \frac{Top - Bottom}{1 + \left(\frac{10^{Log(IC_{50})}}{10^{x}}\right)^{h}}\ \ eq.\ 2$$

Where y = % Activity, Bottom = minimum asymptote, Top = maximum asymptote, x = compound concentration, IC_{50} = the compound concentration where half maximal activity is achieved, and h = the Hill Coefficient.

[0380] In the above assays, compounds of Examples indicated herein were tested and exhibited an ability to reduce levels of phosphorylated ERK-1/2 in cells expressing KRAS and KRAS variants indicating inhibition of constitutive RAS activity in cells expressing KRAS G12C (Examples 1, 3, 8, 9, 19-30, 32-36, 29A-44A, 47A-70A, 72A-79A, 82A-84A, 28B-30B, 33B-94B, 96B-120B, 122B-148B, 1C-49C, 51C, 53C, 54C, 57C, 58C, 60C, 61C, 65C, 67C, 69C-71C, 73C-79C, 81C, 83C-88C, 90C, 92C, 94C-122C, 2D, 3D, 5D, 6D, 8D-10D, 12D, 14D, 16D-99D, 101D-126D, 128D-195D, 197D-201D, 203D-207D, 209D-236D, 239D, 240D, 242D, 244D, 246D-248D, 250D-252D, 254D, 256D-259D, and 262D-275D), KRAS G12D (Examples 1-3, 5-9, 11-15, 19-30, 32-37, 25A, 29A-44A, 47A-67A, 70A, 73A, 74A, 76A, 78A, 79A, 82A-84A, 19B, 28B-30B, 33B-45B, 47B-51B, 53B-65B, 67B-94B, 96B-108B, 110B-148B, 1C-27C, 29C-49C, 51C, 53C, 54C, 57C, 58C, 60C, 61C, 65C, 67C, 69C, 70C, 73C, 75C-79C, 81C, 83C-88C, 90C, 92C, 94C-122C, 2D, 3D, 5D, 6D, 8D, 10D, 12D, 14D, 16D, 18D-20D, 22D-46D, 48D-73D, 75D-81D, 83D-95D, 98D, 99D, 101D, 103D-139D, 141D-159D, 161D, 163D, 165D-178D, 180D, 181D, 183D-195D, 197D-201D, 203D-207D, 209D-236D, 239D, 240D, 242D, 244D, 246D-248D, 250D, 252D, 254D, 256D-259D, and 262D-275D), KRAS G12V (Examples 9, 19-30, 32-36, 29A-44A, 47A-62A, 64A-70A, 72A-74A, 76A, 78A, 79A, 82A-84A, 28B-30B, 33B-53B, 55B-88B, 90B-94B, 96B-107B, 110B-120B, 122B-136B, 138B-146B, 148B, 1C-27C, 29C-49C, 51C, 53C, 54C, 57C, 58C, 60C, 61C, 65C, 67C, 69C, 70C, 73C, 75C-78C, 81C, 83C-88C,

92C, 94C-120C, 122C, 2D, 3D, 6D, 8D, 10D, 12D, 14D, 16D, 18D-46D, 48D-73D, 75D-81D, 83D-96D, 99D, 101D, 104D-133D, 135D-139D, 141D-143D, 145D-159D, 161D, 163D, 165D-173D, 175D, 177D, 178D, 180D, 183D-195D, 197D-203D, 206D, 207D, 209D, 211D-236D, 240D, 242D, 244D, 246D-248D, 250D, 252D, 254D, 256D-259D, and 262D-275D), or KRAS WT (Examples 2, 3, 9, 19-30, 32-36, 29A-44A, 47A-70A, 73A, 74A, 76A, 78A, 79A, 82A-84A, 28B-30B, 33B-88B, 90B-94B, 96B-108B, 110B-120B, 122B-148B, 1C-49C, 51C, 53C, 54C, 57C, 58C, 60C, 61C, 65C, 67C, 69C, 70C, 73C-79C, 81C, 83C-88C, 90C, 92C, 94C-122C, 2D, 3D, 5D, 6D, 8D-10D, 12D, 14D, 16D-46D, 48D-73D, 75D-81D, 83D-99D, 101D-143D, 145D-195D, 197D-207D, 209D-236D, 239D, 240D, 242D, 244D, 246D-248D, 250D, 252D, 254D, 256D-259D, and 262D-275D), with a relative IC50 of <500 nM. Compounds of Examples 1, 2, 4-15, 21, 22, 24-26, 29-34, 37, 29A, 34A-38A, 41A, 43A-47A, 53A, 59A, 60A, 62A-64A, 69A, 71A, 72A, 75A, 77A, 80A, 81A, 18B, 19B, 31B, 32B, 34B, 35B, 39B-43B, 46B, 48B, 51B-54B, 57B, 60B, 63B, 65B, 66B, 68B, 70B, 73B-77B, 83B, 86B, 87B, 89B, 93B, 95B, 98B, 99B, 101B-103B, 108B, 109B, 112B, 115B-121B, 123B, 124B, 136B, 140B-142B, 144B, 147B, 2C, 8C, 14C, 16C, 17C, 20C, 21C, 26C, 28C, 30C, 33C-36C, 38C, 40C, 46C-50C, 52C, 53C, 55C, 56C, 59C, 62C-64C, 66C, 68C, 71C, 72C, 74C, 80C, 82C, 89C, 91C, 93C, 101C, 112C, 113C, 118C, 121C, 1D, 4D, 5D, 7D, 9D, 11D, 13D, 15D, 17D, 18D, 20D-28D, 31D, 33D-35D, 37D, 38D, 40D, 43D, 44D, 46D, 47D, 51D-54D, 56D, 58D-62D, 64D-78D, 80D, 91D, 93D, 96D-106D, 109D-111D, 113D, 114D, 117D, 121D-123D, 126D-128D, 132D-136D, 139D, 140D, 144D, 147D, 148D, 150D, 152D-155D, 157D-162D, 164D, 172D-186D, 188D, 194D, 195D, 199D-210D, 212D, 216D, 218D, 222D, 223D, 225D, 226D, 228D, 229D, 232D, 233D, 237D, 238D, 241D, 243D, 245D, 249D, 251D, 253D, 255D, 259D-261D, 263D, and 268D, were tested in the Mouse Embryonic Fibroblasts cell line assays above (MEF-NRAS, MEF-HRAS) and all exhibited a relative IC50 of >2 μM. Compounds of Examples 8, 9, 19-30, 32-36, 29A-44A, 47A, 49A, 50A, 52A, 54A-69A, 72A, 74A-76A, 78A, 79A, 84A, 28B, 29B, 33B-36B, 39B-53B, 55B-60B, 62B-79B, 82B-87B, 90B, 91B, 96B-103B, 105B-107B, 109B-115B, 117B-120B, 122B-128B, 130B, 131B, 136B, 138B-144B, 147B, 1C-6C, 8C, 9C, 11C-22C, 24C-28C, 30C-38C, 40C-43C, 45C-49C, 51C, 53C, 54C, 57C, 60C, 65C, 67C, 69C, 70C, 73C, 74C, 76C, 77C, 84C, 87C, 88C, 98C, 99C, 101C, 104C-120C, 122C, 2D, 3D, 8D, 10D, 14D, 18D-40D, 42D-46D, 48D-73D, 75D-80D, 83D-87D, 89D-93D, 95D-119D, 121D-145D, 147D-164D, 167D, 168D, 170D-173D, 175D-181D, 183D, 184D, 186D-188D, 190D, 192D-195D, 197D-204D, 206D, 207D, 209D, 212D, 213D, 215D-236D, 240D, 244D,

246D-251D, 254D, 256D, 257D, 259D, 262D-265D, 267D, 268D, 270D-272D, 274D, and 275D were tested in the three assays above (SW620, MEF-NRAS or MEF-HRAS Cellular Phospho-ERK AlphaLISA® Assays) and all showed a significant (i.e., greater than 10-fold) selective inhibition preference for KRas G12V mutant over HRAS and NRAS.

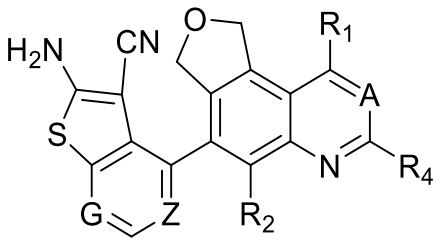
[0381] This data shows that compounds of Formula I as described herein are potent inhibitors of KRAS human cancer cells expressing KRAS demonstrating the ability to inhibit KRAS G12C, G12D or G12V mutants with a significant selective inhibition preference for KRAS mutants over HRAS or NRAS.

Table 32: Abbreviations

KRAS	Kirsten Rat Sarcoma Virus
NRAS	Neuroblastoma RAS Viral Oncogene Homolog
HRAS	Harvey Rat Sarcoma Virus
MEF	Mouse Embryonic Fibroblasts
ERK	Extracellular Signal-Regulated Kinase
AlphaLISA	Alpha-Linked Immunosorbent Assay
DMSO	Dimethyl Sulfoxide
HBSS	Hank's Balanced Salt Solution
FBS	Fetal Bovine Serum
CO_2	Carbon Dioxide

What is Claimed is

1. A compound of the formula:



wherein:

A is -C(H)- or -N-;

Z is -C(R_{3c})- or -N-;

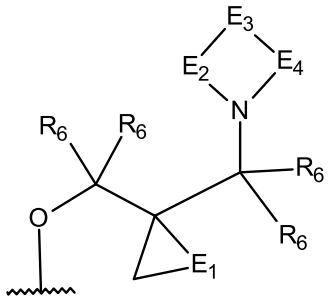
G is -C(R_{3b})- or -N-;

R_1 is H;

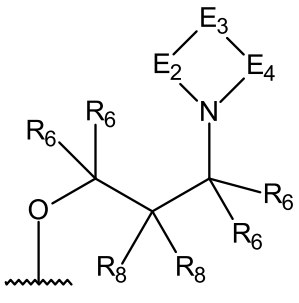
R_2 is H, halogen, or methyl;

R_{3b}, and R_{3c} are each independently H, halogen, or methyl;

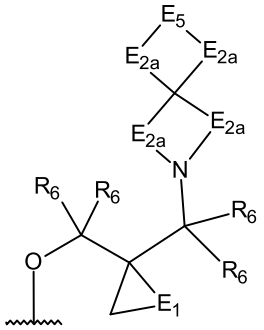
R_4 is a N-linked cyclic amine or a group of the formula



,



, or



;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, morpholine, diazepane, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen; hydroxyl; $-NR_{6a}R_{6a}$; (1-methylpiperidin-4-yl)oxy; C_{1-3} alkoxy optionally substituted with $-NR_{6a}R_{6a}$; C_{1-3} alkyl optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or hydroxyl; an imidazole optionally substituted with a methyl; a monocyclic ring selected from azetidine, piperidine, piperazine, morpholine, oxazepane, or diazepane; a bicycle selected from hexahydro-1H-furo[3,4-c]pyrrole, octahydropyrrolo[3,4-c]pyrrole, or octahydropyrrolo[1,2-a]pyrazine; or a spirocycle selected from 4,7-diazaspiro[2.5]octane, 2-oxa-7-azaspiro[3.5]nonane, 2,6-diazaspiro[3.4]octane, or 2-azaspiro[3.3]heptane; wherein the monocyclic ring is optionally bridged by a C_{1-3} alkylene, and can optionally be substituted with one or more halogen, hydroxyl, -CN, C_{1-3} alkoxy, $-NR_{10}R_{10}$, cyclopropyl, oxetane, $-CO-C_{1-3}$ alkyl, or a C_{1-3} alkyl optionally substituted with hydroxyl, C_{1-3} alkoxy, $-NR_{10}R_{10}$, halogen, or $-CF_3$; and wherein the bicyclo or spirocyclo is each optionally substituted with a methyl or a halogen; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, hexahydro-1H-furo[3,4-b]pyrrole, octahydro-1H-pyrrolo[3,2-b]pyridine, (3as,6as)-tetrahydro-1H,4H-3a,6a-(methanooxymethano)pyrrolo[3,4-c]pyrrole, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, 2-oxa-6-azaspiro[3.4]octane, 2,7-diazaspiro[4.4]nonane, 2-oxa-6-azaspiro[3.4]octane or1-oxa-7-azaspiro[4.4]nonane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$ or hydroxyl;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$;

R_{4b} is H, hydroxyl, or C_{1-3} alkyl;

R_{4c} is independently cyclopropyl, or oxetane;

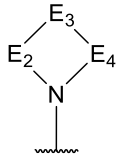
R_{4d} is independently C_{1-3} alkyl;

each R_6 is independently H or deuterium;

each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, a N-methyl pyrrolidine, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, bicyclo[1.1.1]pentan-1-ol, or a C_{1-3} alkyl optionally substituted with one or more deuterium, hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran, -CO-NHMe, or $-CO-NH_2$, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl;

E_1 is $-O-C_{1-3}$ alkylene, or C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl, C_{1-3} alkoxy or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene; and E_3 is -O-, $-CR_7R_7-$, $-NR_9-$, or $-CO-NR_{6a}-$; or



the ring is hexahydro-1H-furo[3,4-c]pyrrole;

each E_{2a} is independently a C_{1-3} alkylene optionally substituted with one or more hydroxyls;

E_5 is -O-, $-CR_7R_7-$, or $-NR_9-$;

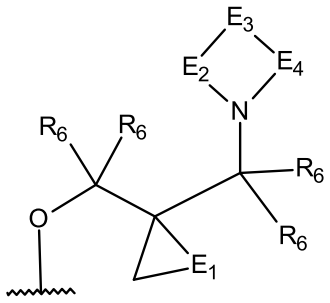
each R_7 is independently H, halogen, CN, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls;

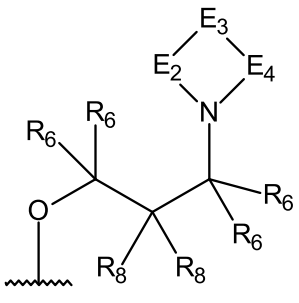
each R_8 is independently a C_{1-3} alkyl;

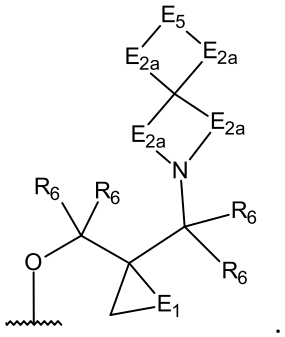
R_9 is each independently H, optionally substituted C_{1-3} alkyl or -CO-C_{1-3} alkyl; wherein the optionally substituted C_{1-3} alkyl is optionally substituted with one or more halogens; and

R_{10} is H or C_{1-3} alkyl optionally substituted with one or more deuterium; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R_4 is a N-linked cyclic amine or a group of the formula



,


, or


;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, morpholine, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, C_{1-3} alkoxy, -$NR_{6a}R_{6a}$, azetidine, piperazine, morpholine, a C_{1-3} alkyl, or an imidazole optionally substituted with a methyl; wherein the azetidine is optionally substituted with hydroxyl or C_{1-3} alkoxy; the piperazine is optionally substituted with a methyl, and the C_{1-3} alkyl is optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or hydroxyl; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-

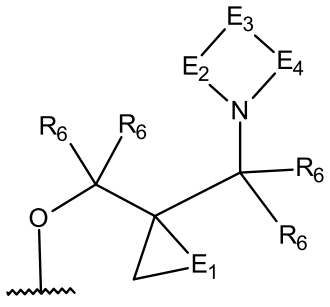
b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, or 2-oxa-6-azaspiro[3.4]octane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$;

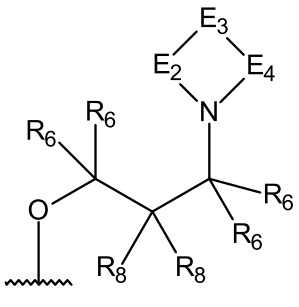
R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$;

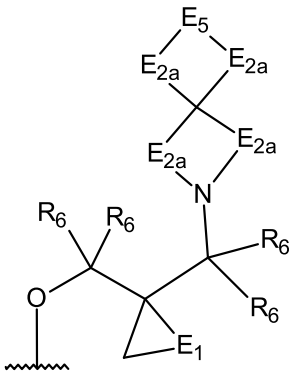
each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, or a C_{1-3} alkyl optionally substituted with one or more hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran,

-CO-NHMe, or $-CO-NH_2$, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl; or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein R_4 is a N-linked cyclic amine or a group of the formula



,


, or


;

wherein the N-linked cyclic amine is a N-linked:

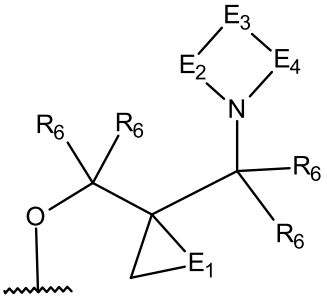
i. azetidine substituted with R_{4a} and R_{4b};

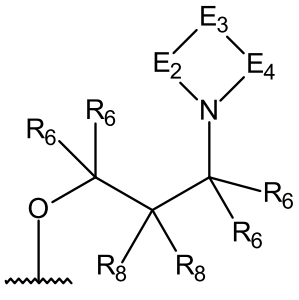
ii pyrrolidine, piperidine, piperazine, morpholine, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, C_{1-3} alkoxy, $-NR_{6a}R_{6a}$, azetidine, a C_{1-3} alkyl, or an imidazole optionally substituted with a methyl; wherein the azetidine is optionally substituted with hydroxyl or C_{1-3} alkoxy; and the C_{1-3} alkyl is optionally substituted with halogen-$NR_{6a}R_{6a}$ or hydroxyl; or

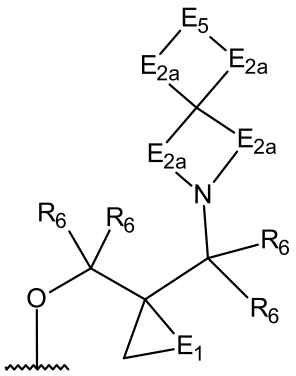
iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-6-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, or 5-azaspiro[2.4]heptane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$; and each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl or a C_{1-3} alkyl optionally substituted with hydroxyl; or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3, wherein R_{3b}, and R_{3c} are each independently H or halogen, and R_4 is a N-linked cyclic amine or a group of the formula



, 

, or 

;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, or morpholine; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, $-NR_{6a}R_{6a}$, imidazole or a C_{1-3} alkyl; wherein the imidazole is optionally substituted with a methyl; and the C_{1-3} alkyl is optionally substituted with $-NR_{6a}R_{6a}$ or hydroxyl; or

iii. octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,4-c]pyrrole, 1,6-diazaspiro[3.3]heptane, or 1,6-diazaspiro[3.4]octane; each of which is optionally substituted with one or more halogen, or a C_{1-3} alkyl;

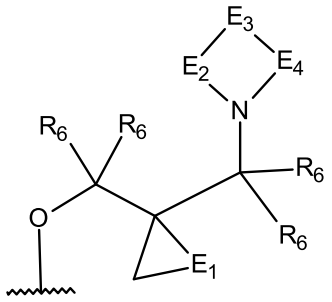
R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, morpholine, wherein the cyclopropyl, azetidine, pyrrolidine or morpholine is optionally substituted with halogen, or $-NR_{6a}R_{6a}$;

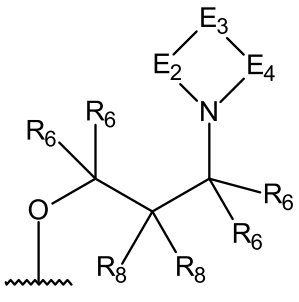
R_{4b} is H, or C_{1-3} alkyl;

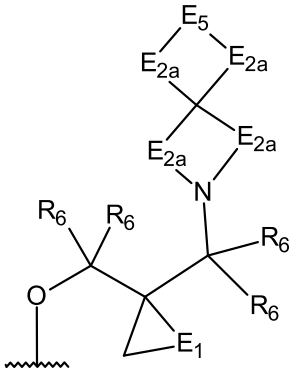
each R_{6a} is independently H or C_{1-3} alkyl;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene; and E_3 is -O-, $-CR_7R_7-$, $-NR_9-$, or $-CO-NR_{6a}-$; or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1-4, wherein R_{3b}, and R_{3c} are each independently H or halogen, and R_4 is a group of the formula



, 

, or 

;

E_1 is C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyls, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene;

E_3 is -O-, $-CR_7R_7$-, $-NR_9$-, or $-CO-NR_{6a}$-;

each R_{6a} is independently H or C_{1-3} alkyl;

each R_7 is independently H, halogen, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls; and

R_9 is each independently H, C_{1-3} alkyl or $-CO-C_{1-3}$ alkyl; or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1-5, wherein G is -N-, or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1-5, wherein G is $-C(R_{3b})$-, or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 7, wherein R_{3b} is F, or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 1-8, wherein Z is -N-, or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1-8, wherein Z is -C(R_{3c})-, or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10, wherein R_{3c} is H or F, or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1-5, 7 or 10, wherein R_{3b}, and R_{3c} are each independently H or halogen, or a pharmaceutically acceptable salt thereof.

13. The compound according to any one of claims 1-12, wherein A is -N-, or a pharmaceutically acceptable salt thereof.

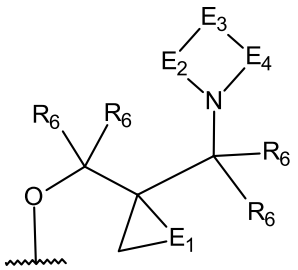
14. The compound according to any one of claims 1-12, wherein A is -C(H)-, or a pharmaceutically acceptable salt thereof.

15. The compound according to any one of claims 1-14, wherein R_2 is F or Cl, or a pharmaceutically acceptable salt thereof.

16. The compound according to any one of claims 1-14, wherein R_2 is F, or a pharmaceutically acceptable salt thereof.

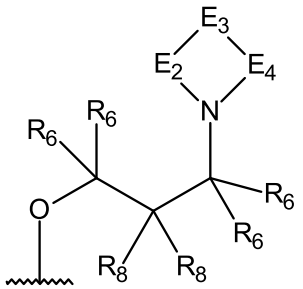
17. The compound according to any one of claims 1-14, wherein R_2 is Cl, or a pharmaceutically acceptable salt thereof.

18. The compound according to any one of claims 1-17, wherein R_4 is



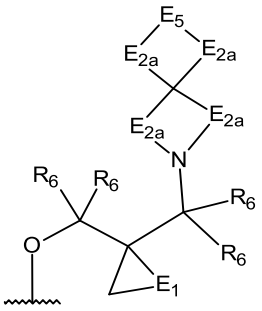
, or a pharmaceutically acceptable salt thereof.

19. The compound according to any one of claims 1-17, wherein R_4 is



, or a pharmaceutically acceptable salt thereof.

20. The compound according to any one of claims 1-17, wherein R_4 is

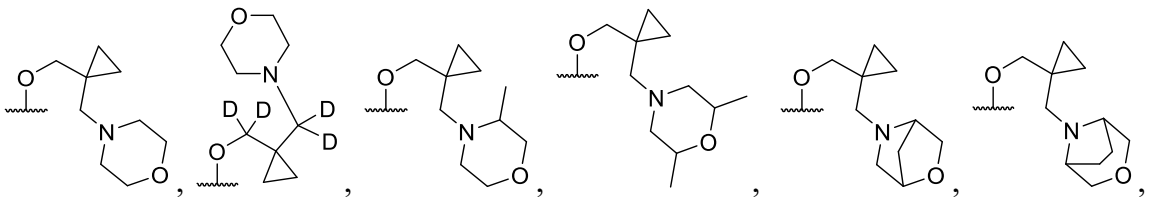


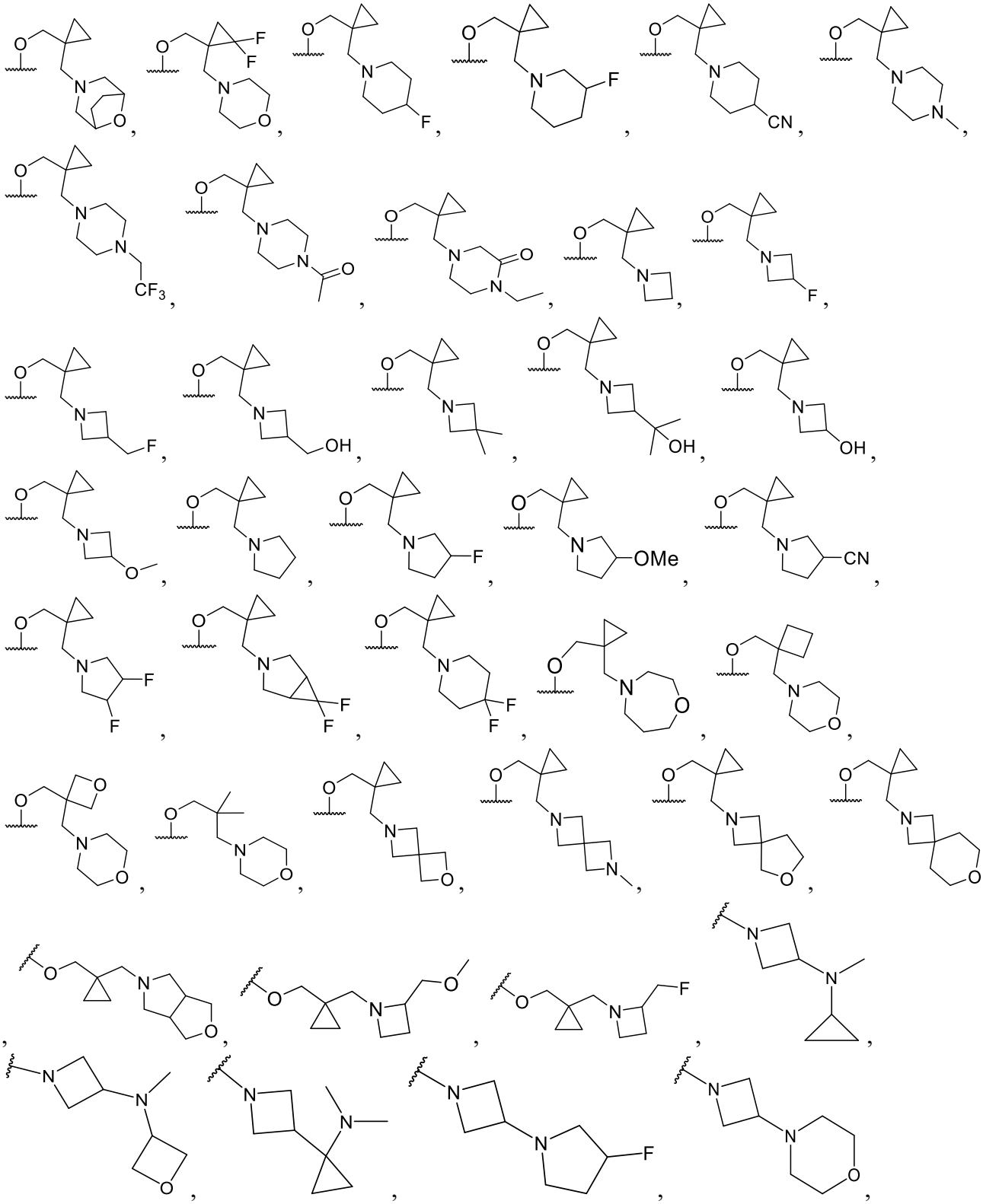
, or a pharmaceutically acceptable salt thereof.

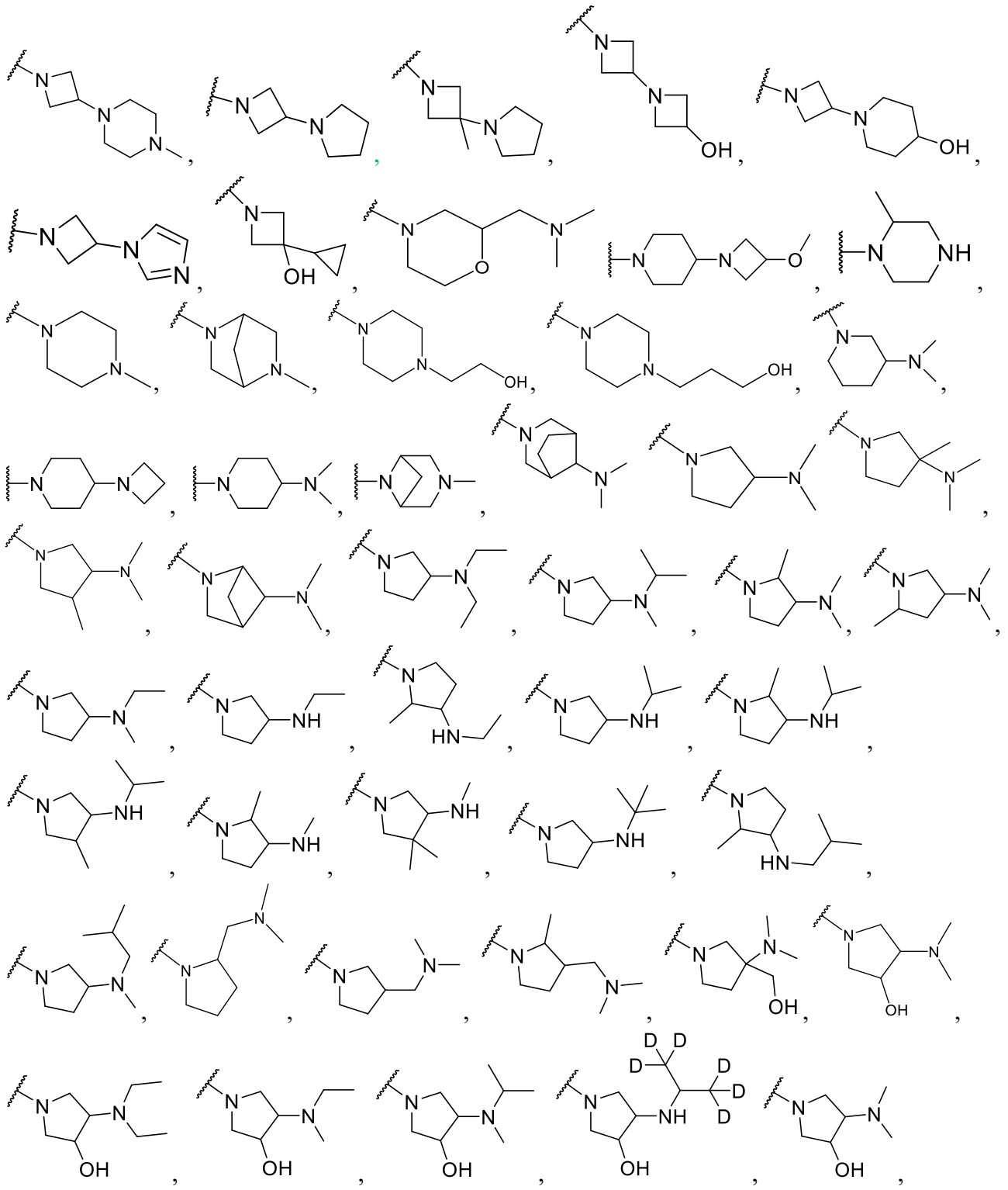
21. The compound according to any one of claims 1-20, wherein each R_6 is H, or a pharmaceutically acceptable salt thereof.

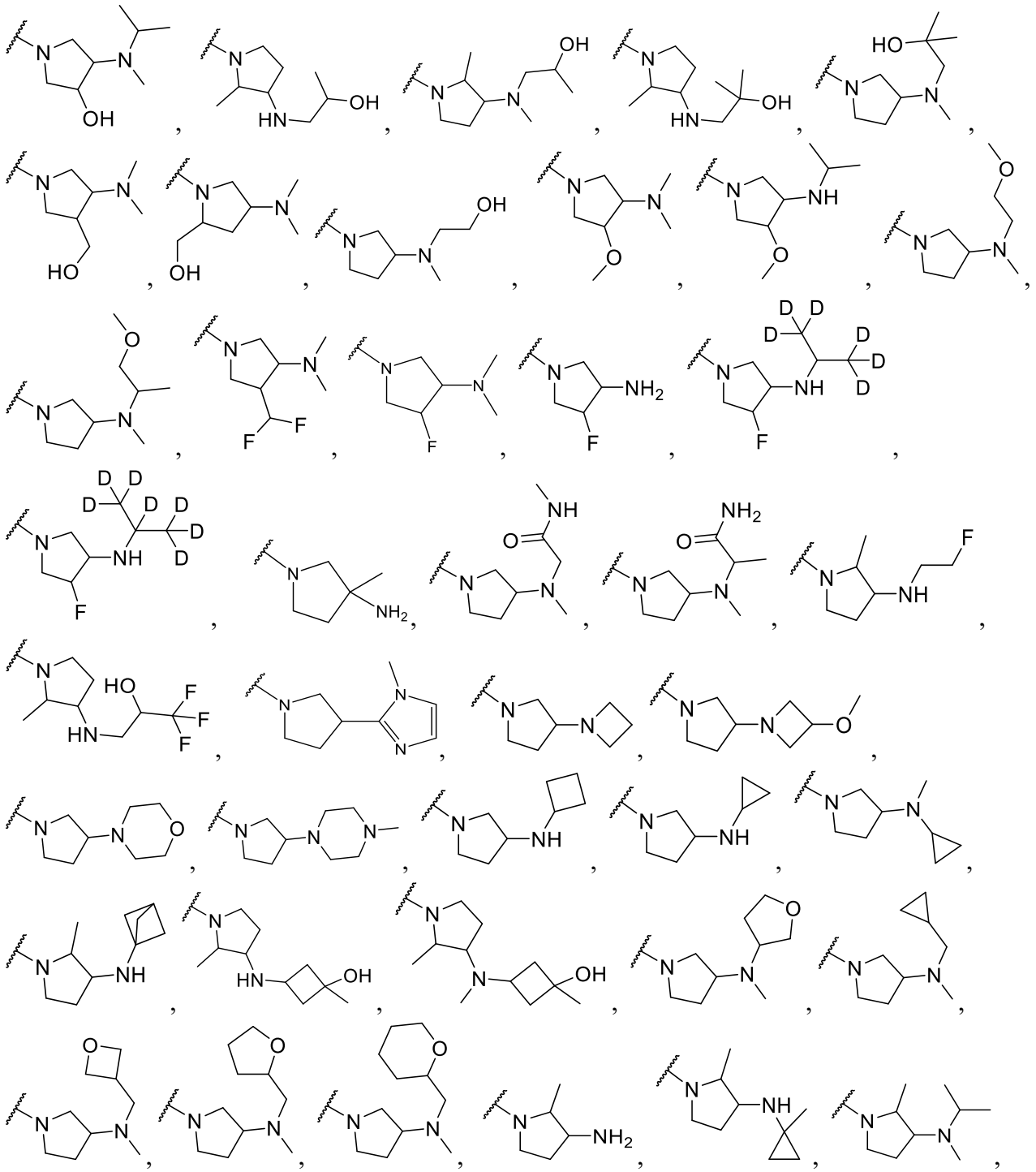
22. The compound according to any one of claims 1-4 and 6-17, wherein R_4 is a N-linked cyclic amine, or a pharmaceutically acceptable salt thereof.

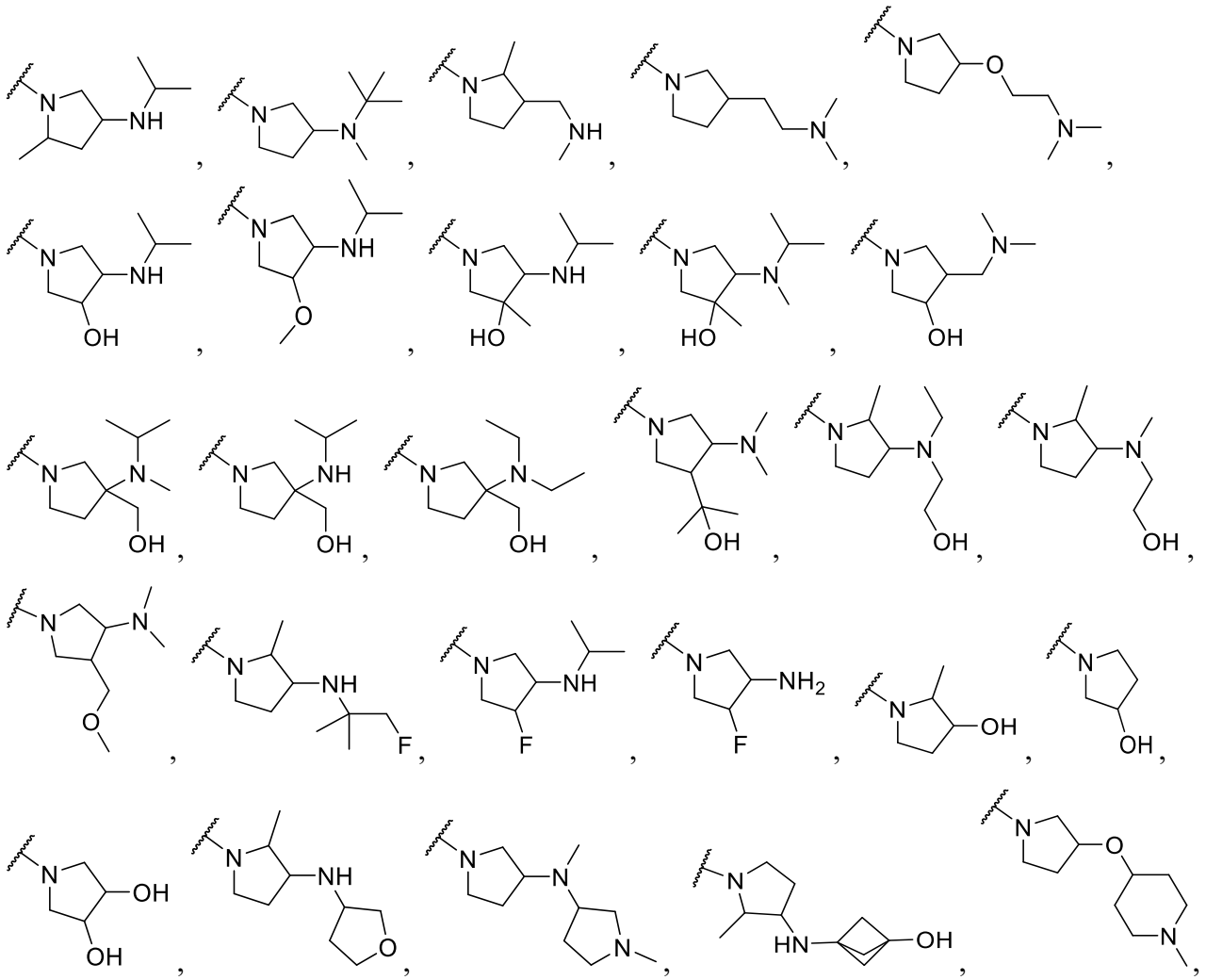
23. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

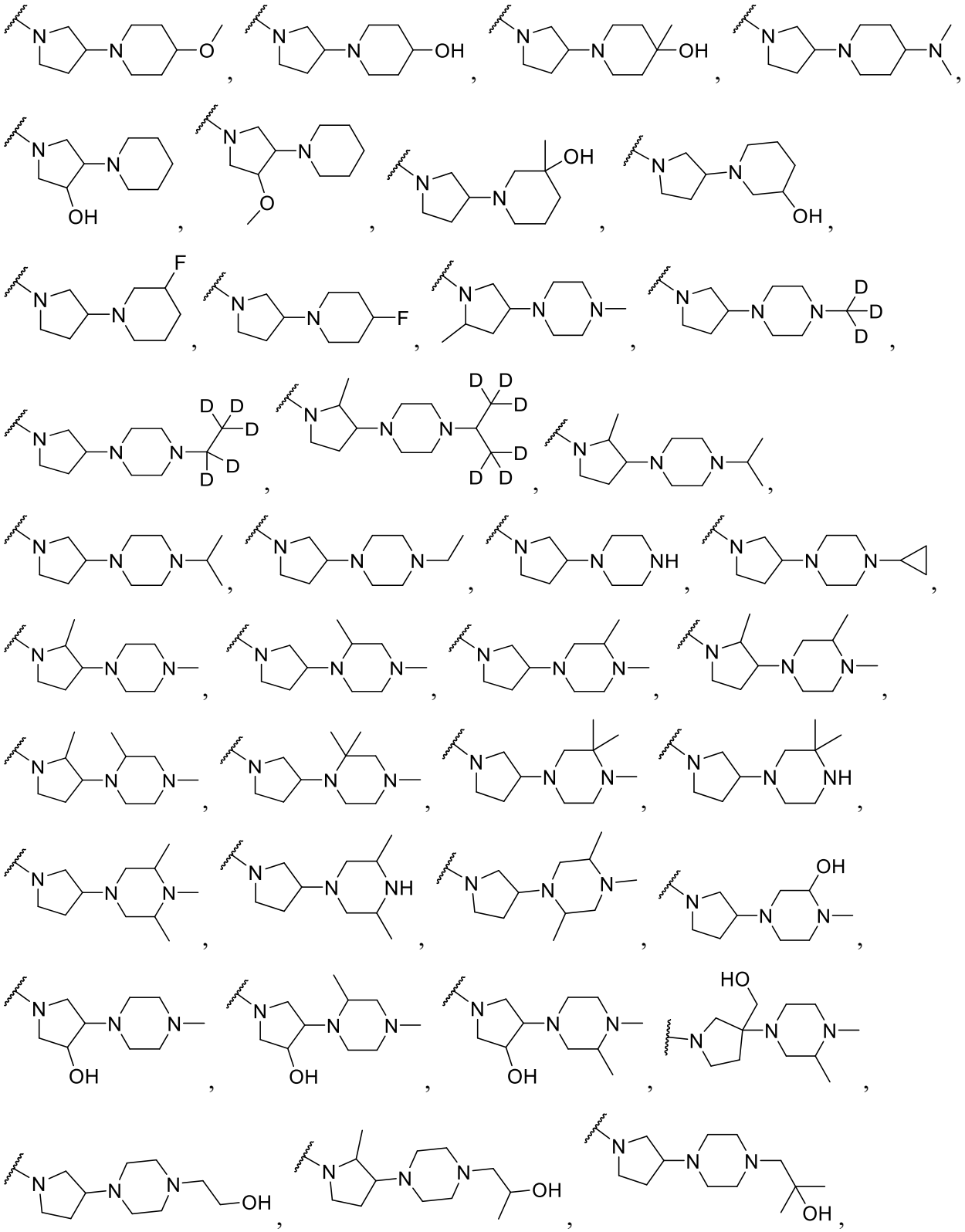


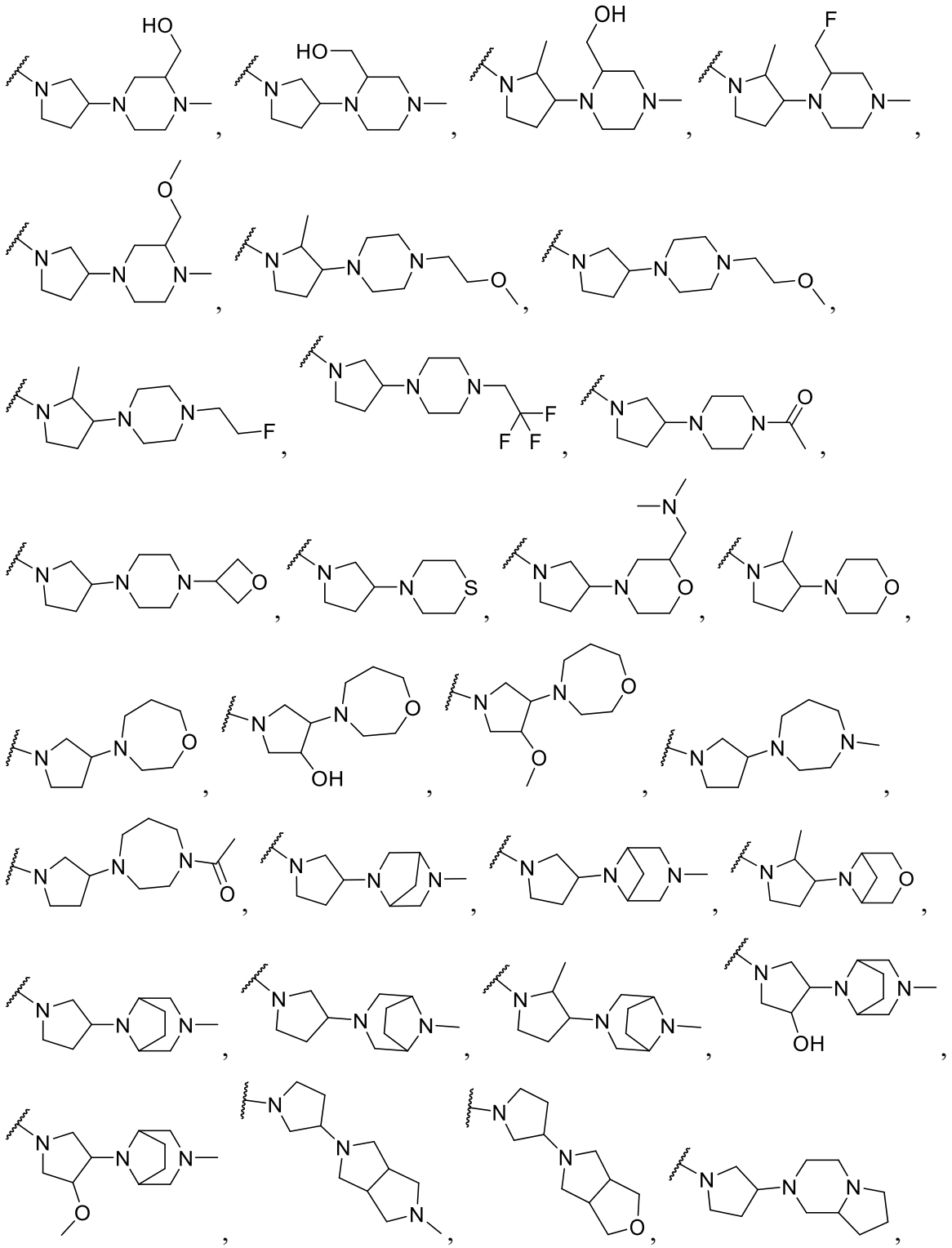


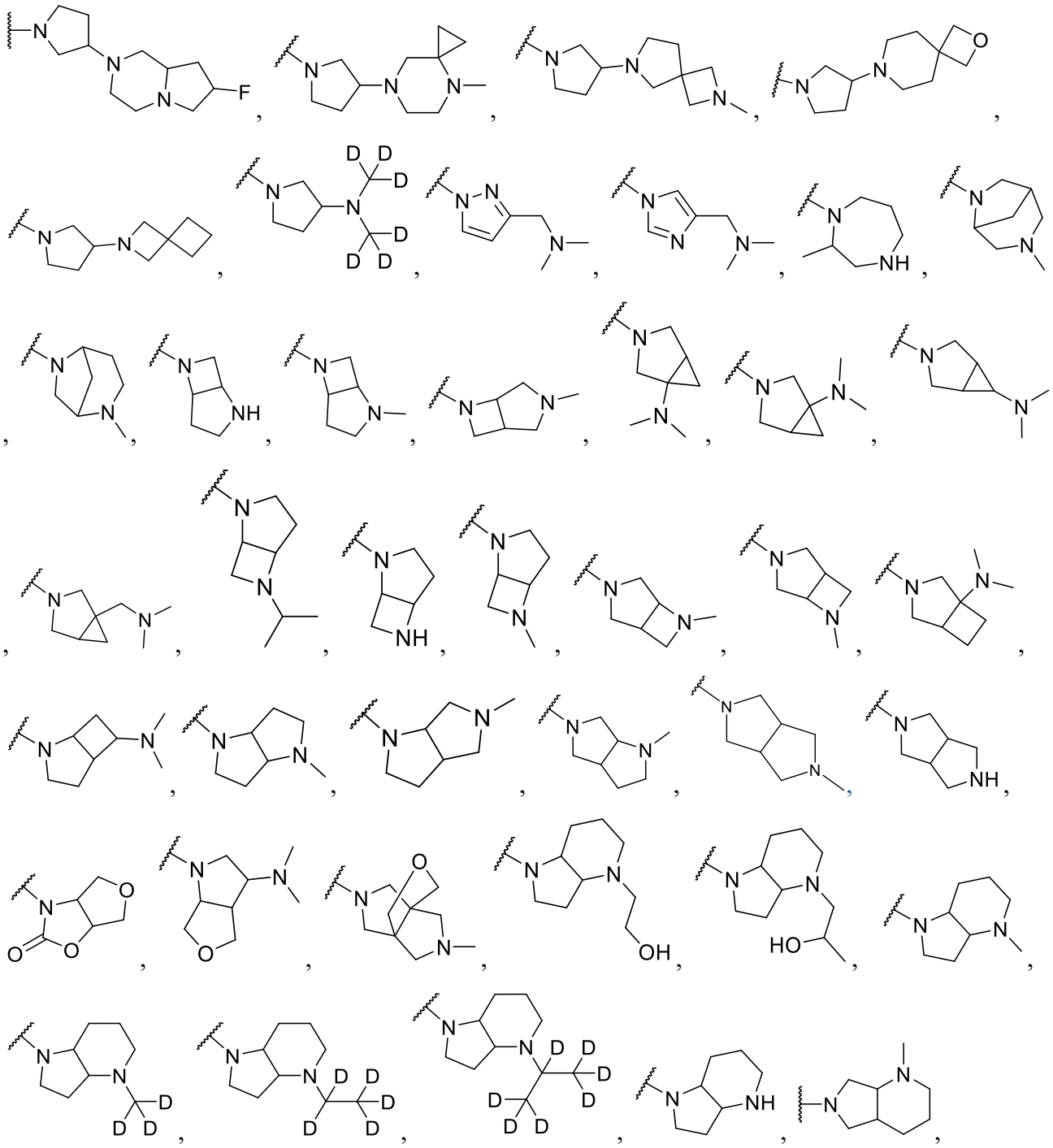


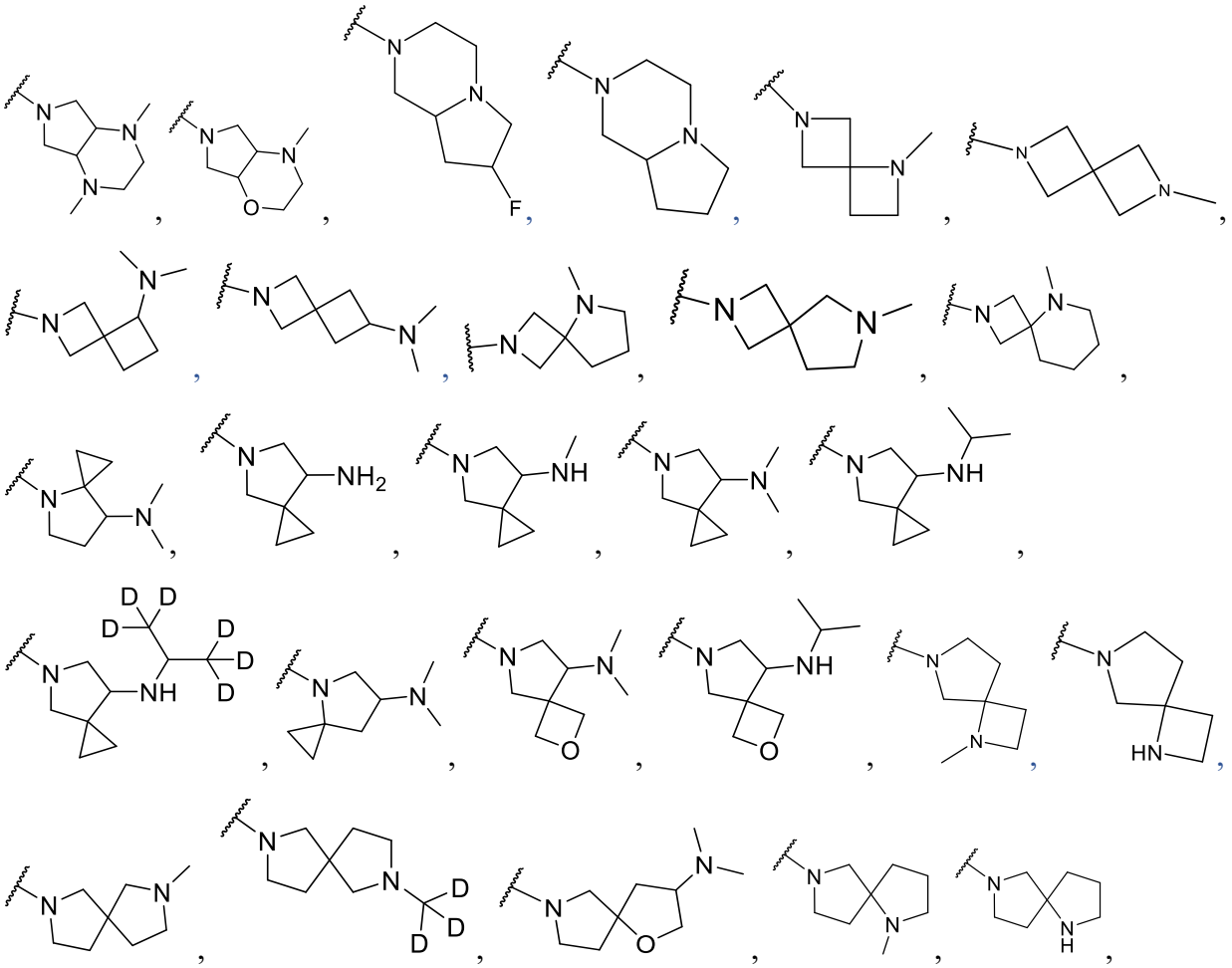






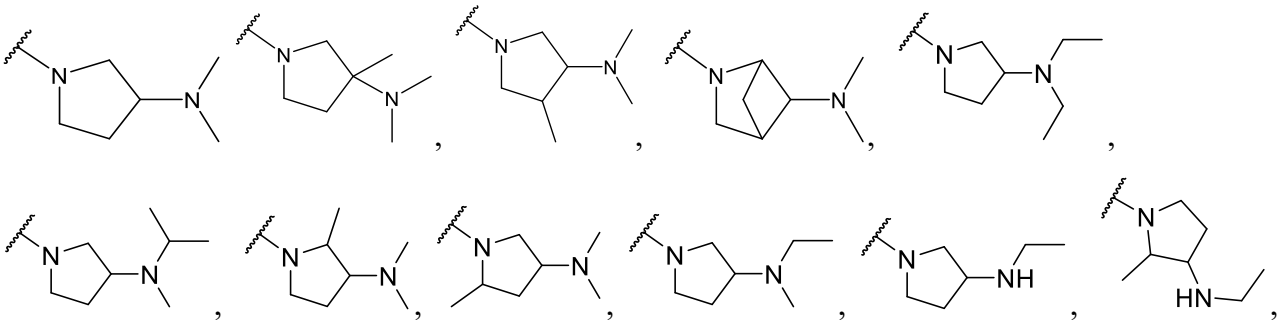


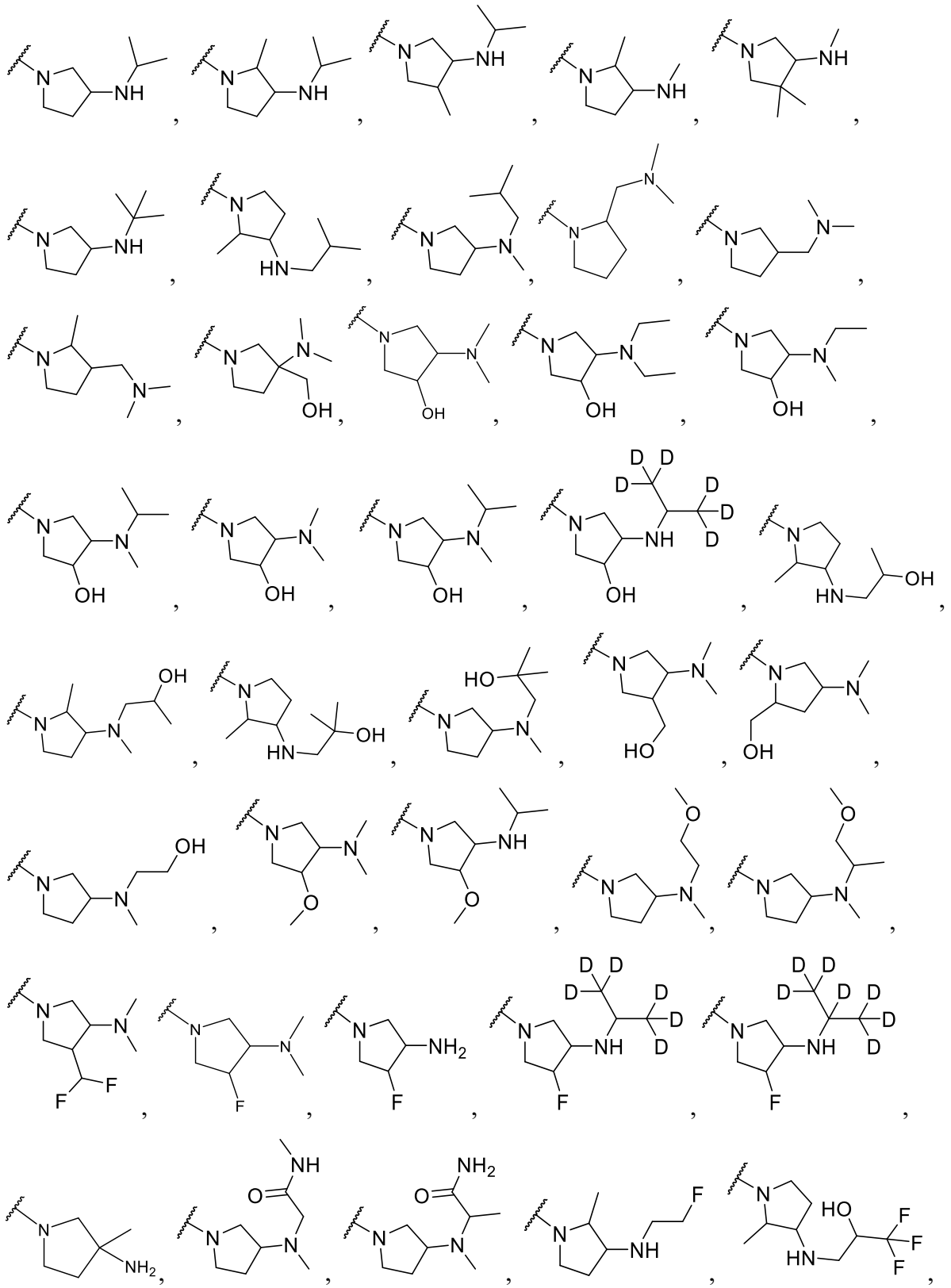


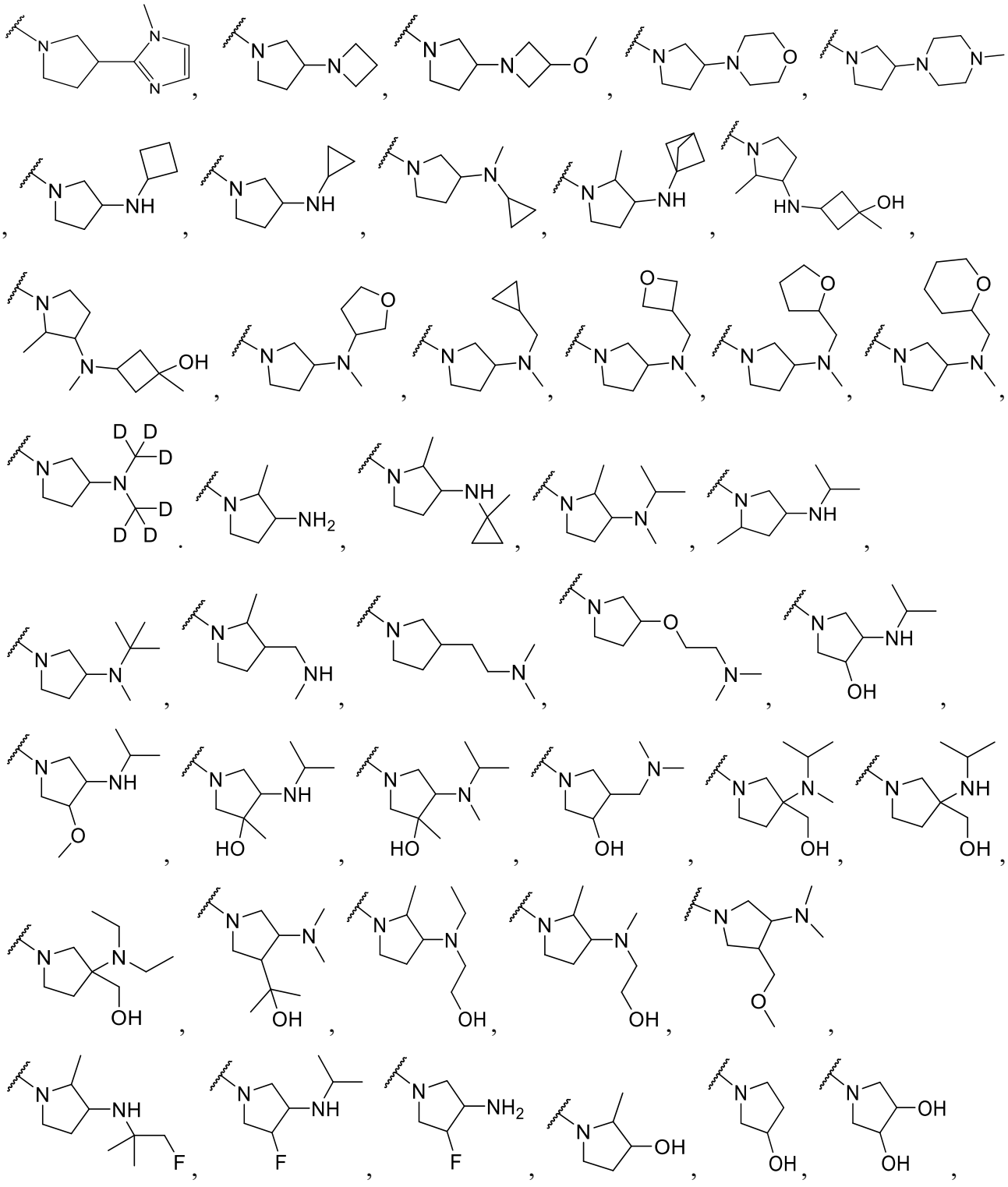


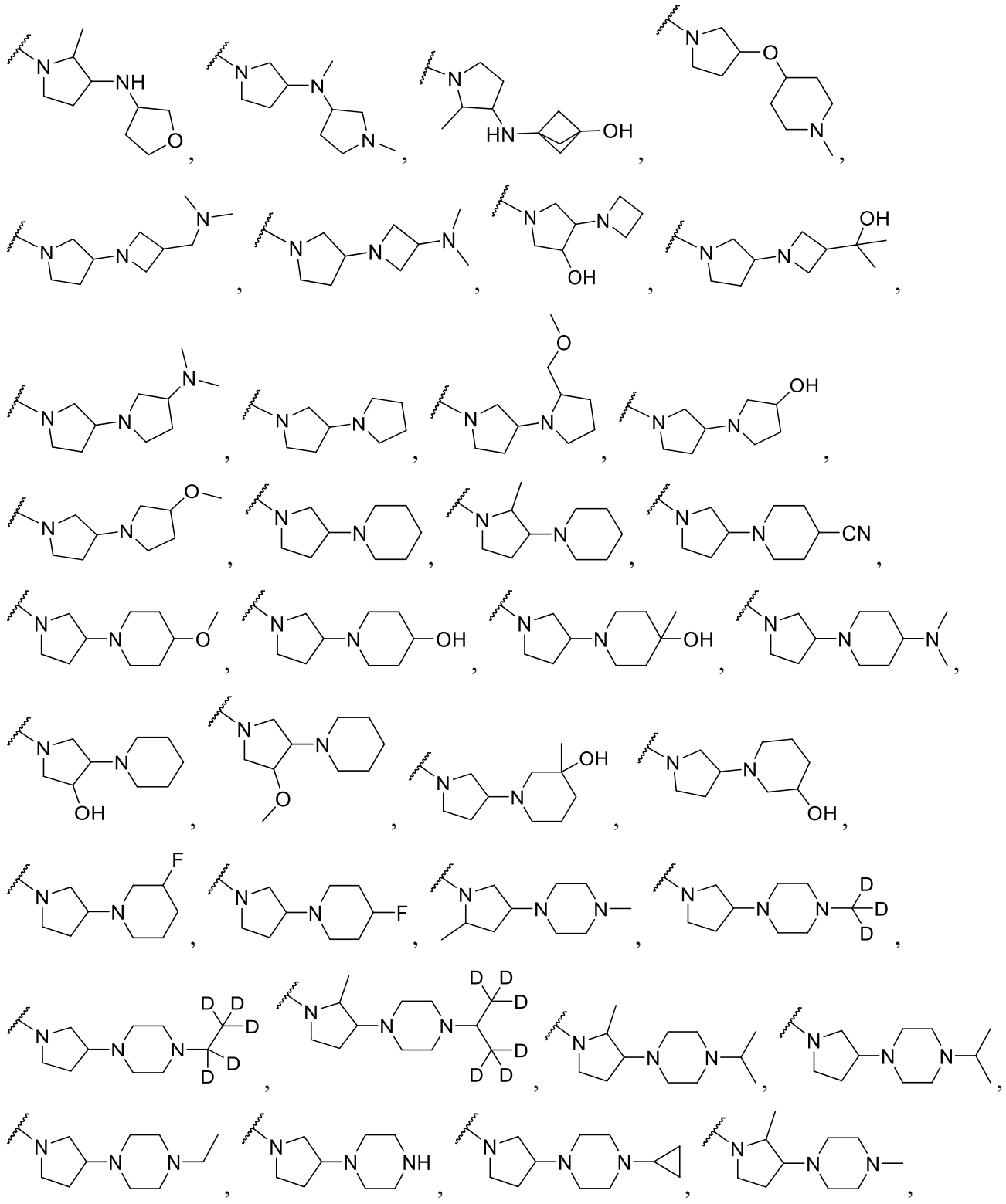
, or , or a pharmaceutically acceptable salt thereof.

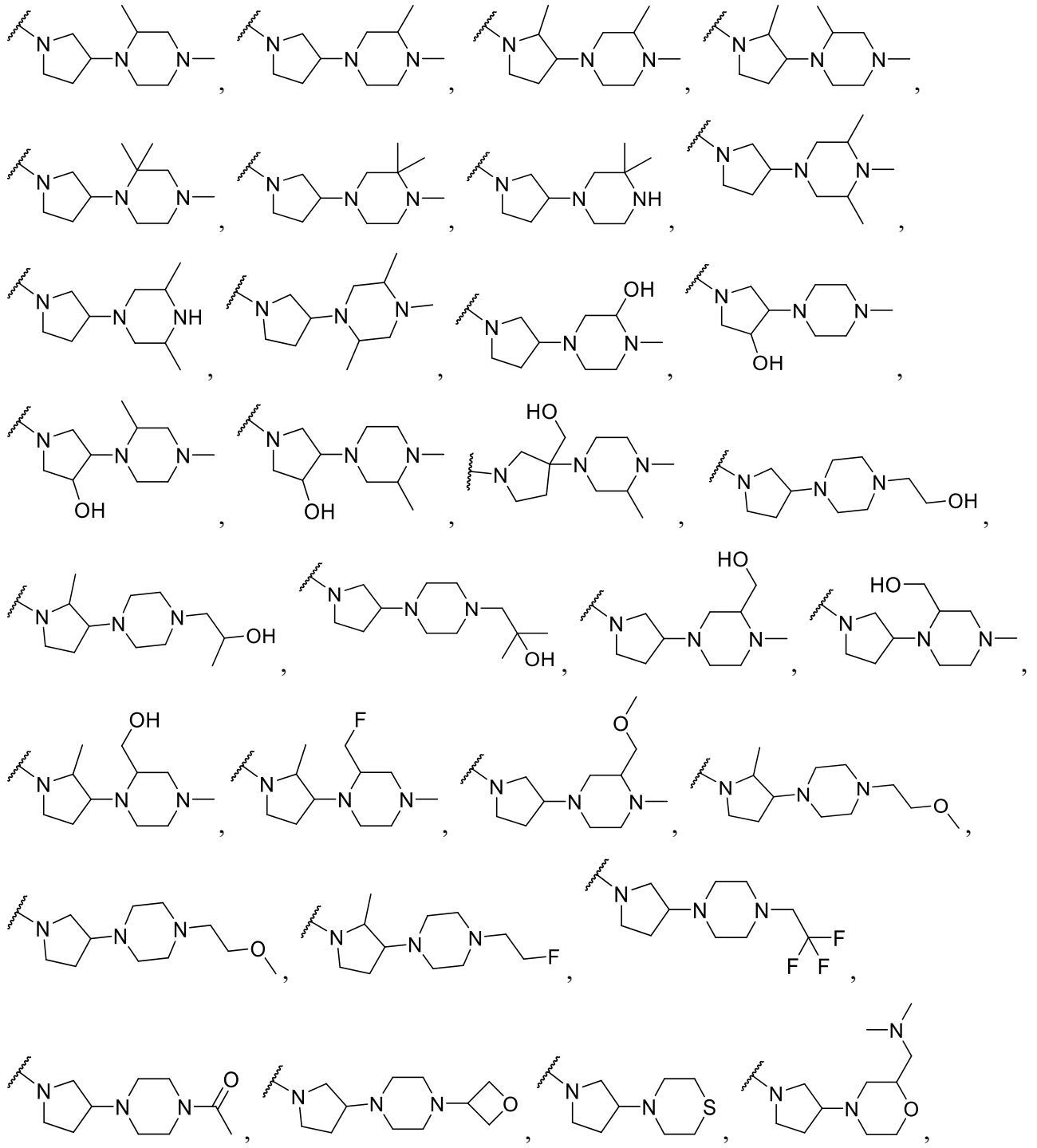
24. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

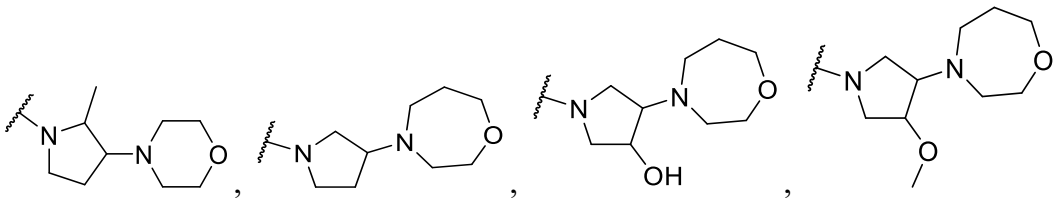
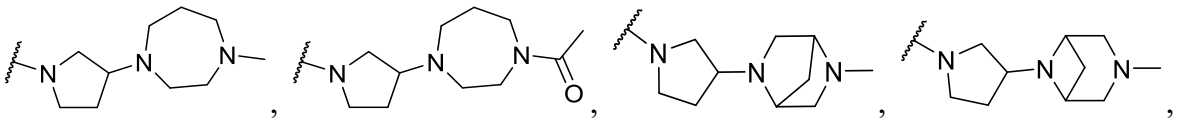
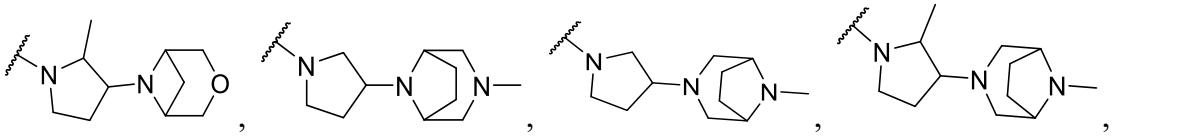
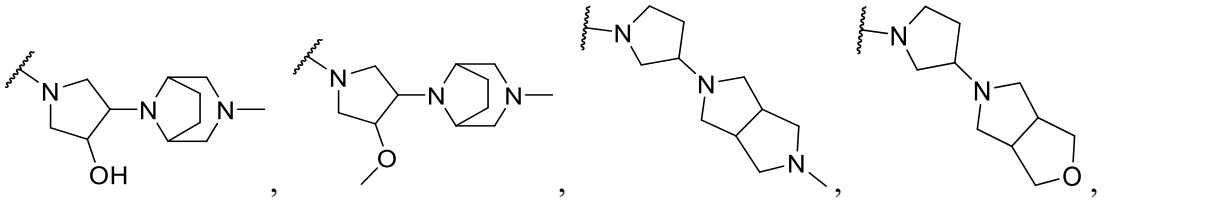
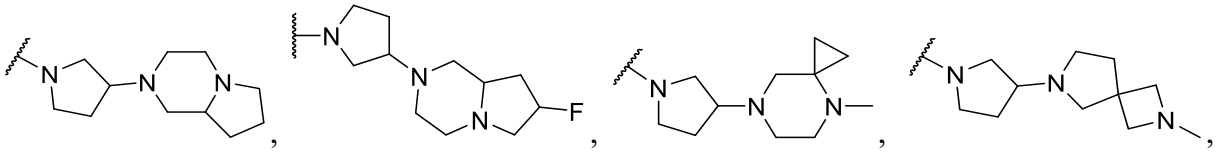
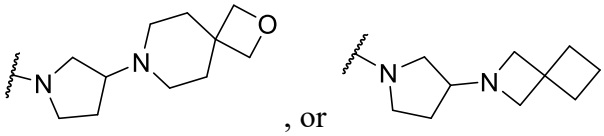




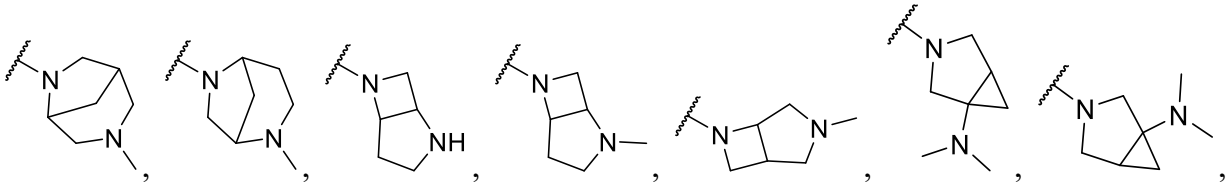
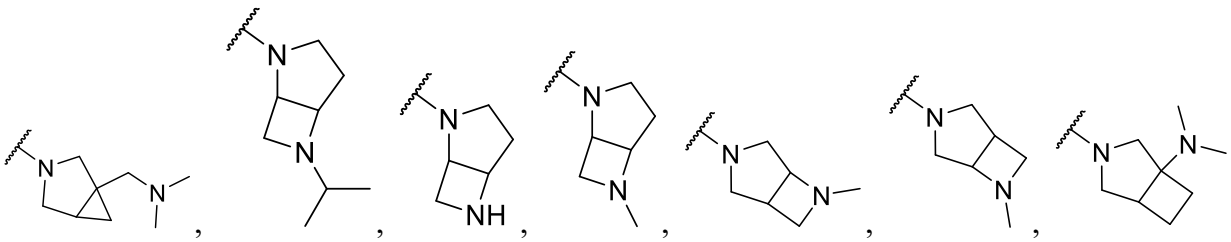


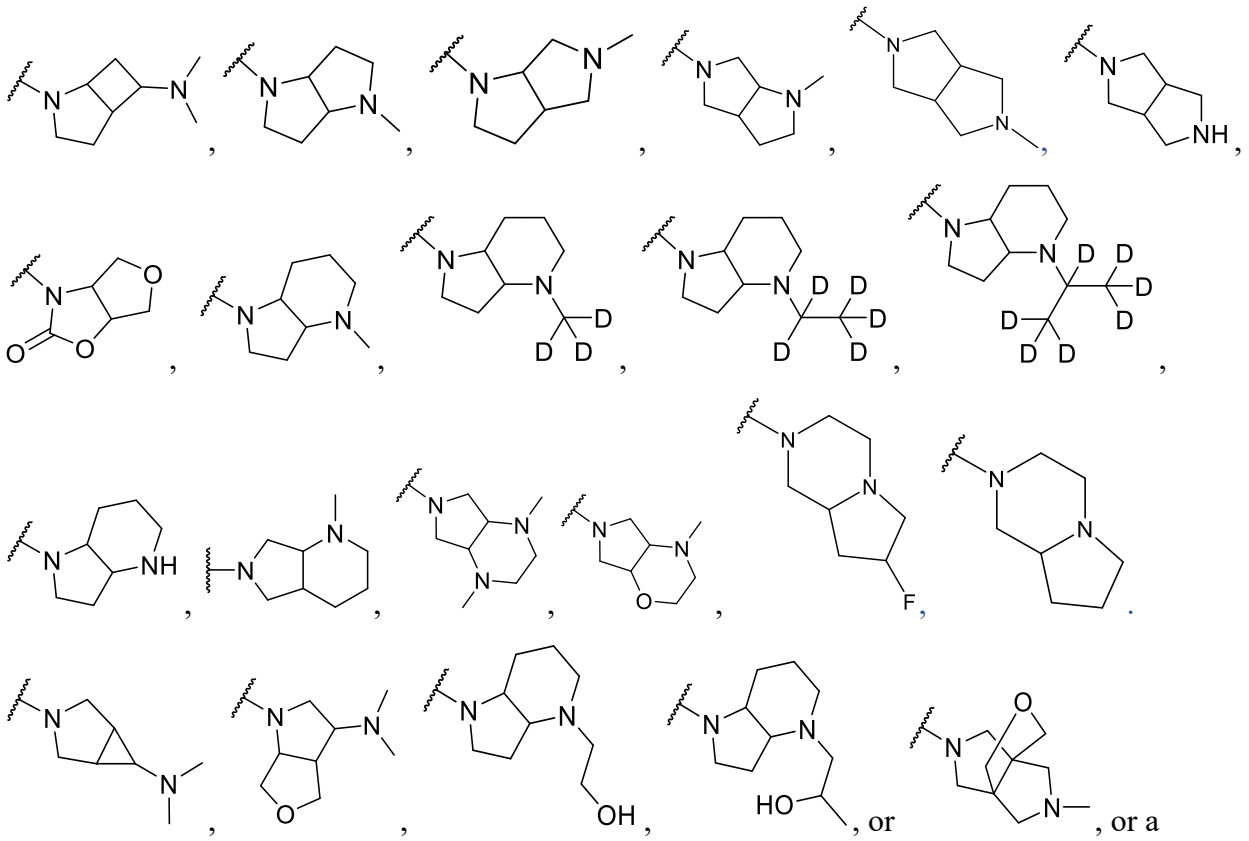










, or a pharmaceutically acceptable salt thereof.

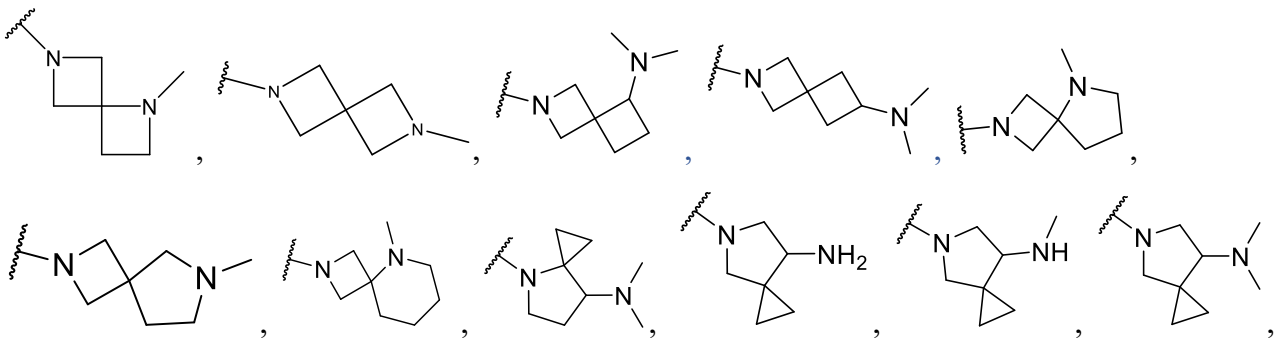
25. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

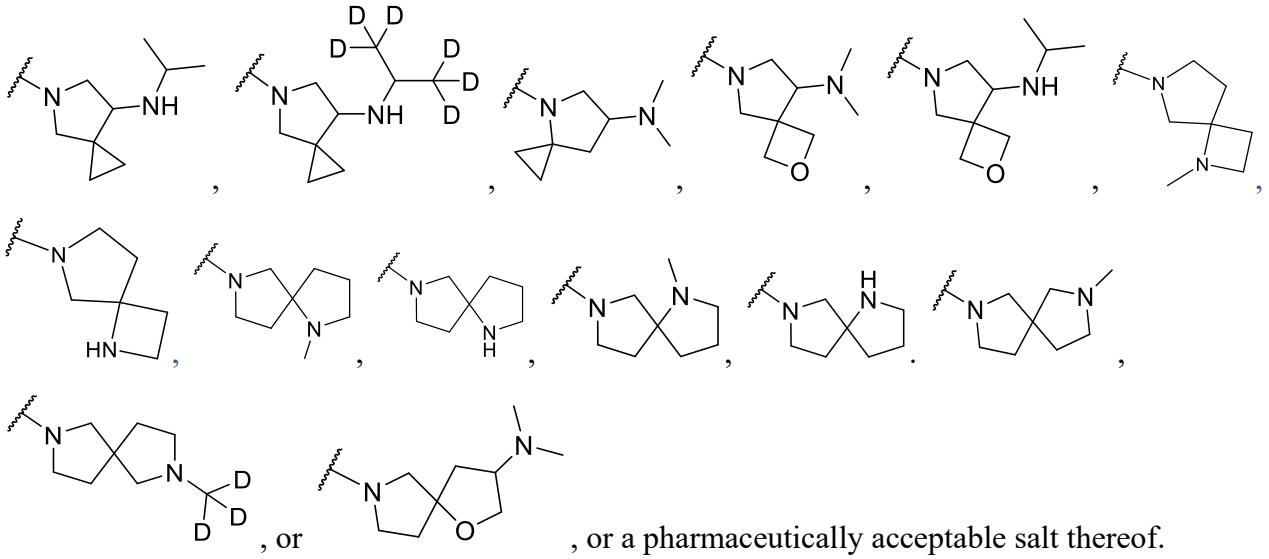





pharmaceutically acceptable salt thereof.

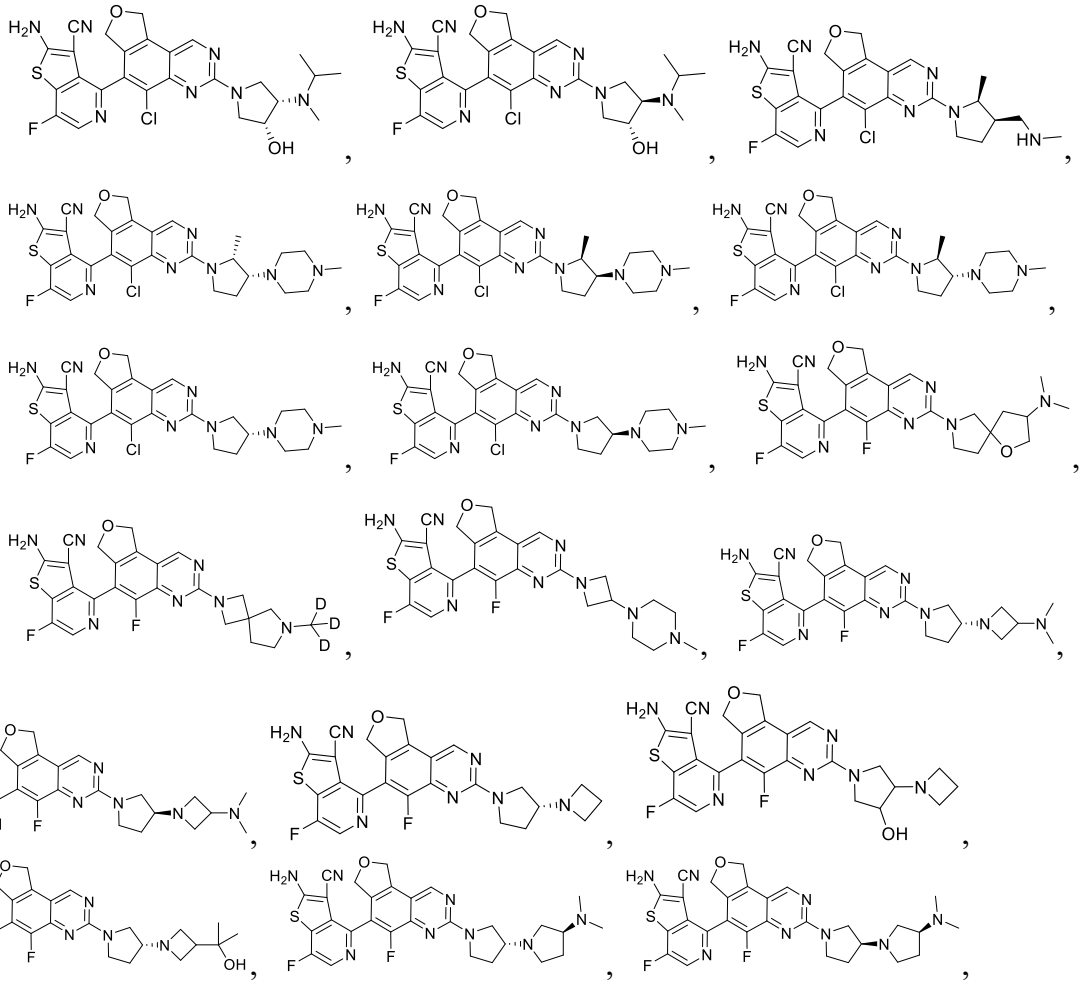
26. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

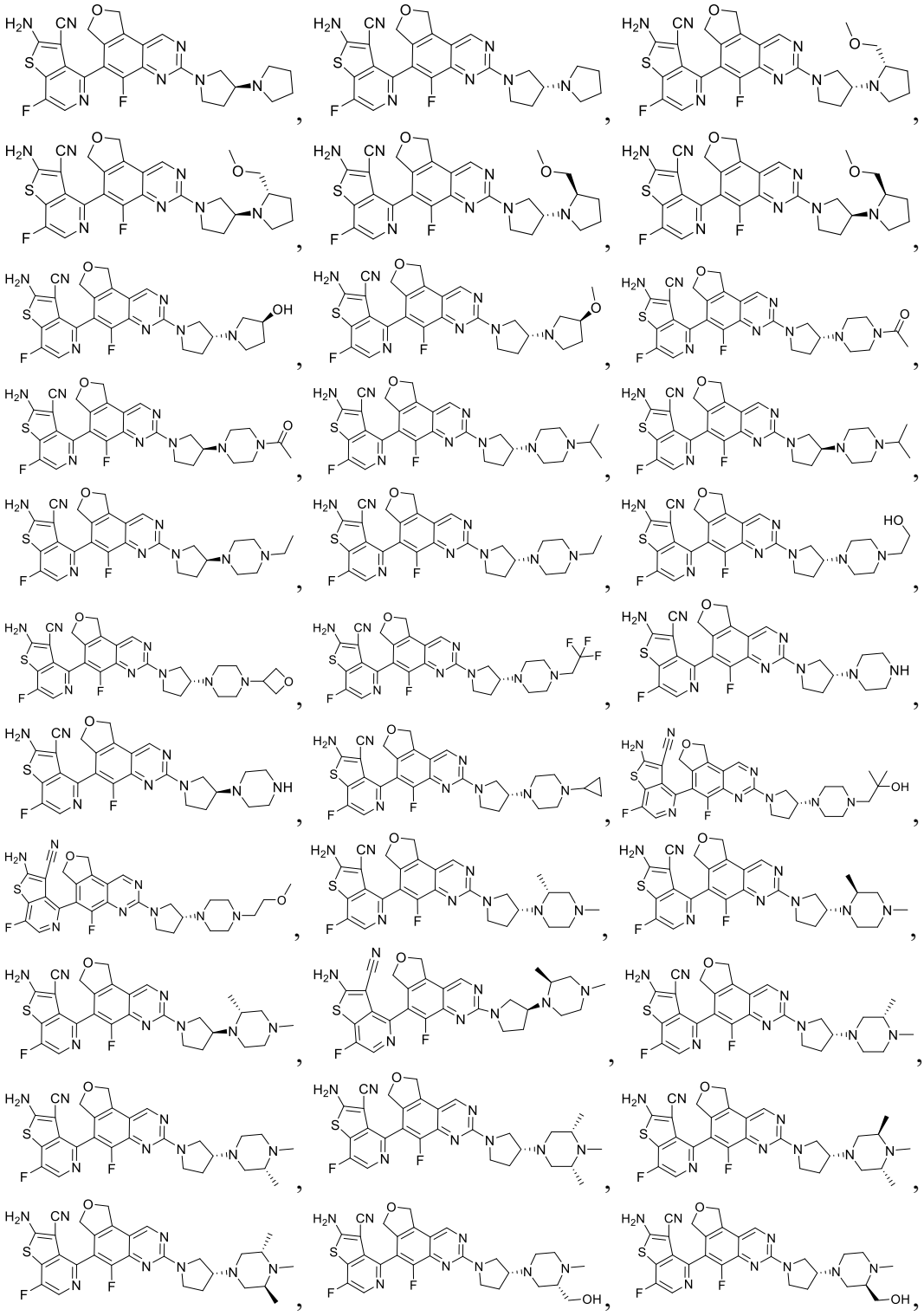


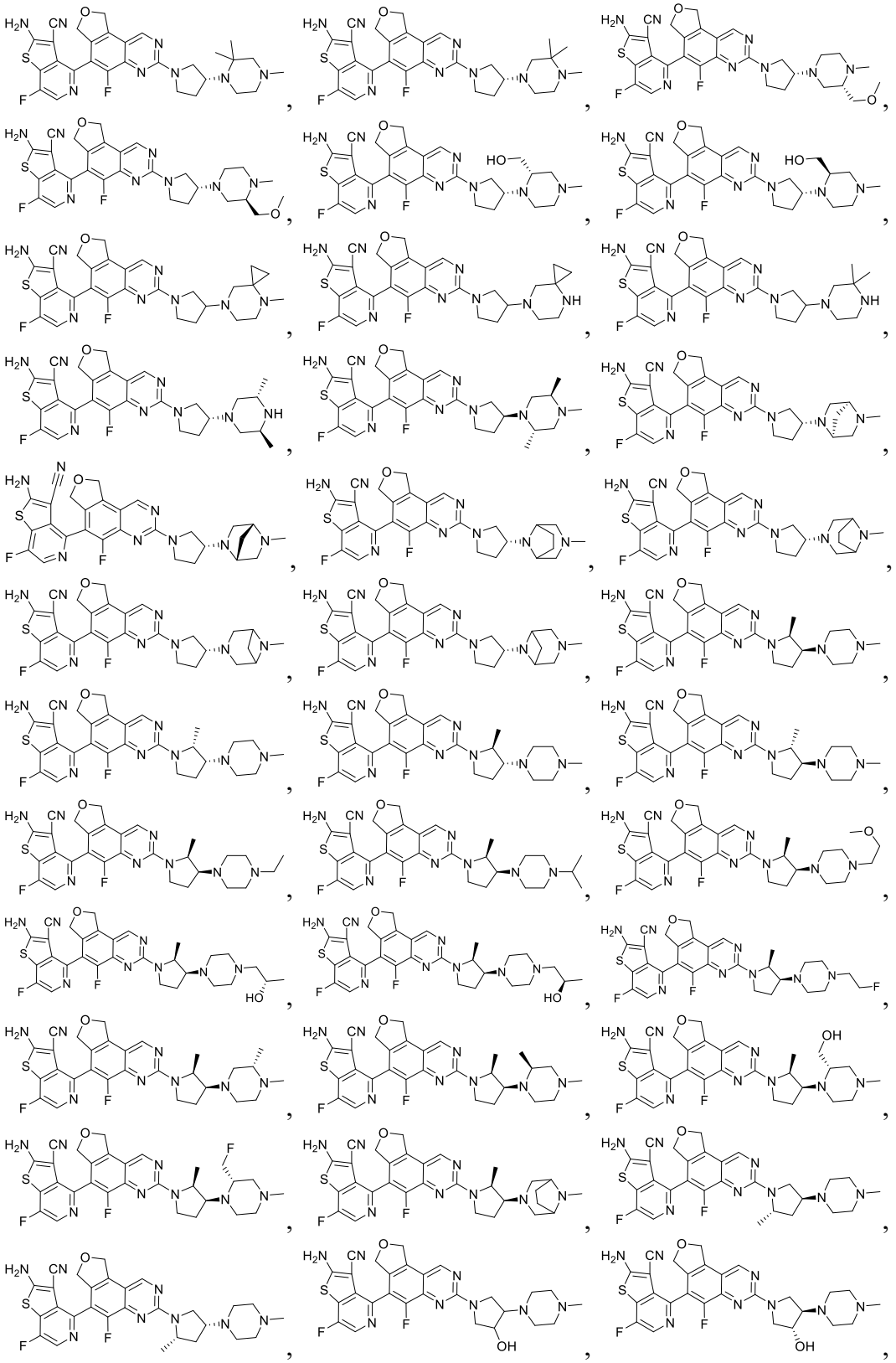


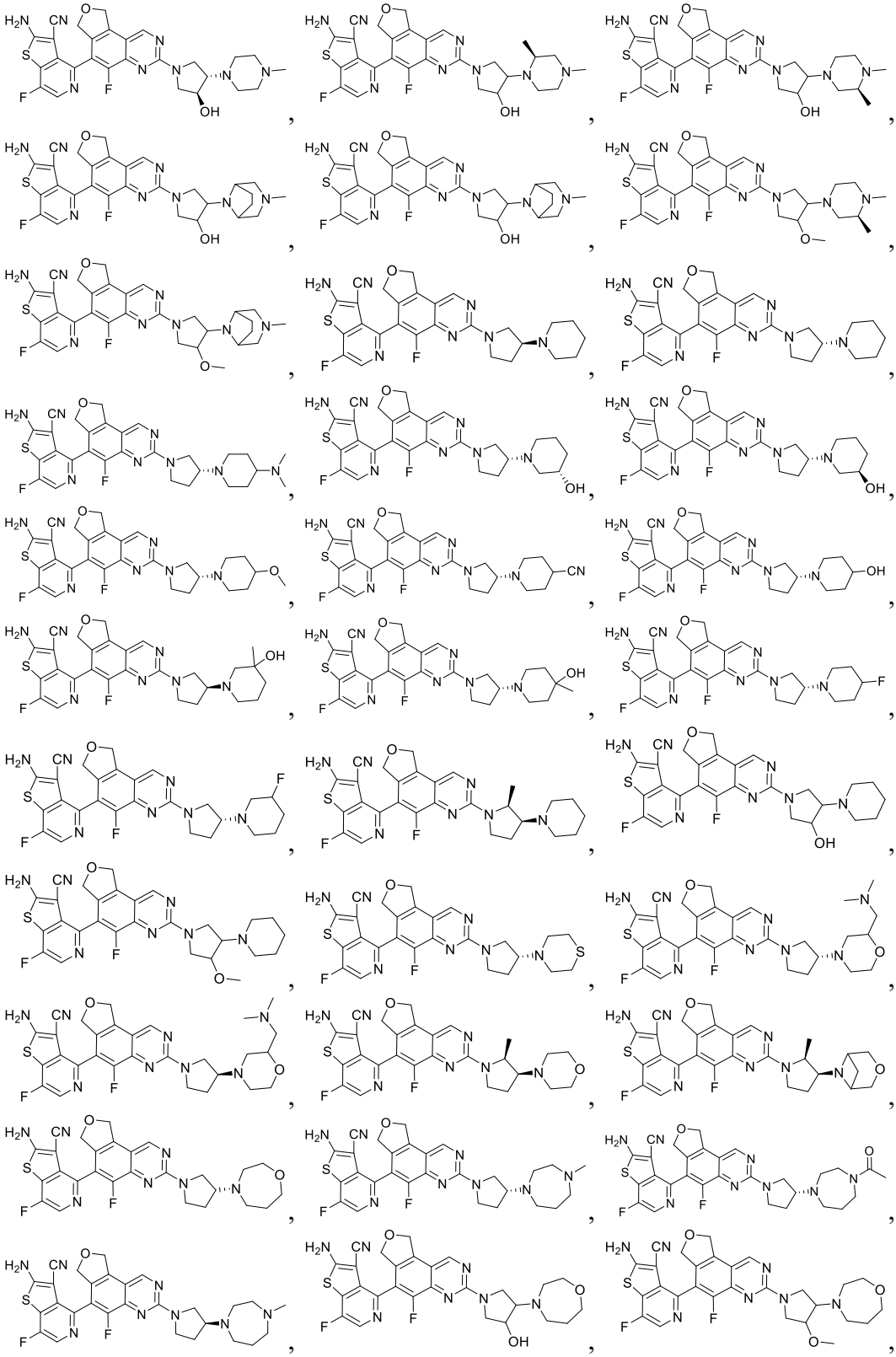
, or a pharmaceutically acceptable salt thereof.

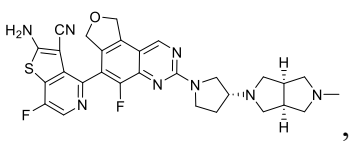
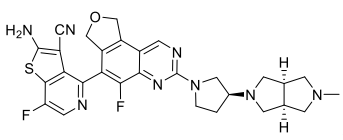
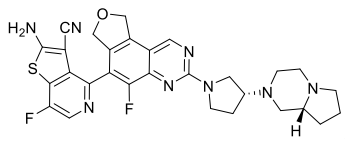
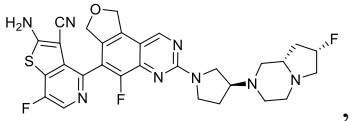
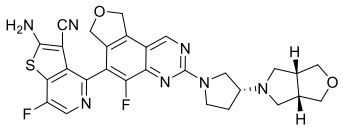
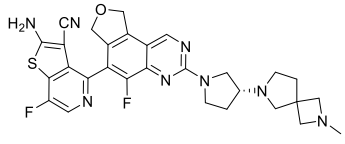
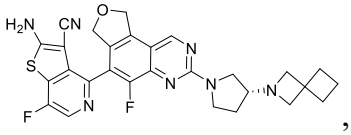
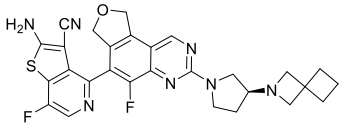
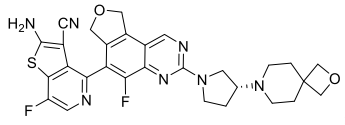
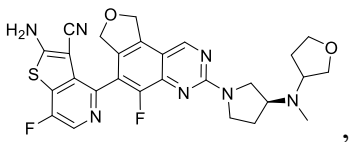
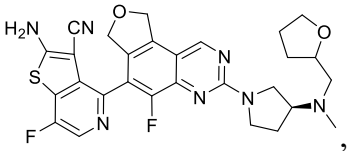
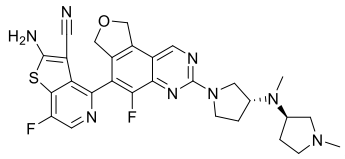
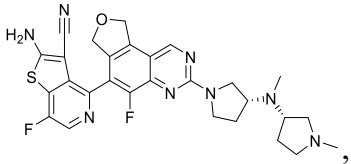
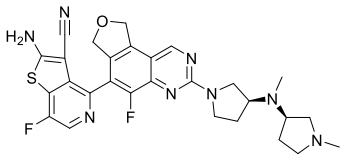
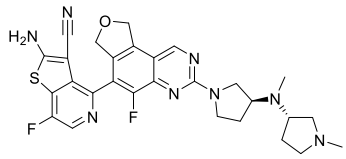
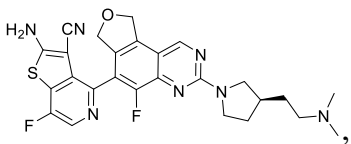
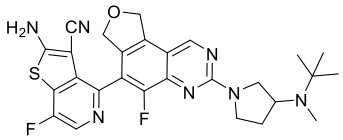
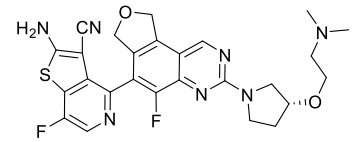
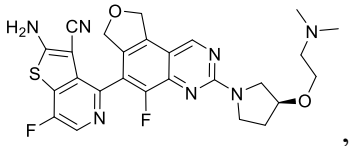
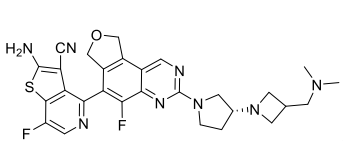
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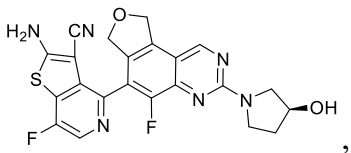
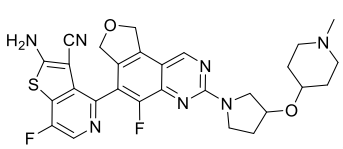
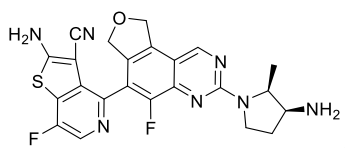
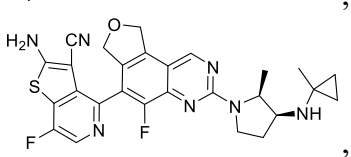
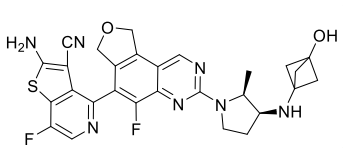
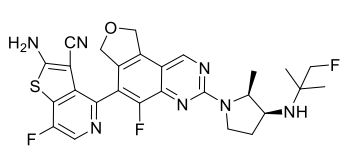
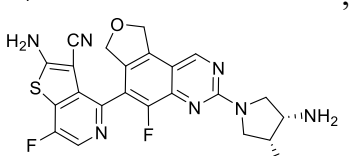
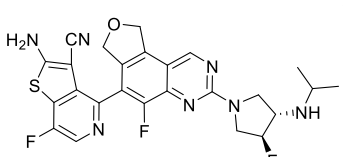
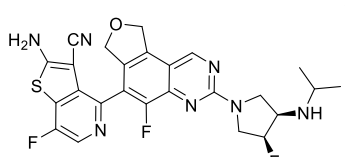








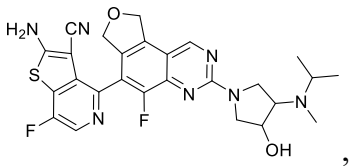
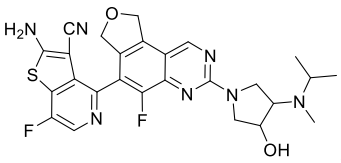
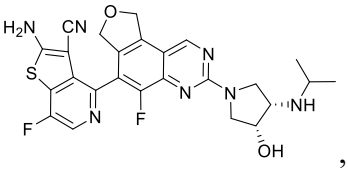
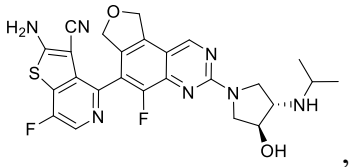
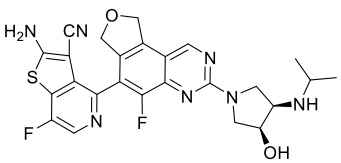
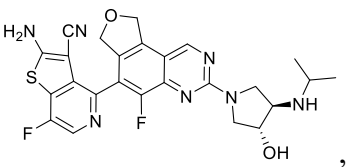
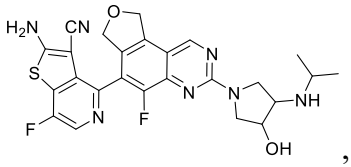
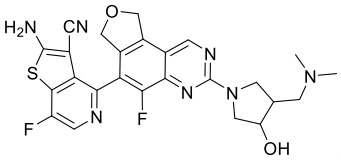
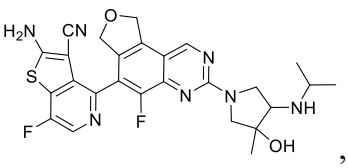
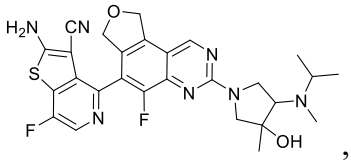
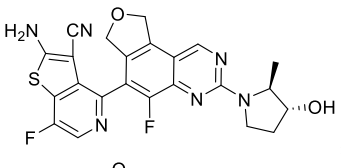
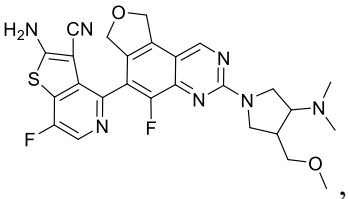
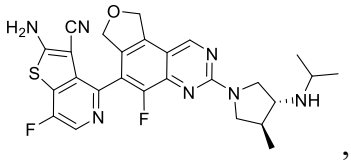
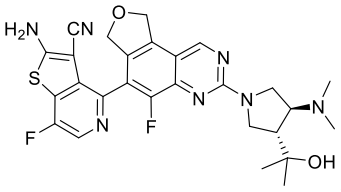
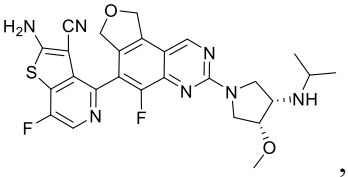
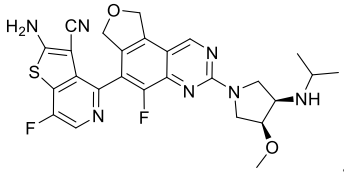
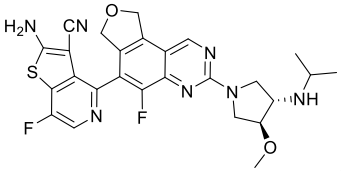
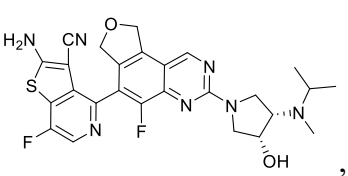
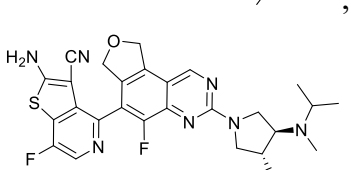
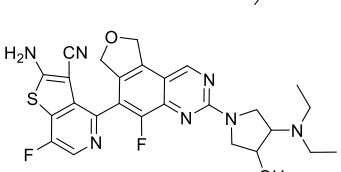
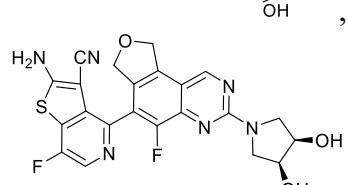
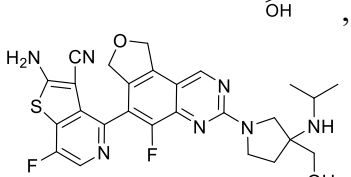
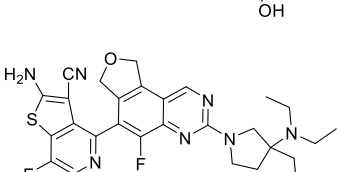
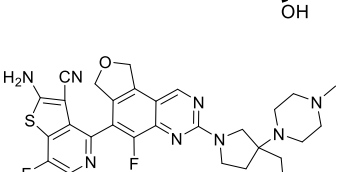
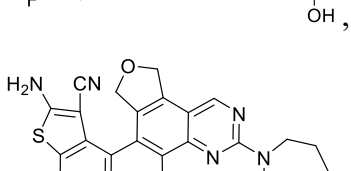
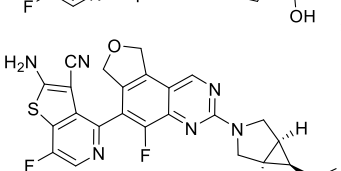
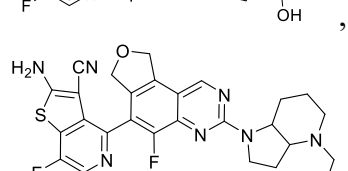
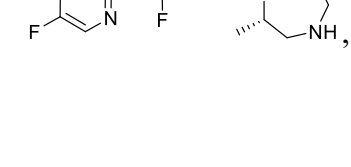
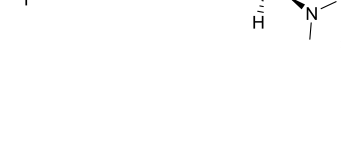
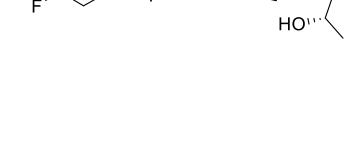

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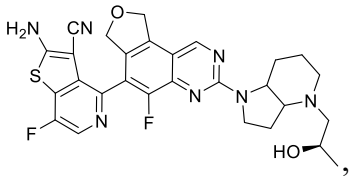
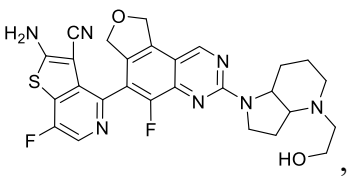
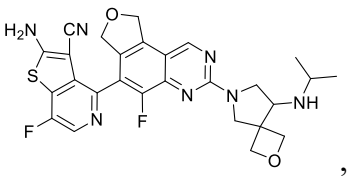
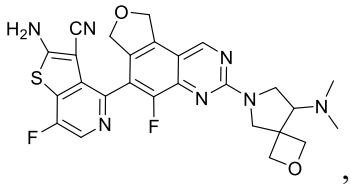
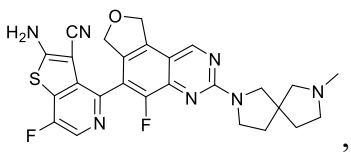
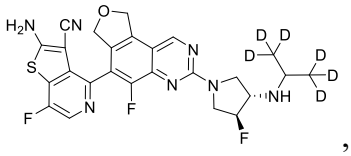
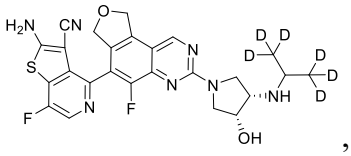
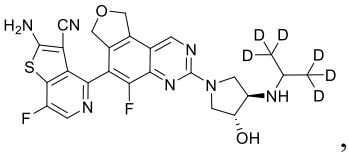
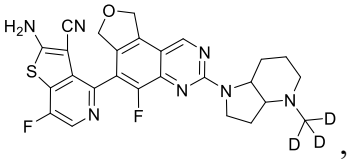
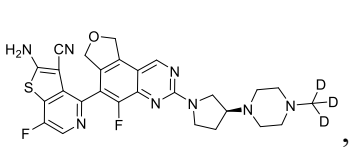
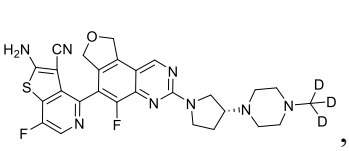
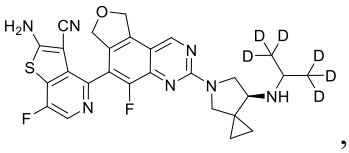
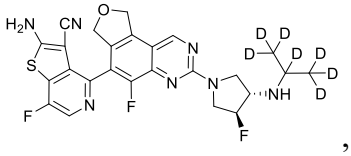
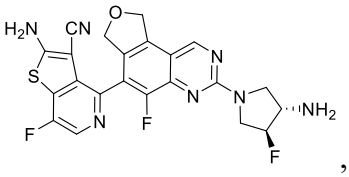
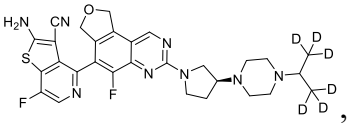
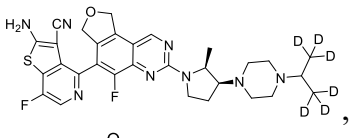
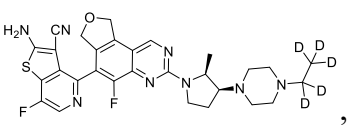
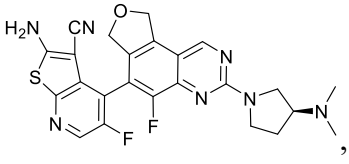
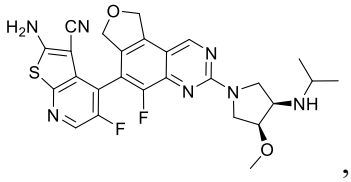
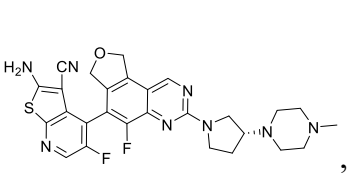
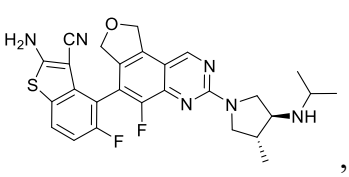
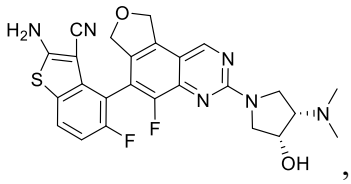
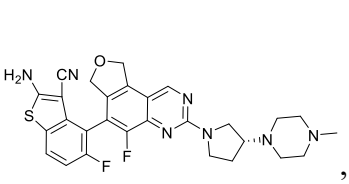
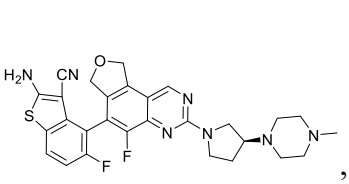
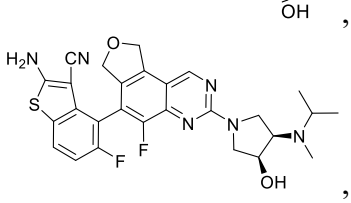
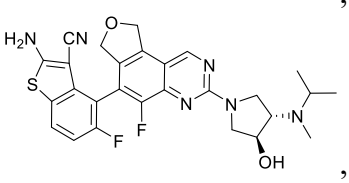
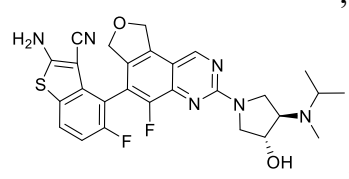
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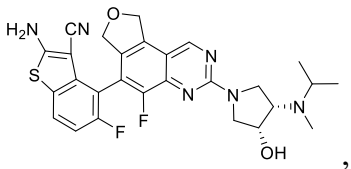
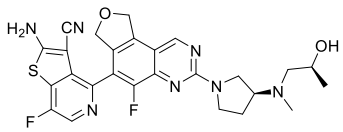
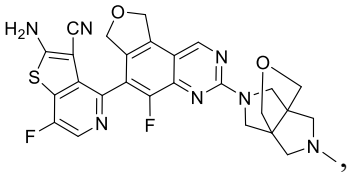
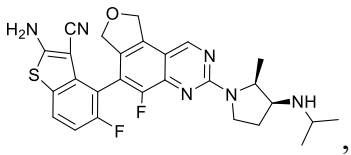
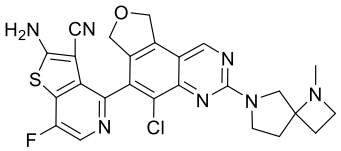
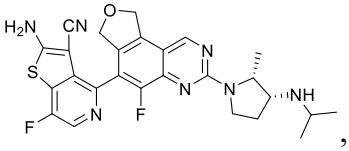
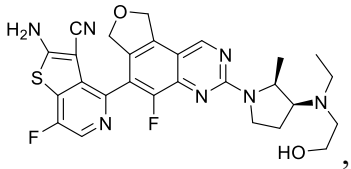
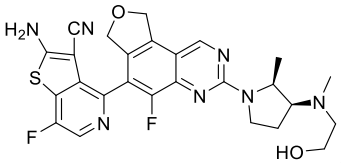
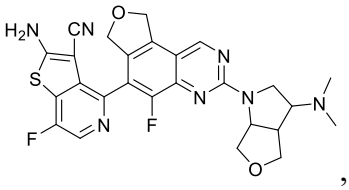
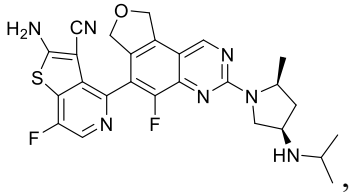
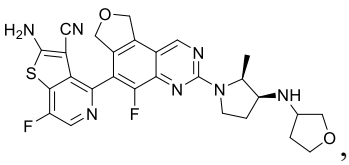
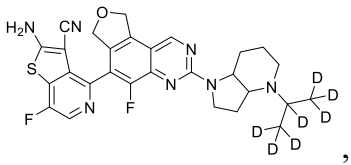
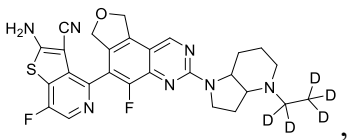
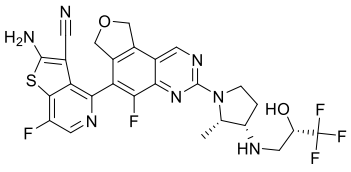
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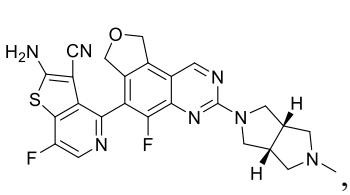
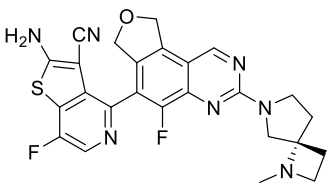
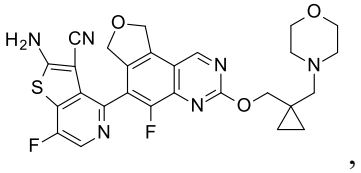
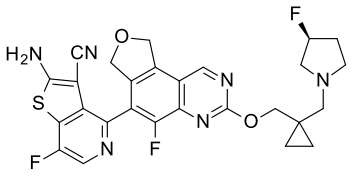
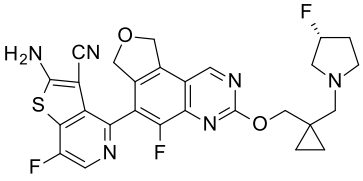
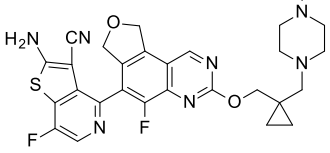
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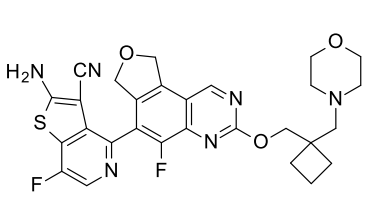
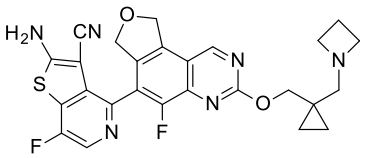
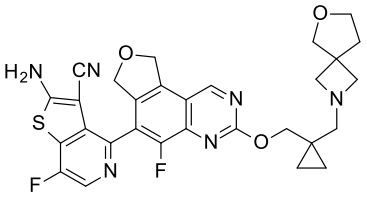
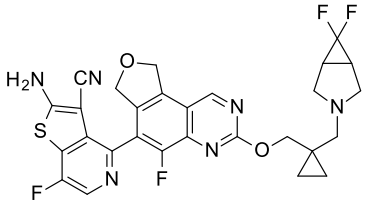
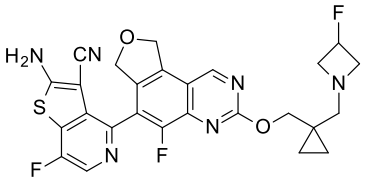
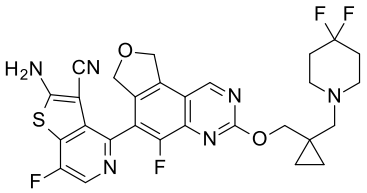
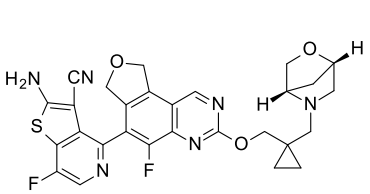
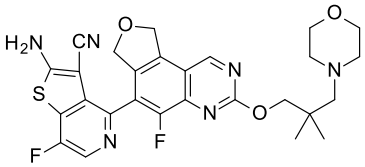
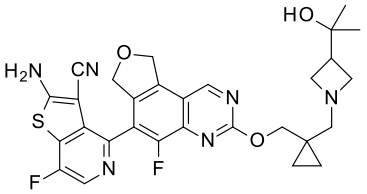
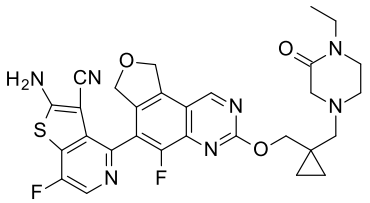
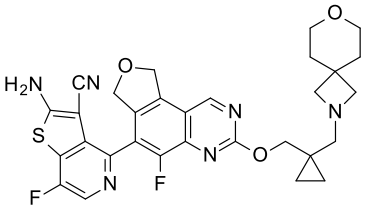
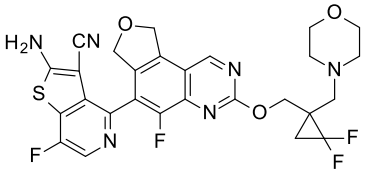
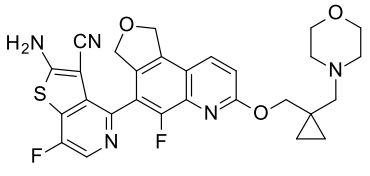
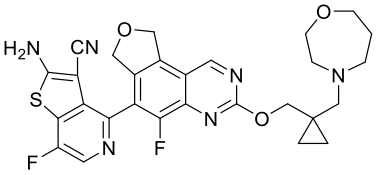
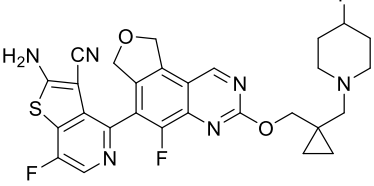
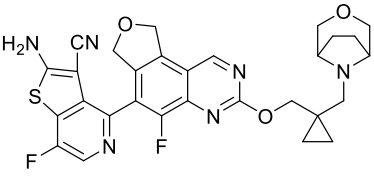
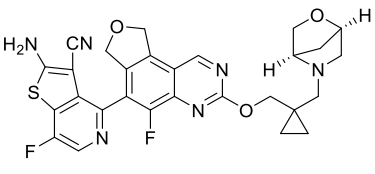
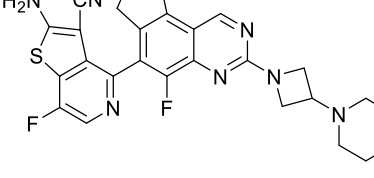

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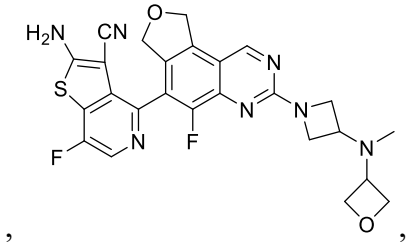
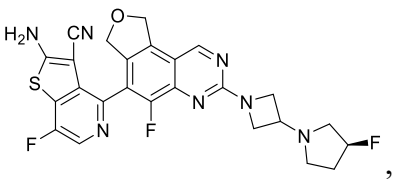
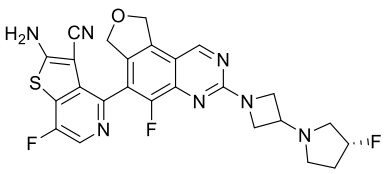
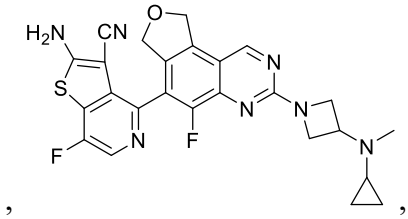
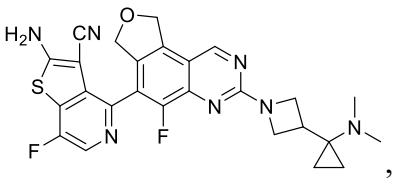
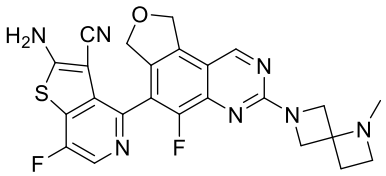
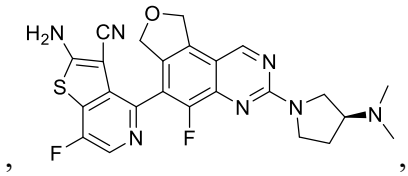
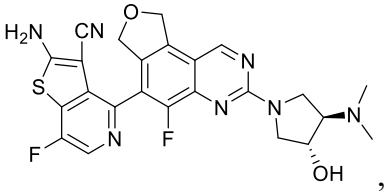
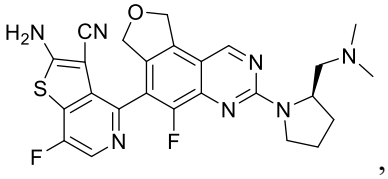
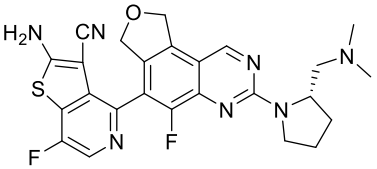
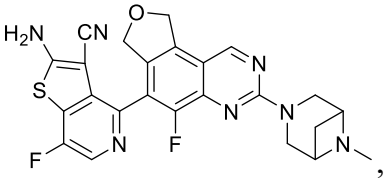
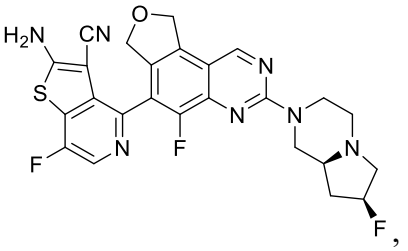
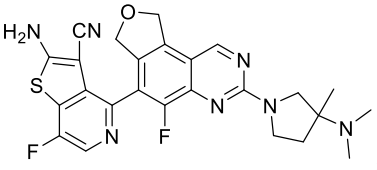
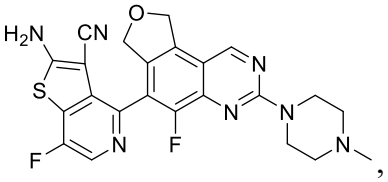
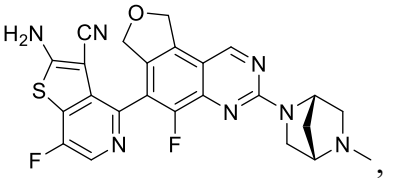
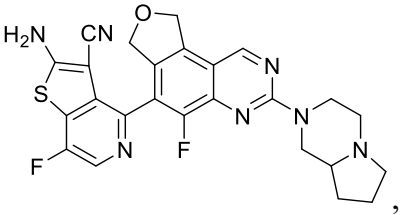
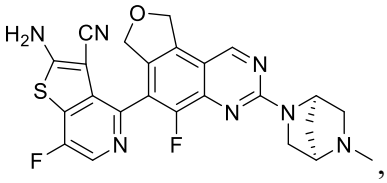
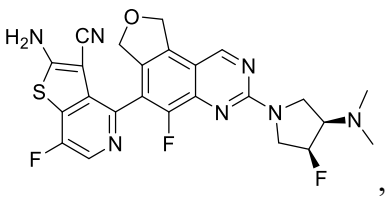
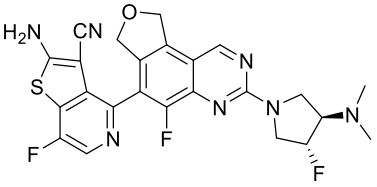
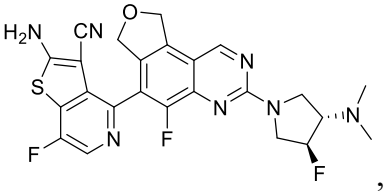
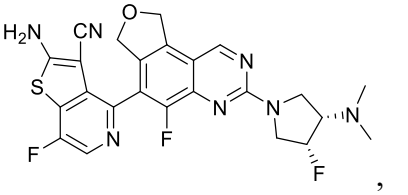
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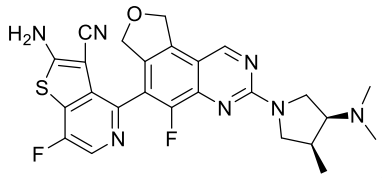
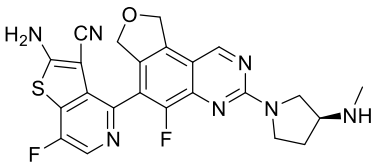
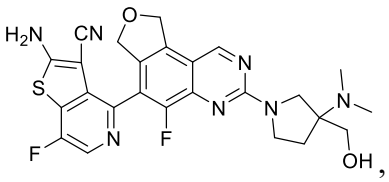
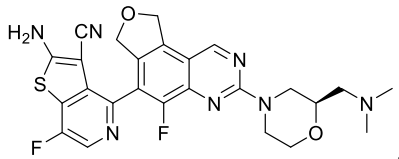
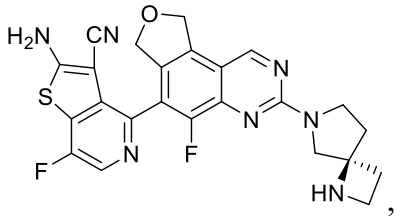
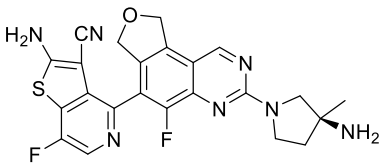
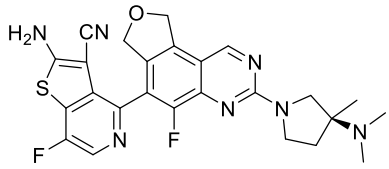
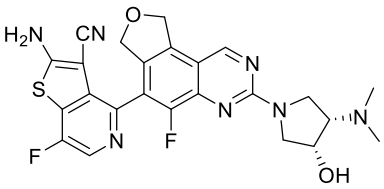
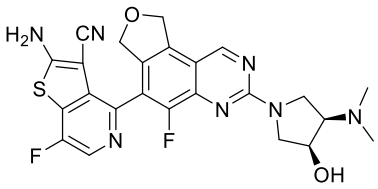
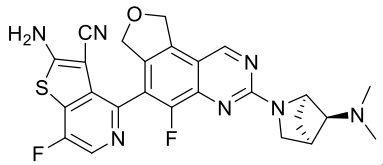
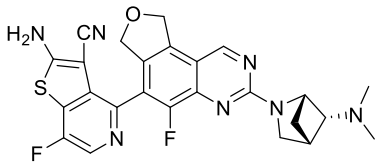
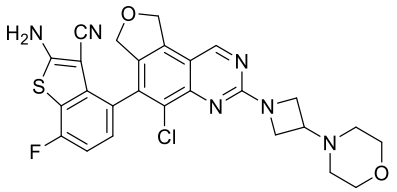
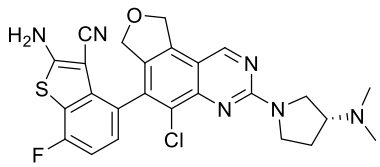
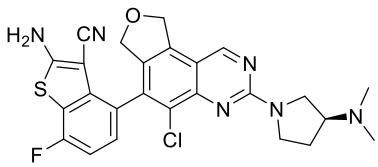
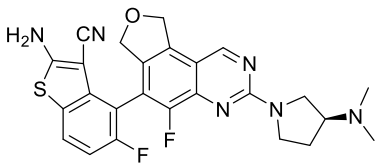
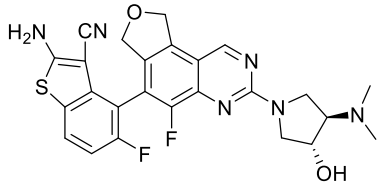
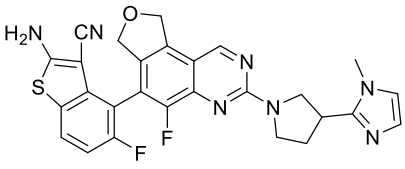
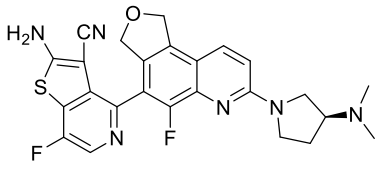
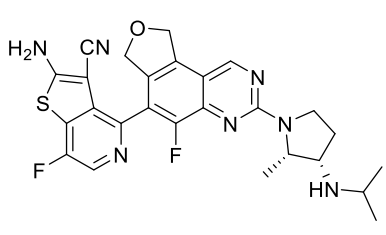
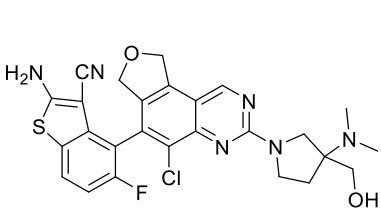
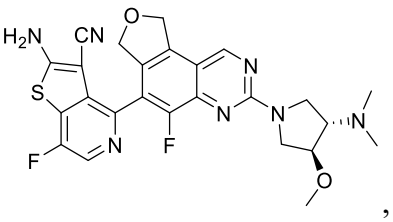
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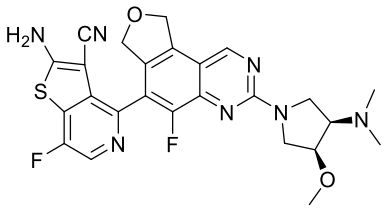
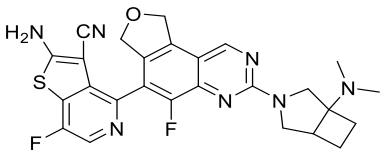
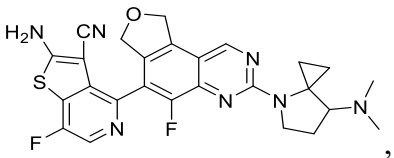
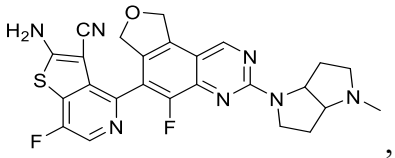
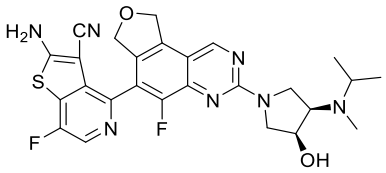
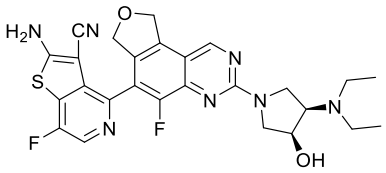
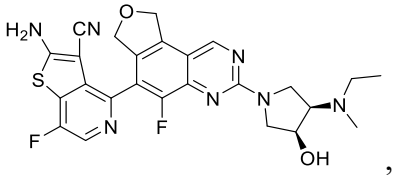
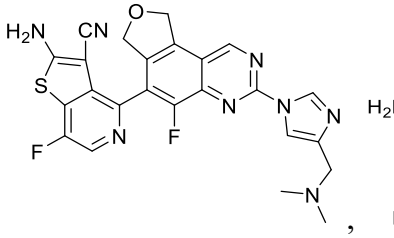
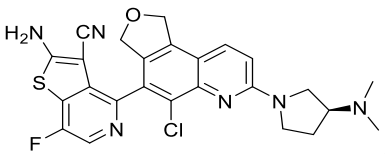
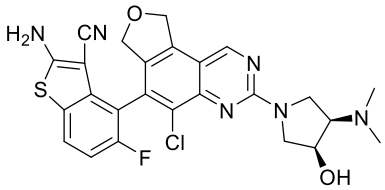
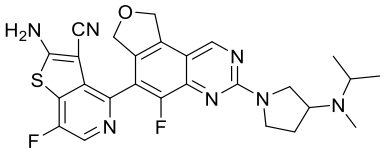
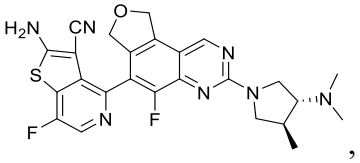
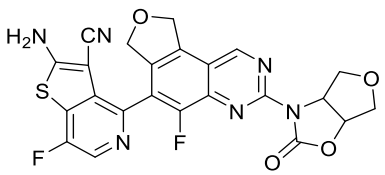
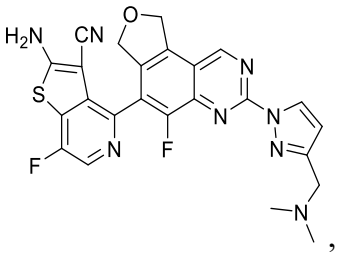
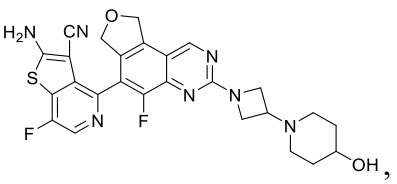
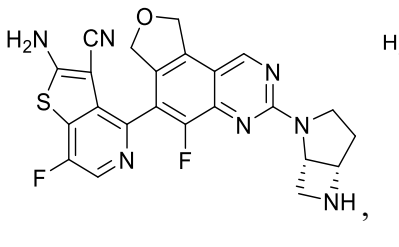
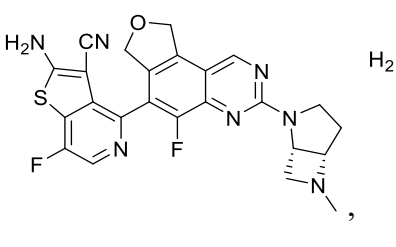
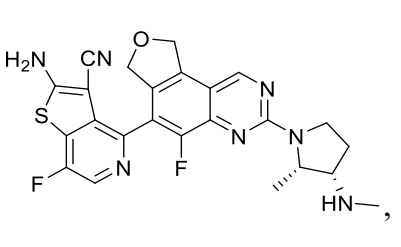
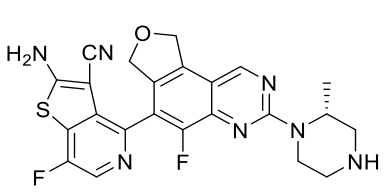
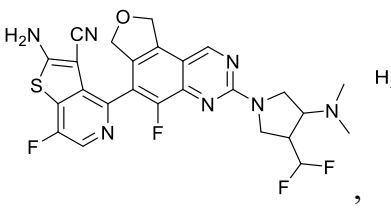
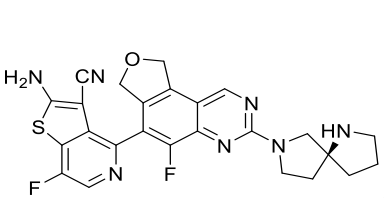

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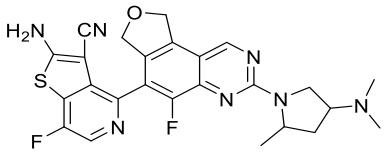
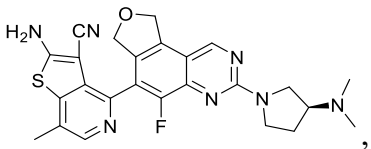
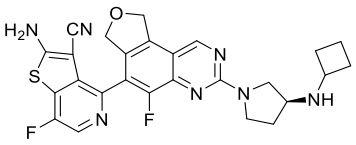
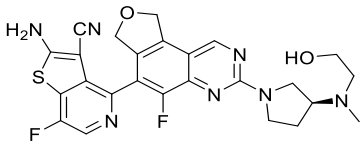
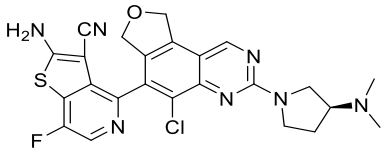
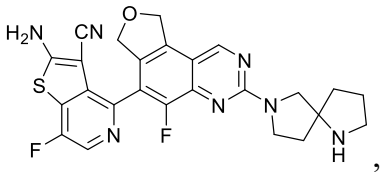
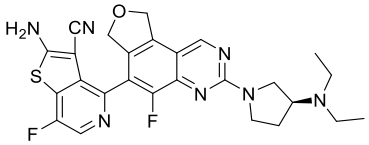
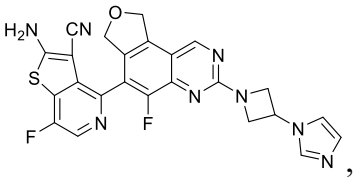
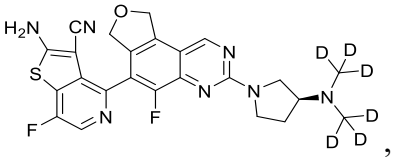
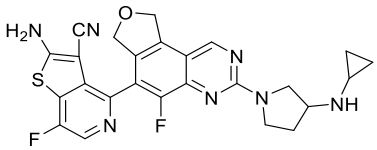
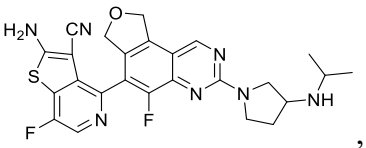
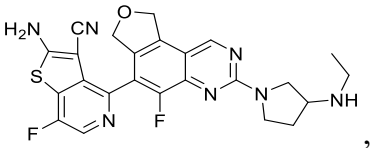
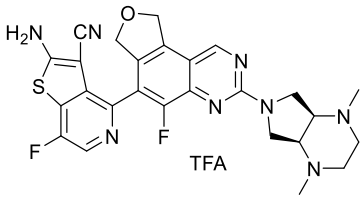
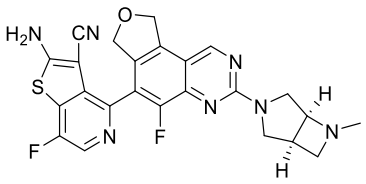
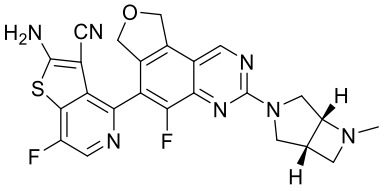
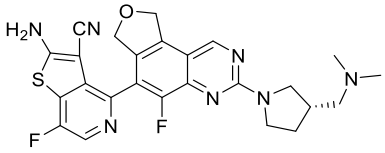
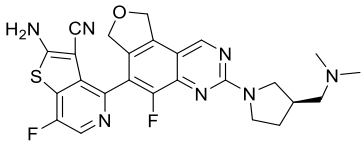
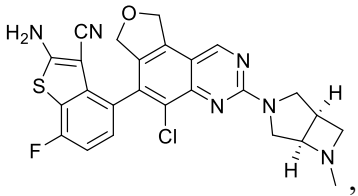
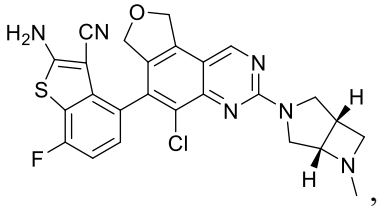
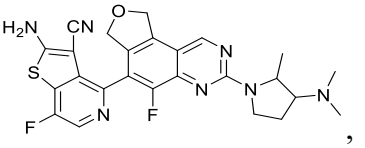
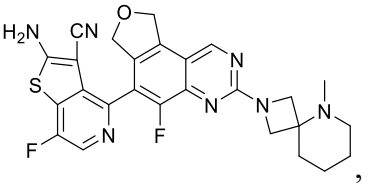
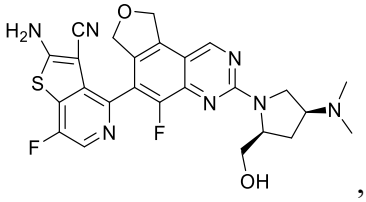
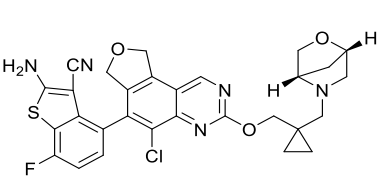
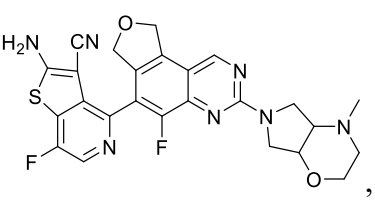

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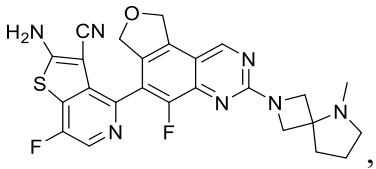
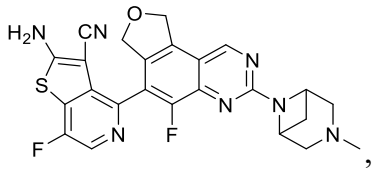
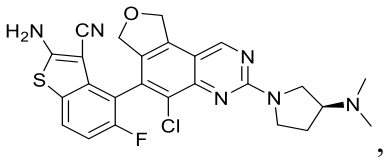
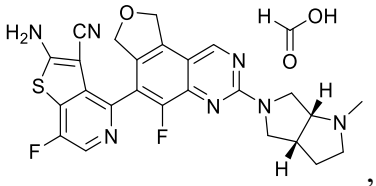
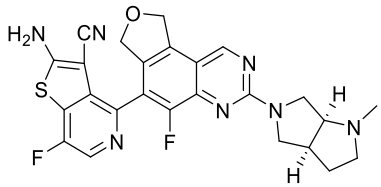
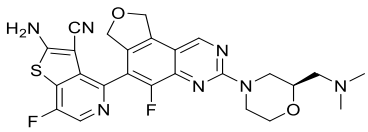
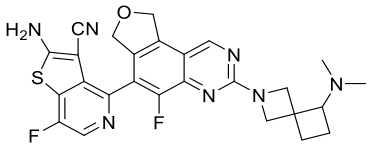
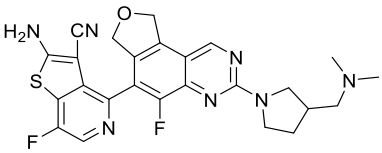
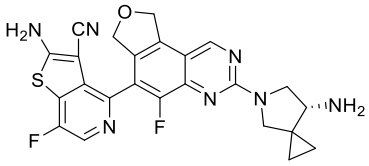
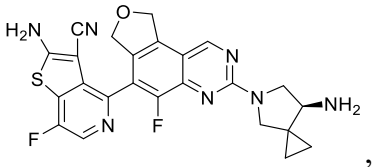
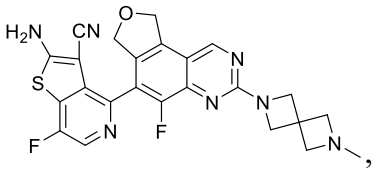
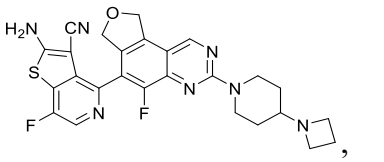
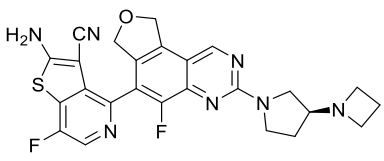
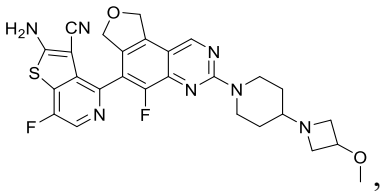
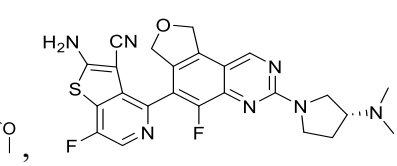
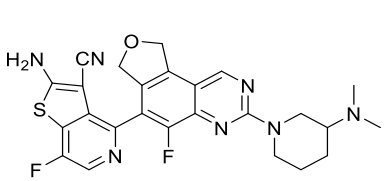
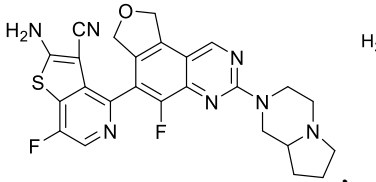
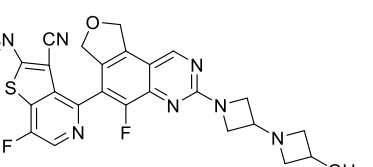
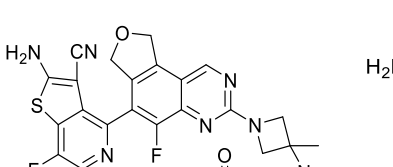
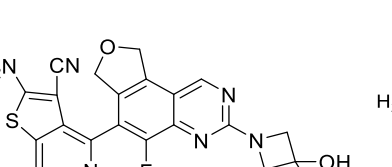
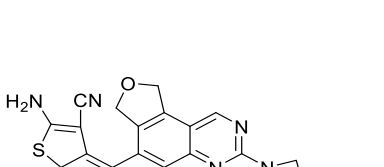
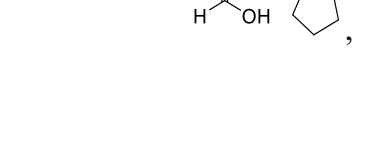
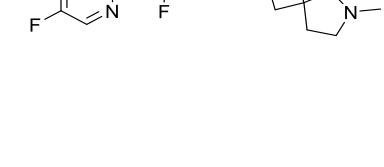
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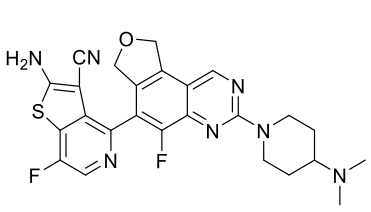
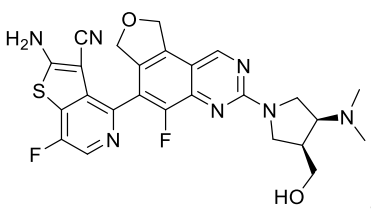
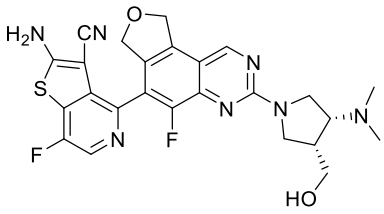
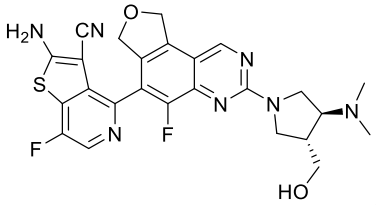
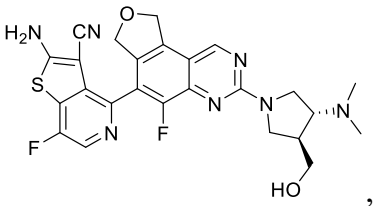
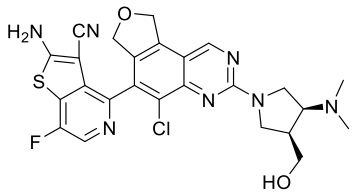
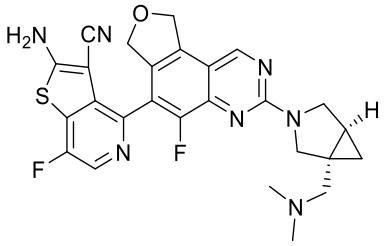
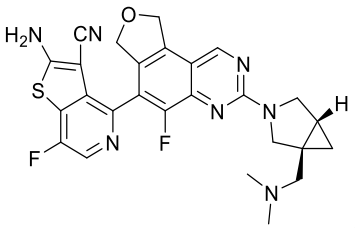
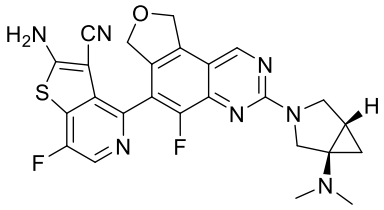
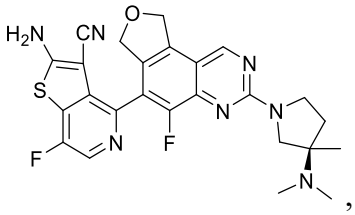
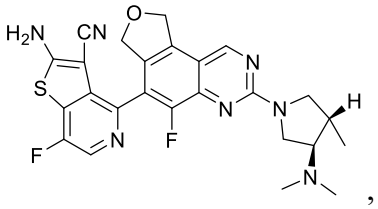
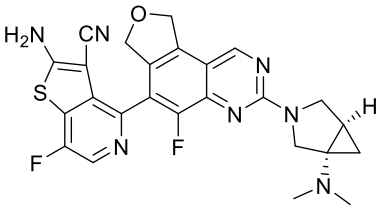
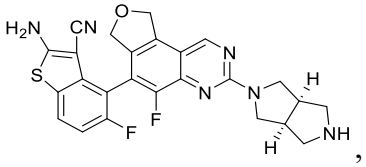
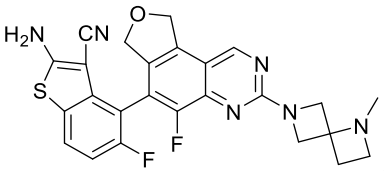
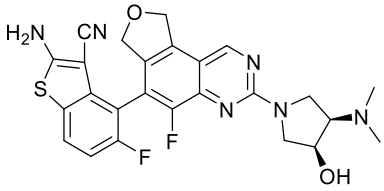
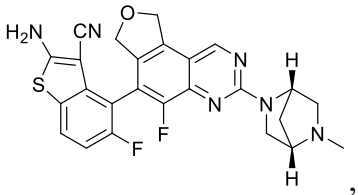
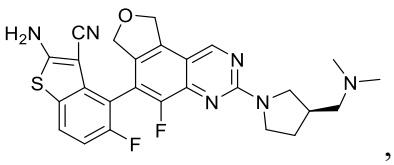
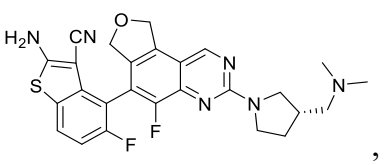
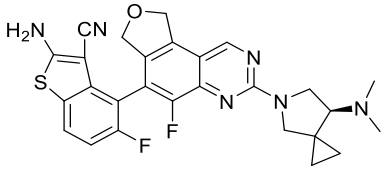
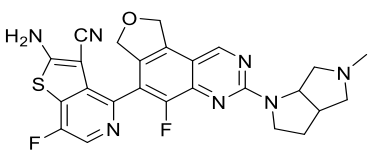
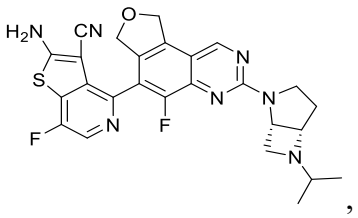
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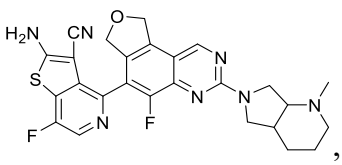
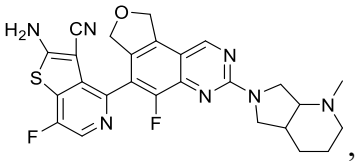
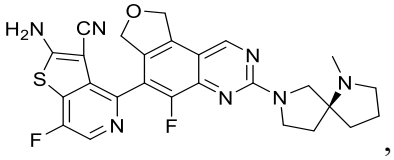
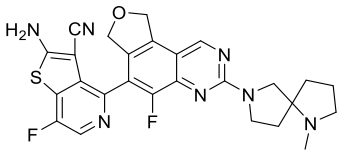
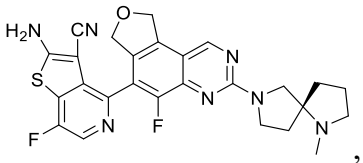
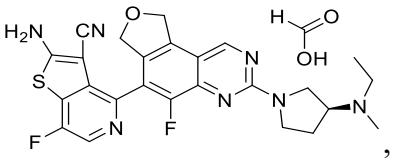
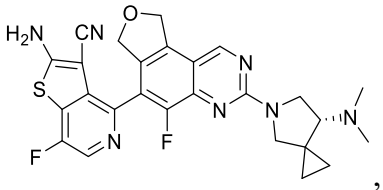
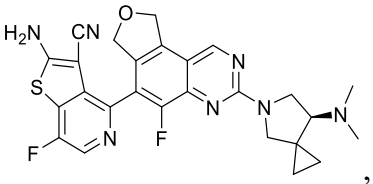
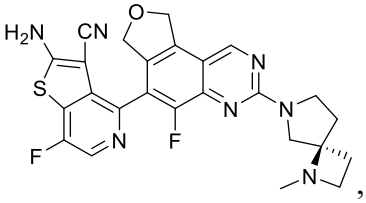
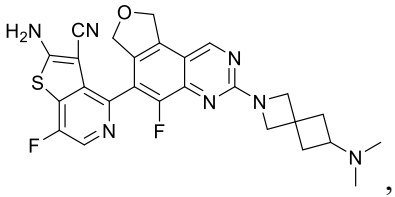
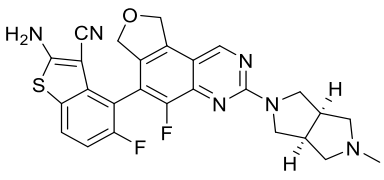
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 , and
 , or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising a compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

30. Use of a pharmaceutical composition according to claim 29 in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

31. Use of a compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

32. The use according to claim 30 or 31 wherein the compound or a pharmaceutically acceptable salt thereof is to be administered to the patient and wherein the patient has a cancer that

was determined to have one or more cells expressing the KRas G12C, G12D, and/or G12V mutant proteins prior to administration of the compound or a pharmaceutically acceptable salt thereof.

33. The use according to claim 30 or 31, wherein the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein.

34. Use of a compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient with a cancer that has a KRas G12C, G12D, and/or G12V mutation.

35. The use according to claim 34, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, mutant ovarian cancer, cholangiocarcinoma, and colorectal cancer.

36. The use according to any one of claims 30-35, wherein the compound or a pharmaceutically acceptable salt thereof and one or more of a PD-1 inhibitor, a PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor, an Aurora A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof are to be administered to the patient.

37. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-28, for use in therapy.

38. Use of the compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-28, in the manufacture of a medicament for the treatment of cancer.

39. The use according to claim 38 wherein the cancer has a KRas G12C, G12D, and/or G12V mutation.

40. The use according to claim 38 or 39 wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

41. The use according to claim 38 wherein the compound, or a pharmaceutically acceptable salt thereof, is to be used in simultaneous, separate, or sequential combination with one or more of a PD-1 or PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor,

an Aurora A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof, in the treatment of cancer.