KRAS INHIBITORS

Background

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.

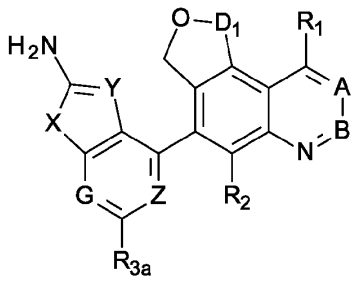
Oncogenic KRas mutations have been identified in approximately 30% of human cancers and have been demonstrated to activate multiple downstream signaling pathways. Despite the prevalence of KRas mutations, it has been a difficult therapeutic target. (Cox, A.D. *Drugging the Undruggable RAS: Mission Possible?* 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).

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 WO2021/041671discloses small molecules inhibitors of KRas G12D and WO2017/011920 discloses small molecule inhibitors of KRas G12C, G12D, and G12V.

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. There is also a need to provide small molecule KRas inhibitors that exhibit greater efficacy at the same or reduced KRas inhibitory 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. The present invention addresses one or more of these needs by providing novel KRas inhibitors.

Summary

Compounds of Formula I are provided herein:



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Formula I

pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof. In Formula I,

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

B is -C(R_4)- or -N-;

D_1 is -CH_2-, -CH_2CH_2-, or -$CH(CH_2CN)$-;

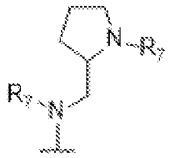
X is -O- or -S-;

Y is -C(CN)- or -N-;

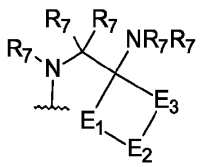
Z is -$C(R_{3c})$- or -N-;

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

R_1 is H, hydroxyl, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, azetidine, N-linked piperazine, piperidine, morpholine, or a group of the formula selected from



or



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wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, azetidine, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, methoxy, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, difluoromethoxy, -O-trideuteromethyl, cyclopropyl, oxetane, pyrazole, imidazole, amino, -$CONR_7R_7$, -O-$(CH_2)_p$-OC_{1-3} alkyl, -O-$(CH_2)_p$-OH, or -O-CO-C_{1-3} alkyl, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a hydroxyl, or a C_{1-3} alkyl substituted with one or more hydroxyl;

E_1 is –$(CR_7R_7–)_n$, E_2 is -CR_7R_7-, -NR_7- or -O- and E_3 is –$(CR_7R_7–)_m$, wherein m + n is 1, 2, 3 or 4;

p is 1, 2, or 3;

R_2 is H, halogen, or methyl;

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

R_4 is H, methyl, -CH_2-OH, -O-R_5-R_6, -O-R_6, or azetidine optionally substituted with NR_7R_7, wherein R_5 is -CH_2-, -$CH(CH_3)$-, or -CH_2-CH_2-, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl, 2-oxo-1,3-dihydrobenzimidazole, imidazole, or pyrazole, wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more oxo, halogen, hydroxyl, methoxy, difluoromethoxy, NR_7R_7, C_{1-4} alkyl, C_{1-4} alkenyl, -CN, or –CO-CH_2OH, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen, hydroxyl, methoxy, or NR_7R_7, wherein the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, or the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally bridged with a C_{1-3} alkyl and wherein if R_4 is H then R_1 is not H; and

each R_7 is independently H, or C_{1-3} alkyl.

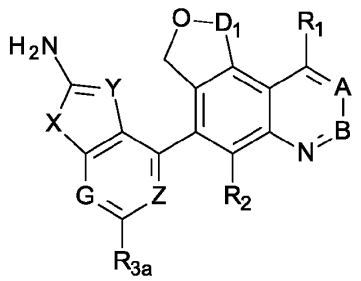
Also provided herein are methods of using the compounds of Formulae I-VIII (including Ia-VIIa), pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, to treat cancer, in particular for the treatment of lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer. The methods include administering a therapeutically effective amount of a compound of Formulae I-VIII (including Ia-VIIa), or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

Further provided herein, are compounds of Formulae I-VIII (including Ia-VIIa), and pharmaceutically acceptable salts thereof, for use in therapy. Additionally provided herein, are the compounds of Formulae I-VIII (including Ia-VIIa), 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 Formulae I-VIII (including Ia-VIIa), 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.

Detailed Description

Novel inhibitors of the KRas gain of function mutation G12D 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 G12D mutant 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 G12D mutant inhibitor compounds are non-selective and inhibit both wild-type KRas and KRas G12D mutants (and possibly other mutant types such as G12C or G12V). Also, some of these new KRas compounds are non-selective and inhibit both wild-type KRas and Kras G12C, G12D, and/or G12V mutants.

The present invention provides a compound of Formula I:



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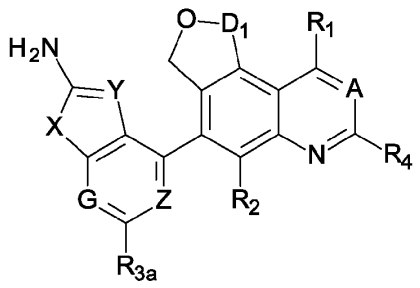
Formula I

wherein A, B, D_1, X, Y, Z, G, R_1, R_2, and R_{3a} are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula II is provided:



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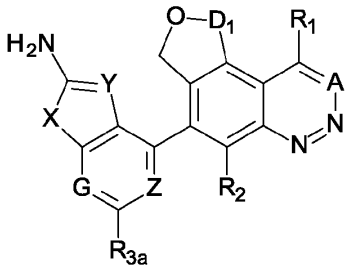
Formula II

wherein R_1, R_2, R_{3a}, R_4, A, D_1, X, Y, Z, and G are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula III is provided:



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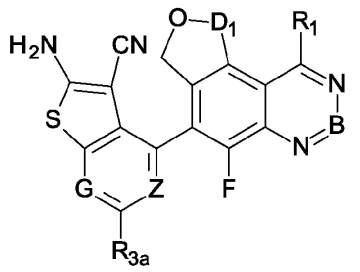
Formula III

wherein R_1, R_2, R_{3a}, A, D_1, X, Y, Z, and G are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula IV is provided:



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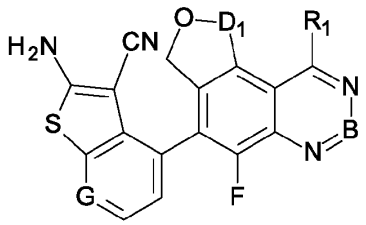
Formula IV

wherein R_1, R_{3a}, B, D_1, Z, and G are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula V is provided:



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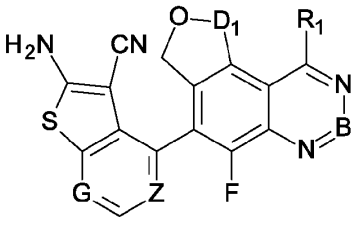
Formula V

wherein R_1, B, D_1, and G are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula VI is provided:



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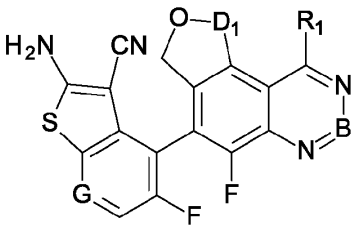
Formula VI

wherein R_1, B, D_1, Z, and G are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula VII is provided:



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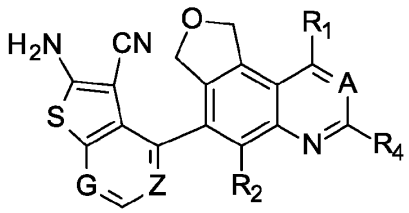
Formula VII

wherein R_1, B, D_1, and G are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula VIII is provided:



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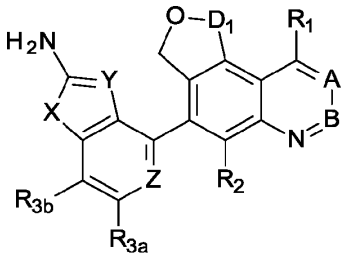
wherein R_1, R_2, R_4, A, Z, and G are as defined above, or a pharmaceutically acceptable salt thereof.

The present invention provides a compound of Formula Ia:



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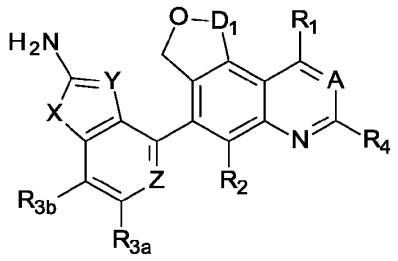
Formula Ia

wherein A, B, D_1, X, Y, Z, R_1, R_2, R_{3a}, and R_{3b} are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula IIa is provided:



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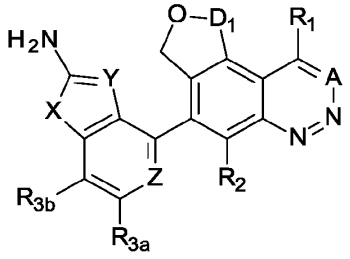
Formula IIa

wherein R_1, R_2, R_{3a}, R_{3b}, R_4, A, D_1, X, Y, and Z are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula IIIa is provided:



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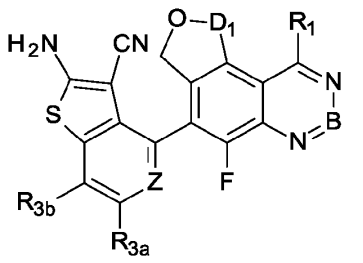
Formula IIIa

wherein R_1, R_2, R_{3a}, R_{3b}, A, D_1, X, Y, and Z are as defined above, or a pharmaceutically acceptable salt thereof.

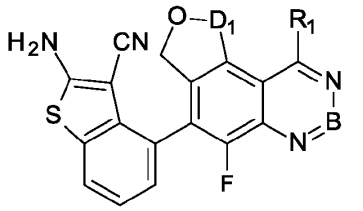
In an embodiment a compound of Formula IVa is provided:



Formula IVa

wherein R_1, R_{3a}, R_{3b}, B, D_1, and Z are as defined above, or a pharmaceutically acceptable salt thereof.

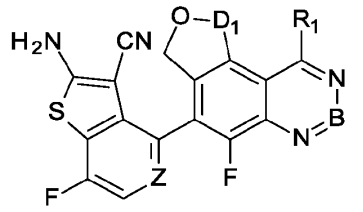
In an embodiment a compound of Formula Va is provided:



Formula Va

wherein R_1, B, and D_1 are as defined above, or a pharmaceutically acceptable salt thereof.

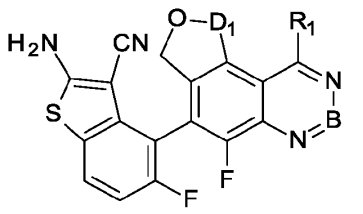
In an embodiment a compound of Formula VIa is provided:



Formula VIa

wherein R_1, B, D_1, and Z are as defined above, or a pharmaceutically acceptable salt thereof.

In an embodiment a compound of Formula VIIa is provided:



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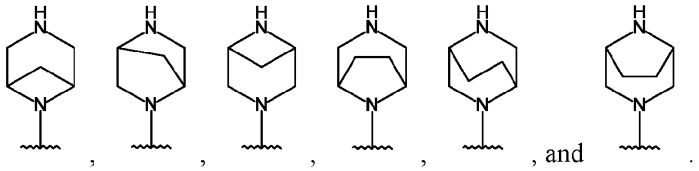
Formula VIIa

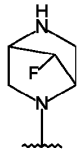
wherein R_1, B, and D_1 are as defined above, or a pharmaceutically acceptable salt thereof.

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 cycloalkyl means saturated cyclic monovalent hydrocarbon radicals containing a specified number of carbon atoms, e.g., "C_{4-6} cycloalkyl." As used herein, the term heteroalkyl means saturated linear or branched-chain monovalent hydrocarbon radicals containing a specified number of atoms including both carbon atoms and one or more heteroatoms, e.g., "C_{2-3} heteroalkyl" and "C_{2-4} heteroalkyl." For example, C_4 heteroalkyl means a saturated linear or branched-chain monovalent hydrocarbon radical containing at least one carbon atoms and at least one heteroatoms, wherein the total number of carbon and heteroatoms adds up to 4 atoms. As used herein, the term heterocycloalkyl means saturated cyclic heteroalkyl groups containing a specified number of atoms including both carbon atoms and one or more heteroatoms, e.g., "C_{4-6} heterocycloalkyl." Examples of heteroatoms include, but are not limited to, nitrogen and oxygen.

For R_1, the N-linked piperazine (or the piperidine) is optionally bridged by the C_{1-3} alkyl. As used herein, the term "bridged" for the R_1 group means the R_1 group is bicyclic with the C_{1-3} alkyl connecting to two, non-adjacent atoms of the N-linked piperazine ring. Examples of bridged N-linked piperazine ring groups include, but are not limited to:

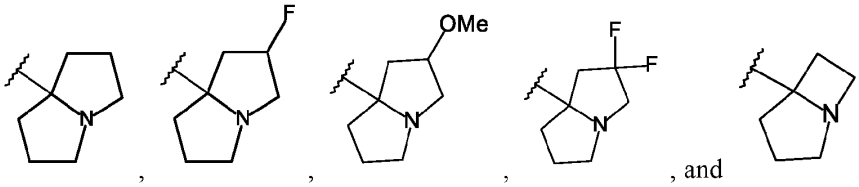


When acting as a bridge, the C_{1-3} alkyl can optionally be substituted as defined, e.g., with a halogen like fluorine such as:



In R_1, the N-linked piperazine group is not specified to be bonded through a carbon or nitrogen and could be either. Similarly, optional substitutions onto the C_{2-4} heteroalkyl, or N-linked piperazine groups of R_1 can be on a carbon or heteroatom.

For R_6, the C_{4-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with a C_{1-4} alkyl to form a bicyclic ring. As used herein, the term "fused" for the R_7 group means the R_6 group is bicyclic with the C_{1-4} alkyl connecting to two, adjacent atoms of the C_{4-6} cycloalkyl or C_{4-6} heterocycloalkyl ring. Examples of fused R_6 groups include:



In R_6, the C_{4-6} heterocycloalkyl group is not specified to be bonded through a carbon or nitrogen and could be either. Similarly, substitutions onto the R_6 C_{4-6} heterocycloalkyl group can be on a carbon or heteroatom.

In an embodiment of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, A is -C(H)- or -N-; B is $-C(R_4)-$ or -N-; D_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH(CH_2CN)-$;

X is -O- or -S-; Y is -C(CN)- or -N-; Z is -C(R_{3c})- or -N-; R_1 is H, C_{1-4} alkyl, C_{1-4} heteroalkyl, or N-linked piperazine, wherein the C_{1-4} alkyl, C_{1-4} heteroalkyl, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, oxetane, and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, cyclopropyl, oxetane, or amino, and wherein the N-linked piperazine is optionally bridged by the C_{1-3} alkyl; R_2 is H, halogen, or methyl; R_{3a}, R_{3b}, and R_{3c} are each independently H or halogen; and R_4 is H, methyl, -CH_2-OH, -O-R_5-R_6, or -O-R_6, wherein R_5 is -CH_2-, -$CH(CH_3)$-, or -CH_2-CH_2-, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heterocycloalkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl, wherein the C_{1-3} alkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more halogen, hydroxyl, methoxy, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{4-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, and wherein if R_4 is H then R_1 is not H.

In an embodiment of a compound of Formulae I, Ia, II, IIa, III, IIIa, or VIII or a pharmaceutically acceptable salt thereof, A is -N-.

In an embodiment of a compound of Formulae I, Ia, II, IIa, III, IIIa, or VIII or a pharmaceutically acceptable salt thereof, A is -C(H)-.

In an embodiment of a compound of Formulae I, Ia, IV, Iva, V, Va, VI, Via, VII, or VIIa or a pharmaceutically acceptable salt thereof, B is -N-.

In an embodiment of a compound of Formulae I, Ia, IV, Iva, V, Va, VI, Via, VII, or VIIa or a pharmaceutically acceptable salt thereof, B is -CH-.

In an embodiment of a compound of Formulae I, Ia, IV, Iva, V, Va, VI, Via, VII, or VIIa or a pharmaceutically acceptable salt thereof, B is -C(R_4)-.

In an embodiment of a compound of Formulae I, Ia, II, IIa, III, IIIa, IV, Iva, V, Va, VI, Via, VII, or VIIa or a pharmaceutically acceptable salt thereof, D_1 is -CH_2-.

In an embodiment of a compound of Formulae I, Ia, II, IIa, III, or IIIa or a pharmaceutically acceptable salt thereof, X is -S-.

In an embodiment of a compound of Formulae I, Ia, II, IIa, III, or IIIa or a pharmaceutically acceptable salt thereof, Y is -C(CN)-.

In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, or IVa or a pharmaceutically acceptable salt thereof, Z is -C(R_{3c})-.

In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, or IVa or a pharmaceutically acceptable salt thereof, Z is -N-.

In an embodiment of a compound of any of Formulae I, II, III, IV, V, or VII or a pharmaceutically acceptable salt thereof, G is -C(R_{3b})-.

In an embodiment of a compound of any of Formulae I, II, III, IV, V, or VII or a pharmaceutically acceptable salt thereof, G is -N-.

In an embodiment of a compound of any of Formulae I, II, III, IV, or VII or a pharmaceutically acceptable salt thereof, G is -N-, and Z is -C(R_{3c})-.

In an embodiment of a compound of any of Formulae I, II, III, IV, V, or VII or a pharmaceutically acceptable salt thereof, G is -C(R_{3b})-.

In an embodiment of a compound of any of Formulae I, II, III, IV, or VII or a pharmaceutically acceptable salt thereof, G is -C(R_{3b})-, and Z is -N-.

In an embodiment of a compound of any of Formulae I, II, III, or IV or a pharmaceutically acceptable salt thereof, R_{3b} is F, or a pharmaceutically acceptable salt thereof.

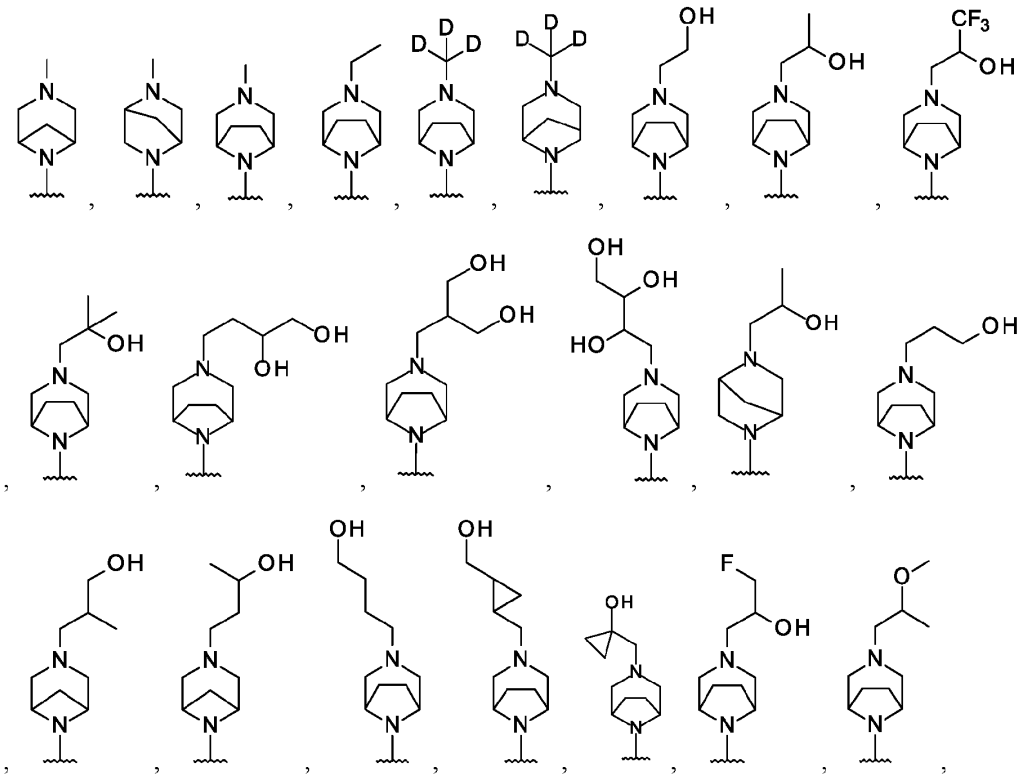
In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is H.

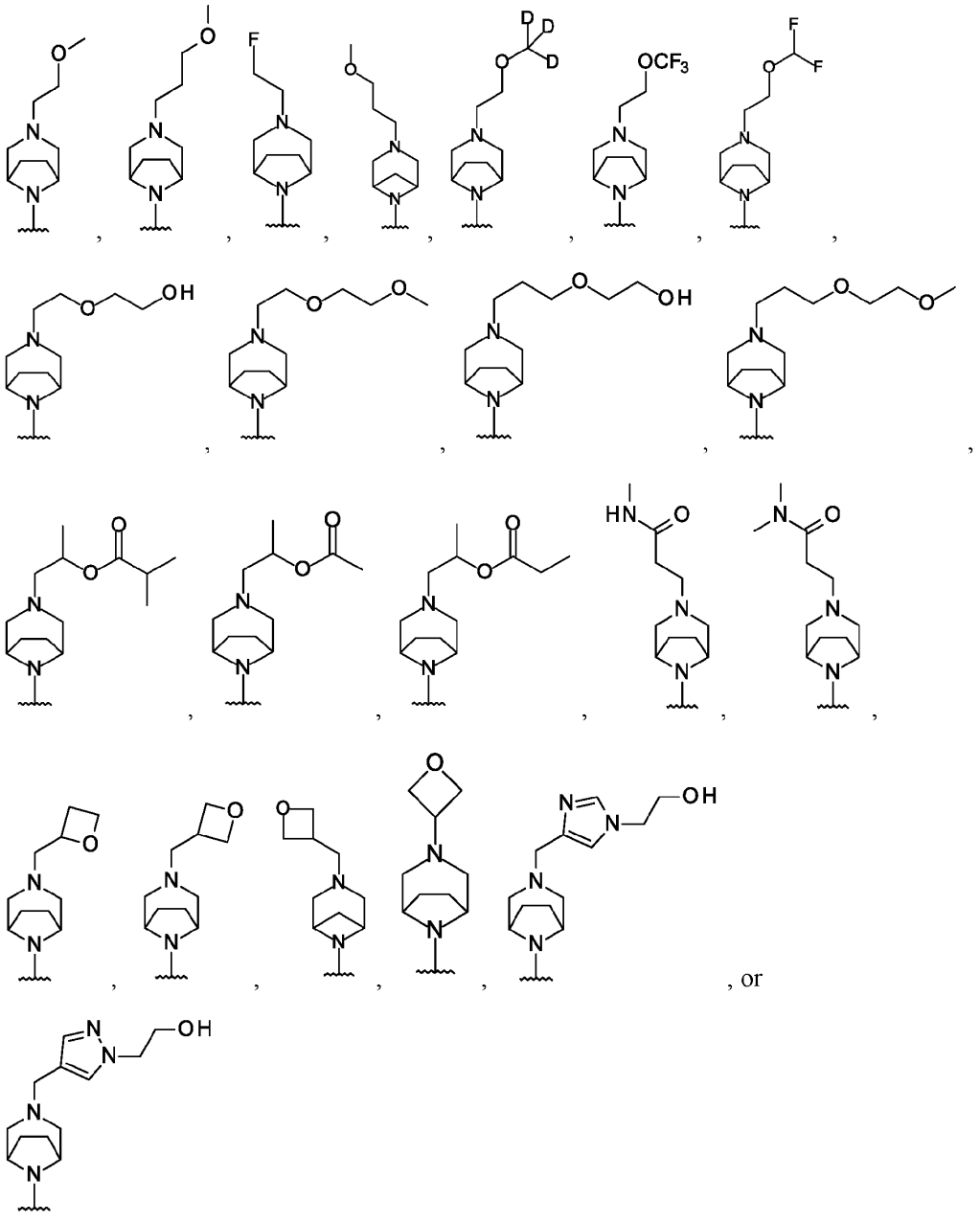
In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is N-linked piperazine, which can be optionally substituted as defined above.

In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is an optionally substituted N-linked piperazine bridged by a C_{1-3} alkyl.

In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is N-linked piperazine substituted with one or more of methyl, trideuteromethyl, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, difluoromethoxy, -O-trideuteromethyl, cyclopropyl, oxetane, pyrazole, imidazole, $-CONR_7R_7$, $-O-(CH_2)_p-OC_{1-3}$ alkyl, $-O-(CH_2)_p-OH$, or $-O-CO-C_{1-3}$ alkyl, and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a hydroxyl or a C_{1-3} alkyl substituted with one or more hydroxyl;, and wherein the N-linked piperazine is bridged by a C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is selected from





, or

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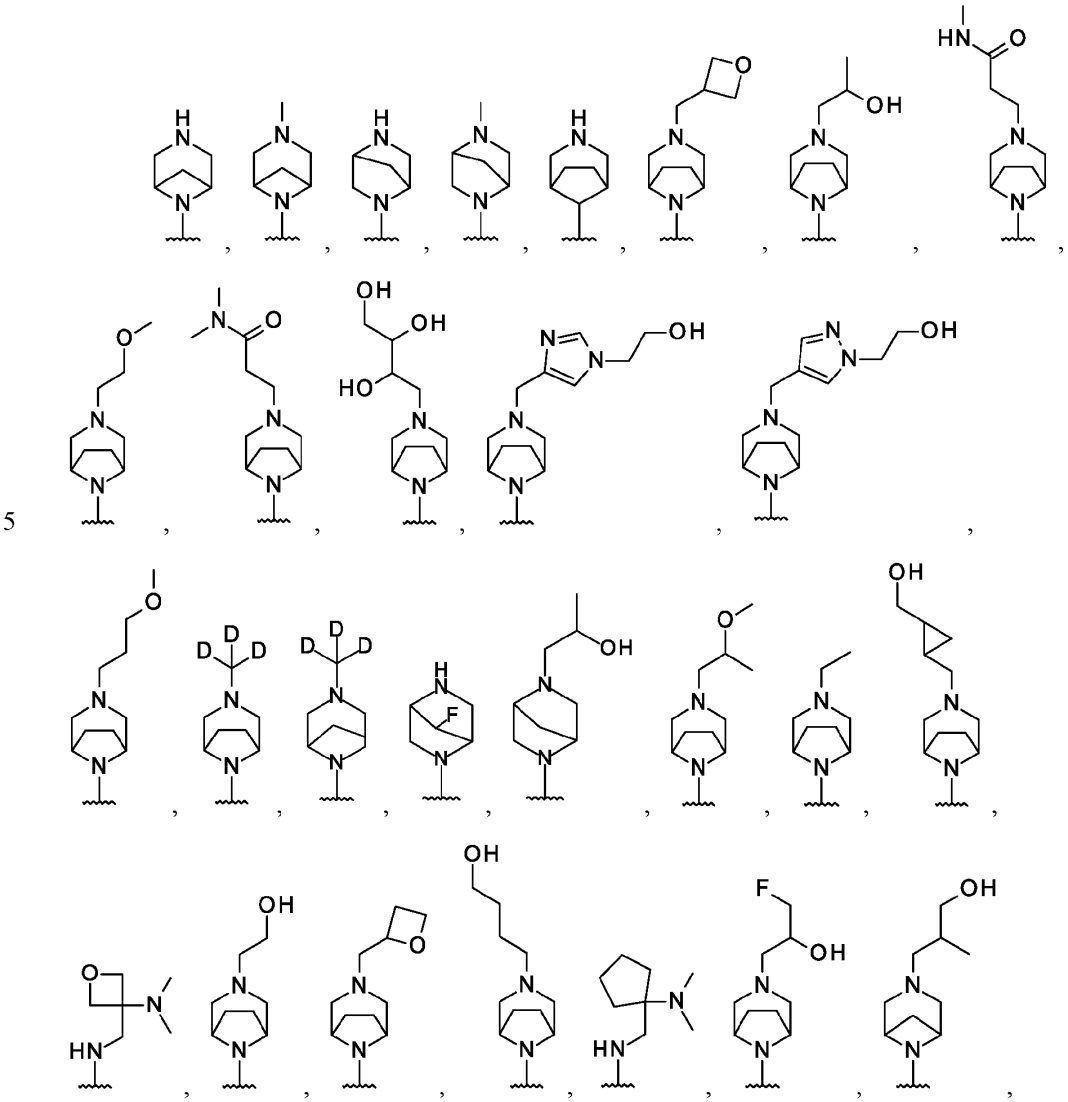
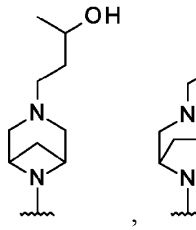
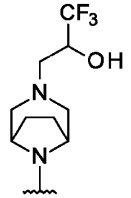
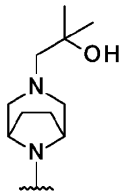
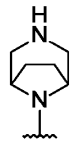
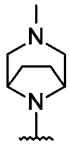
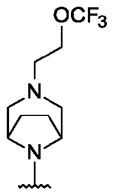
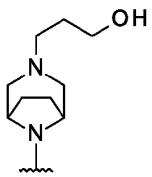
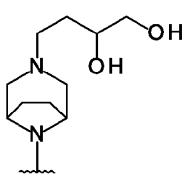
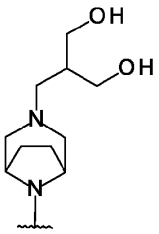
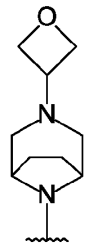
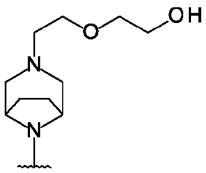
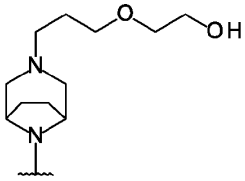
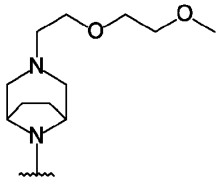
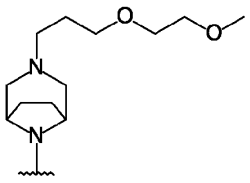
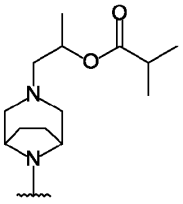
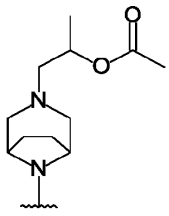
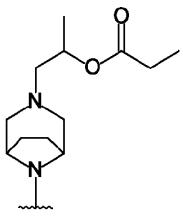
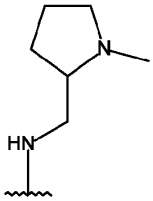
In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is H, methoxy, $-CH_2-CH_2-NH_2$, or a group of the formula





















, or .

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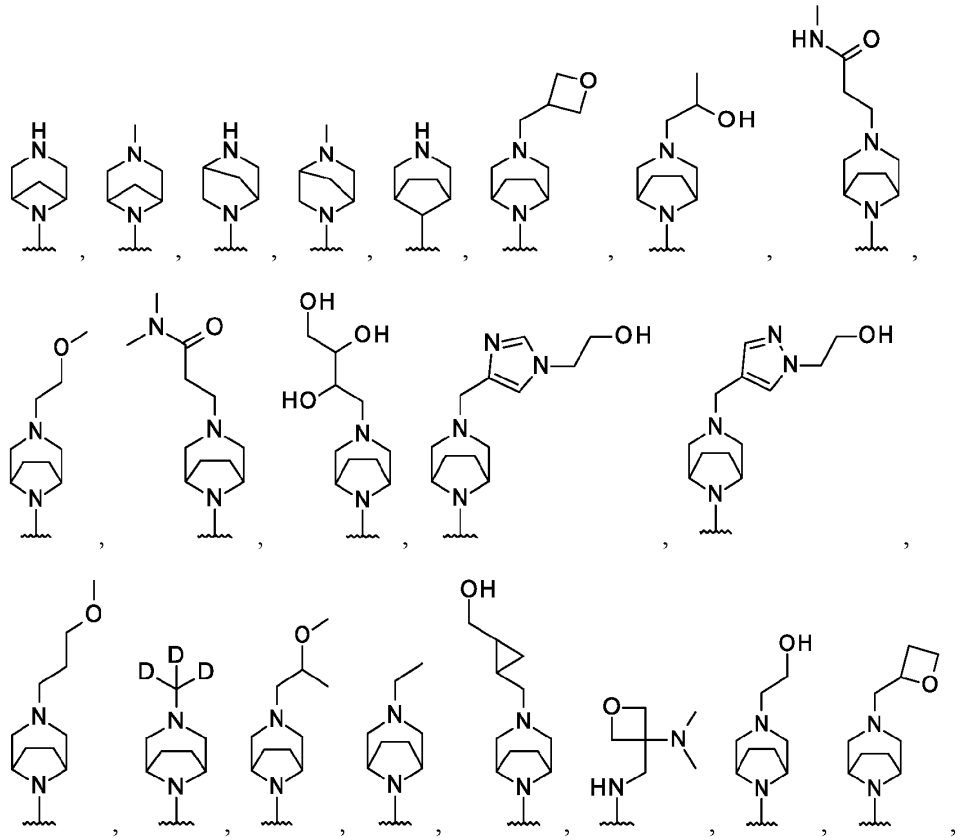
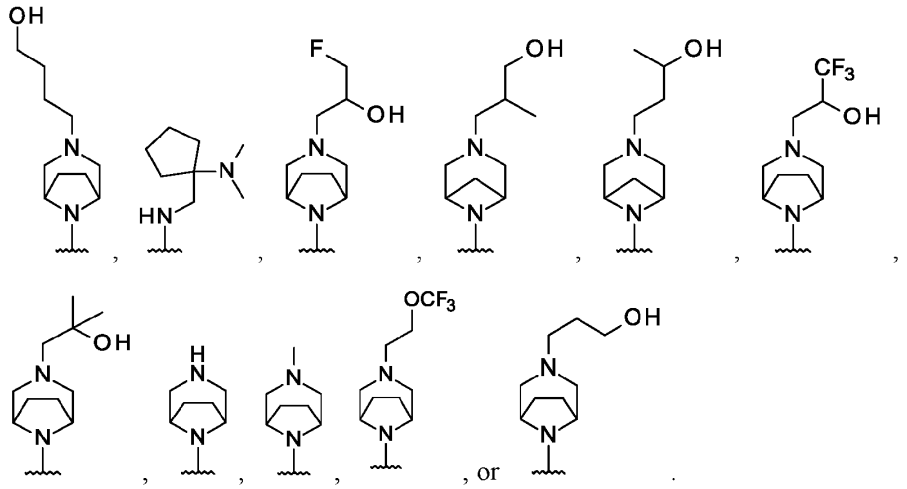
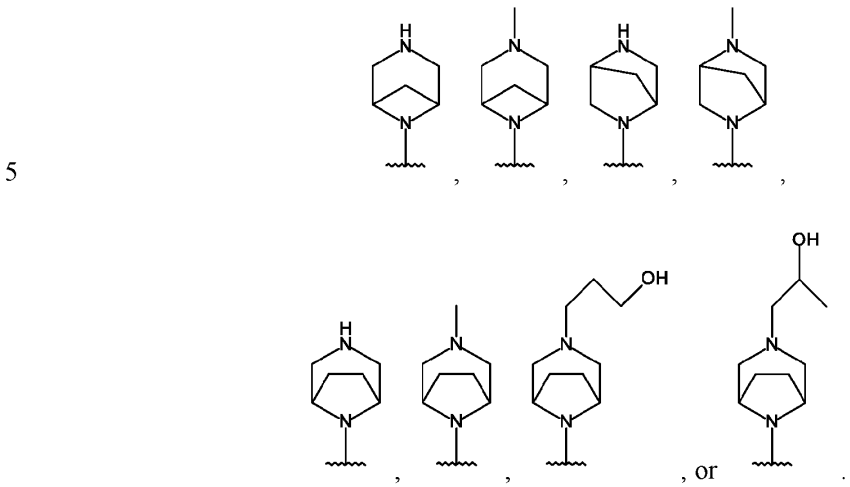
In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is

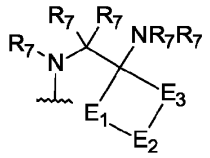




In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is



In an embodiment of a compound of any of Formulae I, Ia, II, IIa, III, IIIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_1 is H, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, N-linked piperazine, piperidine, or a group of the formula



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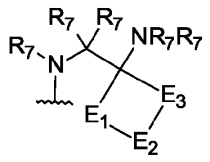
wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, cyclopropyl, oxetane, pyrazole, imidazole, amino, $-CONR_7R_7$, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a C_{1-3} alkyl substituted with one or more hydroxyl.

In an embodiment of a compound of Formulae I, Ia, II, IIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is H, methyl, $-CH_2$-OH, -O-R_5-R_6, or -O-R_6, wherein R_5 is $-CH_2$-, $-CH_2(CH_3)$-, or $-CH_2$-CH_2-, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heterocycloalkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl, wherein the C_{1-3} alkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more halogen, hydroxyl, methoxy, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{4-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, and wherein if R_4 is H then R_1 is not H.

In an embodiment of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, R_{3a}, R_{3b}, and R_{3c} are each independently H, or halogen; and R_1 is H, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, N-linked piperazine, piperidine, or a group of the formula



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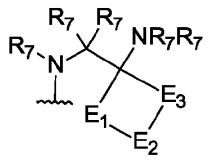
wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, cyclopropyl, oxetane, pyrazole, imidazole, amino, $-CONR_7R_7$, $-O-(CH_2)_p-OC_{1-3}$ alkyl, $-O-(CH_2)_p-OH$, or $-O-CO-C_{1-3}$ alkyl, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a C_{1-3} alkyl substituted with one or more hydroxyl; and R_4 is H, methyl, $-CH_2-OH$, $-O-R_5-R_6$, $-O-R_6$, or azetidine optionally substituted with NR_7R_7, wherein R_5 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2-CH_2-$, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl or 2-oxo-1,3-dihydrobenzimidazole, wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more halogen, hydroxyl, methoxy, NR_7R_7, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, or the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally bridged with a C_{1-3} alkyl and wherein if R_4 is H then R_1 is not H; or a pharmaceutically acceptable salt thereof.

In an embodiment of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, R_{3a}, R_{3b}, and R_{3c} are each independently H, or halogen; and R_1 is H, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, N-linked piperazine, piperidine, or a group of the formula



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wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, cyclopropyl, oxetane, pyrazole, imidazole, amino, or $-CONR_7R_7$, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a C_{1-3} alkyl substituted with one or more hydroxyl; and R_4 is H, methyl, $-CH_2-OH$, $-O-R_5-R_6$, $-O-R_6$, or azetidine optionally substituted with NR_7R_7, wherein R_5 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2-CH_2-$, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl or 2-oxo-1,3-dihydrobenzimidazole, wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more halogen, hydroxyl, methoxy, NR_7R_7, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, or the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally bridged with a C_{1-3} alkyl and wherein if R_4 is H then R_1 is not H; or a pharmaceutically acceptable salt thereof.

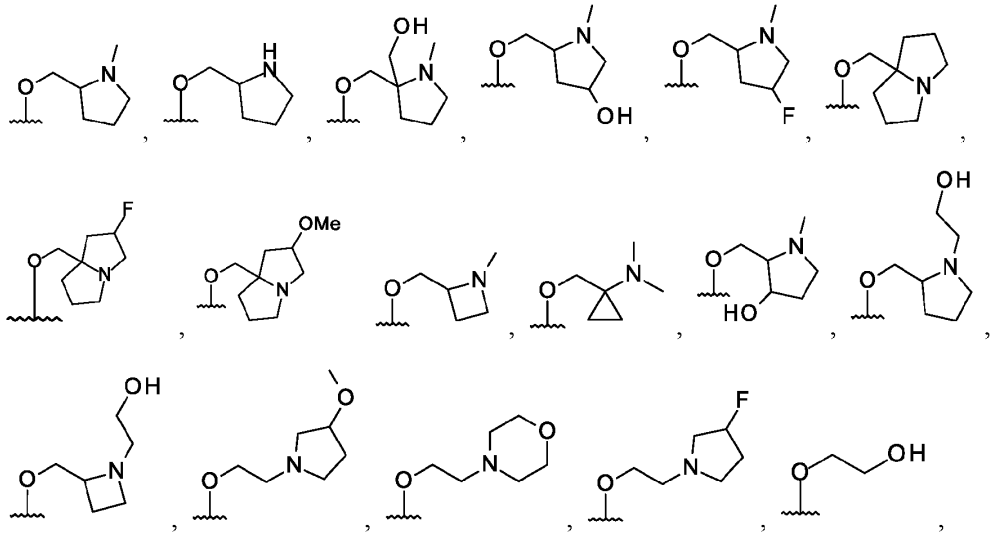
In an embodiment of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, R_{3a}, R_{3b}, and R_{3c} are each independently H, or halogen; R_1 is H, C_{1-4} alkyl, C_{2-4} heteroalkyl, or N-linked piperazine, wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, cyclopropyl, oxetane, or amino, and wherein the

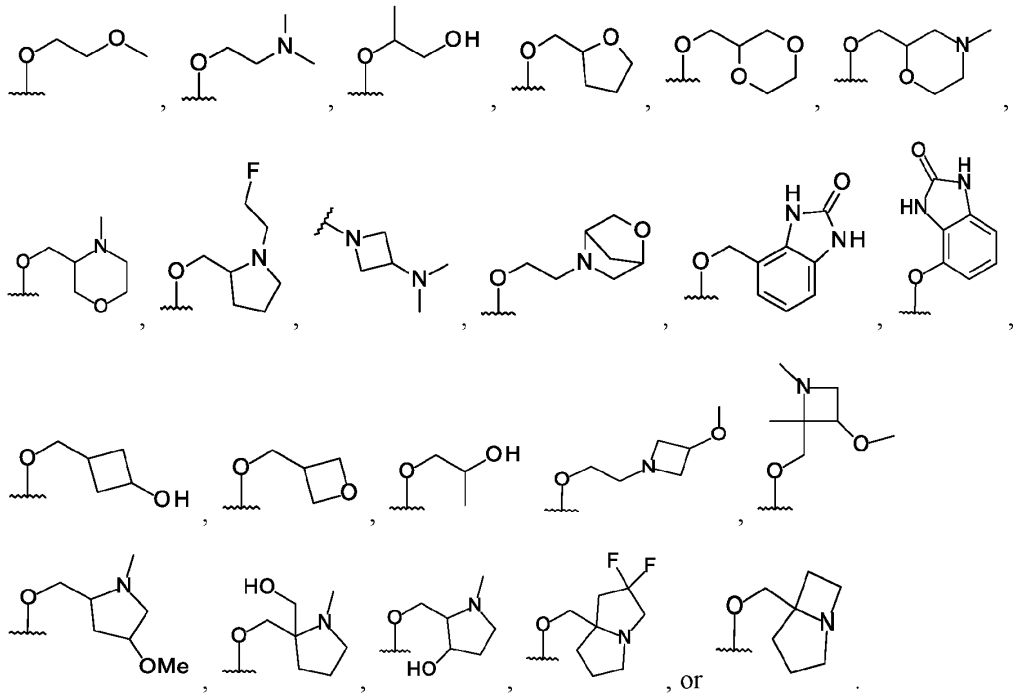
N-linked piperazine is optionally bridged by the C_{1-3} alkyl; and R_4 is H, methyl, $-CH_2$-OH, -O-R_5-R_6, or -O-R_6, wherein R_5 is $-CH_2$-, $-CH_2(CH_3)$-, or $-CH_2-CH_2$-, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl, wherein the C_{1-3} alkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more halogen, hydroxyl, methoxy, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{4-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, and wherein if R_4 is H then R_1 is not H; or a pharmaceutically acceptable salt thereof.

In an embodiment of a compound of Formulae Formulae I, Ia, II, IIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is $-O-CH_2-R_6$.

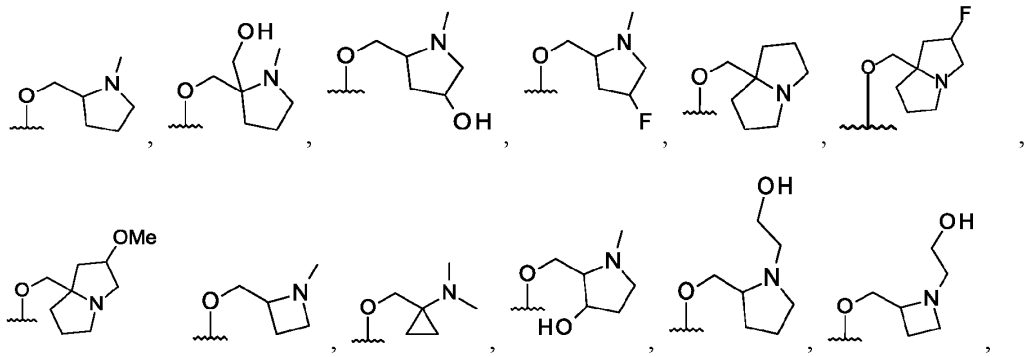
In an embodiment of a compound of Formulae II, IIa, IV or IVa or a pharmaceutically acceptable salt thereof, R_6 is azetidine, pyrrolidine, piperidine, oxetane, tetrahydrofuran, morpholine, cyclobutane, or 1,4-dioxane.

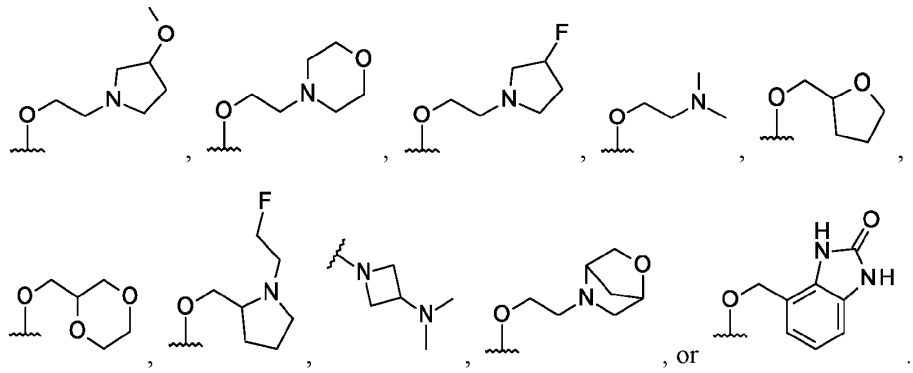
In an embodiment of a compound of Formulae Formulae I, Ia, II, IIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is methyl, methoxy, $-CH_2$-OH, or a group of the formula



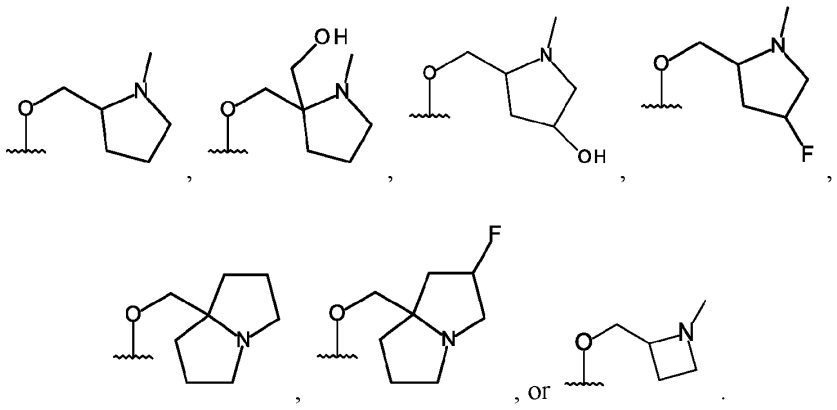


In an embodiment of a compound of Formulae Formulae I, Ia, II, IIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is

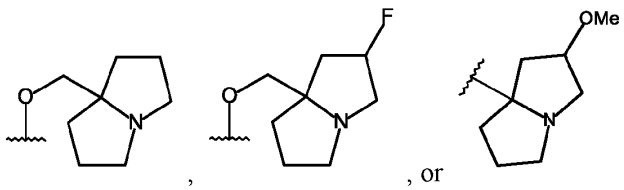




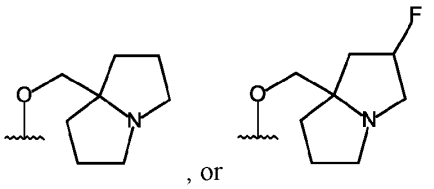
In an embodiment of a compound of Formulae I, Ia, II, IIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is



In an embodiment of a compound of Formulae Formulae I, Ia, II, IIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is

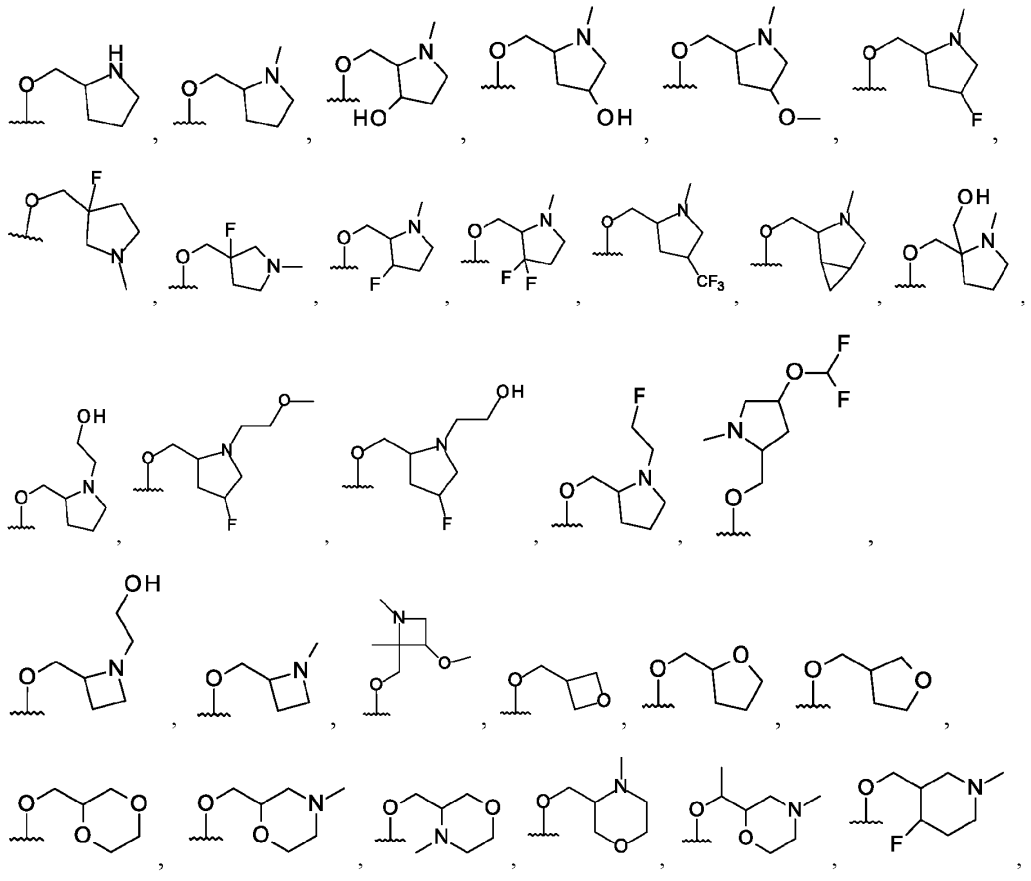


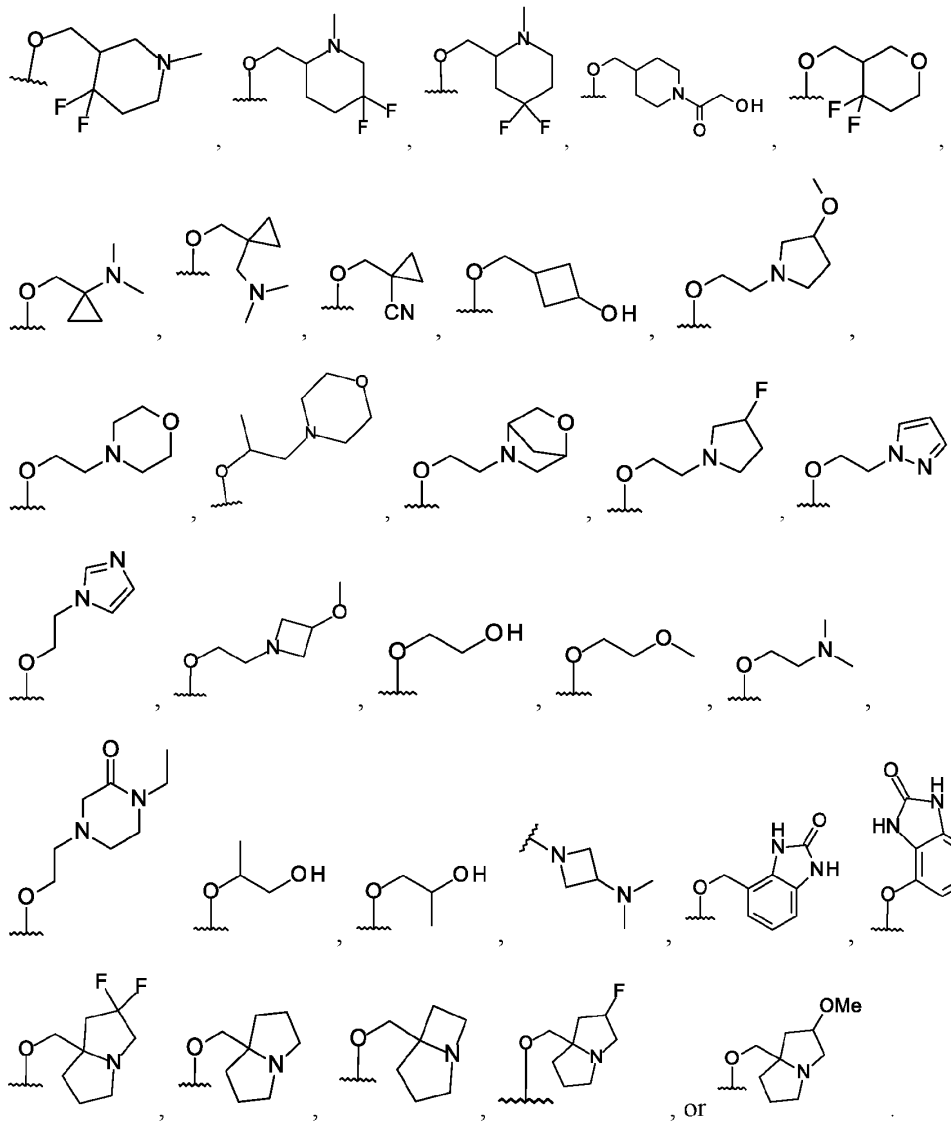
In an embodiment of a compound of Formulae Formulae I, Ia, II, IIa, IV, IVa, V, Va, VI, VIa, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is



, or .

In an embodiment of a compound of Formulae Formulae I, Ia, II, IIa, IV, Iva, V, Va, VI, Via, VII, VIIa, or VIII or a pharmaceutically acceptable salt thereof, R_4 is selected from





In an embodiment of a compound of Formulae I, Ia, II, IIa, III, IIIa or VIII or a pharmaceutically acceptable salt thereof, R_2 is F or Cl.

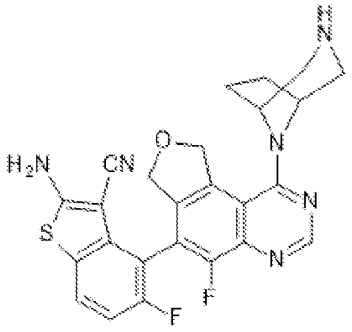
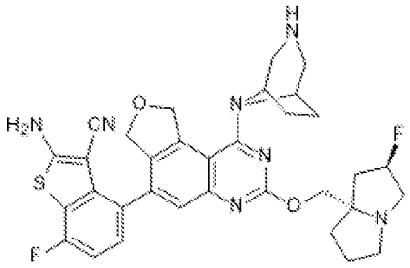
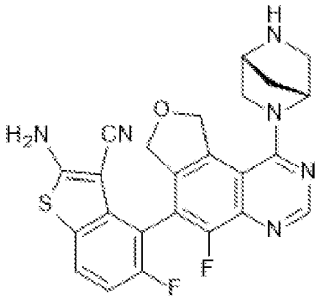
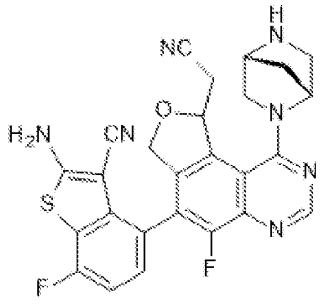
In an embodiment of a compound of Formulae I, Ia, II, IIa, III, IIIa, IV, or IVa or a pharmaceutically acceptable salt thereof, R_{3b} and R_{3c} are each independently H or F.

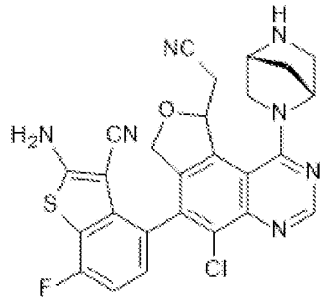
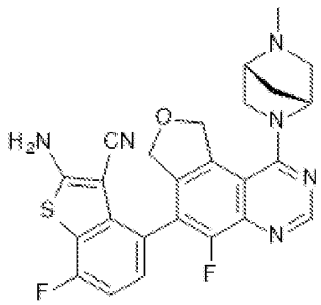
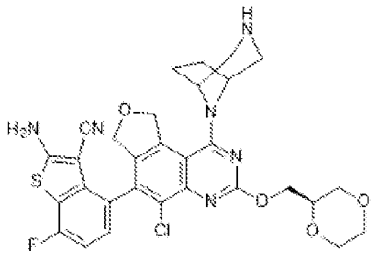
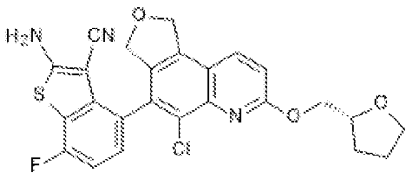
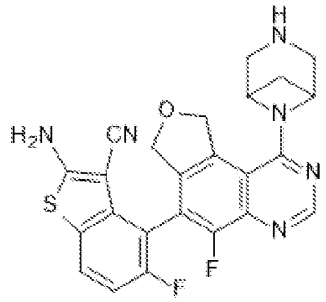
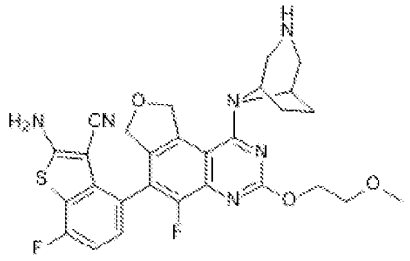
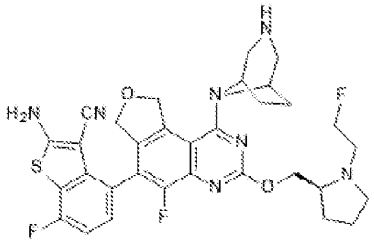
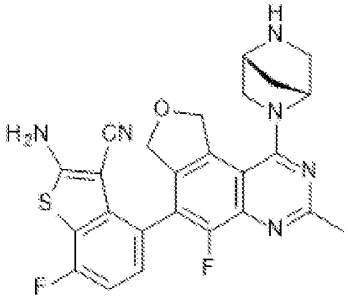
In an embodiment of a compound of Formulae I, Ia, II, or IIa or a pharmaceutically acceptable salt thereof, X is S, Y is -C(CN)-, R_2 is F or Cl, R_{3a} is H, R_{3b} is H, R_{3c} is F, and D_1 is $-CH_2-$.

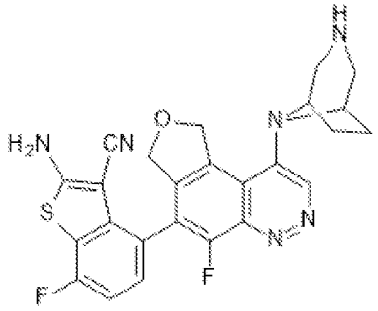
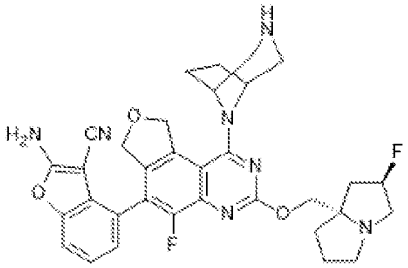
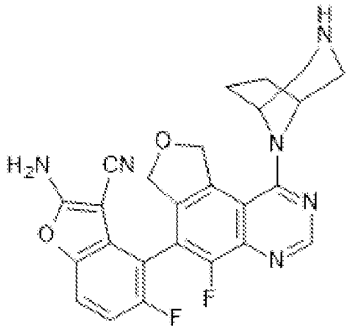
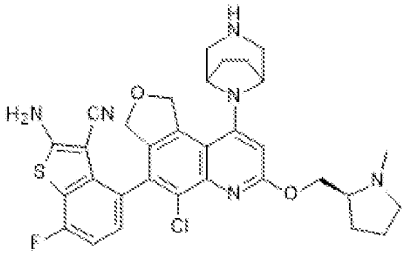
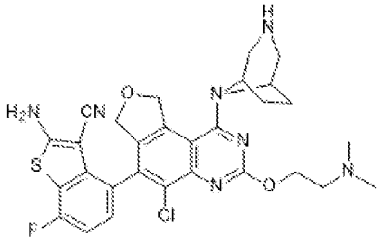
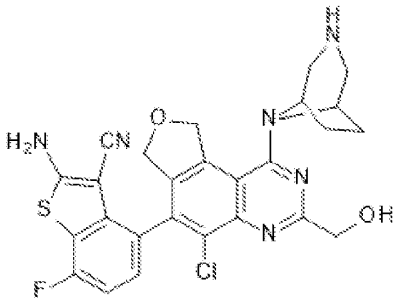
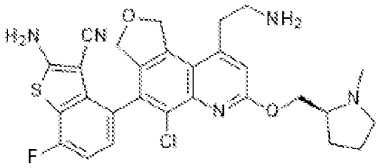
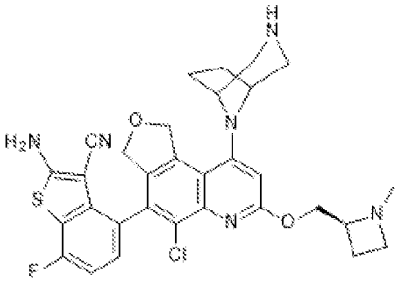
In the above embodiments of the compounds of Formulae I – VIII (including Ia-VIIa), the chemical drawings are shown flat without chiral information. These compounds often have multiple chiral centers and are contemplated to exist is various forms with various combinations of chiral centers. Additionally, these compounds have various enantiomers, diastereomers, and atropisomers that can exist and are included herein.

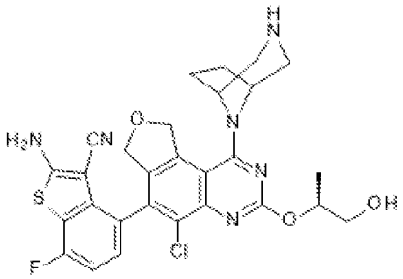
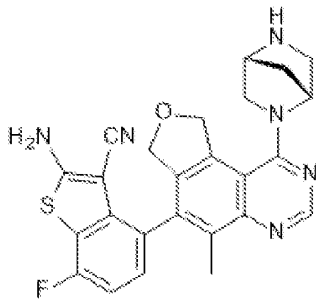
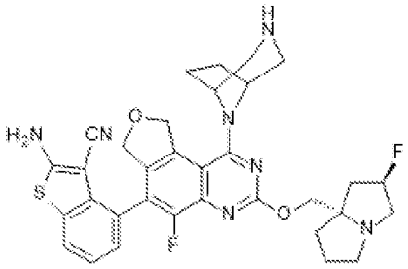
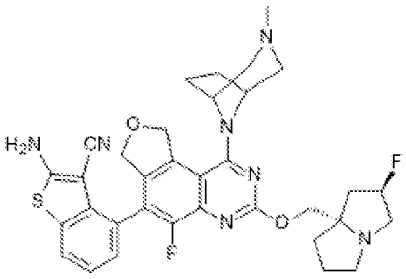
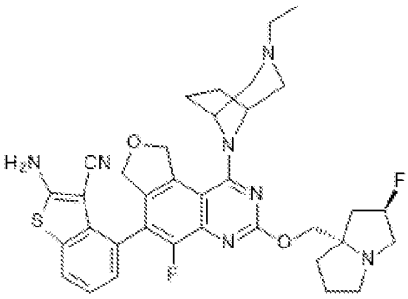
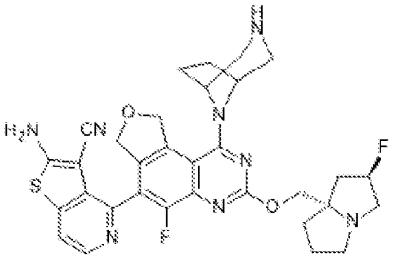
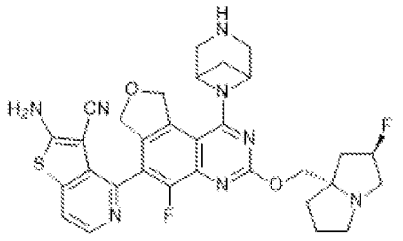
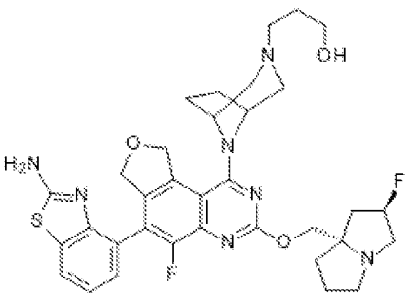
Examples of compounds described herein include the compounds of Table A and pharmaceutically acceptable salts thereof.

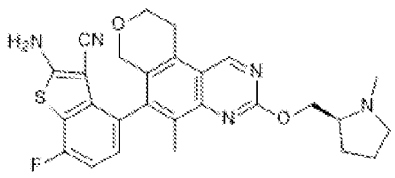
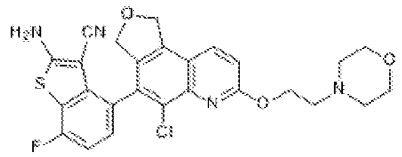
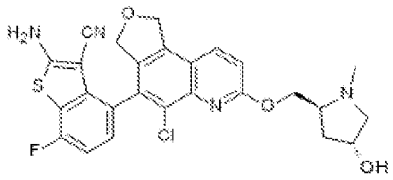
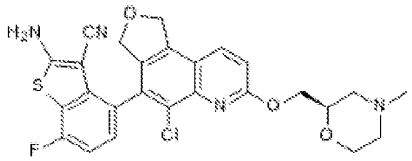
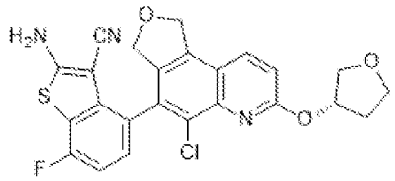
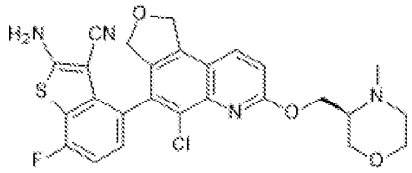
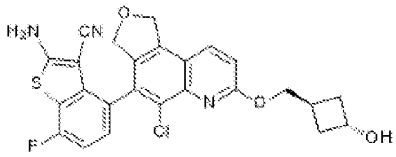
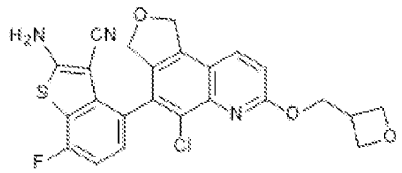
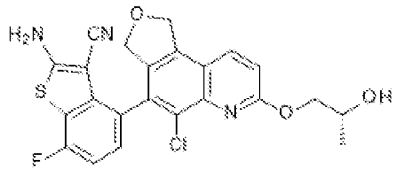
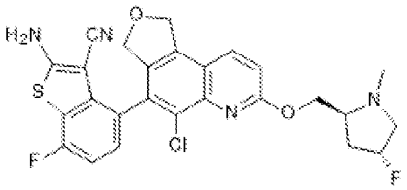
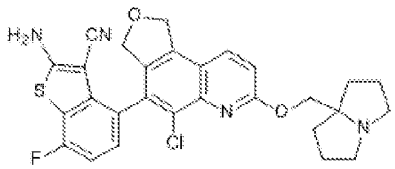
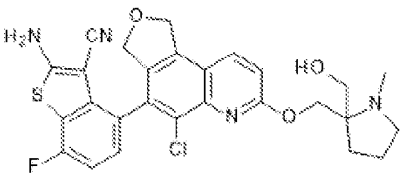
Table A: Example Compounds

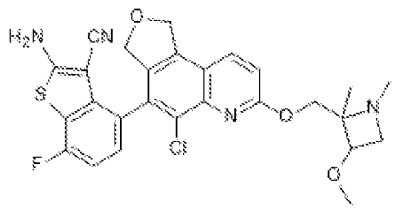
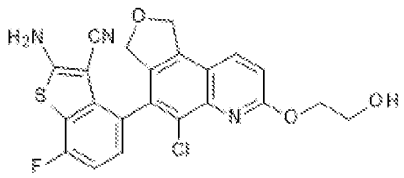
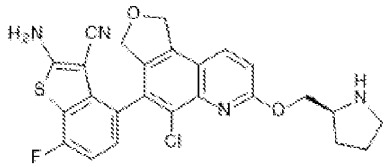
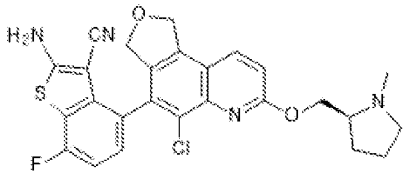
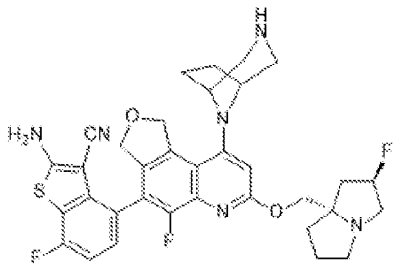
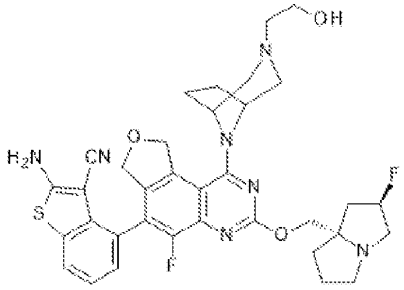
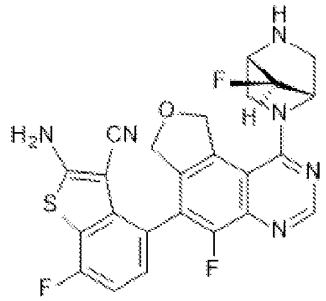
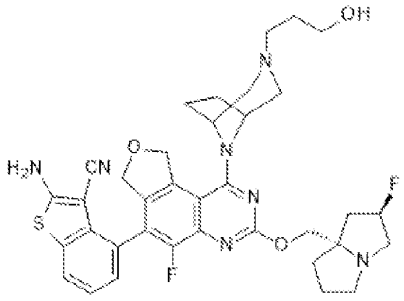
Ex. #	Compound	Ex. #	Compound
1		2	
3		4	

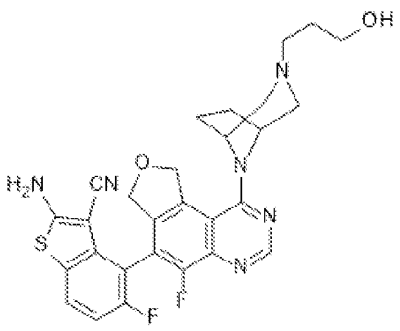
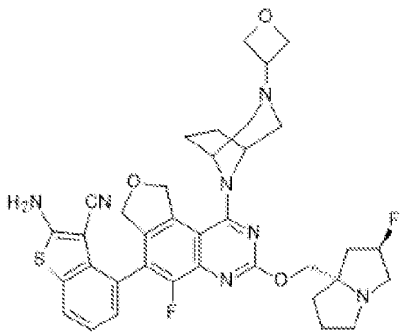
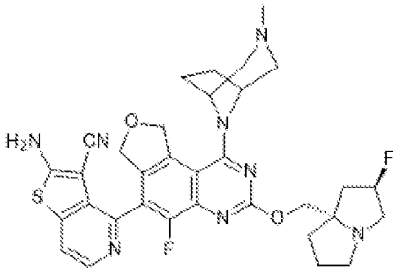
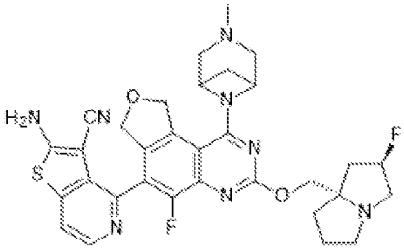
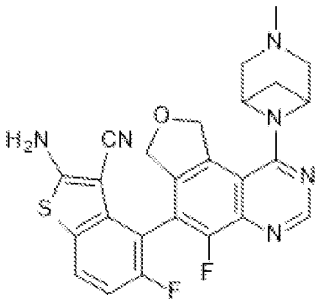
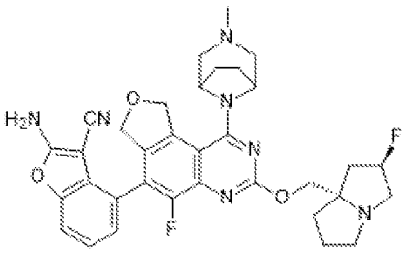
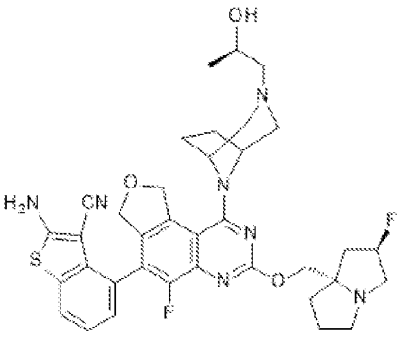
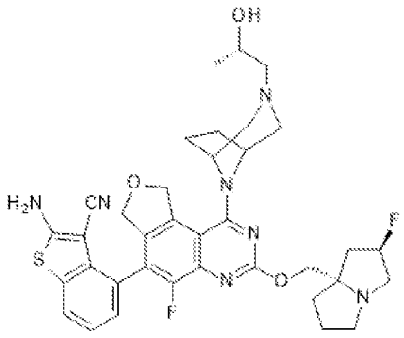
5		6	
7		8	
9		10	
11		12	

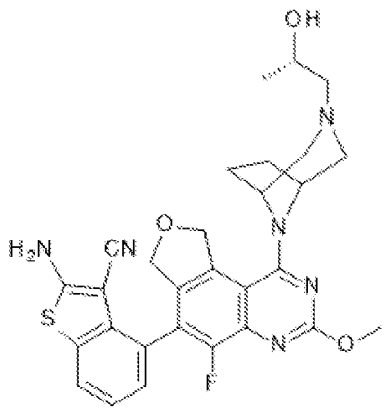
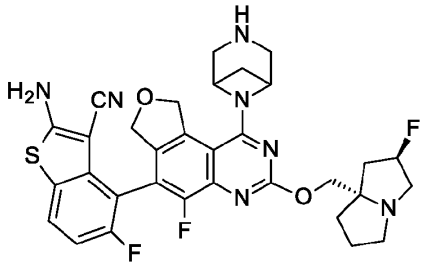
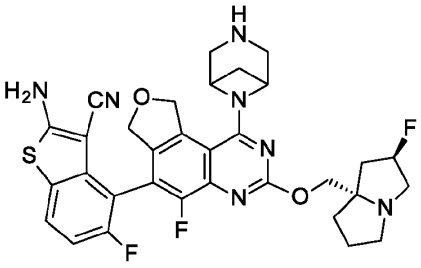
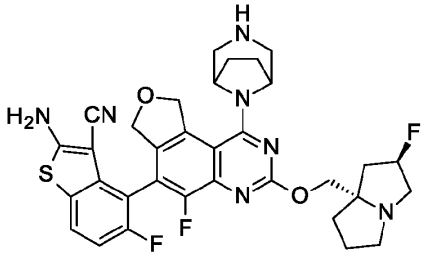
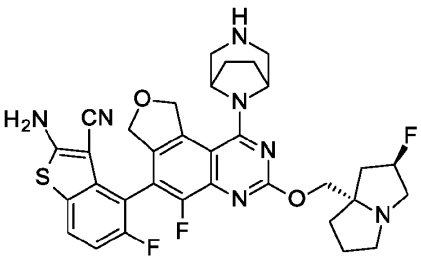
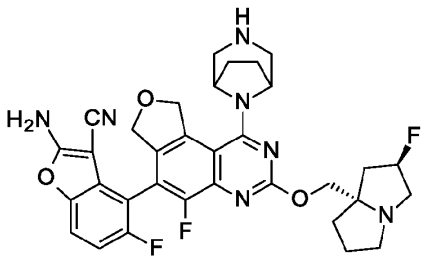
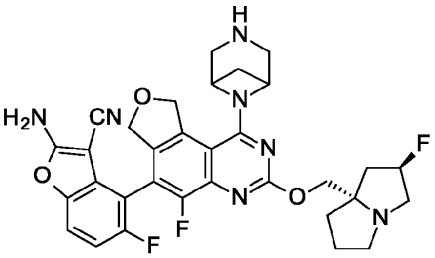
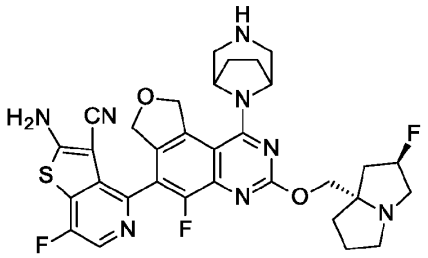
13		14	
15		16	
17		18	
19		20	

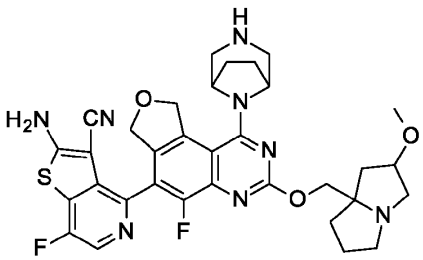
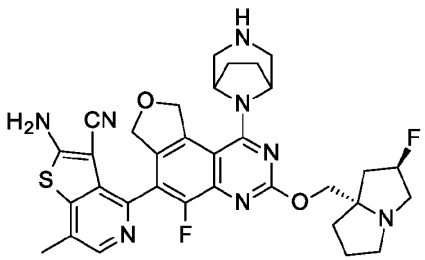
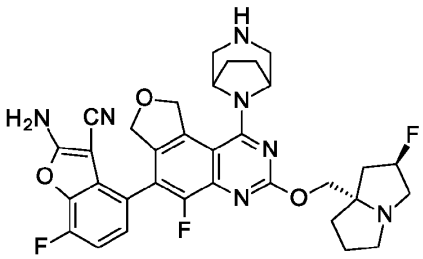
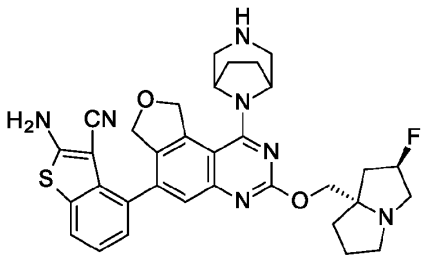
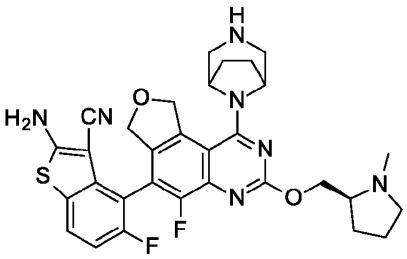
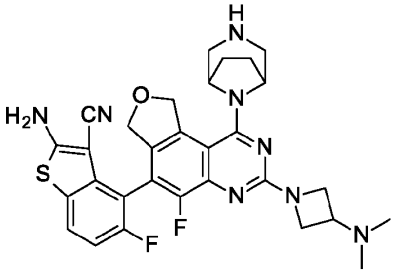
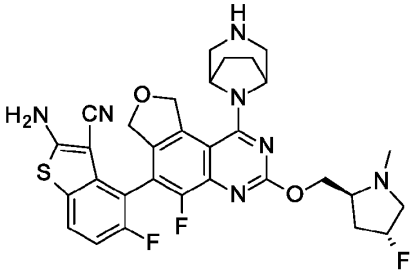
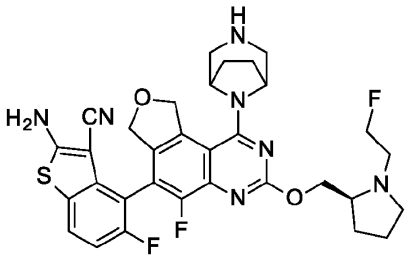
21		22	
23		24	
25		26	
27		28	

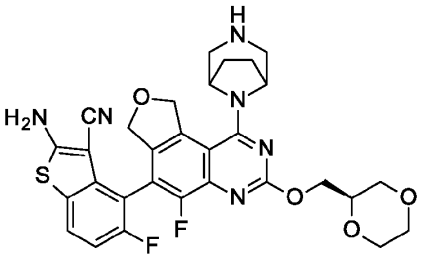
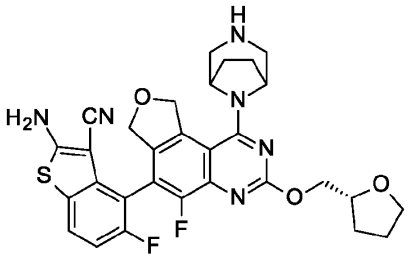
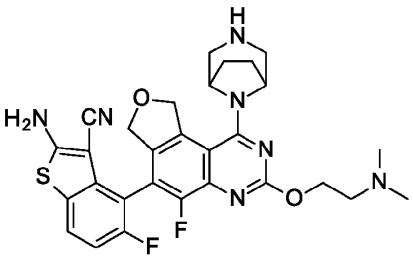
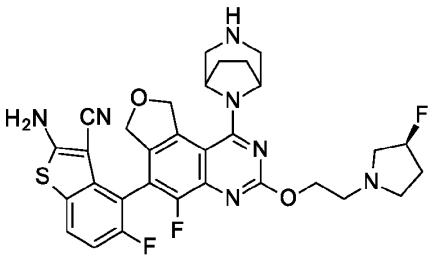
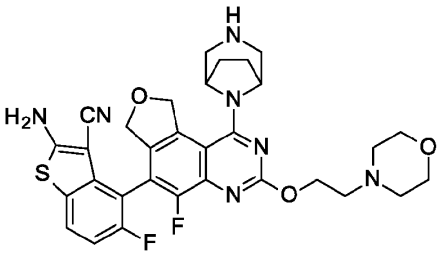
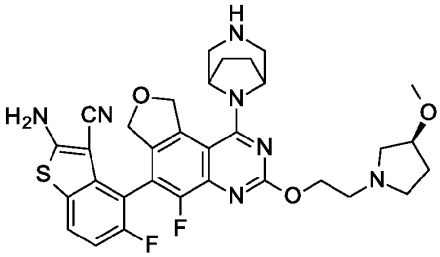
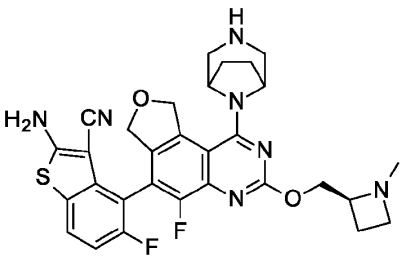
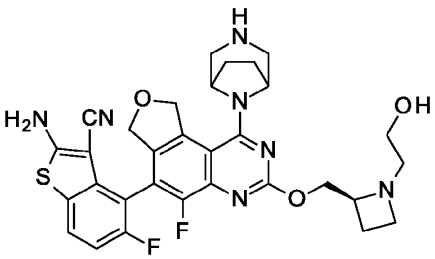
29		30	
31		32	
33		34	
35		36	
37		38	
39		40	

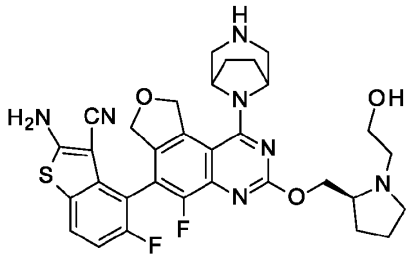
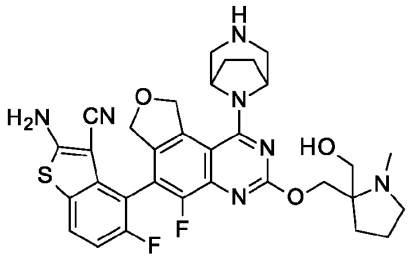
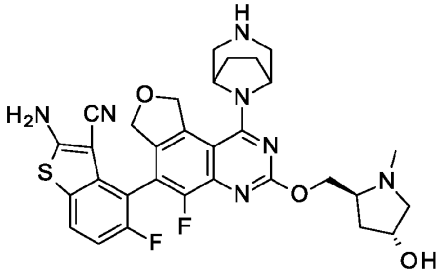
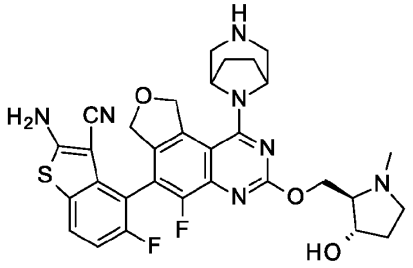
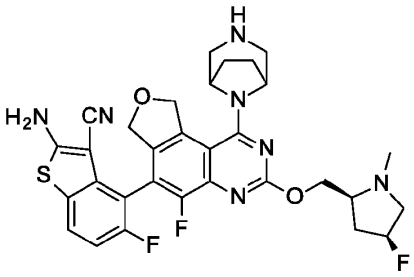
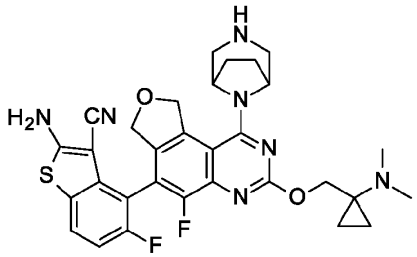
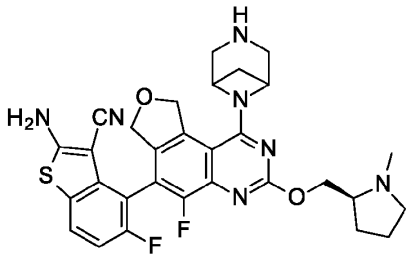
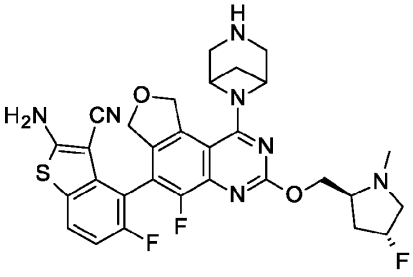
41		42	
43		44	
45		46	
47		48	

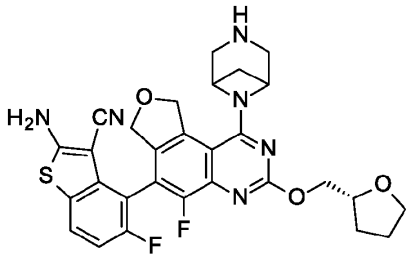
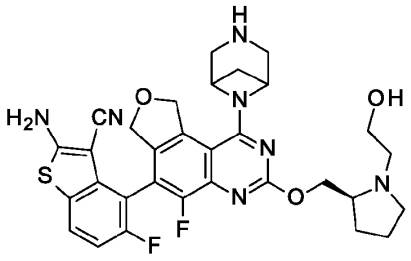
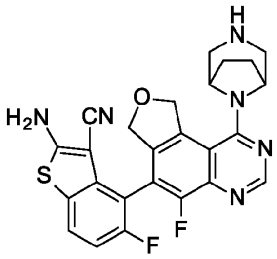
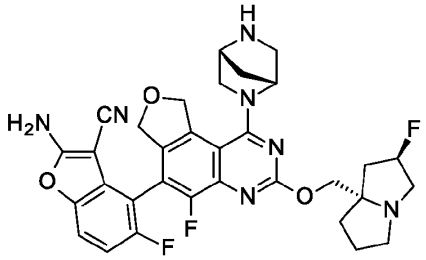
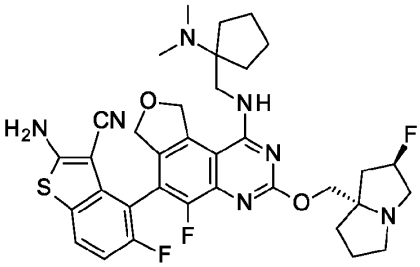
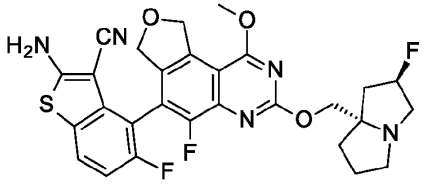
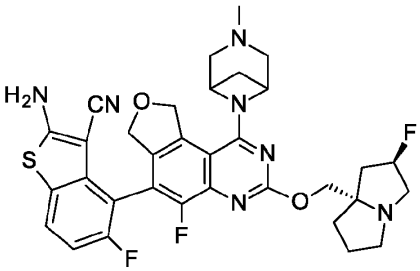
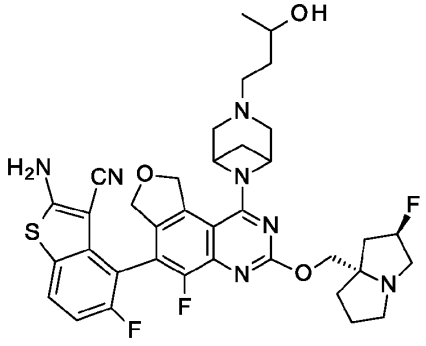
49		50	
51		52	
53		54	
55		56	

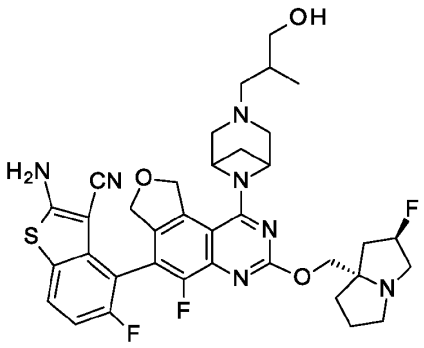
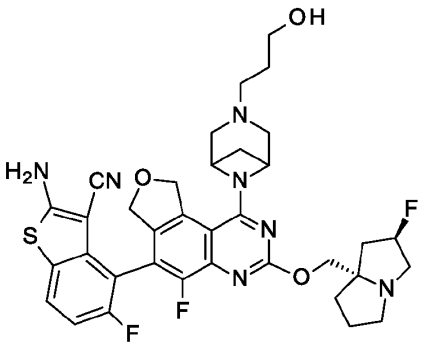
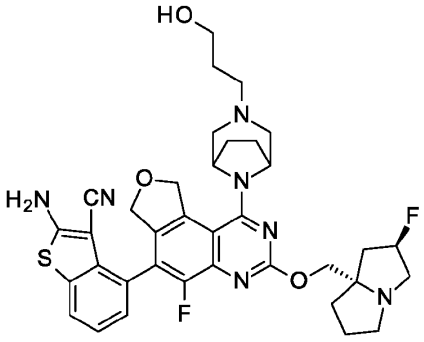
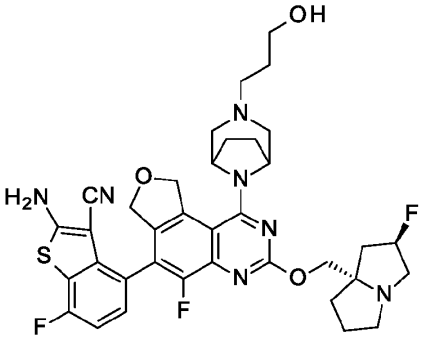
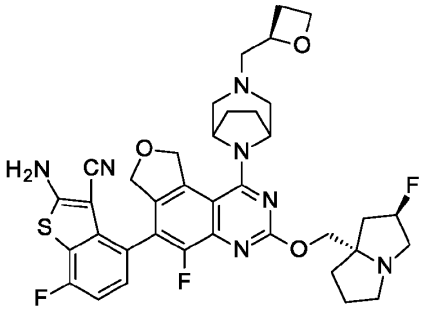
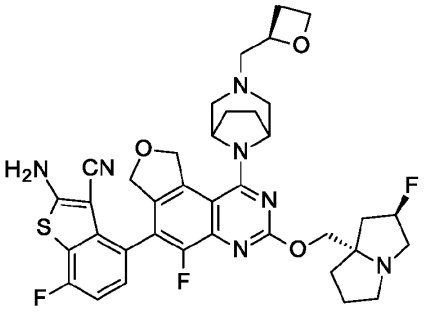
57		58	
59		60	
61		62	
63		64	

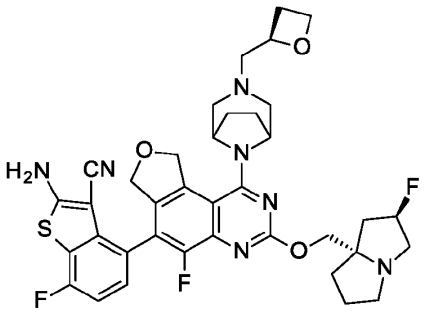
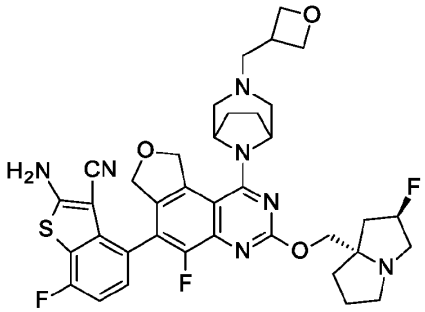
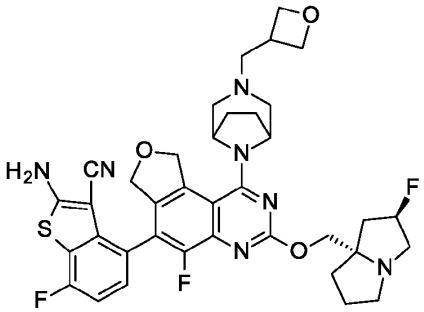
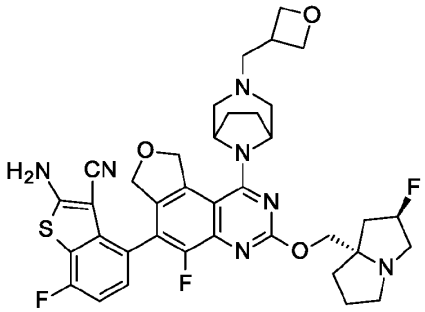
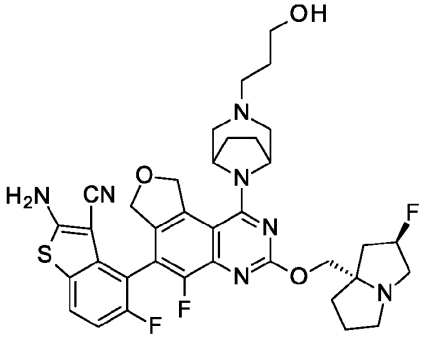
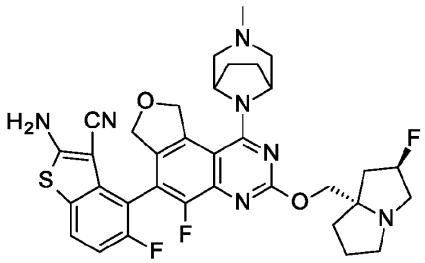
65		66	
67		68	
69		70	
71		72	

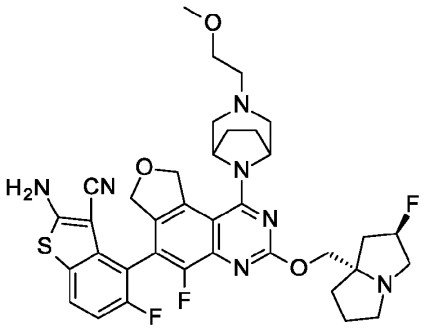
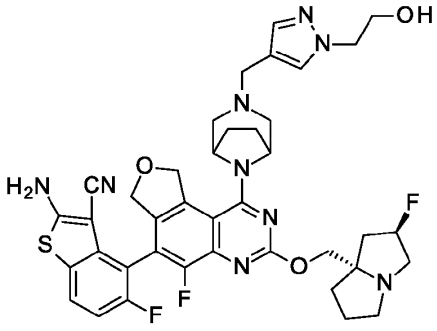
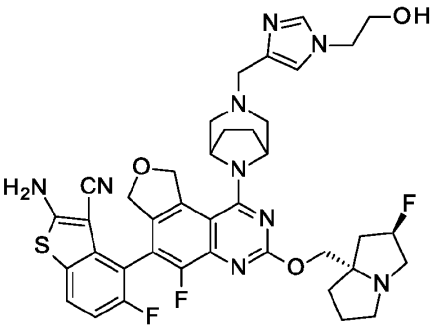
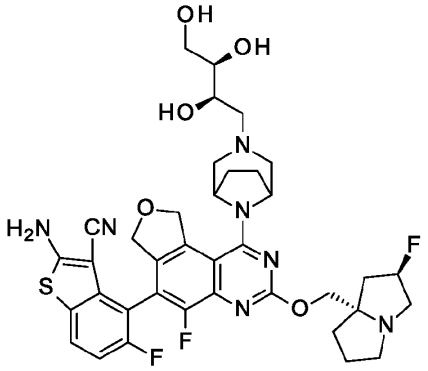
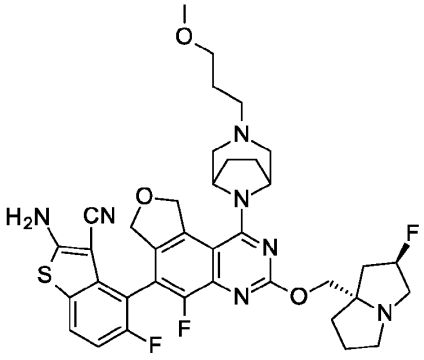
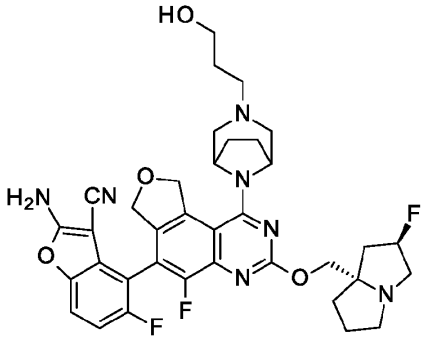
73		74	
75		76	
77		78	
79		80	

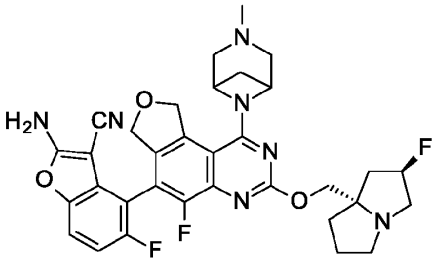
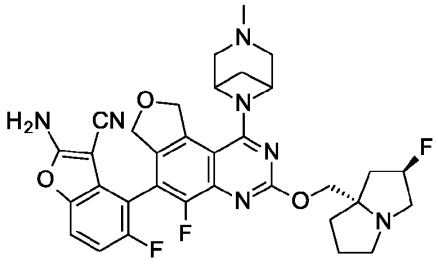
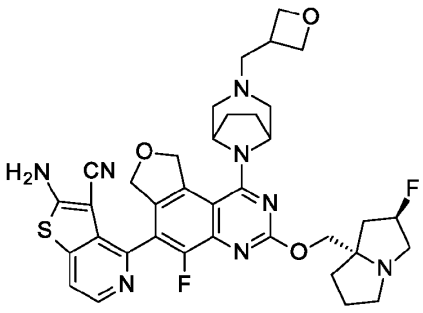
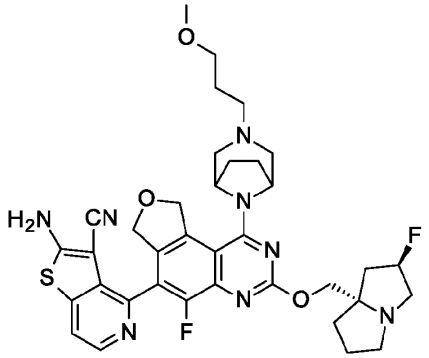
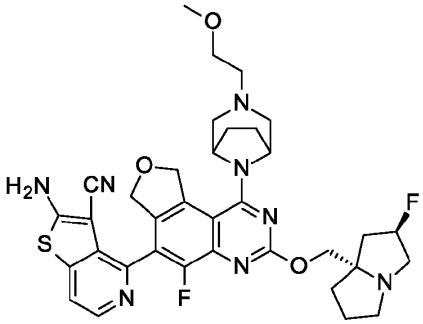
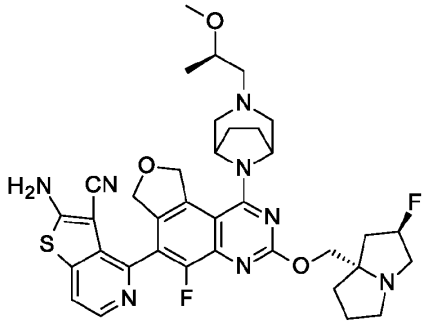
81		82	
83		84	
85		86	
87		88	

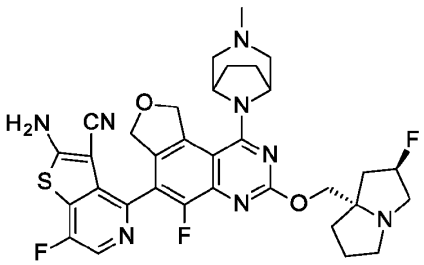
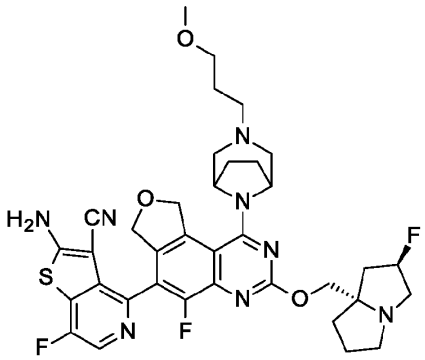
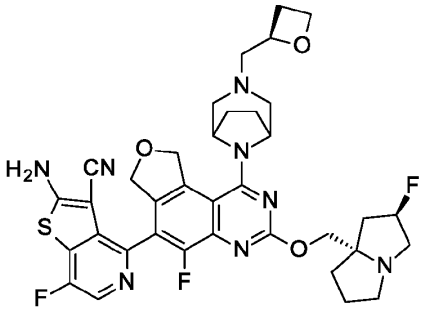
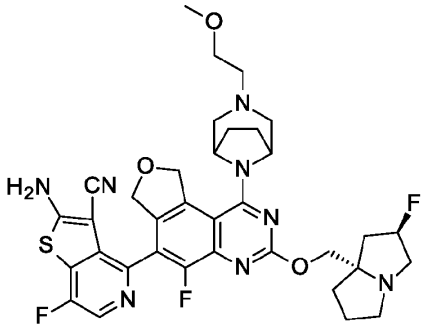
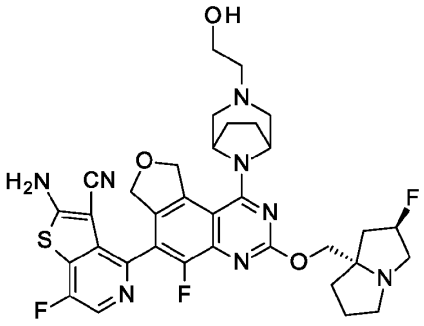
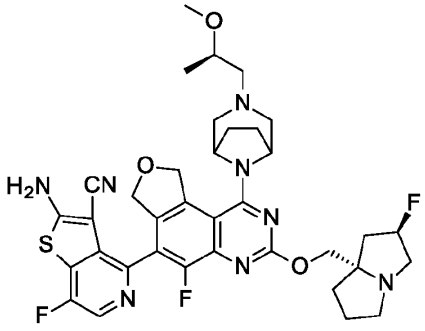
89		90	
91		92	
93		94	
95		96	

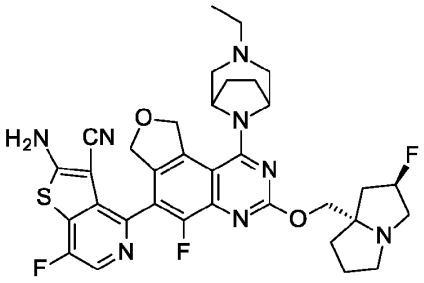
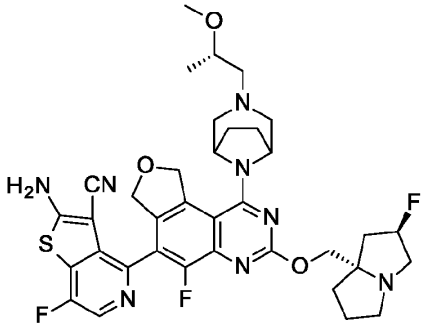
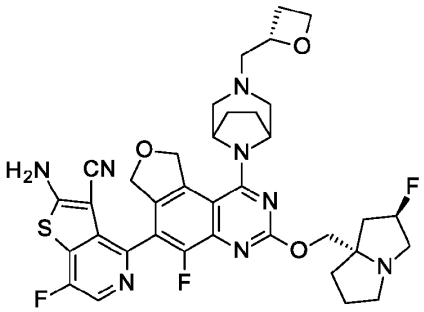
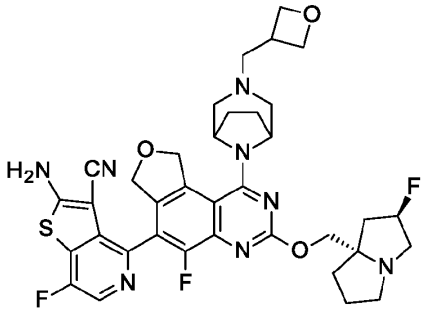
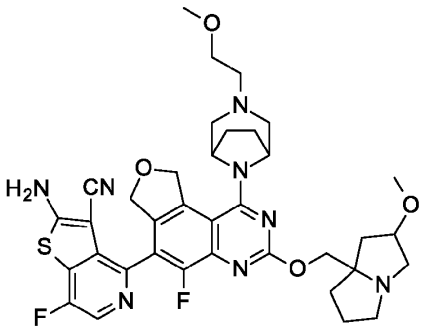
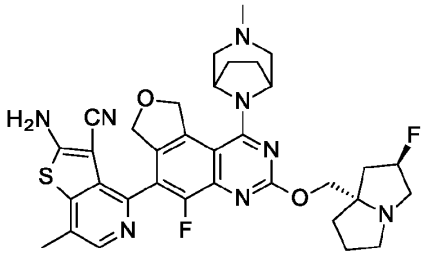
97		98	
99		100	
101		102	

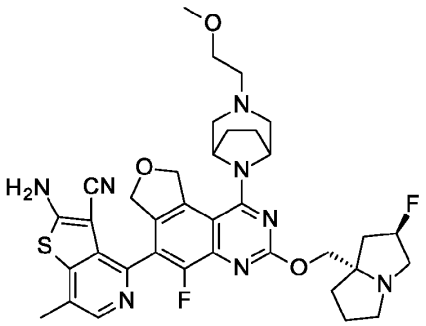
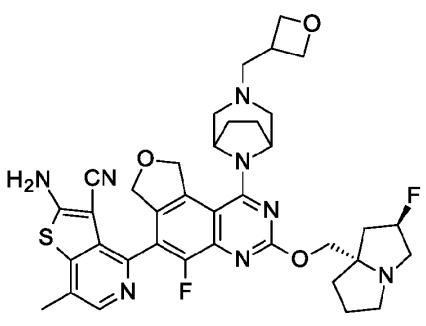
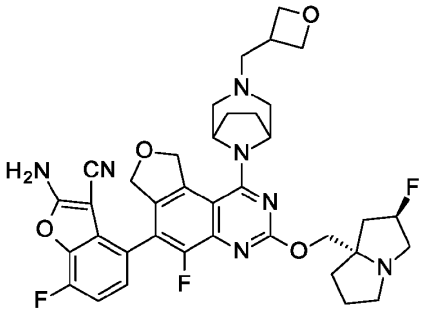
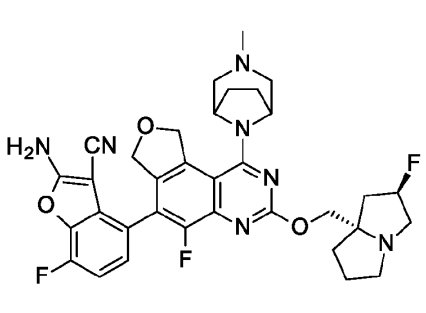
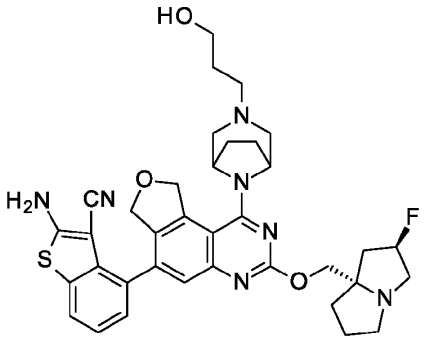
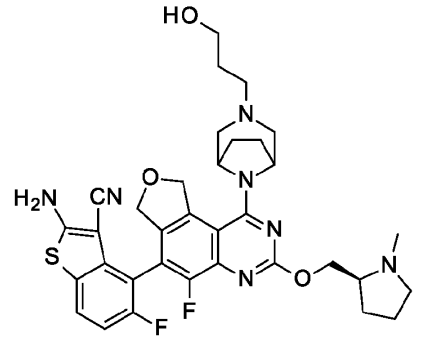
103		104	
105		106	
107		108	

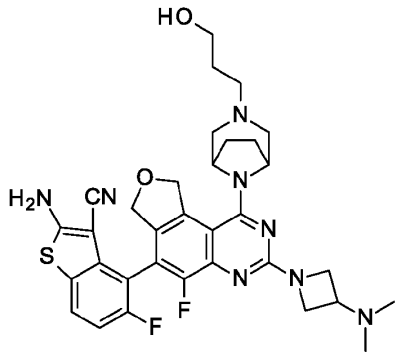
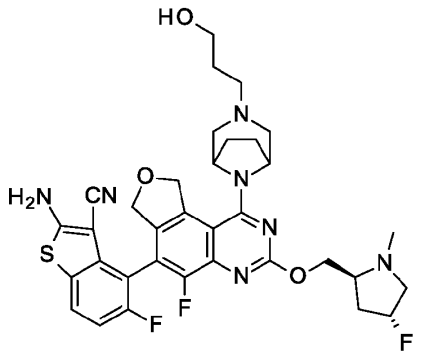
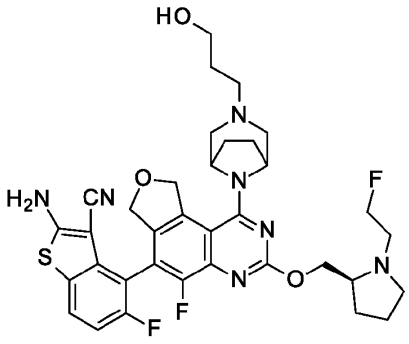
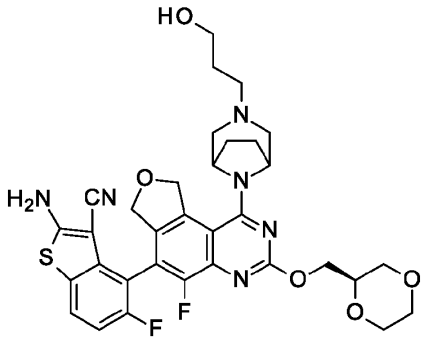
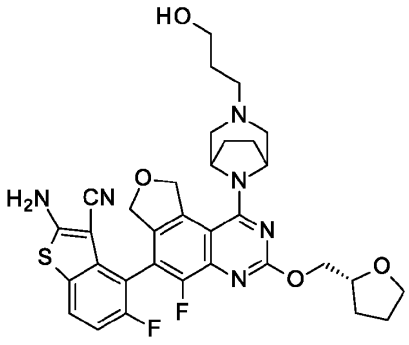
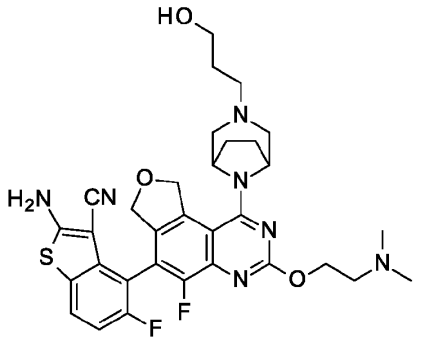
109		110	
111		112	
113		114	

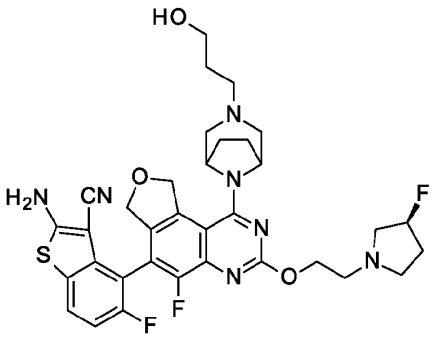
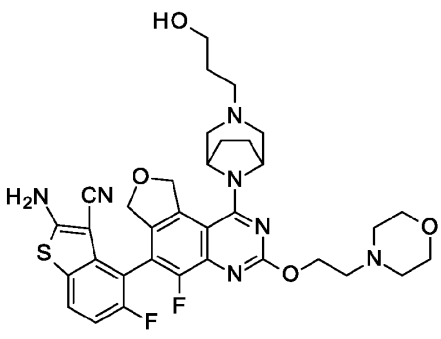
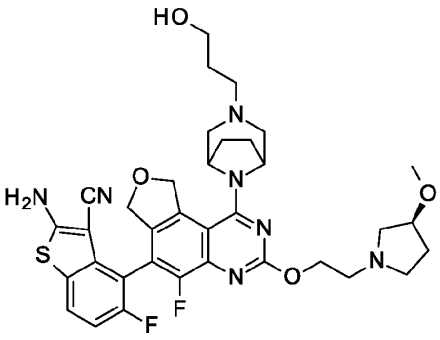
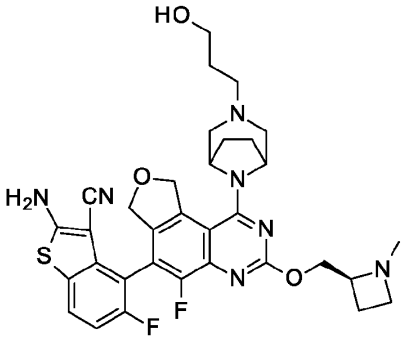
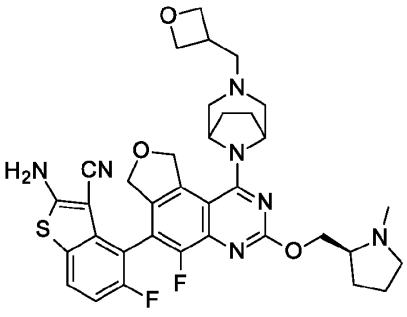
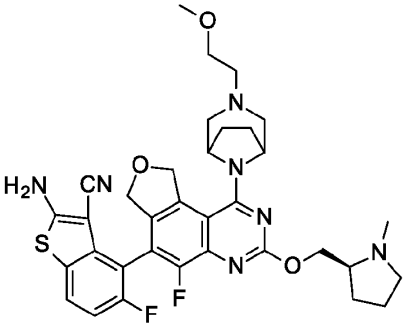
115		116	
117		118	
119		120	

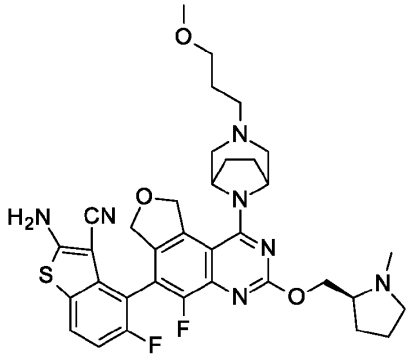
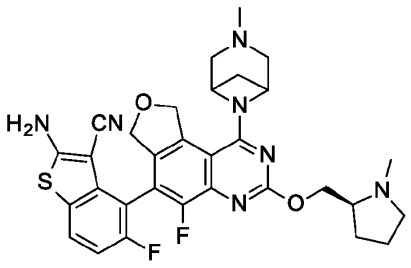
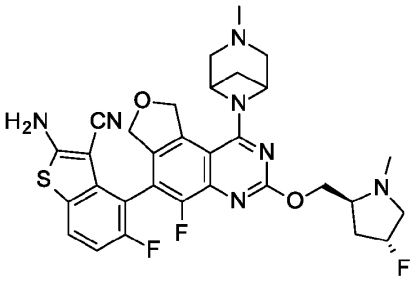
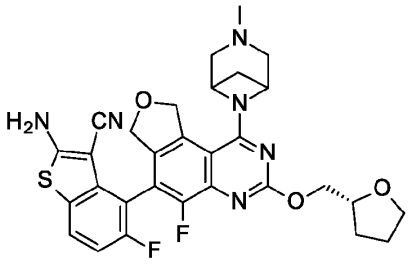
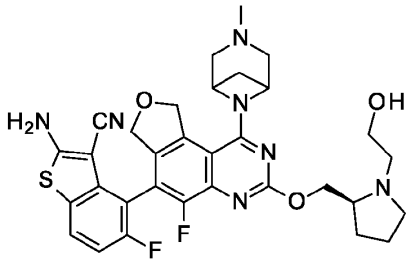
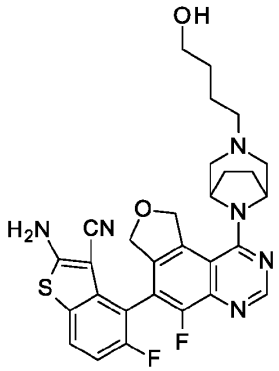
121		122	
123		124	
125		126	

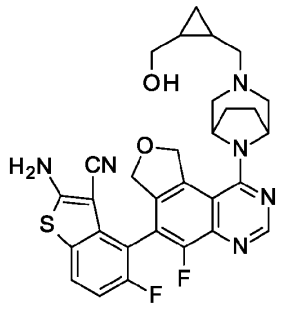
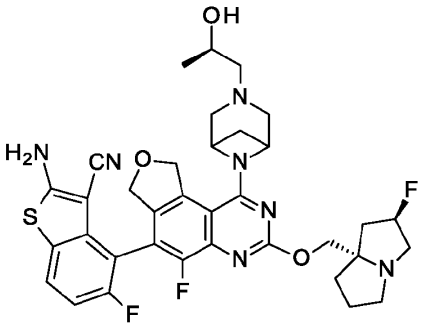
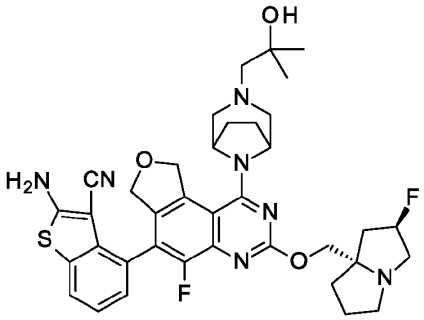
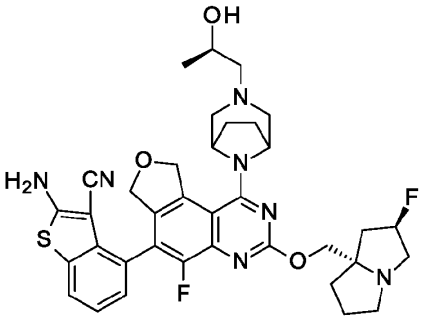
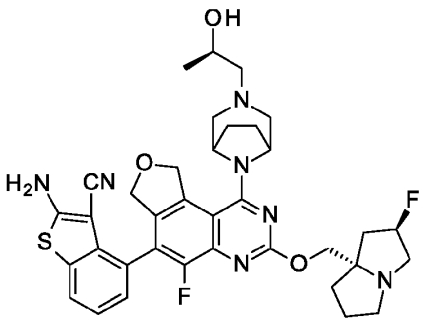
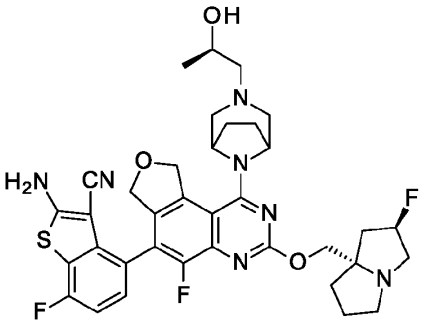
127		128	
129		130	
131		132	

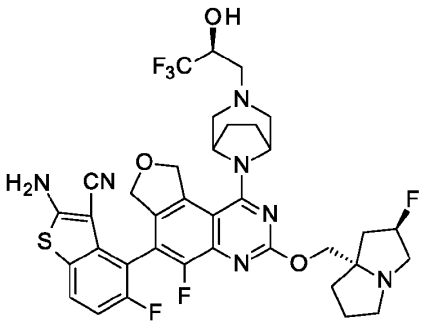
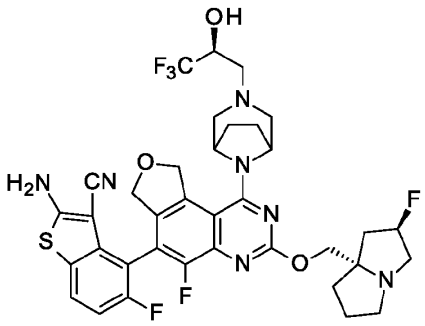
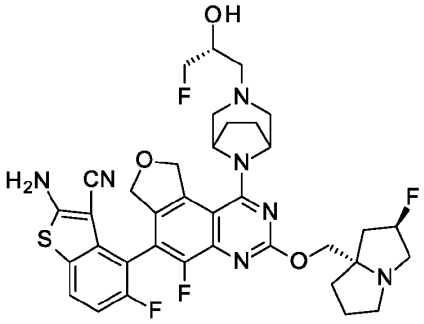
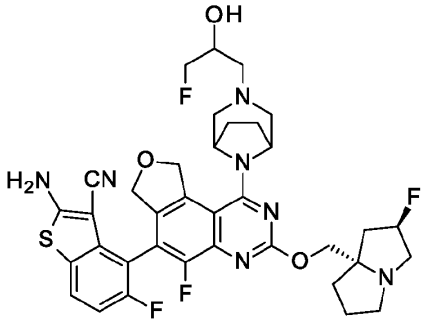
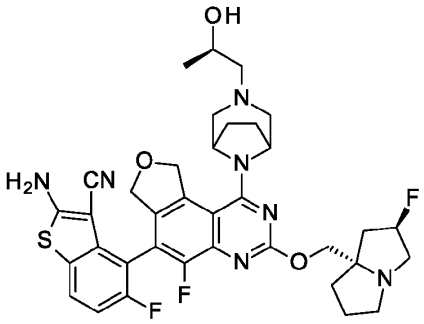
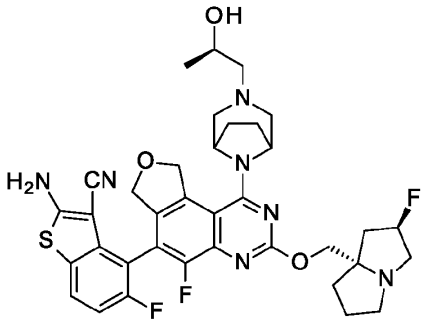
133		134	
135		136	
137		138	

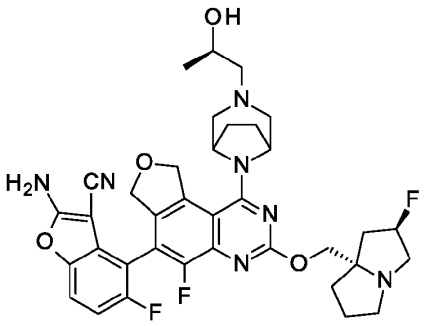
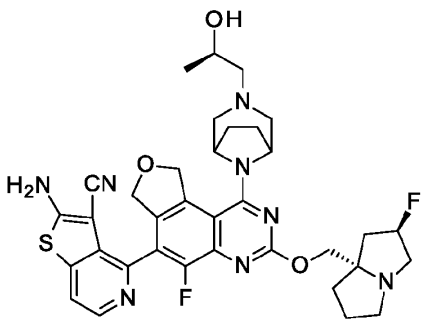
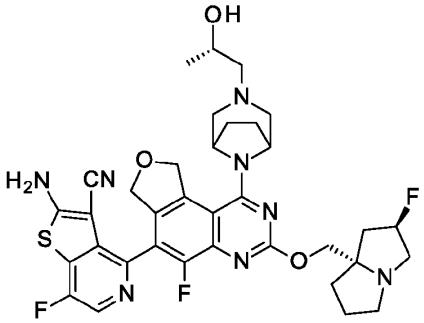
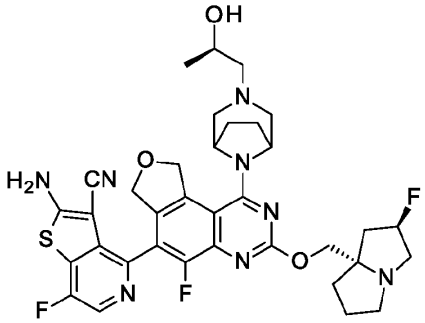
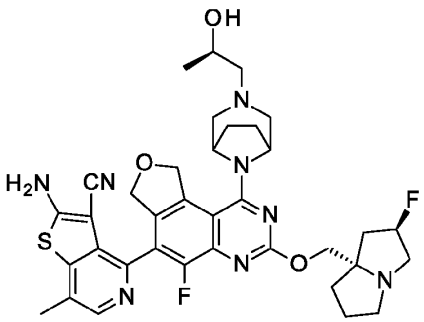
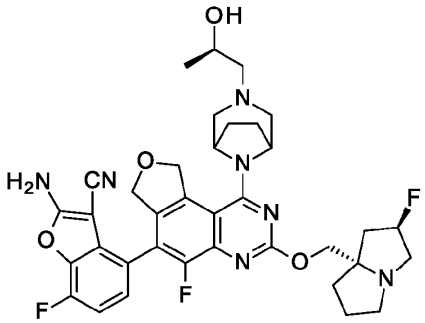
139		140	
141		142	
143		144	

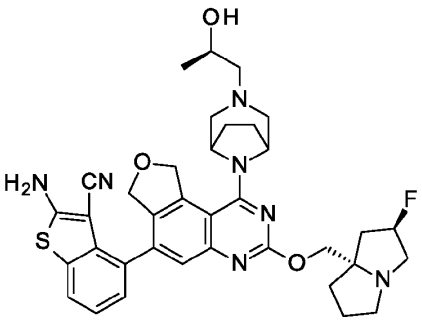
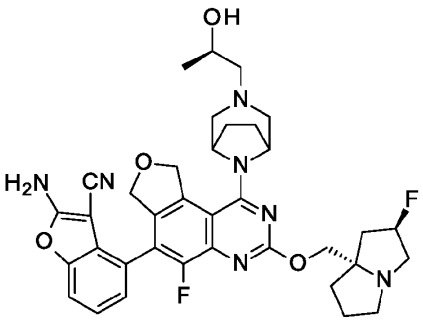
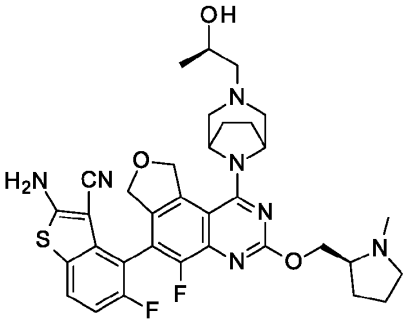
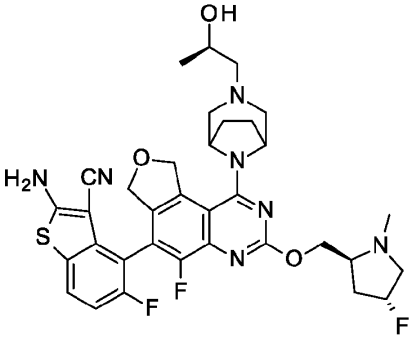
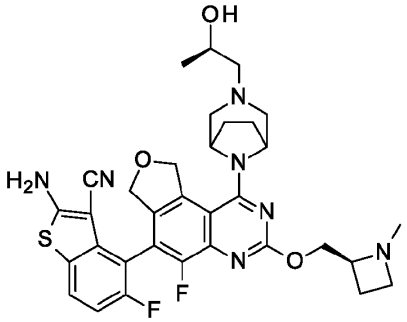
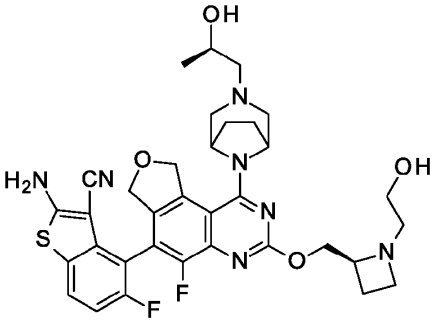
145		146	
147		148	
149		150	

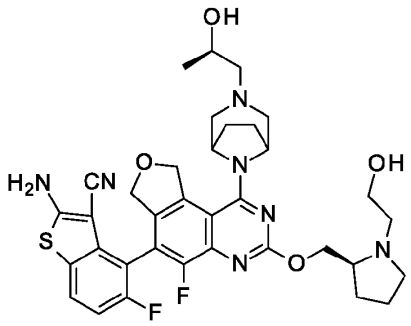
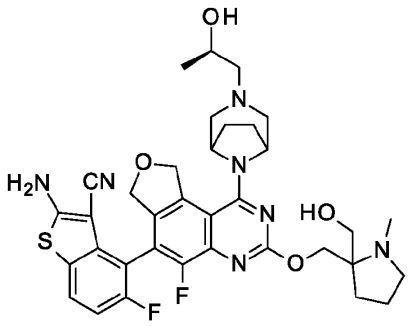
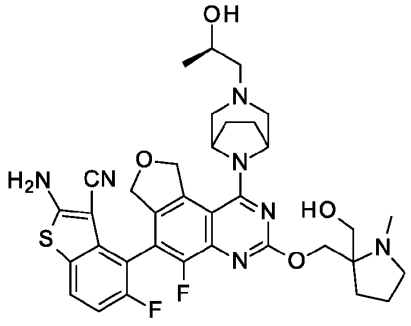
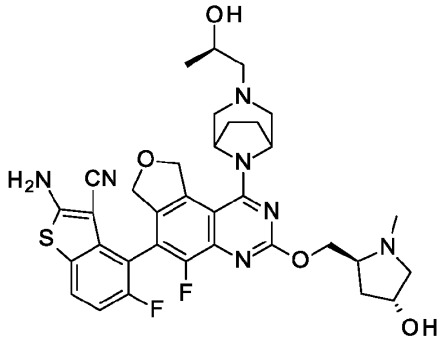
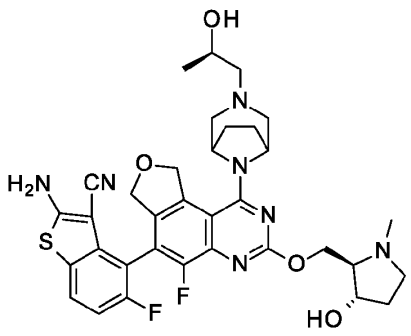
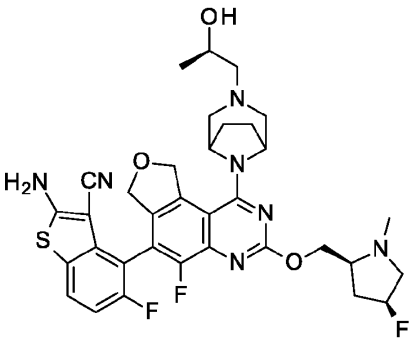
151		152	
153		154	
155		156	

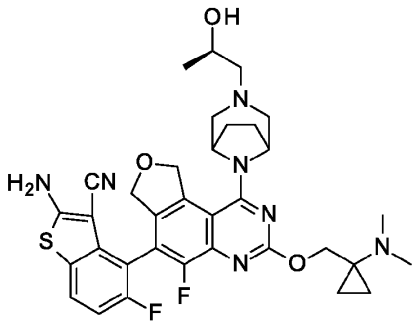
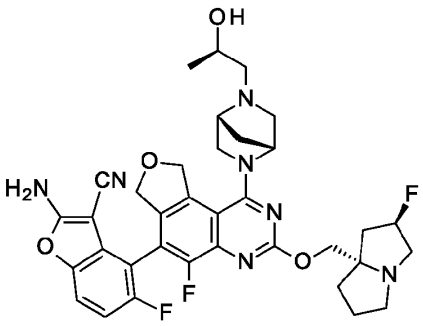
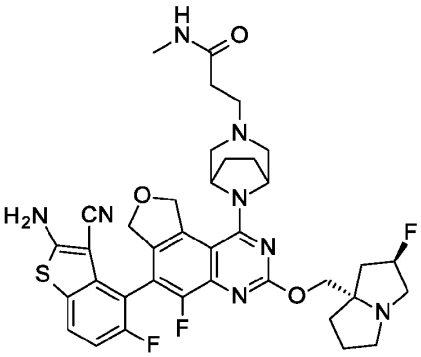
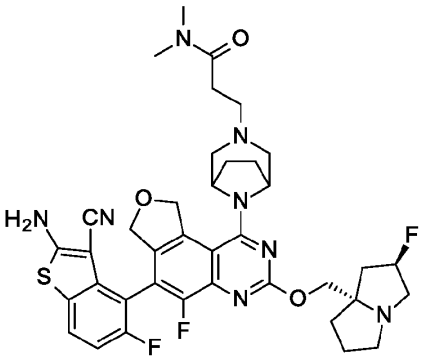
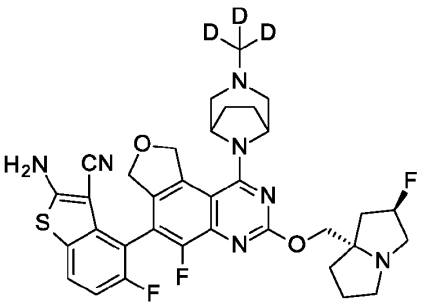
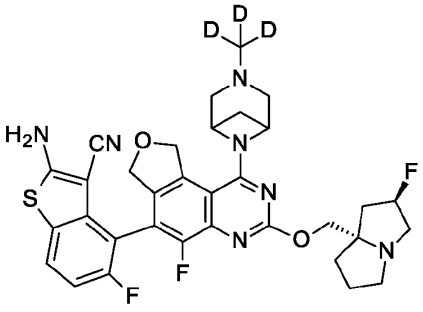
157		158	
159		160	
161		162	

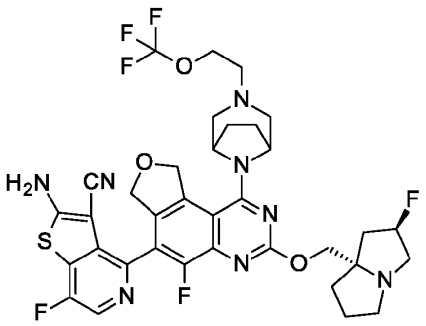
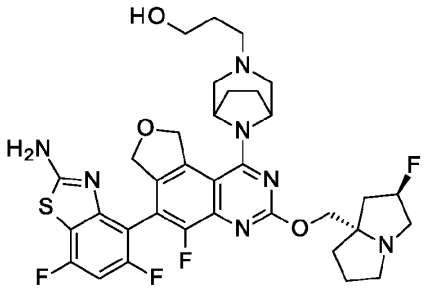
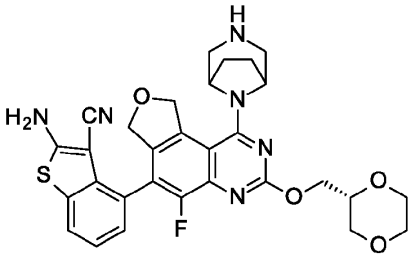
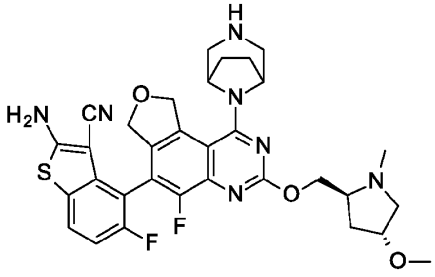
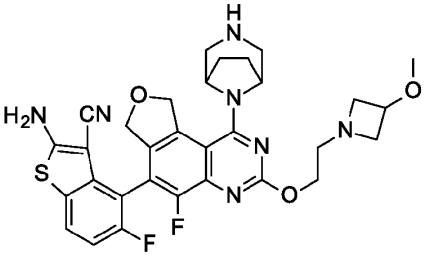
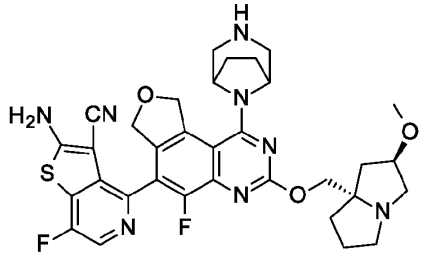
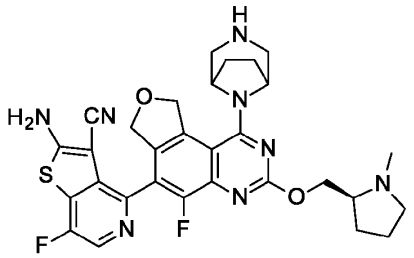
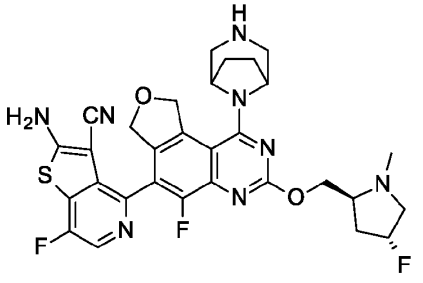
163		164	
165		166	
167		168	

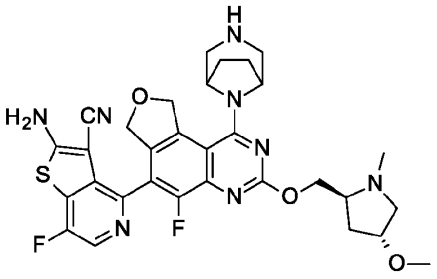
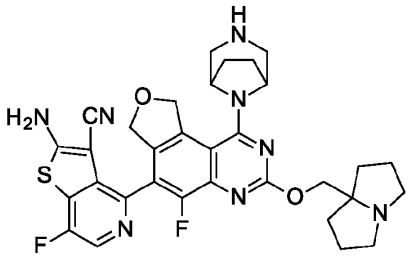
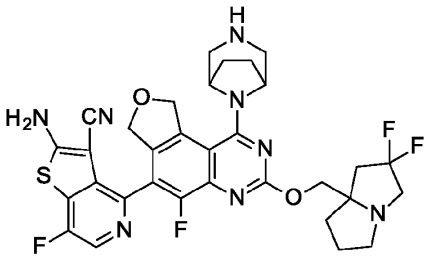
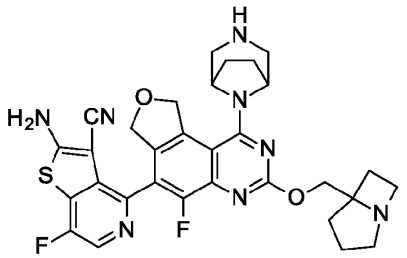
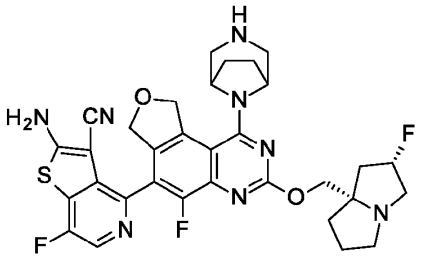
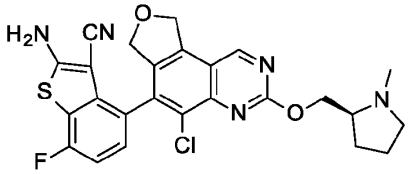
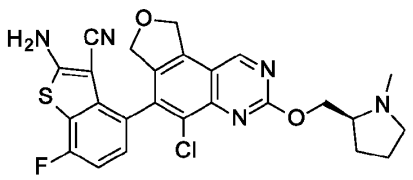
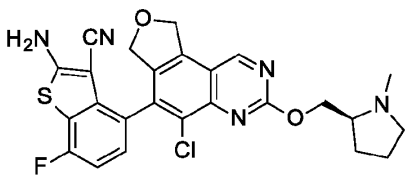
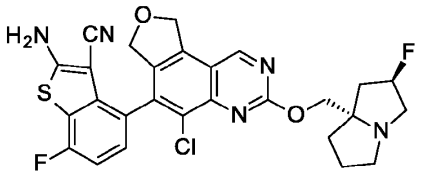
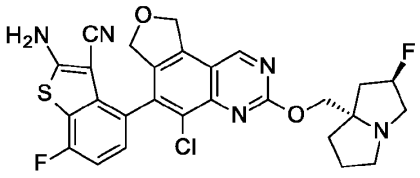
169		170	
171		172	
173		174	

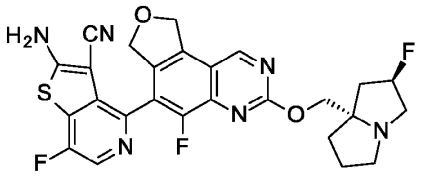
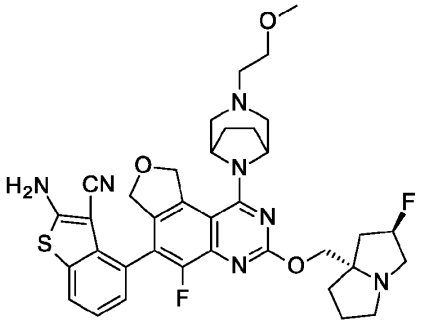
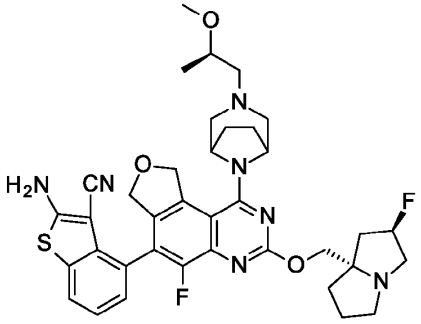
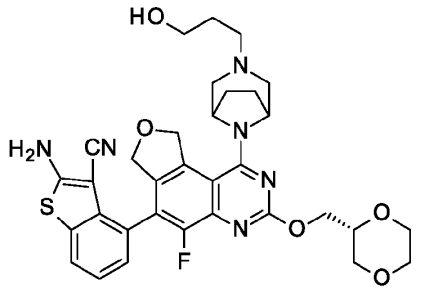
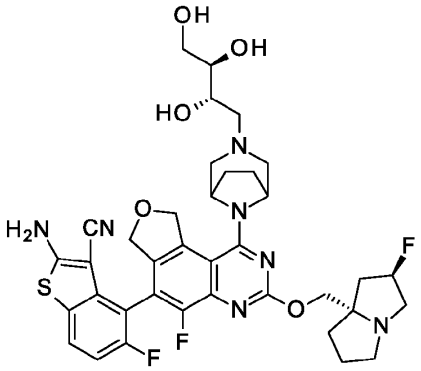
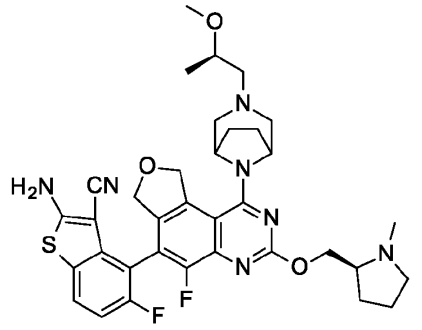
175		176	
177		178	
179		180	

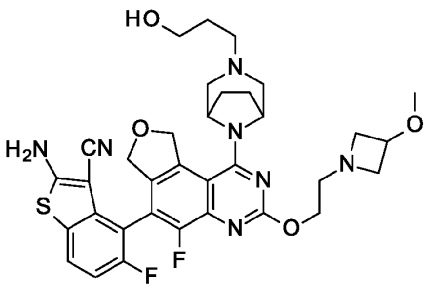
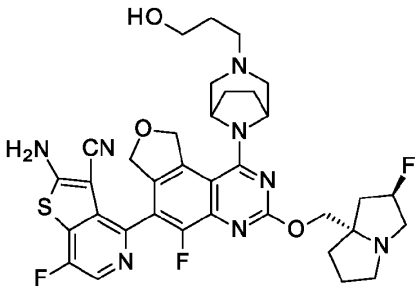
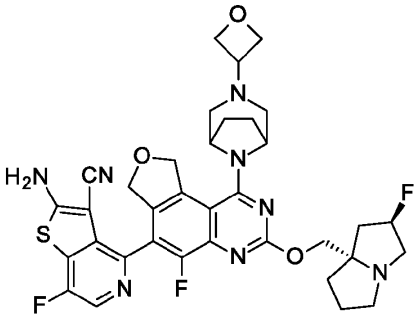
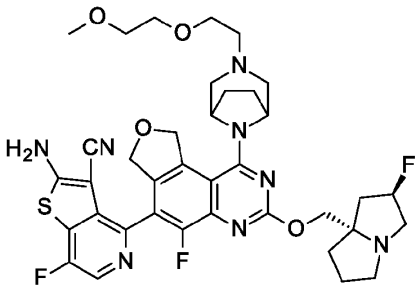
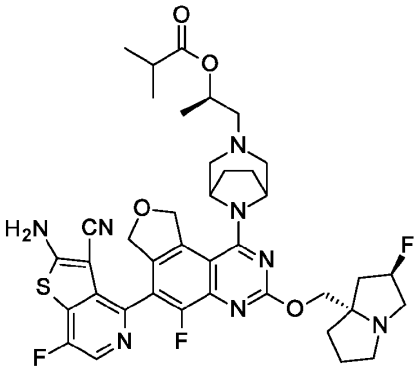
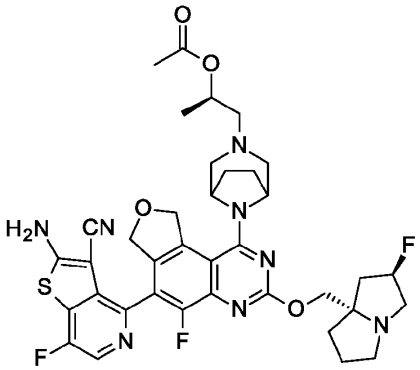
181		182	
183		184	
185		186	

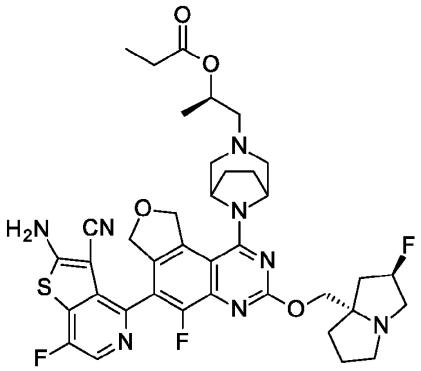
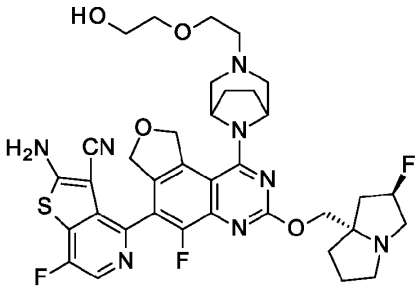
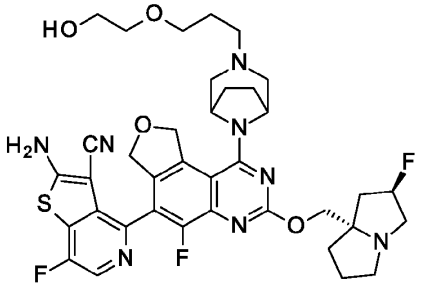
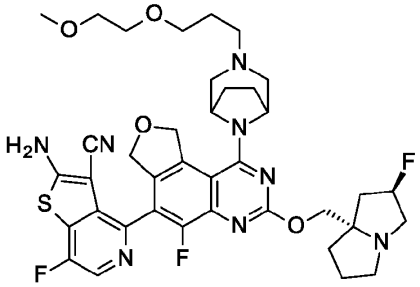
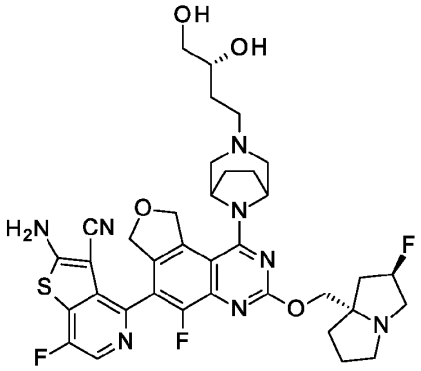
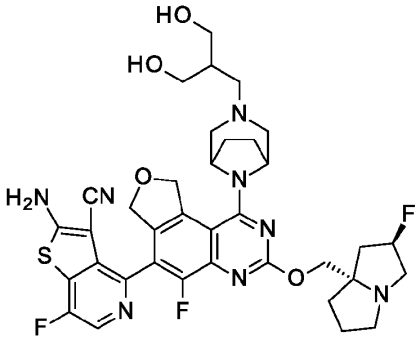
187		188	
189		190	
191		192	

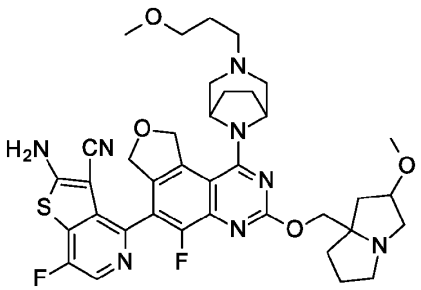
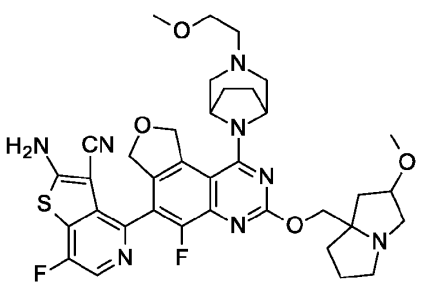
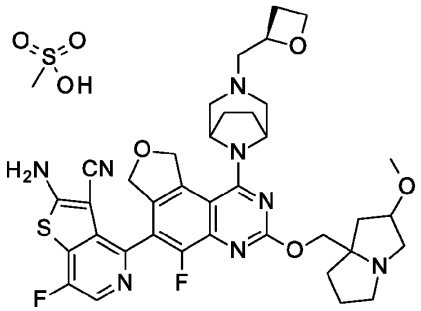
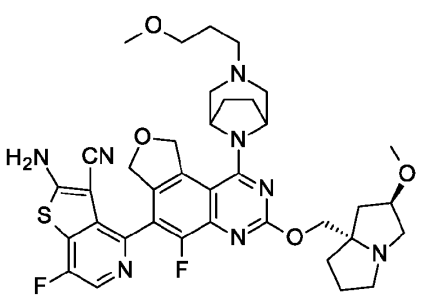
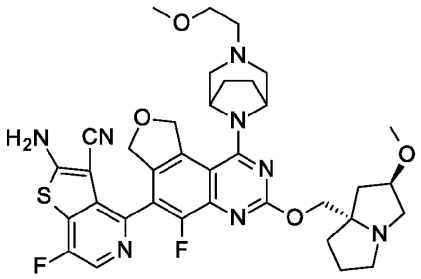
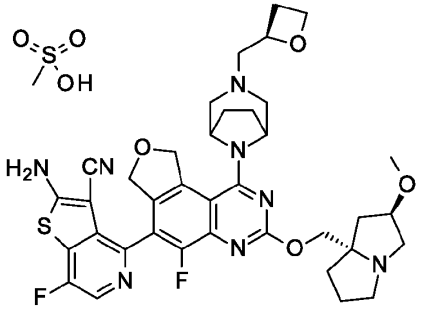
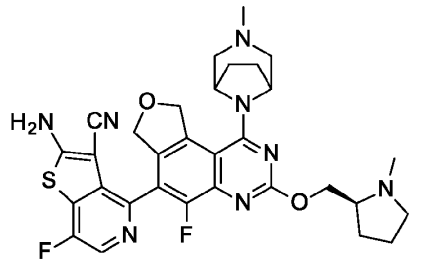
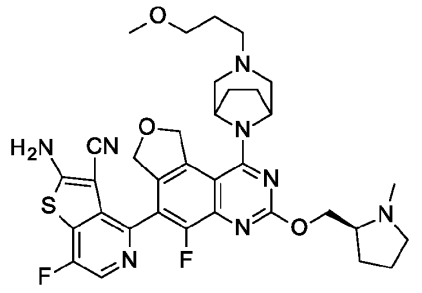
193		194	
195		196	
197		198	
199		200	

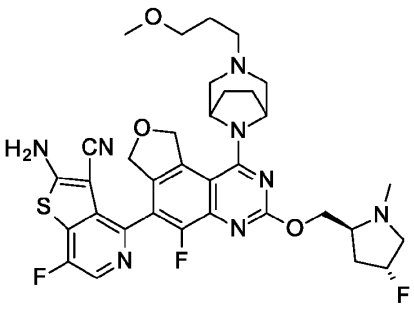
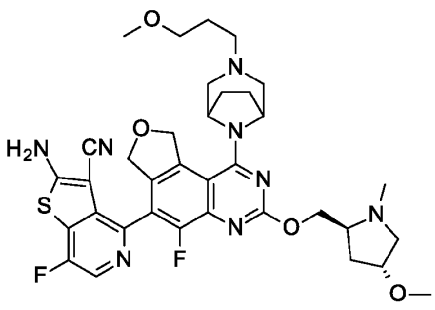
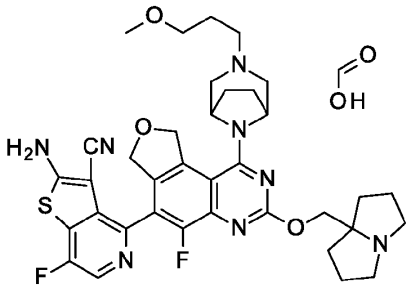
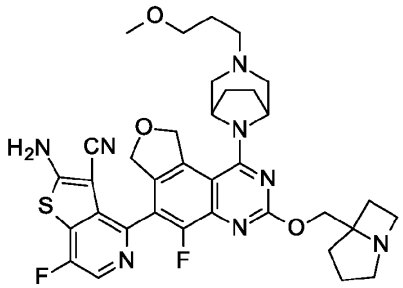
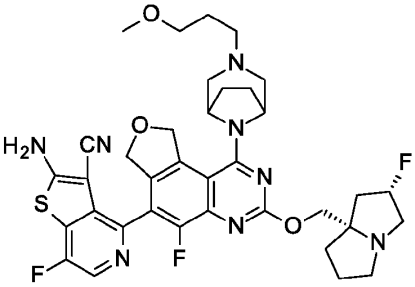
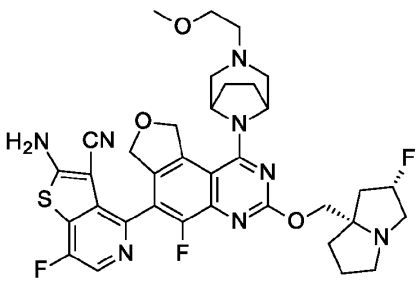
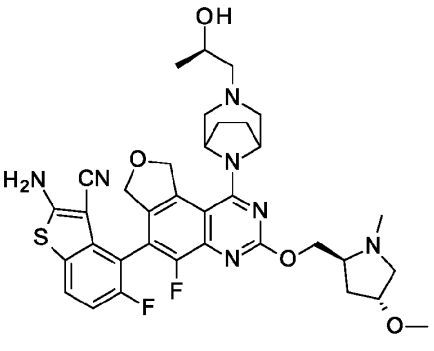
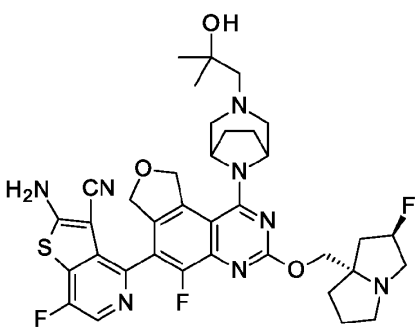
201		202	
203		204	
205		206	
207		208	
209		210	

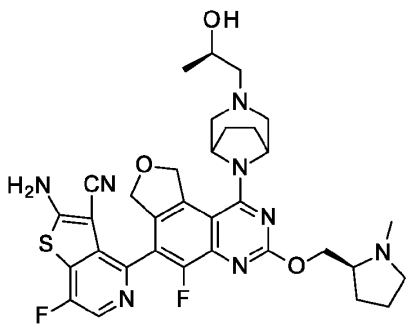
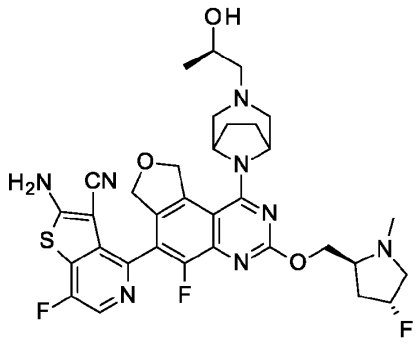
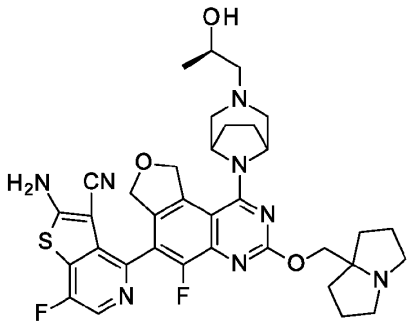
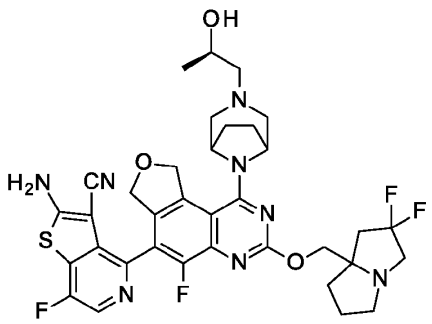
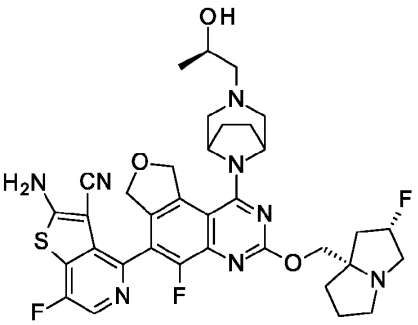
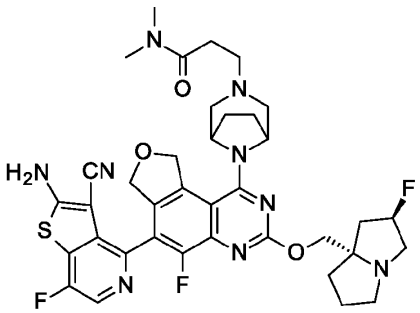
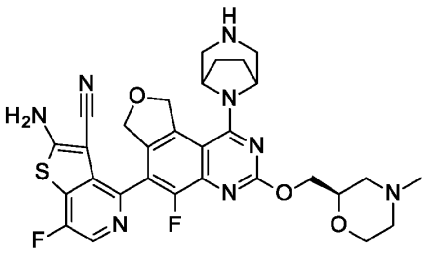
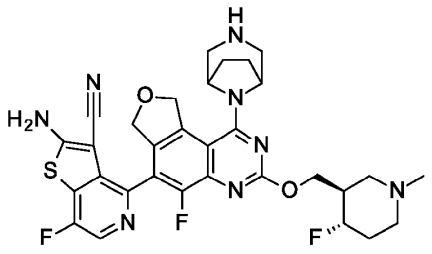
211		212	
213		214	
215		216	

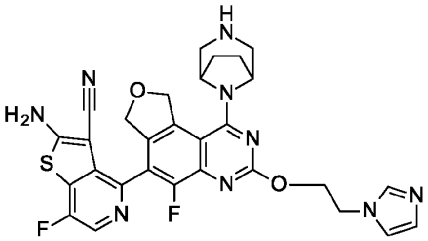
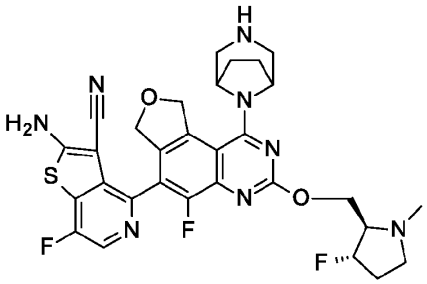
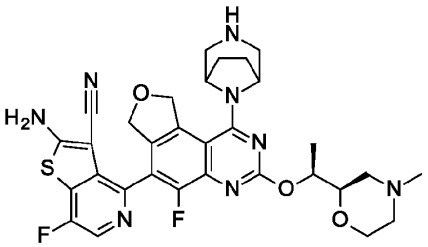
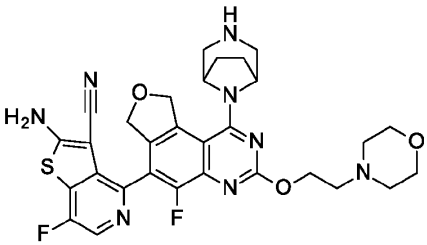
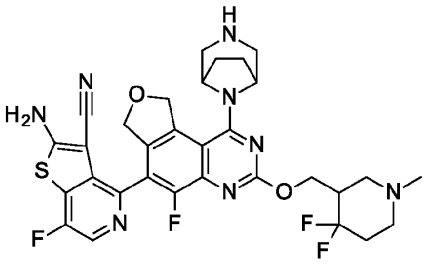
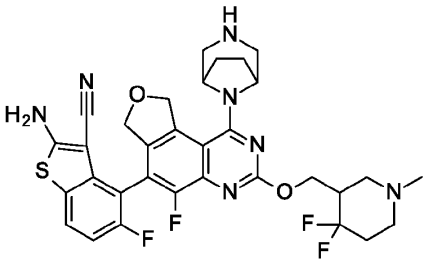
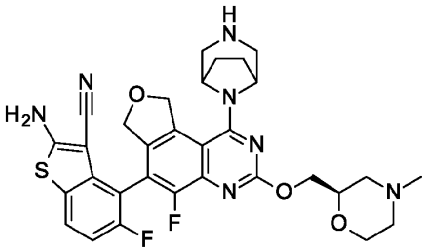
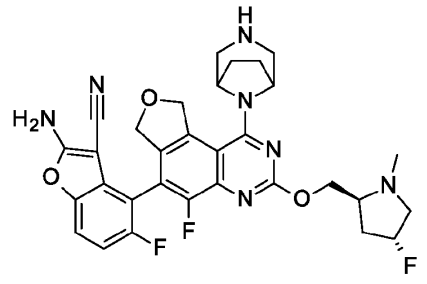
217		218	
219		220	
221		222	

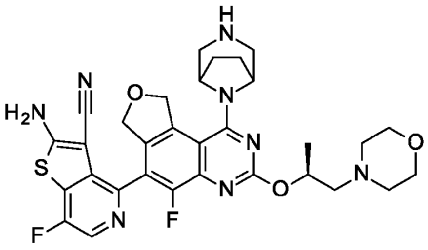
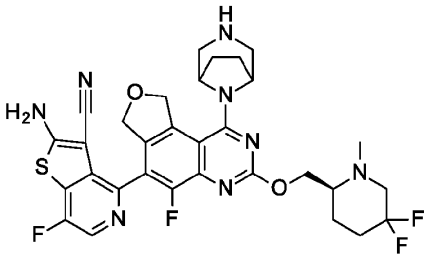
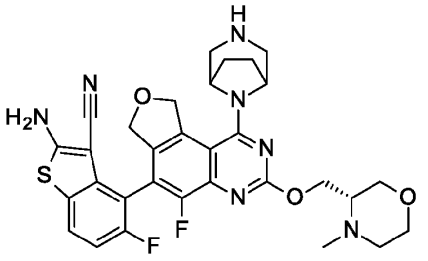
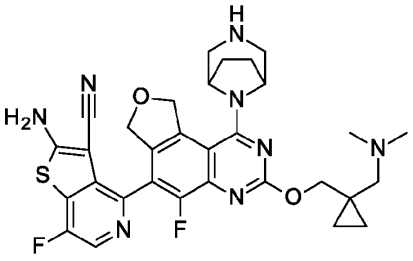
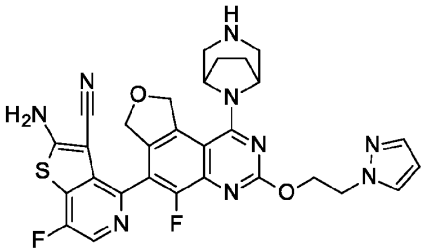
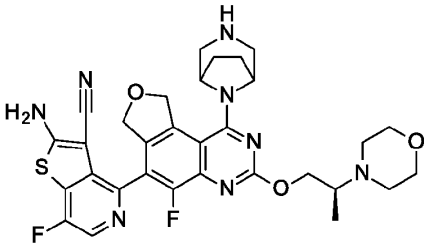
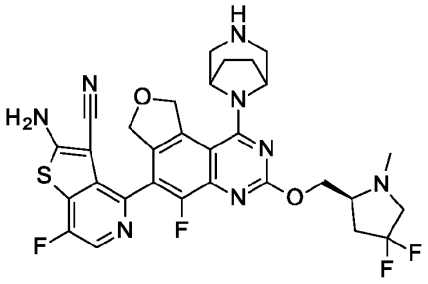
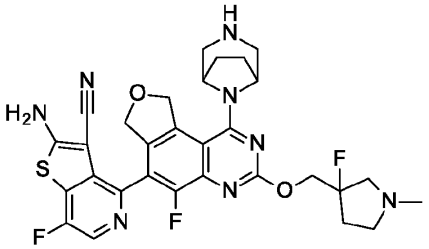
223		224	
225		226	
227		228	

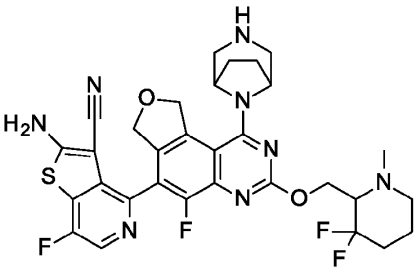
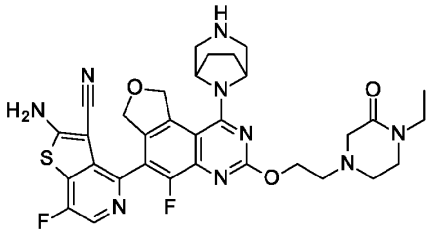
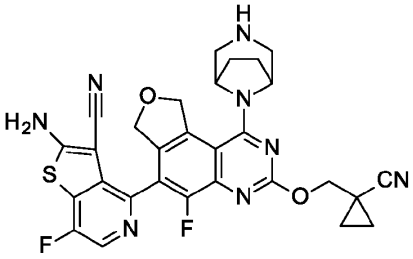
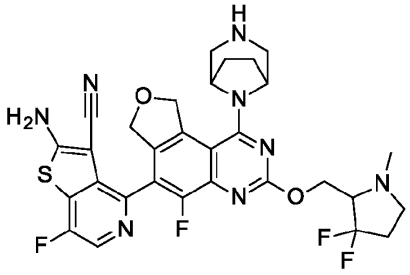
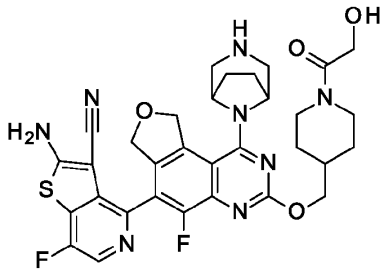
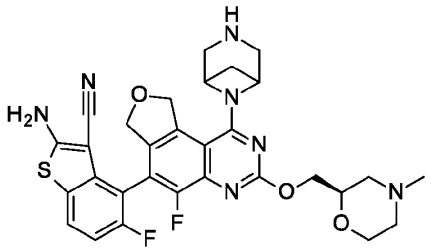
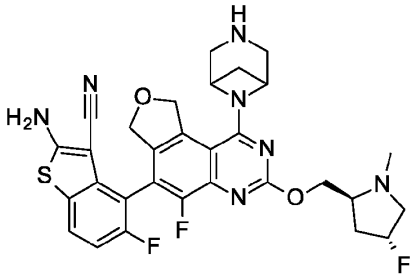
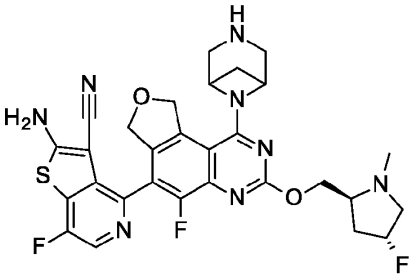
229		230	
231		232	
233		234	
235		236	

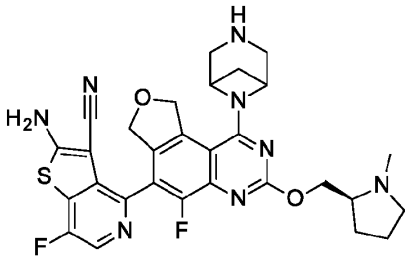
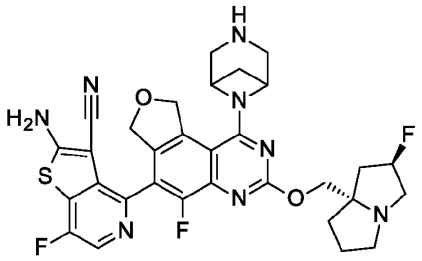
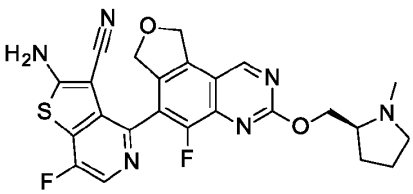
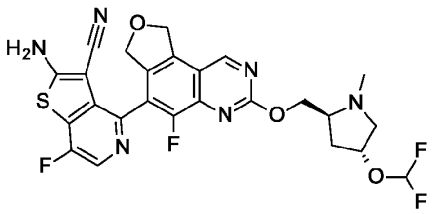
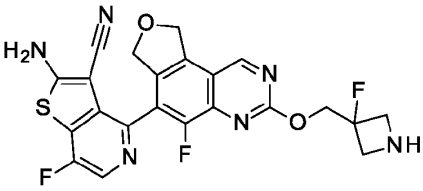
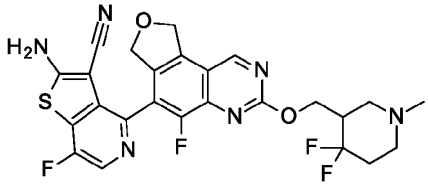
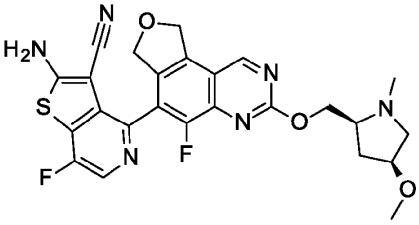
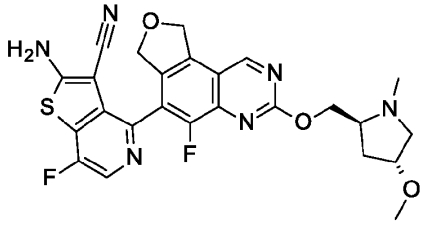
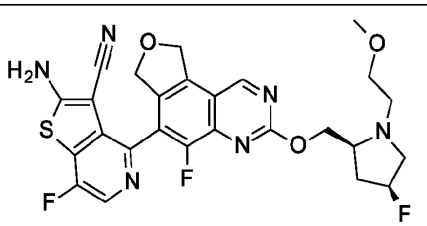
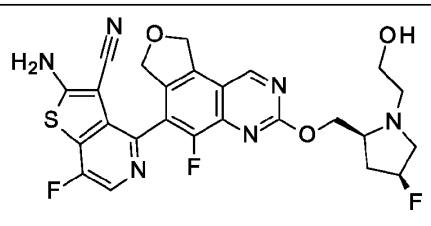
237		238	
239		240	
241		242	
243		244	

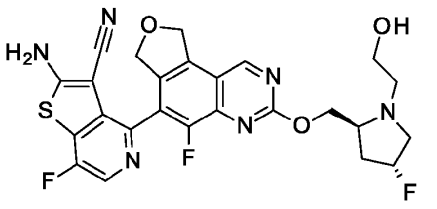
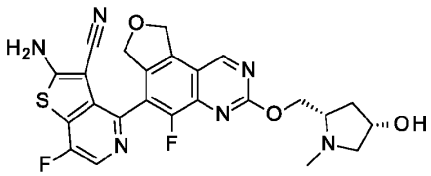
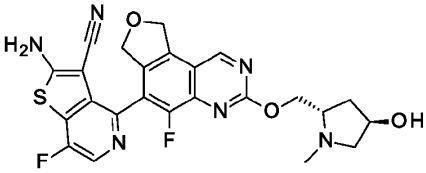
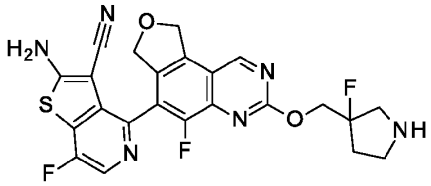
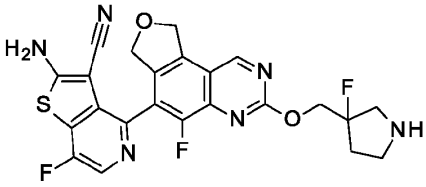
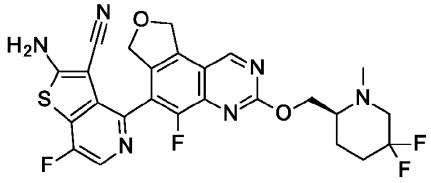
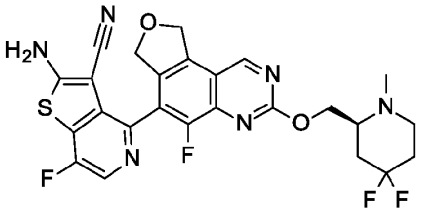
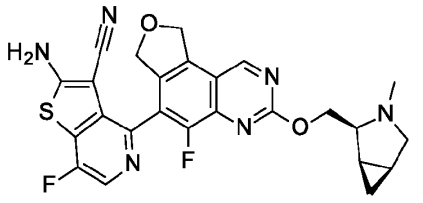
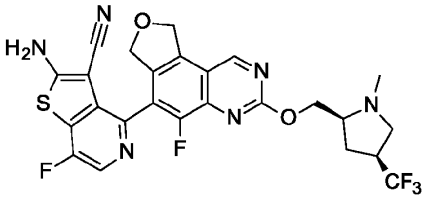
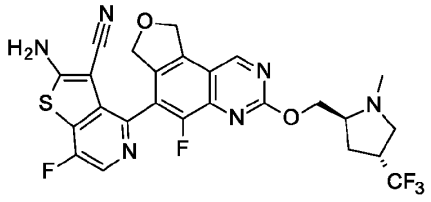
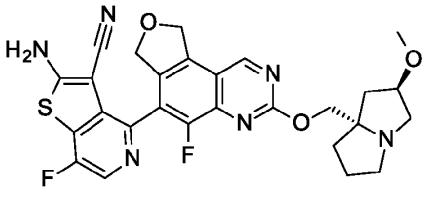
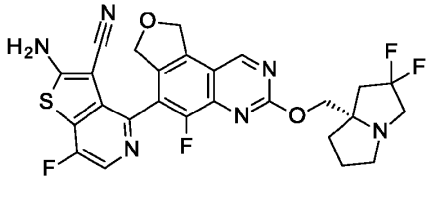
245		246	
247		248	
249		250	
251		252	

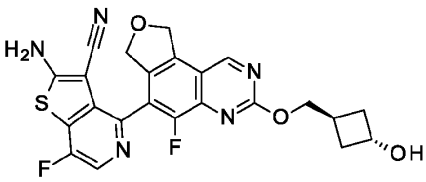
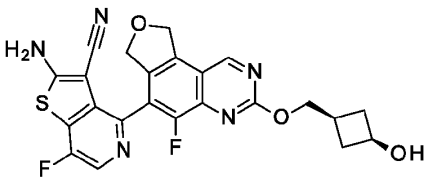
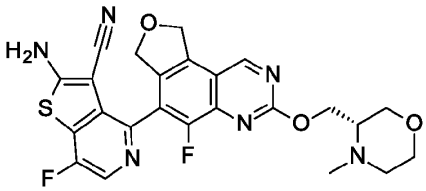
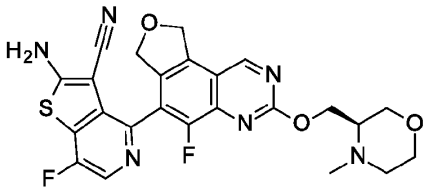
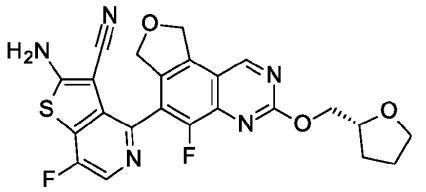
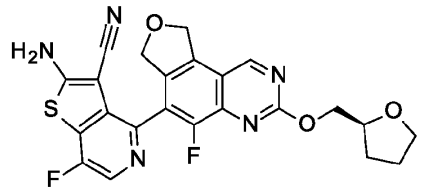
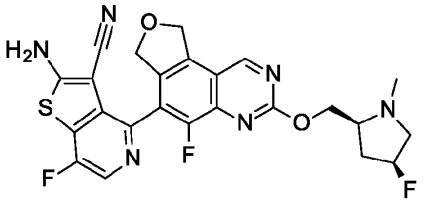
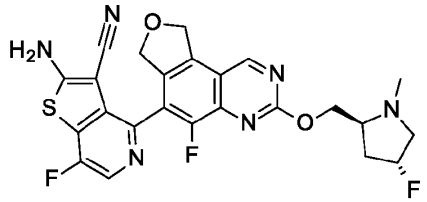
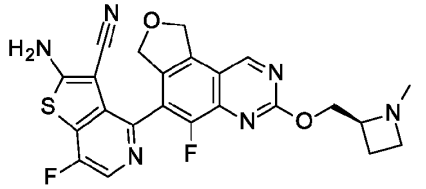
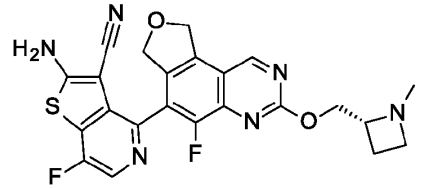
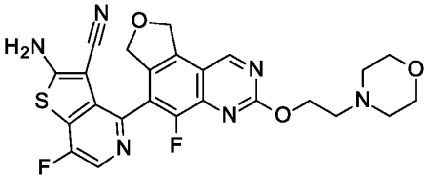
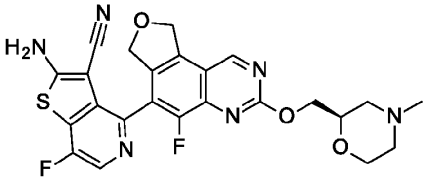
253		254	
255		256	
257		258	
259		260	

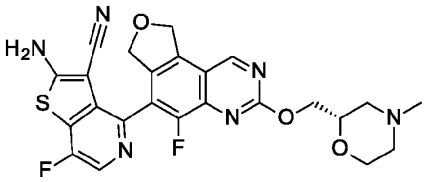
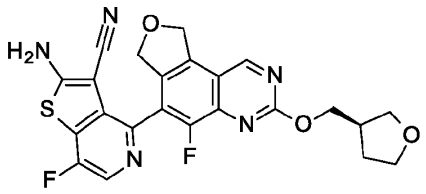
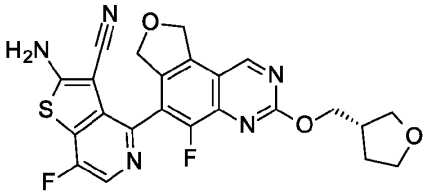
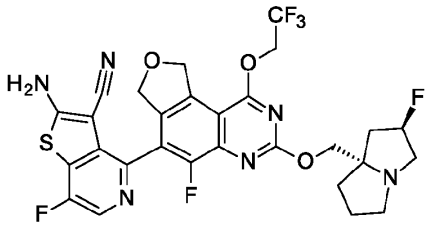
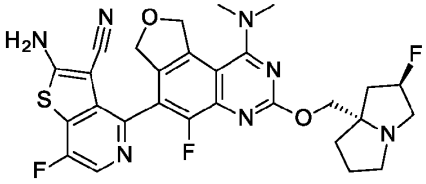
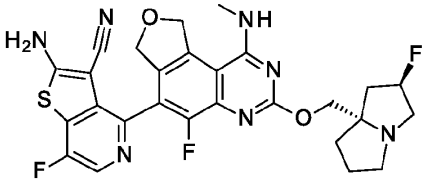
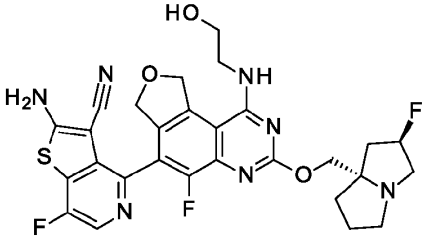
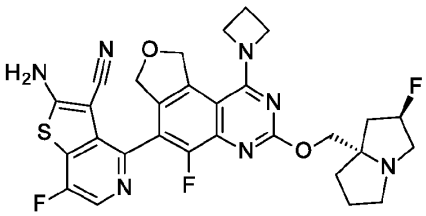
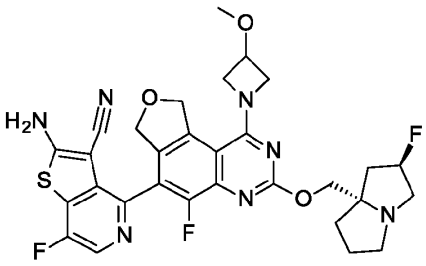
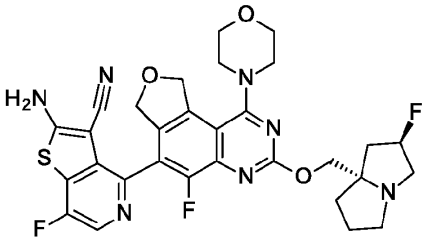
261		262	
263		264	
265		266	
267		268	

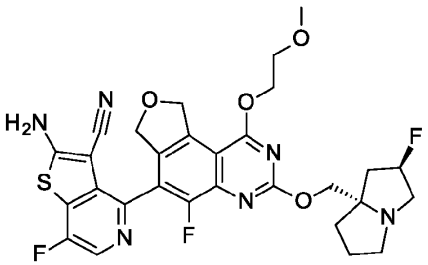
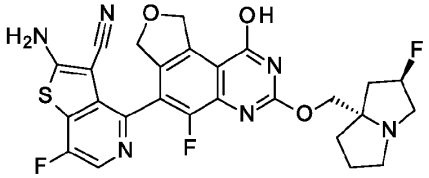
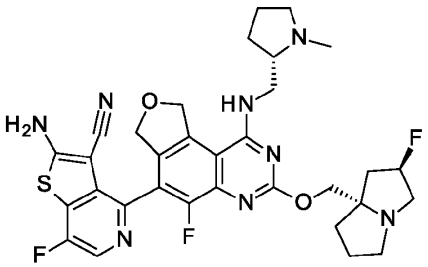
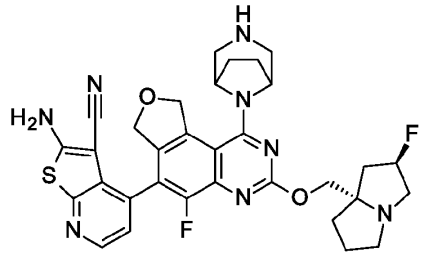
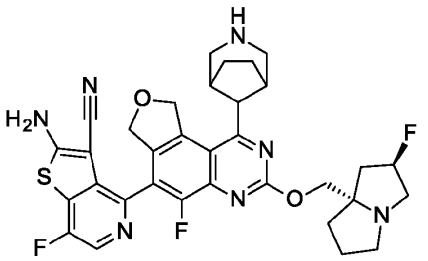
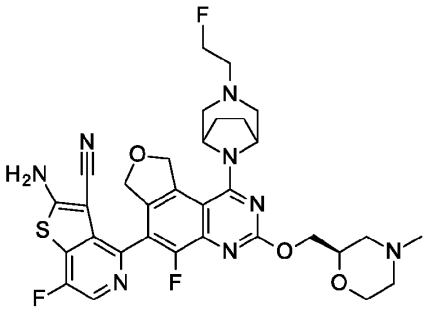
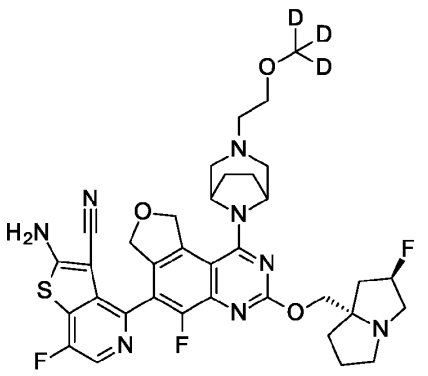
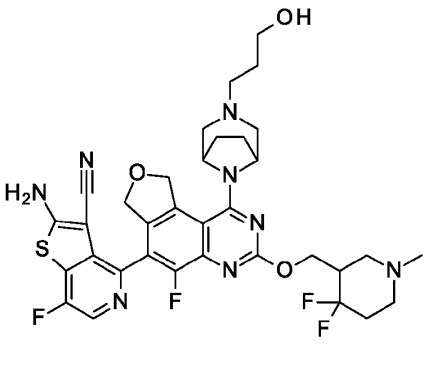
269		270	
271		272	
273		274	
275		276	

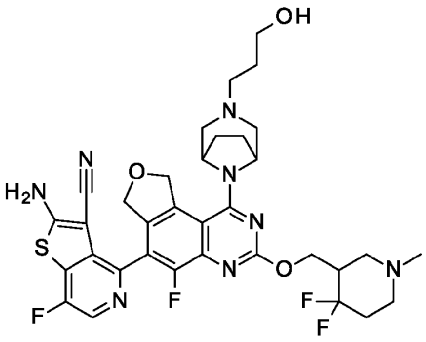
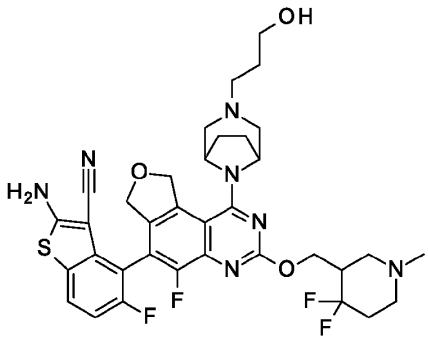
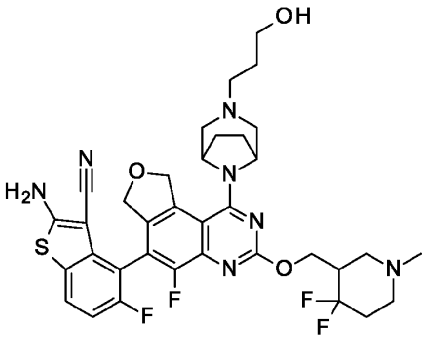
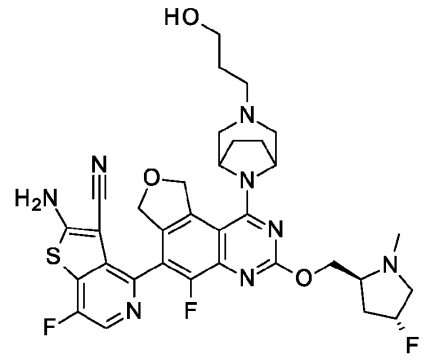
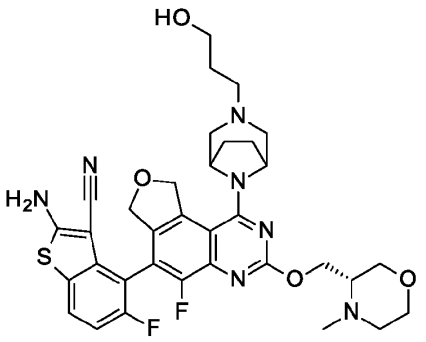
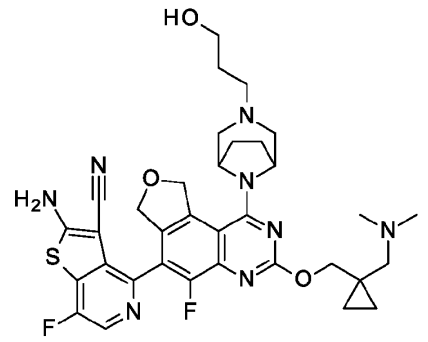
277		278	
279		280	
281		282	
283		284	
285		286	

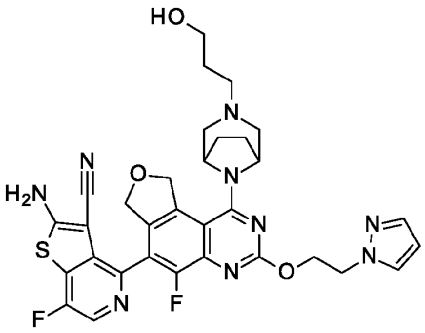
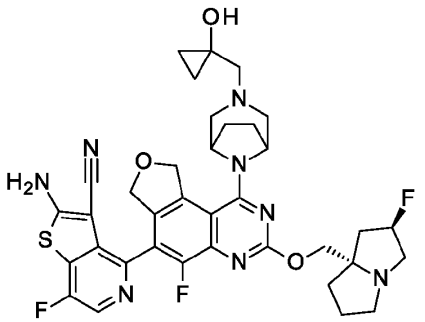
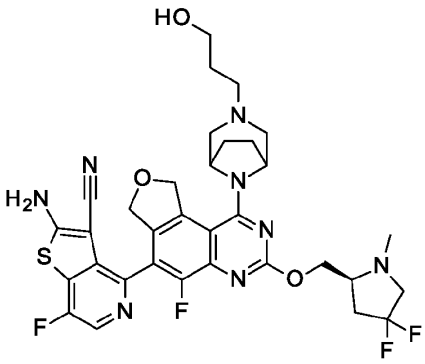
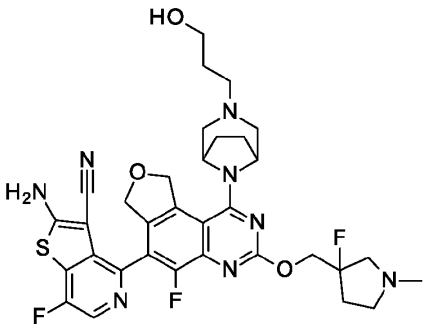
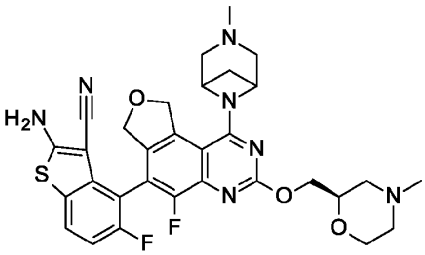
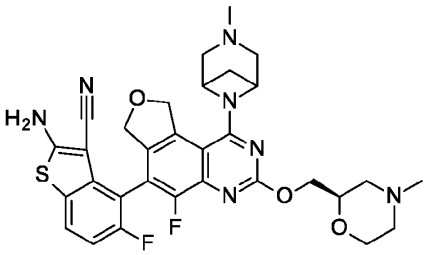
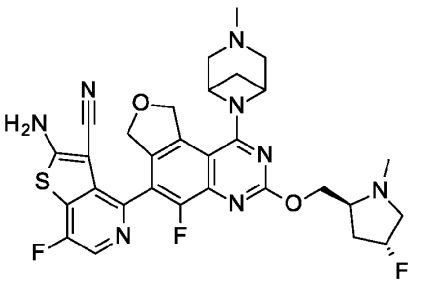
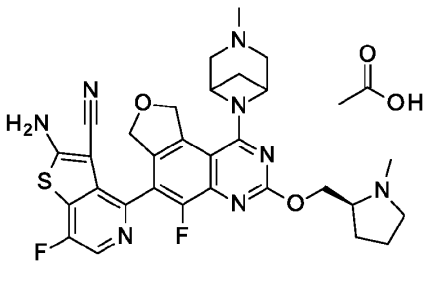
287		288	
289		290	
291		292	
293		294	
295		296	
297		298	

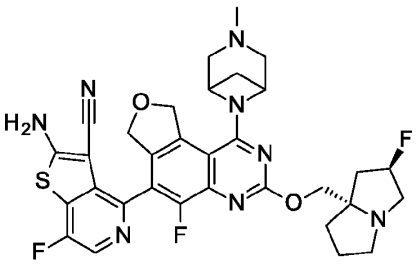
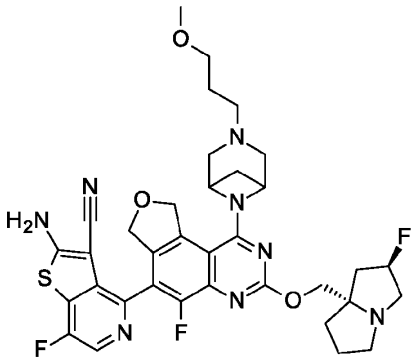
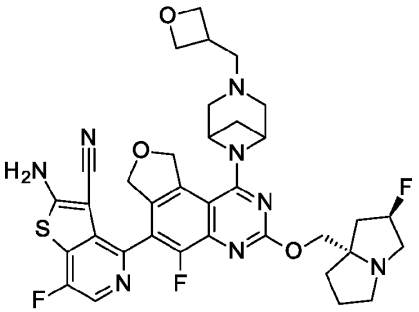
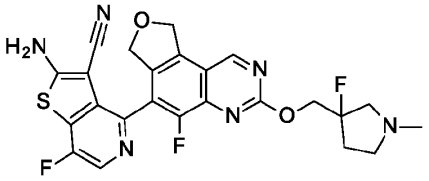
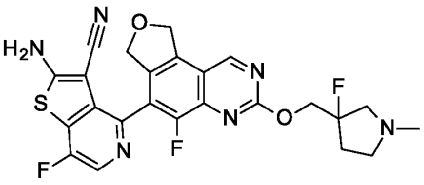
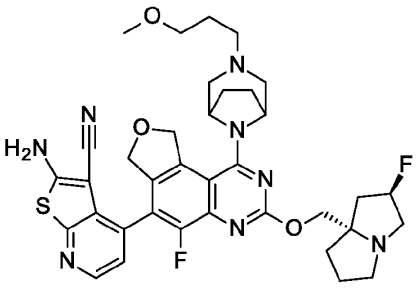
299		300	
301		302	
303		304	
305		306	
307		308	
309		310	

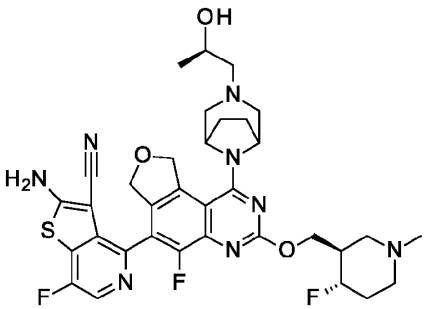
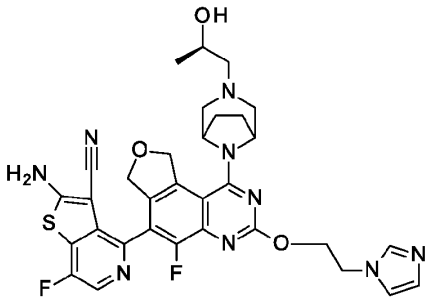
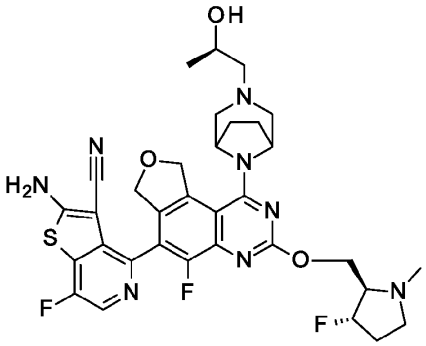
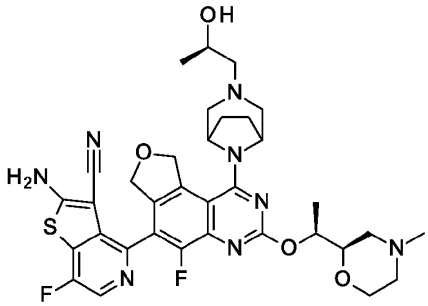
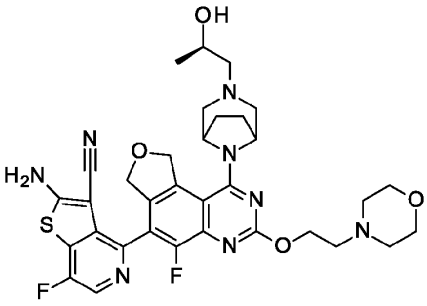
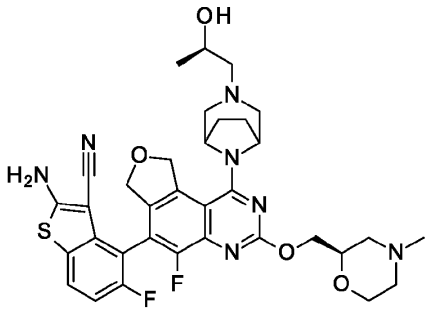
311		312	
313		314	
315		316	
317		318	
319		320	

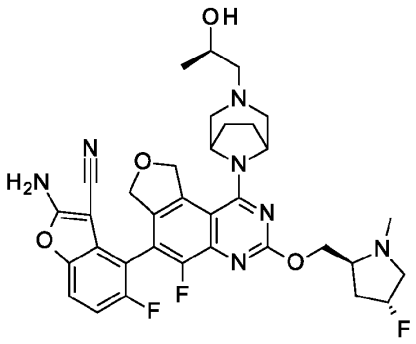
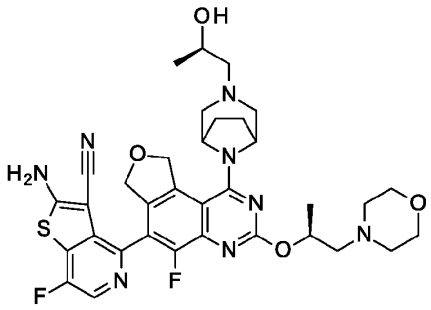
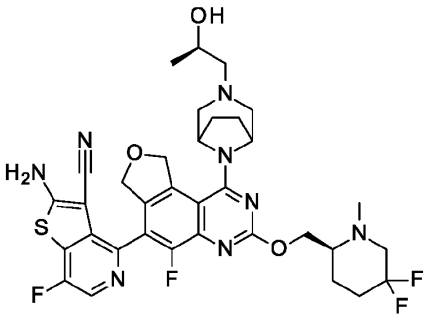
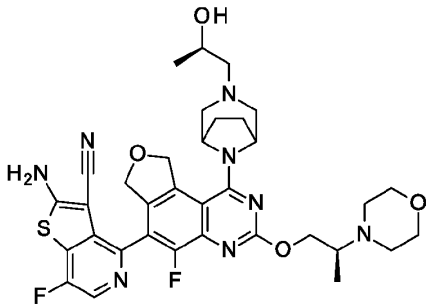
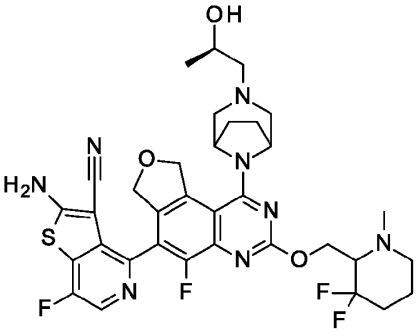
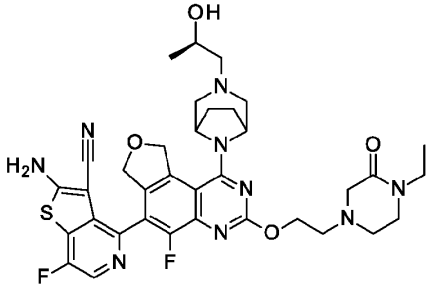
321		322	
323		324	
325		326	
327		328	

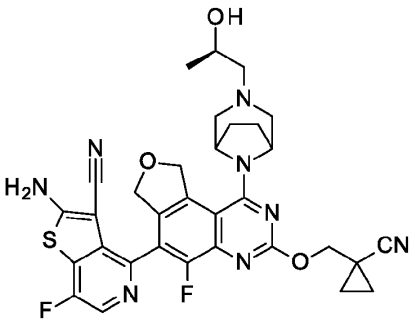
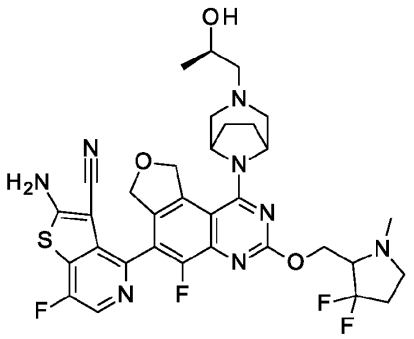
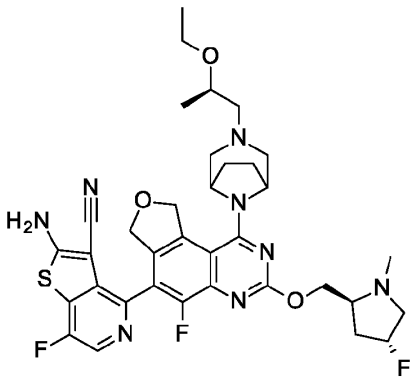
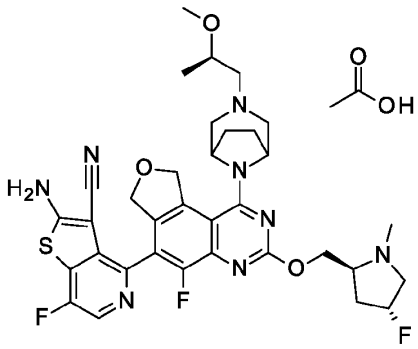
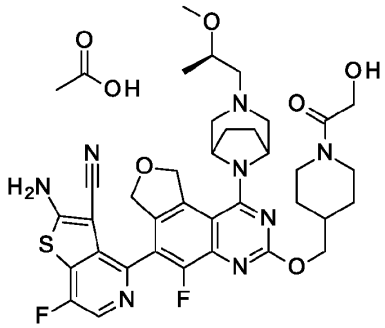
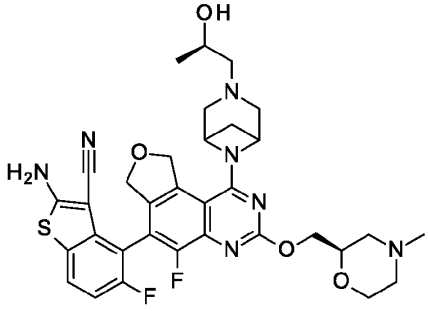
329		330	
331		332	
333		334	

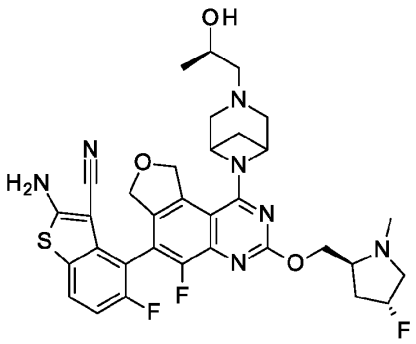
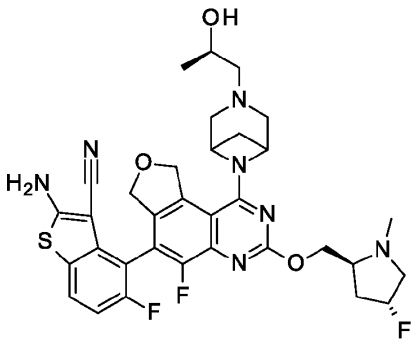
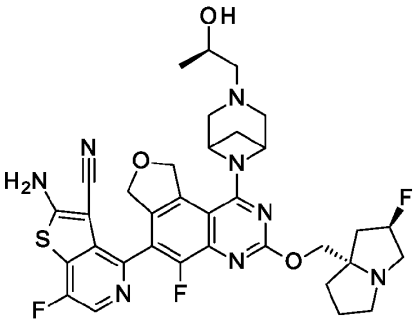
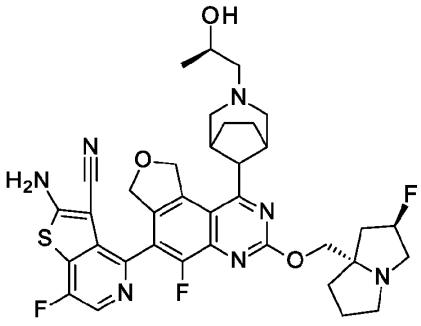
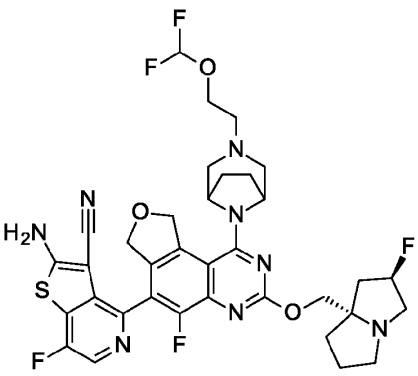
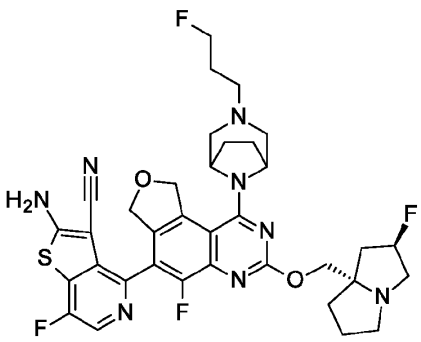
335		336	
337		338	
339		340	
341		342	

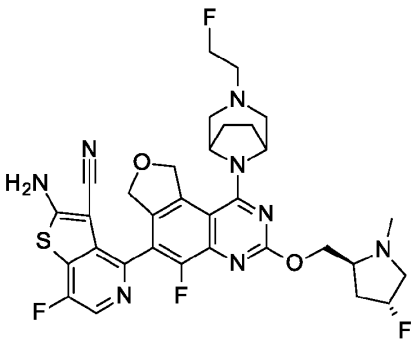
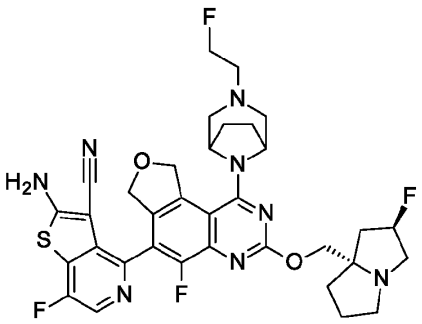
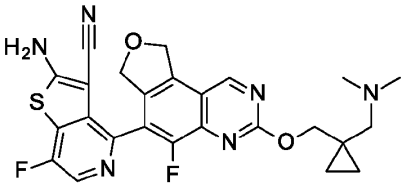
343		344	
345		346	
347		348	

349		350	
351		352	
353		354	

355		356	
357		358	
359		360	

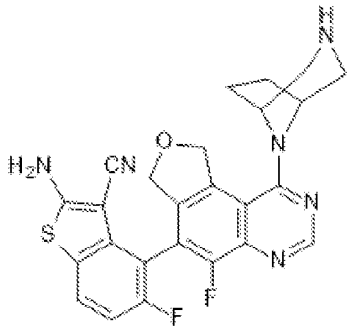
361		362	
363		364	
365		366	

367		368	
369		370	
371		372	

373		374	
375			

The chemical drawings in Table A contain indications of chiral aspects of the specific compounds shown. However, the chemical drawings in Table A 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.

In a compound of Formulae I, Ia, II, IIa, III, IIIa, IV or IVa or a pharmaceutically acceptable salt thereof, the compound is selected from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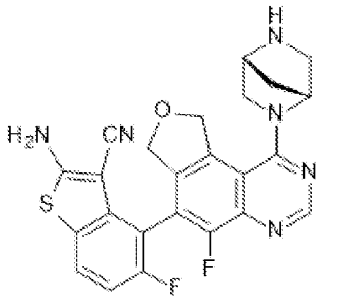
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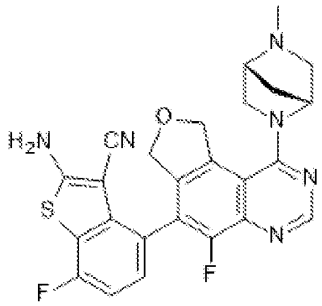
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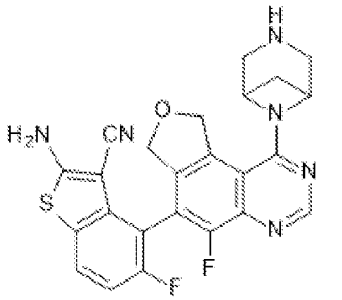
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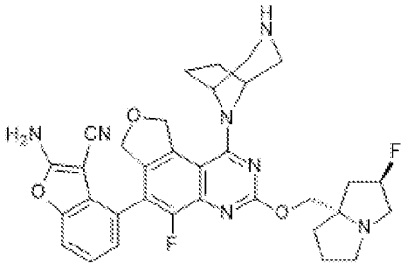
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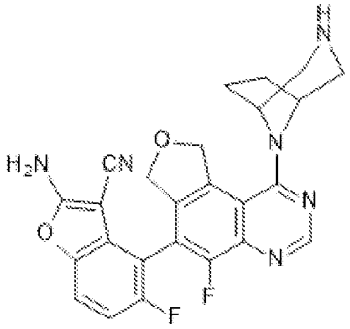
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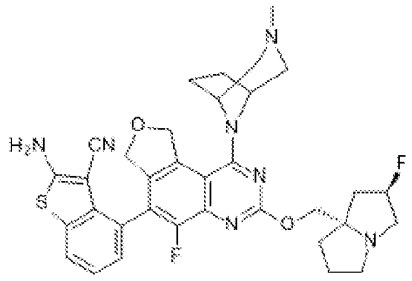
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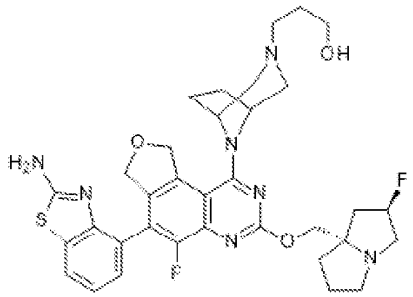
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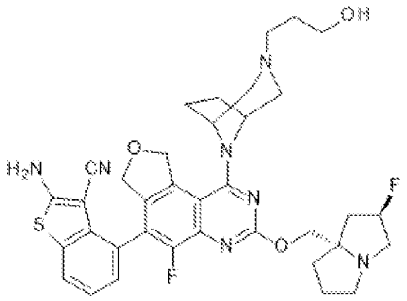
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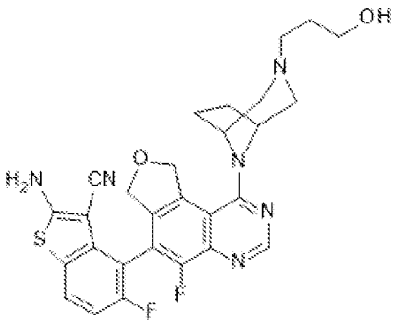
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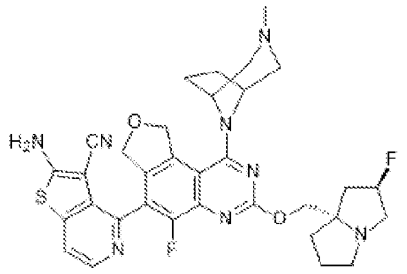
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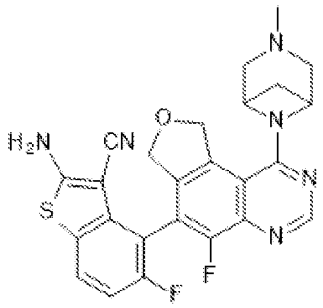
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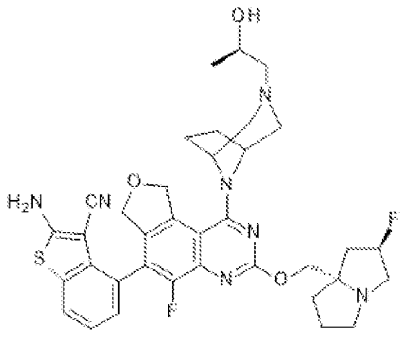
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or a pharmaceutically acceptable salt thereof.

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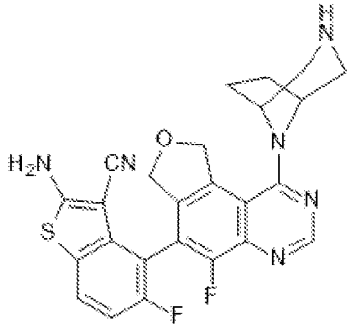
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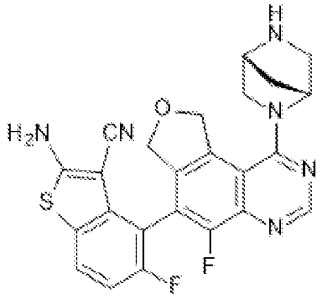
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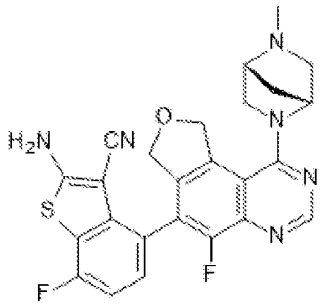
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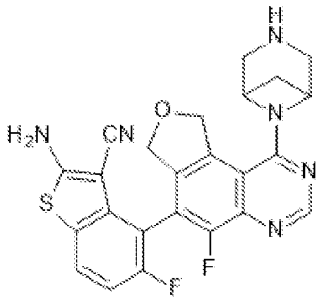
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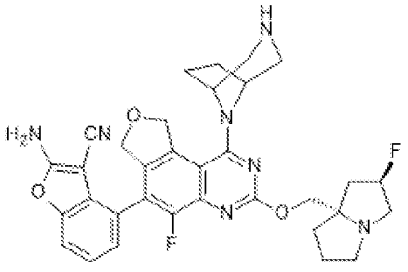
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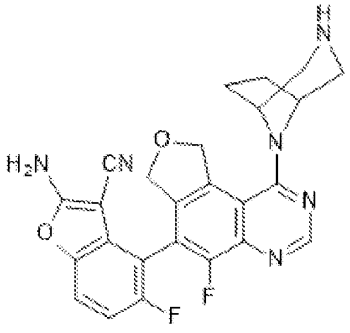
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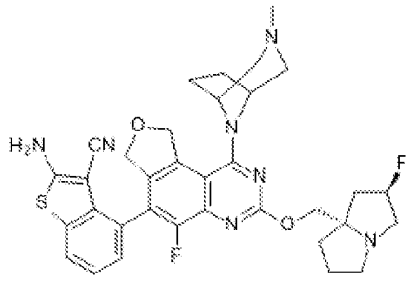
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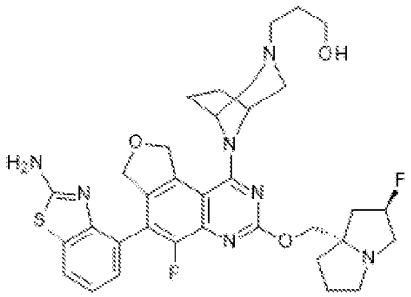
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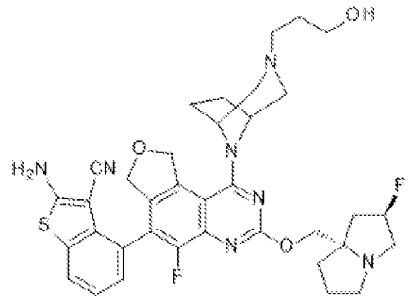
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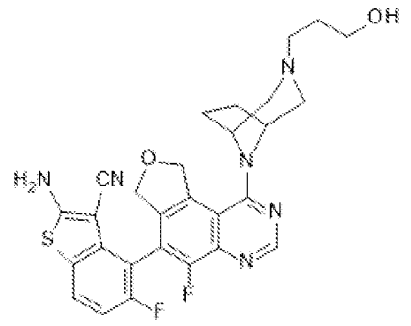
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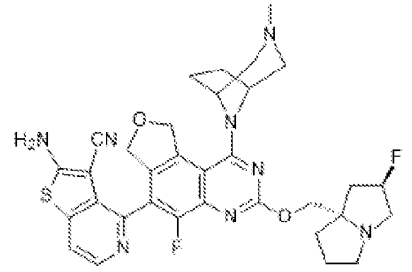
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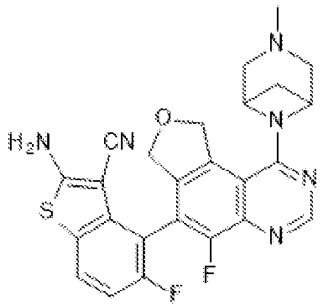
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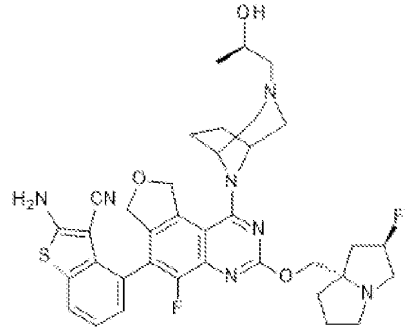
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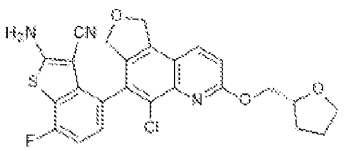
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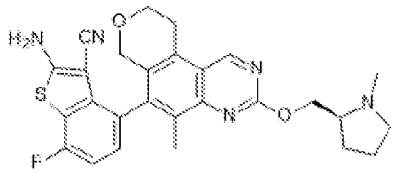
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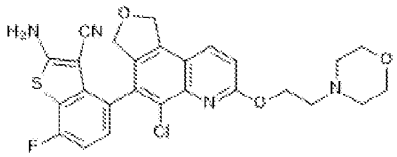
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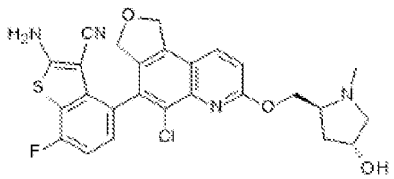
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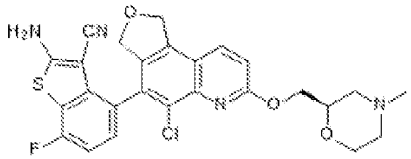
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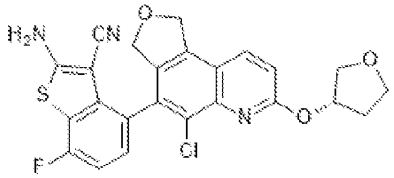
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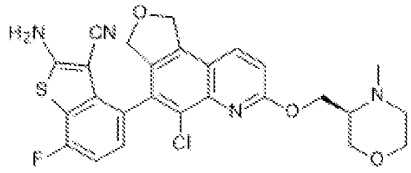
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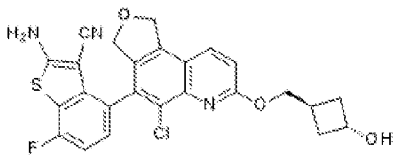
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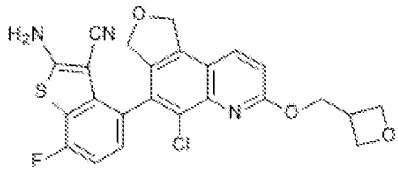
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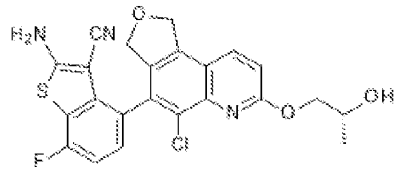
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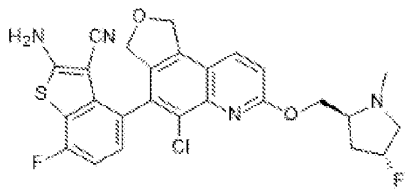
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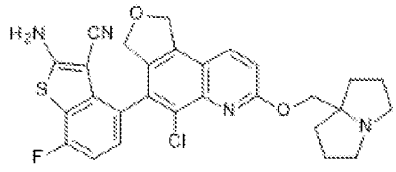
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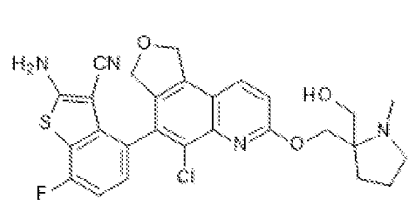
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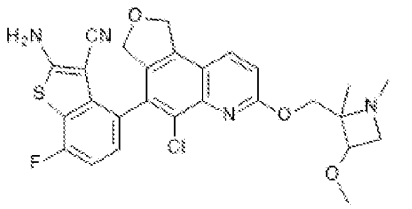
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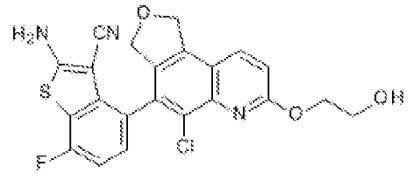
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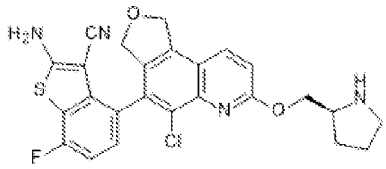
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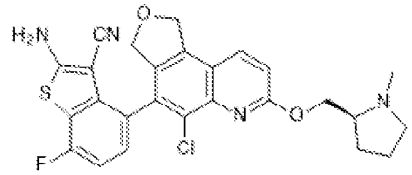
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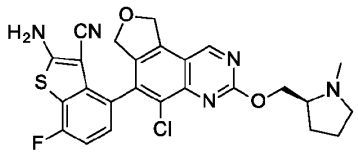
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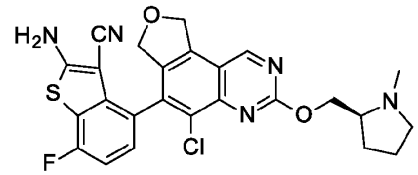
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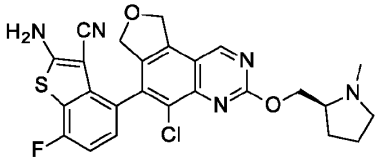
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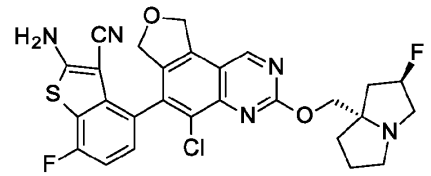
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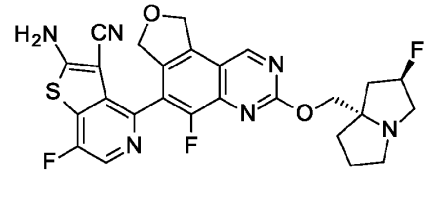
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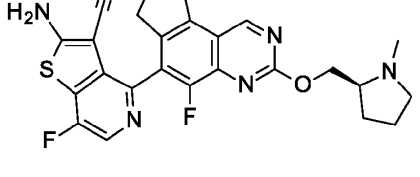
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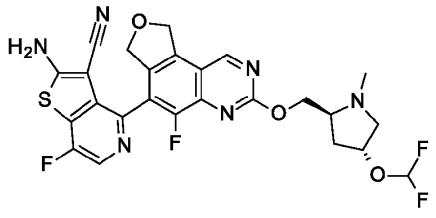
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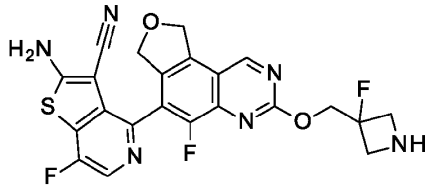
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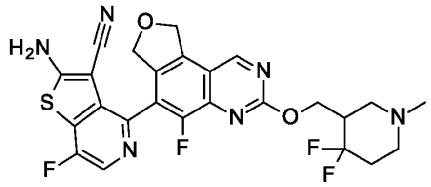
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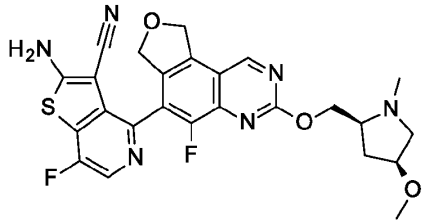
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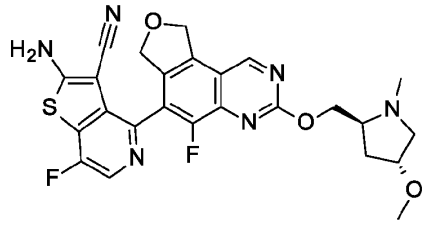
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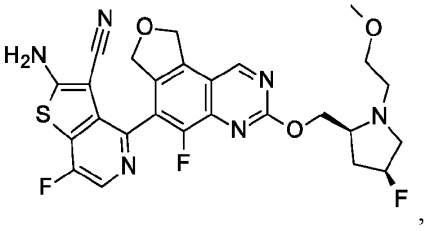
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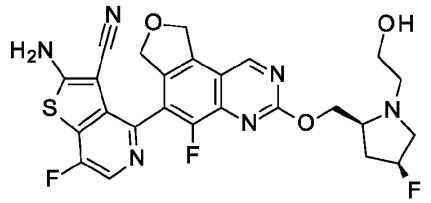
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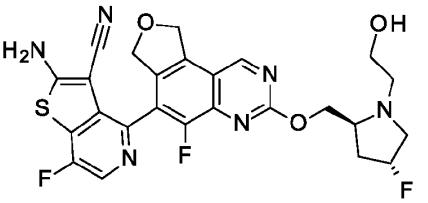
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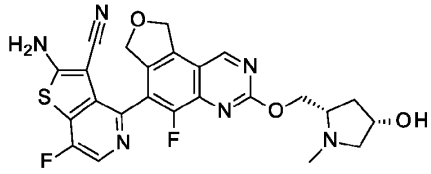
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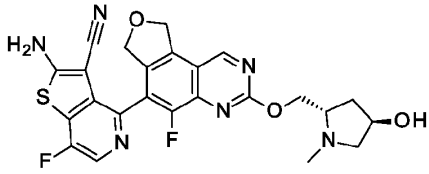
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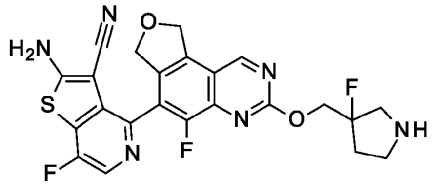
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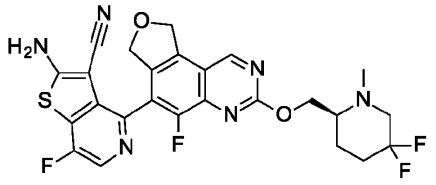
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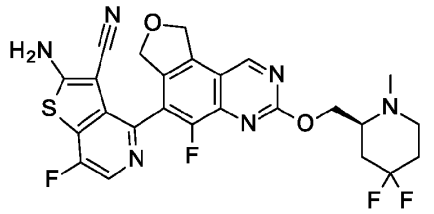
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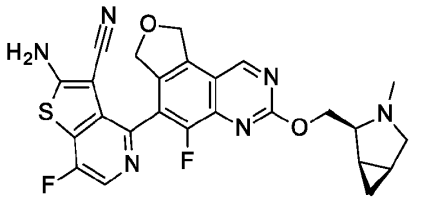
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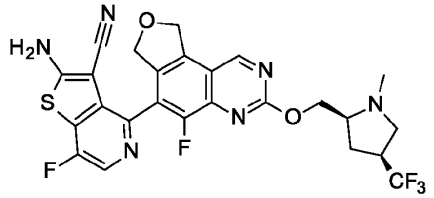
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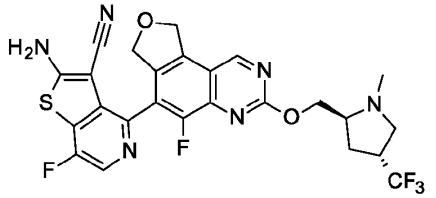
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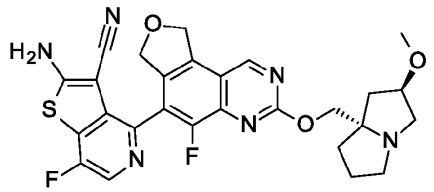
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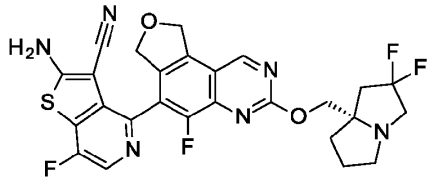
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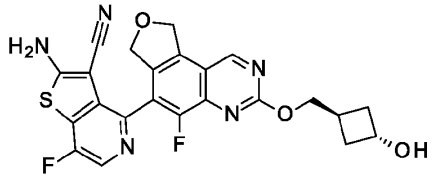
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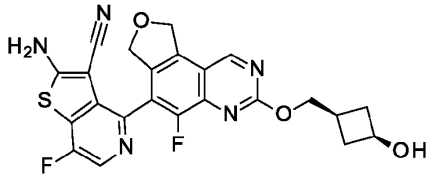
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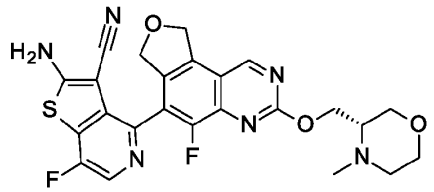
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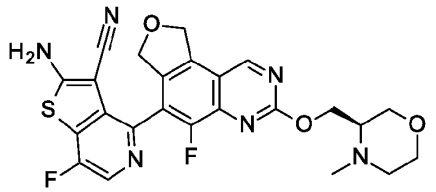
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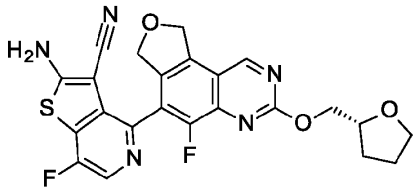
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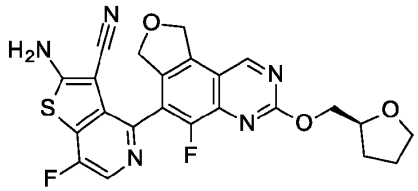
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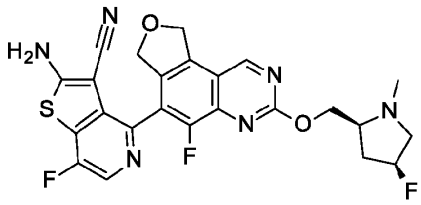
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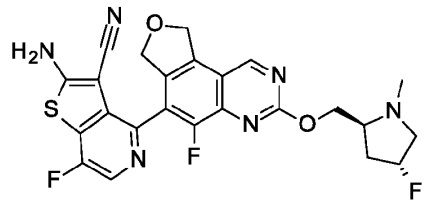
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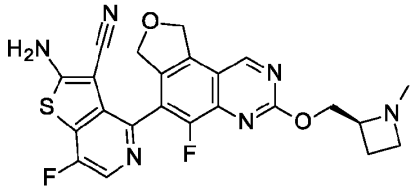
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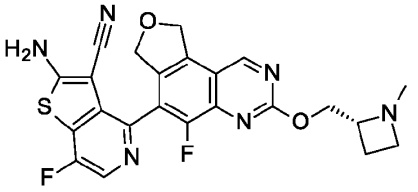
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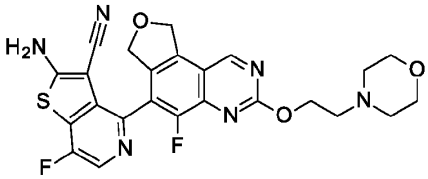
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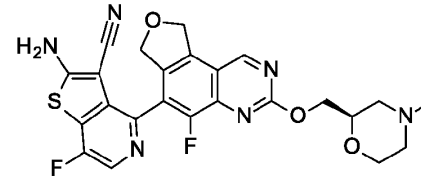
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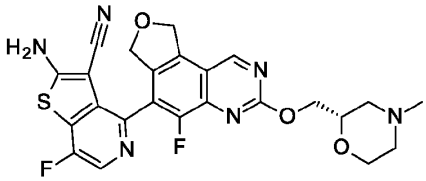
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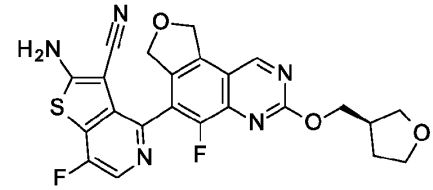
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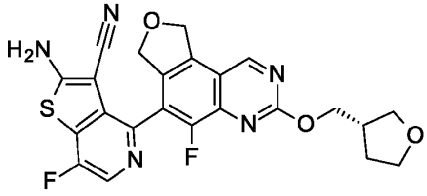
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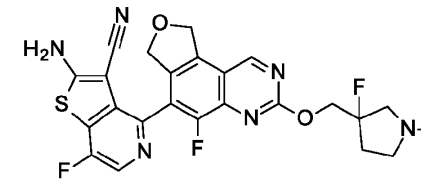
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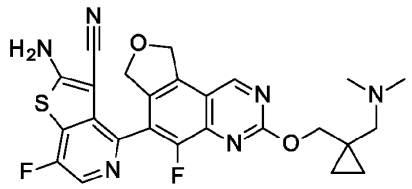

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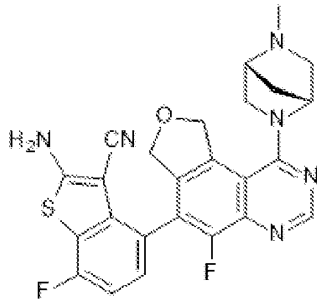
A further compound of Formulae I, Ia, II, IIa, III, IIIa, IV, or IVa or a pharmaceutically acceptable salt thereof, the compound is selected from



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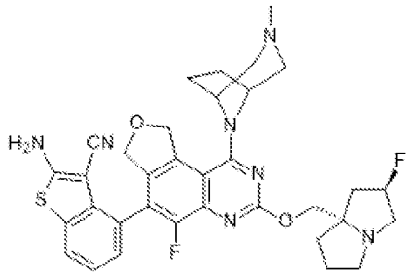

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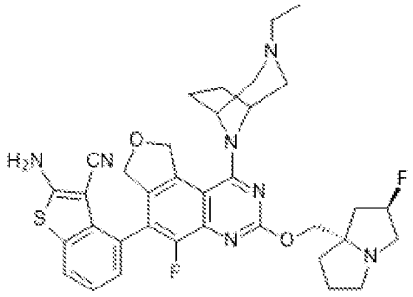

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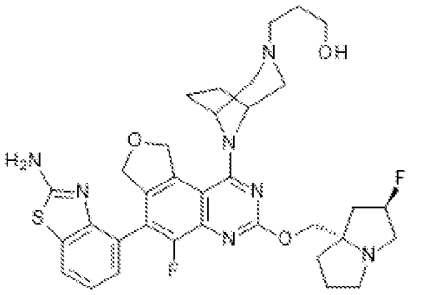

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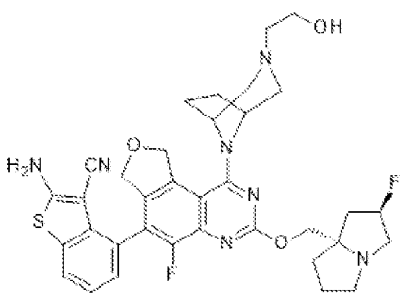
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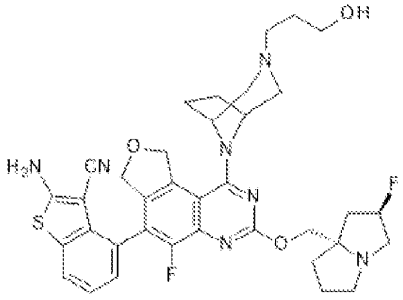
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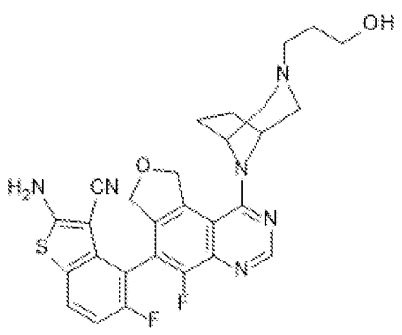
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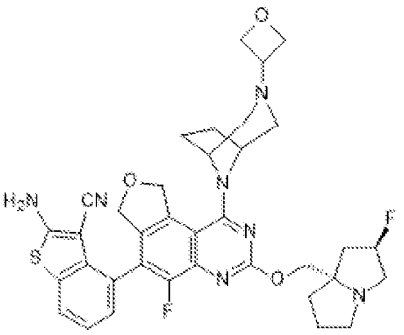
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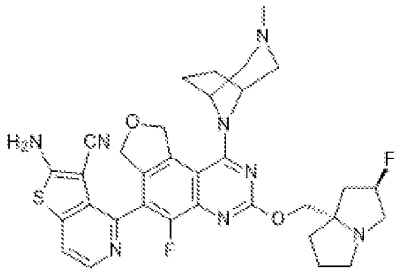
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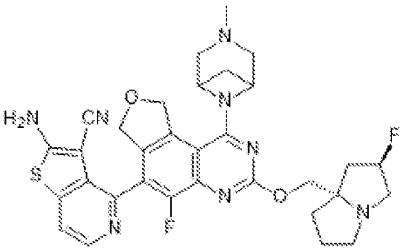
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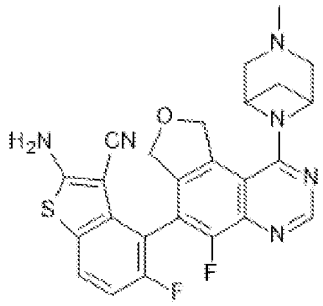
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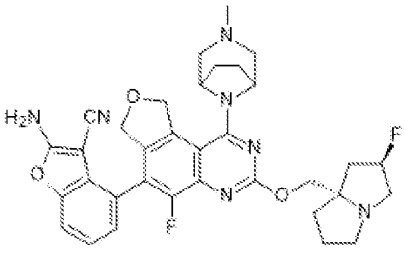
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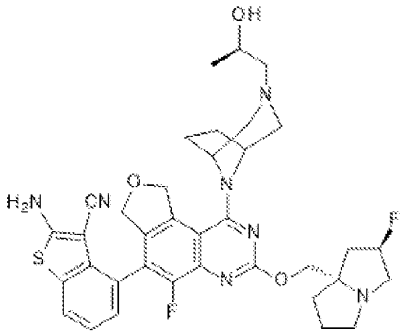
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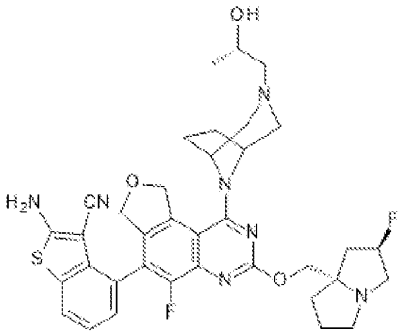
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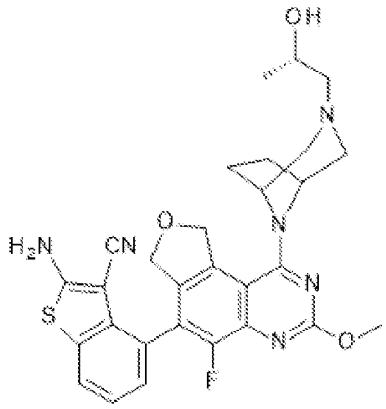
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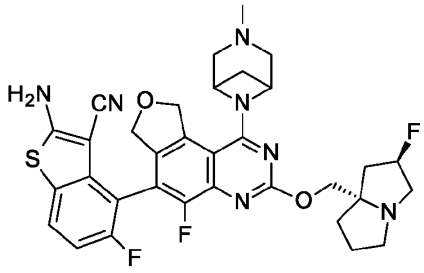
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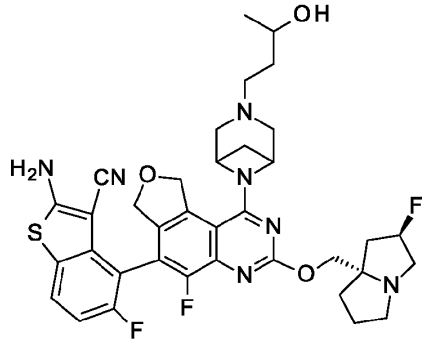
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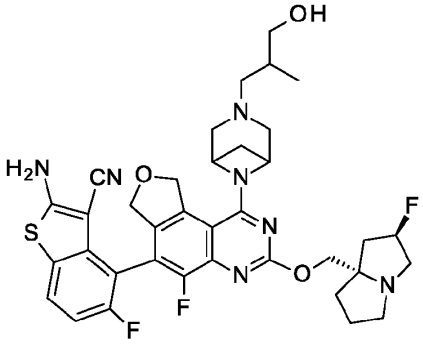
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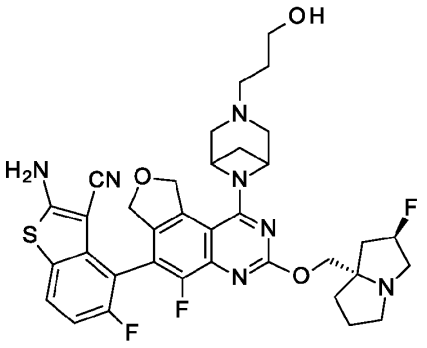
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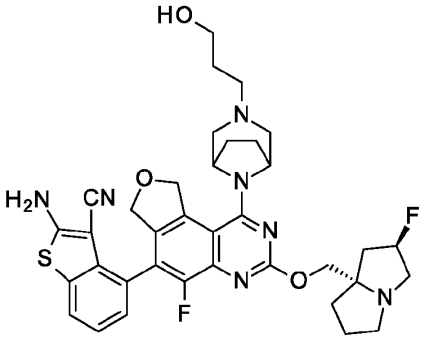
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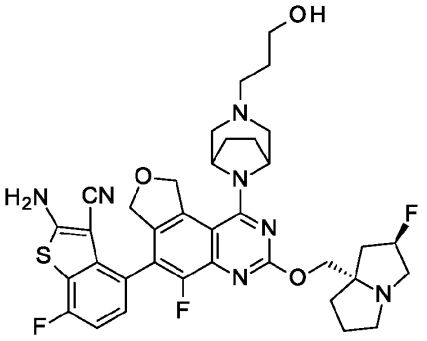
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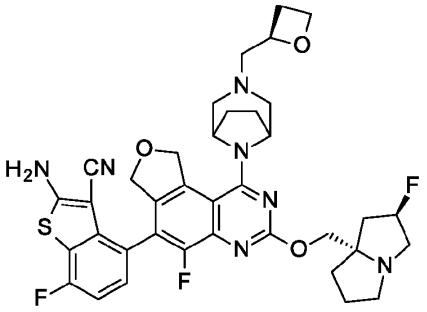
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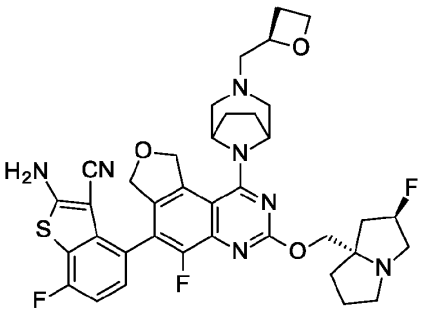
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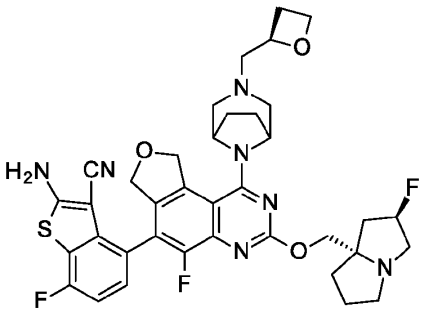
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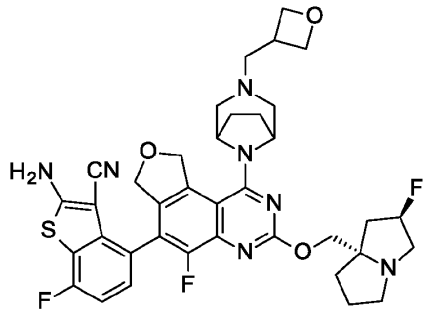
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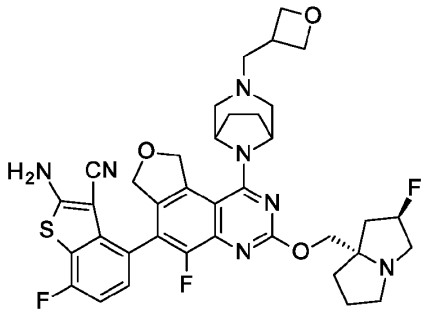
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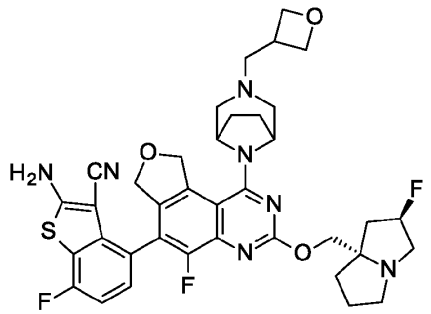
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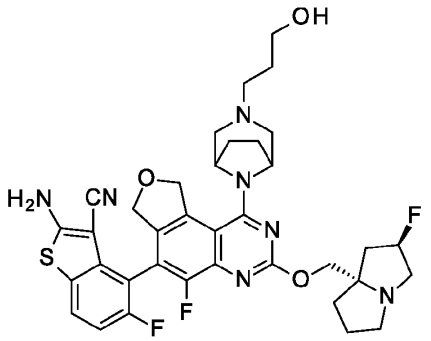
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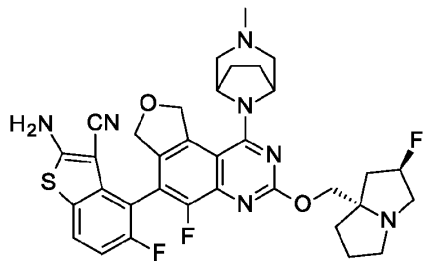
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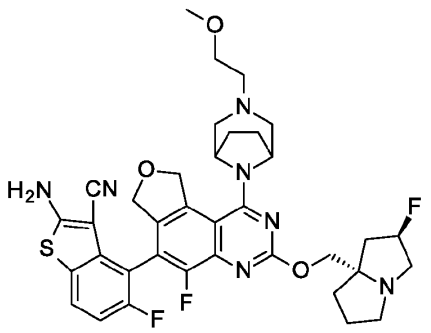
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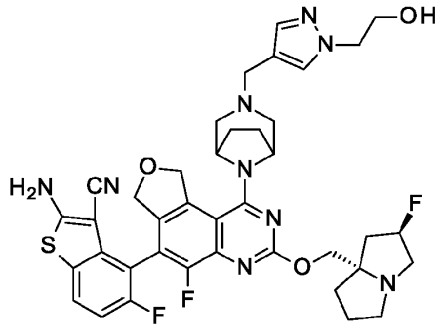
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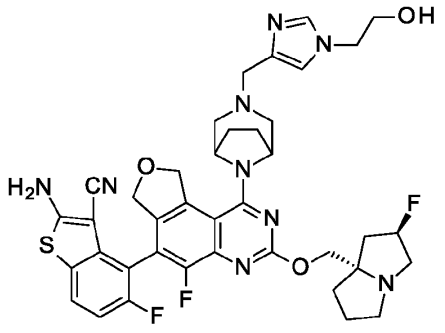
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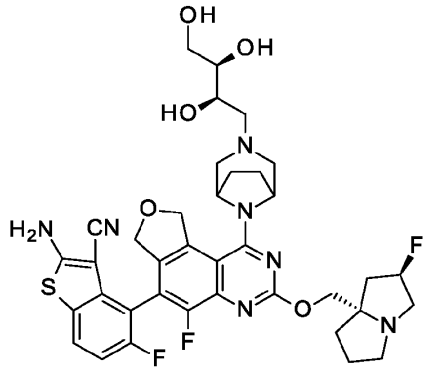
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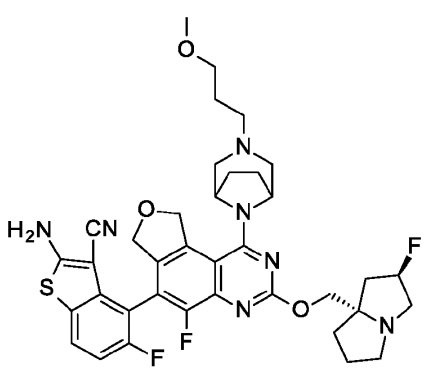
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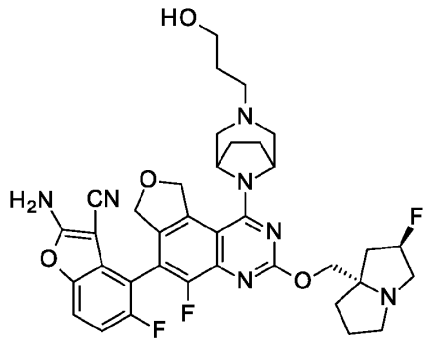
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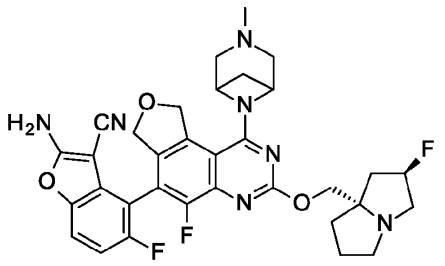
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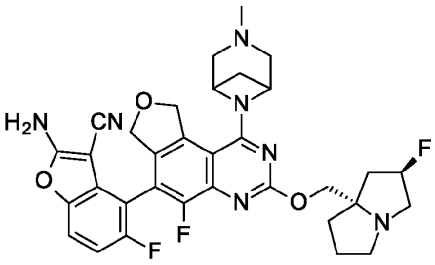
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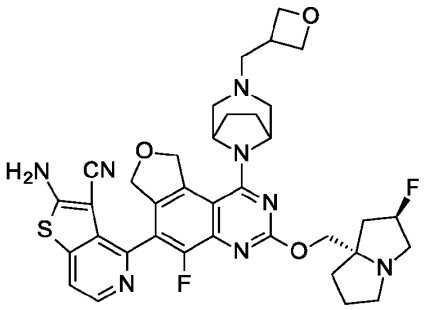
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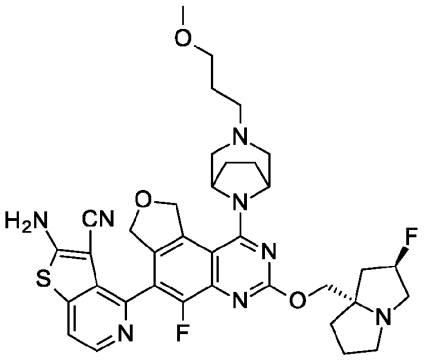
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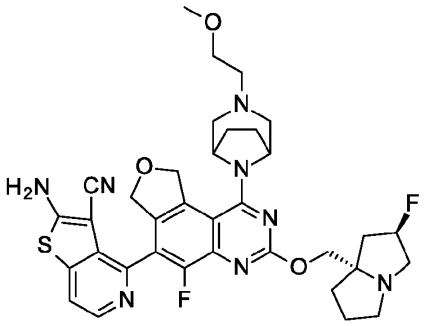
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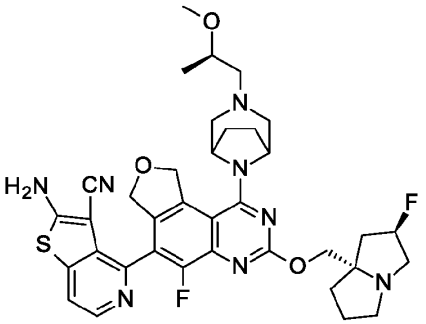
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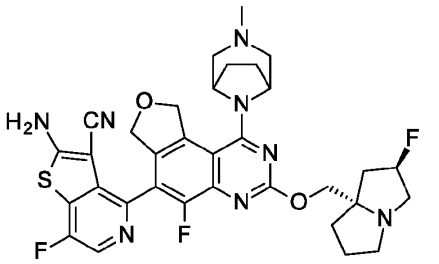
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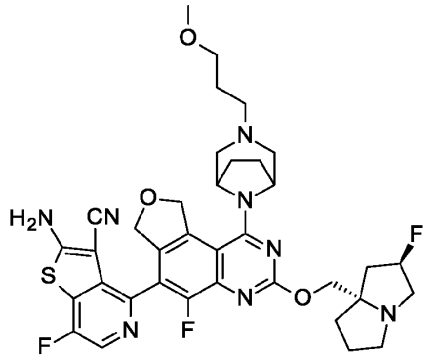
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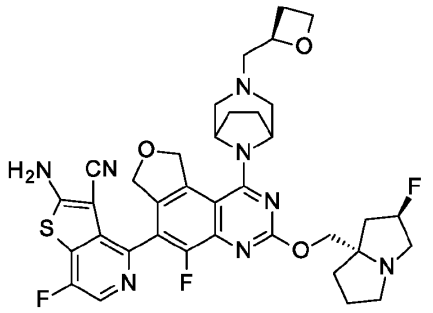
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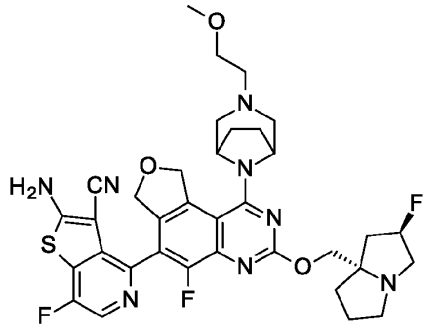
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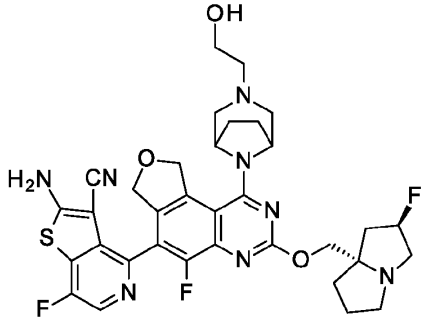
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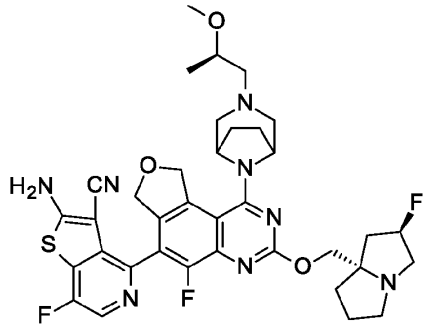
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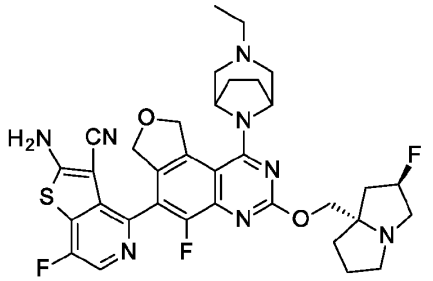
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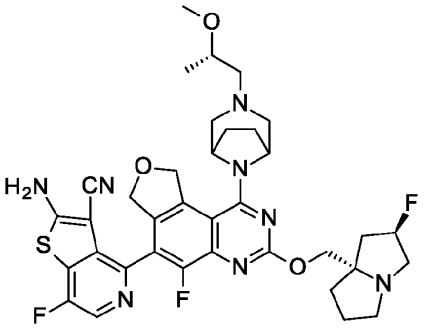
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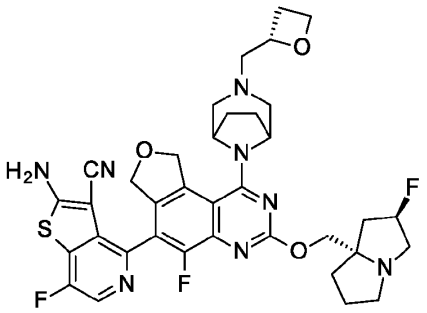
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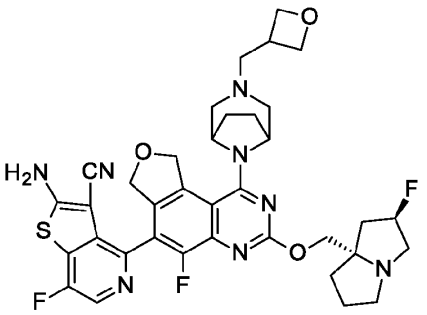
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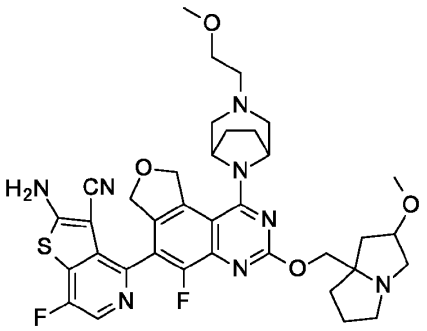
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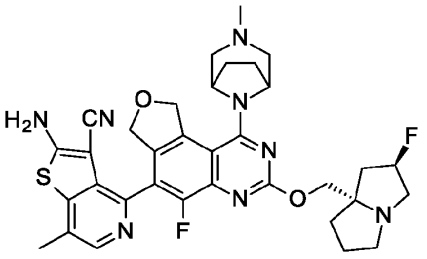
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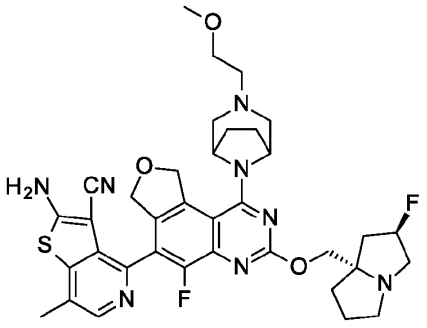
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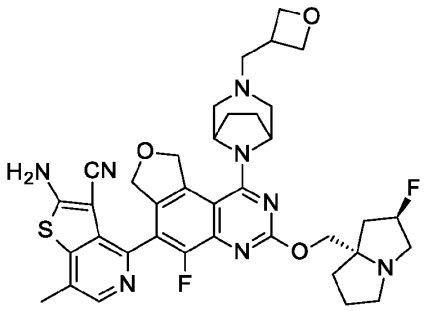
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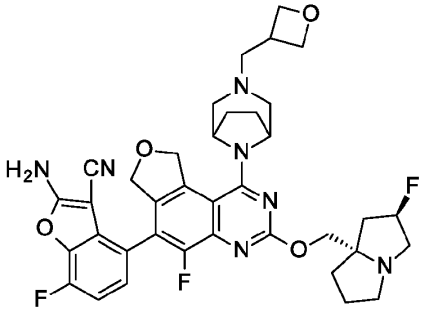
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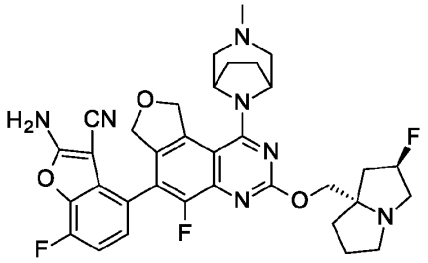
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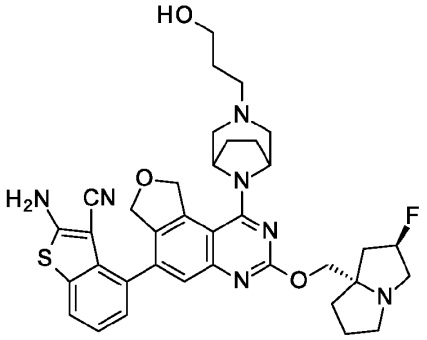
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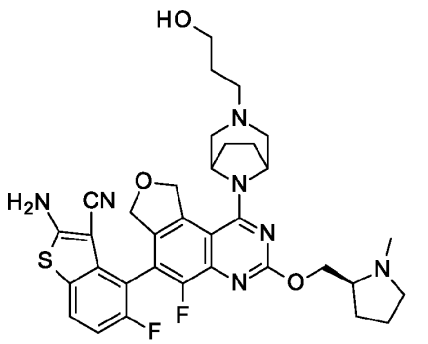
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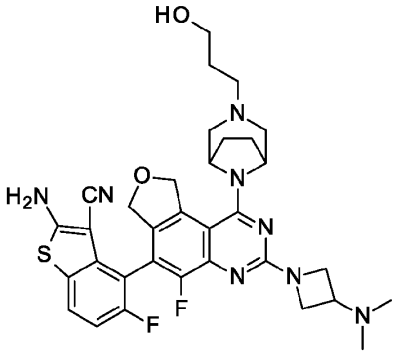
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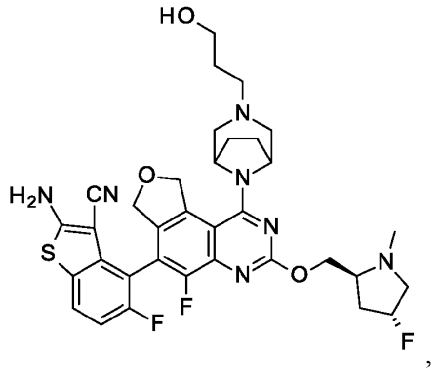
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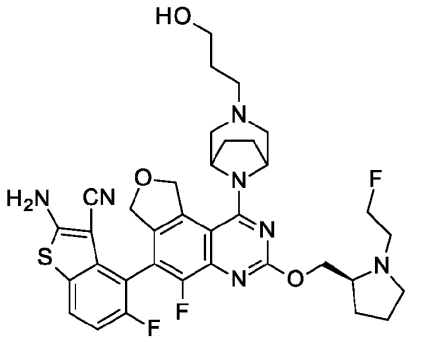
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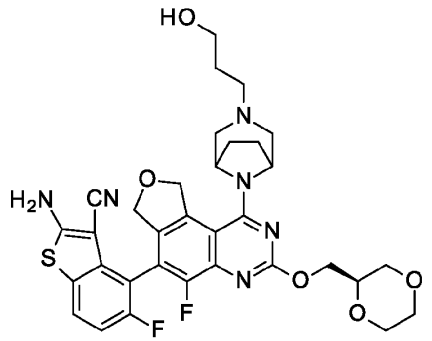
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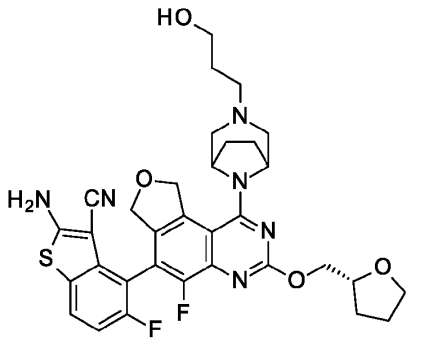
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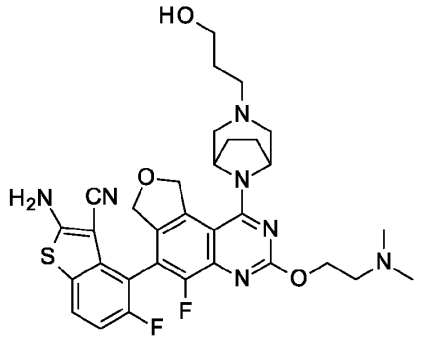
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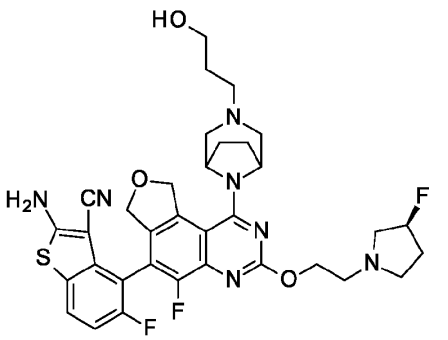
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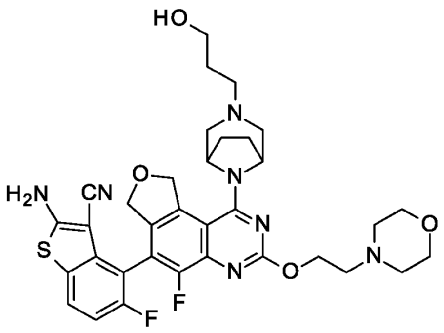
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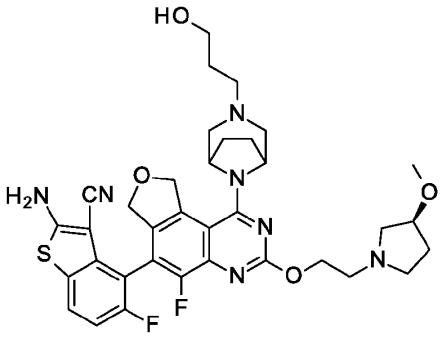
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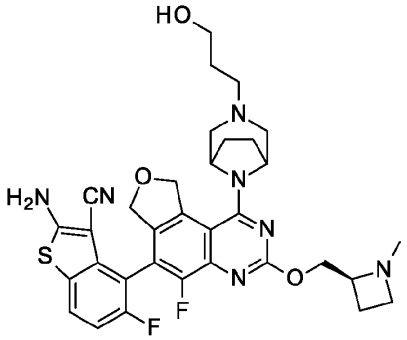
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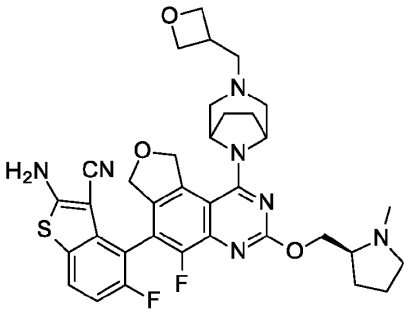
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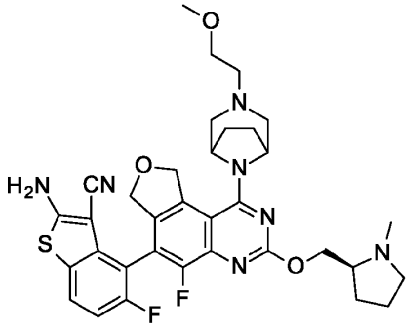
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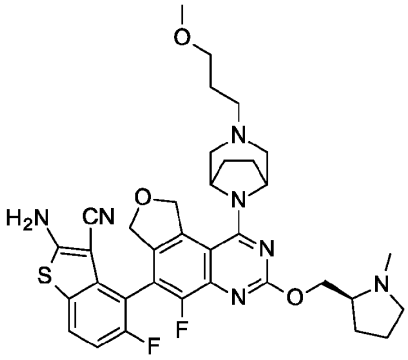
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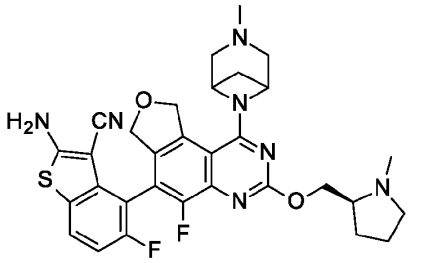
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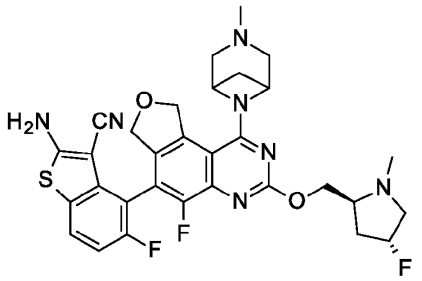
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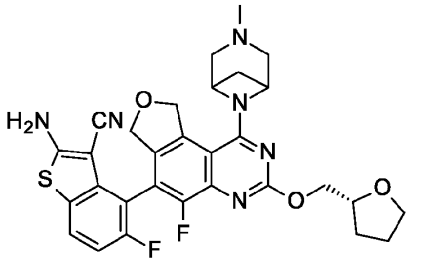
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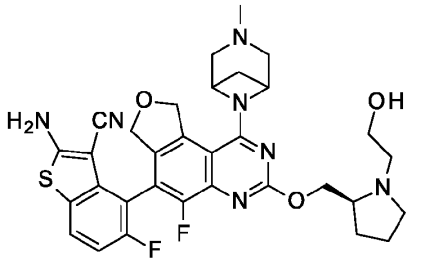
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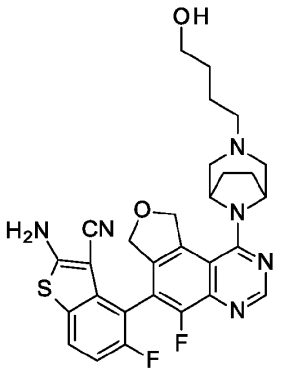
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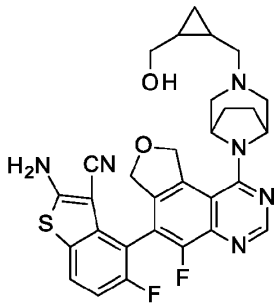
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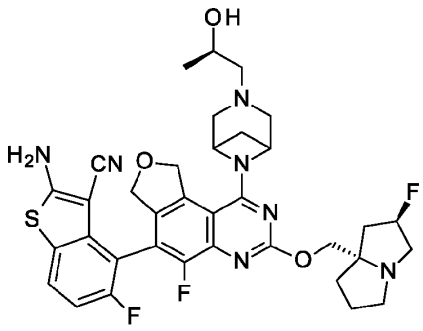
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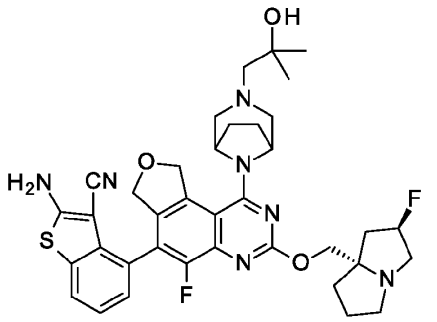
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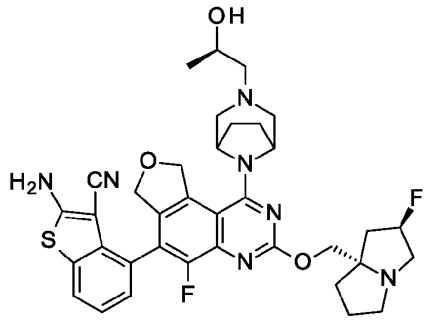
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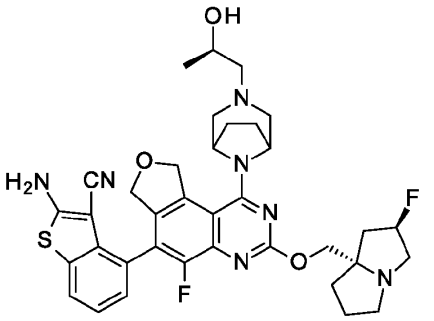
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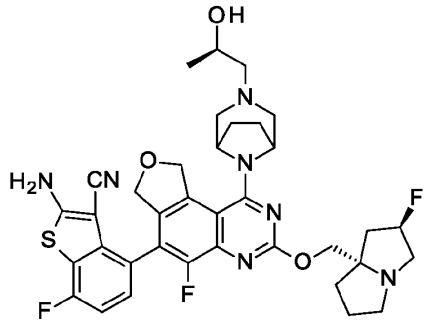
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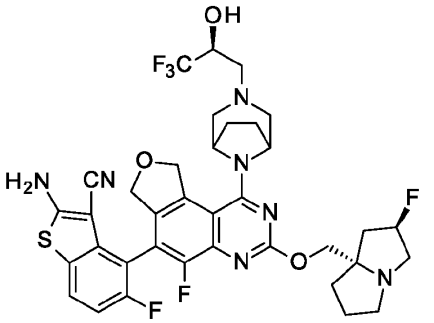
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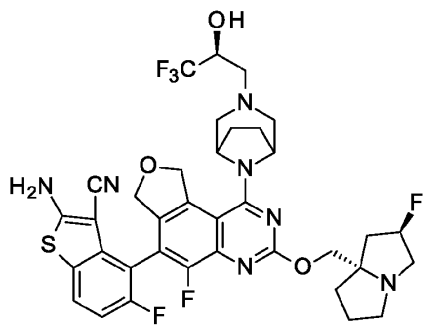
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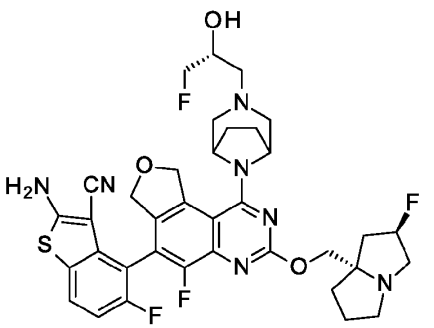
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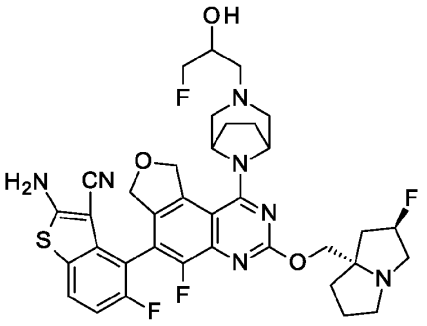
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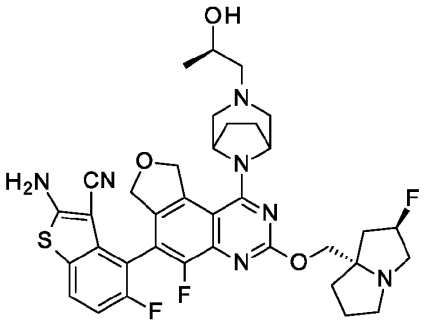
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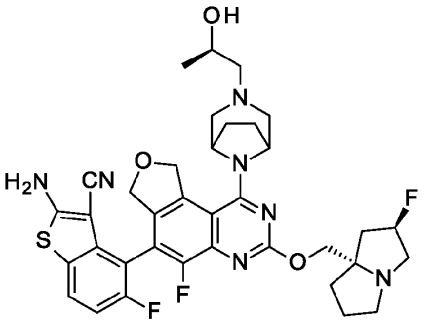
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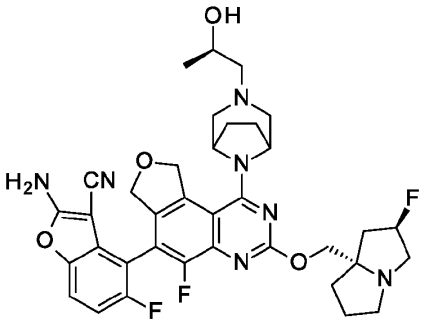
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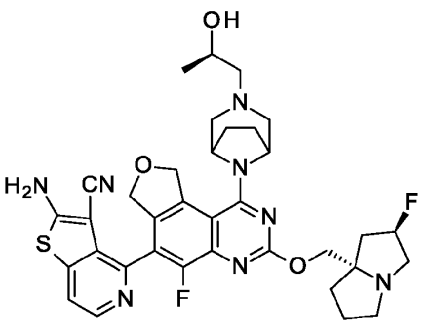
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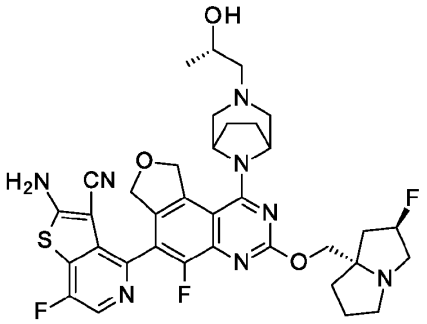
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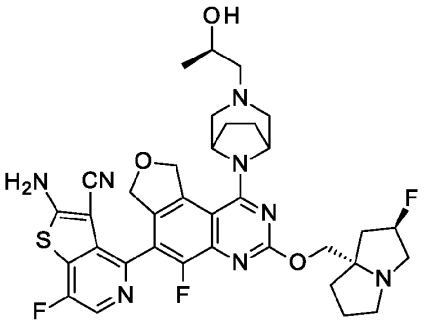
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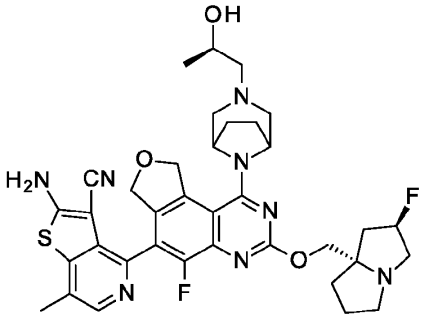
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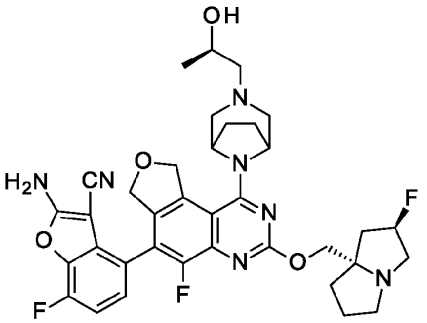
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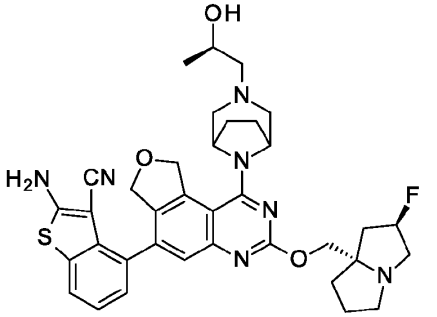
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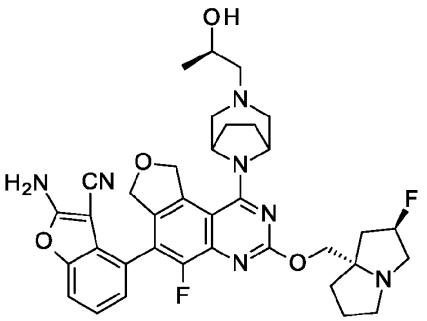
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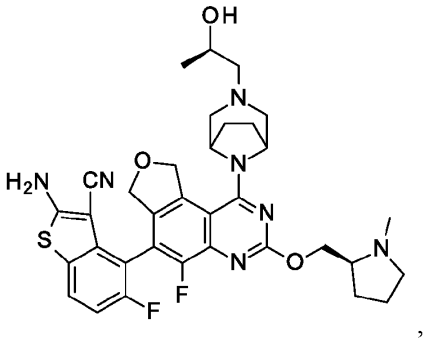
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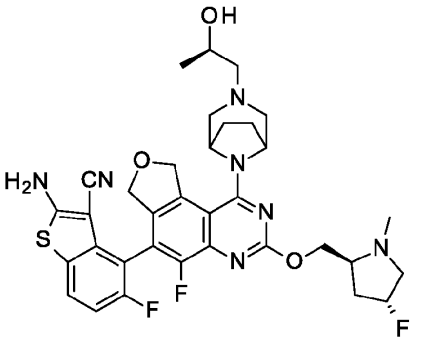
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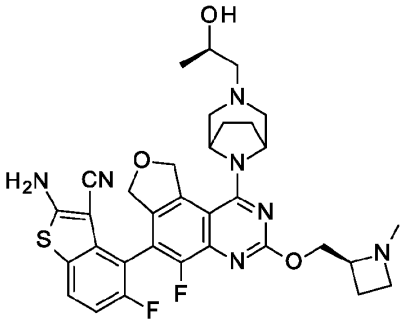
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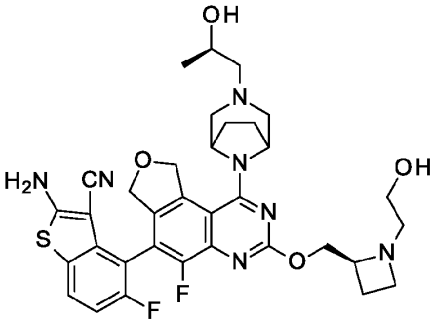
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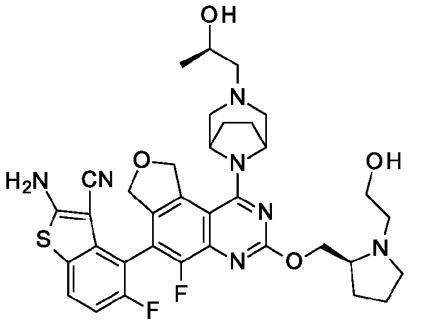
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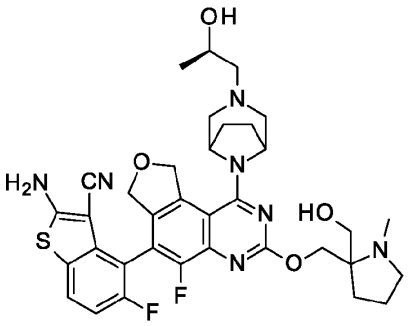
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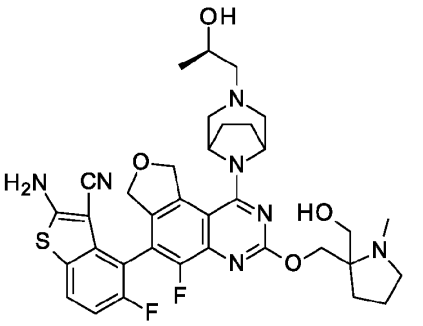
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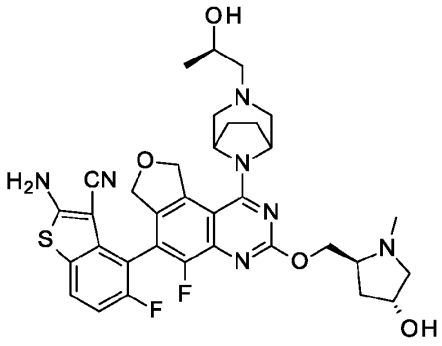
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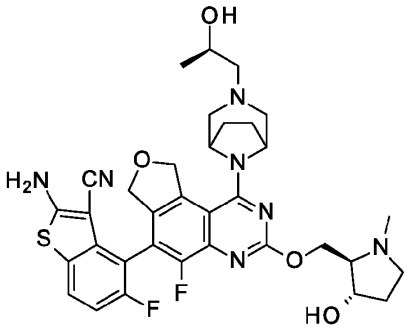
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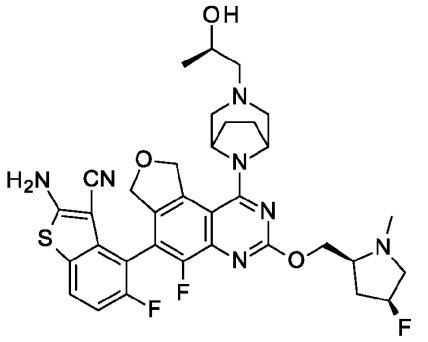
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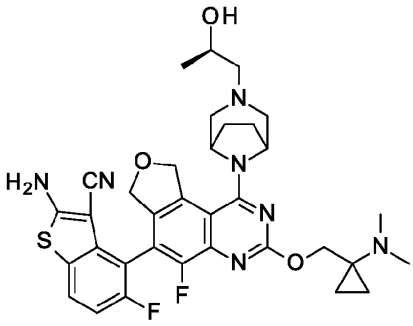
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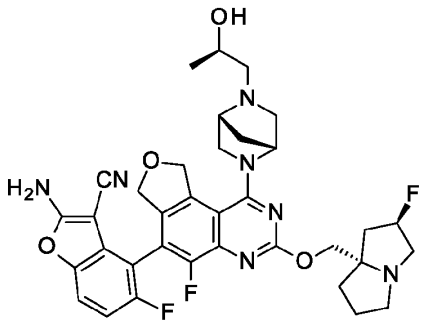
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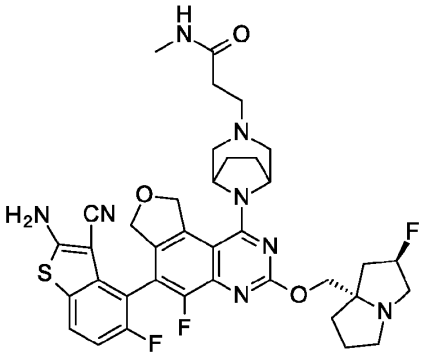
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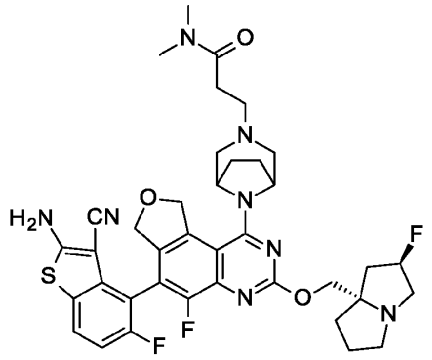
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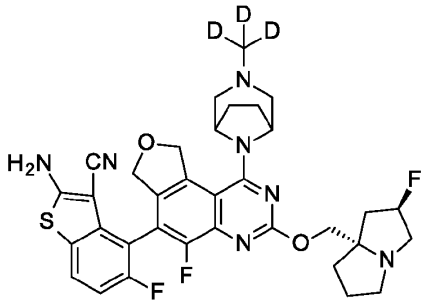
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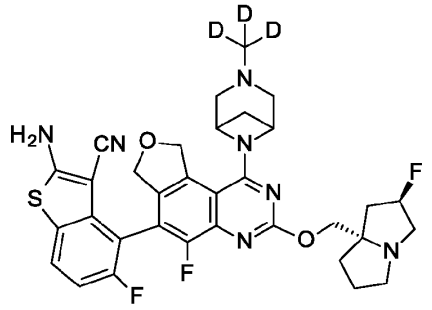
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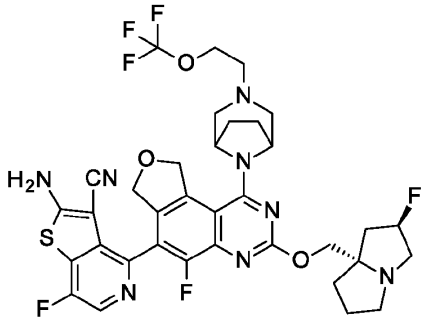
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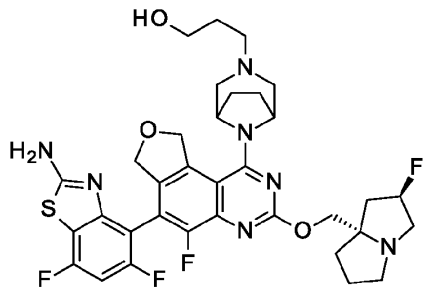
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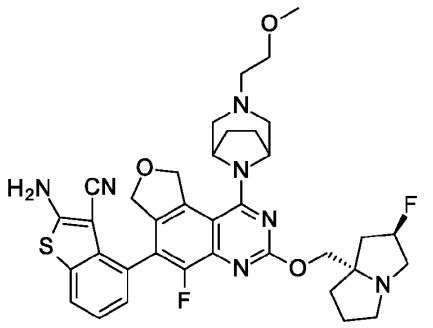
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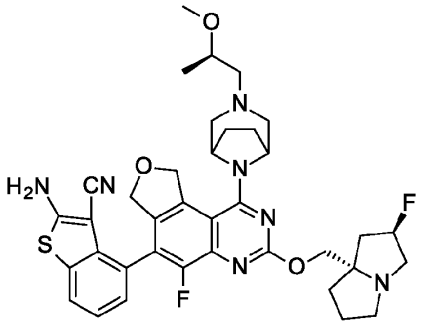
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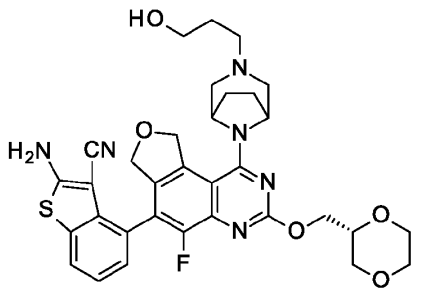
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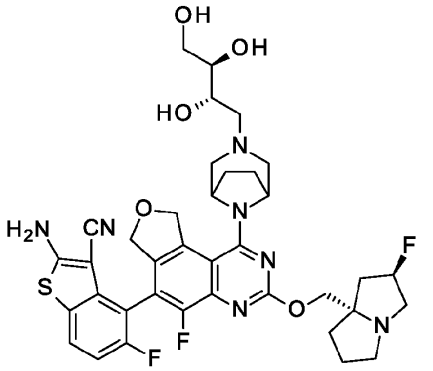
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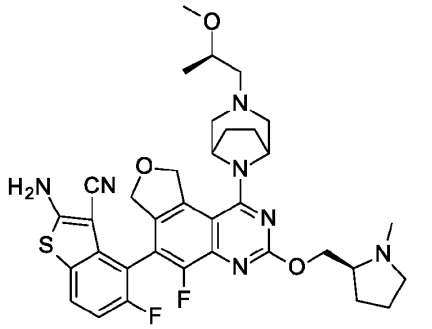
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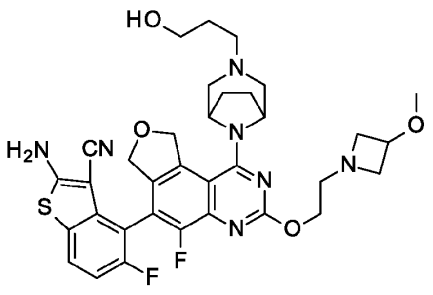
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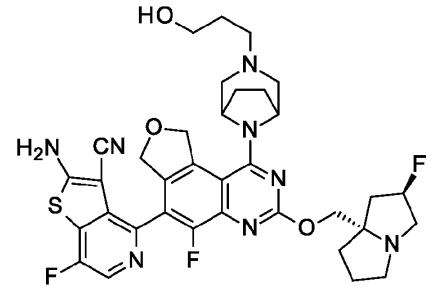
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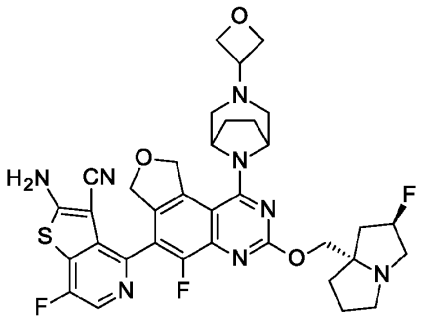
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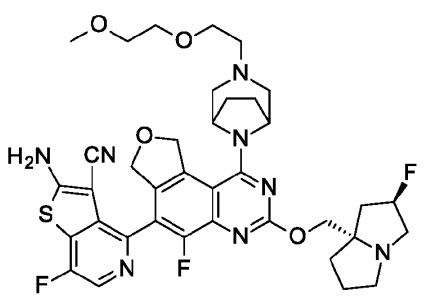
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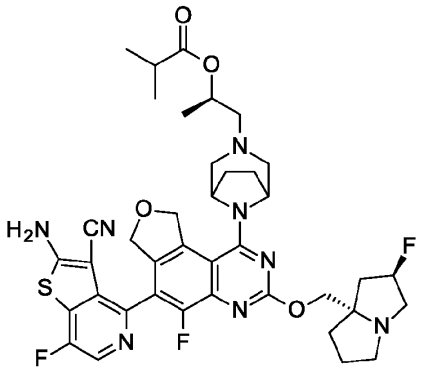
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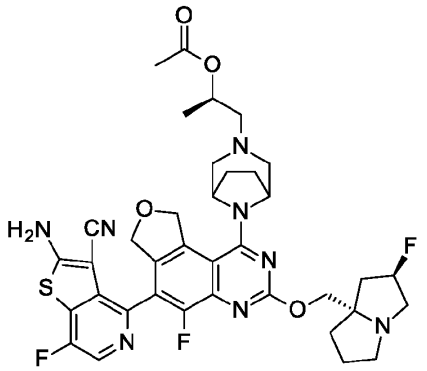
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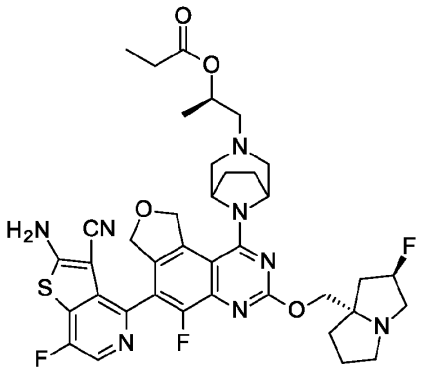
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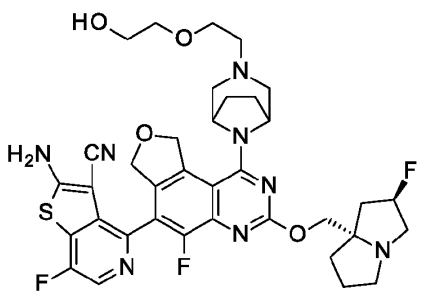
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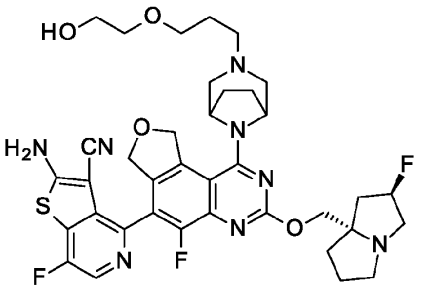
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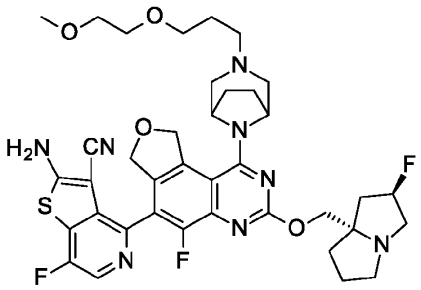
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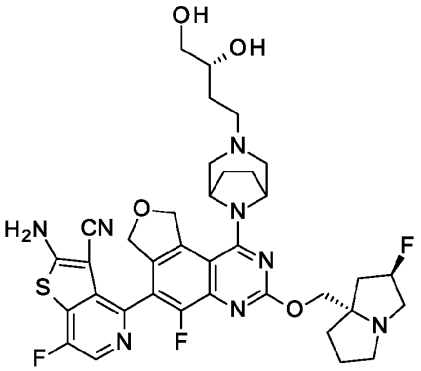
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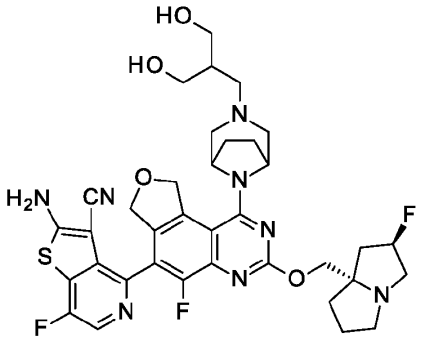
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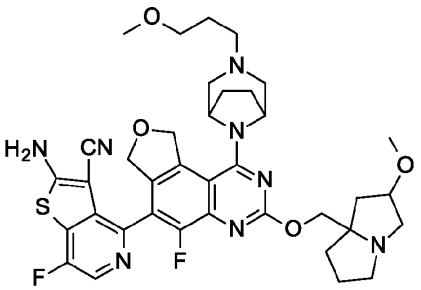
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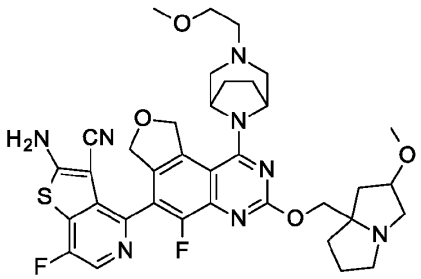
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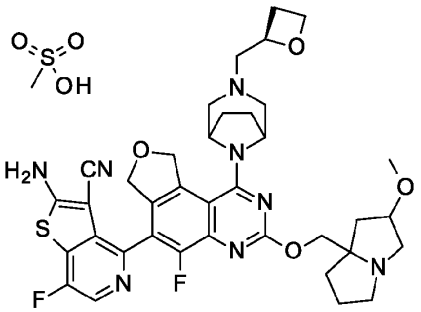
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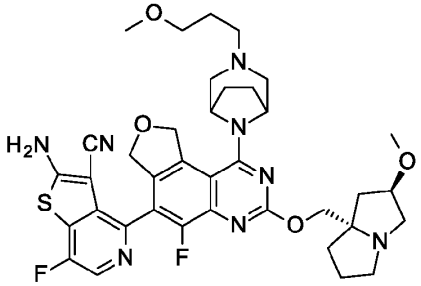
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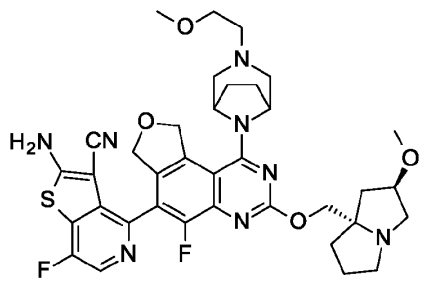
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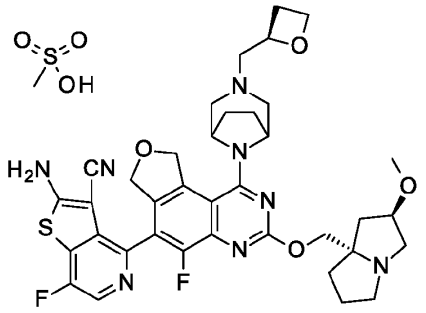
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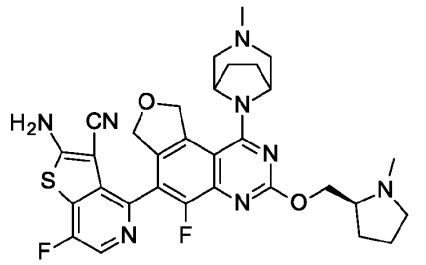
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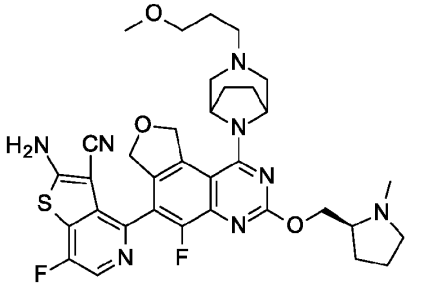
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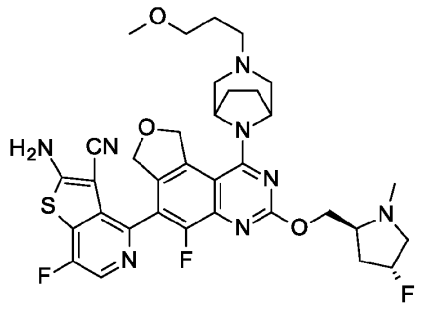
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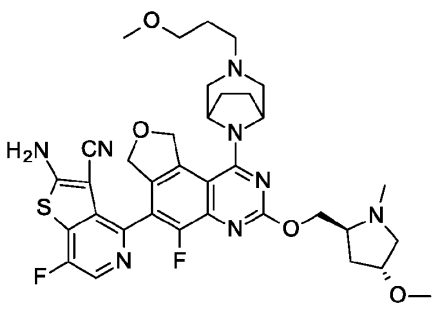
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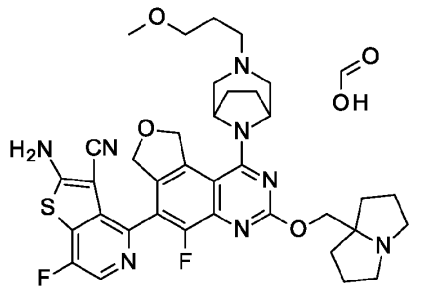
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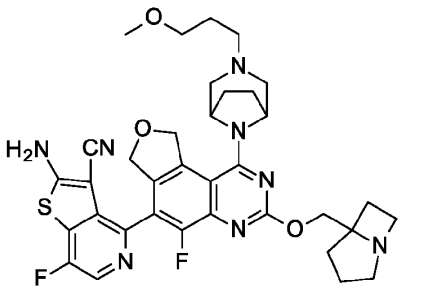
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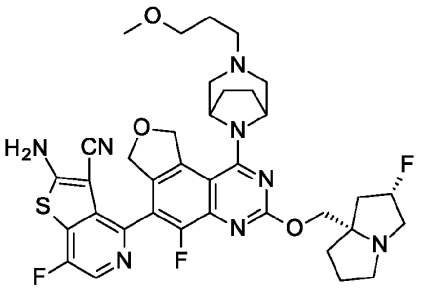
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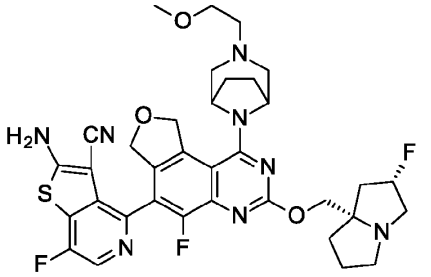
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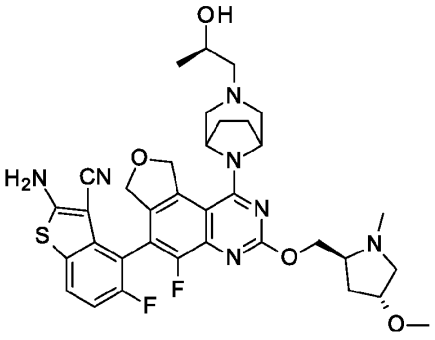
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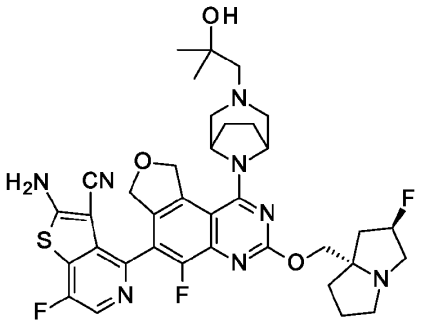
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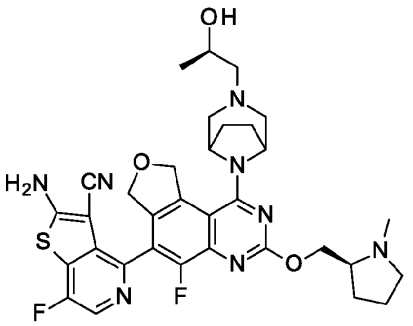
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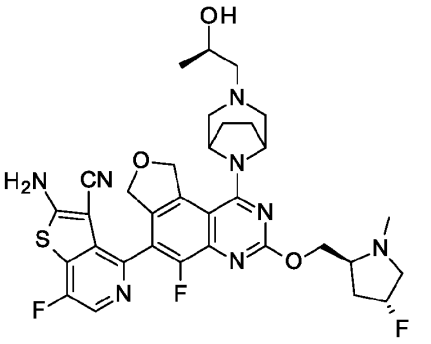
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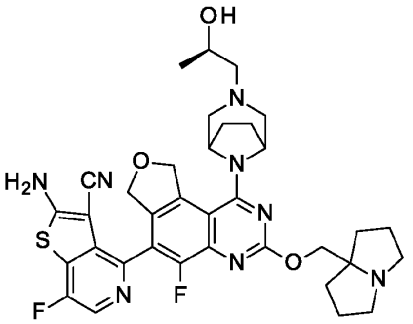
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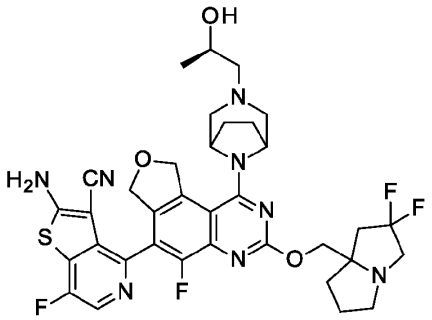
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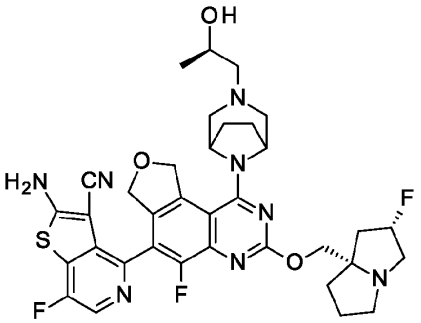
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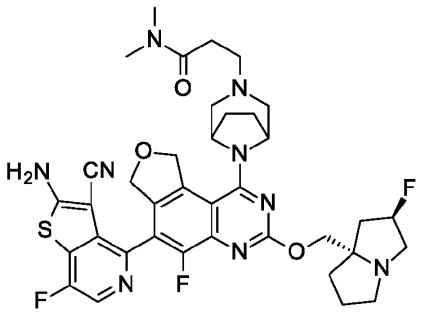
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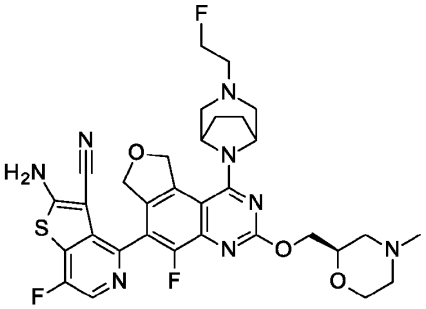
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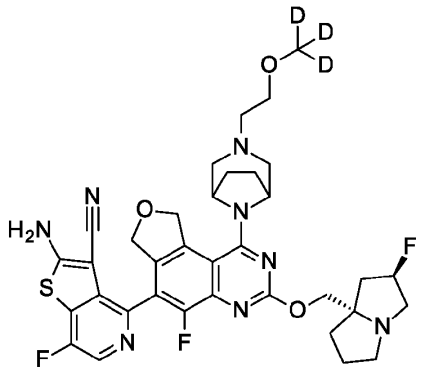
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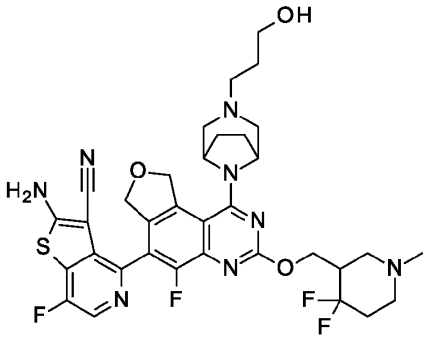
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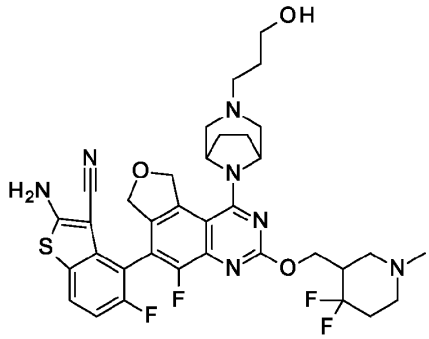
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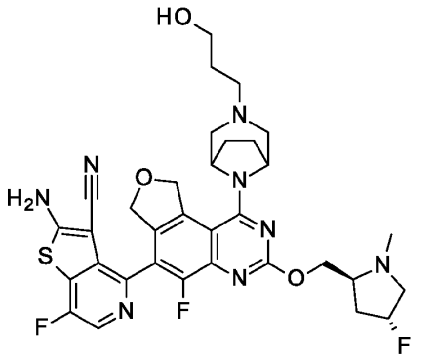
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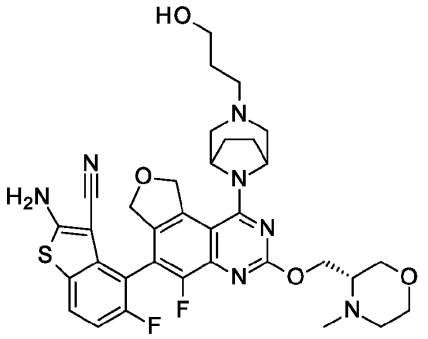
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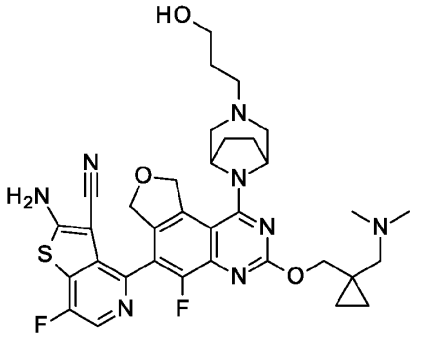
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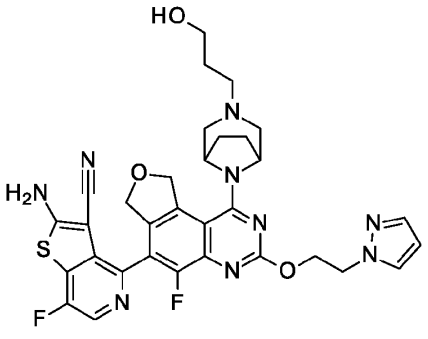
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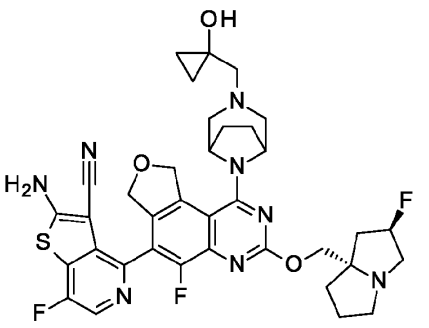
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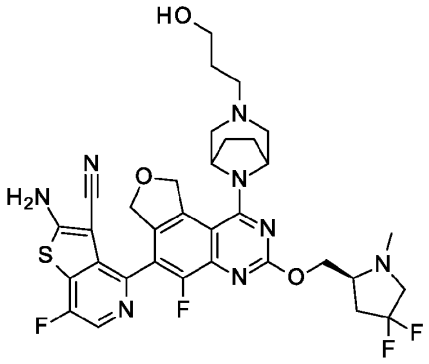
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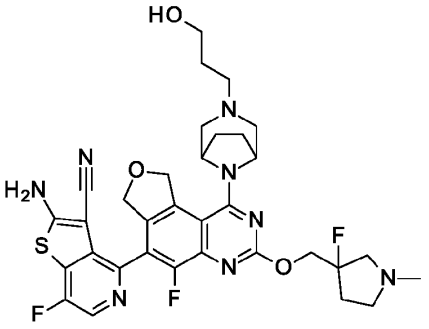
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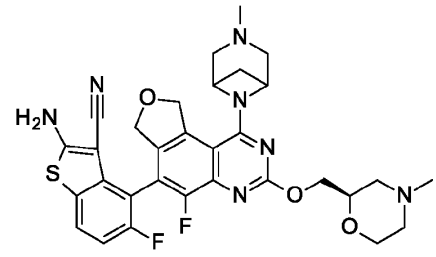
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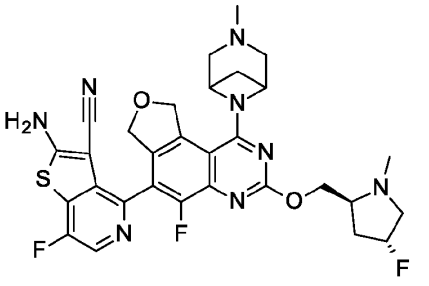
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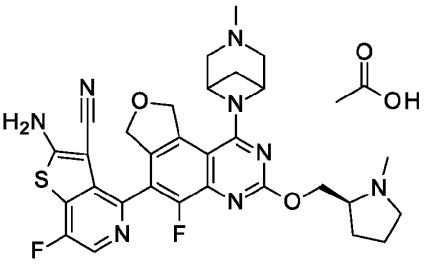
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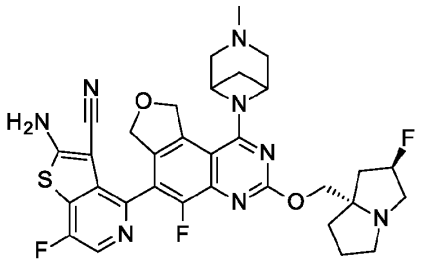
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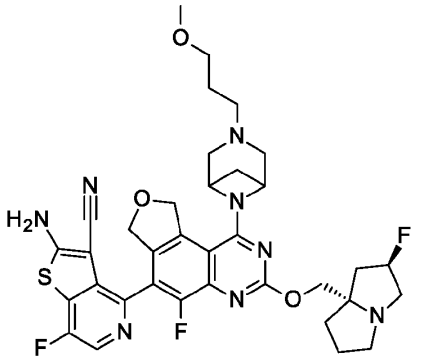
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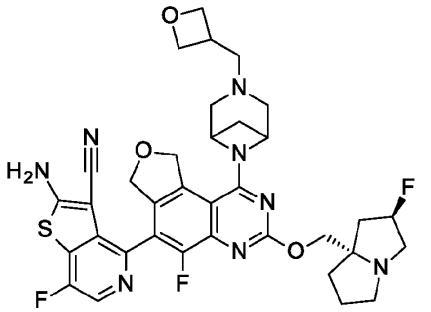
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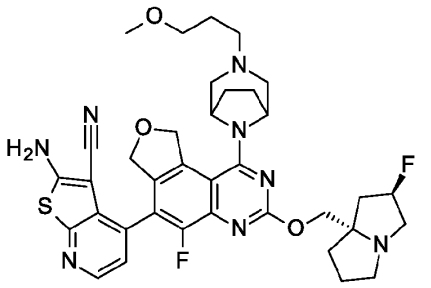
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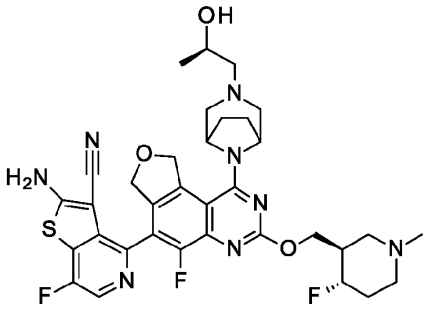
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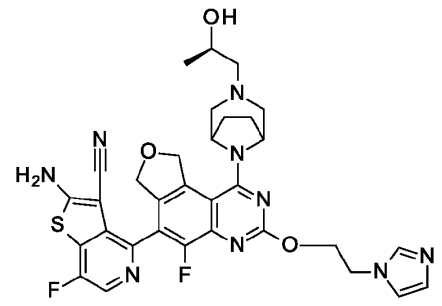
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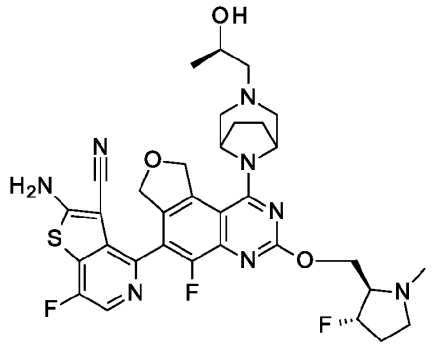
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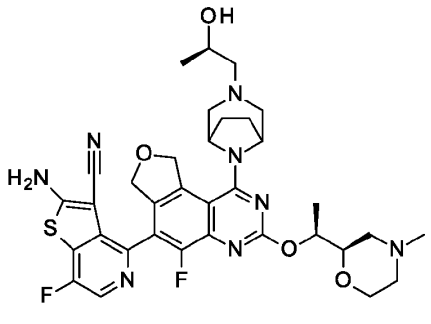
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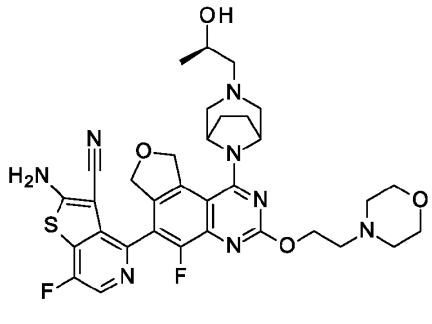
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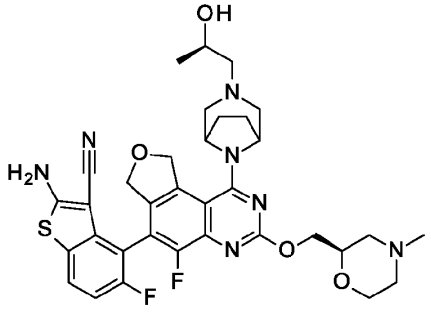
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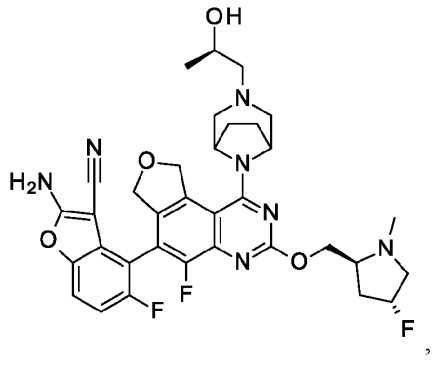
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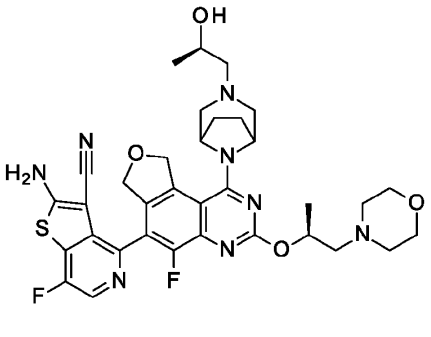
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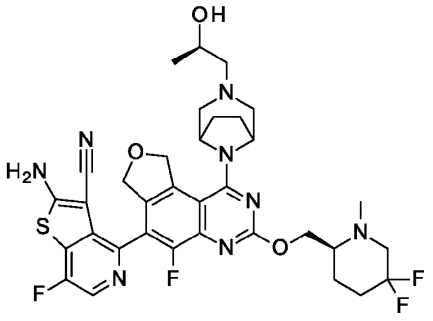
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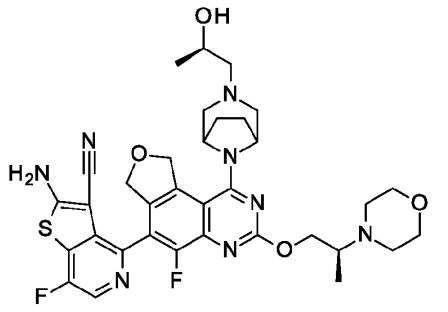
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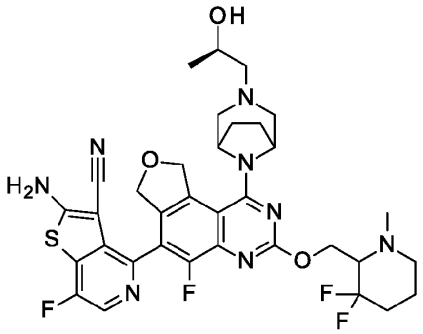
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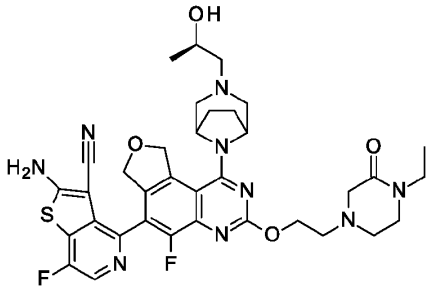
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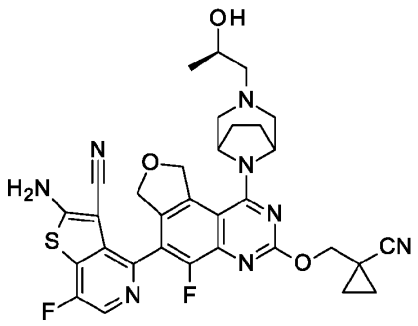
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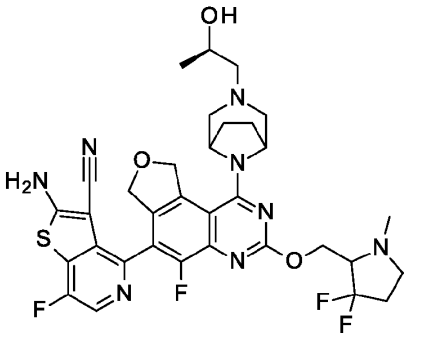
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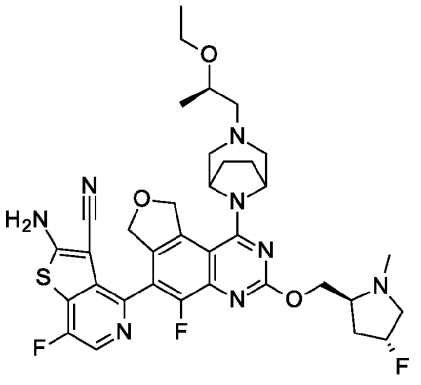
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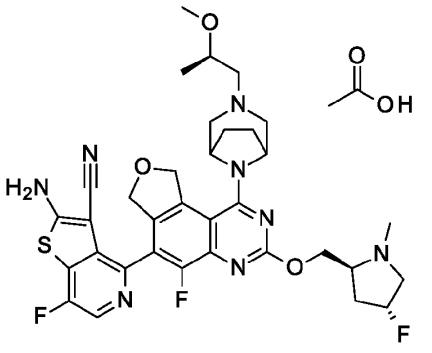
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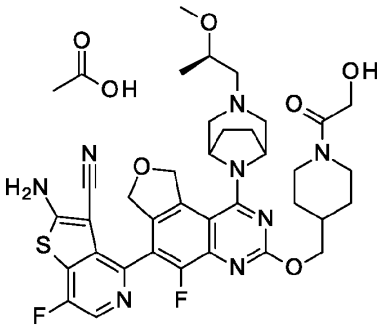
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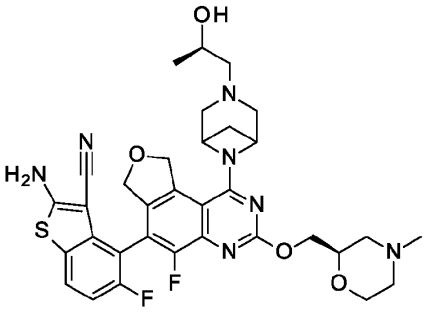
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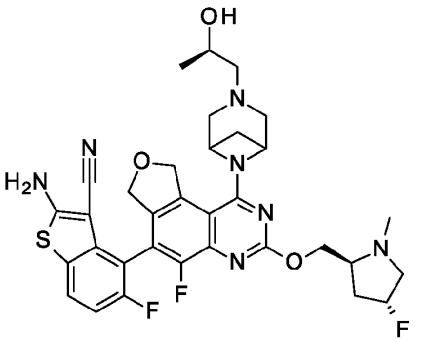
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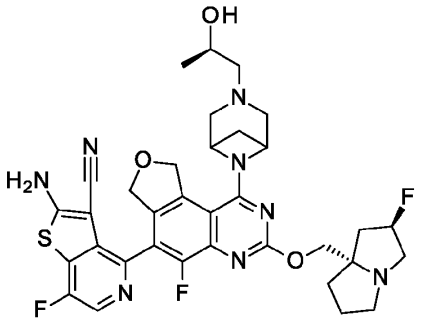
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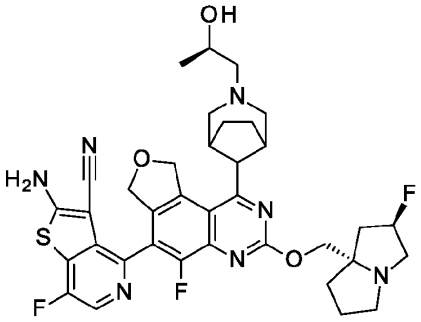
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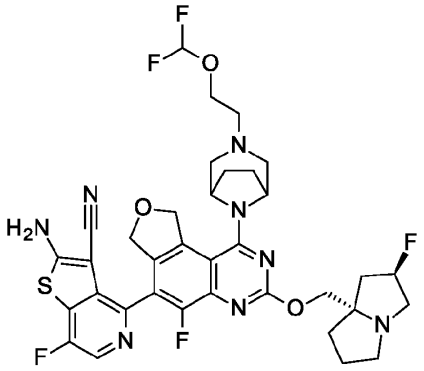
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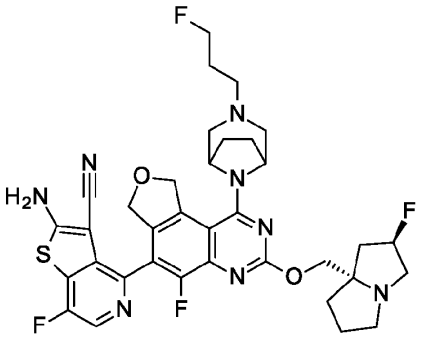
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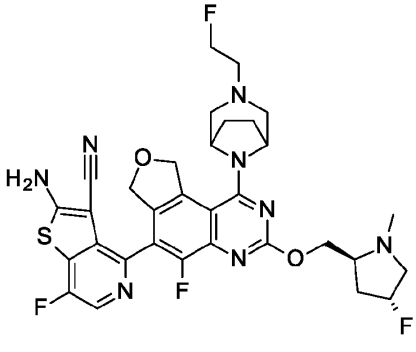
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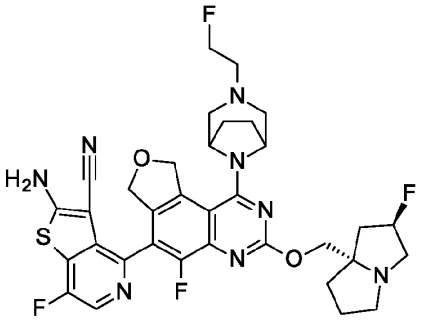
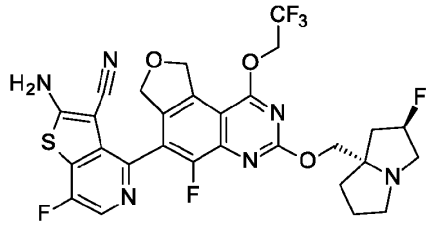

, or a pharmaceutically acceptable salt thereof.

A further compound of Formulae I, Ia, II, IIa, III, IIIa, IV, or IVa or a pharmaceutically acceptable salt thereof, the compound is selected from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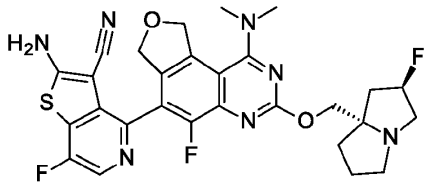
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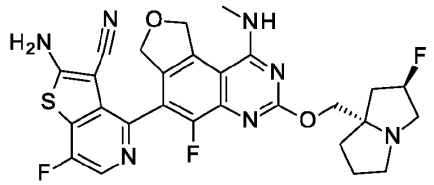
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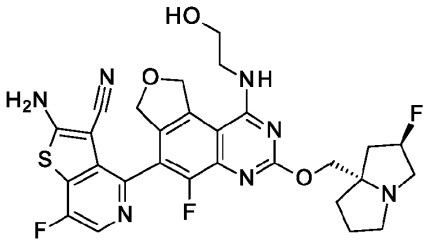
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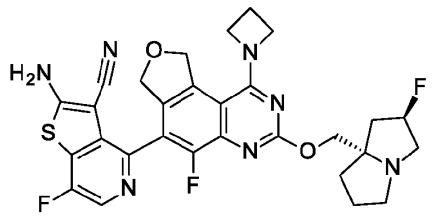
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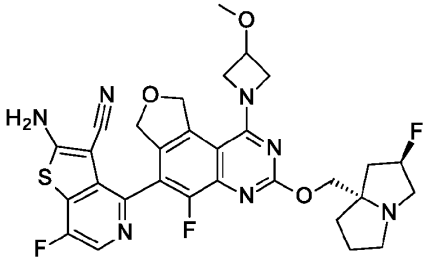
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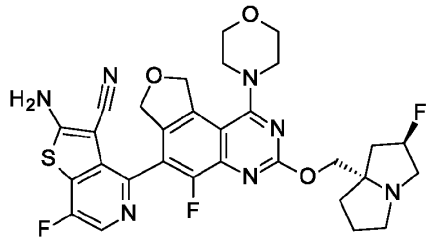
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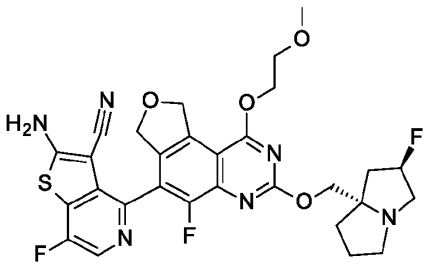
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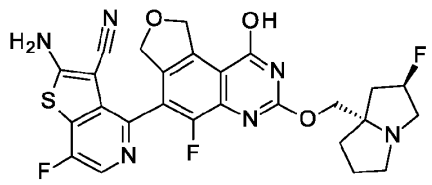

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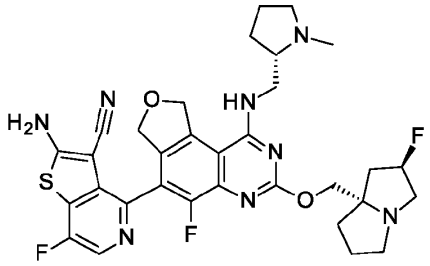


, or a pharmaceutically acceptable salt thereof.

Also provided herein are pharmaceutical compositions comprising a compound according to any one of Formulae I-VIII (including Ia-VIIa), or a pharmaceutically acceptable salt thereof, examples of which include, but are not limited to, the compounds in Table A, and a pharmaceutically acceptable carrier, diluent, or excipient.

Further provided herein are methods of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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.

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 any one of Formulae I-VIII (including Ia-VIIa), 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.

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 any one of Formulae I-VII 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.

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 any one of I-VIII (including Ia-VIIa), or a pharmaceutically acceptable salt thereof. In one embodiment this method comprises inhibiting a human mutant KRas G12D enzyme.

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 any one of I-VIII (including Ia-VIIa), or a pharmaceutically acceptable salt thereof. The G12D 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., G12D 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.

Further provided herein is a compound or a pharmaceutically acceptable salt thereof according to any one of Formulae I-VII 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 patient may have been treated with a different course of treatment prior to being treated as described herein.

The compounds provided herein according to any one of I-VIII (including Ia-VIIa), 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.

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 any one of I-VIII (including Ia-VIIa), 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. Further provided herein is a compound according to any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of I-VIII (including Ia-VIIa), 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. Further

provided is a compound according to any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of I-VIII (including

Ia-VIIa), 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. Further provided is a compound according to any one of I-VIII (including Ia-VIIa), 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. Additionally provided is a combination comprising a compound according to any one of I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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. Additionally provided is a combination comprising a compound according to any one of I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of I-VIII (including Ia-VIIa), 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. Further provided is a compound according to any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of I-VIII (including Ia-VIIa), 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 any one of I-VIII (including Ia-VIIa), 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. Additioinally provided is a combination comprising a compound according to any one of I-VIII (including Ia-VIIa), 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 herein is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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.

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 any one of Formulae I-VII 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.

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 any one of Formulae I-VIII (including Ia-VIIa), or a pharmaceutically acceptable salt thereof. In one embodiment this method comprises inhibiting a human mutant KRas G12C, G12D, and/or G12V enzyme.

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 any one of Formulae I-VIII (including Ia-VIIa), or a pharmaceutically acceptable salt thereof. The G12D 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., G12D 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.

Further provided herein is a compound or a pharmaceutically acceptable salt thereof according to any one of Formulae I-VII 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 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.

The compounds provided herein according to any one of Formulae I-VIII (including Ia-VIIa), 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 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.

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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of

Formulae I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII

(including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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. Further provided is a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 G12C, G12D, and/or G12V protein. Additionally provided is a combination comprising a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 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.

Also provided is a method of treating cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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 any one of Formulae I-VIII (including Ia-VIIa), 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.

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.

Pharmaceutical compositions containing the compounds of Formulae I-VII 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.

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.

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.

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.

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 G12D mutant bearing cancers.

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(β-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_2O" 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.

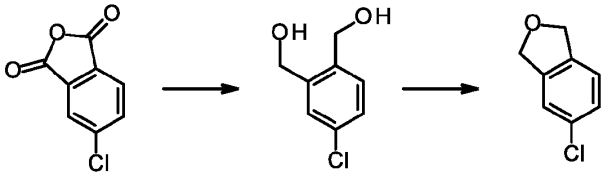
Individual isomers, enantiomers, diastereomers, and atropisomers may be separated or resolved at any convenient point in the synthesis of compounds listed below, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., "*Enantiomers, Racemates, 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.

Compounds of any one of Formulae I-VII 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*

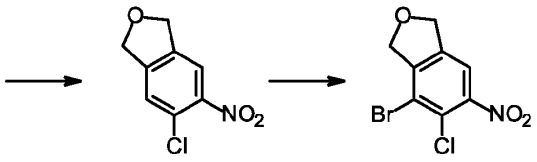
Development, 4: 427-435 (2000); and Berge, S.M., *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, 66: 1-19, (1977).

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.

Scheme 1a



(1) (2) (3)

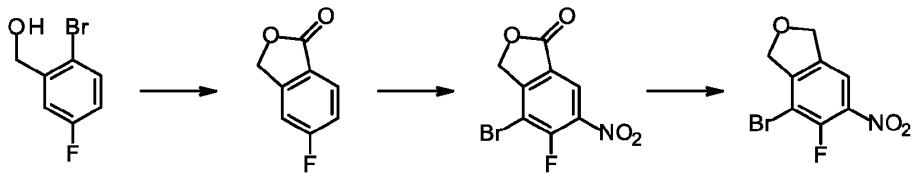


(4) (5)

Scheme 1a depicts the preparation of dihydroisobenzofuran (5). Commercially available 4-chlorophthalic anhydride (1) may undergo reductive ring opening with $LiAlH_4$ in THF to give diol (2). Subsequent ring closure using a dialkyl carbonate such as dimethyl carbonate and a strong base such as NaOMe may be used to furnish heterocycle (3). Subsequent electrophilic aromatic substitution may yield nitroaryl compound (4) using KNO_3 or HNO_3 in conjunction with a strong acid like H_2SO_4. Heterocycle (4) may be brominated with a variety of suitable reagents such as, but not limited to, NBS, $POBr_3$, Br_2, and 1,3-

dibromo-5,5-dimethylimidazolidine-2,4-dione, to furnish 4-bromo-5-chloro-6-nitro-1,3-dihydroisobenzofuran (5).

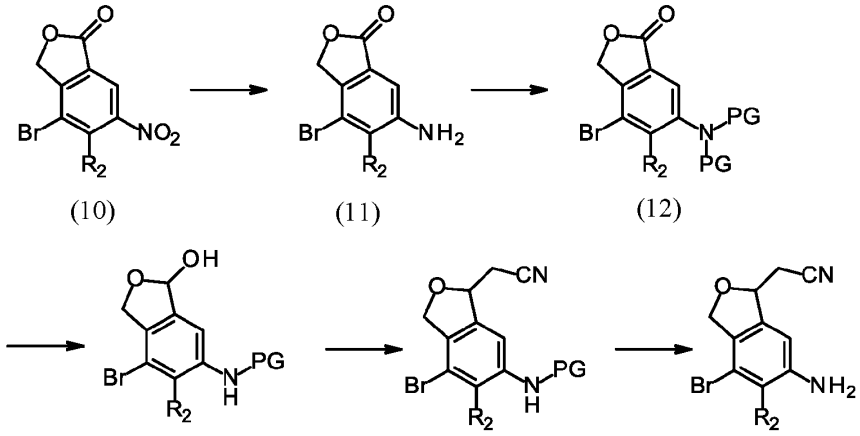
Scheme 1b



(6) (7) (8) (9)

Scheme 1b illustrates the preparation of dihydroisobenzofuran (9). Using commercially available (2-bromo-5-fluorophenyl)methanol (6), a palladium-catalyzed carbonylation may be accomplished using a ligand such as XantPhos and a palladium source such as $Pd(OAc)_2$ with a suitable base, for example, triethylamine and a polar aprotic solvent such as acetonitrile to give lactone (7). A person skilled in the art will appreciate that a variety of bidentate phosphine ligands may be used. Subsequent nitration and bromination using conditions mentioned previously may afford functionalized isobenzofuranone (8). Reduction of compound (8) may be accomplished by using a hydride reagent such as DIBAL-H to give an intermediate lactol compound which is then further reduced by triethylsilane and TFA to afford 4-bromo-5-fluoro-6-nitro-1,3-dihydroisobenzofuran (9).

Scheme 2

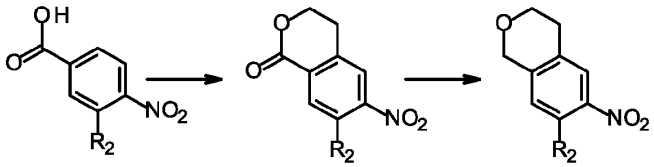


(10) (11) (12)

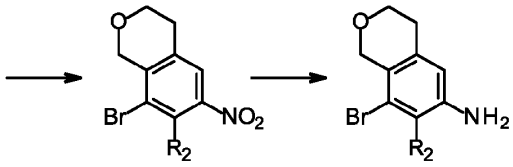
(13) (14) (15)

Scheme 2 depicts the preparation of cyanomethyl-substituted heterocyclic compounds of (15). Nitroaryl compounds of (10) may be reduced to the corresponding aniline compounds of (11) under hydrogenation conditions utilizing a Pt/C catalyst doped with sulfur. Alternatively, a person skilled in the art will also appreciate that the reduction may also be achieved with iron or zinc powder and NH_4Cl in a polar solvent such as THF, EtOH or MeOH. Protection of the amino moiety may be accomplished with di-*tert*-butyl dicarbonate, or Boc group, using a catalytic amount of DMAP under refluxing conditions in acetonitrile. A person skilled in the art will also be aware that other suitable carbamate protecting groups such as Alloc, Fmoc and Cbz may also be used in place of the Boc protecting group. Reduction of the lactone moiety of compounds (12) at low temperatures, obtained using a dry ice / acetone bath for instance, with an appropriate hydride agent, for example, DIBAL-H, may furnish the hydroxy compounds of (13). Cyanomethyl compounds of (14) may be obtained by using diethyl cyanomethyl phosphonate in a miscible solvent such as THF under Horner-Emmons reaction conditions. Deprotection of the amino group on cyanomethyl-substituted heterocycle (14) may be achieved by using HCl dissolved in 1,4-dioxane which upon basic work-up gives the aniline compounds of (15).

Scheme 3



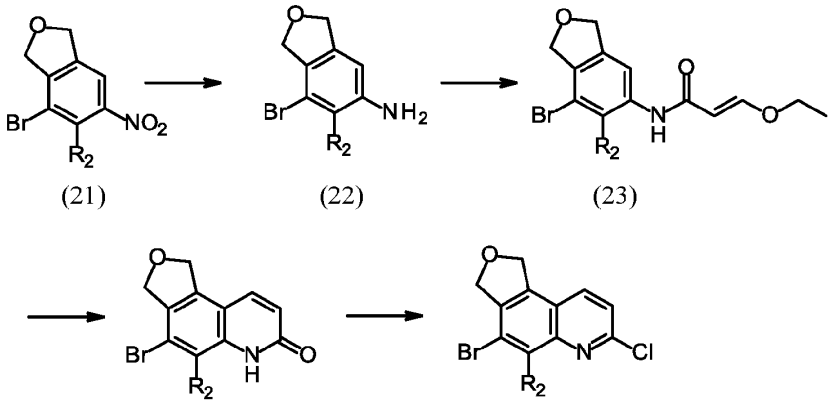
(16) (17) (18)



(19) (20)

Scheme 3 depicts the preparation of isochromane compounds of (20). Starting from the benzoic acid compounds of (16), ring closure is achieved by a palladium-catalyzed C-H insertion reaction followed by oxidative addition to ethylene oxide, dissolved in THF, to afford isochromanone compounds of (17). A person skilled in the art would understand that a variety of N-acyl amino acids may be used as a ligand for the palladium. For example, N-acetyl valine may be used. A polar acidic solvent such as trifluoroethanol, TFA or hexafluoroisopropanol may be used as the solvent. Preferred is trifluoroethanol and hexafluoroisopropanol. Reduction of the carbonyl moiety may be achieved by utilizing a two-step procedure. In the first step, $LiBH_4$ in THF may be used to furnish an isochromanol intermediate which in the second step is then reacted with *p*-toluenesulfonic acid under refluxing conditions in toluene to give the isochromane compounds of (18). Subsequent bromination using conditions as mentioned previously, for example, NBS, may afford aryl bromide compounds of (19). Iron powder and NH_4Cl in a mixed solvent system such as THF and water may be used to reduce the nitro moiety to give the aniline compounds of (20).

Scheme 4a

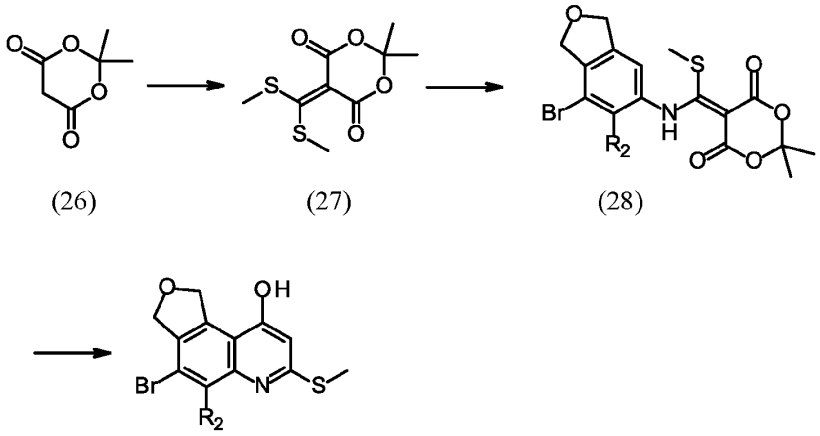


(21) (22) (23)

(24) (25)

Scheme 4a illustrates the preparation of quinoline compounds of (25). Nitroaryl compounds of (21) may be reduced to the corresponding aniline compounds of (22) by aforementioned reaction conditions using iron or zinc powder. Acylation of amine compounds of (22) using 3-ethoxyprop-2-enoyl chloride in THF and a suitable base such as pyridine may yield the enamide compounds of (23). Cyclization using H_2SO_4 as the solvent followed by trituration in ice water affords quinolinone compounds of (24). Subsequent chlorination may be achieved with a suitable reagent such as (chloromethylene)dimethyliminium chloride or $POCl_3$ to furnish the chloroquinoline compounds of (25).

Scheme 4b

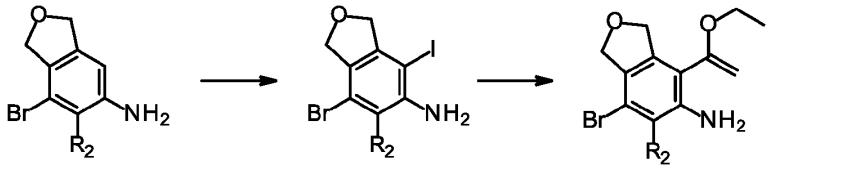


(26) (27) (28)

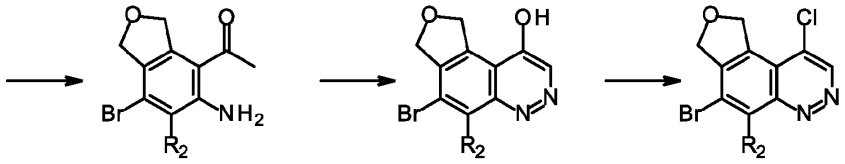
(29)

Scheme 4b depicts the preparation of methylsulfanyl quinoline compounds of (29). Commercially available Meldrum's acid may be converted to the sulfanyl compound (27) using CS_2 and a polar aprotic solvent such as DMSO followed by alkylation with methyl iodide. N-alkylation of the aniline compounds of (22) with methyl sulfanyl compound (27) by heating in a nonpolar solvent such as toluene followed by trituration in a suitable solvent system, for example, Et_2O/EtOAc, affords the functionalized compounds of (28). Refluxing at about 180 °C in a suitable high-boiling solvent, for instance, diphenyl ether may allow cyclization to occur to furnish quinolinol compounds of (29).

Scheme 5



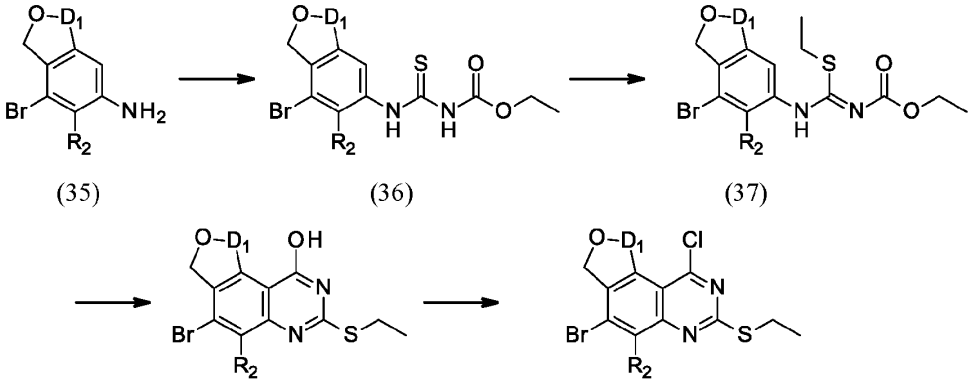
(22) (30) (31)



(32) (33) (34)

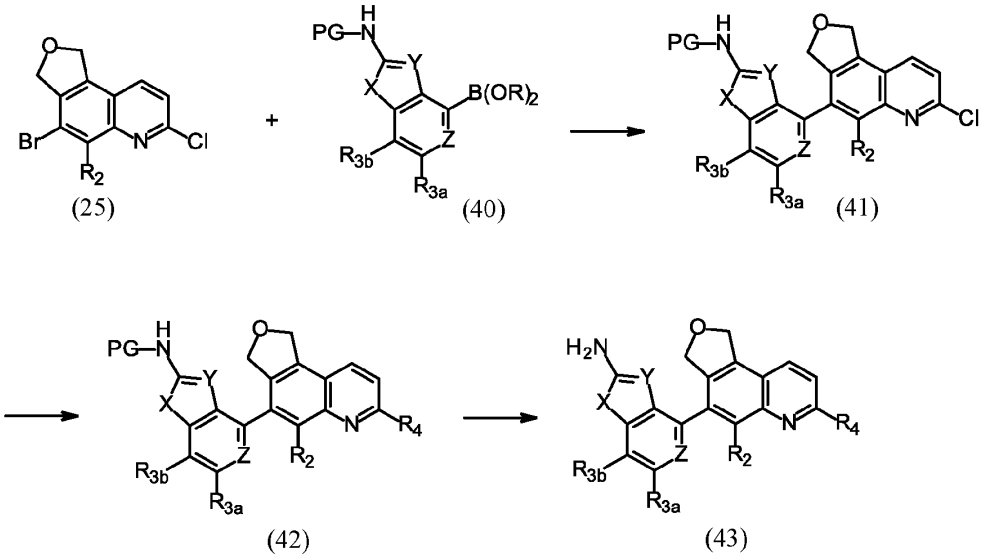
Scheme 5 shows the preparation of the cinnoline compounds of (34). Dihydroisobenzofuran compounds of (22) may be iodinated by several reagents known by those skilled in the art, such as NIS, I_2 and pyridinium iodo-chloride, to afford iodo-aniline compounds of (30). Stille coupling of iodide (30) using a Pd^0 source such as $Pd(PPh_3)_4$ and an appropriate tributylstannane, such as tributyl(1-ethoxyvinyl)stannane, may afford the vinyl compounds of (31). Acid hydrolysis using aqueous HCl may furnish acetophenone compounds of (32). A person of skill in the art will be familiar with conditions for diazotization of the amine moiety by use of sodium nitrite and TFA, followed by ring closure to obtain the hydroxycinnoline compounds of (33). Standard chlorination conditions, such as oxalyl chloride and DMF in DCM may be used to furnish the chlorocinnoline compounds of (34).

Scheme 6



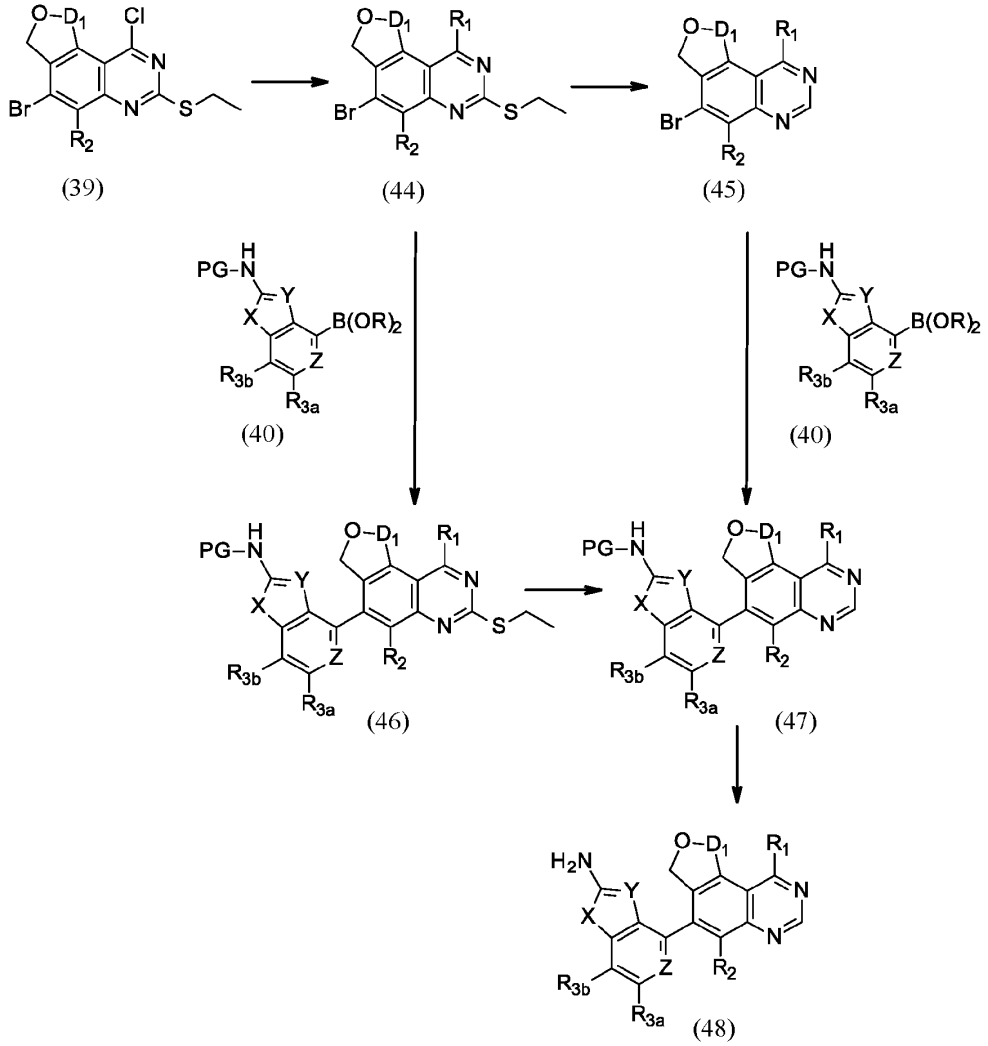
Scheme 6 depicts the preparation of the quinazolinyl compounds of (39). Thioacylation of the aniline compounds of (35) may be achieved with an appropriate isothiocyanate, for example ethoxycarbonyl isothiocyanate, to afford the carbamothioyl compounds of (36). S-Alkylation may be achieved by using a mild base, such as K_2CO_3, in a polar solvent such as acetone followed by the slow addition of ethyl iodide to give the sulfanyl compounds of (37). Ring closure in a solvent such as anhydrous NMP or diphenyl ether at 175 °C may furnish the hydroxyquinazoline compounds of (38) followed by chlorination using, for instance, oxalyl chloride, thionyl chloride, (chloromethylene)dimethyliminium chloride or $POCl_3$ plus adjusting the solvent as necessary may afford the chloroquinazolinyl compounds of (39).

Scheme 7



Scheme 7 illustrates the preparation of the bicyclic-substituted quinolinyl compounds of (43). Suzuki coupling of boronic ester compounds of (40) with bromoquinoline compounds of (25) using a base such as Cs_2CO_3 in THF with a suitable palladium complex well known by one skilled in the art, for example, dichloro[bis(2-(diphenylphosphino)phenyl)ether]palladium(II), may furnish the biaryl compounds of (41). A nucleophilic aromatic substitution reaction, commonly known as a S_NAR, of the chloro-moiety ortho to the quinoline nitrogen, using a strong base such as LiHMDS in THF and appropriate nucleophile, such as a primary or secondary alcohol, may yield the substituted-quinolinyl compounds of (42). Removal of the protecting group on the amine-moiety by using an appropriate acid, such as TFA in DCM, may furnish the functionalized quinolinyl compounds of (43).

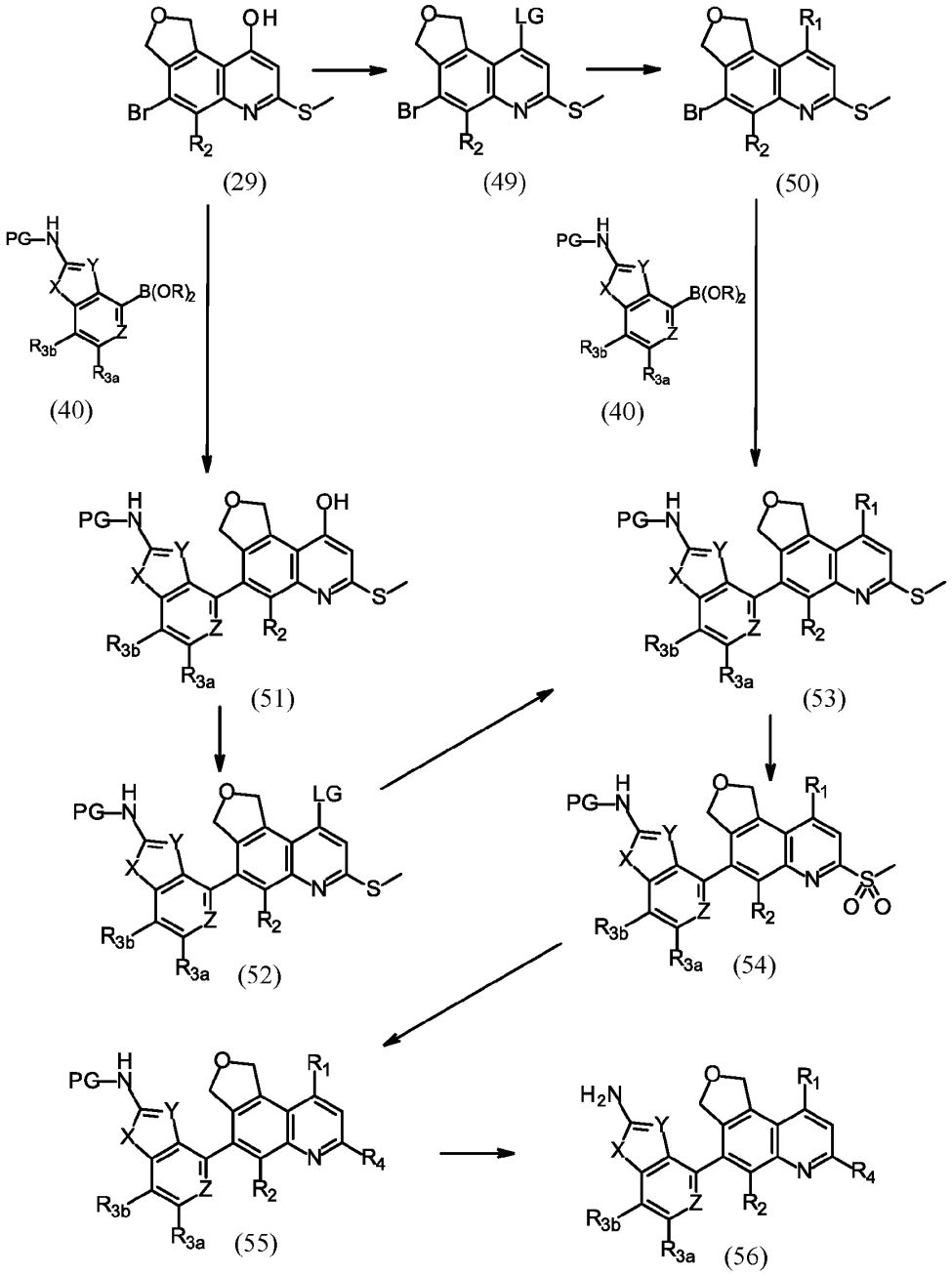
Scheme 8



Scheme 8 depicts two routes for the preparation of bicyclic-substituted quinazoline compounds of (48). Chloroquinazolinyl compounds of (39) may undergo a SNAR with an appropriate nucleophile, such as a substituted piperazine. A person of skill in the art will be aware that a variety of non-nucleophilic bases may be employed, such as, but not limited to, DIPEA, TEA, or NMM in the reaction along with a polar, aprotic solvent such as acetonitrile or DMF to furnish the substituted quinazolinyl compounds of (44). In one route, the

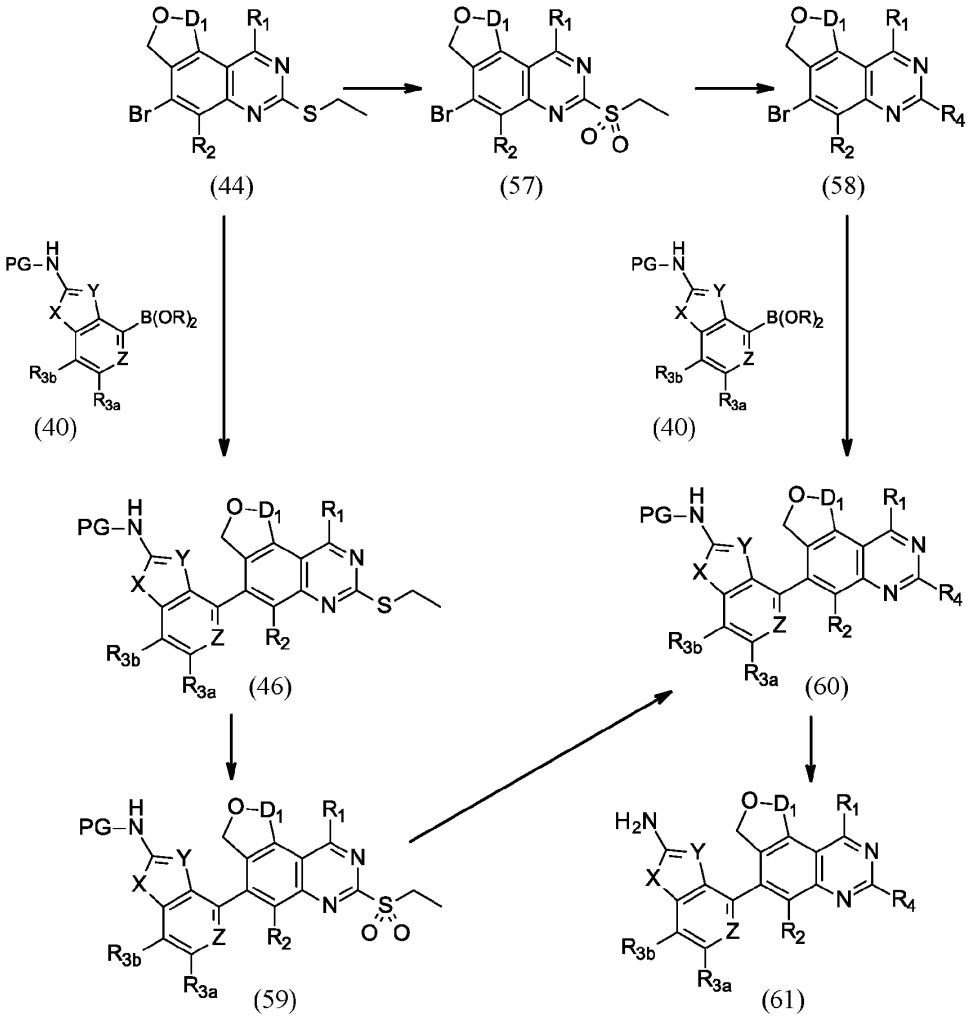
compounds of (44) may first undergo desulfurization with triethylsilane and $PdCl_2$ to afford quinazolinyl compounds of (45). An alternative method for desulfurization involves oxidation of the thioether compounds of (44) with *m*CPBA to afford an intermediate sulfone moiety which may then be removed using the well-known conditions to one with skill in the art, for instance, $NaBH_4$ in DCM/MeOH to furnish the quinazolinyl compounds of (45). This is then followed by a reaction with the bicyclic boronates of (40) using previously mentioned Suzuki coupling conditions to furnish bicyclic-substituted quinazolinyl compounds of (47). Another route utilizes the Suzuki coupling first to afford bicyclic-substituted quinazolinyl compounds of (46) before undergoing a desulfurization reaction to obtain the quinazolinyl compounds of (47). The amine moiety on the compounds of (47) may then be suitably deprotected using well known methods to one of skill in the art, for instance using TFA to remove a Boc-protecting group, to furnish the substituted quinazolinyl compounds of (48).

Scheme 9



Scheme 9 illustrates the preparation of the dihydrofuroquinoline compounds of (56), also via two routes. Persons with skill in the art may choose the route based upon the order in which they desired to functionalize the dihydrofuroquinolinyl core. In one route, the hydroxy moiety of the quinolinyl compounds of (29) may be converted to a leaving group (LG) moiety, such as a chloride. Chlorination may be accomplished with oxalyl chloride and DMF in DCM to furnish the quinolinyl compounds of (49). Subsequent nucleophilic displacement at elevated temperatures, ~ 130 °C, by a substituted piperazine using an appropriate hindered base such as DIPEA in an aprotic solvent such as DMSO may afford the substituted quinolinyl compounds of (50). Aryl coupling of the bromo-quinolinyl compounds of (50) with the bicyclic boronates of (40) under Suzuki conditions may furnish biaryl compounds of (53). Alternatively, to install the bicyclic aryl group first, the Suzuki coupling of bromide (29) with boronate (40) may be done using conditions well known by one with skill in the art, such as using K_3PO_4 as the base and the palladium complex 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride as well as refluxing in dioxane/water, to obtain the biaryl compounds of (51). Then the hydroxy moiety of the quinolinyl compounds of (51) may be converted to a leaving group (LG) moiety, for example, a chloride, a bromide or a triflate by standard methods that one with skill in the art would appreciate. For example, the triflate may be obtained from the hydroxy-quinoline compounds of (51) by using trifluoromethanesulfonic anhydride and DMAP in DCM at 0 °C which may then be used in a S_NAR, as previously described, using a substituted piperazine to give the dihydrofuroquinolinyl compounds of (53). The compounds of (53) may then be oxidized with *m*CPBA, or other suitable oxidizing agents known to those with skill in the art, along with an appropriate solvent, if needed, to furnish the sulfone compounds of (54). The sulfone moiety may then undergo nucleophilic displacement with a suitable nucleophile, such as a primary or secondary alcohol, using a strong base such as LiHMDS in THF to afford the substituted quinolinyl compounds of (55). Subsequent removal of the protecting group(s) may be achieved by methods appropriate to the protecting group used, such as Boc removal by TFA in DCM, to give the dihydrofuroquinoline compounds of (56).

Scheme 10

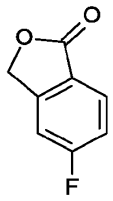


Scheme 10 depicts the preparation of dihydrofuroquinazoline compounds of (61) with route options to functionalize the quinazolinyl core in two different ways. One route to the intermediate compounds of (60) starts from the oxidation of the thioether compounds of (44), as previously mentioned with *m*CPBA, to furnish the sulfone compounds of (57). Nucleophilic displacement of the sulfone moiety may then provide the bifunctionalized quinazolinyl compounds of (58). Suzuki coupling of the bromide compounds of (58) with

boronate compounds of (40), such as substituted benzothiophenes, benzothiazoles and benzofurans, may then yield the biaryl compounds of (60). The Suzuki coupling may also be achieved in the reverse, by reacting the bromide compounds of (58) with bis(neopentyl glycolato)diboron in the presence of a mild base such as KOAc and a palladium complex, such as dichloro[bis(2-(diphenylphosphino)phenyl)ether]palladium(II), to form the boronate ester on the quinazolinyl core followed by the coupling to a Boc-protected chlorothienopyridine, such as *tert*-butyl N-(4-chlorothieno[3,2-c]pyridin-2-yl)carbamate, to furnish the biaryl compounds of (60). Another route to the intermediate compounds of (60) involves incorporating the Suzuki coupling up front so the bromide compounds of (44) may undergo arylation with the boronate compounds of (40) to provide the biaryl compounds of (46). Oxidation of the sulfide moiety on the compounds of (46) with previously mentioned standard conditions may then afford the sulfone compounds of (59) which through a S_NAR with a nucleophile such as a primary or secondary alcohol may furnish the functionalized compounds of (60). Subsequent removal of the protecting group(s) may be achieved by methods appropriate to the protecting group used, such as Boc removal by TFA in DCM, to give the dihydrofuroquinazoline compounds of (61).

Preparation 1

5-Fluoro-3H-isobenzofuran-1-one

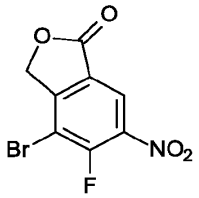


To a stirred mixture of (2-bromo-5-fluorophenyl)methanol (500 g, 2.44 mol) and TEA (474.6 mL, 3.41 mol, 1.4 eq.) in ACN (2500 mL) was added $Pd(OAc)_2$ (10.95 g, 48.77 mmol, 0.02 eq.) and XantPhos (42.33 g, 73.16 mmol, 0.03 equiv.) at RT, then stirred for 3 days at 120 °C under 10 atm of carbon monoxide.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

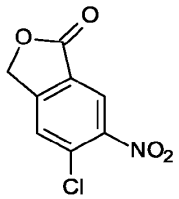
4-Bromo-5-fluoro-6-nitro-3H-isobenzofuran-1-one



To a stirred mixture of 5-fluoro-3H-isobenzofuran-1-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-*d6*) δ 8.58 (s, 1H), 5.51 (s, 2H).

Preparation 3

5-Chloro-6-nitro-3H-isobenzofuran-1-one

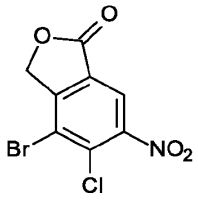


In a 1L, 3-necked round bottom flask a solution of 5-chloro-3H-isobenzofuran-1-one (60 g, 355.91 mmol) in HNO_3 (46 mL) and H_2SO_4 (277 mL) was heated at 100 °C under N_2 for 4 h. The mixture was added slowly to ice water (1 L) and stirred for 30 min. The resulting

precipitate was filtered and rinsed with H_2O (2 x 300 mL) and dried under vacuum at 45 °C to obtain the title compound (57 g, 70%) as a yellow solid. MS (ES) *m/z*=214 (M+1).

Preparation 4

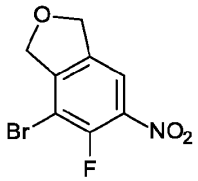
4-Bromo-5-chloro-6-nitro-3H-isobenzofuran-1-one



In a 1L, 3-necked RBF a solution of 5-chloro-6-nitro-3H-isobenzofuran-1-one (65 g, 283 mmol) was dissolved in H_2SO_4 (600 mL) and cooled to 0 °C. NBS (60 g, 337 mmol) was added under N_2 portion wise at such a rate to keep the temperature at 0 °C. The reaction was then stirred at 50 °C for ~18 h. The mixture was added slowly to ice water (1 L) and stirred for 30 min. The resulting precipitate was filtered and rinsed with H_2O (2 x 300 mL) and dried under vacuum at 45 °C to obtain the title compound (65 g, 72%) as a yellow solid. MS (ES) *m/z*=292 (M+1).

Preparation 5

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

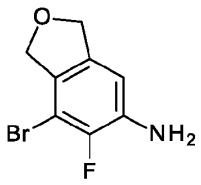


To a stirred mixture of 4-bromo-5-fluoro-6-nitro-3H-isobenzofuran-1-one (270 g, 978 mmol) in DCM (2,500 mL) was added DIBAL-H (1M in THF, 1,467 mL, 1.467 mol, 1.5 eq.) dropwise at -78 °C under N_2. The reaction was stirred for 5 h at -78 °C, then was quenched with 5N NaOH (300 mL) at -78 °C. The resulting 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. ^1H 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 6

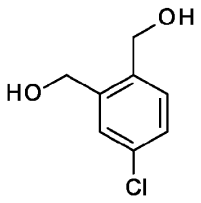
7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-amine



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 7

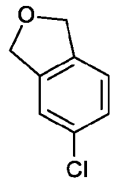
[4-Chloro-2-(hydroxymethyl)phenyl]methanol



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 8

5-Chloro-1,3-dihydroisobenzofuran

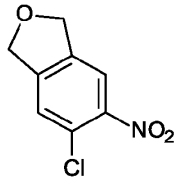


To a stirred mixture of [4-chloro-2-(hydroxymethyl)phenyl]methanol (219.5 g, 1.271 mol) and dimethyl carbonate (458.2 g, 5.082 mol, 4 eq.) in ACN (3 L) was added NaOMe (137.4 g, 2.544 mol, 2 eq.) in portions at RT. The resulting mixture was stirred for ~18 h at 80 °C under N_2. The mixture was concentrated 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. ^{1}H 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 9

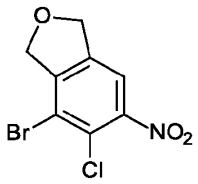
5-Chloro-6-nitro-1,3-dihydroisobenzofuran



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 10

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

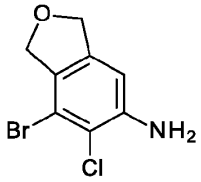


To a stirred solution of 5-chloro-6-nitro-1,3-dihydroisobenzofuran (125 g, 626 mmol) in H_2SO_4 (700 mL) was added 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (179.1 g, 626.3 mmol, 1 eq.) in portions at -10 °C. The mixture was stirred for 1 h at -10 °C then slowly was added to stirred ice-cooled 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 11

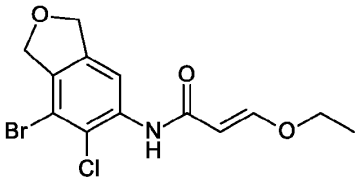
7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-amine



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 12

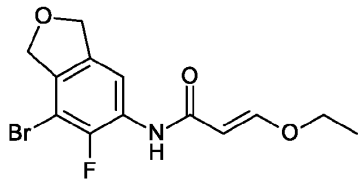
N-(7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxy-prop-2-enamide



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 13

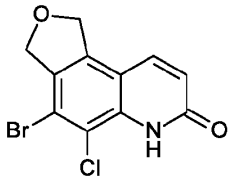
N-(7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxy-prop-2-enamide



7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-amine was used in a manner analogous to the method of Preparation 12 to afford the title compound (1.4 g, 89%) as a pale-yellow solid. MS (ES) *m/z*=332 (M+1).

Preparation 14

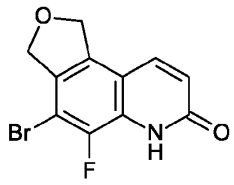
4-Bromo-5-chloro-3,6-dihydro-1H-furo[3,4-f]quinolin-7-one



To a stirred solution of H_2SO_4 (20 mL) was added N-(7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxy-prop-2-enamide (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 15

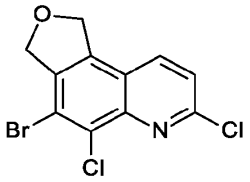
4-Bromo-5-fluoro-3,6-dihydro-1H-furo[3,4-f]quinolin-7-one



N-(7-Bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)-3-ethoxy-prop-2-enamide was used in a manner analogous to that described for Preparation 14 to obtain the title compound (1.2 g, quantitative) as a tan solid. MS (ES) *m/z*=284 (M+1).

Preparation 16

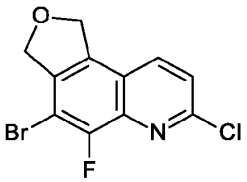
4-Bromo-5,7-dichloro-1,3-dihydrofuro[3,4-f]quinoline



To a stirred solution of 4-bromo-5-chloro-3,6-dihydro-1H-furo[3,4-f]quinolin-7-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 17

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

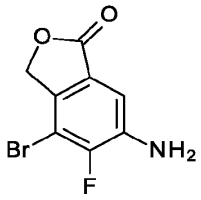


A suspension of 6-bromo-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-

1-ol (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 18

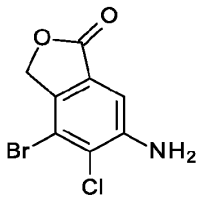
6-Amino-4-bromo-5-fluoro-3H-isobenzofuran-1-one



A suspension of 4-bromo-5-fluoro-6-nitro-3H-isobenzofuran-1-one (1.11 g, 4.02 mmol) in AcOH (4 mL), H_2O (2 mL) and EtOH (20 mL) was charged with iron (1.0 g, 18 mmol) and heated at 70 °C for 2 h. The reaction was cooled to RT, partitioned between DCM and sat. aq. $NaHCO_3$ and filtered through a pad of diatomaceous earth. The pad was rinsed with DCM, the filtrate partitioned, and the organics were dried over $MgSO_4$ and concentrated to afford the title compound (0.90 g, 91%) as a white solid. MS (ES) *m/z* = 246 (M-1).

Preparation 19

6-Amino-4-bromo-5-chloro-3H-isobenzofuran-1-one

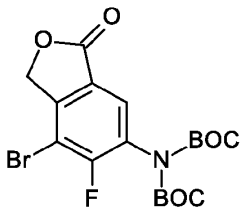


To a mixture of 4-bromo-5-chloro-6-nitro-3H-isobenzofuran-1-one (7.98 g, 27.3

mmol) in EtOH (200 mL) and H_2O (40 mL) was added NH_4Cl (5.84 g, 109 mmol), followed by iron powder (6.09 g, 109 mmol). The mixture was stirred at 80 °C in an oil bath for 20 h. The mixture was filtered through a pad of diatomaceous earth and washed with acetone. The filtrate was concentrated to ~50 mL. The resultant precipitate was collected by filtration and dried under vacuum overnight to afford a first batch of product (2.57 g) as beige solid. The diatomaceous earth mixture was stirred in acetone/MeOH (2/1) and filtered. The process was repeated twice. The combined filtrate was concentrated and dried in a vacuum oven at 60 °C overnight to afford a second batch of product (3.70 g). The batches were combined to give the title compound (6.27 g, 87.5%). MS (ES) *m/z* = 279 ($M+H_2O+1$).

Preparation 20

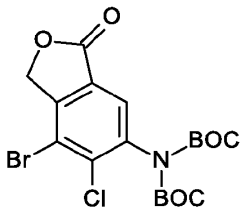
tert-Butyl N-(7-bromo-6-fluoro-3-oxo-1H-isobenzofuran-5-yl)-N-*tert*-butoxycarbonyl-carbamate



A mixture of 6-amino-4-bromo-5-fluoro-3H-isobenzofuran-1-one (36.0 g, 146 mmol), di-*tert*-butyl dicarbonate (100 g, 444 mmol) and DMAP (4.50 g, 37.0 mmol) in ACN (1,000 mL) was heated to reflux. After refluxing for 30 min, the reaction mixture was allowed to cool to RT. The solvent was removed under reduced pressure and the residue was dissolved in DCM (1,000 mL), washed with ice cold 10% citric acid, sat. aq. $NaHCO_3$, brine, and then was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by silica column chromatography (100% A to 100% B; A = 4% MTBE and 20% DCM in Hex, B = 10% MTBE and 20% DCM in Hex) to afford the title compound (36.0 g, 55%). ^1H NMR (300 MHz, DMSO-d_6) δ 8,11 (s, 1H), 5.49 (s, 2H), 1.40 (s, 18H).

Preparation 21

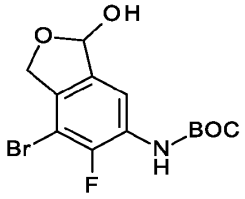
tert-Butyl N-(7-bromo-6-chloro-3-oxo-1H-isobenzofuran-5-yl)-N-*tert*-butoxycarbonyl-carbamate



6-Amino-4-bromo-5-chloro-3H-isobenzofuran-1-one was used in a manner analogous to the method of Preparation 20 to afford the title compound (34.6 g, 61%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (s, 1H), 5.48 (s, 2H), 1.40 (s, 18H).

Preparation 22

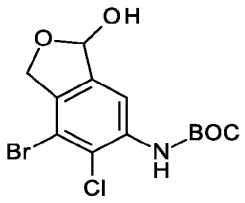
tert-Butyl N-(7-bromo-6-fluoro-3-hydroxy-1,3-dihydroisobenzofuran-5-yl)carbamate



To a solution of *tert*-butyl N-(7-bromo-6-fluoro-3-oxo-1H-isobenzofuran-5-yl)-N-*tert*-butoxycarbonyl-carbamate (36.0 g, 80.7 mmol) in DCM (1,600 mL) at -70 °C was added DIBAL-H (1M in DCM, 245 mL, 245 mmol) dropwise over 2 h. The reaction mixture was stirred for 1h at -70 °C after addition. The reaction was quenched by adding NaOH solution (1M in H_2O, 164 mL, 164 mmol) dropwise at -70 °C. The mixture was diluted with DCM (1,000 mL) and stirred up to RT. After addition of $MgSO_4$ (200 g), the mixture was stirred for 10 min and then left to stand over $MgSO_4$ overnight at RT. The mixture was filtered through diatomaceous earth and washed with 10% MeOH in DCM (1,000 mL). The filtrate was concentrated and purified by silica column chromatography (5-40% EtOAc/Hex) to afford the title compound (25.0g, 89%) as white solid. MS (ES) *m/z*=346 (M-1).

Preparation 23

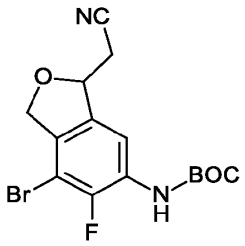
tert-Butyl N-(7-bromo-6-chloro-3-hydroxy-1,3-dihydroisobenzofuran-5-yl)carbamate



tert-Butyl N-(7-bromo-6-chloro-3-oxo-1H-isobenzofuran-5-yl)-N-*tert*-butoxycarbonyl-carbamate was used in a manner analogous to the method of Preparation 22 to afford the title compound (5.10 g, 65.4%) as a white solid. MS (ES) *m/z*=346 (M-H_2O+1).

Preparation 24

tert-Butyl N-[7-bromo-3-(cyanomethyl)-6-fluoro-1,3-dihydroisobenzofuran-5-yl]carbamate

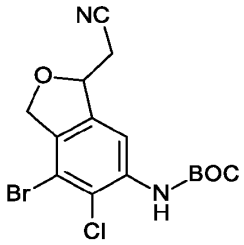


To a flask was added *tert*-butyl N-(7-bromo-6-fluoro-3-hydroxy-1,3-dihydroisobenzofuran-5-yl)carbamate (9.70 g, 27.9 mmol), THF (200 mL), diethyl cyanomethylphosphonate (7.00 mL, 42.3 mmol) and Cs_2CO_3 (10.0 g, 30.7 mmol). The flask was fitted with a condenser and the mixture was heated to reflux. After 3 h, the mixture was allowed to cool and was filtered through diatomaceous earth and rinsed with EtOAc. The combined filtrate and washings were concentrated. The crude oil was diluted with EtOAc (500 mL) and H_2O (500 mL) was added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was back extracted with EtOAc (500 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash silica column chromatography, eluting with 5-40% EtOAc/Hex to afford the title compound (9.15 g, 89%) as a white solid. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 9.28 (s, 1H), 7.68 (s, 1H), 5.52 (s, H), 5.02 (m, 2H), 3.18

(m, 2H), 1.49 (s, 9H).

Preparation 25

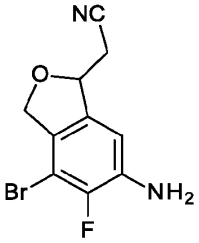
tert-Butyl N-[7-bromo-6-chloro-3-(cyanomethyl)-1,3-dihydroisobenzofuran-5-yl]carbamate



tert-Butyl N-(7-bromo-6-chloro-3-hydroxy-1,3-dihydroisobenzofuran-5-yl)carbamate was used in a manner analogous to the method of Preparation 24 to afford the title compound (3.92 g, 72%) as white solid. MS (ES) *m/z*=385 (M-1).

Preparation 26

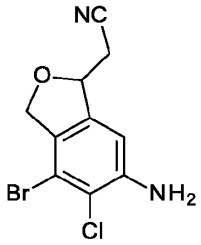
2-(6-Amino-4-bromo-5-fluoro-1,3-dihydroisobenzofuran-1-yl)acetonitrile



To a suspension of *tert*-butyl N-[7-bromo-3-(cyanomethyl)-6-fluoro-1,3-dihydroisobenzofuran-5-yl]carbamate (9.10 g, 24.5 mmol) in MeOH (150 mL) cooled in an ice bath was added HCl solution (4M in 1,4-dioxane, 64.0 mL, 256 mmol). The reaction was stirred at RT for 6 h. The mixture was cooled in an ice bath, neutralized first with 2N NaOH solution, and then with sat. aq. $NaHCO_3$. The mixture was concentrated and the resultant solid was collected and dried *in vacuo* at 60 °C overnight to afford the title compound as white solid (6.10 g, 92%). MS (ES) *m/z*=269 (M-1).

Preparation 27

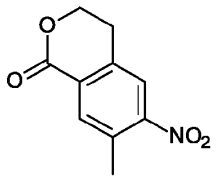
2-(6-Amino-4-bromo-5-chloro-1,3-dihydroisobenzofuran-1-yl)acetonitrile



tert-Butyl N-[7-bromo-6-chloro-3-(cyanomethyl)-1,3-dihydroisobenzofuran-5-yl]carbamate was used in a manner analogous to the method of Preparation 26 to afford the title compound (2.64 g, 99%) as an off-white solid. MS (ES) *m/z*=287 (M+1).

Preparation 28

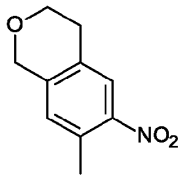
7-Methyl-6-nitro-isochroman-1-one



To a stirred mixture of 3-methyl-4-nitrobenzoic acid (70.0 g, 386 mmol) and N-acetyl-L-leucine (13.4 g, 77.3 mmol) in hexafluoroisopropanol (750 mL) was added KOAc (37.9 g, 386 mmol), and $Pd(OAc)_2$ (8.68 g, 38.6 mmol) followed by ethylene oxide (155 mL, 386 mmol, 1 eq., 2.5M in THF) at RT. The reaction mixture was stirred at 80 °C for 8 h under N_2. The mixture was diluted with EtOAc (1,000 mL). The organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE:EtOAc (3:1 to 1:1) to afford the product (56.0 g, 52.4%) as a yellow solid. MS (ES) *m/z*=249 (M+1).

Preparation 29

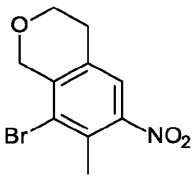
7-Methyl-6-nitro-isochromane



To a stirred mixture of 7-methyl-6-nitro-isochroman-1-one (66.0 g, 319 mmol) in THF (800 mL) was added $LiBH_4$ (2M in THF, 400 mL, 800 mmol) dropwise at -78 °C under N_2. The reaction mixture was allowed to warm to RT and was stirred for 3 h. The reaction was diluted by sat. aq. NH_4Cl (300 mL) and was extracted with EtOAc (2 x 600 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. To the crude 2-[2-(hydroxymethyl)-4-methyl-5-nitrophenyl]ethanol (50.0 g, 237 mmol) was added 4-methylbenzene-1-sulfonic acid (44.8 g, 260 mmol) and toluene (500 mL). The resulting reaction mixture was heated at 115 °C for ~ 18 h. The reaction was allowed to cool down to RT. The mixture was diluted with EtOAc (1,000 mL) and was washed with brine (500 mL), then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE:EtOAc (3:1 to 1:1) to afford the product (30.0 g, 36.3%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 6.96 (s, 1H), 4.82 – 4.74 (m, 2H), 4.02 – 3.96 (m, 2H), 2.96 – 2.82 (m, 2H), 2.5 (s, 3H).

Preparation 30

8-Bromo-7-methyl-6-nitro-isochromane

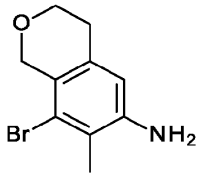


To a mixture of 7-methyl-6-nitro-isochromane (30 g, 150 mmol) in conc. H_2SO_4 (300 mL) was added NBS (32.1 g, 180 mmol) in portions at RT. The reaction was stirred at RT for

~ 18 h. The reaction mixture was poured into ice water (500 mL) and was filtered. The filter cake was washed with sat. aq. Na_2CO_3 (2 x 50 mL), then was dissolved in EtOAc (500 mL), washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE:EtOAc (3:1 to 1:1) to afford the product (23.0 g, 56.5%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 4.78 – 4.68 (m, 2H), 4.02 – 3.92 (m, 2H), 2.98 – 2.86 (m, 2H), 2.57 (s, 3H).

Preparation 31

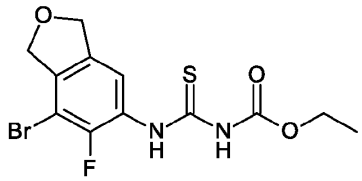
8-Bromo-7-methyl-isochroman-6-amine



To a mixture of 8-bromo-7-methyl-6-nitro-isochromane (23.0 g, 84.5 mmol) and NH_4Cl (22.6 g, 423 mmol) in EtOH (250 mL) and H_2O (50 mL) was added iron powder (23.6 g, 423 mmol) at RT. The resulting reaction mixture was heated at 80 °C for 6 h. The mixture was filtered, and the filter cake was washed with EtOAc (2 x 200 mL). The filtrate was diluted with EtOAc (100 mL), washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE:EtOAc (2:1 to 1:2) to afford the product (17.0 g, 83%) as a yellow solid. MS (ES) *m/z*=242 (M+1).

Preparation 32

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

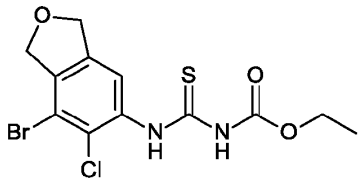
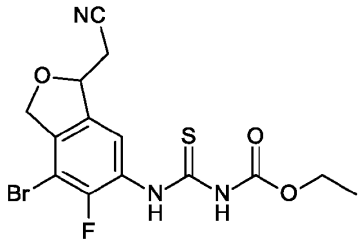


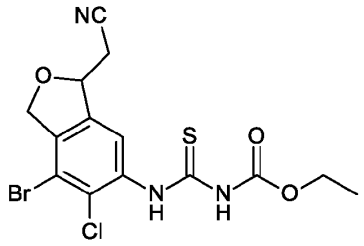
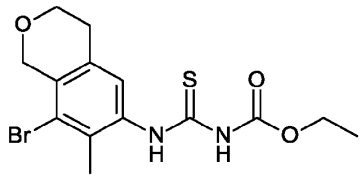
A solution of 7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-amine (20.4 g, 87.9

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).

The following compounds in Table 1 were prepared in a similar manner as described in Preparation 32. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

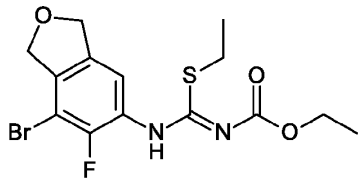
Table 1:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
33	Ethyl N-[(7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)carbamothioyl]carbamate		379
34	Ethyl N-[[7-bromo-3-(cyanomethyl)-6-fluoro-1,3-dihydroisobenzofuran-5-yl]carbamothioyl]carbamate		402

35	Ethyl N-[[7-bromo-6-chloro-3-(cyanomethyl)-1,3-dihydroisobenzofuran-5-yl]carbamothioyl]carbamate		418
36	Ethyl N-[(8-bromo-7-methyl-isochroman-6-yl)carbamothioyl]carbamate		373

Preparation 37

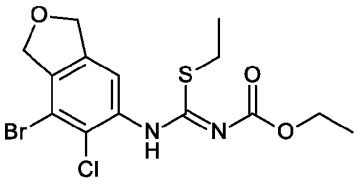
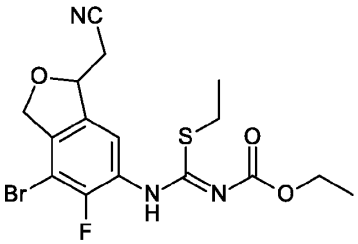
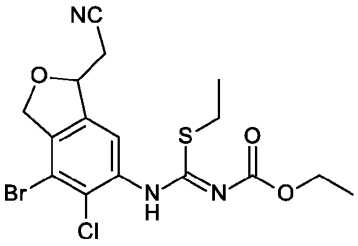
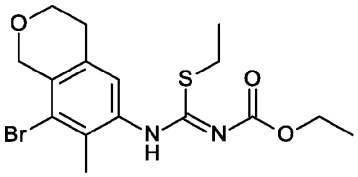
Ethyl (NZ)-N-[[(7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)amino]-ethylsulfanyl-methylene]carbamate



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).

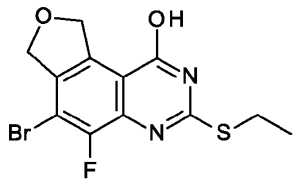
The following compounds in Table 2 were prepared in a similar manner as described for Preparation 37. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 2:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
38	Ethyl (NZ)-N-[[(7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)amino]-ethylsulfanyl-methylene]carbamate		407
39	Ethyl (NZ)-N-[[[7-bromo-3-(cyanomethyl)-6-fluoro-1,3-dihydroisobenzofuran-5-yl]amino]-ethylsulfanyl-methylene]carbamate		430
40	Ethyl (NZ)-N-[[[7-bromo-6-chloro-3-(cyanomethyl)-1,3-dihydroisobenzofuran-5-yl]amino]-ethylsulfanyl-methylene]carbamate		446
41	Ethyl (NZ)-N-[[(8-bromo-7-methyl-isochroman-6-yl)amino]-ethylsulfanyl-methylene]carbamate		401

Preparation 42

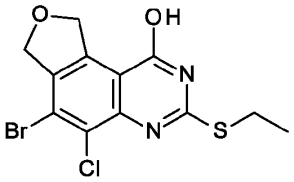
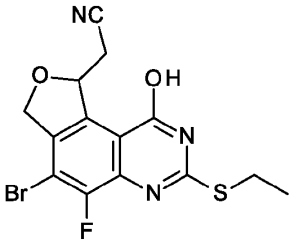
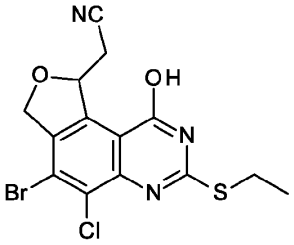
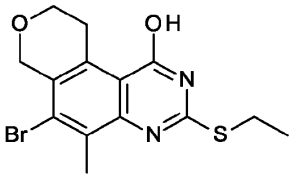
6-Bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-ol



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 (NZ)-N-[[(7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-yl)amino]-ethylsulfanyl-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).

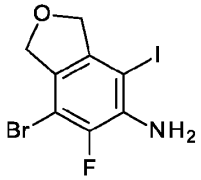
The following compounds in Table 3 were prepared in a similar manner as described for Preparation 42. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 3:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
43	6-Bromo-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-ol		361
44	2-(6-Bromo-3-ethylsulfanyl-5-fluoro-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-9-yl)acetonitrile		382
45	2-(6-Bromo-5-chloro-3-ethylsulfanyl-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-9-yl)acetonitrile		400
46	6-bromo-3-ethylsulfanyl-5-methyl-9,10-dihydro-7H-pyrano[4,3-f]quinazolin-1-ol		355

Preparation 47

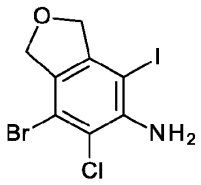
7-Bromo-6-fluoro-4-iodo-1,3-dihydroisobenzofuran-5-amine



A mixture of 7-bromo-6-fluoro-1,3-dihydroisobenzofuran-5-amine (15.0 g, 64.6 mmol) and NIS (16.0 g, 71.1 mmol) in $CHCl_3$ (400 mL) was stirred at 50 °C under N_2 for ~18 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with PE / EtOAc (10:1-5:1) to afford the product (16.0 g, 69.2%) as an orange solid. MS (ES) *m/z*=358 (M+1).

Preparation 48

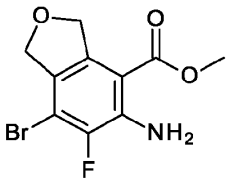
7-Bromo-6-chloro-4-iodo-1,3-dihydroisobenzofuran-5-amine



7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-amine was used in a manner analogous to the method of Preparation 47 to afford the title compound (0.19 g, 60%) as white solid. MS (ES) *m/z*=372 (M+1).

Preparation 49

Methyl 5-amino-7-bromo-6-fluoro-1,3-dihydroisobenzofuran-4-carboxylate

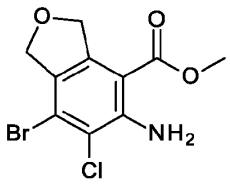


To a stirred solution of 7-bromo-6-fluoro-4-iodo-1,3-dihydroisobenzofuran-5-amine

(1.62 g, 4.53 mmol) in MeOH (20 mL) and DMF (20 mL) was added TEA (1.89 mL, 13.6 mmol) and $Pd(dppf)Cl_2$ (331 mg, 0.45 mmol) at RT under CO atmosphere. The mixture was stirred at 60 °C for ~18 h under CO atmosphere using a CO balloon. The resulting mixture was concentrated under reduced pressure and was diluted with EtOAc (300 mL). The mixture was washed with H_2O (3 x 200 mL), brine (200 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc in PE, 20% to 40% gradient in 30 min to afford the product (1.00 g, 76.1%) as a yellow solid. MS (ES) *m/z*=290 (M+1).

Preparation 50

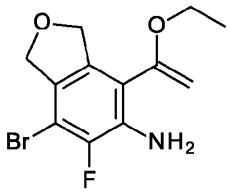
Methyl 5-amino-7-bromo-6-chloro-1,3-dihydroisobenzofuran-4-carboxylate



7-Bromo-6-chloro-4-iodo-1,3-dihydroisobenzofuran-5-amine was used in a manner analogous to the method of Preparation 49 to afford the title compound (6.2 g, 58%) as light-yellow solid. MS (ES) *m/z*=306 (M+1).

Preparation 51

7-Bromo-4-(1-ethoxyvinyl)-6-fluoro-1,3-dihydroisobenzofuran-5-amine

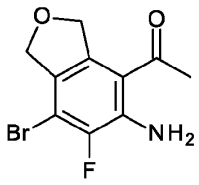


To a stirred mixture of 7-bromo-6-fluoro-4-iodo-1,3-dihydroisobenzofuran-5-amine (6.00 g, 16.8 mmol) and tributyl(1-ethoxyvinyl)stannane (22.7 g, 62.9 mmol) in DMF (60 mL) was added $Pd(PPh_3)_4$ (3.88 g, 3.34 mmol) in portions at RT. The reaction was then

stirred for ~ 18 h at 80 °C. The mixture was allowed to cool down to RT and was extracted with EtOAc (200 mL). The organic layers were washed with H_2O (3 x 50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the product (5.07 g, quantitative) which was used in the subsequent step without further purification. MS (ES) *m/z*=301 (M+1).

Preparation 52

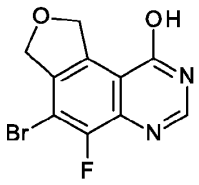
1-(5-Amino-7-bromo-6-fluoro-1,3-dihydroisobenzofuran-4-yl)ethanone



To a stirred mixture of 7-bromo-4-(1-ethoxyvinyl)-6-fluoro-1,3-dihydroisobenzofuran-5-amine (5.00 g, 16.6 mmol) in THF (50 mL) was added 1M HCl in water (50 mL) dropwise at 0 °C, then stirred for 3 h at RT. The resulting mixture was extracted with EtOAc (100 mL) and the organic layers were washed with 1M aq. Na_2CO_3 solution (100 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE:EtOAc (3:1 to 1:1) to afford the product (2.00 g, 44.1%) as a yellow solid. MS (ES) *m/z*=274 (M+1).

Preparation 53

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

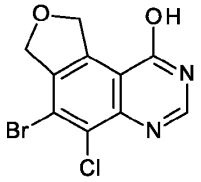


A mixture of methyl 5-amino-7-bromo-6-fluoro-1,3-dihydroisobenzofuran-4-carboxylate (6.00 g, 20.7 mmol) and formamide (48.0 mL, 1,200 mmol) was stirred for 12 h at 160 °C under N_2. The mixture was allowed to cool down to RT and diluted with H_2O (300

mL) at 0 °C. The precipitated solids were collected by filtration and washed with H_2O (3 x 50 mL). The solids were dried under vacuum to afford the product (5.2 g, 88.1%) as a brown solid. MS (ES) *m/z*=285 (M+1).

Preparation 54

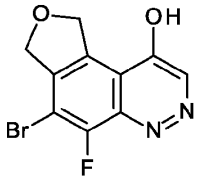
6-Bromo-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-1-ol



Methyl 5-amino-7-bromo-6-chloro-1,3-dihydroisobenzofuran-4-carboxylate was used in a manner analogous to the method of Preparation 53 to afford the title compound (3.5 g, 58%) as black solid. MS (ES) *m/z*=301 (M+1).

Preparation 55

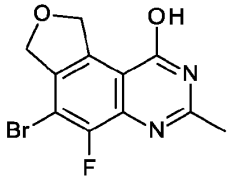
4-Bromo-5-fluoro-1,3-dihydrofuro[3,4-f]cinnolin-9-ol



To a stirred mixture of 1-(5-amino-7-bromo-6-fluoro-1,3-dihydroisobenzofuran-4-yl)ethanone (2.00 g, 7.30 mmol) in TFA (40 mL) was added $NaNO_2$ (0.600 g, 8.76 mmol) at RT and stirred for 2 h at 70 °C. The reaction was allowed to cool to RT and then concentrated under reduced pressure, H_2O (100 mL) was added, and the resulting mixture was extracted with EtOAc (2 x 100 mL), the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with DCM:MeOH (10:1) to afford the product (1.20 g, 57.7%) as a yellow solid. MS (ES) *m/z*=285 (M+1).

Preparation 56

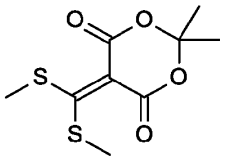
6-Bromo-5-fluoro-3-methyl-7,9-dihydrofuro[3,4-f]quinazolin-1-ol



A stirred mixture of methyl 5-amino-7-bromo-6-fluoro-1,3-dihydro-2-benzofuran-4-carboxylate (350 mg, 1.21 mmol) and ACN (594 mg, 14.5 mmol) in 4M HCl in 1,4-dioxane (10 mL) was heated at 100 °C under N_2. The resulting mixture was stirred for ~ 18 h at 100 °C under N_2. The mixture was diluted with H_2O (100 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were concentrated under reduced pressure to afford the product (290 mg, 80.4%) as a yellow solid. MS (ES) *m/z*=299 (M+1).

Preparation 57

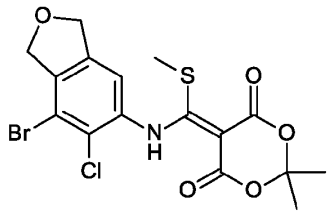
5-[Bis(methylsulfanyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione



To a stirred mixture of Meldrum's acid (20 g, 138.76 mmol) and TEA (42.13 g, 416.30 mmol, 3 eq.) in DMSO (100 mL) was added CS_2 (15.85 g, 208.15 mmol, 1.5 eq.). The resulting mixture was stirred at RT for 3 h under N_2. CH_3I (59.09 g, 416.30 mmol, 3 eq.) was added dropwise at 0 °C. The temperature was allowed to warm to RT and reaction was stirred for ~ 18 h. The resulting mixture was diluted with EtOAc (1,000 mL), washed with H_2O (2 x 200 mL), then brine (200 mL) and was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified on silica, eluting with PE:EtOAc (4:1 to 2:1) to afford the title compound (23 g, 67%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.64 (s, 6H), 1.68 (s, 6H).

Preparation 58

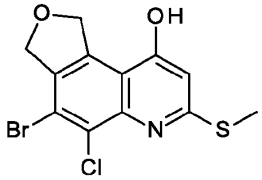
5-[[(7-Bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)amino]-methylsulfanyl-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione



A stirred mixture of 5-[bis(methylsulfanyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (16.49 g, 66.40 mmol, 1.1 eq.) and 7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-amine (15 g, 60 mmol, 1 eq.) in toluene (150 mL) was heated at 80 °C for 2 days. The reaction mixture was concentrated under reduced pressure and the residue was purified by trituration with 10:1 PE:EtOAc (250 mL). The solid was collected by filtration and dried under vacuum to afford the title compound (20 g, 73%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.97 (s, 1H), 7.52 (s, 1H), 5.14 (s, 2H), 5.03 (s, 2H), 2.37 (s, 3H), 1.67 (s, 6H).

Preparation 59

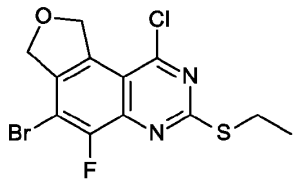
4-Bromo-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-9-ol



A solution of 5-[[(7-bromo-6-chloro-1,3-dihydroisobenzofuran-5-yl)amino]-methylsulfanyl-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (18 g, 40 mmol, 1 eq.) in diphenyl ether (200 mL) was stirred for 1h at 180 °C. The reaction was allowed to cool down to RT then was diluted with PE (500 mL) and stirred for 20 min at RT. After filtration, the filter cake was washed with PE (2 x 50 mL) and was dried under reduced pressure to afford the title compound (11.3 g, 81%) as a yellow solid which was used in the next step without further purification. MS (ES) *m/z*=346 (M+1).

Preparation 60

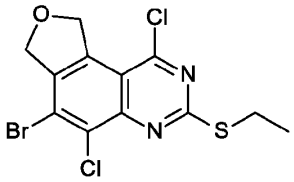
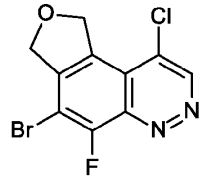
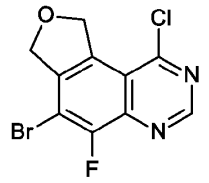
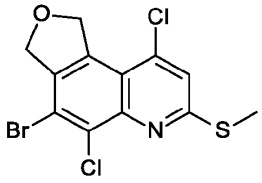
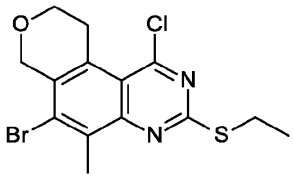
6-Bromo-1-chloro-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline



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-ethylsulfanyl-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).

The following compounds in Table 4 were prepared in a similar manner as described for Preparation 60. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

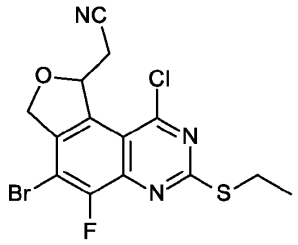
Table 4:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
61	6-Bromo-1,5-dichloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazoline		379
62	4-Bromo-9-chloro-5-fluoro-1,3-dihydrofuro[3,4-f]cinnoline		303
63	6-Bromo-1-chloro-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline		303
64[a]	4-bromo-5,9-dichloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinoline		366
65	6-bromo-1-chloro-3-ethylsulfanyl-5-methyl-9,10-dihydro-7H-pyrano[4,3-f]quinazoline		375

[a] After removal of ice bath, the reaction was heated at 37 °C for ~24 h.

Preparation 66

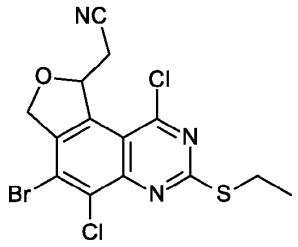
2-(6-Bromo-1-chloro-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-9-yl)acetonitrile



To a solution of DMF (60 mL) and $POCl_3$ (50.00 mL, 538 mmol) was added 2-(6-bromo-3-ethylsulfanyl-5-fluoro-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-9-yl)acetonitrile (4.6 g, 12 mmol) portion wise. The mixture was heated at 90 °C in an oil bath for 1 h. The reaction mixture was cooled to RT, and then was slowly added to a mixture of ice-water with stirring. The resultant solid was collected by filtration, washed with cold water and dried in vacuum oven at 55 °C overnight to obtain the title compound (4.5g, 75%) as a light-brown solid. MS (ES) *m/z*=402 (M+1).

Preparation 67

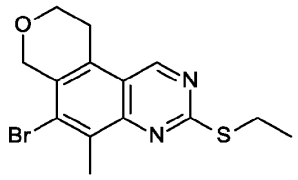
2-(6-Bromo-1,5-dichloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-9-yl)acetonitrile



2-(6-Bromo-5-chloro-3-ethylsulfanyl-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-9-yl)acetonitrile was used in a manner analogous to the method of Preparation 66 to afford the title compound (0.9 g, 81%) as off-white solid. MS (ES) *m/z*=418 (M+1).

Preparation 68

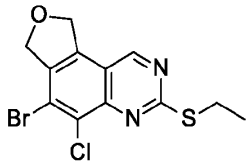
6-Bromo-3-ethylsulfanyl-5-methyl-9,10-dihydro-7H-pyrano[4,3-f]quinazoline



A mixture of 6-bromo-1-chloro-3-ethylsulfanyl-5-methyl-9,10-dihydro-7H-pyrano[4,3-f]quinazoline (1.10 g, 2.94 mmol) and TMEDA (500 mg, 4.30 mmol) in THF (20 mL) was purged with argon. $Pd(ddpf)Cl_2 \cdot DCM$ complex (120 mg, 0.144 mmol) and $NaBH_3CN$ (280 mg, 4.46 mmol) were added. The reaction mixture was purged again with argon and heated to 45 °C. After 2 h, the reaction mixture was cooled down to RT and diluted with EtOAc, washed with sat. aq. NH_4Cl, brine and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc in hexanes (0 to 40%) to afford the product (998 mg, quantitative) as a yellow solid. MS (ES) *m/z*=339 (M+1).

Preparation 300

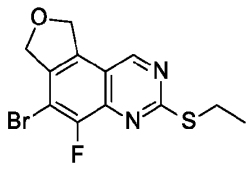
6-Bromo-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazoline



6-Bromo-1,5-dichloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazoline was used in an analogous manner to the method of Preparation 68 to obtain the title compound (0.38 g, 51%) as a white solid. MS (ES) *m/z*=345,347 (M+1, Br).

Preparation 301

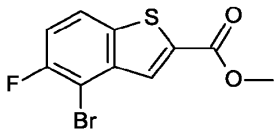
6-Bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline



6-Bromo-1-chloro-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline was used in an analogous manner to the method of Preparation 68 to obtain the title compound (1.00 g, 92%). MS (ES) *m/z*=329,331 (M+1, Br).

Preparation 69

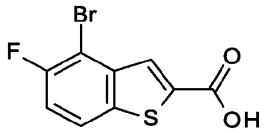
Methyl 4-bromo-5-fluoro-benzothiophene-2-carboxylate



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 70

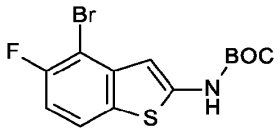
4-Bromo-5-fluoro-benzothiophene-2-carboxylic acid



A solution of methyl 4-bromo-5-fluoro-benzothiophene-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 71

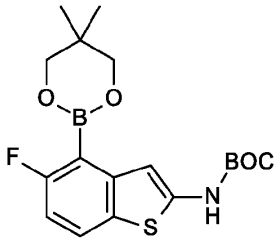
tert-Butyl N-(4-bromo-5-fluoro-benzothiophen-2-yl)carbamate



A solution of 4-bromo-5-fluoro-benzothiophene-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 72

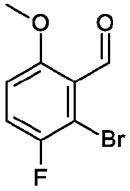
tert-Butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluoro-benzothiophen-2-yl]carbamate



A mixture of *tert*-butyl N-(4-bromo-5-fluoro-benzothiophen-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 73

2-Bromo-3-fluoro-6-methoxy-benzaldehyde



In a 2L 3-necked RBF equipped with a thermocouple, dropping funnel and condenser, a solution of 2-bromo-3,6-difluoro-benzaldehyde (95.0 g, 430 mmol) in MeOH (850 mL) was charged dropwise with NaOMe (30 mass%) in MeOH (95 mL, 475 mmol, 1.1 eq.) over ~ 15 min and stirred at 60 °C for 5 h. The reaction was cooled to RT.

The reaction mixture was poured slowly into H_2O (2 L) while stirring. A thick precipitate formed in the flask. The mixture was stirred at RT for 15 min and was filtered. The filter cake was dried under vacuum at 50 °C for ~18 h to afford the title compound (75.4 g, 75%) as a white solid. MS (ES) *m/z*=232 (M+1).

Preparation 74

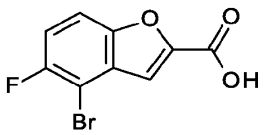
2-Bromo-3-fluoro-6-hydroxy-benzaldehyde



A 3-necked 2L RBF, equipped with a thermometer, overhead stirrer and dropping funnel was charged with a solution of 2-bromo-3-fluoro-6-methoxy-benzaldehyde (79.2 g, 340 mmol) in DCM (700 ml). The flask was placed in a dry ice/acetone bath and was cooled to -76 °C. BBr_3 (1.0 M in DCM, 340 mL, 340 mmol, 1 eq.) was added dropwise at such a rate to keep internal temperature below -70 °C. The reaction was stirred in the dry ice/acetone bath for 15 min, then the ice bath was removed and the reaction was left to stir at RT for ~ 18 h. The reaction flask was placed in an ice/water bath. Once the internal temperature settled at ~2.5 °C, H_2O (250 mL) was added dropwise via an addition funnel. The ice bath was removed and the reaction was allowed to come to RT and was stirred another 15 min. The reaction mixture was partitioned and the aqueous phase was treated with DCM (200 mL) and brine (100 mL) and was partitioned again. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to a tan solid. Hexanes (250 mL) were added and the slurry was stirred for 30 min. The solids were filtered and the filtrate, upon standing, precipitated additional solids that were filtered and combined with the previously filtered solids (Batch 1). The combined batches were dried under vacuum at 50 °C overnight. The filtrate was concentrated and purified on silica (5% to 30% DCM/Hex) to obtain more product (Batch 2). The two batches were combined to afford the title compound (66.7 g, 90%) as white solid. GCMS (EI) *m/z*=219 $(M)^+$.

Preparation 75

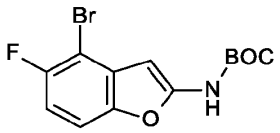
4-Bromo-5-fluoro-benzofuran-2-carboxylic acid



In a 2L, 3-necked RBF, equipped with overhead stirrer, thermocouple, a solution of 2-bromo-3-fluoro-6-hydroxy-benzaldehyde (64.45 g, 294.3 mmol) in DMF (600 mL, 7,760 mmol) was charged with K_2CO_3 (89.5 g, 648 mmol, 2.2 eq.), NaI (8.83 g, 58.9 mmol, 0.2 eq.) and ethyl bromoacetate (36 mL, 324.2 mmol, 1.1 eq.) was heated at 70 °C for ~18 h. The temperature was increased to 120 °C for 4 h. The reaction was cooled to ~45 °C, then the heat was removed and the reaction was allowed to cool. When the internal temperature reached ~45 °C, a thick precipitate formed in the flask. H_2O (1 L) was added in a slow stream via addition funnel to obtain a nearly homogeneous mixture. The pH was adjusted to ~3 with conc. HCl and the mixture was stirred at RT for 30 min. Solids were filtered, rinsed with H_2O (500 mL) and dried under vacuum at 50 °C to obtain the title compound (52.4 g, 69%) as a white solid. MS (ES), *m/z*=212 (M-1-CO_2).

Preparation 76

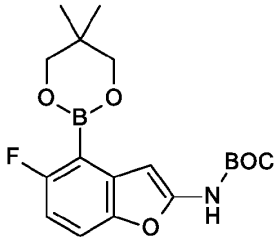
tert-Butyl N-(4-bromo-5-fluoro-benzofuran-2-yl)carbamate



4-Bromo-5-fluoro-benzofuran-2-carboxylic acid was used in a manner analogous to the method of Preparation 71 and then the product was purified on silica, eluting with MTBE/Hex (5% to 30%) to obtain the title compound (29.1 g, 35%) as a yellow solid, MS (ES), *m/z*=274 (M+1-*t*Bu).

Preparation 77

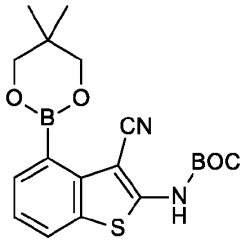
tert-Butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluoro-benzofuran-2-yl]carbamate



tert-Butyl N-(4-bromo-5-fluoro-benzofuran-2-yl)carbamate was used in an analogous manner to the method of Preparation 72 to obtain the title compound (21.3 g, 71%) as a light-tan solid. MS (ES), *m/z*=240 (M+1, mass of boronic acid was observed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (bs, 1H), 8.43 (s, 1H), 7.82 (dd, *J*=5.1, 8.8 Hz, 1H), 6.91 (dd, *J*=8.8, 9.5 Hz, 1H), 7.15 (s, 1H), 3.81 (s, 4H), 1.50 (s, 9H), 1.03 (s, 6H).

Preparation 78

tert-Butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzothiophen-2-yl]carbamate

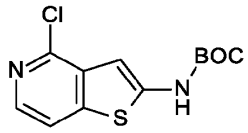


A mixture of *tert*-butyl N-(4-bromo-3-cyano-benzothiophen-2-yl)carbamate (United States Patent Application Publication US 2021/0179633 A1, Preparation 7) (19.0 g, 53.8 mmol), bis(neopentyl glycolato)diboron (18.2 g, 80.6 mmol) and KOAc (15.8 g, 161 mmol) in 1,4-dioxane (350 mL) was sparged with N_2 for 40 min. Pd-117 (3.93 g, 5.38 mmol) was added, and the resulting mixture was heated at 95 °C for 1.5 h. The reaction was cooled, filtered through diatomaceous earth and rinsed with DCM. The filtrate was concentrated and the residue was purified on silica, eluting with EtOAc/Hex (10-50%) to give the title compound (11.7 g, 56%) as an off-white solid. MS (ES), *m/z*=317 (M-1, mass of boronic

acid was observed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 7.95 (dd, J= 1.0, 8.0 Hz, 1H), 7.54 (dd, J= 1.0, 7.2 Hz, 1H), 7.31 (t, J= 7.6 Hz, 1H), 3.78 (s, 4H), 1.53 (s, 9H), 1.04 (s, 6H).

Preparation 79

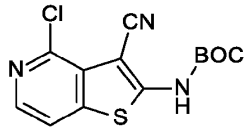
tert-Butyl N-(4-chlorothieno[3,2-c]pyridin-2-yl)carbamate



To a suspension of 4-chlorothieno[3,2-c]pyridine-2-carboxylic acid (78 g, 365.1 mmol) in *t*-BuOH (1,500 mL) was added TEA (155 mL, 1,110 mmol) and diphenylphosphoryl azide (100 g, 356.1 mmol). The mixture was stirred and heated to ~ 80 °C. After 14 h, the reaction was allowed to cool to RT and the solids were allowed to settle. The liquid above the solids was decanted and the solids were filtered and rinsed with DCM. The filtrate and decanted solution were combined and concentrated. The crude material was purified on silica, eluting with MTBE/Hex (10-50%) to afford the title compound (65 g, 58.3%) as a white solid. MS (ES) m/z=285 (M+1).

Preparation 80

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

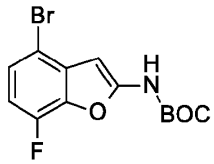


tert-Butyl N-(4-chlorothieno[3,2-c]pyridin-2-yl)carbamate (5.0 g, 18 mmol) in THF (120 mL) was cooled with an ice/water bath. CSI (4.7 mL, 53 mmol) was added dropwise all at once at a steady rate and stirred under N_2. After 1.5 h, the cold reaction mixture was transferred to an addition funnel and was added dropwise over a 14 min period to cold DMF (125 mL) in an ice bath. After addition, the ice bath was removed, and the reaction was stirred at RT for 1 h. The reaction was diluted with EtOAc and washed with brine and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the oil

containing DMF was evaporated over a stream of N_2 to obtain a brown solid. EtOH (25 mL) was added to the solid and it was sonicated, filtered and the solids were rinsed with DCM and air dried to obtain the product (2.2 g, 37%) as a white solid. MS (ES) *m/z*=310 (M+1).

Preparation 227

tert-Butyl N-(4-bromo-7-fluoro-benzofuran-2-yl)carbamate



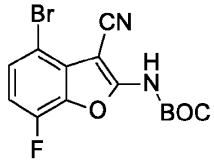
Ethyl 4-bromo-7-fluoro-benzofuran-2-carboxylate. 6-Bromo-3-fluoro-2-hydroxy-benzaldehyde (2.9 g, 13 mmol) was combined with potassium carbonate (2.0 g, 14 mmol) and sodium iodide (0.40 g, 2.7 mmol) in DMF (45 mL). Ethyl bromoacetate (1.6 mL, 14 mmol) was added and the reaction mixture was stirred at room temperature overnight. Potassium carbonate (2.0 g, 14 mmol) was added. The reaction mixture was stirred at 120 °C for 3 h and cooled to room temperature. The reaction mixture was diluted with water (60 mL), stirred for 30 min, and filtered the resulting solid. The solids were washed with water and dried in a vacuum oven (40 °C) to give ethyl 4-bromo-7-fluoro-benzofuran-2-carboxylate (1.2 g, 32%) as a light tan solid. MS (ES) *m/z*=287,289 (M+1, Br).

4-Bromo-7-fluoro-benzofuran-2-carboxylic acid. Ethyl 4-bromo-7-fluoro-benzofuran-2-carboxylate was used in an analogous manner to the method of Preparation 70 to obtain 4-bromo-7-fluoro-benzofuran-2-carboxylic acid (0.97 g, 90%) as a white solid. MS (ES) *m/z*=256,258 (M-1,Br).

tert-Butyl N-(4-bromo-7-fluoro-benzofuran-2-yl)carbamate. 4-Bromo-7-fluoro-benzofuran-2-carboxylic acid was used in an analogous manner to the method of Preparation 79 to obtain the title compound (0.42 g, 66%). MS (ES) *m/z*=328,330 (M-1,Br).

Preparation 228

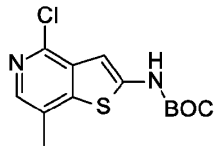
tert-Butyl N-(4-bromo-3-cyano-7-fluoro-benzofuran-2-yl)carbamate



tert-Butyl N-(4-bromo-7-fluoro-benzofuran-2-yl)carbamate was used in an analogous manner to the method of Preparation 80 to obtain the title compound (1.75 g, 63%). MS (ES) *m/z*=354,356 (M+1,Br).

Preparation 229

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



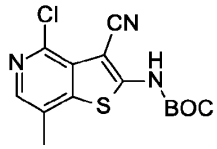
Methyl 4-chloro-7-methyl-thieno[3,2-c]pyridine-2-carboxylate. 2,4-Dichloro-5-methyl-pyridine-3-carbaldehyde (7.25 g, 38.2 mmol), potassium carbonate (10.5 g, 76.0 mmol), and DMF (127 mL) were combined, heated at 70 °C overnight, and cooled to room temperature. The reaction mixture was added to water (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).

4-Chloro-7-methyl-thieno[3,2-c]pyridine-2-carboxylic acid. Methyl 4-chloro-7-methyl-thieno[3,2-c]pyridine-2-carboxylate was used in an analogous manner to the method of Preparation 70 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).

tert-Butyl N-(4-chloro-7-methyl-thieno[3,2-c]pyridin-2-yl)carbamate. 4-Chloro-7-methyl-thieno[3,2-c]pyridine-2-carboxylic acid was used in an analogous manner to the method of Preparation 79 to obtain the title compound (0.83 g, 63%). MS (ES) *m/z*=299 (M+1).

Preparation 230

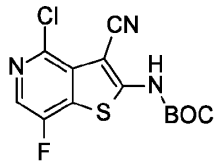
tert-Butyl N-(4-chloro-3-cyano-7-methyl-thieno[3,2-c]pyridin-2-yl)carbamate



tert-Butyl N-(4-chloro-7-methyl-thieno[3,2-c]pyridin-2-yl)carbamate was used in an analogous manner to the method of Preparation 80 to obtain the title compound (0.542 g, 31%). MS (ES) *m/z*=324 (M+1).

Preparation 231

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



Ethyl N-(3-cyano-7-fluoro-thieno[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 room temperature 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).

2-Amino-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile. A suspension of ethyl N-(3-cyano-7-fluoro-thieno[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 room temperature. 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.

tert-Butyl N-(3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate. A mixture of crude 2-amino-7-fluoro-thieno[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 room temperature 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).

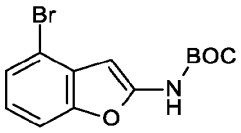
tert-Butyl N-(3-cyano-7-fluoro-5-oxido-thieno[3,2-c]pyridin-5-ium-2-yl)carbamate. 3-Chloroperoxybenzoic acid (9.00 g, 40.2 mmol) was added to a solution of *tert*-butyl N-(3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate (7.85 g, 26.8 mmol) in DCM (180 mL). The reaction mixture was stirred at room temperature 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).

tert-Butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate. A suspension of *tert*-butyl N-(3-cyano-7-fluoro-5-oxido-thieno[3,2-c]pyridin-5-ium-2-yl)carbamate (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 room temperature for 30 min, at 45 °C for 90 min, and cooled to room temperature. 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 81

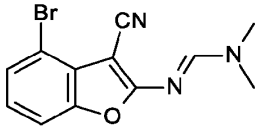
tert-Butyl N-(4-bromobenzofuran-2-yl)carbamate



4-Bromobenzofuran-2-carboxylic acid was used in an analogous manner to the method of Preparation 71 to obtain the title compound (6.48 g, 50%). MS (ES) *m/z*=310 (M-1).

Preparation 82

N'-(4-Bromo-3-cyano-benzofuran-2-yl)-N,N-dimethyl-formamidine

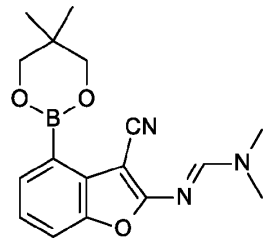


To a RBF was added *tert*-butyl N-(4-bromobenzofuran-2-yl)carbamate (6.48 g, 20.8 mmol) and THF (0.3 M, 69.2 mL). The solution was cooled to -78 °C under N_2 and CSI (6.0 mL, 68.5 mmol, 3.3 eq.) was added slowly over 5 min. The reaction was stirred for 30 min, then it was transferred via cannula into stirred DMF (100 mL) at RT and rinsed with THF. The reaction mixture was stirred for 16 h at RT. The reaction was then chilled in ice bath and sat. aq. $NaHCO_3$ (~160 mL) was added slowly until effervescence subsided, then the mixture was diluted with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$ (2x), brine (3x) and was dried over $MgSO_4$, filtered, and concentrated. The resulting material was mixed

with EtOAc to loosen solids. Hexane was added and the mixture was sonicated to break up larger clumps. The solids were filtered, rinsed with 20% EtOAc/Hexanes and dried *in vacuo* to obtain the title compound (3.39 g, 55.9%) as a light-green solid, MS (ES) *m/z*=292 (M+1).

Preparation 83

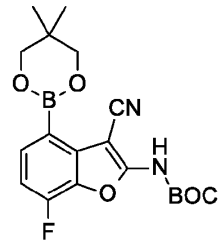
N'-[3-Cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzofuran-2-yl]-N,N-dimethyl-formamidine



To a RBF was added N'-(4-bromo-3-cyano-benzofuran-2-yl)-N,N-dimethyl-formamidine (3.38 g, 11.6 mmol), bis(neopentyl glycolato)diboron (7.84 g, 34.7 mmol, 3.0 eq.), KOAc (3.75 g, 38.2 mmol, 3.3 eq.), and 1,4-dioxane (96 mL). The mixture was sparged with N_2 and Pd-117 (0.83 g, 1.16 mmol, 0.1 eq.) was added and the reaction was stirred for 2.5 h at 100 °C. The reaction mixture was cooled, filtered through diatomaceous earth and rinsed with 20% EtOAc/hexane. The filtrate was concentrated and the residue was purified on silica, eluting with EtOAc/Hex (0-100%). Fractions containing desired material were concentrated and EtOAc was added to the resulting solid. Solids were filtered and rinsed with EtOAc and hexanes and dried *in vacuo* at RT to obtain the title compound (2.64 g, 70%) as a tan solid. MS (ES) *m/z*=258 (M+1) of corresponding boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.48 – 7.44 (m, 2H), 7.17 (dd, *J*= 7.4, 8.0 Hz, 1H), 3.78 (s, 4H), 3.2 (s, 3H), 3.1 (s, 3H) 1.00 (s, 6H).

Preparation 232

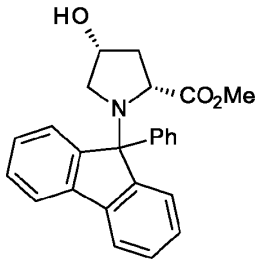
tert-Butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzofuran-2-yl]carbamate



tert-Butyl N-(4-bromo-3-cyano-7-fluoro-benzofuran-2-yl)carbamate was used in an analogous manner to the method of Preparation 83 to obtain the title compound (0.75 g, 73%). MS (ES) *m/z*=321 (M+1, corresponding boronic acid).

Preparation 84

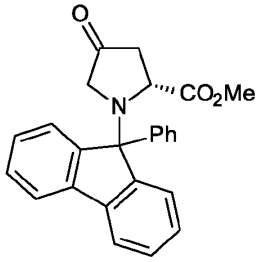
Methyl (2R,4R)-4-hydroxy-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate



To a stirred mixture of methyl (2R,4R)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (20.0 g, 138 mmol) and 9-bromo-9-phenylfluorene (53.1 g, 165 mmol) in DCM (400 mL) was added chlorotrimethylsilane (37.4 g, 344 mmol), TEA (13.9 g, 138 mmol) and $Pb(NO_3)_2$ (41.1 g, 124 mmol) portion wise at RT. The resulting mixture was stirred for ~ 18h at 70 °C under N_2. The reaction was cooled to RT and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:1) to afford the product (42 g, 79.2%) as a white solid. MS (ES) *m/z*=386 (M+1).

Preparation 85

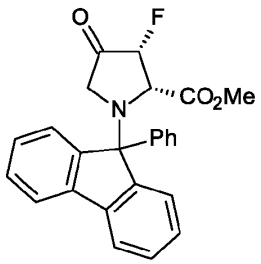
Methyl (2R)-4-oxo-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate



To a stirred solution of methyl (2R,4R)-4-hydroxy-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate (30.0 g, 77.8 mmol) and oxalyl chloride (83.0 g, 654 mmol) in DCM (1,000 mL) was added TEA (243 g, 2397 mmol) and DMSO (85.1 g, 1090 mmol) at -40 °C. The resulting mixture was stirred for 8 h at -40 °C under N_2. The mixture was allowed to warm to RT and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (2:1) to afford methyl the product (25.7 g, 85.6%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (dd, J=14.0 Hz, 2H), 7.51 – 7.23 (m, 11H), 3.76 – 3.59 (m, 2H), 3.36 (s, 1H), 3.04 (s, 3H), 2.66 (dd, J=17.9, 8.5 Hz, 1H), 2.28 – 2.16 (m, 1H).

Preparation 86

Methyl (2S,3R)-3-fluoro-4-oxo-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate

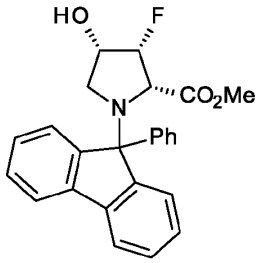


To a stirred solution of methyl (2R)-4-oxo-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate (40.0 g, 104 mmol) and TEA (31.7 g, 312 mmol) in DCM (1000 mL) was added trimethylsilyl trifluoromethanesulfonate (119 g, 208 mmol) dropwise at -40 °C. The resulting mixture was stirred for 2 h at -40 °C under N_2. Concentrated under reduced

pressure, diluted with pentane (1,000 mL) and washed with sat. aq. $NaHCO_3$ (2 x 500 mL) and brine and the organics dried over anhydrous Na_2SO_4. The solution was concentrated under vacuum to give the crude silyl enol ether (47.3 g, quantitative). To a solution of crude silyl enol ether (13.0 g, 28.5 mmol) in DCM (200 mL) was added Selectfluor (131 g, 37.0 mmol) in portions at RT. The resulting mixture was stirred at RT ~ 18 h. The mixture was then concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:1) to afford the title compound (3.96 g, 34.4%) as a light-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.70 (m, 2H), 7.51 – 7.28 (m, 11H), 5.10 (dd, *J*=50.9, 7.9 Hz, 1H), 4.10 – 3.96 (m, 2H), 3.74 – 3.61 (m, 1H), 3.25 (s, 3H).

Preparation 87

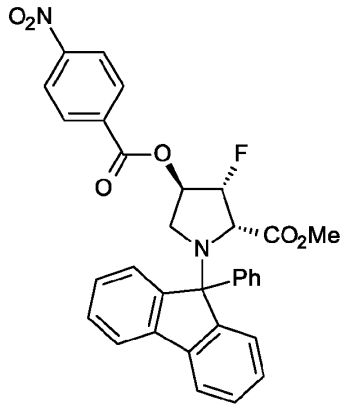
Methyl (2S,3R,4S)-3-fluoro-4-hydroxy-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate



To a stirred solution of methyl (2S,3R)-3-fluoro-4-oxo-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate (8.00 g, 19.93 mmol) in THF (60 mL) and EtOH (60 mL) was added $NaBH_4$ (0.83 g, 21.9 mmol) in portions at 0 °C under N_2. The resulting mixture was stirred for 1 h at 0 °C under N_2. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified with silica gel, eluting with PE:EtOAc (4:1 to 2:1) to afford the title compound (6.66 g, 83%) as a light-yellow solid. MS (ES) *m/z*=426 (M+Na).

Preparation 88

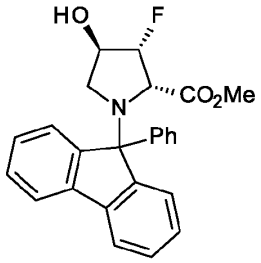
Methyl (2S,3R,4R)-3-fluoro-4-(4-nitrobenzoyloxy)-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate



To a stirred mixture of PPh_3 (3.25 g, 12.4 mmol) and DIAD (2.41 g, 11.9 mmol) in THF (100 mL) was added methyl (2S,3R,4S)-3-fluoro-4-hydroxy-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate (1.00 g, 2.48 mmol) and 4-nitrobenzoic acid (0.41 g, 2.48 mmol) dropwise at 0 °C under N_2. The reaction was stirred for 1 h at 0 °C, then diluted with H_2O and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with H_2O (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified with silica gel, eluting with PE:EtOAc (4:1 to 2:1) to afford the title compound (450 mg, 38.6%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.26 (m, 2H), 8.16 – 8.10 (m, 2H), 7.76 – 7.72 (m, 1H), 7.70 – 7.66 (m, 1H), 7.53 – 7.49 (m, 2H), 7.41 – 7.35 (m, 4H), 7.28 – 7.24 (m, 4H), 7.22 – 7.18 (m, 1H), 5.74 – 5.70 (m, 1H), 5.15 – 5.09 (m, 1H), 4.06 – 4.02 (m, 1H), 3.68 – 3.64 (m, 1H), 3.35 (s, 3H), 3.10 – 3.06 (m, 1H).

Preparation 89

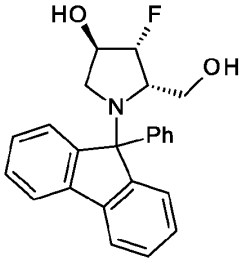
Methyl (2S,3R,4R)-3-fluoro-4-hydroxy-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate



To a stirred mixture of methyl (2S,3R,4R)-3-fluoro-4-(4-nitrobenzoyloxy)-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate (3.00 g, 5.43 mmol) in THF (100 mL) and H_2O (25 mL) was added a solution of $LiOH·H_2O$ (255 mg, 6.08 mmol) dissolved in H_2O (25 mL) dropwise at 0 °C. After stirring for 2 h at 0 °C the reaction mixture was adjusted to pH 7 with formic acid and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel, eluting with PE:EtOAc (1:1) to afford the title compound (1.76 g, 80.7%) as a yellow solid. MS (ES) *m/z*=426 (M+Na).

Preparation 90

(3R,4R,5S)-4-Fluoro-5-(hydroxymethyl)-1-(9-phenylfluoren-9-yl)pyrrolidin-3-ol

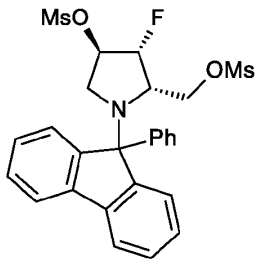


To a stirred mixture of methyl (2S,3R,4R)-3-fluoro-4-hydroxy-1-(9-phenylfluoren-9-yl)pyrrolidine-2-carboxylate (3.00 g, 7.44 mmol) in THF (100 mL) was added 1M $LiAlH_4$ in THF (15.0 mL, 15.0 mmol) dropwise at -60 °C under N_2. The reaction was stirred for 2 h at -60 °C. The reaction mixture was diluted with EtOAc (200 mL), washed with aq. potassium

sodium tartrate (100 mL), then brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified on silica gel, eluting with PE:EtOAc (1:1) to afford the title compound (1.85 g, 66.3%) as a light-yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dt, *J*=7.6, 0.9 Hz, 1H), 7.74 – 7.63 (m, 2H), 7.61 – 7.43 (m, 4H), 7.37 – 7.20 (m, 6H), 4.61 – 4.43 (m, 2H), 3.54 (d, *J*=10.0 Hz, 1H), 3.25 – 3.22 (m, 1H), 2.89 – 2.63 (m, 3H), 2.25 (s, 1H).

Preparation 91

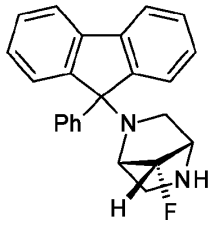
((2S,3R,4R)-3-Fluoro-4-((methylsulfonyl)oxy)-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidin-2-yl)methyl methanesulfonate



To a stirred mixture of (3R,4R,5S)-4-fluoro-5-(hydroxymethyl)-1-(9-phenylfluoren-9-yl)pyrrolidin-3-ol (1.00 g, 2.66 mmol) in THF (50 mL) was added TEA (1.62 g, 16.0 mmol) and methanesulfonyl chloride (1.22 g, 10.7 mmol) dropwise at 0 °C under N_2. When the reaction was complete by LC-MS, the resulting mixture was diluted with H_2O (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified with silica gel, eluting with PE:EtOAc (4:1 to 2:1) to afford the title compound (1.32 g, 93.4%) as a white solid. MS (ES) *m/z*=532 (M+1).

Preparation 92

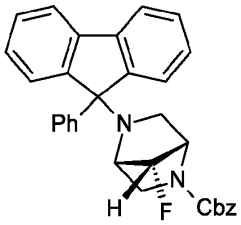
(1S,4S,7S)-7-Fluoro-2-(9-phenyl-9H-fluoren-9-yl)-2,5-diazabicyclo[2.2.1]heptane



A mixture of [(2S,3R,4R)-3-fluoro-4-(methanesulfonyloxy)-1-(9-phenylfluoren-9-yl)pyrrolidin-2-yl]methyl methanesulfonate (4.00 g, 7.52 mmol) in 2.0M NH_3 in IPA (210 mL, 420 mmol) was heated at 100 °C overnight. The mixture was allowed to cool to RT and was concentrated under reduced pressure. The residue was purified with silica gel, eluting with DCM:MeOH (12:1 to 10:1) to afford the title compound (1.00 g, 37.3%) as a light-yellow solid. MS (ES) *m/z*=357 (M+1).

Preparation 93

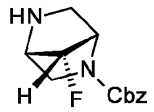
Benzyl (1S,4S,7S)-7-fluoro-2-(9-phenyl-9H-fluoren-9-yl)-2,5-diazabicyclo[2.2.1]heptane



To a stirred mixture of (1S,4S,7S)-7-fluoro-2-(9-phenylfluoren-9-yl)-2,5-diazabicyclo[2.2.1]heptane (1.20 g, 3.37 mmol) and DIEA (1.31 g, 10.1 mmol) in DCM (100 mL) was added Cbz-Cl (0.86 g, 5.05 mmol) in portions at 0 °C. The resulting mixture was stirred for 2 h at RT, then was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (9:1~5:1) to afford the product (1.41 g, 85.4%) as a white solid. MS (ES) *m/z*=491 (M+1).

Preparation 94

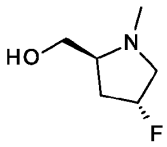
Benzyl (1S,4S,7R)-7-fluoro-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



To a stirred solution of benzyl (1S,4S,7R)-7-fluoro-5-(9-phenylfluoren-9-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (1.41 g, 2.88 mmol) in DCM (16 mL) was added TFA (8.00 mL, 106 mmol) at RT. The resulting mixture was stirred for 1 h, then was concentrated under reduced pressure. The residue was dissolved in EtOAc (300 mL) and washed with sat. aq. $NaHCO_3$ (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the product as a white solid (1.3 g, crude) which was used in a subsequent step without further purification. MS (ES) *m/z*=251 (M+1).

Preparation 95

((2S,4R)-4-Fluoro-1-methylpyrrolidin-2-yl)methanol

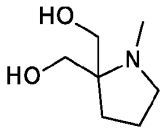


To a stirred solution of 1-(*tert*-butyl) 2-methyl (2S,4R)-4-fluoropyrrolidine-1,2-dicarboxylate (20.0 g, 80.9 mmol, 1.0 eq.) in THF (200 mL) was added $LiAlH_4$ (485.3 mL, 485.3 mmol, 6.0 eq., 1M in THF) dropwise at -50 °C under N_2. The resulting mixture was stirred for 1 h at -50 °C under N_2. Then the mixture was stirred for 2 h at 70 °C under N_2. The mixture was cooled to 0 °C and quenched by the addition of H_2O. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl and were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (5:1) to afford the product (2.94 g, 27.3%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (dm, *J*=55.7 Hz, 1H), 3.74 (dd, *J*= 3.3, 11.4 Hz, 1H), 3.54 (ddd, *J*=

26.4, 11.9, 5.1 Hz, 1H), 3.48 (dd, *J*= 2.0, 11.2 Hz, 1H), 2.89 (s, 1H), 2.82 (m, 1H), 2.67 (ddd, *J*= 32.4, 11.9, 2.5 Hz, 1H), 2.43 (s, 3H), 2.13 (m, 1H), 2.06 (m, 1H).

Preparation 96

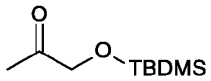
[2-(Hydroxymethyl)-1-methylpyrrolidin-2-yl]methanol



[2-(Hydroxymethyl)pyrrolidin-2-yl]methanol (500 mg, 3.81 mmol, 1.0 eq.) and HCHO (343 mg, 11.4 mmol, 3.0 eq.) in MeOH (10.00 mL) was stirred for 0.5 h at RT. Then $NaBH_3CN$ (479 mg, 7.62 mmol, 2.00 eq.) was slowly added at 0 °C. The resulting mixture was stirred for 4 h at RT. The reaction was quenched with H_2O (5 mL) at 0 °C and then diluted with H_2O. The mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified on silica gel, eluting with DCM/MeOH/NH_4OH (100:10:1 to 100:20:1) to afford the product (400 mg, 72.3%) as a yellow oil. (M+1). ^1H NMR (300 MHz, DMSO-*d6*+D_2O) δ 4.31 – 4.08 (m, 2H), 3.38 – 3.23 (m, 4H), 2.72 (t, *J*=6.3 Hz, 2H), 2.33 s, 3H), 1.76 – 1.50 (m, 4H).

Preparation 97

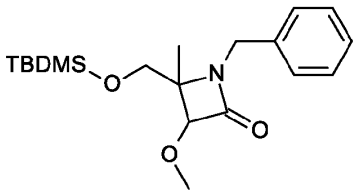
1-[*tert*-Butyl(dimethyl)silyl]oxypropan-2-one



A solution of 1-hydroxypropan-2-one (25.00 g, 337.48 mmol, 1.0 eq.), *tert*-butyldimethylchlorosilane (76.30 g, 506.22 mmol, 1.50 eq.) and imidazole (50.54 g, 742.45 mmol, 2.20 eq.) in DCM (100 mL) was stirred for 4 h at RT under N_2. The resulting mixture was diluted with EtOAc (400 mL), washed with H_2O (3 x 500 mL), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (0-5%) to afford the product (56.00 g, 88.10%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (s, 2H), 2.17 (s, 3H), 0.93 (s, 9H), 0.09 (s, 6H).

Preparation 98

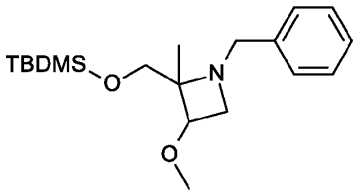
1-Benzyl-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-methoxy-4-methyl-azetidin-2-one



A mixture of 1-[*tert*-butyl(dimethyl)silyl]oxypropan-2-one (30.00 g, 159.28 mmol, 1.00 eq.), benzylamine (17.07 g, 159.30 mmol, 1.00 eq.) and 4Å molecular sieves (30 g) in DCM (300 mL) was stirred for 12 h at 45 °C under N_2. To the mixture was added TEA (37.23 g, 367.92 mmol, 2.31 eq.) and then methoxyacetyl chloride (22.47 g, 207.06 mmol, 1.30 eq.) was added dropwise over 30 min at -78 °C. The reaction was allowed to warm to RT and stirred for 12 h. The mixture was filtered and the filter cake was washed with DCM (200 mL). The filtrate was diluted with H_2O (300 mL) and was extracted with DCM (3 x 300 mL). The combined organic layers were washed with sat. aq. NaCl (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (10%) to afford the product (9.00 g, 12.12%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 5H), 4.45 – 4.27 (m, 2H), 4.10 (s, 1H), 3.71 – 3.56 (m, 2H), 3.50 (s, 3H), 1.22 (s, 3H), 0.86 (s, 9H), 0.05 – -0.09 (m, 6H).

Preparation 99

(1-Benzyl-3-methoxy-2-methyl-azetidin-2-yl)methoxy-*tert*-butyl-dimethyl-silane

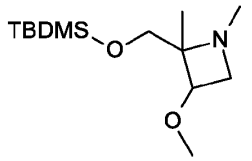


To a stirred mixture of $AlCl_3$ (1.85 g, 13.85 mmol, 1.21 eq.) in THF (20 mL) was added a solution of $LiAlH_4$ (0.64 g, 16.82 mmol, 1.47 eq.) in THF (10 mL) dropwise at -10 °C under N_2. The resulting mixture was allowed to warm to RT and stir for 3 h. After cooling

to -10 °C a solution of 1-benzyl-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-methoxy-4-methyl-azetidin-2-one (4.00 g, 11.4 mmol, 1.0 eq.) in THF (10 mL) was added dropwise. The mixture was allowed to warm to RT and stir for additional 1 h. Then H_2O (0.64 mL) was added followed by 15% NaOH (0.64 mL) and additional H_2O (1.92 mL). The mixture was filtered and the filter cake was washed with THF (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc/PE (0-10%) to afford the product (1.56 g, 40.63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.10 (m, 5H), 3.80 – 3.65 (m, 3H), 3.61 (dd, *J*=6.4, 4.7 Hz 1H), 3.53 (d, *J*=13.2 Hz, 1H), 3.23 (d, *J*=4.9 Hz, 4H), 2.98 (dd, *J*=7.7, 4.7 Hz, 1H), 1.22 (s, 3H), 0.83 (s, 9H), 0.00 (d, 6H).

Preparation 100

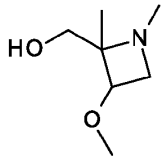
tert-Butyl-[(3-methoxy-1,2-dimethyl-azetidin-2-yl)methoxy]-dimethyl-silane



To a solution of (1-benzyl-3-methoxy-2-methyl-azetidin-2-yl)methoxy-*tert*-butyl-dimethyl-silane (1.1 g, 3.28 mmol, 1.00 eq.) in MeOH (10 mL) was added Pd/C (110 mg, 10%wt) under N_2. The mixture was hydrogenated at RT for 24 h under H_2 atmosphere using a hydrogen balloon. To the above mixture was added $(HCHO)_n$ (0.20 g, 6.66 mmol, 2.03 eq.) at RT. The resulting mixture was placed under a H_2 atmosphere again (balloon) and stirred for additional 10 h at RT. The mixture was filtered and the filter cake was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to give the product (0.8 g, crude) as a colorless oil, which was used in a subsequent step without further purification.

Preparation 101

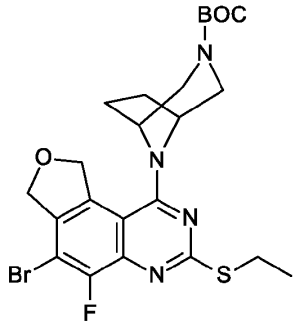
(3-Methoxy-1,2-dimethyl-azetidin-2-yl)methanol



A solution of *tert*-butyl-[(3-methoxy-1,2-dimethyl-azetidin-2-yl)methoxy]-dimethyl-silane (800 mg, 3.08 mmol, 1 eq.) in 4M HCl/MeOH (10.00 mL) was stirred for 10 h at RT under N_2. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH/NH_3H_2O (15:3:0.2) to afford the product (250 mg, 55.84%) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, *J*=6.3, 4.8 Hz, 1H), 3.78 – 3.66 (m, 2H), 3.46 (dd, *J*=8.0, 6.3 Hz, 1H), 3.36 – 3.28 (m, 4H), 2.35 (s, 3H), 1.18 (s, 3H).

Preparation 102

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

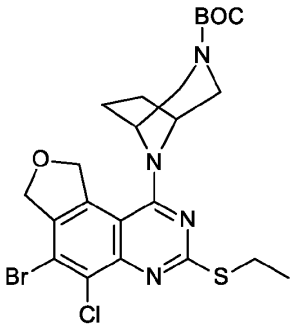
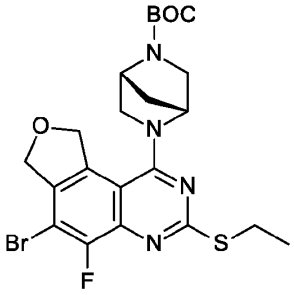


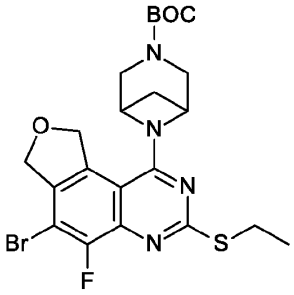
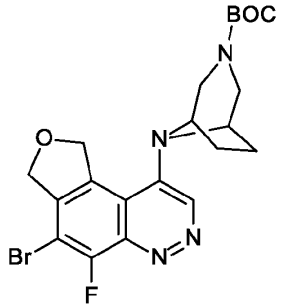
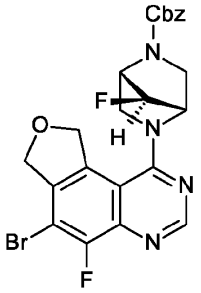
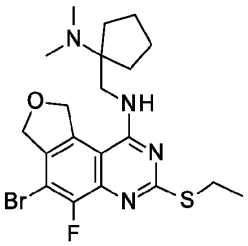
A suspension of 6-bromo-1-chloro-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline (21.0 g, 57.8 mmol) in ACN (580 mL) was charged with *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (15.2 g, 69.5 mmol, 1.20eq.) and DIPEA (40 mL, 229 mmol, 4 eq.) and was stirred at RT for 90 min. H_2O (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)

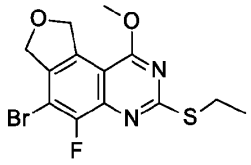
as a white solid, MS (ES) *m/z*=539 (M+1).

The following compounds in Table 5 were prepared in similar manner as described in Preparation 102. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 5:

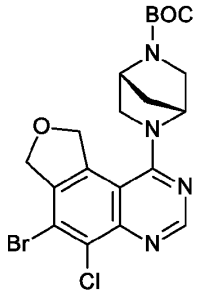
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
103	*tert*-Butyl 8-(6-bromo-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		555
104	*tert*-Butyl (1R,4R)-5-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		525

105	*tert*-Butyl 6-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		525
106	*tert*-Butyl 8-(4-bromo-5-fluoro-1,3-dihydrofuro[3,4-f]cinnolin-9-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		479
107	Benzyl (1S,4S,7R)-5-(6-bromo-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-7-fluoro-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		517
233	6-Bromo-N-[[1-(dimethylamino)cyclopentyl]methyl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-amine		469

234	6-Bromo-3-ethylsulfanyl-5-fluoro-1-methoxy-7,9-dihydrofuro[3,4-f]quinazoline		359

Preparation 108

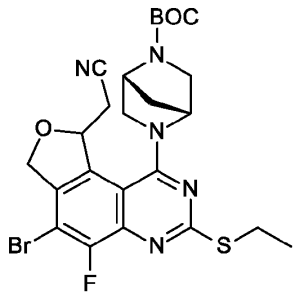
tert-Butyl (1R,4R)-5-(6-bromo-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



To a stirred mixture of 6-bromo-5-chloro-7H,9H-furo[3,4-f]quinazolin-1-ol (3 g, 9.95 mmol) and BrOP (5.79 g, 14.92 mmol) in 1,4-dioxane (30 mL) was added TEA (6.92 mL, 49.75 mmol) dropwise at RT. The resulting mixture was stirred for 4 h at 80 °C under N_2. Cooled to RT, and added *tert*-butyl (1R,4R)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3.95 g, 19.90 mmol). Heating was resumed at 80 °C under N_2. After 2h, the mixture was allowed to cool to RT, diluted with H_2O (200 mL) and extracted with EtOAc (3 x 500mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (3:1 to 2:1) to afford the title compound (780 mg, 14.6%) as a yellow solid. MS (ES) *m/z* = 481 (M+1).

Preparation 109

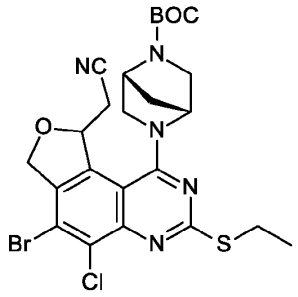
tert-Butyl (1R,4R)-5-[6-bromo-9-(cyanomethyl)-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



A suspension of 2-(6-bromo-1-chloro-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-9-yl)acetonitrile (4.40 g, 8.85 mmol) in DMF (80 mL) cooled in an ice bath was charged with *tert*-butyl (1R,4R)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.00 g, 9.78 mmol) and DIPEA (3.10 mL, 17.8 mmol). The reaction was stirred at RT for 2 h. DMF was removed under reduced pressure. The residue was dissolved in EtOAc (500 mL), washed with sat. aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica column chromatography, eluting with EtOAc/Hex (10-100%) to afford the title compound (4.00g, 80%) as a light-brown solid. MS (ES) *m/z*=564 (M+1).

Preparation 110

tert-Butyl (1R,4R)-5-[6-bromo-5-chloro-9-(cyanomethyl)-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

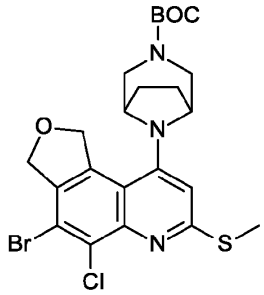


2-(6-Bromo-1,5-dichloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-9-

yl)acetonitrile was used in an analogous manner to the method of Preparation 108 to obtain the title compound (0.53 g, 76%) as yellow solid. MS (ES) *m/z*=580 (M+1).

Preparation 111

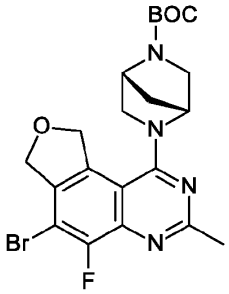
tert-Butyl 8-(4-bromo-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



In a dry reaction vessel, DMSO (198 mL) was purged with N_2 using a gas dispersion tube for 5 min. DIPEA (3.9 mL, 22 mmol) was added and purged for an additional 3 min. Solid 4-bromo-5,9-dichloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinoline (8.1 g, 22 mmol) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (19 g, 89 mmol, 4 eq.) was added and the reaction vessel was sealed and heated to 130 °C for 48 h. After cooling to RT, the reaction was poured into a separatory funnel and diluted with DCM (1.5 L), washed with H_2O (3 x 500 mL), separated and concentrated. The residue was purified on silica (100% DCM to 5% EtOAc/DCM) to obtain the title compound (5.36 g. 45%) as a white solid. MS (ES) *m/z*= 540 (M+1).

Preparation 112

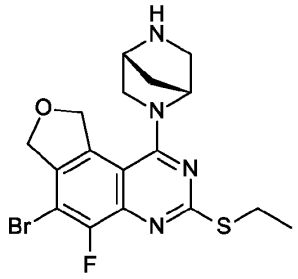
tert-Butyl (1R,4R)-5-(6-bromo-5-fluoro-3-methyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



A mixture of 6-bromo-5-fluoro-3-methyl-7,9-dihydrofuro[3,4-f]quinazolin-1-ol (280 mg, 0.936 mmol), phosphonitrilic chloride trimer (423 mg, 1.22 mmol) and DIEA (605 mg, 4.68 mmol) in ACN was stirred for 5 h at 50 °C under N_2. After cooling to RT, added *tert*-butyl (1R,4R)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (119 mg, 0.602 mmol) and DIEA (605 mg, 4.68 mmol) and the resulting mixture was stirred at for 2h. The reaction was stirred for additional 2 h at RT. The mixture was diluted with H_2O (150 mL), extracted with EtOAc (3 x 50 mL) and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (3:1 to 1:1) to afford the title compound (280 mg, 62.3%) as a yellow solid. MS (ES) *m/z*=479 (M+1).

Preparation 113

6-Bromo-1-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline

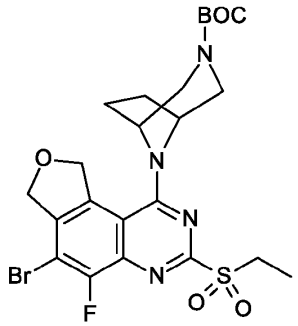


tert-Butyl (1R,4R)-5-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-

f]quinazolin-1-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (500 mg, 0.951 mmol) was stirred in DCM (5 mL, 78.00 mmol). TFA (2 mL, 26.45 mmol) was added. The reaction vessel was capped and stirred at RT for ~ 18 h. The reaction solution was placed over an 10g SCX column, washed with 3 column volumes of MeOH, then eluting with 3 column volumes of 2N NH_3 in MeOH. The basic fraction was concentrated to give the title compound (426 mg, quantitative) as a thick oil. MS (ES) *m/z*=426 (M+1).

Preparation 114

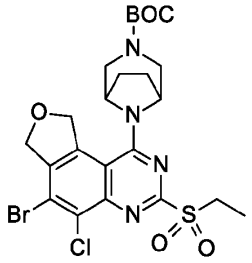
tert-Butyl 8-(6-bromo-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



A solution of *tert*-butyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (4.3 g, 8.0 mmol) in DCM (40 mL) was charged with *m*CPBA (6.21 g, 25.2 mmol, 3.2 eq.) and stirred at RT for 90 min. The mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$, and brine. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica, eluting with EtOAc/Hex (20-80%) to obtain the title compound (3.0 g, 66%) as a white solid. MS (ES) *m/z*=571 (M+1).

Preparation 235

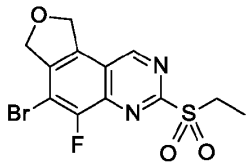
tert-Butyl 8-(6-bromo-5-chloro-3-ethylsulfonyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl 8-(6-bromo-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate was used in an analogous manner to the method of Preparation 114 to obtain the title compound (13.5 g, 86%). MS (ES) *m/z*=587,589 (M+1, Br).

Preparation 302

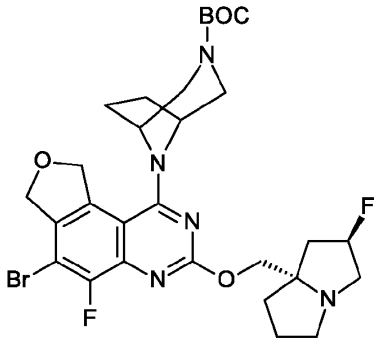
6-Bromo-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline



6-Bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline was used in an analogous manner to the method of Preparation 114 to obtain the title compound (1.00 g, 92%). MS (ES) *m/z*=361,363 (M+1, Br).

Preparation 115

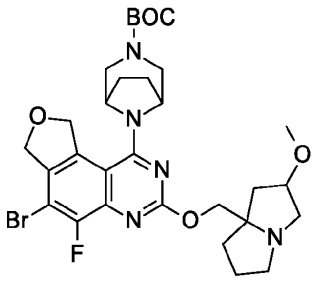
tert-Butyl 8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



To a mixture of [(2R,8S)-2-Fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (2.26 g, 13.8 mmol) in THF (110 mL) under N_2 was added dropwise LiHMDS in THF (13.7 mL, 13.7 mmol, 1.0 M) and stirred for 20 min. To this solution was added dropwise via syringe, *tert*-butyl 8-(6-bromo-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (6.54 g, 11.4 mmol) in THF (40 mL). After 35 min, the reaction was diluted with EtOAc (250 mL) and washed with brine. The aqueous was extracted with EtOAc (2 x 200 mL) and the combined organics were dried over Na_2SO_4 and concentrated to a tan solid. The crude material was purified by silica, eluting with 0-10% MeOH/DCM to afford the title compound (7.0 g, 96%) as a light-tan solid. MS (ES) *m/z*= 636 (M+1).

Preparation 236

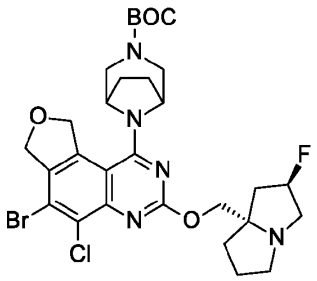
tert-Butyl 8-[6-bromo-5-fluoro-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



(2-Methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methanol was used in an analogous manner to the method of Preparation 115 to obtain the title compound (4.5 g, 85%). MS (ES) *m/z*=648,650 (M+1, Br).

Preparation 237

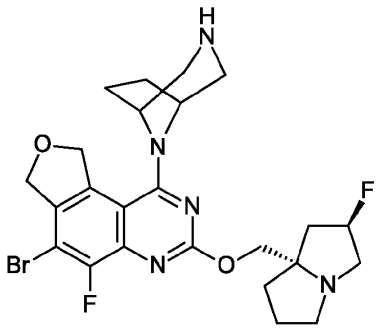
tert-Butyl 8-[6-bromo-5-chloro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl 8-(6-bromo-5-chloro-3-ethylsulfonyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate was used in an analogous manner to the method of Preparation 115 to obtain the title compound (12.8 g, 85%). MS (ES) *m/z*=652,654 (M+1, Br).

Preparation 116

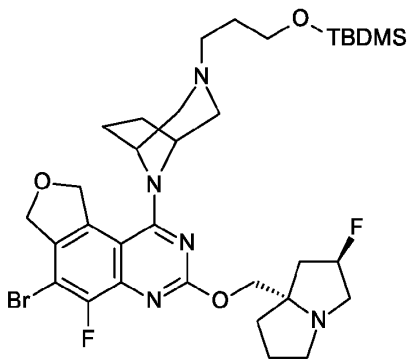
6-Bromo-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazoline



tert-Butyl 8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate was used in an analogous manner to the method of Preparation 113 and was isolated by partitioning between DCM and sat. aq. $NaHCO_3$ to obtain the title compound (0.83 g, 99%) as a pale-yellow foam. MS (ES) *m/z*=536 (M+1).

Preparation 117

3-[8-[6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]propoxy-*tert*-butyl-dimethyl-silane

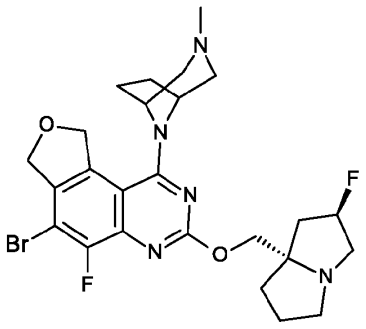


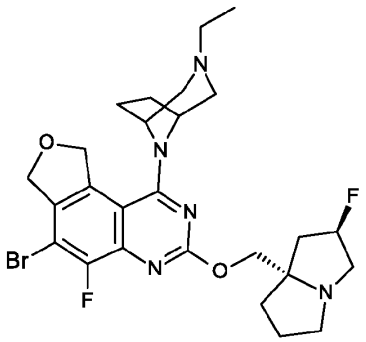
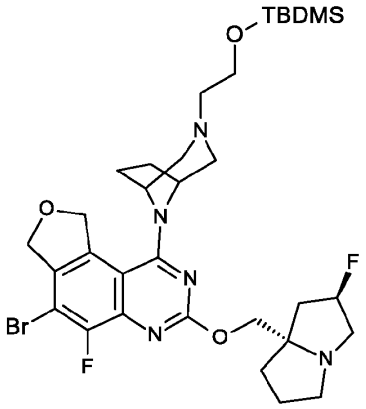
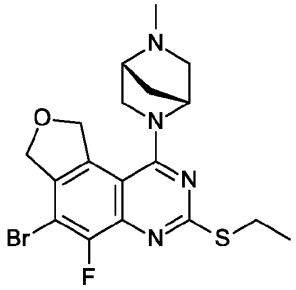
A solution of 6-bromo-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-

fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazoline (0.900 g, 1.68 mmol) in DCM (17 mL) was treated with 3-[(*tert*-butyldimethylsilyl)oxy]-1-propanal (0.998 g, 5.03 mmol) and $NaBH(OAc)_3$ (1.12 g, 5.02 mmol) and was stirred at RT for 2 h. The reaction mixture was treated with sat. aq. $NaHCO_3$ and was stirred for 15 min. H_2O was added and the layers were separated. The aqueous layer was extracted 2x with DCM. The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica, eluting with 0% to 4% 7N NH_3/MeOH in DCM to afford the title compound (0.844 g, 71%) as an off-white solid. MS (ES) *m/z*=708 (M+1).

The following compounds in Table 6 were prepared in a similar manner as described for Preparation 117, using the appropriate aldehyde. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

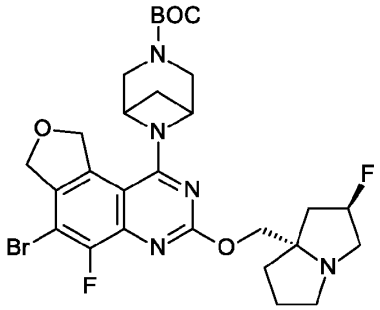
Table 6:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
118	6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazoline		550

119	6-Bromo-1-(3-ethyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazoline		564
120	2-[8-[6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]ethoxy-*tert*-butyl-dimethyl-silane		694
121	6-Bromo-3-ethylsulfanyl-5-fluoro-1-[(1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7,9-dihydrofuro[3,4-f]quinazoline		439

Preparation 122

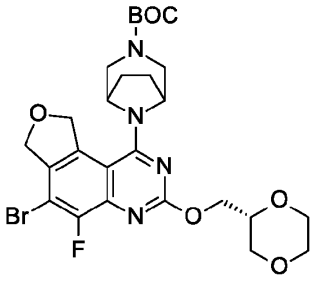
tert-Butyl 6-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate



tert-Butyl 6-(6-bromo-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate was used in an analogous manner to the method of Preparation 115 to obtain the title compound (0.8 g, 84%) as light-yellow foam. MS (ES) *m/z*=622 (M+1).

Preparation 303

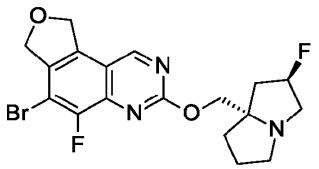
tert-Butyl 8-[6-bromo-3-[[(2R)-1,4-dioxan-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



[(2S)-1,4-Dioxan-2-yl]methanol was used in an analogous manner to the method of Preparation 115 to obtain the title compound (1.72 g, 97%) as white solid. MS (ES) *m/z*=595,597 (M+1, Br).

Preparation 304

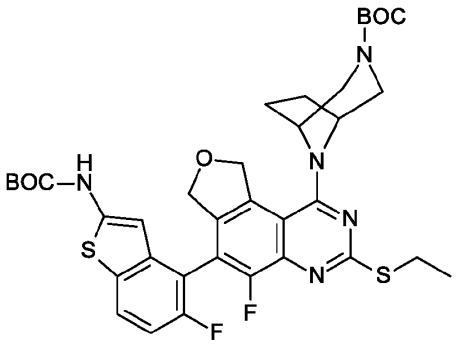
6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolinediazabicyclo[3.2.1]octane-3-carboxylate



6-Bromo-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline was used in an analogous manner to the method of Preparation 115 to obtain the title compound (0.11 g, 62%) as off-white solid. MS (ES) *m/z*=426,428 (M+1, Br).

Preparation 123

tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

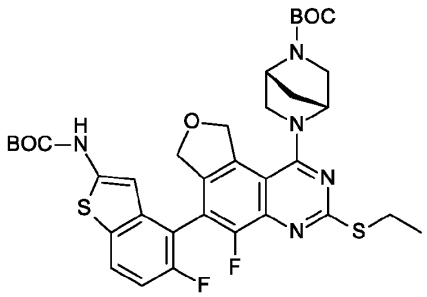


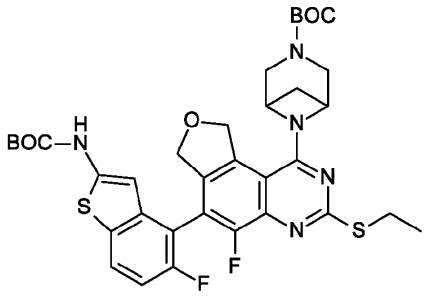
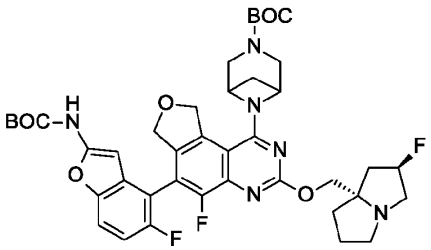
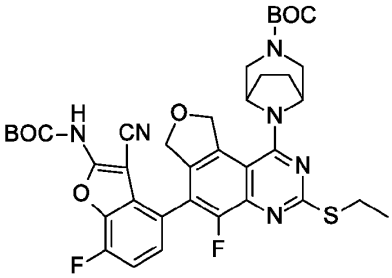
A 250 mL 3-necked RBF, equipped with a thermocouple, condenser and N_2 sparge line, was charged with a suspension of *tert*-butyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (5.00 g, 9.27 mmol) and *tert*-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluoro-benzothiophen-2-yl]carbamate (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

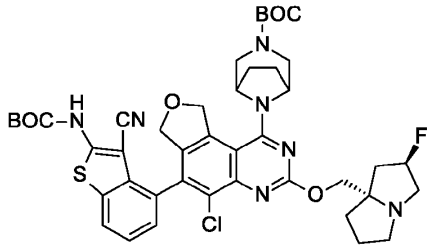
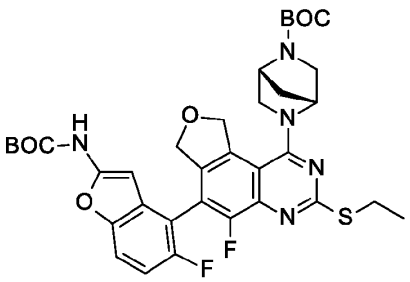
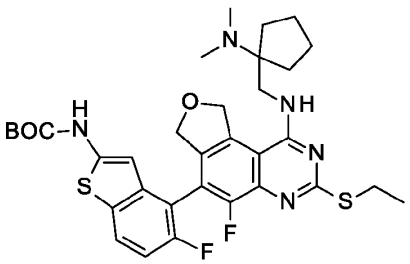
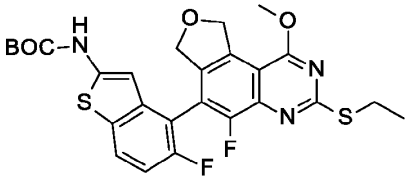
temperature was allowed to reach 70 °C and was stirred for 90 min. The reaction was cooled to RT, then the mixture was diluted with EtOAc, washed with H_2O and partitioned. The aqueous phase was extracted with EtOAc (100 mL), and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, 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).

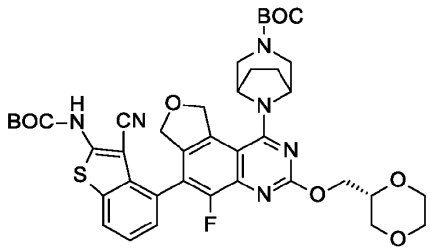
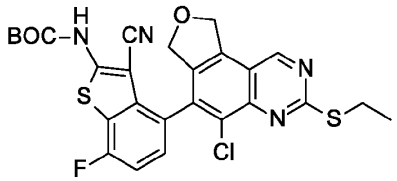
The following compounds in Table 7 were prepared in similar manner as described in Preparation 123. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 7:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
124	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		712

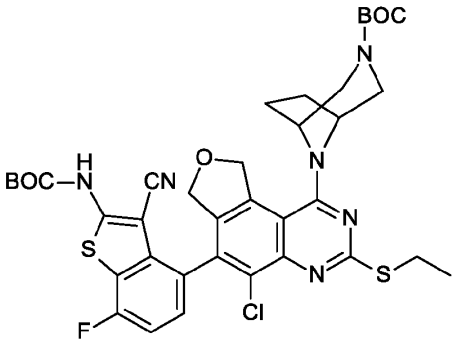
125	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		712
238	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		793
239	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzofuran-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		735

240	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-benzothiophen-4-yl]-5-chloro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		846
241	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzofuran-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		696
242	*tert*-Butyl N-[4-[1-[[1-(dimethylamino)cyclopentyl]methylamino]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophen-2-yl]carbamate		656
243	*tert*-Butyl N-[4-(3-ethylsulfanyl-5-fluoro-1-methoxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluoro-benzothiophen-2-yl]carbamate		546

305	*tert*-Butyl 8-[6-[2-(tert-butoxycarbonylamino)-3-cyano-benzothiophen-4-yl]-3-[[(2R)-1,4-dioxan-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		789
306	*tert*-Butyl N-[4-(5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		557

Preparation 126

tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

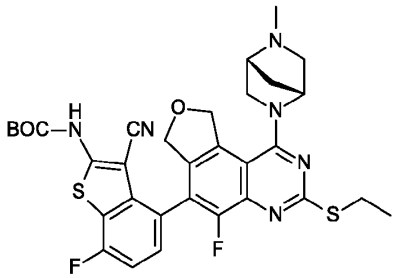
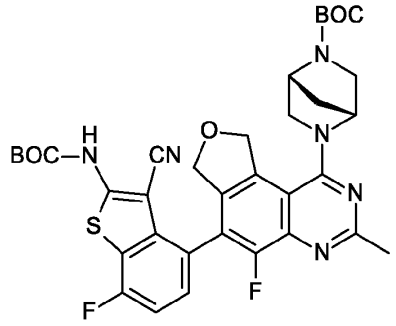


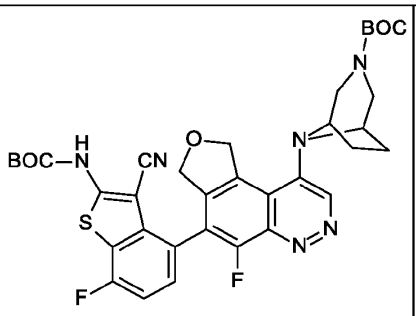
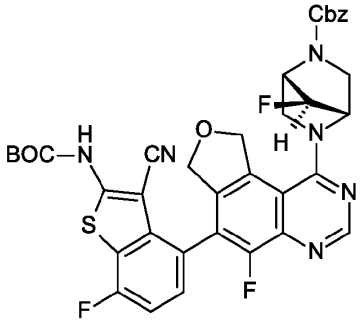
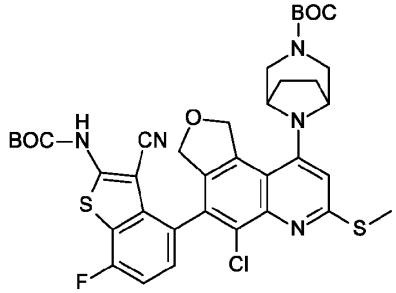
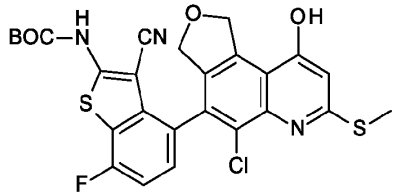
A solution of *tert*-butyl 8-(6-bromo-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.785 g, 1.36 mmol) in THF (10 mL) was charged with *tert*-butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-yl]carbamate (0.826 g, 2.04 mmol, 1.5 eq.) and Cs_2CO_3 (1.39 g, 4.27

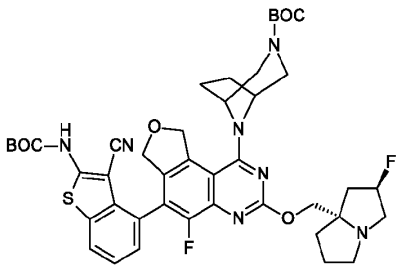
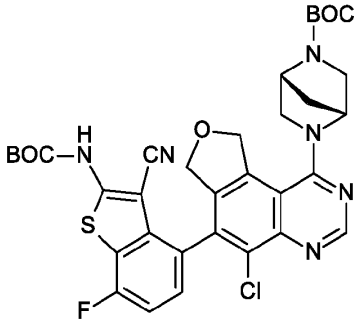
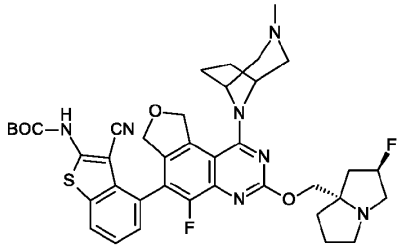
mmol, 3.15 eq.). The mixture was stirred and sparged with N_2 for 10 min. Pd-117 (0.202 g, 0.274 mmol, 0.20 eq.) was added and the mixture was sparged for another 5 min, then the reaction flask was fitted with a reflux condenser and heated at 70 °C for 6 h. The reaction was cooled to RT, diluted with H_2O (1 mL) and was stirred for 5 min. The mixture was filtered through a 3.0 g ISOLUTE® cartridge (Biotage, LLC; Charlotte, NC), eluting with EtOAc until the effluent came off clear and colorless. The filtrate was concentrated and purified on silica, eluting with 20% EtOAc/Hex to obtain the title compound (0.743 g, 70%) as a white solid. MS (ES) *m/z*=767 (M+1).

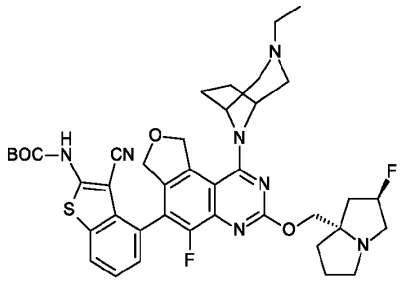
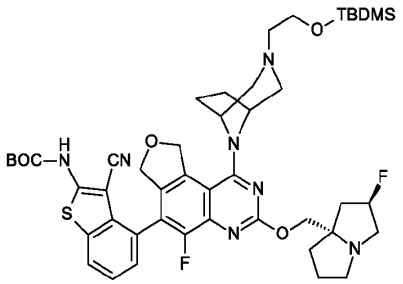
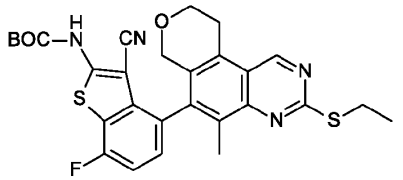
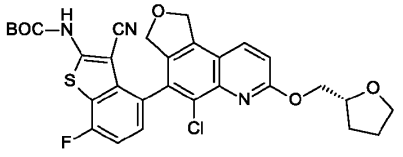
The following compounds in Table 8 were prepared in similar manner as described for Preparation 126. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

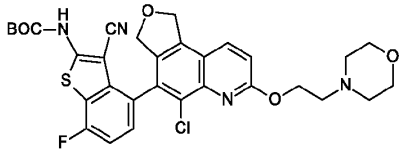
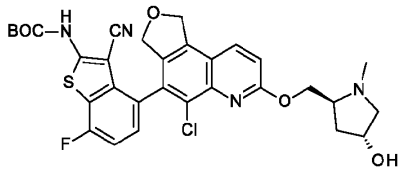
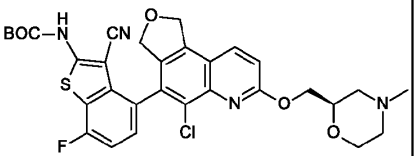
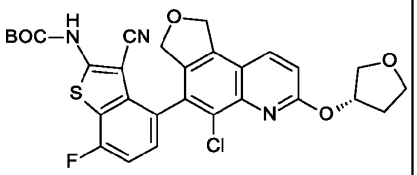
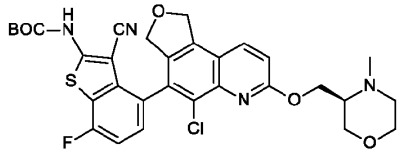
Table 8:

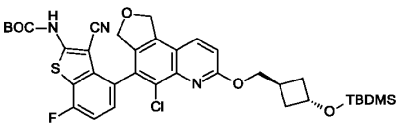
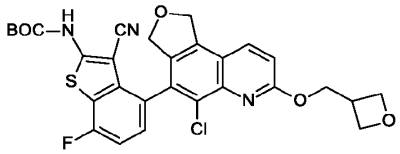
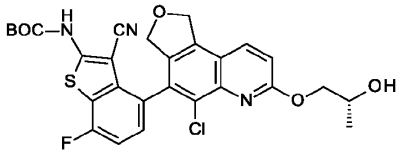
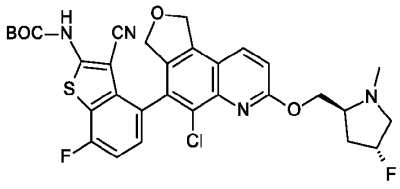
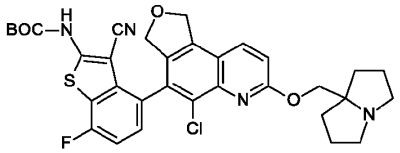
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
127	*tert*-Butyl N-[3-cyano-4-[3-ethylsulfanyl-5-fluoro-1-[(1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophen-2-yl]carbamate		651
128	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-3-methyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		691

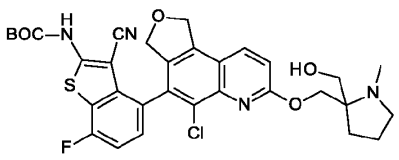
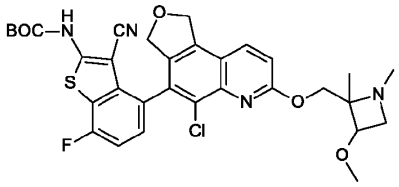
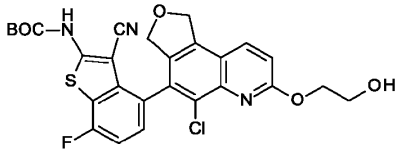
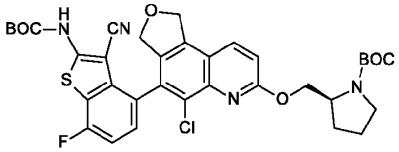
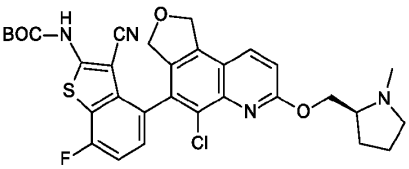
129	*tert*-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-1,3-dihydrofuro[3,4-f]cinnolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		691
130	Benzyl (1S,4S,7R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-7-fluoro-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		729
131	*tert*-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		752
132	*tert*-Butyl N-[4-(5-chloro-9-hydroxy-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		558

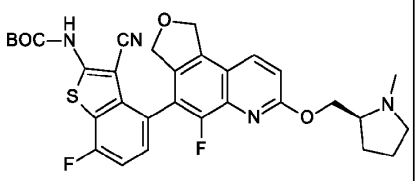
133	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-benzothiophen-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		830
134	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		693
135	*tert*-Butyl N-[3-cyano-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophen-2-yl]carbamate		744

136	*tert*-Butyl N-[3-cyano-4-[1-(3-ethyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophen-2-yl]carbamate		758
137	*tert*-Butyl N-[4-[1-[3-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-benzothiophen-2-yl]carbamate		888
138	*tert*-Butyl N-[3-cyano-4-(3-ethylsulfanyl-5-methyl-9,10-dihydro-7H-pyrano[4,3-f]quinazolin-6-yl)-7-fluoro-benzothiophen-2-yl]carbamate		551
139	*tert*-Butyl N-[4-[5-chloro-7-[[(2R)-tetrahydrofuran-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		596

140	*tert*-Butyl N-[4-[5-chloro-7-(2-morpholinoethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		625
141	*tert*-Butyl N-[4-[5-chloro-7-[[(2S,4R)-4-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		625
142	*tert*-Butyl N-[4-[5-chloro-7-[[(2R)-4-methylmorpholin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		625
143	*tert*-Butyl N-[4-[5-chloro-7-[(3S)-tetrahydrofuran-3-yl]oxy-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		582
144	*tert*-Butyl N-[4-[5-chloro-7-[[(3S)-4-methylmorpholin-3-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		625

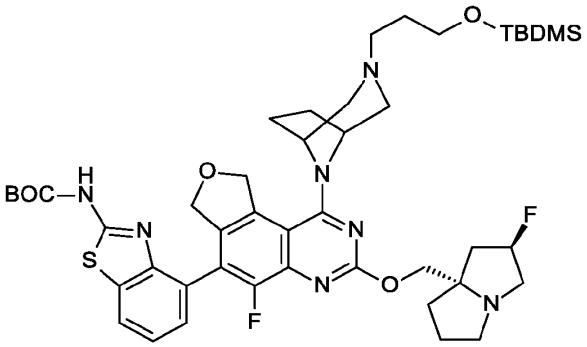
145	*tert*-Butyl N-[4-[7-[[3-[*tert*-butyl(dimethyl)silyl]oxycyclobutyl]methoxy]-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		710
146	*tert*-Butyl N-[4-[5-chloro-7-(oxetan-3-ylmethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		582
147	*tert*-Butyl N-[4-[5-chloro-7-[(2R)-2-hydroxypropoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		570
148	*tert*-Butyl N-[4-[5-chloro-7-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		627
149	*tert*-Butyl N-[4-[5-chloro-7-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		635

150	*tert*-Butyl N-[4-[5-chloro-7-[[2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		639
151	*tert*-Butyl N-[4-[5-chloro-7-[(3-methoxy-1,2-dimethyl-azetidin-2-yl)methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		639
152	*tert*-Butyl N-[4-[5-chloro-7-(2-hydroxyethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		556
153	*tert*-Butyl (2S)-2-[[4-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl]oxymethyl]pyrrolidine-1-carboxylate		695
154	*tert*-Butyl N-[4-[5-chloro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		609

155	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]benzothiophen-2-yl]carbamate, Isomer 1		593

Preparation 156

tert-Butyl N-[4-[1-[3-[3-[*tert*-butyl(dimethyl)silyl]oxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-1,3-benzothiazol-2-yl]carbamate

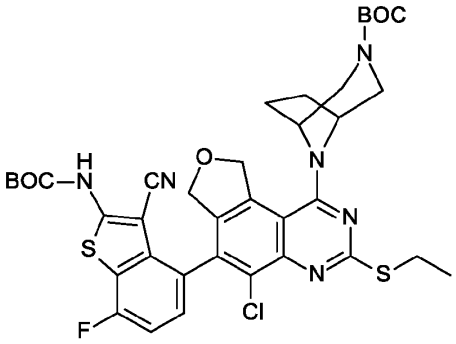


A mixture of 3-[8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]propoxy-*tert*-butyl-dimethyl-silane (0.110 g, 0.155 mmol), [2-(*tert*-butoxycarbonylamino)-1,3-benzothiazol-4-yl]boronic acid (US 10,968,214 B2; Preparation 17) (0.064 g, 0.217 mmol) and K_2CO_3 (0.064 g, 0.466 mmol) in 1,4-dioxane (1.5 mL) and H_2O (0.5 mL) was sparged with N_2 for 5 min before $Pd(PPh_3)_4$ (0.036 g, 0.310 mmol) was added. The resulting mixture was heated at 100 °C for 1.5 h, then cooled to RT and was partitioned between DCM and H_2O. The layers were separated, and the aqueous layer was extracted 2x with DCM. The organic layers were combined, passed through a hydrophobic frit (ISOLUTE® phase separator cartridge), and concentrated *in vacuo*. The residue was purified on silica (gradient 0 to 4% 7N NH_3/MeOH in DCM) to obtain the title

compound (0.098 g, 55%) as a pale-yellow solid. MS (ES) *m/z*=878 (M+1).

Preparation 157

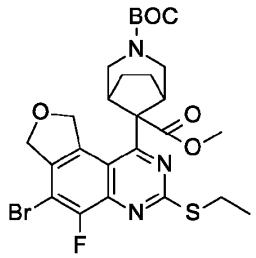
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, Isomer 2



tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (5.30 g, 6.94 mmol) was purified by SFC (Chiralpak® IC, 21x250 mm, 35% MeOH (with 0.5% DMEA), 65% CO_2, 80 mL/min). The second eluting isomer (t_{R2}=10.77 min) was collected, concentrated and lyophilized to afford the title compound (1.37 g, 42%) as a white solid with 96 % ee. MS (ES) *m/z*=767 (M+1).

Preparation 323

O3-*tert*-Butyl O8-methyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3-azabicyclo[3.2.1]octane-3,8-dicarboxylate



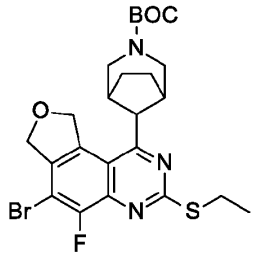
6-Bromo-1-chloro-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline (0.10 g, 0.28 mmol), O3-*tert*-butyl O8-methyl 3-azabicyclo[3.2.1]octane-3,8-dicarboxylate (0.22 g, 0.82 mmol), and bis(tri-*tert*-butylphosphine)palladium(0) (0.022 g, 0.042 mmol) were combined under nitrogen. Toluene (4 mL) was added and the mixture was sparged with nitrogen for 3 min and cooled to 0 °C. LiHMDS (0.8 mL, 0.8 mmol, 1M in THF) was added dropwise over 1.5 min and the reaction mixture was allowed to warm to room temperature. After 3 h, the reaction was poured into brine and extracted with ethyl acetate (2x). The combined organics were dried over $MgSO_4$, filtered and concentrated.

6-Bromo-1-chloro-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline (0.30 g, 0.83 mmol), O3-*tert*-butyl O8-methyl 3-azabicyclo[3.2.1]octane-3,8-dicarboxylate (0.67 g, 2.5 mmol), and bis(tri-*tert*-butylphosphine)palladium(0) (0.065 g, 0.12 mmol) were combined under nitrogen. Toluene (11 mL) was added and the mixture was sparged with nitrogen for 3 min and cooled to 0 °C. LiHMDS (2.4 mL, 2.4 mmol, 1M in THF) was added dropwise over 3 min and the reaction mixture was allowed to warm to room temperature. After 3 h, the reaction was poured into brine and extracted with ethyl acetate (2x). The combined organics were dried over $MgSO_4$, filtered and concentrated.

The two residues were combined and purified by silica gel column chromatography, eluting with 0 to 30% ethyl acetate in hexanes to afford the product (0.55 g, 83%). MS (ES) *m/z*=596,598 (M+1,Br).

Preparation 324

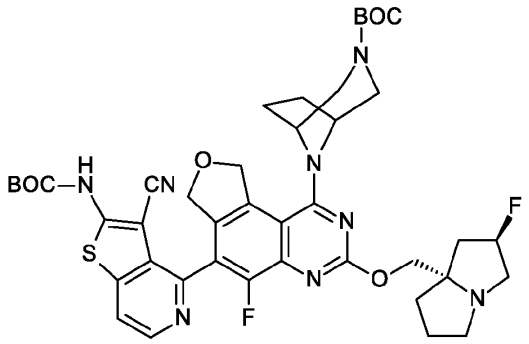
tert-Butyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3-azabicyclo[3.2.1]octane-3-carboxylate



A mixture of O3-*tert*-butyl O8-methyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3-azabicyclo[3.2.1]octane-3,8-dicarboxylate (0.99 g, 1.7 mmol) and LiCl (1.1 g, 25 mmol) in DMSO (9 mL) was stirred under microwave irradiation at 150 °C for 10 min. The reaction was diluted with water and extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with 0 to 30% ethyl acetate in hexanes to afford the product (0.11 g, 12%) as the faster eluting isomer. MS (ES) *m/z*=538,540 (M+1,Br).

Preparation 158

tert-Butyl 8-[6-[2-(tert-butoxycarbonylamino)-3-cyano-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

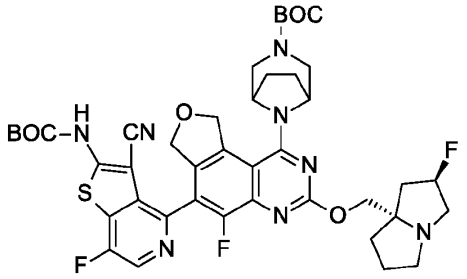


A mixture of *tert*-butyl 8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.500 g, 0.786 mmol), KOAc (0.231 g, 2.35 mmol) and bis(neopentyl glycolato)diboron (0.266 g, 1.18 mmol) in 1,4-dioxane (8 mL) was sparged with N_2 for 10 min. Pd-117 (0.057 g, 0.078 mmol) was added, and the resulting mixture was heated at 95 °C for 2 h. The reaction mixture was cooled to RT. H_2O (2.6 mL) was added, and the mixture was sparged with N_2 for 10 min. *tert*-Butyl N-(4-chloro-3-cyano-thieno[3,2-c]pyridin-2-yl)carbamate (0.245 g, 0.791 mmol), XPhos Pd G4 (0.071 g, 0.078 mmol) and K_3PO_4 (0.250 g, 1.18 mmol) were added, and the resulting mixture was heated at

85 °C for 1 h. The reaction mixture was cooled to RT and was partitioned between DCM and H_2O. The layers were separated, and the aqueous layer was extracted 2x with DCM. The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica (gradient 0 to 6% 7N NH_3/MeOH in DCM) to obtain the title compound (0.404 g, 62%) as a yellowish-tan solid. MS (ES) *m/z*=831 (M+1).

Preparation 244

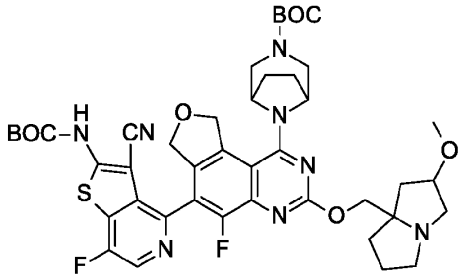
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate was used in an analogous manner to the method of Preparation 158 to obtain the title compound (0.667 g, 46%). MS (ES) *m/z*=849 (M+1).

Preparation 245

tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

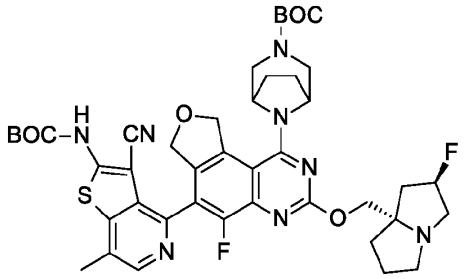


tert-Butyl 8-[6-bromo-5-fluoro-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-

yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were used in an analogous manner to the method of Preparation 158 to obtain the title compound (0.43 g, 42%). MS (ES) *m/z*=861 (M+1).

Preparation 246

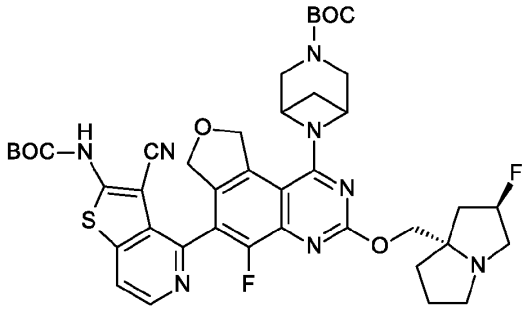
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-methyl-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl N-(4-chloro-3-cyano-7-methyl-thieno[3,2-c]pyridin-2-yl)carbamate was used in an analogous manner to the method of Preparation 158 to obtain the title compound (0.10 g, 24%). MS (ES) *m/z*=845 (M+1).

Preparation 159

tert-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate

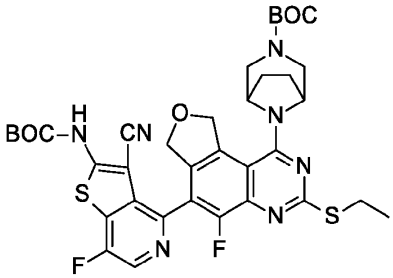


tert-Butyl 6-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-

8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate was used in an analogous manner to the method of Preparation 158 to obtain the title compound (0.101 g, 42.5%) as light-yellow solid. MS (ES) *m/z*=617 (M+1).

Preparation 307

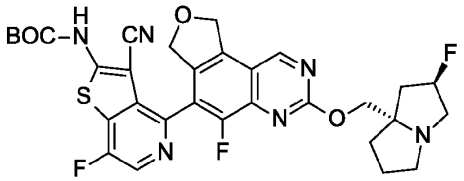
tert-Butyl 8-[6-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were used in an analogous manner to the method of Preparation 158 to obtain the title compound (2.15 g, 61%) as white solid. MS (ES) *m/z*=752 (M+1).

Preparation 308

tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate

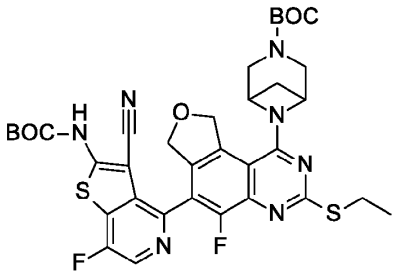


6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazoline and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were used in an analogous manner to the method of

Preparation 158 to obtain the title compound (0.080 g, 35%). MS (ES) *m/z*=639 (M+1).

Preparation 325

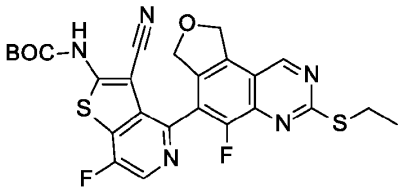
tert-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate



tert-Butyl 6-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were used in an analogous manner to the method of Preparation 158 to obtain the title compound. MS (ES) *m/z*=738 (M+1).

Preparation 326

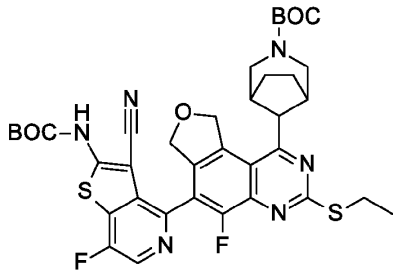
tert-Butyl N-[3-cyano-4-(3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate



6-Bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were used in an analogous manner to the method of Preparation 158 to obtain the title compound (43.0 g, 72%) as brown solid. MS (ES) *m/z*=542 (M+1).

Preparation 327

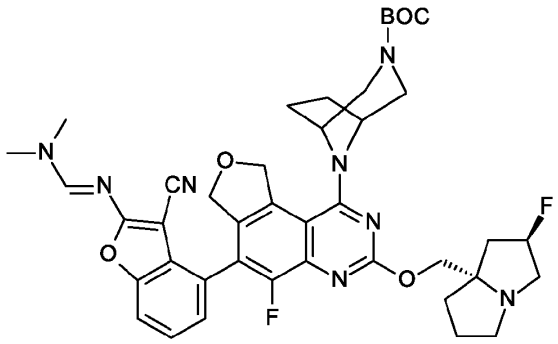
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3-azabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3-azabicyclo[3.2.1]octane-3-carboxylate and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were used in an analogous manner to the method of Preparation 158 to obtain the title compound (0.050 g, 9%). MS (ES) *m/z*=751 (M+1).

Preparation 160

tert-Butyl 8-[6-[3-cyano-2-[dimethylaminomethyleneamino]benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



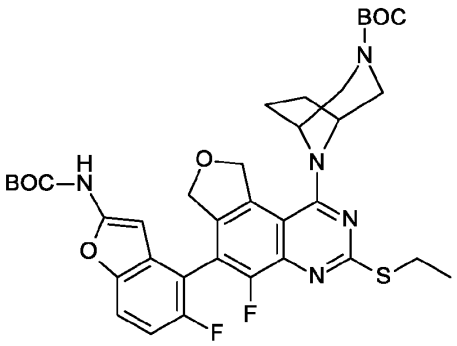
To a RBF was added *tert*-butyl 8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-

tert-butyl 8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-

carboxylate (1.10 g, 1.73 mmol), N'-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzofuran-2-yl]-N,N-dimethyl-formamidine (0.67 g, 2.07 mmol, 1.2 eq.), K_3PO_4 (0.550 g, 2.59 mmol, 1.5 eq.), Pd-118 (0.11 g, 0.173 mmol, 0.10 eq.), 1,4-dioxane (8.6 mL), and H_2O (1.7 mL). The mixture sparged with N_2, then heated at 90 °C for 3 h. The reaction was cooled, diluted with EtOAc and was washed with sat. aq. $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica (0-10% MeOH/DCM) to obtain the title compound (0.78 g, 58.7%). MS (ES) *m/z*=769 (M+1).

Preparation 161

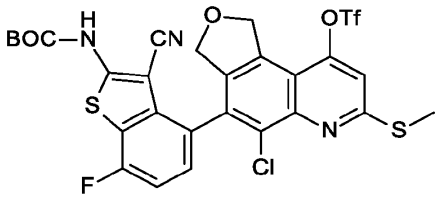
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzofuran-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl 8-(6-bromo-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate and *tert*-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluoro-benzofuran-2-yl]carbamate were used in an analogous manner to the method of Preparation 160 to obtain the title compound (0.375 g, 95.0%). MS (ES) *m/z*=710 (M+1).

Preparation 162

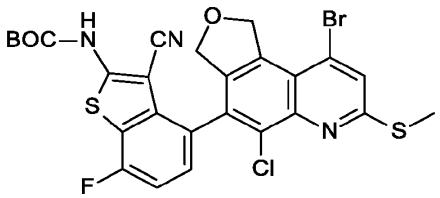
[4-[2-(*tert*-Butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl] trifluoromethanesulfonate



To a stirred mixture of *tert*-butyl N-[4-(5-chloro-9-hydroxy-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (7.5 g, 13.44 mmol, 1 eq.) and 2,6-lutidine (3.31 g, 30.91 mmol, 2.3 eq.) in DCM (100 mL) were added DMAP (0.25 g, 2.01 mmol, 0.15 eq.) and Tf_2O (7.58 g, 26.88 mmol, 2 eq.) dropwise at 0 °C under N_2. The resulting mixture was stirred for 2 h at 0 °C. The mixture was concentrated under reduced pressure and the residue was purified on silica, eluting with PE:EtOAc (3:1 to 1:1) to afford the title compound (8.0 g, 86%) as a light-yellow solid. MS (ES) *m/z*=690 (M+1).

Preparation 163

tert-Butyl N-[4-(9-bromo-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate

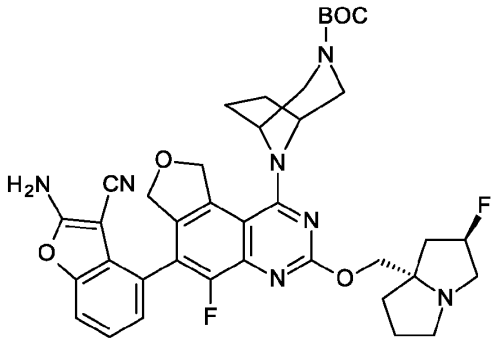


To a stirred solution of [4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl] trifluoromethanesulfonate (8.0 g, 11.5 mmol, 1 eq.) in ACN (100 mL) was added LiBr (20.13 g, 231.8 mmol, 20 eq.). The resulting mixture was stirred for 18 h at 85 °C. The mixture was concentrated under reduced pressure, then poured into H_2O (200 mL). After filtration, the filtrate cake was dried under vacuum at 40 °C to afford the crude, which was then suspended

in 1,4-dioxane (70 mL) and charged with di-*tert*-butyl dicarbonate (3.77 g, 17.28 mmol, 1.5 eq.) and DMAP (0.31 g, 2.53 mmol, 0.22 eq.). The resulting mixture was stirred for 2 h at RT, then concentrated under reduced pressure. The residue was purified on silica, eluting with DCM/EtOAc (15:1 to 10:1) to obtain the title compound (6.0 g, 84%) as a yellow solid. MS (ES) *m/z*=620 (M-1).

Preparation 164

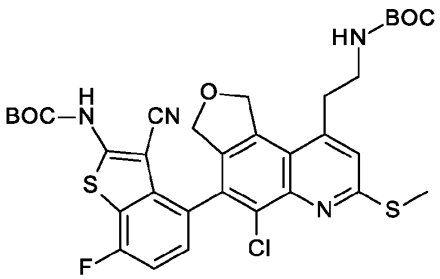
tert-Butyl 8-[6-(2-amino-3-cyano-benzofuran-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



To a RBF was added *tert*-butyl 8-[6-[3-cyano-2-[dimethylaminomethyleneamino]benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (780 mg, 1.02 mmol), MeOH (20 mL), and 1M NaOH (2.5 mL, 2.5 mmol, 2.5 eq.). The mixture was heated to 60 °C and stirred for 5 h. The reaction was cooled to 0 °C and 5N HCl was added to adjust to pH 4. The reaction mixture was placed over a 20g SCX column, washed with 3 column volumes of MeOH then eluting with 3 column volumes of 2N NH_3 in MeOH. The basic fractions were concentrated to give the title compound (588 mg, 81.2%) as an oil. MS (ES) *m/z*=715(M+1).

Preparation 165

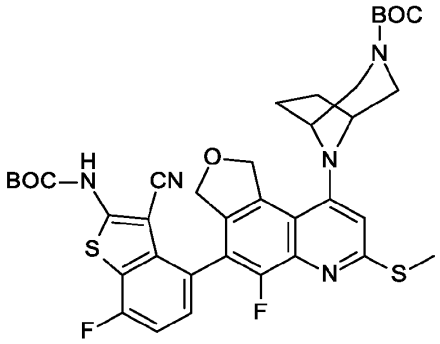
tert-Butyl N-[2-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl]ethyl]carbamate



A mixture of *tert*-butyl N-[4-(9-bromo-5-chloro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (0.500 g, 0.805 mmol), *tert*-butyl N-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]carbamate (0.466 g, 1.65 mmol) and Cs_2CO_3 (0.787 g, 2.42 mmol) in 1,4-dioxane (8 mL) and water (0.8 mL) was sparged with N_2 for 15 min. $Pd(ddpf)Cl_2$ (0.059 g, 0.081 mmol) was added, and the resulting mixture was heated at 70 °C for ~ 18 h. The reaction mixture was cooled to RT and partitioned between DCM and H_2O. The layers were separated, and the aqueous layer was extracted 2x with DCM and 2x with $CHCl_3$:IPA (4:1). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica, eluting with EtOAc/Hex (10-70%) to obtain the title compound (0.367 g, 67%) as a white solid. MS (ES) *m/z*=685 (M+1).

Preparation 166

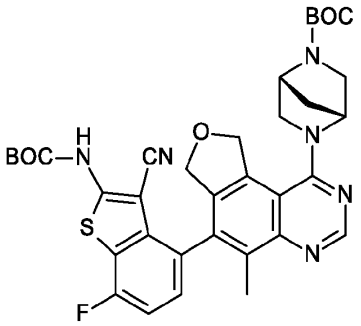
tert-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



A suspension of *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.416 g, 1.90 mmol, 2.5 eq.), *tert*-butyl N-[4-(9-bromo-5-fluoro-7-methylsulfanyl-1,3-dihydrofuro[3,4-f]quinolin-4-yl)-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (0.446 g, 0.70 mmol) and Cs_2CO_3 (0.481 g, 1.47 mmol, 2 eq.) in DMF (25 mL) was purged with N_2 for ~ 5 min. $Pd_2(dba)_3$ (0.085g, 0.15 mmol, 0.2 eq.) and BrettPhos (0.165 g, 0.292 mmol, 0.4 eq.) were added and the flask was sealed and heated to 100 °C for 6 h. The reaction mixture was cooled to RT, diluted with EtOAc and washed with brine. The aqueous layer was extracted with EtOAc and the combined organics were dried over Na_2SO_4 and concentrated. The residue was purified on silica, eluting with EtOAc/Hex (0% to 60%) to obtain the title compound (0.221g, 39%) as a yellow solid. MS (ES) *m/z*=737 (M+1).

Preparation 167

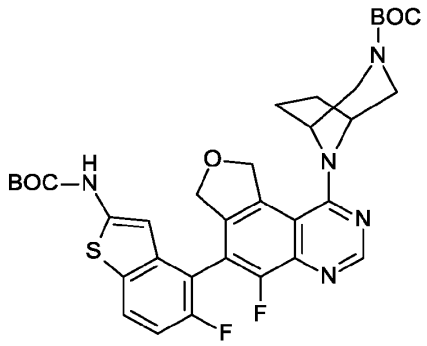
tert-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-methyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



To a stirred mixture of *tert*-butyl (1R,4R)-5-[6-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (470 mg, 0.68 mmol), K_2CO_3 (281 mg, 2.03 mmol) and methylboronic acid (406 mg, 6.78 mmol) in 1,4-dioxane (20 mL) was added RuPhos (94.9 mg, 0.20 mmol) and XPhos Palladacycle Gen.4 (117 mg, 0.14 mmol) in portions at RT. The resulting mixture was stirred for 2 h at 100 °C under N_2. The mixture was allowed to cool to RT, diluted with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:1 to 1:2) to afford the title compound (350 mg, 69.0%) as a red solid. MS (ES) *m/z*=673 (M+1).

Preparation 168

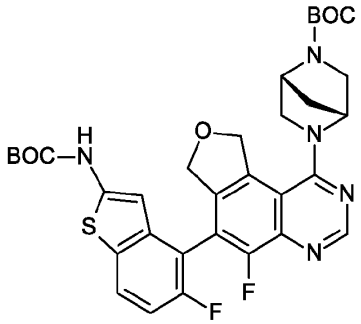
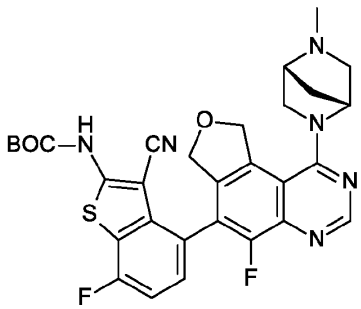
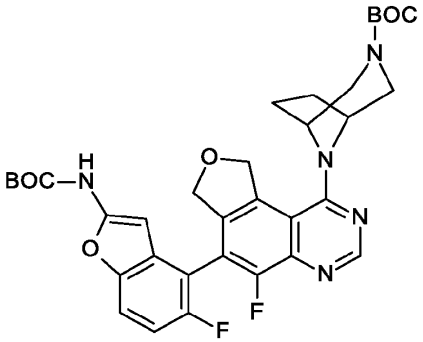
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



A solution of *tert*-butyl 8-[6-[2-(tert-butoxycarbonylamino)-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (28.6 g, 37.4 mmol) in THF (375 mL) was charged with TES (24 mL, 150 mmol, 4.00 eq.) and $PdCl_2$ (0.688 g, 3.69 mmol, 0.10 eq.) and stirred at RT for 4 h. H_2O (100 mL) was added dropwise, and the mixture was stirred at RT for 15 min. The mixture was filtered through diatomaceous earth, rinsed with EtOAc (100 mL). The filtrate was partitioned, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica, eluting with EtOAc/Hexanes (10-60%) to obtain the title compound (22.35 g, 90%) as a white foam. MS (ES) *m/z*=666 (M+1).

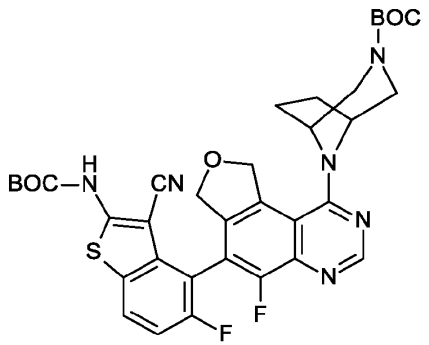
The following compounds in Table 9 were prepared in similar manner to Preparation 168. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 9:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
169	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		652
170	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-1-[(1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophen-2-yl]carbamate		591
171	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzofuran-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		650

Preparation 172

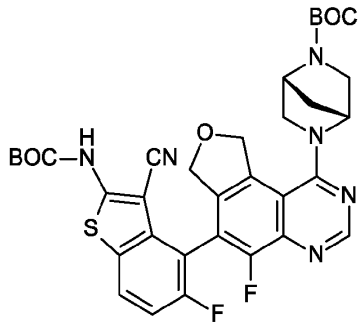
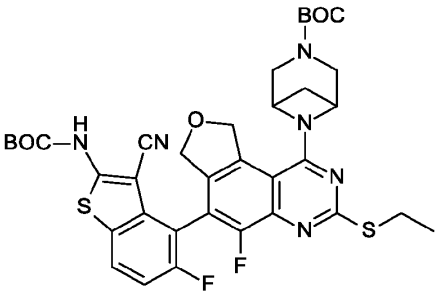
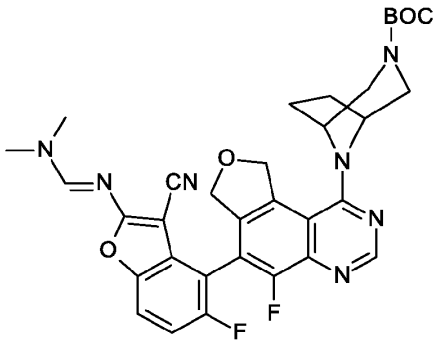
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

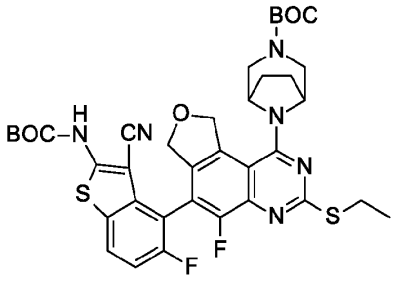
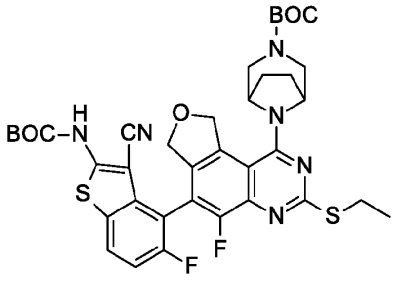
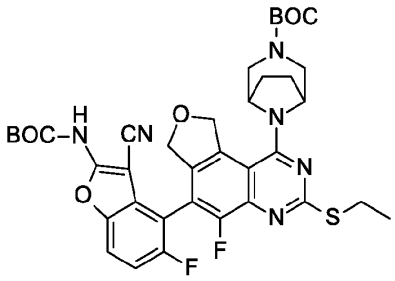


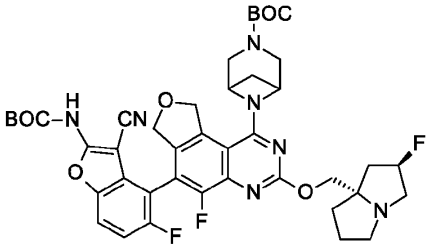
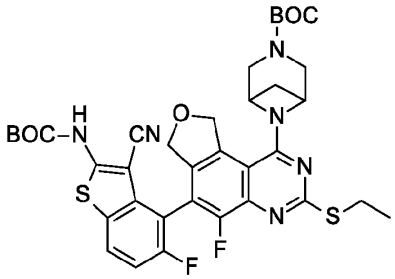
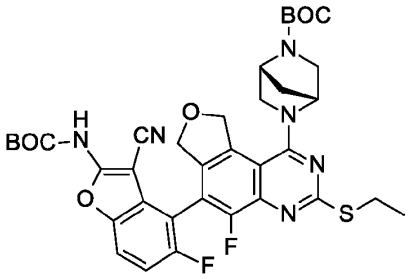
In a 250 mL 3-necked RBF, equipped with a thermocouple, N_2 inlet and dropping funnel, *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.640 g, 0.961 mmol) was dissolved in THF (10 mL). The flask was placed in a -45 °C bath (ACN/Dry ice) and flushed with N_2. Once the internal temperature had reached -45 °C chlorosulfonyl isocyanate (0.42 mL, 4.8 mmol, 5.0 eq.) was added dropwise at such a rate to keep the internal temperature below -30 °C. After 90 min, the cold reaction mixture was poured into DMF (15 mL) and stirred at RT for 1 h. The mixture was diluted with EtOAc, then was washed with 0.2M LiCl (3 x 300 mL) and brine. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica, eluting with EtOAc/hexanes (10% to 100%) to obtain the title compound (0.553g, 83%) as a white solid. MS (ES) *m/z*=691 (M+1).

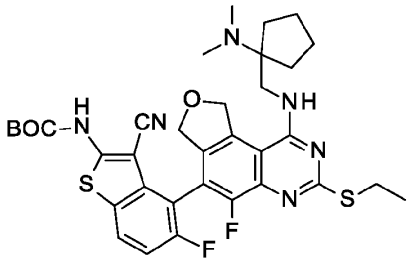
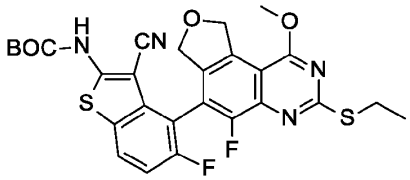
The following compounds in Table 10 were prepared in a similar manner as described for Preparation 172. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 10:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
173	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		677
174	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		737
175	*tert*-Butyl 8-[6-[3-cyano-2-[dimethylaminomethyleneamino]-5-fluoro-benzofuran-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		630

247	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		751
248[1]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, Isomer 2		751
249	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		735

250	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		818
251[2]	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate, Isomer 2		737
252	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		721

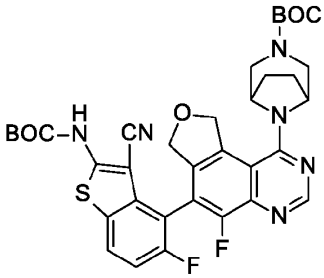
253	*tert*-Butyl N-[3-cyano-4-[1-[[1-(dimethylamino)cyclopentyl]methylamino]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophen-2-yl]carbamate		681
254	*tert*-Butyl N-[3-cyano-4-(3-ethylsulfanyl-5-fluoro-1-methoxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluoro-benzothiophen-2-yl]carbamate		571

[1]Chiralpak® AD-H, 50 x 250 mm, 30% EtOH : 70% CO_2, 180 mL/min

[2]Chiralpak® AD-H, 30 x 250 mm, 35% IPA(0.2% DEA) : 65% CO_2, 50 mL/min

Preparation 255

tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, Isomer 2

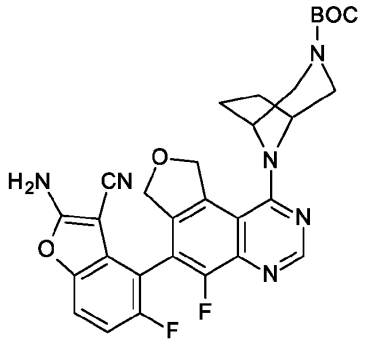


tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate was used in an analogous manner to the method of Preparation 168, followed by chiral purification (Chiralpak® AD-H, 30 x 250 mm, 30% IPA

: 70% CO_2, 100 mL/min) to obtain the title compound (1.02 g, 35%). MS (ES) *m/z*=691 (M+1).

Preparation 176

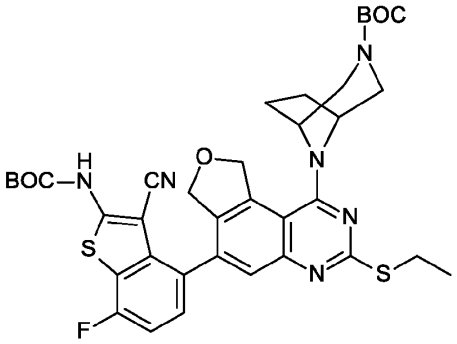
tert-Butyl 8-[6-(2-amino-3-cyano-5-fluoro-benzofuran-4-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



To a RBF was added *tert*-butyl 8-[6-[3-cyano-2-[dimethylaminomethyleneamino]-5-fluoro-benzofuran-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.225 g, 0.357 mmol), MeOH (2 mL), and 1M NaOH (0.9 mL, 0.893 mmol, 2.5 eq.) and was heated at 60 °C for 90 min. The reaction was cooled to 0 °C and 5N HCl was added to adjust to pH 4. The mixture was washed with brine, extracted with EtOAc (3x), dried over $MgSO_4$, filtered, and concentrated to afford the title compound (0.188 g, 92%). MS (ES) *m/z*=576 (M+1).

Preparation 177

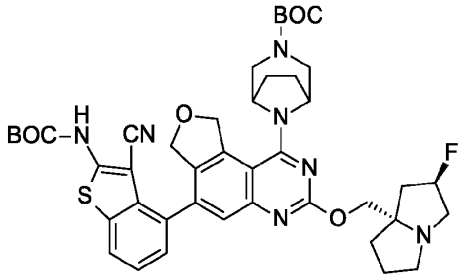
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



A solution of *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-ethylsulfanyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.390 g, 0.498 mmol), in 1,4-dioxane (5 mL) and IPA (1 mL) was charged with Cs_2CO_3 (0.489 g, 1.50 mmol, 3.0eq) and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.041 g, 0.051 mmol, 0.10 eq.) and was heated at 100 °C for ~18 h. The reaction was cooled to RT. The mixture was diluted with EtOAc and was washed with sat. aq. NH_4Cl, and brine. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluting with EtOAc/Hex (10-50%) to obtain the title compound (0.289g, 60%) as a 75% pure off-white solid, which was used in a subsequent step without further purification. MS (ES) *m/z*=733 (M+1).

Preparation 256

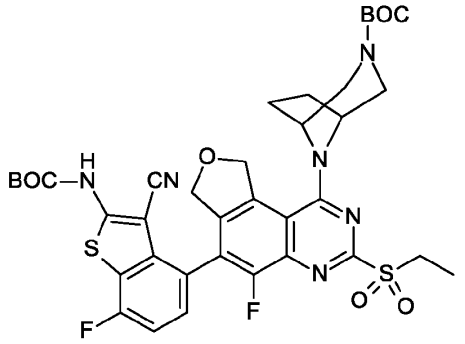
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-benzothiophen-4-yl]-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-benzothiophen-4-yl]-5-chloro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate was used in an analogous manner to the method of Preparation 177 to obtain the title compound (0.57 g, 83%). MS (ES) *m/z*=812 (M+1).

Preparation 178

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

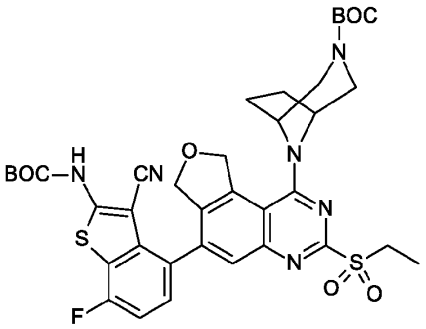
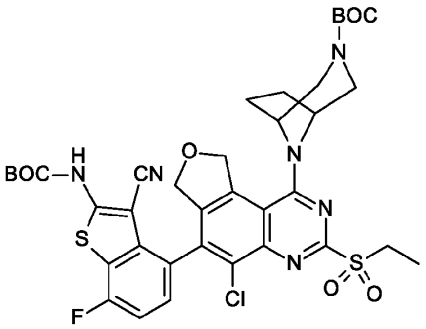


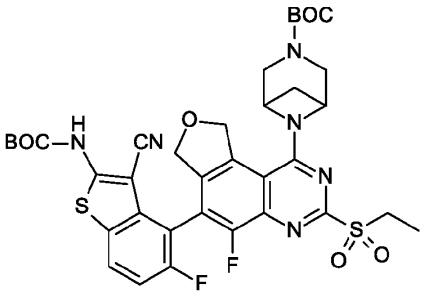
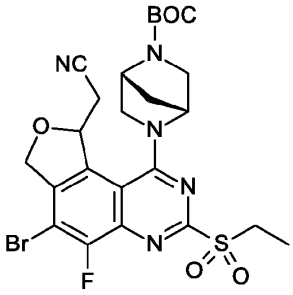
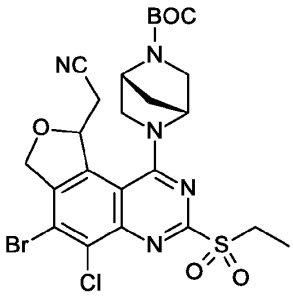
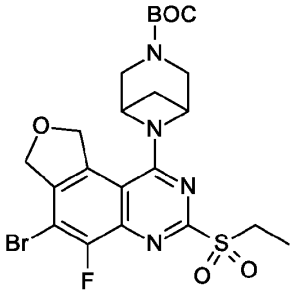
A solution of *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-3-ethylsulfanyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-

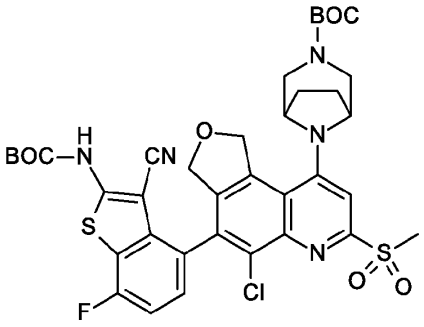
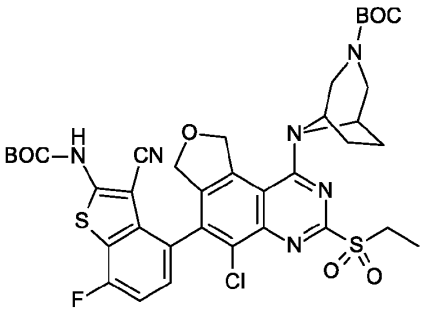
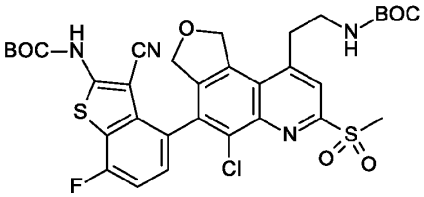
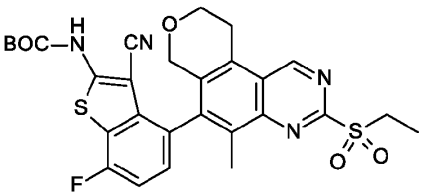
diazabicyclo[3.2.1]octane-3-carboxylate (1.13 g, 1.47 mmol) in DCM (15 mL) was charged with *m*CPBA (0.842 g, 4.88 mmol, 3.3 eq.) and was stirred at RT for 2 h. The mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$, and brine. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica, eluting with 40% EtOAc/Hex to obtain the title compound (1.15 g, 75%) as a white solid, MS (ES) *m/z*=783 (M+1).

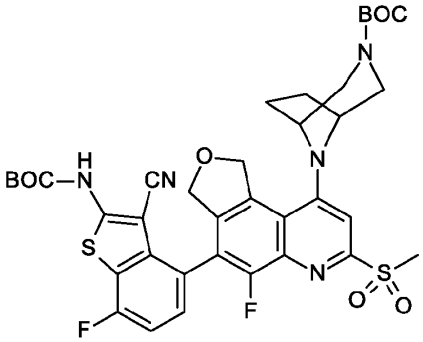
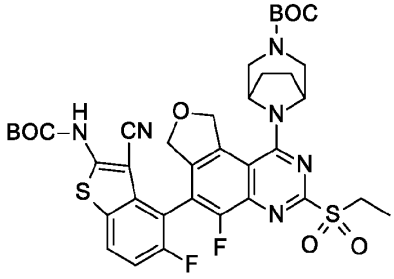
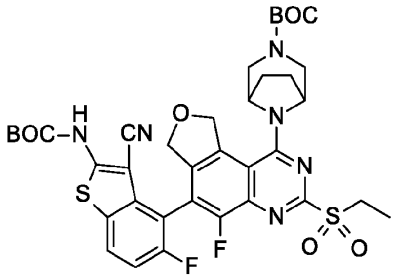
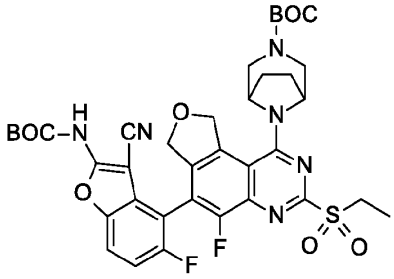
The following compounds in Table 11 were prepared in a similar manner as described for Preparation 178. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

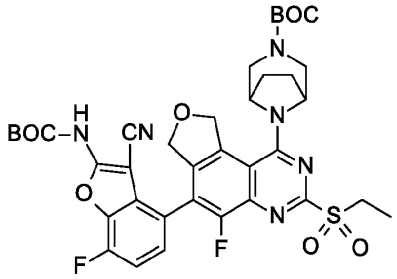
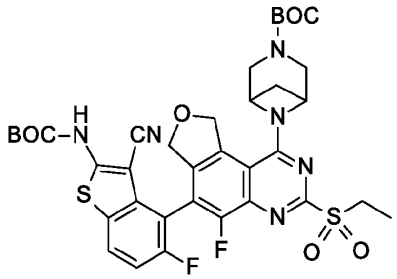
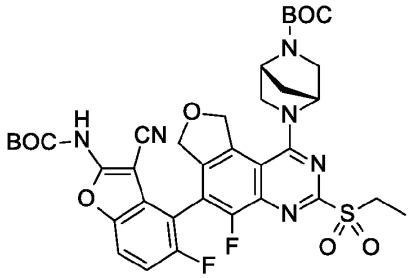
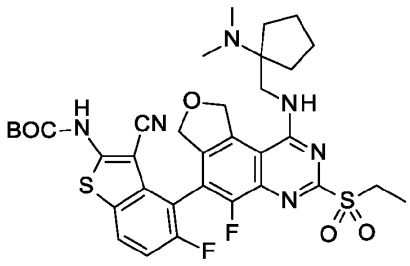
Table 11:

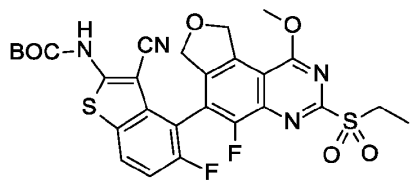
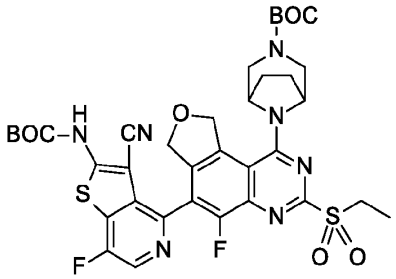
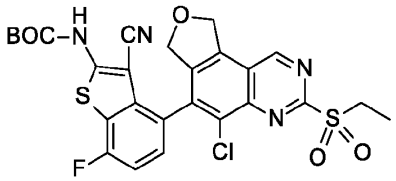
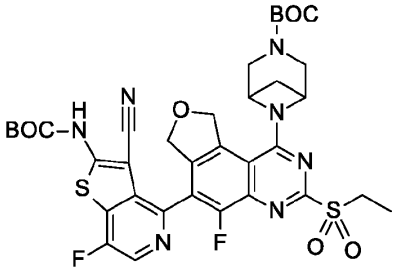
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
179	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-3-ethylsulfonyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		765
180	tert-butyl 8-[6-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-ethylsulfonyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		799

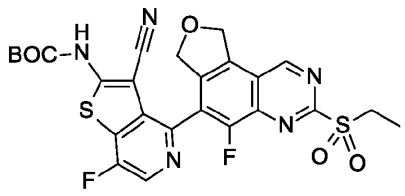
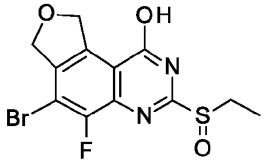
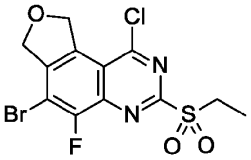
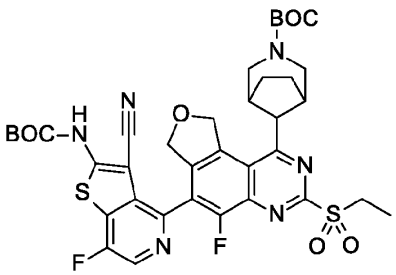
181	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		769
182	*tert*-Butyl (1R,4R)-5-[6-bromo-9-(cyanomethyl)-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		596
183	*tert*-Butyl (1R,4R)-5-[6-bromo-5-chloro-9-(cyanomethyl)-3-ethylsulfonyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		612
184	*tert*-Butyl 6-(6-bromo-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		557

185	*tert*-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-methylsulfonyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		784
186[1]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-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
187	*tert*-Butyl N-[2-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-methylsulfonyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl]ethyl]carbamate		717
188	*tert*-Butyl N-[3-cyano-4-(3-ethylsulfonyl-5-methyl-9,10-dihydro-7H-pyrano[4,3-f]quinazolin-6-yl)-7-fluoro-benzothiophen-2-yl]carbamate		583

189	*tert*-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-7-methylsulfonyl-1,3-dihydrofuro[3,4-f]quinolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		769
257	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-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
258[2]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-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
259	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		767

260	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzofuran-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		767
261[3]	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		769
262	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		753
263	*tert*-Butyl N-[3-cyano-4-[1-[[1-(dimethylamino)cyclopentyl]methylamino]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophen-2-yl]carbamate		713

264	*tert*-Butyl N-[3-cyano-4-(3-ethylsulfonyl-5-fluoro-1-methoxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-5-fluoro-benzothiophen-2-yl]carbamate		603
309	*tert*-Butyl 8-[6-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[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		784
310	*tert*-Butyl N-[4-(5-chloro-3-ethylsulfonyl-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		589
328	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		770

329	*tert*-Butyl N-[3-cyano-4-(3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl)-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		574
330	6-Bromo-3-ethylsulfinyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-ol		361,363
331	6-Bromo-1-chloro-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline		419 $M+Na^+$
332	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3-azabicyclo[3.2.1]octane-3-carboxylate		742

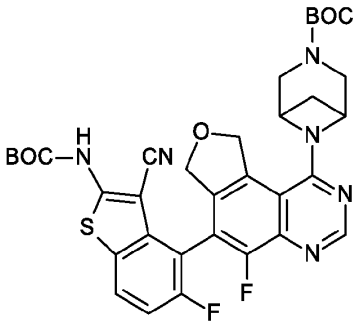
[1]single atropisomer (from precursor in Preparation 157)

[2]single atropisomer (from precursor in Preparation 248)

[3]single atropisomer (from precursor in Preparation 251)

Preparation 190

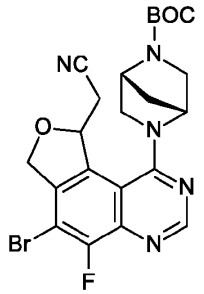
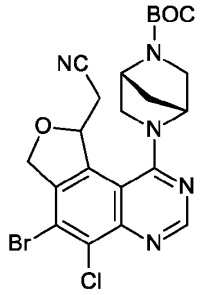
tert-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate



To a stirring solution of *tert*-butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (1.16 g, 1.50 mmol) in DCM (15 mL) and MeOH (15 mL) at RT was added $NaBH_4$ (0.58 g, 15 mmol, 10 eq.). After 15 min, the reaction mixture was diluted with DCM (300 mL), then sat. aq. $NaHCO_3$ (100 mL) and H_2O (500 mL) were added. The reaction mixture was stirred at RT until gas evolution stopped. The organic layer was separated and the aqueous layer was extracted with DCM (300 mL). The organic layers were combined and then were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica, eluting with MeOH/DCM (0-2%) to obtain the title compound (0.80 g, 77%). MS (ES) *m/z*=677 (M+1).

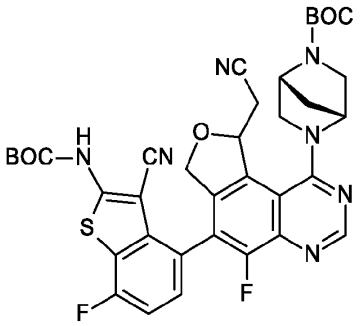
The following compounds in Table 12 were prepared in a similar manner as described in Preparation 190. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

Table 12:

Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
191	*tert*-Butyl (1R,4R)-5-[6-bromo-9-(cyanomethyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		504
192	*tert*-Butyl (1R,4R)-5-[6-bromo-5-chloro-9-(cyanomethyl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		520

Preparation 193

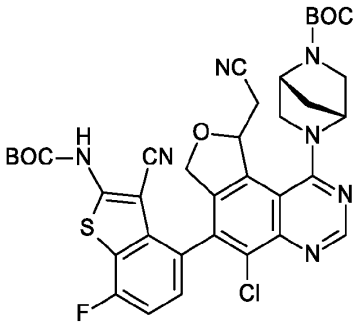
tert-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-9-(cyanomethyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



To a sealed flask were added *tert*-butyl(1R,4R)-5-[6-bromo-9-(cyanomethyl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (1.00 g, 1.98 mmol) in THF (20.0 mL) and *tert*-butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-yl]carbamate (1.20 g, 2.97 mmol). The flask was sparged with N_2 for 15 min and then Pd-117 (430 mg, 0.601 mmol) was added, followed by Cs_2CO_3 (1.30 g, 3.99 mmol). The flask was sealed and heated with stirring at 70 °C in an oil bath for 2 h. The reaction mixture was cooled to RT and diluted with THF, filtered through a pad of diatomaceous earth. The filter cake was washed with 10% MeOH in DCM. The filtrate was concentrated, and the residue was purified by silica column chromatography with acetone/hexanes (0-40%) to afford crude product, which was repurified on silica with 1% to 5% 7N NH_3/MeOH in DCM to afford title compound (0.795 g, 56%) as a yellow solid. MS (ES) *m/z*=716 (M+1).

Preparation 194

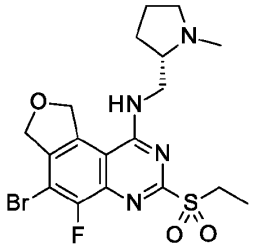
tert-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-9-(cyanomethyl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



tert-Butyl (1R,4R)-5-[6-bromo-5-chloro-9-(cyanomethyl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was used in an analogous manner to the method of Preparation 193 to obtain the title compound (0.25 g, 54.7%) as yellow solid. MS (ES) *m/z*=732 (M+1).

Preparation 333

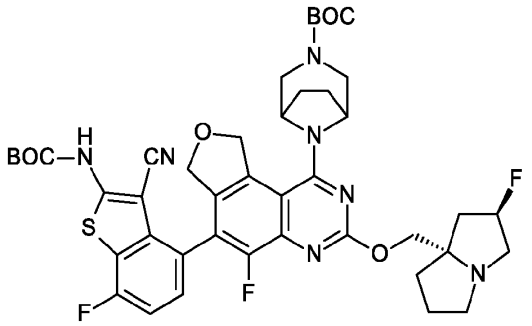
6-Bromo-3-ethylsulfonyl-5-fluoro-N-[[(2S)-1-methylpyrrolidin-2-yl]methyl]-7,9-dihydrofuro[3,4-f]quinazolin-1-amine



6-Bromo-1-chloro-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazoline and [(2S)-1-methylpyrrolidin-2-yl]methanamine were used in an analogous manner to the method of Preparation 102 to obtain the title compound. MS (ES) *m/z*=473,475 (M+1,Br).

Preparation 195

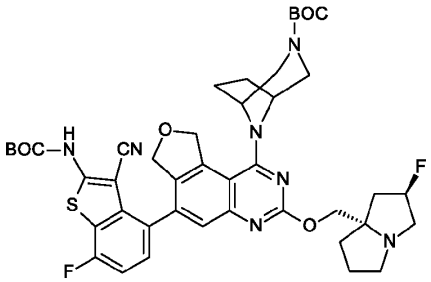
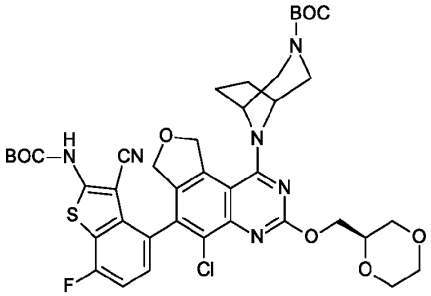
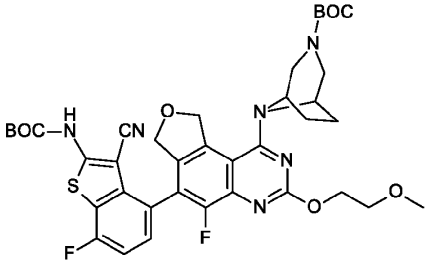
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

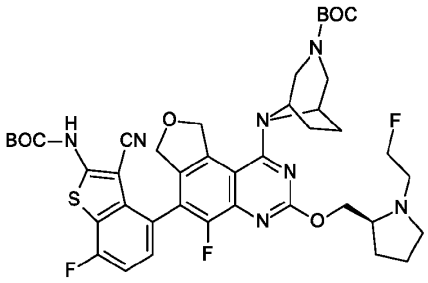
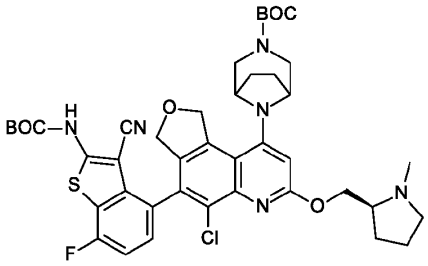
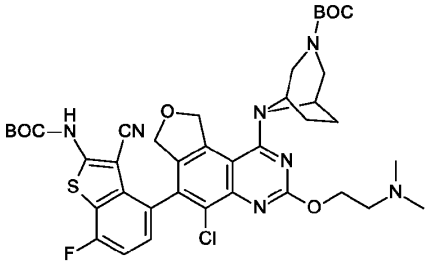


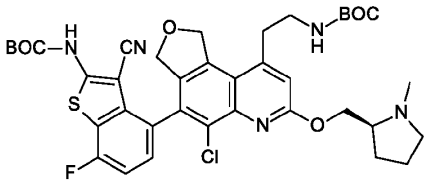
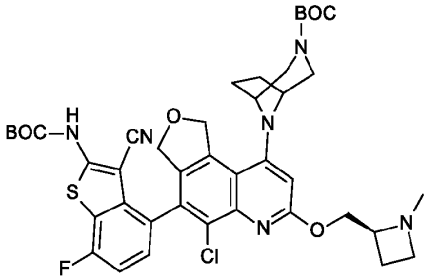
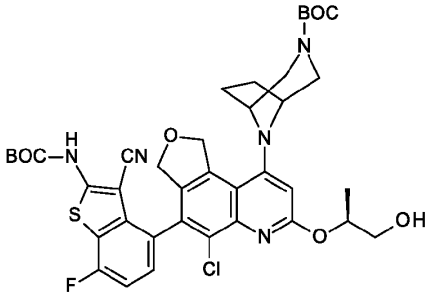
To [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (1.15 g, 7.01 mmol) in THF (30 mL) under N_2 at RT was added dropwise LiHMDS (6.7 mL, 6.7 mmol, 1M in THF) and stirred for 20 min at RT. To this solution was added dropwise via syringe, *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-3-ethylsulfonyl-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (2.3 g, 2.9 mmol) in THF (20 mL). After 40 min, the reaction was diluted with EtOAc and washed with brine. The aqueous layer was extracted 2x EtOAc and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated to a tan solid. The material was purified by silica (0% to 3.5% 7N NH_3/MeOH in DCM) to afford the title compound (2.26 g, 91%) as a yellow solid. MS (ES) *m/z*= 848 (M+1).

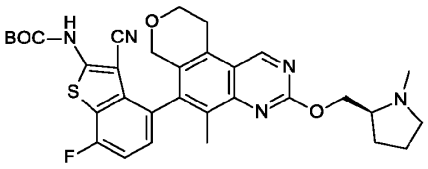
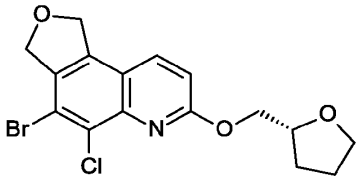
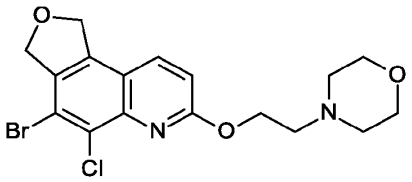
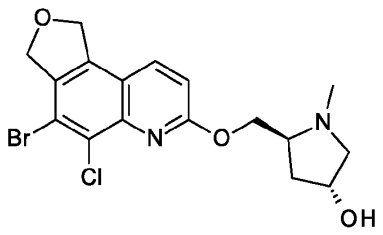
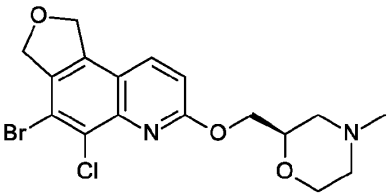
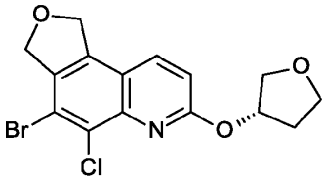
The following compounds in Table 13 were prepared in a similar manner described in Preparation 195. Various methods were used to purify the compounds, which would be apparent to one skilled in the art.

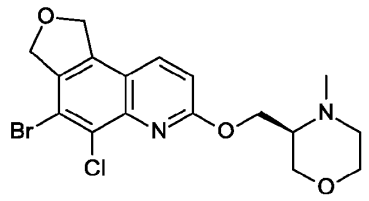
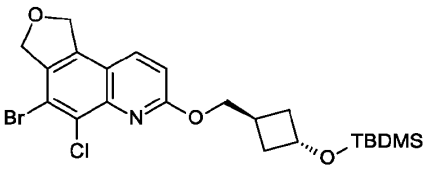
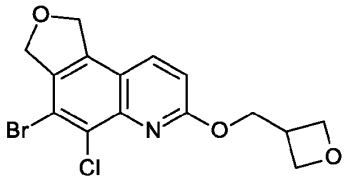
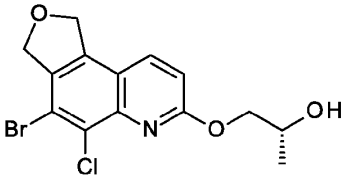
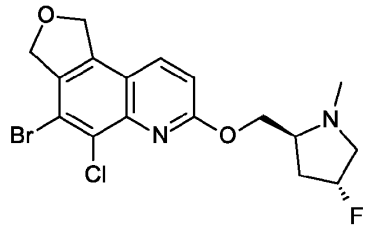
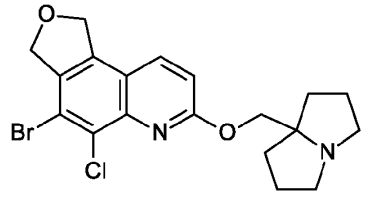
Table 13:

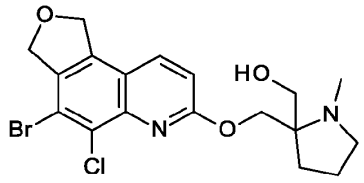
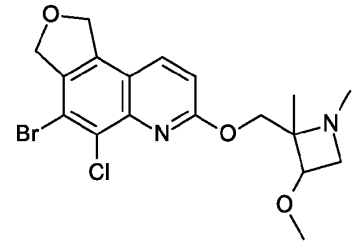
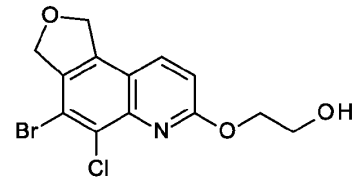
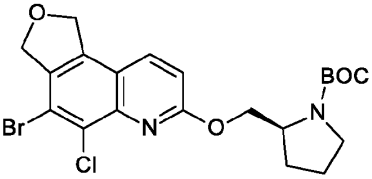
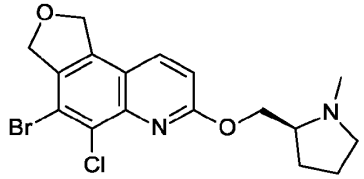
Preparation	Chemical Name	Structure	MS (ES) *m/z* (M+1)
196	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate)		831
197	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-[[(2R)-1,4-dioxan-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		823
198	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-3-(2-methoxyethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		765

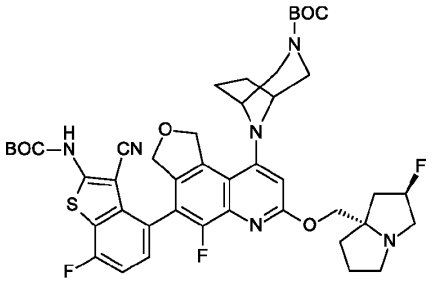
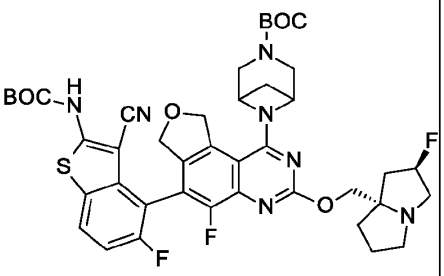
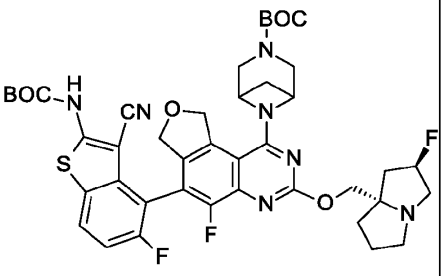
199	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-(2-fluoroethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		836
200[1]	*tert*-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820
201[2]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-[2-(dimethylamino)ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		794

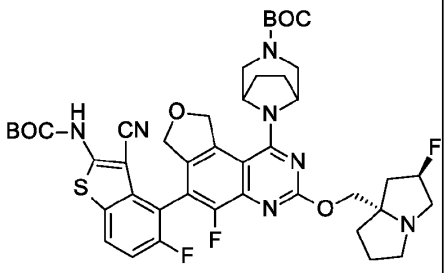
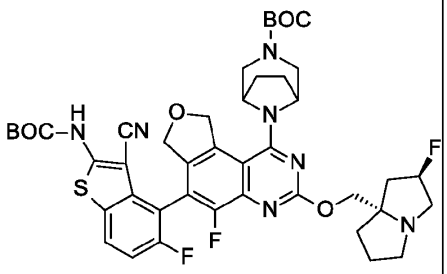
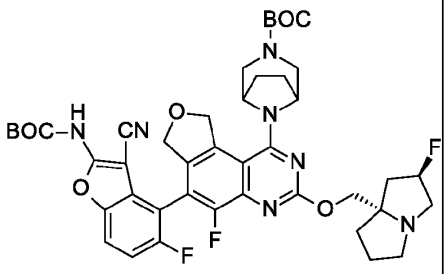
202[1]	*tert*-Butyl N-[2-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-9-yl]ethyl]carbamate		752
203[1]	*tert*-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-7-[[(2S)-1-methylazetidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		805
204[1]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-[(1S)-2-hydroxy-1-methyl-ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		781

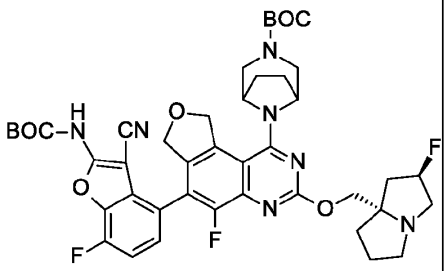
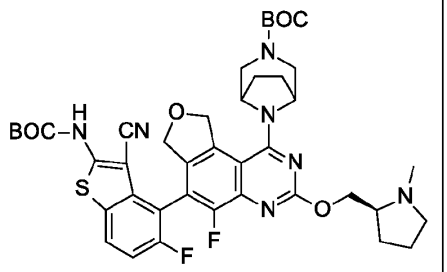
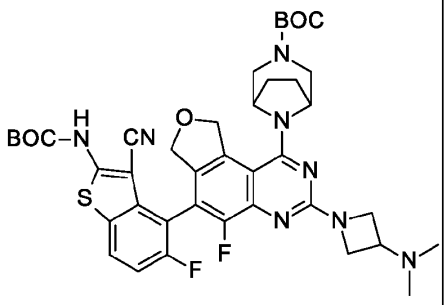
205	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-methyl-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-9,10-dihydro-7H-pyrano[4,3-f]quinazolin-6-yl]benzothiophen-2-yl]carbamate		604
206[3]	4-Bromo-5-chloro-7-[[(2R)-tetrahydrofuran-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinoline		384
207[1]	4-Bromo-5-chloro-7-(2-morpholinoethoxy)-1,3-dihydrofuro[3,4-f]quinoline		413
208[1]	(3R,5S)-5-[(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxymethyl]-1-methyl-pyrrolidin-3-ol		413
209[1]	4-Bromo-5-chloro-7-[[(2R)-4-methylmorpholin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinoline		413
210[1]	4-Bromo-5-chloro-7-[(3S)-tetrahydrofuran-3-yl]oxy-1,3-dihydrofuro[3,4-f]quinoline		370

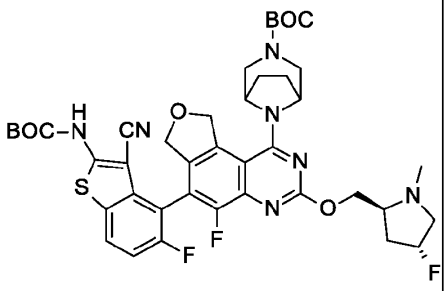
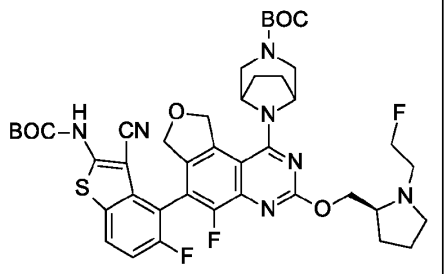
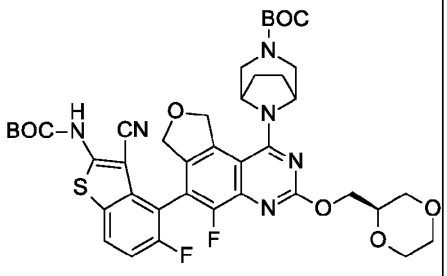
211[1]	4-Bromo-5-chloro-7-[[(3S)-4-methylmorpholin-3-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinoline		413
212[1]	[3-[(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxymethyl]cyclobutoxy]-*tert*-butyl-dimethyl-silane		498
213[1]	4-Bromo-5-chloro-7-(oxetan-3-ylmethoxy)-1,3-dihydrofuro[3,4-f]quinoline		370
214[1]	(2R)-1-[(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxy]propan-2-ol		358
215[1]	4-Bromo-5-chloro-7-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinoline		415
216[1]	4-Bromo-5-chloro-7-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-1,3-dihydrofuro[3,4-f]quinoline		423

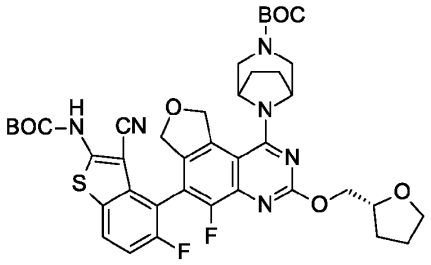
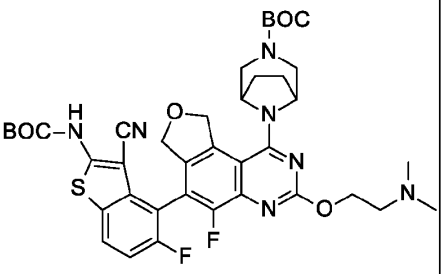
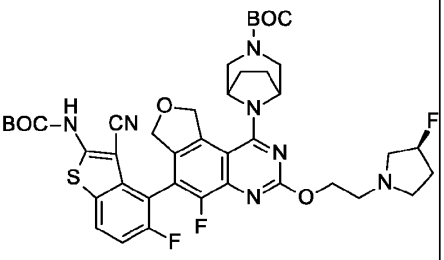
217[1]	[2-[(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxymethyl]-1-methyl-pyrrolidin-2-yl]methanol		427
218[1]	4-Bromo-5-chloro-7-[(3-methoxy-1,2-dimethyl-azetidin-2-yl)methoxy]-1,3-dihydrofuro[3,4-f]quinoline		427
219[1]	2-[(4-Bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxy]ethanol		344
220[1]	*tert*-Butyl (2S)-2-[(4-bromo-5-chloro-1,3-dihydrofuro[3,4-f]quinolin-7-yl)oxymethyl]pyrrolidine-1-carboxylate		483
221[3]	4-Bromo-5-chloro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinoline		397

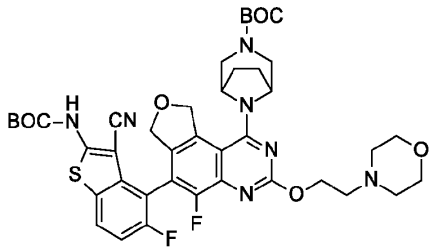
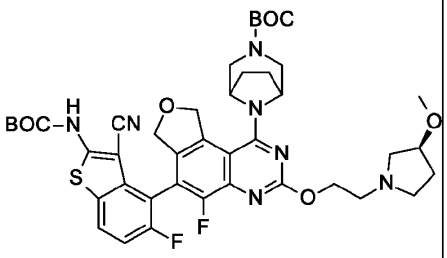
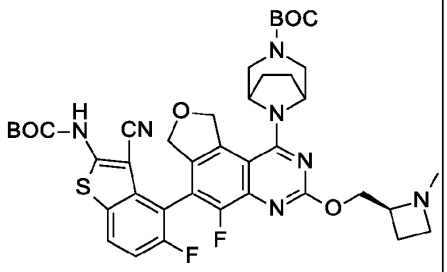
222[4]	*tert*-Butyl 8-[4-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-7-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-9-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		847
265	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		834
266[5]	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate, Isomer 2		834

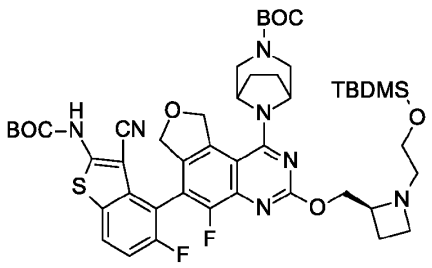
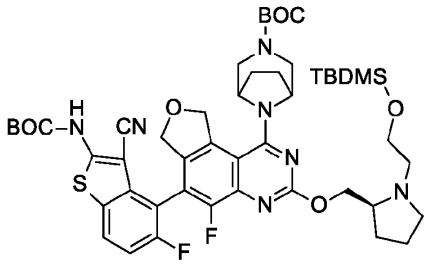
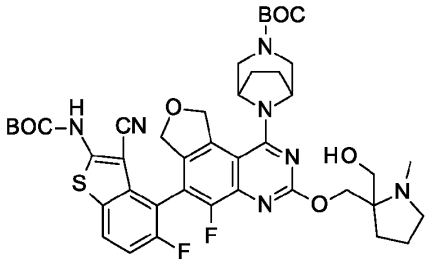
267	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		848
268[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		848
269	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		832

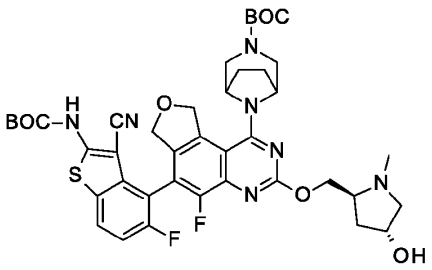
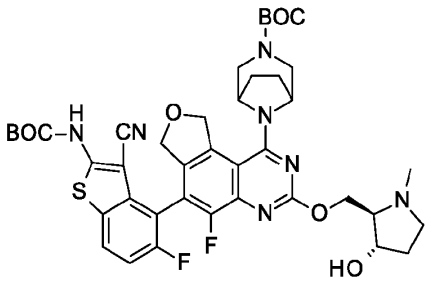
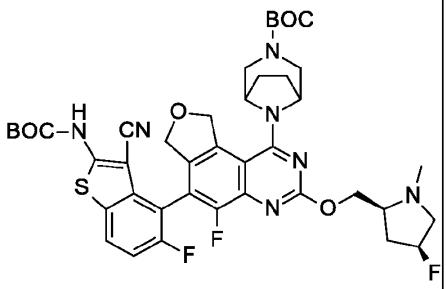
270	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		832
271[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		804
272[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-[3-(dimethylamino)azetidin-1-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		789

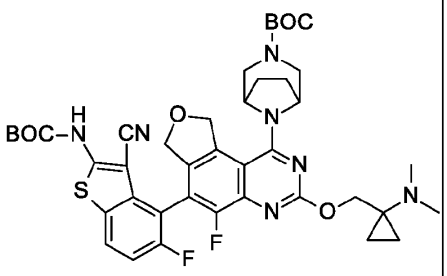
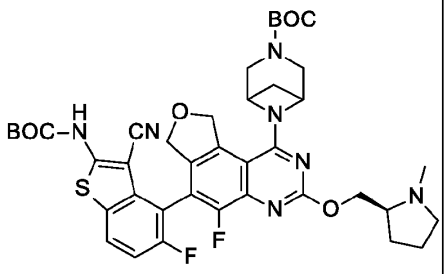
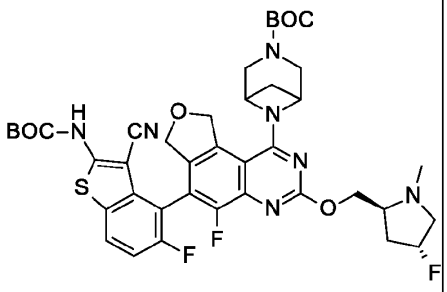
273[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		822
274[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-(2-fluoroethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		836
275[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-[[(2R)-1,4-dioxan-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		807

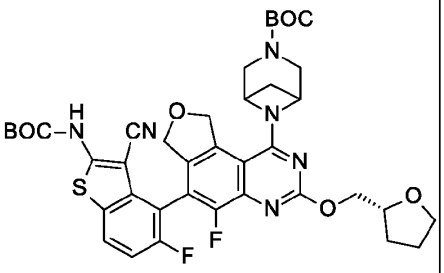
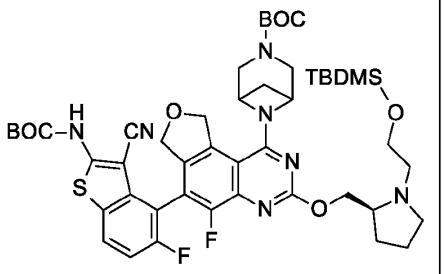
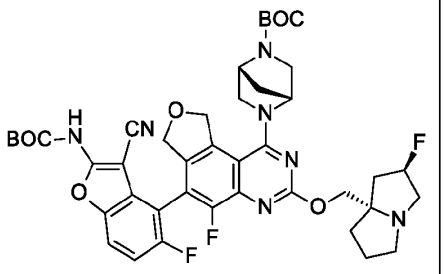
276[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		791
277[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-[2-(dimethylamino)ethoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		778
278[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[2-[(3S)-3-fluoropyrrolidin-1-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		822

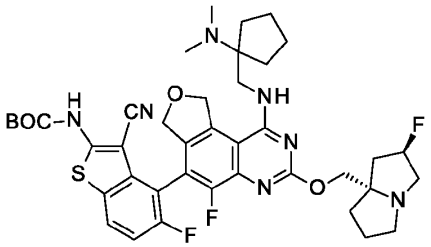
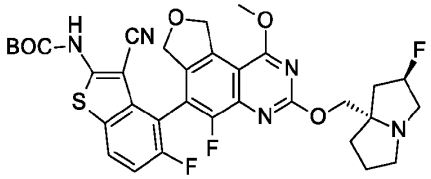
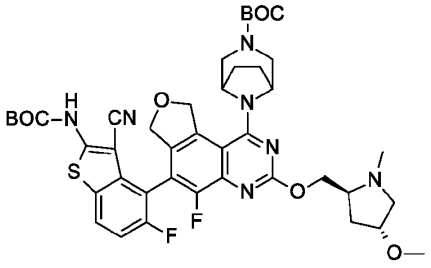
279[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820
280[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[2-[(3S)-3-methoxypyrrolidin-1-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		834
281[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		790

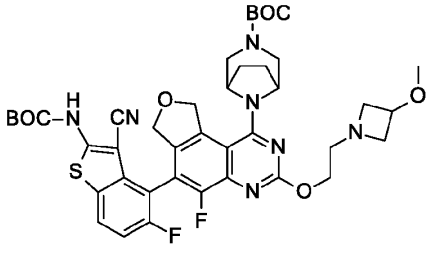
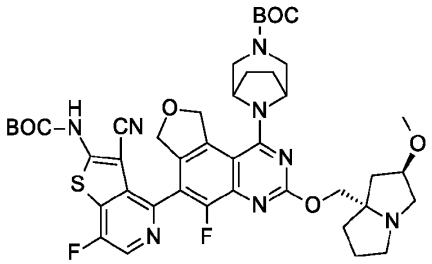
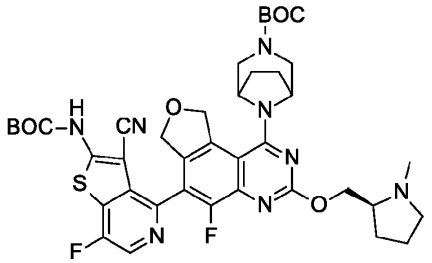
282[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)azetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		934
283[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		948
284[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		834

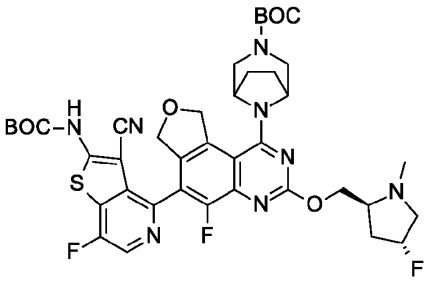
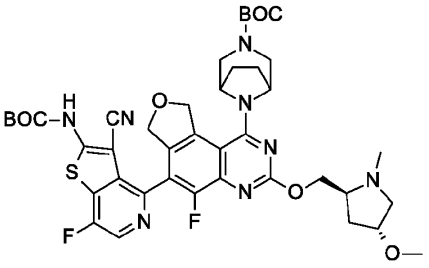
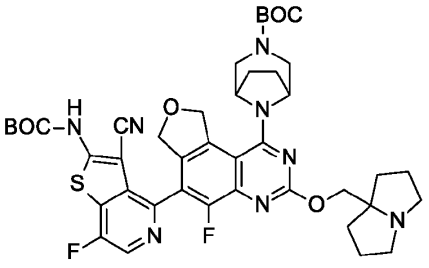
285[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S,4R)-4-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820
286[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R,3S)-3-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820
287[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		822

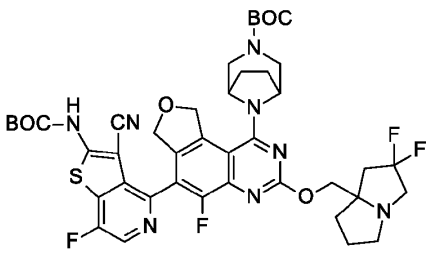
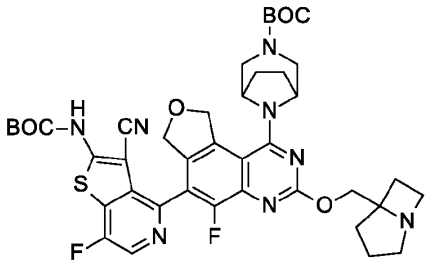
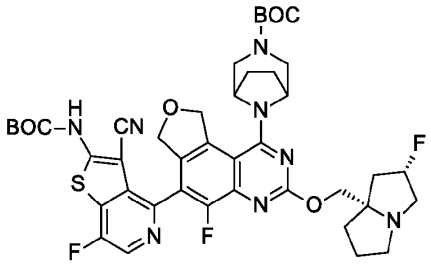
288[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-[[1-(dimethylamino)cyclopropyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		804
289[7]	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		790
290[7]	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		808

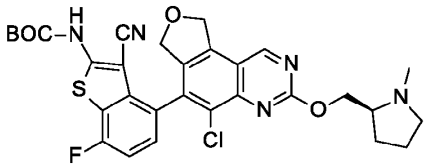
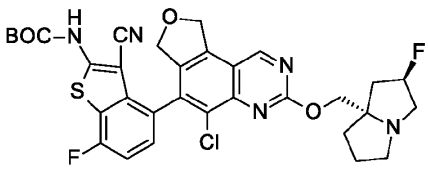
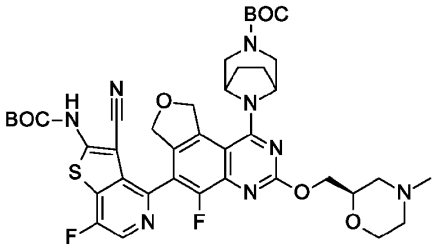
291[7]	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		777
292[7]	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		934
293	*tert*-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate		818

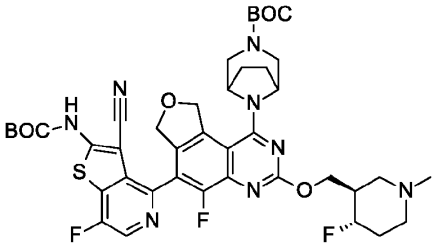
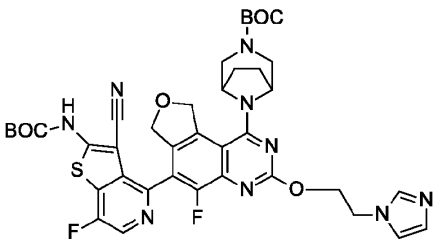
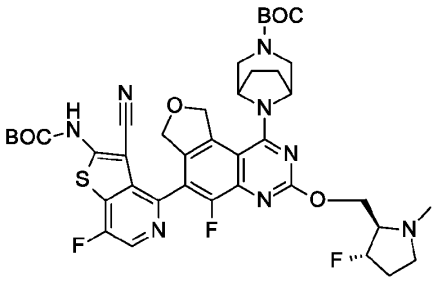
294	*tert*-Butyl N-[3-cyano-4-[1-[[1-(dimethylamino)cyclopentyl]methylamino]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophen-2-yl]carbamate		778
295	*tert*-Butyl N-[3-cyano-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-methoxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophen-2-yl]carbamate		668
311[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		834

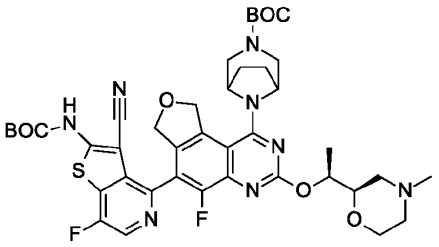
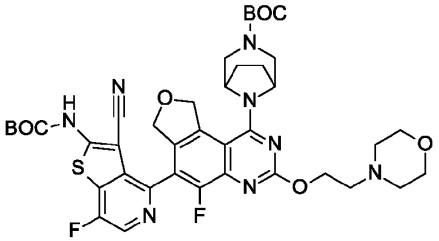
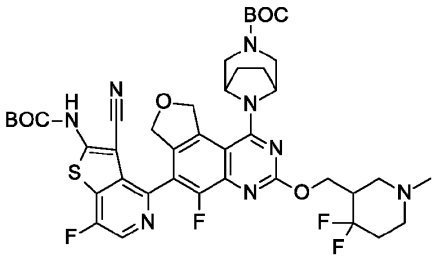
312[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[2-(3-methoxyazetidin-1-yl)ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820
313	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		861
314	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		805

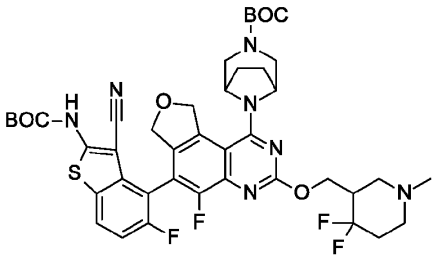
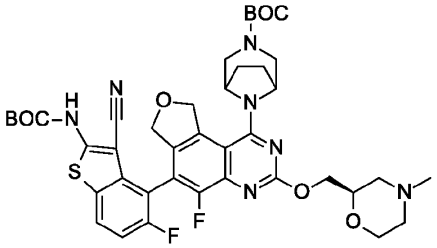
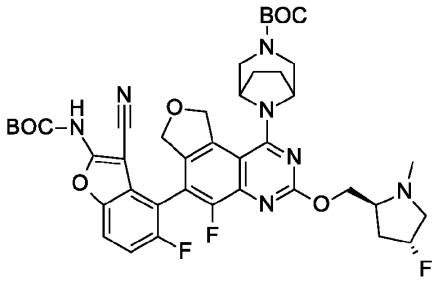
315	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		823
316	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		835
317	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		831

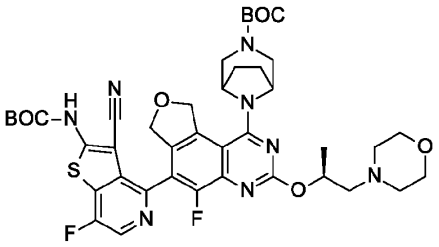
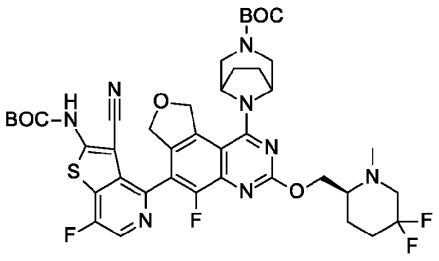
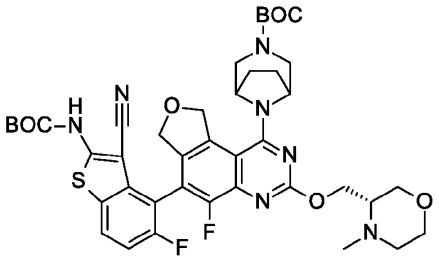
318	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[(6,6-difluoro-2,3,5,7-tetrahydro-1H-pyrrolizin-8-yl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		867
319	*tert*-Butyl 8-[3-(1-azabicyclo[3.2.0]heptan-5-ylmethoxy)-6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[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		817
320	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2SR,8SR)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		849

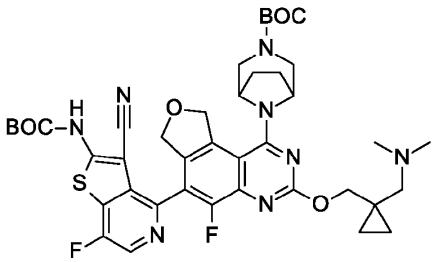
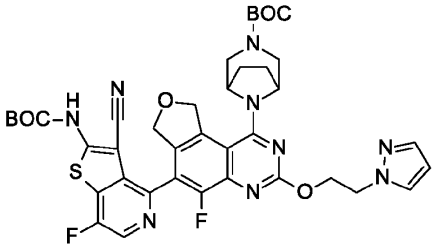
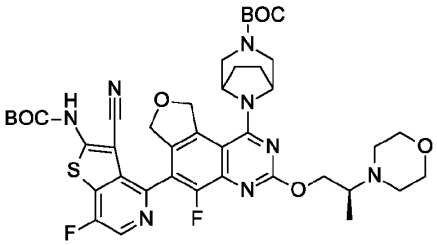
321	*tert*-Butyl N-[4-[5-chloro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		610
322	*tert*-Butyl N-[4-[5-chloro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate		654
334	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		821

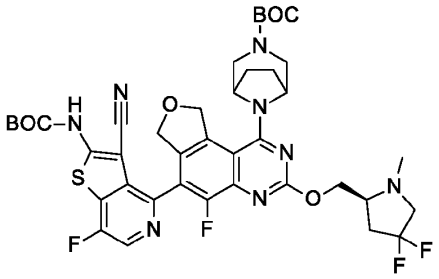
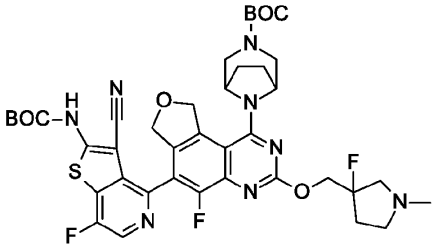
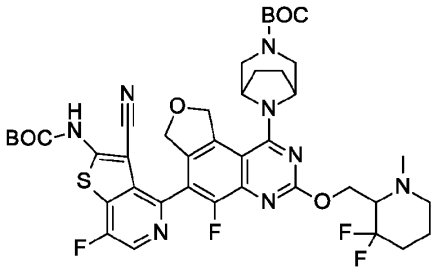
335	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(3R,4S)-4-fluoro-1-methyl-3-piperidyl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		837
336	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-(2-imidazol-1-ylethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		802
337	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,3S)-3-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		823

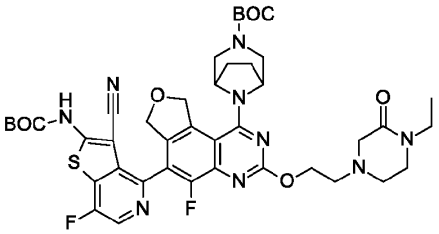
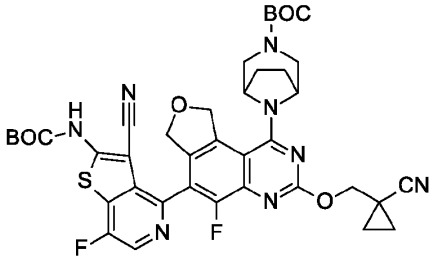
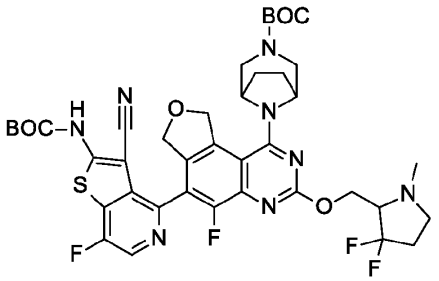
338	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[(1S)-1-[(2R)-4-methylmorpholin-2-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		835
339	*tert*-Butyl 8-[6-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		821
340	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		855

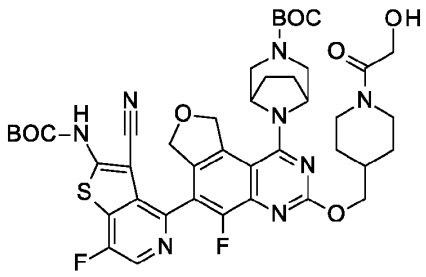
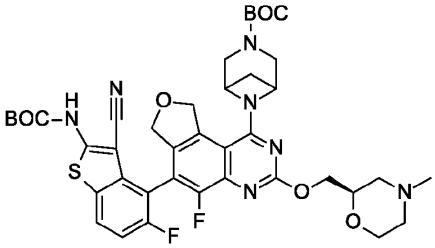
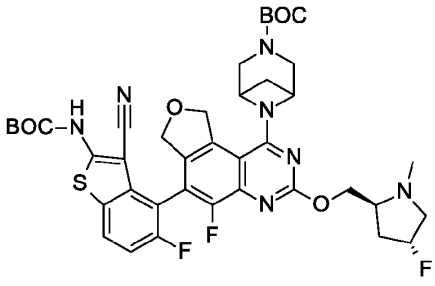
341[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		854
342[6]	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820
343	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		806

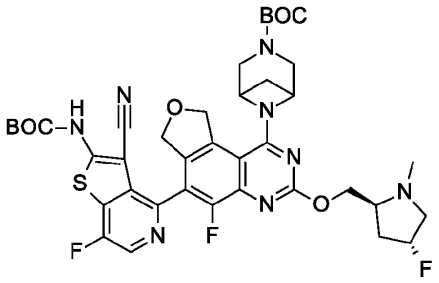
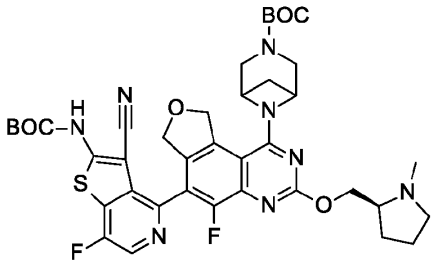
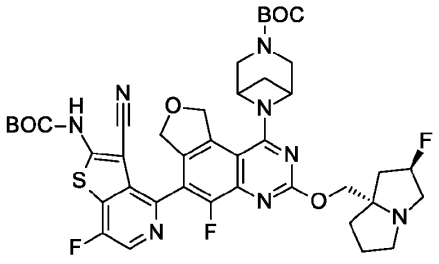
344	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[(1S)-1-methyl-2-morpholino-ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		835
345	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[[(2S)-5,5-difluoro-1-methyl-2-piperidyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		855
346	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(3S)-4-methylmorpholin-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		820

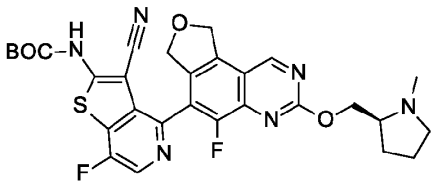
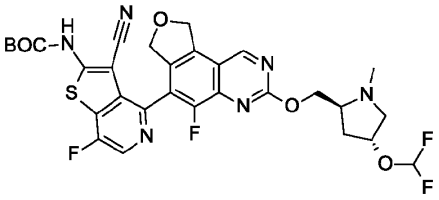
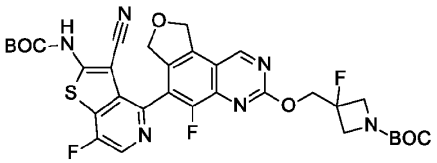
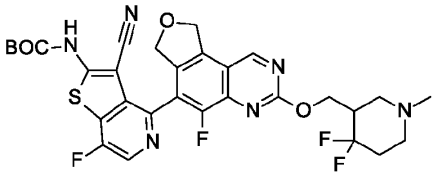
347	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		819
348	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-(2-pyrazol-1-ylethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		802
349	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[(2S)-2-morpholinopropoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		835

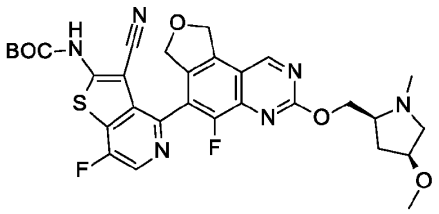
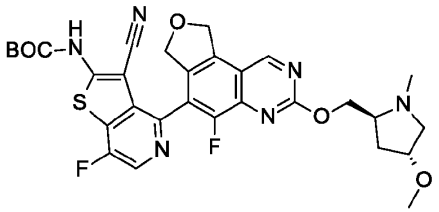
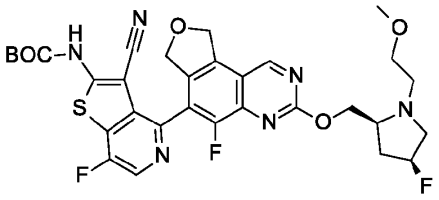
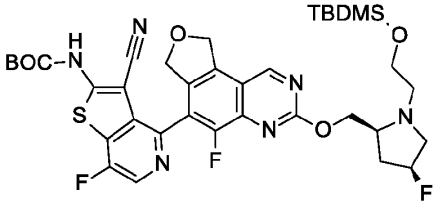
350	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[[(2S)-4,4-difluoro-1-methyl-pyrrolidin-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		841
351	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[(3-fluoro-1-methyl-pyrrolidin-3-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		722
352	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[(3,3-difluoro-1-methyl-2-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		855

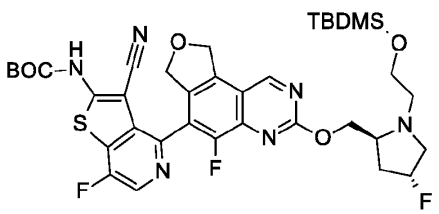
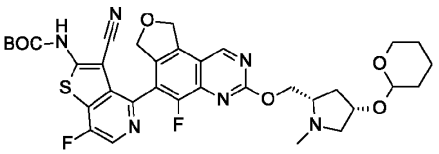
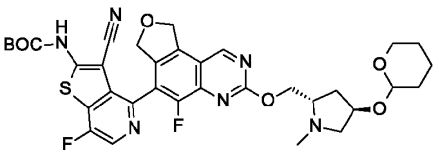
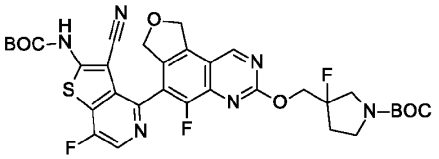
353	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[2-(4-ethyl-3-oxo-piperazin-1-yl)ethoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		862
354	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[(1-cyanocyclopropyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		787
355	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-3-[(3,3-difluoro-1-methyl-pyrrolidin-2-yl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		841

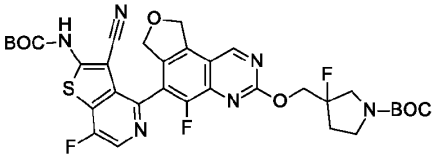
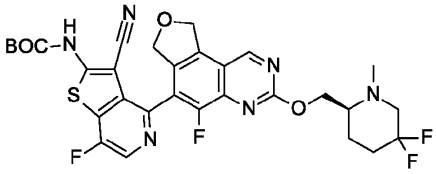
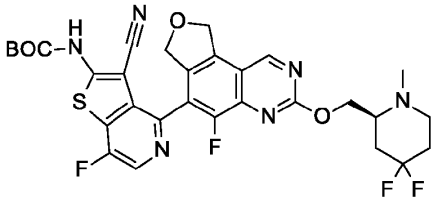
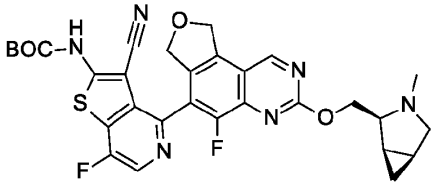
356	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[1-(2-hydroxyacetyl)-4-piperidyl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate		
357	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		806
358	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		808

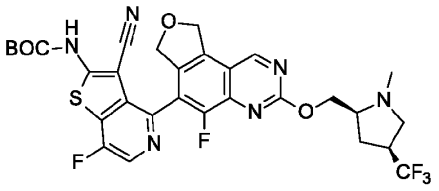
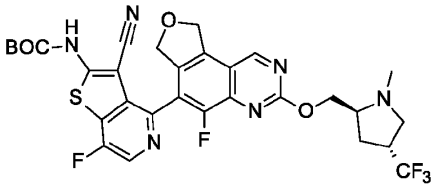
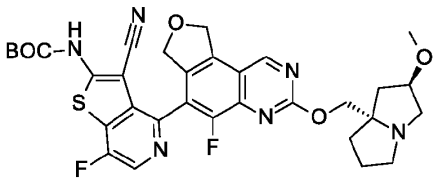
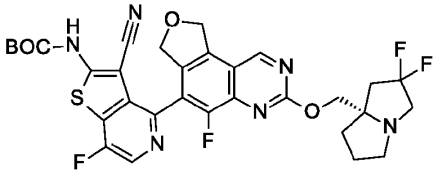
359	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		809
360	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		791
361	*tert*-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate		835

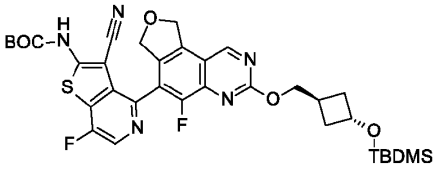
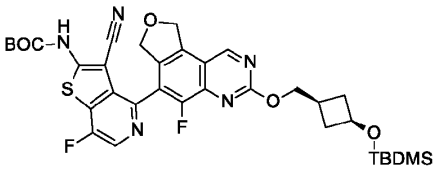
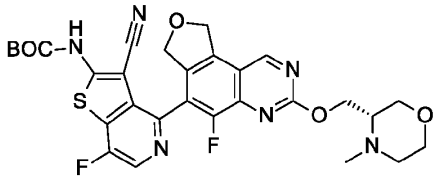
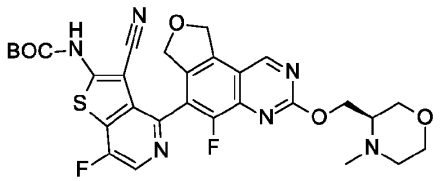
362	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		595
363	*tert*-Butyl N-[3-cyano-4-[3-[[(2S,4R)-4-(difluoromethoxy)-1-methyl-pyrrolidin-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		661
364	*tert*-Butyl 3-[[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl]oxymethyl]-3-fluoro-azetidine-1-carboxylate		585
365	*tert*-Butyl N-[3-cyano-4-[3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		645

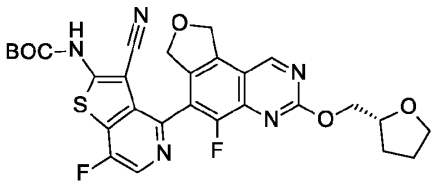
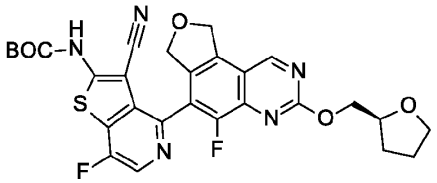
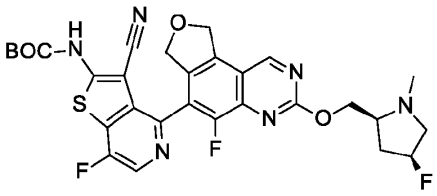
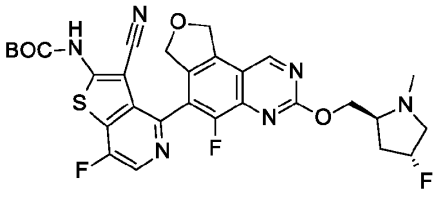
366	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		625
367	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		625
368	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-fluoro-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		657
369	*tert*-Butyl N-[4-[3-[[(2S,4S)-1-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-fluoro-pyrrolidin-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		757

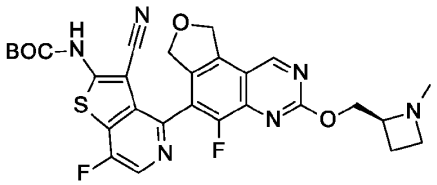
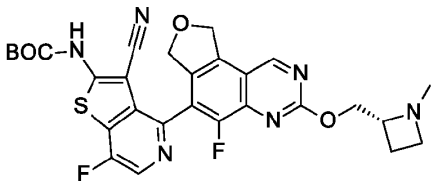
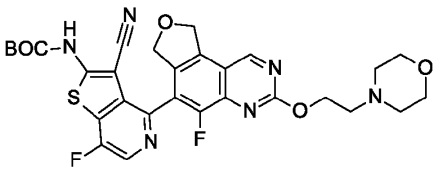
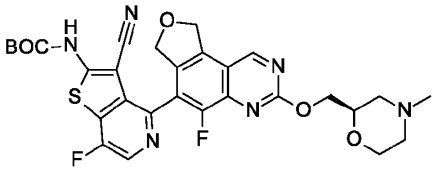
370	*tert*-Butyl N-[4-[3-[[(2S,4R)-1-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-4-fluoro-pyrrolidin-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		757
371	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-1-methyl-4-tetrahydropyran-2-yloxy-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		695
372	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-1-methyl-4-tetrahydropyran-2-yloxy-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		695
373[8]	*tert*-Butyl 3-[[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl]oxymethyl]-3-fluoro-pyrrolidine-1-carboxylate, Isomer 1		699

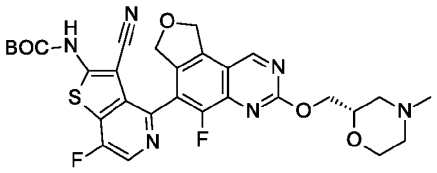
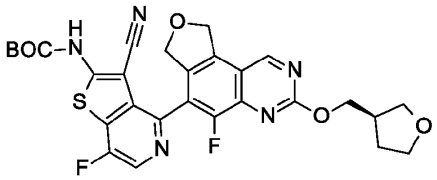
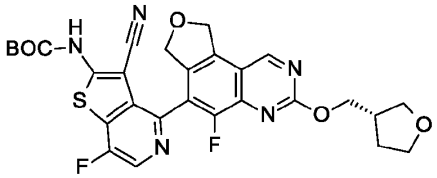
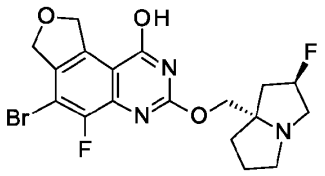
374[8]	*tert*-Butyl 3-[[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-3-yl]oxymethyl]-3-fluoro-pyrrolidine-1-carboxylate, Isomer 2		699
375	*tert*-Butyl N-[3-cyano-4-[3-[[(2S)-5,5-difluoro-1-methyl-2-piperidyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		645
376	*tert*-Butyl N-[3-cyano-4-[3-[[(2S)-4,4-difluoro-1-methyl-2-piperidyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		645
377	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(1R,2S,5S)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		607

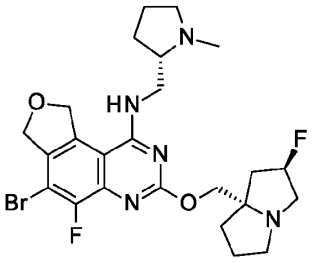
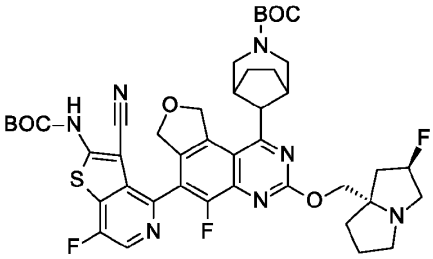
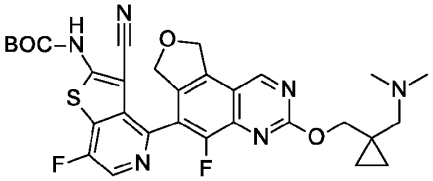
378	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-1-methyl-4-(trifluoromethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		663
379	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-1-methyl-4-(trifluoromethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		663
380	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		651
381	*tert*-Butyl N-[3-cyano-4-[3-[[(8S)-6,6-difluoro-2,3,5,7-tetrahydro-1H-pyrrolizin-8-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		657

382	*tert*-Butyl N-[4-[3-[[3-[*tert*-butyl(dimethyl)silyl]oxycyclobutyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		696
383	*tert*-Butyl N-[4-[3-[[3-[*tert*-butyl(dimethyl)silyl]oxycyclobutyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		696
384	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(3S)-4-methylmorpholin-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		611
385	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(3R)-4-methylmorpholin-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		611

386	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		582
387	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		582
388	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		613
389	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		613

390	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		581
391	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		581
392	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		611
393	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		611

394	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2S)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		611
395	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(3R)-tetrahydrofuran-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		582
396	*tert*-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(3S)-tetrahydrofuran-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate		582
397	6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-ol		442,444

398	6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-N-[[(2S)-1-methylpyrrolidin-2-yl]methyl]-7,9-dihydrofuro[3,4-f]quinazolin-1-amine		538,540
399	*tert*-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3-azabicyclo[3.2.1]octane-3-carboxylate		848
416	*tert*-Butyl N-[3-cyano-4-[3-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate		609

[1]The reaction was heated at 55 °C for ~ 18 h.

[2]single atropisomer (from precursor in Preparation 157)

[3]The reaction was heated at 80 °C for 1 h.

[4]The reaction was heated at 60 °C ~ 48 h.

[5]Chiralpak® AD-H, 21 x 150 mm, 25% IPA (0.5% DMEA) : 75% CO_2, 70 mL/min

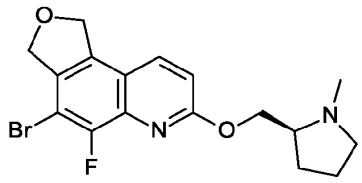
[6]single atropisomer (from precursor in Preparation 248)

[7]single atropisomer (from precursor in Preparation 251)

[8]Chiralcel® OD, 20 x 250 mm, 20% EtOH (0.5% DMEA) : 80% CO_2, 80 mL/min

Preparation 223

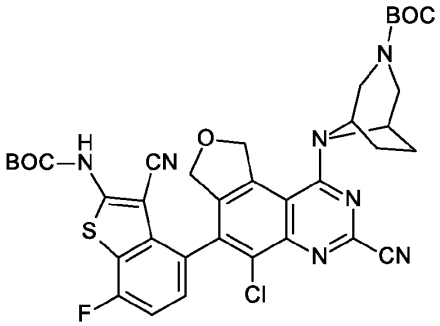
4-Bromo-5-fluoro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinoline



A solution of LHMDS (1M in THF, 7.3 mL, 7.3 mmol) and N-methyl-l-prolinol (0.9 mL, 7 mmol) in DMF (15 mL) was stirred for 5 min. A suspension of 4-bromo-7-chloro-5-fluoro-1,3-dihydrofuro[3,4-f]quinoline (1.0 g, 3.3 mmol) in DMF (30 mL) was added and stirred at RT for ~18 h. The reaction solution was added to H_2O (150 mL) and the resulting solid was filtered, washed with H_2O and placed under vacuum at 40 °C overnight to obtain the title compound (1.1 g, 85%) as a white solid. MS (ES) *m/z*=381 (M+1).

Preparation 224

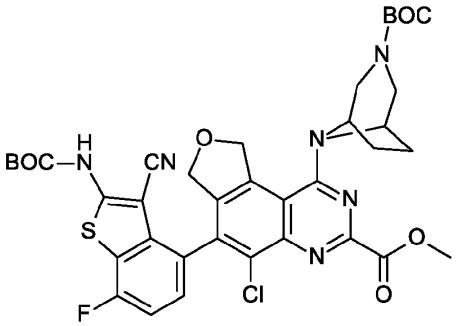
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-cyano-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



A mixture of *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-ethylsulfonyl-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, Isomer 2 (Preparation 157; 765 mg, 0.957 mmol) and NaCN (93.8 mg, 1.91 mmol) in DMSO (10 mL) was stirred at RT for 1 h. The resulting mixture was diluted with EtOAc (200 mL), washed with H_2O (3 x 200 mL), brine (200 mL), then was dried over anhydrous Na_2SO_4, filtered and was concentrated under reduced pressure to afford the title compound (650 mg, 93%) as a yellow solid. MS (ES) *m/z*=732 (M+1).

Preparation 225

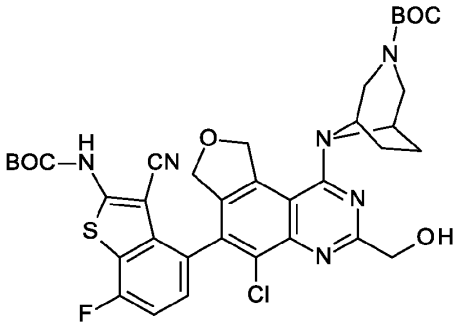
Methyl 6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-1-(3-*tert*-butoxycarbonyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-chloro-7,9-dihydrofuro[3,4-f]quinazoline-3-carboxylate



To a stirred solution of *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-cyano-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (650 mg, 0.888 mmol) in MeOH (10 mL) was added a solution of NaOH (71.0 mg, 1.78 mmol) in H_2O (10 mL) dropwise at RT. The resulting mixture was stirred for 2 h at RT. The mixture was cooled to 0 °C and was acidified to pH 2-3 with 1N HCl solution and was stirred for 2 h at RT. The resulting mixture was concentrated under reduced pressure and extracted with EtOAc (300 mL). The combined organic layers were washed with H_2O (3 x 200 mL), brine (200 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (580 mg, 85%) as a yellow solid. MS (ES) *m/z*=765 (M+1).

Preparation 226

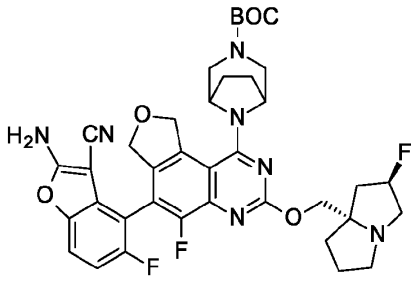
tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-chloro-3-(hydroxymethyl)-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



To a stirred mixture of methyl 6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-1-(3-*tert*-butoxycarbonyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-chloro-7,9-dihydrofuro[3,4-f]quinazoline-3-carboxylate (200 mg, 0.261 mmol) in EtOH (20 mL) at 0 °C was added $NaBH_4$ (19.8 mg, 0.522 mmol) in portions. The resulting mixture was stirred for 1h at RT under N_2. The reaction was quenched with H_2O at 0 °C. The resulting mixture was concentrated under reduced pressure and was extracted with EtOAc (300 mL). The organic layer was washed with H_2O (3 x 200 mL), brine (200 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (150 mg, 78%) as a yellow solid. MS (ES) *m/z*=737 (M+1).

Preparation 296

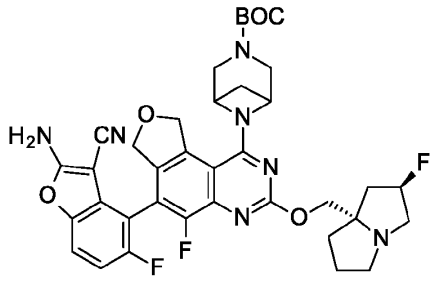
tert-Butyl 8-[6-(2-amino-3-cyano-5-fluoro-benzofuran-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate, Isomer 1



A mixture of *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.548 g, 0.659 mmol) and hexafluoroisopropanol (3 mL) was stirred under microwave irradiation at 110 °C for 4 min. The mixture was concentrated and purified by reversed phase flash purification on C18, eluting with 0% to 100% ACN in 10 mM aq. NH_4HCO_3 with 5% MeOH to obtain the racemate, followed by chiral purification (Chiralpak® IC, 21 x 250 mm, 35% EtOH (w/ 0.5% DMEA): 65% CO_2, 80 mL/min) to obtain the title compound (0.126 g) as a white solid. MS (ES) *m/z*=732 (M+1).

Preparation 297

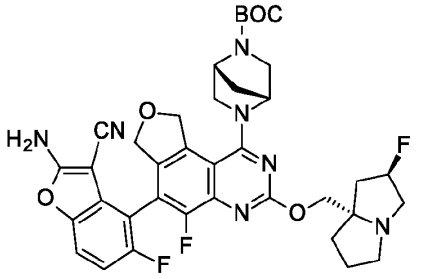
tert-Butyl 6-[6-(2-amino-3-cyano-5-fluoro-benzofuran-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate



tert-Butyl 6-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate was used in an analogous manner to the method of Preparation 296 to obtain the title compound (0.28 g). MS (ES) *m/z*=718 (M+1).

Preparation 298

tert-Butyl (1R,4R)-5-[6-(2-amino-3-cyano-5-fluoro-benzofuran-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate, Isomer 2

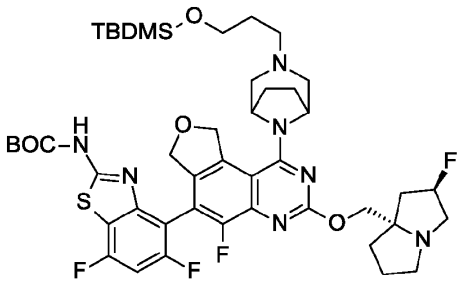


tert-Butyl (1R,4R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzofuran-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was used in an analogous manner to the method of Preparation 296, followed by chiral purification

(Chiralpak® IC, 21 x 250 mm, 40% MeOH : 60% CO_2, 70 mL/min) to obtain the title compound (0.14 g). MS (ES) *m/z*=718 (M+1).

Preparation 299

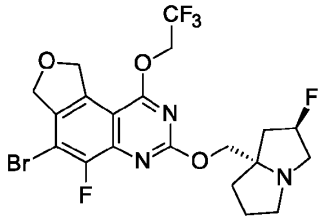
tert-Butyl N-[4-[1-[3-[3-[*tert*-butyl(dimethyl)silyl]oxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5,7-difluoro-1,3-benzothiazol-2-yl]carbamate



[2-(*tert*-Butoxycarbonylamino)-5,7-difluoro-1,3-benzothiazol-4-yl]boronic acid was used in an analogous manner to the method of Preparation 156 to obtain the title compound (0.50 g). MS (ES) *m/z*=914 (M+1).

Preparation 400

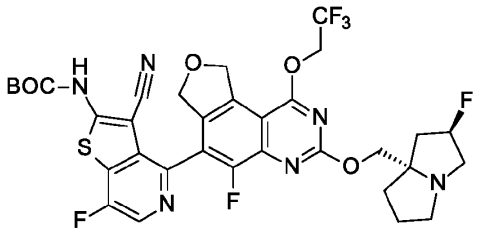
6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazoline



6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-ol and trifluoroethanol were used in an analogous manner to the method of Preparation 112 to obtain the title compound (2.2 g, 77%) as light yellow solid. MS (ES) *m/z*=524,526 (M+1,Br).

Preparation 401

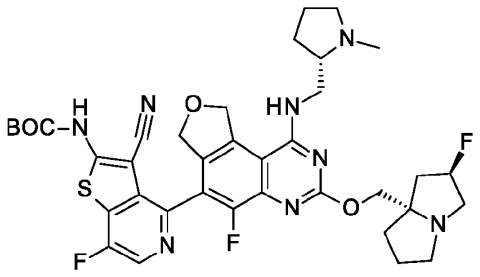
tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate



6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazoline and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were used in an analogous manner to the method of Preparation 158 to obtain the title compound (1.5 g) as light yellow solid. MS (ES) *m/z*=737 (M+1).

Preparation 402

tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[[(2S)-1-methylpyrrolidin-2-yl]methylamino]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate

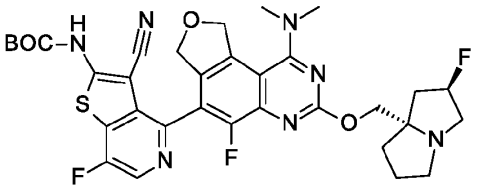


6-Bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-N-[[(2S)-1-methylpyrrolidin-2-yl]methyl]-7,9-dihydrofuro[3,4-f]quinazolin-1-amine and *tert*-butyl N-(4-chloro-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl)carbamate were

used in an analogous manner to the method of Preparation 158 to obtain the title compound. MS (ES) *m/z*=751 (M+1).

Preparation 403

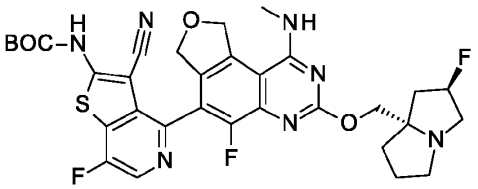
tert-Butyl N-[3-cyano-4-[1-(dimethylamino)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate



tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate and dimethylamine were used in an analogous manner to the method of Preparation 111 to obtain the title compound. MS (ES) *m/z*=682 (M+1).

Preparation 404

tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(methylamino)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate

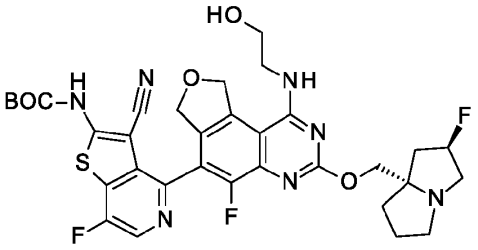


tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate and methylamine were used in an

analogous manner to the method of Preparation 111 to obtain the title compound. MS (ES) *m/z*=668 (M+1).

Preparation 405

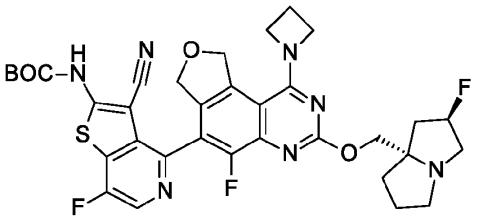
tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2-hydroxyethylamino)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate



tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate and ethanolamine were used in an analogous manner to the method of Preparation 111 to obtain the title compound. MS (ES) *m/z*=698 (M+1).

Preparation 406

tert-Butyl N-[4-[1-(azetidin-1-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-7-fluoro-thieno[3,2-c]pyridin-2-yl]carbamate

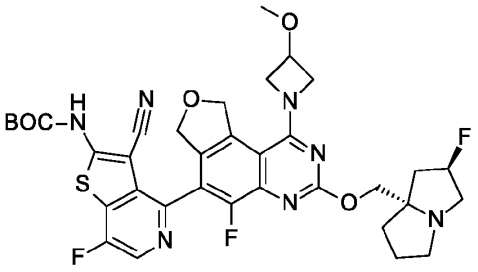


tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate and azetidine were used in an

analogous manner to the method of Preparation 111 to obtain the title compound. MS (ES) *m/z*=694 (M+1).

Preparation 407

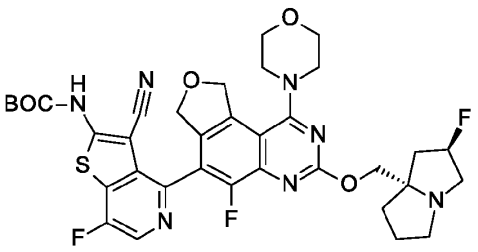
tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methoxyazetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate



tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate and 3-methoxyazetidine were used in an analogous manner to the method of Preparation 111 to obtain the title compound. MS (ES) *m/z*=724 (M+1).

Preparation 408

tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-morpholino-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate

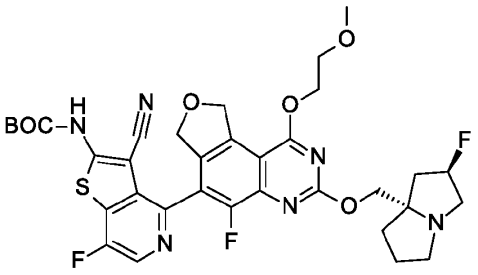


tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-

f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate and morpholine were used in an analogous manner to the method of Preparation 111 to obtain the title compound. MS (ES) *m/z*=724 (M+1).

Preparation 409

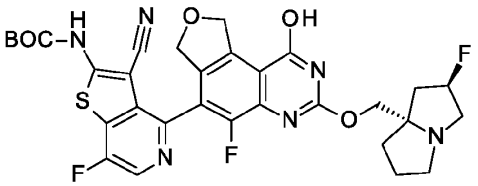
tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2-methoxyethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate



tert-Butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate and 2-methoxyethanol were used in an analogous manner to the method of Preparation 195 to obtain the title compound. MS (ES) *m/z*=713 (M+1).

Preparation 410

tert-butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate

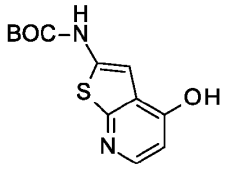


To a solution of *tert*-butyl N-[3-cyano-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-

dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridin-2-yl]carbamate (0.15 g, 0.20 mmol) in THF (2 mL) was added a solution of NaOH (0.041 g, 1.02 mmol) in H_2O (0.2 mL) dropwise under nitrogen. After 2h, the mixture was diluted with H_2O (50 mL) and extracted with EtOAc (2 x 100mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was diluted with DMF (2 mL) and purified by reversed phase flash purification on C18, eluting with 24% to 37% ACN in 10 mM aq. NH_4HCO_3 with 0.05% NH_4OH, to give the title compound (0.022 g, 16%) as a white solid. MS (ES) *m/z*=655 (M+1).

Preparation 411

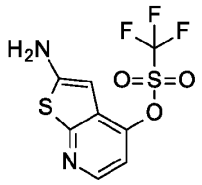
tert-Butyl N-(4-hydroxythieno[2,3-b]pyridin-2-yl)carbamate



A mixture of 4-hydroxythieno[2,3-b]pyridine-2-carboxylic acid;hydrochloride (1.96 g, 8.5 mmol) and triethylamine (4.8 mL, 34 mmol, 4.0 eq) in *tert*-butanol (40 mL) was heated to form a solution, then cooled to RT. Diphenylphosphoryl azide (2.5 mL, 11 mmol, 1.3 eq) was added. The reaction mixture was stirred at RT for 10 min, then heated at 85 °C overnight. The mixture was concentrated *in vacuo*. The residue was purified on silica, eluting with 10-100% acetone in hexanes to obtain the title compound (1.70 g, 76%). MS (ES) *m/z*=267 (M+1).

Preparation 412

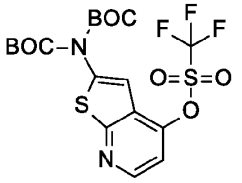
(2-Aminothieno[2,3-b]pyridin-4-yl) trifluoromethanesulfonate



To a suspension of *tert*-butyl N-(4-hydroxythieno[2,3-b]pyridin-2-yl)carbamate (1.45 g, 5.4 mmol) in DCM (110 mL) was added 2,6-lutidine (1.2 mL, 10 mmol, 1.9 eq) and 4-dimethylaminopyridine (0.067 g, 0.54 mmol, 0.10 eq). The reaction mixture was cooled in an ice bath, treated dropwise with trifluoromethanesulfonic anhydride (1.2 mL, 7.0 mmol, 1.3 eq), and stirred in the ice bath for 1 h. Additional 2,6-lutidine (1.2 mL, 10 mmol, 1.9 eq) and trifluoromethanesulfonic anhydride (1.2 mL, 7.0 mmol, 1.3 eq) were added. The reaction mixture was stirred in the ice bath for 30 min, then quenched with saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organics were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified on silica, eluting with 0-75% MTBE in hexanes to give impure fractions. The impure fractions were concentrated *in vacuo* and further purified on silica, eluting with 50-100% DCM in hexanes. The aqueous layer was extracted four times with 4:1 $CHCl_3$:isopropanol. The combined organics were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified on silica, eluting with 10-50% MTBE in hexanes. Clean fractions from the second and third silica purifications were combined and concentrated *in vacuo* to obtain the title compound (0.71 g, 44%) as an off-white solid. MS (ES) *m/z*=299 (M+1).

Preparation 413

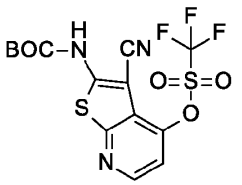
[2-[Bis(*tert*-butoxycarbonyl)amino]thieno[2,3-b]pyridin-4-yl] trifluoromethanesulfonate



To a solution of (2-aminothieno[2,3-b]pyridin-4-yl) trifluoromethanesulfonate (0.67 g, 2.26 mmol) in 1,4-dioxane (45 mL) was added di-*tert*-butyl dicarbonate (1.23 g, 5.64 mmol, 2.5 eq) and 4-dimethylaminopyridine (0.028 g, 0.227 mmol, 0.10 eq). The reaction mixture was stirred at RT for 6 days, and concentrated *in vacuo*. The residue was purified on silica, eluting with 0-50% MTBE in hexanes to obtain the title compound (0.93 g, 82%). MS (ES) *m/z*=499 (M+1).

Preparation 414

[2-(*tert*-Butoxycarbonylamino)-3-cyano-thieno[2,3-b]pyridin-4-yl] trifluoromethanesulfonate

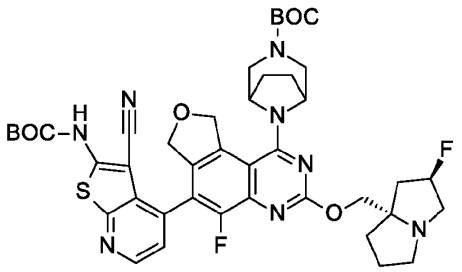


A solution of [2-[bis(*tert*-butoxycarbonyl)amino]thieno[2,3-b]pyridin-4-yl] trifluoromethanesulfonate (0.550 g, 1.10 mmol) in acetonitrile (11 mL) was cooled in an ice bath. Chlorosulfonyl isocyanate (0.3 mL, 3 mmol, 3 eq) was added dropwise and the reaction mixture was stirred in the ice bath for 5 h, placed in a -20 °C freezer overnight, allowed to warm to RT, and stirred for 3.5 h. The reaction mixture was cooled in an ice bath, added dropwise to N,N-dimethylformamide (8.5 mL, cooled in an ice bath), stirred for 1 h, slowly poured into cold saturated aqueous sodium bicarbonate, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organics were washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified on silica, eluting with 0-50% DCM in

hexanes to obtain the title compound (0.118 g, 25%) as an off-white solid. MS (ES) *m/z*=424 (M+1).

Preparation 415

tert-Butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-thieno[2,3-b]pyridin-4-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate



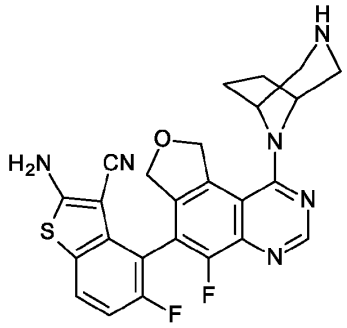
Reaction mixture A: A mixture of *tert*-butyl 8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.370 g, 0.581 mmol), KOAc (0.171 g, 1.74 mmol) and bis(neopentyl glycolato)diboron (0.197 g, 0.872 mmol) in 1,4-dioxane (6 mL) was sparged with N_2 for 10 min. Dichloro[bis(2-(diphenylphosphino)phenyl)ether]palladium(II) (0.043 g, 0.059 mmol) was added, and the resulting mixture was sealed and heated at 95 °C for 2.5 h. The reaction mixture was cooled to RT and kept overnight.

Reaction mixture B: A mixture of tert-butyl 8-[6-bromo-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.370 g, 0.581 mmol), KOAc (0.171 g, 1.74 mmol) and bis(neopentyl glycolato)diboron (0.197 g, 0.872 mmol) in 1,4-dioxane (6 mL) was sparged with N2 for 10 min. Dichloro[bis(2-(diphenylphosphino)phenyl)ether]palladium(II) (0.043 g, 0.059 mmol) was added, and the resulting mixture was sealed and heated at 95 °C overnight. The reaction mixture was cooled to RT.

Reaction mixture C: A mixture of [2-(*tert*-butoxycarbonylamino)-3-cyano-thieno[2,3-b]pyridin-4-yl] trifluoromethanesulfonate (0.162 g, 0.383 mmol), 1,4-dioxane (4 mL) and water (1.2 mL) was sparged with N_2 for 15 min. Potassium phosphate (0.162 g, 0.763 mmol) and XPhos Pd G4 (CAS# 1599466-81-5; 0.035 g, 0.039 mmol) were added, and the resulting mixture was sealed and heated at 85 °C. Reaction mixture A was added via syringe and heated for 1 h before cooling to RT. The reaction mixture was again heated at 85 °C. One-third of Reaction mixture B was added via syringe and heated for 1 h. The remainder of Reaction mixture B was added via syringe and heated for 1 h. The reaction mixture was partitioned between DCM and water. The layers were separated, and the aqueous layer was extracted 2x with DCM. The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica, eluting with 1-5% 7N ammoniated methanol/DCM to afford the title compound (0.200 g, 45%). MS (ES) *m/z*= 831 (M+1).

Example 1

2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile, Isomer 2

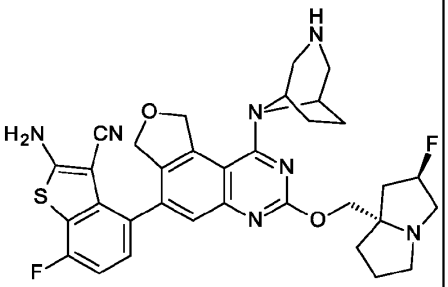
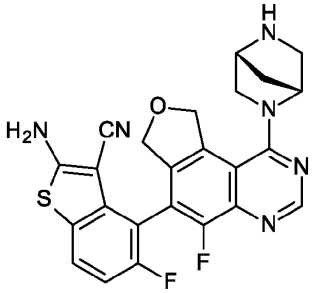


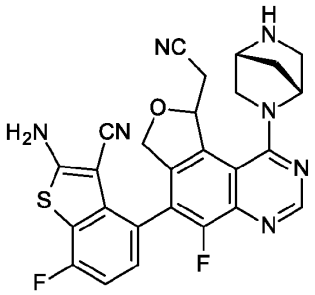
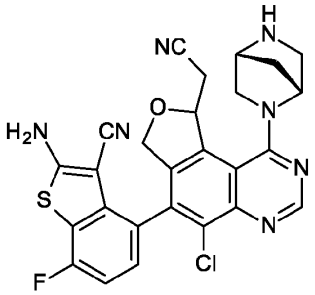
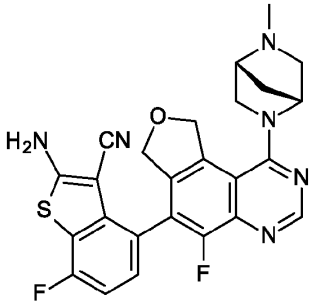
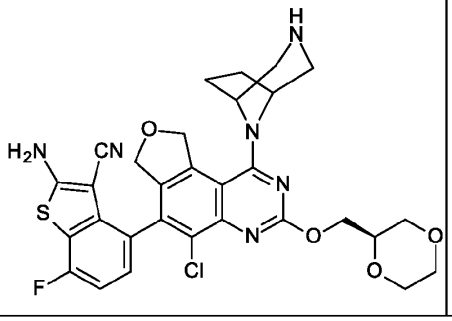
A solution of *tert*-butyl 8-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-5-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (0.605 g, 0.876 mmol) in DCM (5 mL) was charged with TFA (4 mL) and stirred at RT for 25 min. The mixture was concentrated, DCM was added and the mixture was concentrated again, repeating 3x. The mixture was filtered

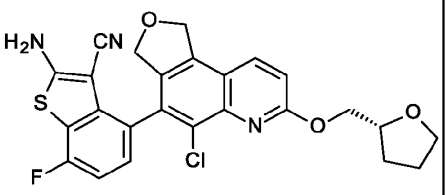
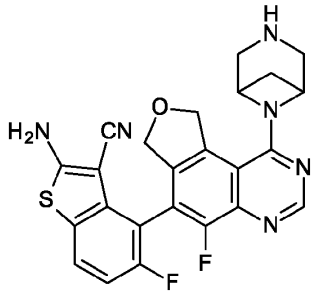
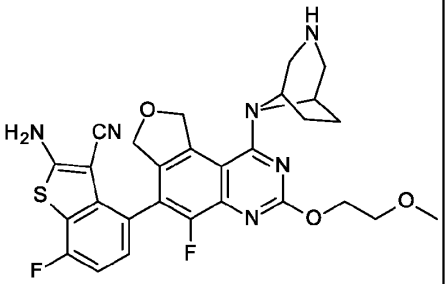
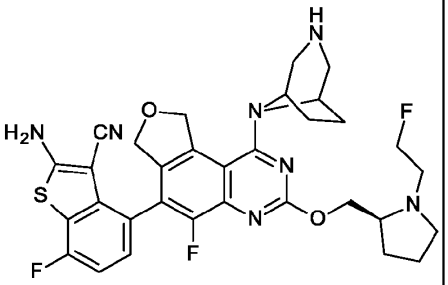
through an SCX column, eluting with MeOH (4 CV), followed by 7N NH_3/MeOH (4 CV) to obtain the crude product which was purified on silica gel, eluting with a gradient of 1% to 10% 7N NH_3/MeOH in DCM to obtain the racemate, followed by chiral purification (Chiralpak® AS-H, 21 x 250 mm, 35% MeOH (w/ 0.5% DMEA): 65% CO_2, 80 mL/min) to obtain the title compound (0.129 g, 30%) as a white solid. MS (ES) *m/z*=491 (M+1).

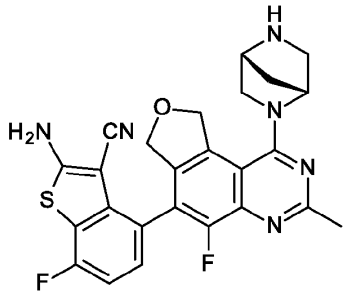
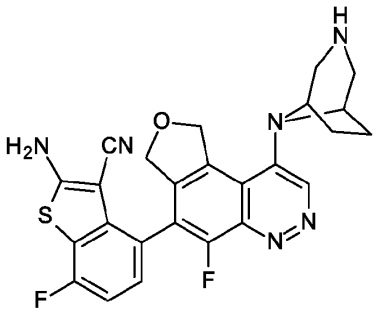
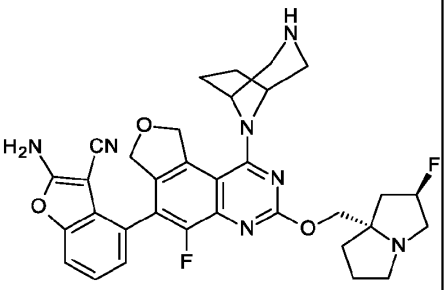
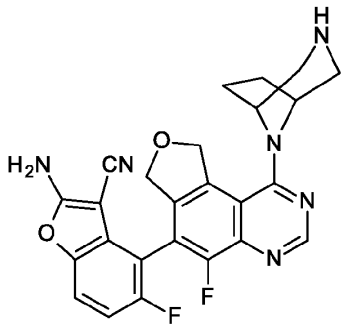
The Example compounds in Table 14 were prepared in a similar manner as described for Preparation 296 or Example 1. Various methods were used to purify the compounds, which would be apparent to one skilled in the art. Chiral purification methods (if applicable) for the Examples of Table 14 are located in Table 18.

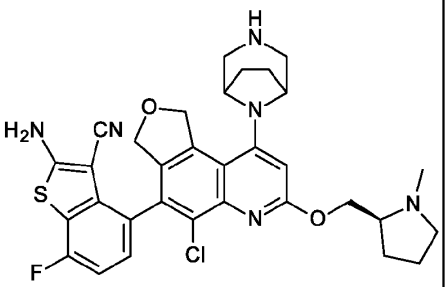
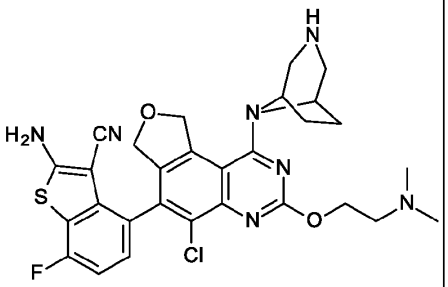
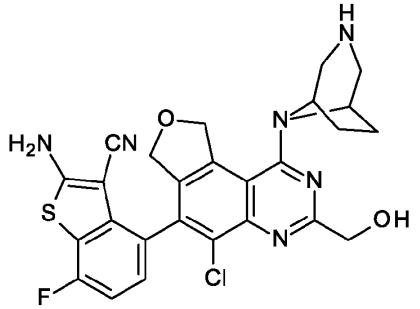
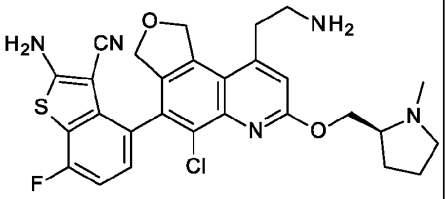
Table 14:

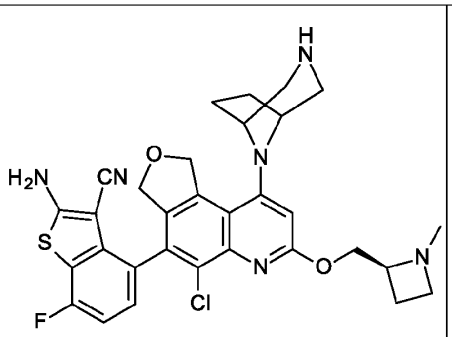
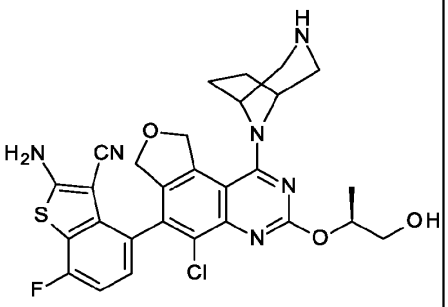
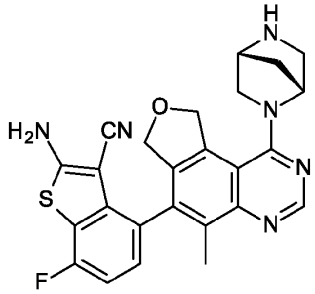
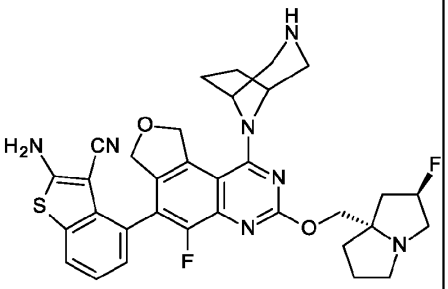
Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)
2	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		630
3	2-Amino-4-[1-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile, Isomer 2		477

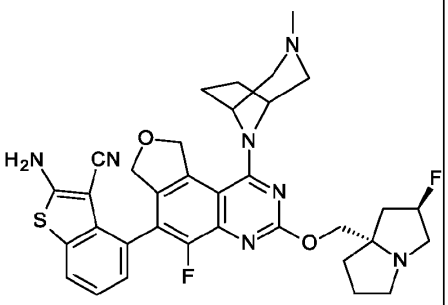
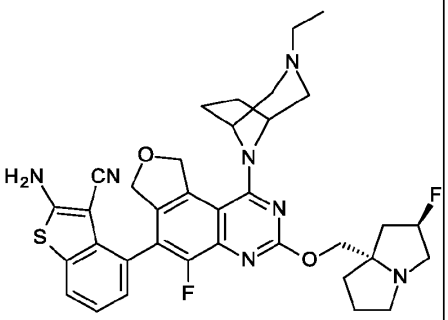
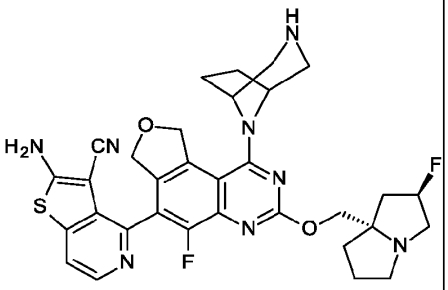
4[1]	2-Amino-4-[9-(cyanomethyl)-1-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		516
5[1]	2-Amino-4-[5-chloro-9-(cyanomethyl)-1-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 2		532
6	2-Amino-7-fluoro-4-[5-fluoro-1-[(1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		491
7	2-Amino-4-[5-chloro-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2R)-1,4-dioxan-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		623

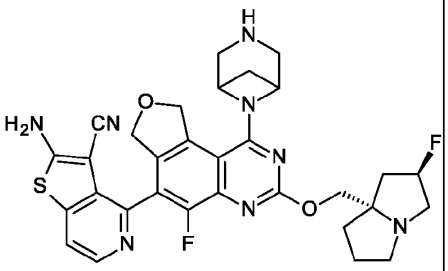
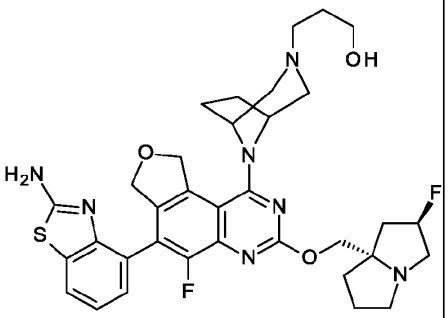
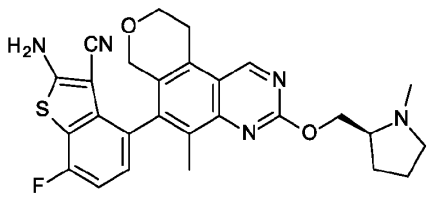
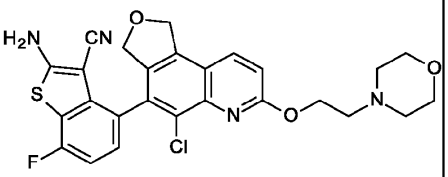
8	2-Amino-4-[5-chloro-7-[[(2R)-tetrahydrofuran-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile		496
9	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile, Isomer2		477
10	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(2-methoxyethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		565
11	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-(2-fluoroethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		636

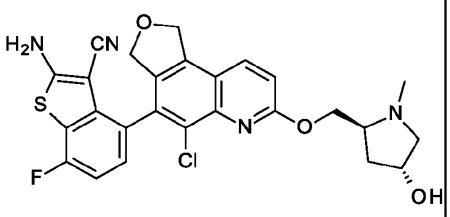
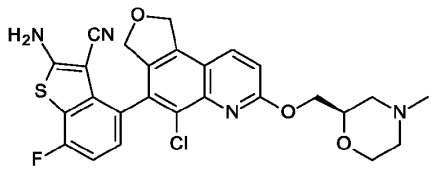
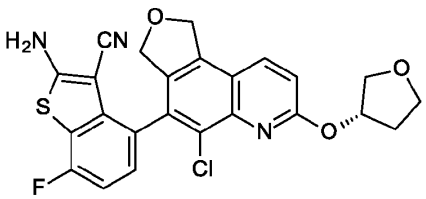
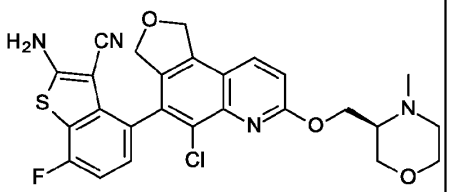
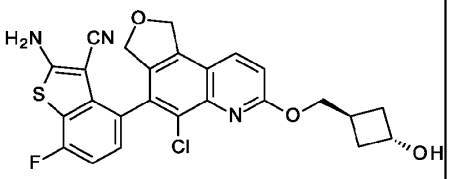
12	2-Amino-4-[1-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-5-fluoro-3-methyl-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		491
13	2-Amino-4-[9-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-1,3-dihydrofuro[3,4-f]cinnolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile		491
14	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		614
15	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzofuran-3-carbonitrile, Isomer 2		475

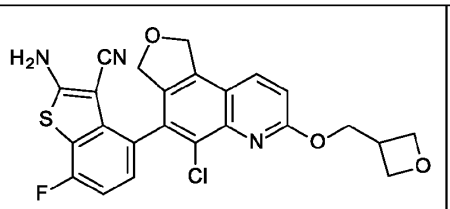
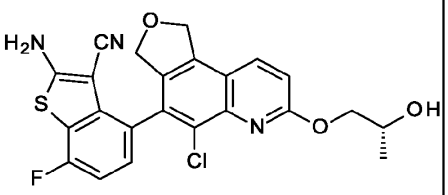
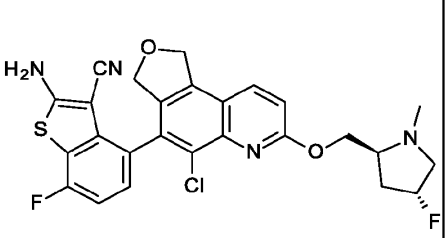
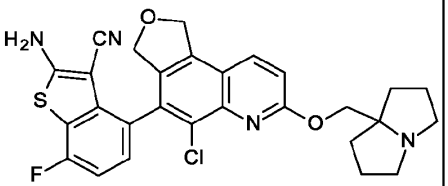
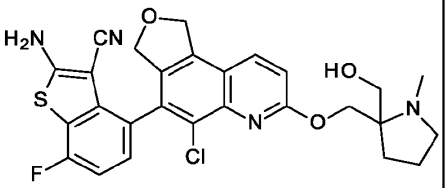
16	2-Amino-4-[5-chloro-9-(3,8-diazabicyclo[3.2.1]octan-8-yl)-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile		619
17[2]	2-Amino-4-[5-chloro-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[2-(dimethylamino)ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		594
18	2-Amino-4-[5-chloro-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-(hydroxymethyl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 2		537
19	2-Amino-4-[9-(2-aminoethyl)-5-chloro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile		552

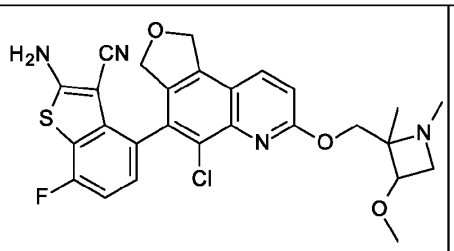
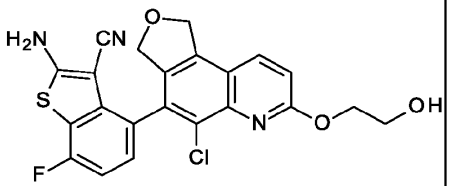
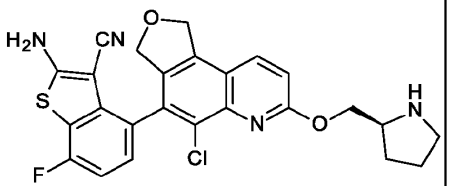
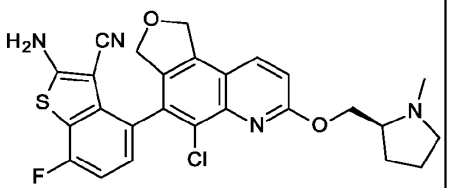
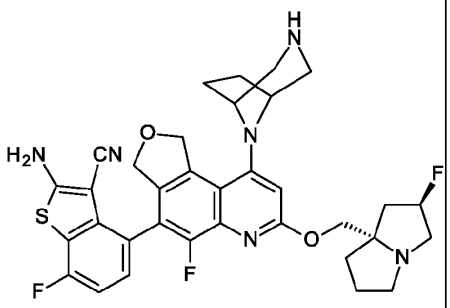
20	2-Amino-4-[5-chloro-9-(3,8-diazabicyclo[3.2.1]octan-8-yl)-7-[[(2S)-1-methylazetidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile		605
21	2-Amino-4-[5-chloro-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[(1S)-2-hydroxy-1-methyl-ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		581
22	2-Amino-4-[1-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-5-methyl-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		473
23	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		630

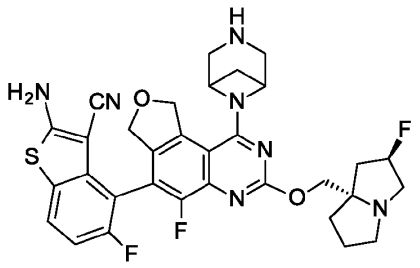
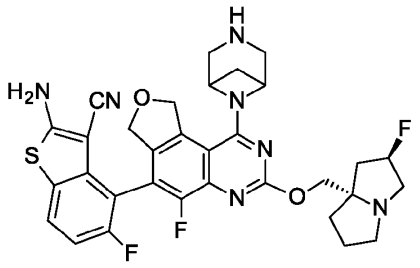
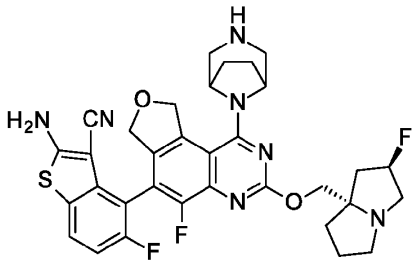
24	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		644
25	2-Amino-4-[1-(3-ethyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		658
26	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		631

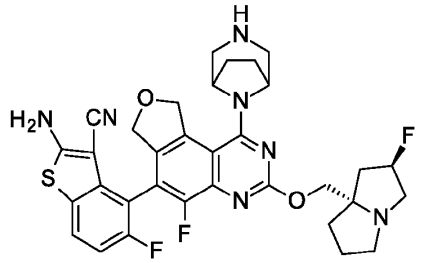
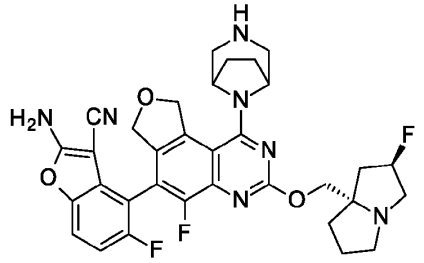
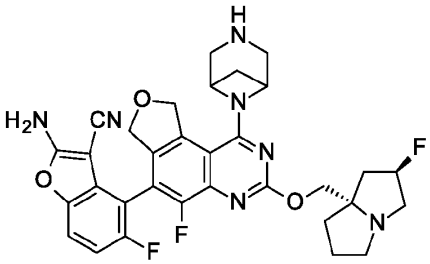
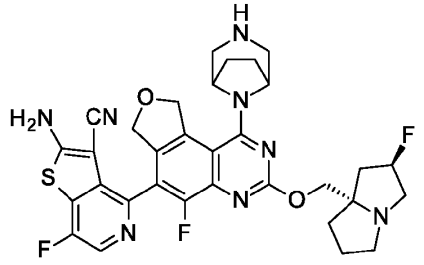
27	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		617
28	3-[8-[6-(2-Amino-1,3-benzothiazol-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]propan-1-ol		664
29	2-Amino-7-fluoro-4-[5-methyl-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-9,10-dihydro-7H-pyrano[4,3-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		502[a]
30	2-Amino-4-[5-chloro-7-(2-morpholinoethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		525

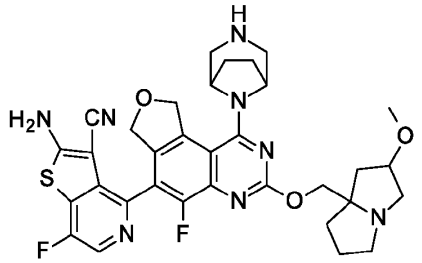
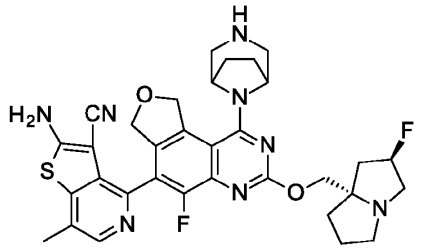
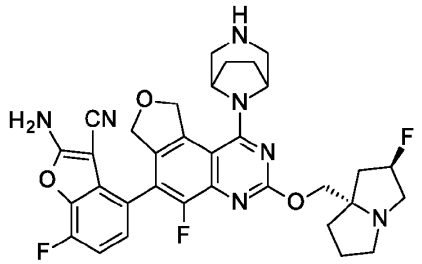
31	2-Amino-4-[5-chloro-7-[[(2S,4R)-4-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		525
32	2-Amino-4-[5-chloro-7-[[(2R)-4-methylmorpholin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 2		525
33	2-Amino-4-[5-chloro-7-[(3S)-tetrahydrofuran-3-yl]oxy-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 2		482
34	2-Amino-4-[5-chloro-7-[[(3S)-4-methylmorpholin-3-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		525
35	2-Amino-4-[5-chloro-7-[(3-hydroxycyclobutyl)methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		496

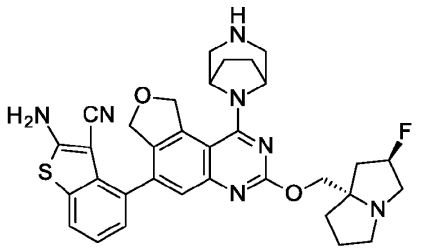
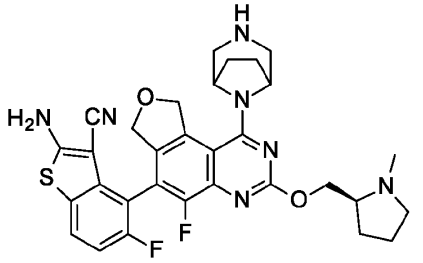
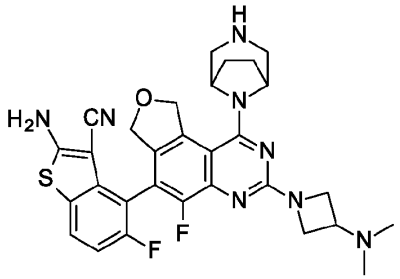
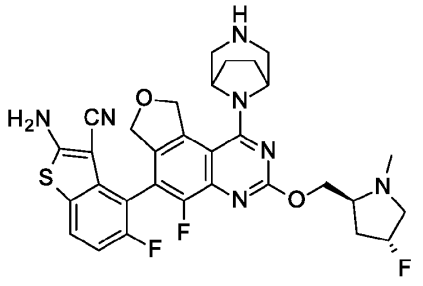
36	2-Amino-4-[5-chloro-7-(oxetan-3-ylmethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		482
37	2-Amino-4-[5-chloro-7-[(2R)-2-hydroxypropoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile		470
38	2-Amino-4-[5-chloro-7-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		527
39	2-Amino-4-[5-chloro-7-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		535
40	2-Amino-4-[5-chloro-7-[[2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		539

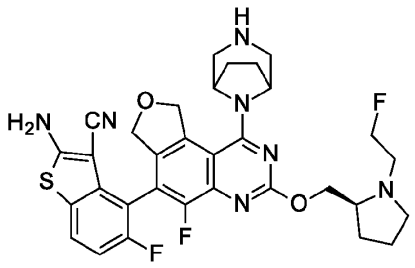
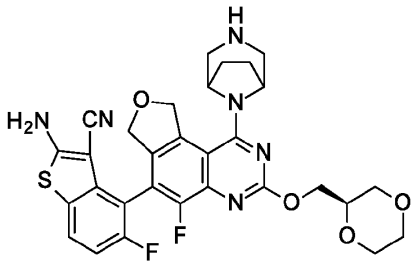
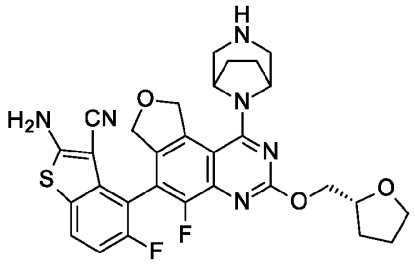
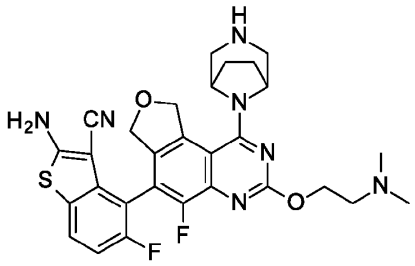
41	2-Amino-4-[5-chloro-7-[(3-methoxy-1,2-dimethyl-azetidin-2-yl)methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		539
42	2-Amino-4-[5-chloro-7-(2-hydroxyethoxy)-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile		456
43	2-Amino-4-[5-chloro-7-[[(2S)-pyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		495
44	2-Amino-4-[5-chloro-7-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		509
45	2-Amino-4-[9-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1,3-dihydrofuro[3,4-f]quinolin-4-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		647

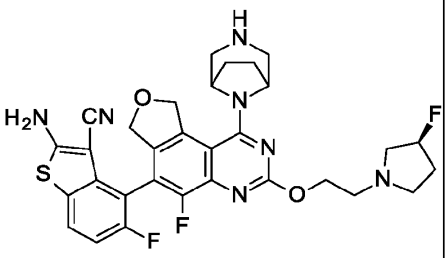
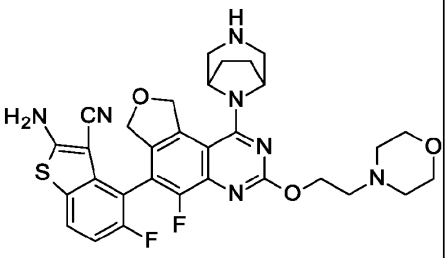
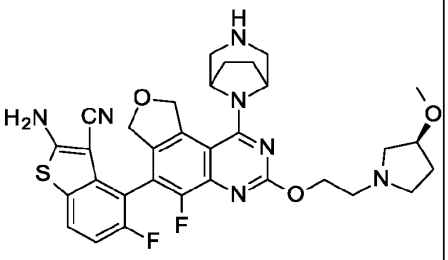
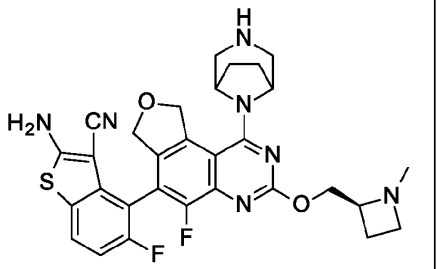
58	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		634
59[3]	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		634
60	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		648

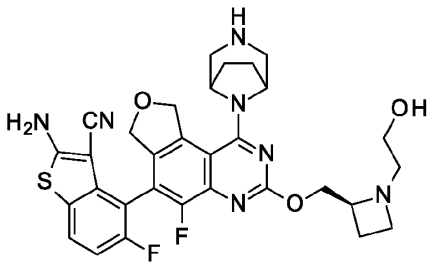
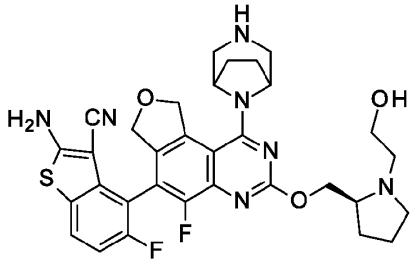
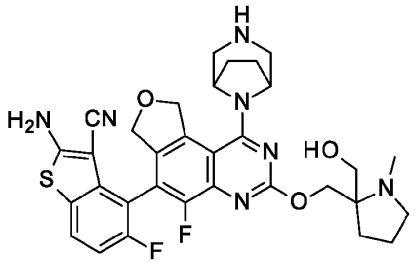
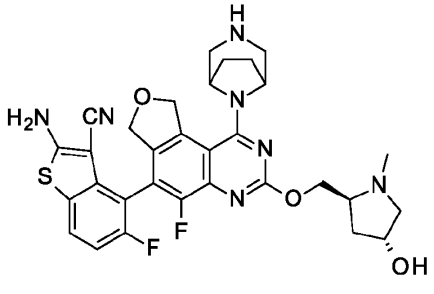
61[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		648
62[5]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzofuran-3-carbonitrile		632
63	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzofuran-3-carbonitrile		618
64	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		649

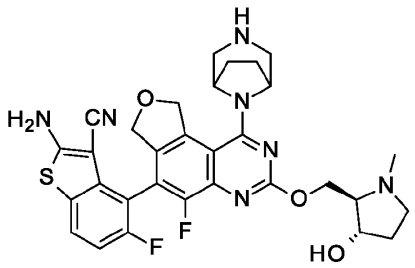
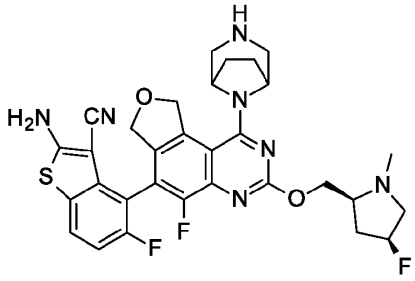
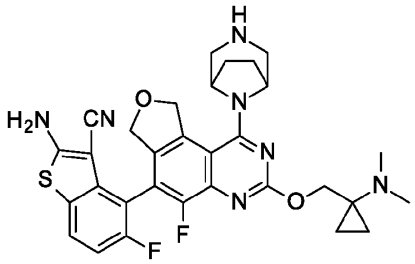
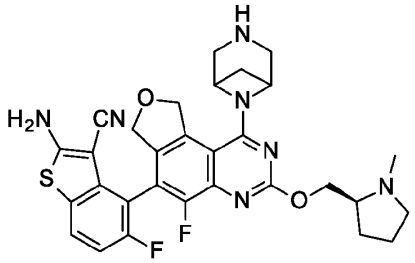
65	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		661
66	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-methyl-thieno[3,2-c]pyridine-3-carbonitrile		645
67	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzofuran-3-carbonitrile		632

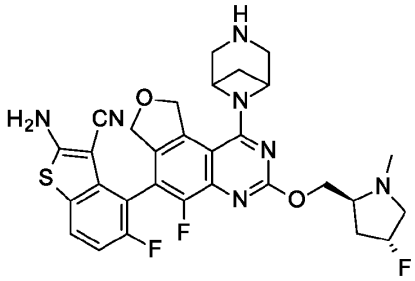
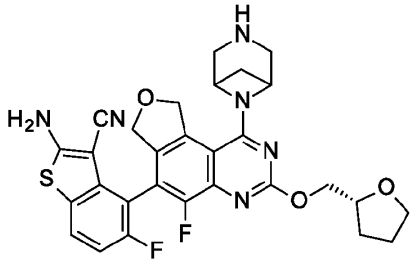
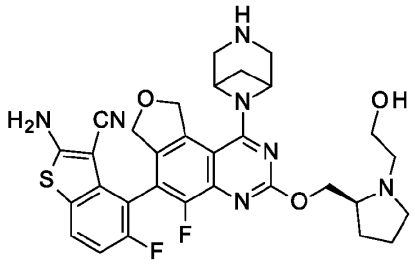
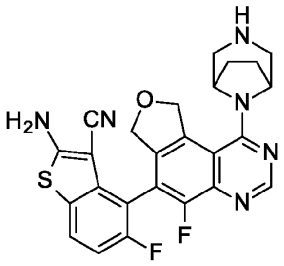
68	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		612
69[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		604
70[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[3-(dimethylamino)azetidin-1-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		589
71[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		622

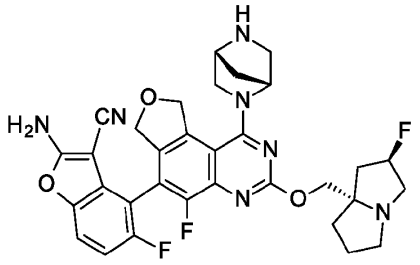
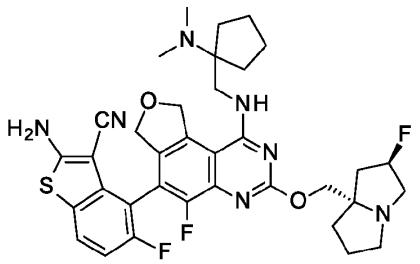
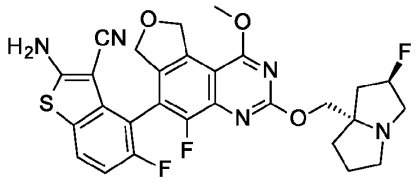
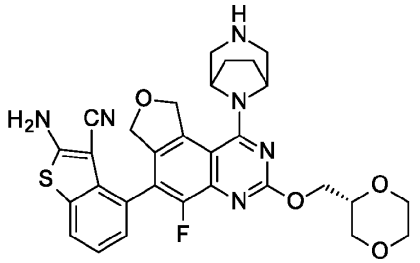
72[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-(2-fluoroethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		636
73[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2R)-1,4-dioxan-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		607
74[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		591
75[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[2-(dimethylamino)ethoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		578

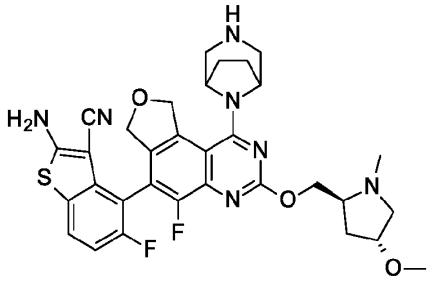
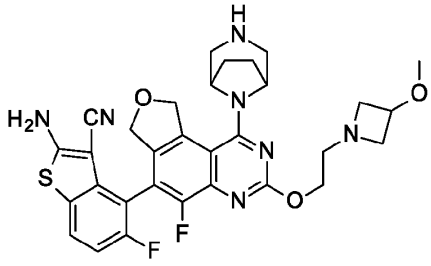
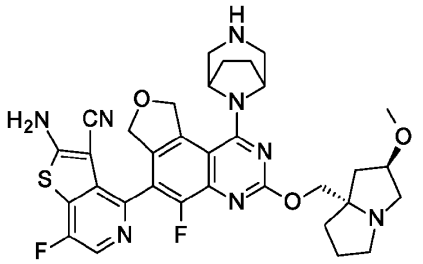
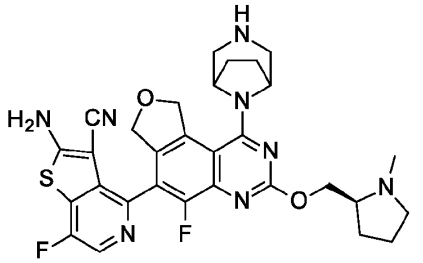
76[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[2-[(3S)-3-fluoropyrrolidin-1-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		622
77[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620
78[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[2-[(3S)-3-methoxypyrrolidin-1-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		634
79[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		590

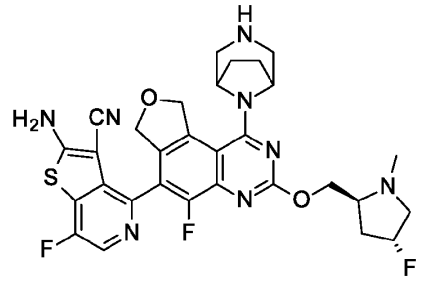
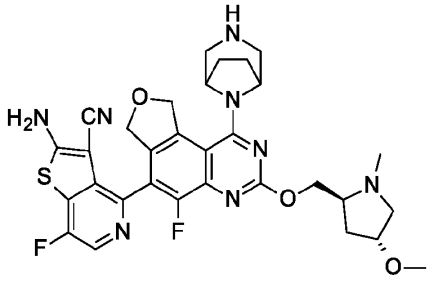
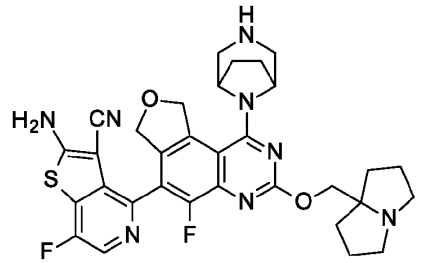
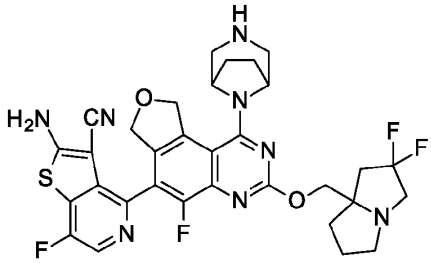
80[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)azetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620
81[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		634
82[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		634
83[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S,4R)-4-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620

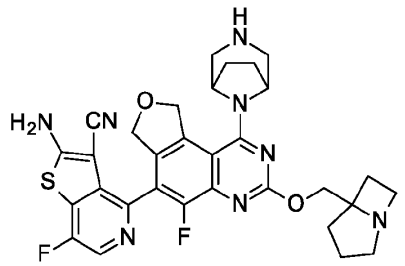
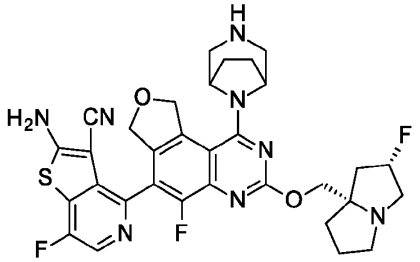
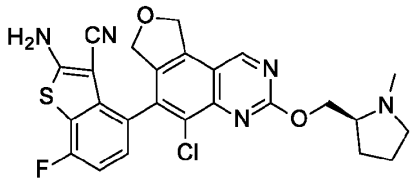
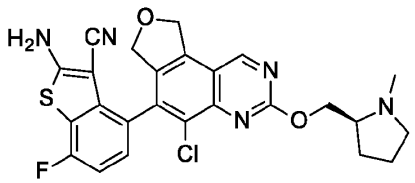
84[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,3S)-3-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620
85[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		622
86[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[1-(dimethylamino)cyclopropyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		604
87[6]	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		590

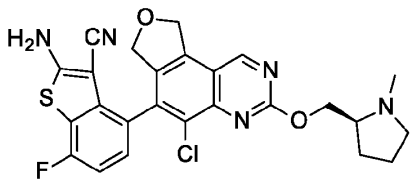
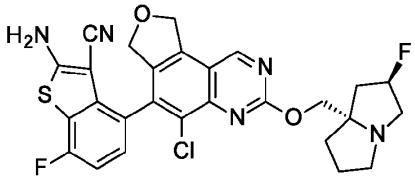
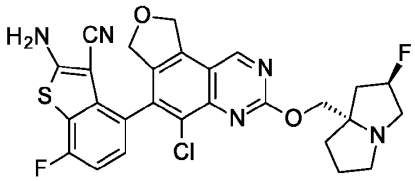
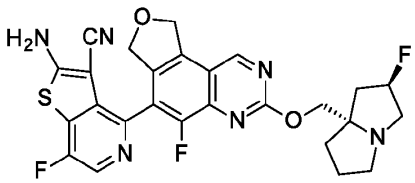
88[6]	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		608
89[6]	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		577
90[6]	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620
91[7]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		491

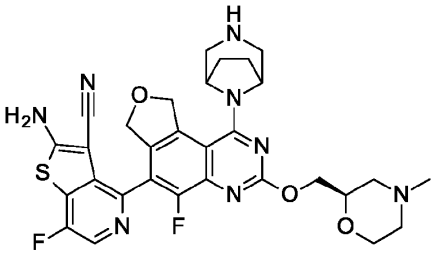
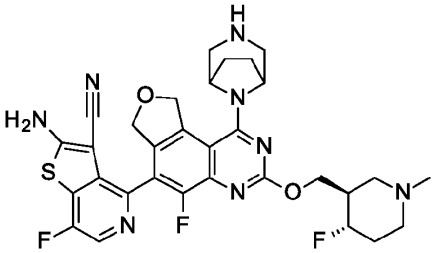
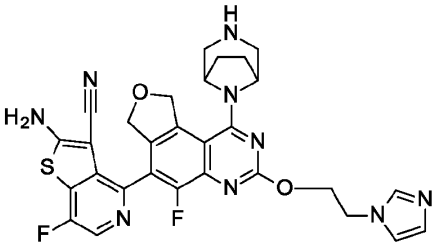
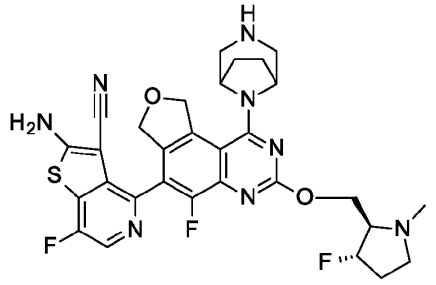
92[8]	2-Amino-4-[1-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzofuran-3-carbonitrile		618
93	2-Amino-4-[1-[[1-(dimethylamino)cyclopentyl]methylamino]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		678
94	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-methoxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		568
195	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2R)-1,4-dioxan-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		589

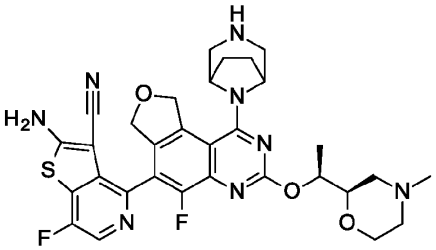
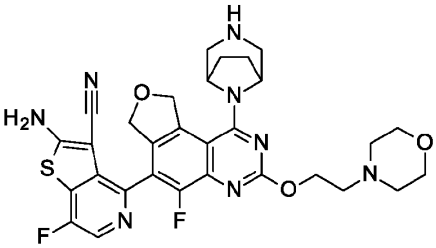
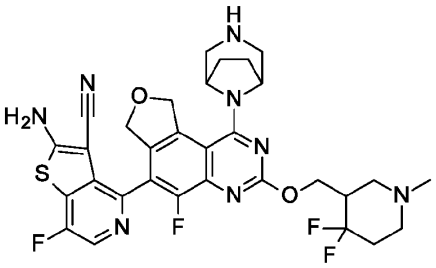
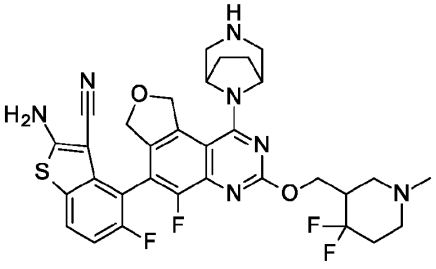
196[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		634
197[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[2-(3-methoxyazetidin-1-yl)ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620
198	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		661
199	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		605

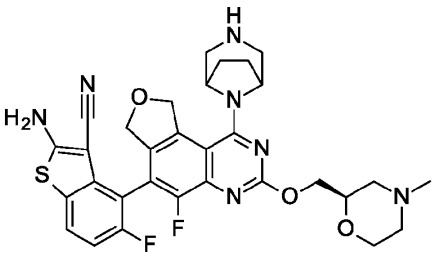
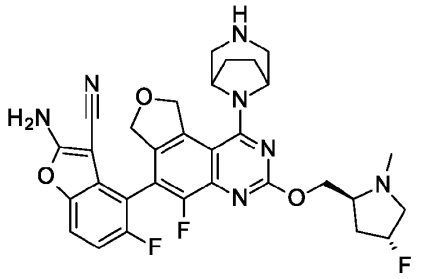
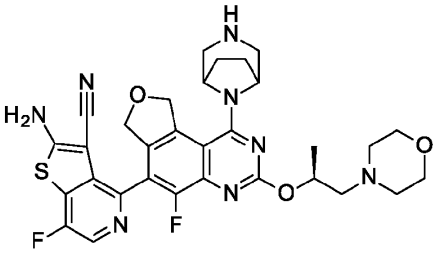
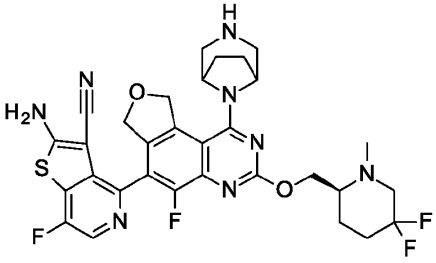
200	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		623
201	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		635
202	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		631
203	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[(6,6-difluoro-2,3,5,7-tetrahydro-1H-pyrrolizin-8-yl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		667

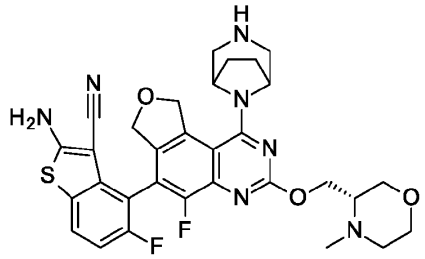
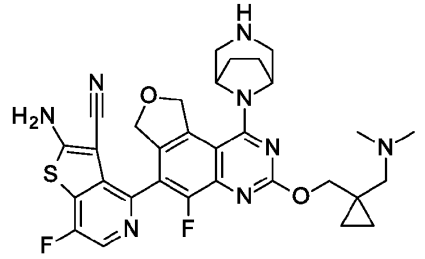
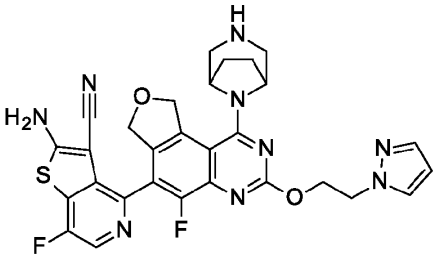
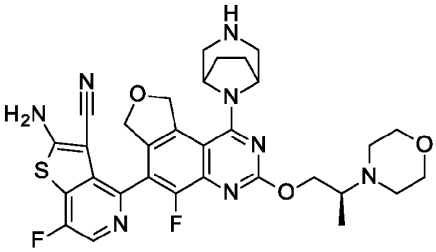
204	2-Amino-4-[3-(1-azabicyclo[3.2.0]heptan-5-ylmethoxy)-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		617
205	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2SR,8SR)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		649
206	2-Amino-4-[5-chloro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile		510
207	2-Amino-4-[5-chloro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		510

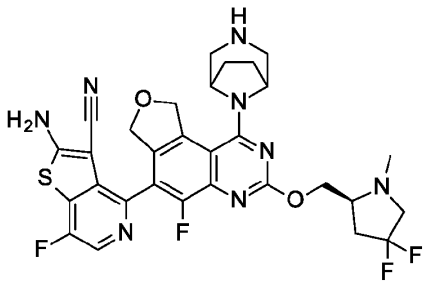
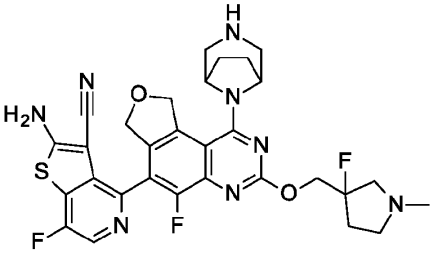
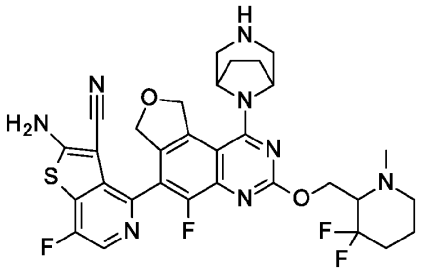
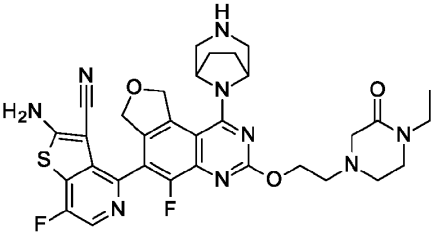
208	2-Amino-4-[5-chloro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 2		510
209	2-Amino-4-[5-chloro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 1		554
210	2-Amino-4-[5-chloro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-benzothiophene-3-carbonitrile, Isomer 2		554
211	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		539

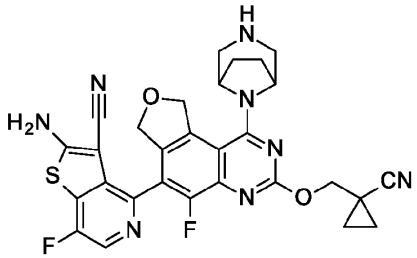
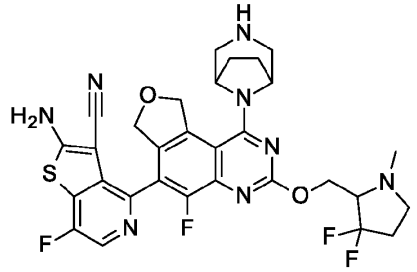
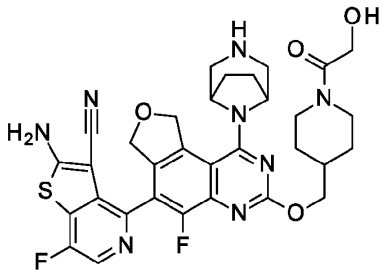
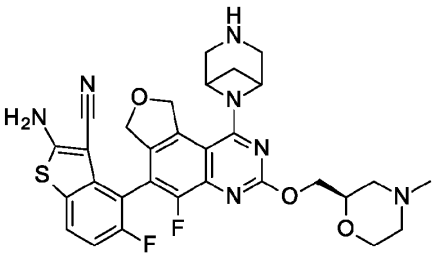
251	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		621
252	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(3R,4S)-4-fluoro-1-methyl-3-piperidyl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		637
253	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(2-imidazol-1-ylethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		602
254	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,3S)-3-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		623

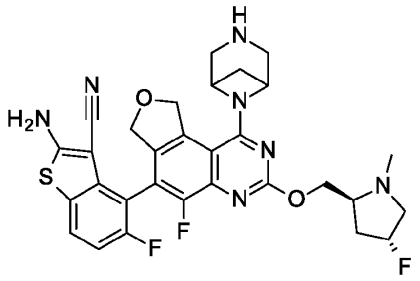
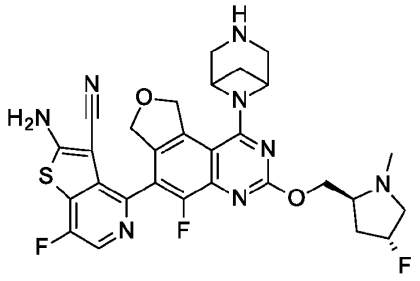
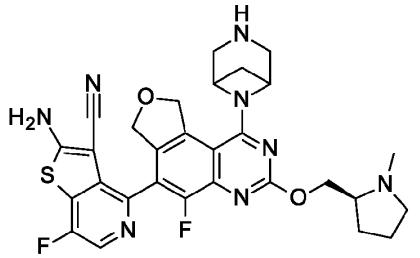
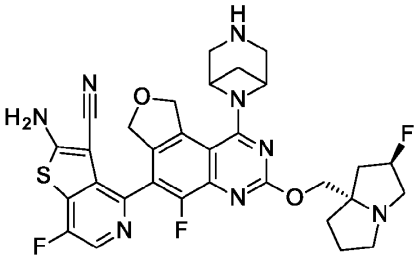
255	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[(1S)-1-[(2R)-4-methylmorpholin-2-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		635
256	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		621
257	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		655
258[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		654

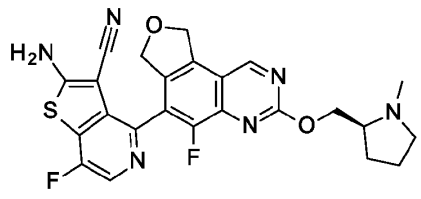
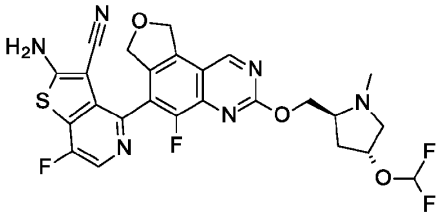
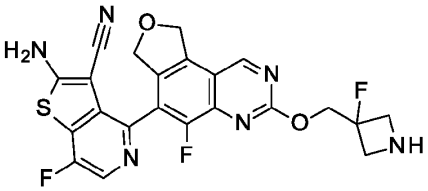
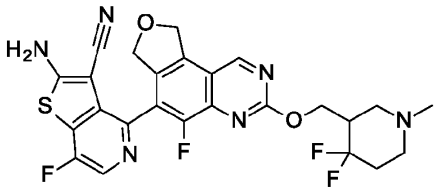
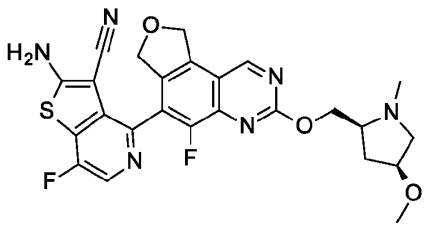
259[4]	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620
260	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzofuran-3-carbonitrile		606
261	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[(1S)-1-methyl-2-morpholino-ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		635
262	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2S)-5,5-difluoro-1-methyl-2-piperidyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		655

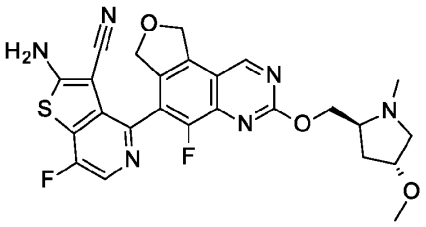
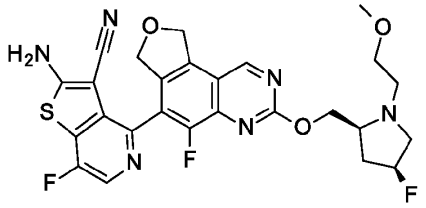
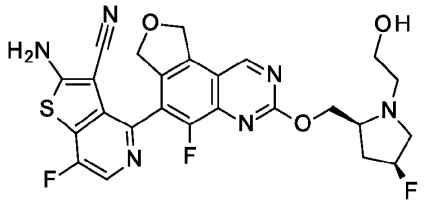
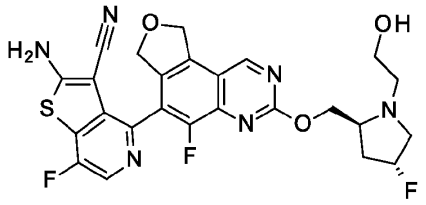
263	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(3S)-4-methylmorpholin-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		620
264	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		619
265	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-(2-pyrazol-1-ylethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		602
266	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[(2S)-2-morpholinopropoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		635

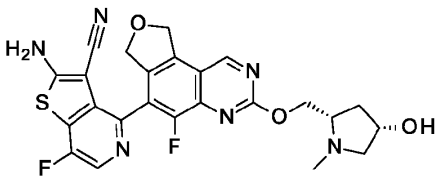
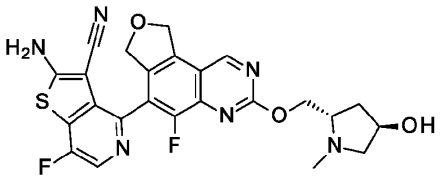
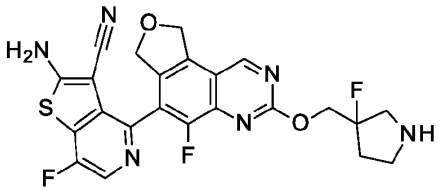
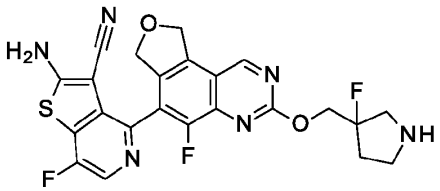
267	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2S)-4,4-difluoro-1-methyl-pyrrolidin-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		641
268	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[(3-fluoro-1-methyl-pyrrolidin-3-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		623
269	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[(3,3-difluoro-1-methyl-2-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		655
270	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[2-(4-ethyl-3-oxo-piperazin-1-yl)ethoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		662

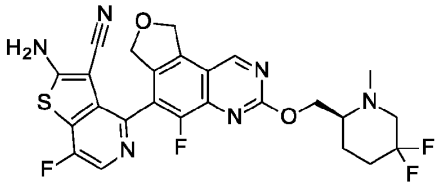
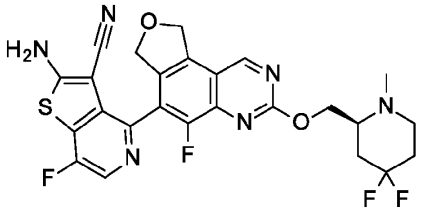
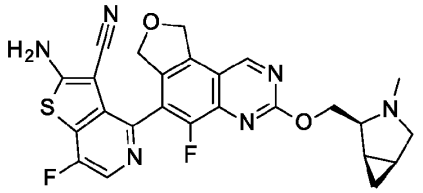
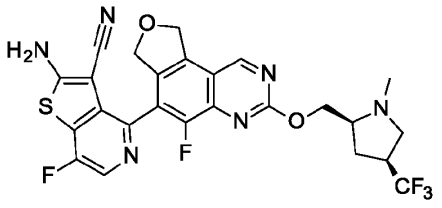
271	2-Amino-4-[3-[(1-cyanocyclopropyl)methoxy]-1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		587
272	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[(3,3-difluoro-1-methyl-pyrrolidin-2-yl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		641
273	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[1-(2-hydroxyacetyl)-4-piperidyl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		663
274	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		606

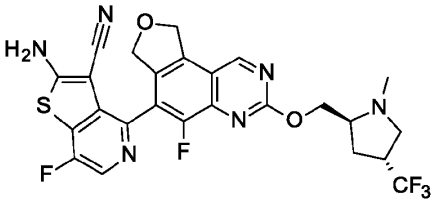
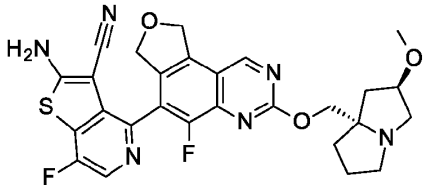
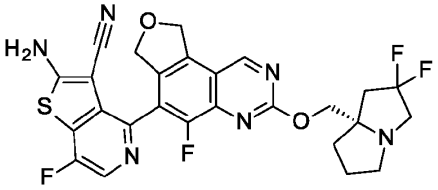
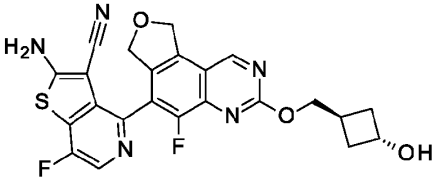
275	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		608
276	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		609
277	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		591
278	2-Amino-4-[1-(3,6-diazabicyclo[3.1.1]heptan-6-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		635

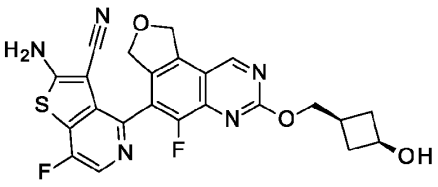
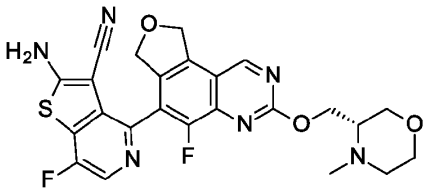
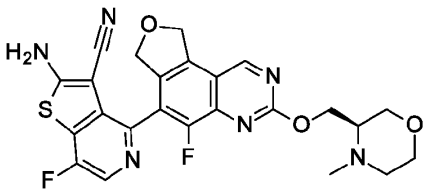
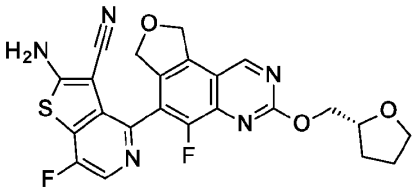
279	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		495
280	2-Amino-4-[3-[[(2S,4R)-4-(difluoromethoxy)-1-methyl-pyrrolidin-2-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		561
281	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-fluoroazetidin-3-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		485
282	2-Amino-4-[3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		545
283	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		525

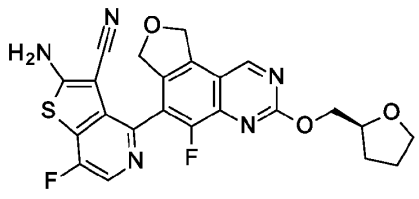
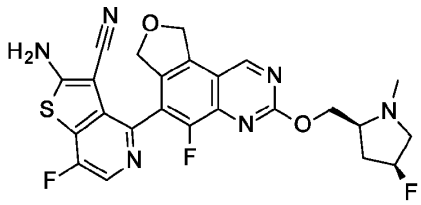
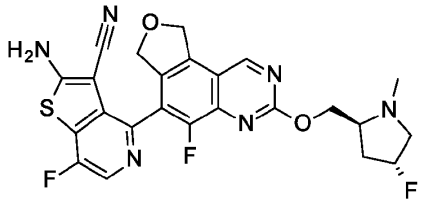
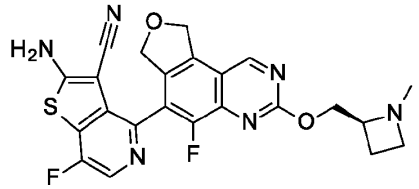
284	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		525
285	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-fluoro-1-(2-methoxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		557
286	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-fluoro-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		543
287	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		543

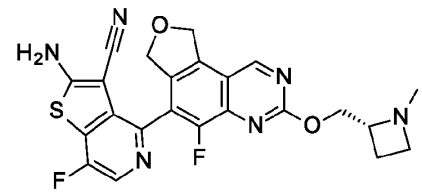
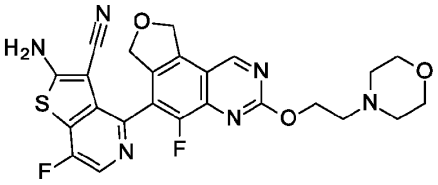
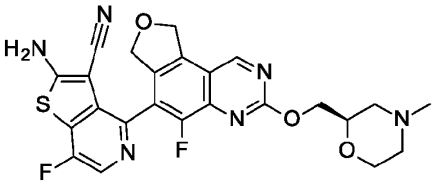
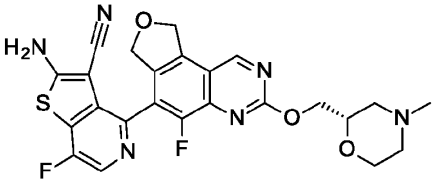
288	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		511
289	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		511
290	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-fluoropyrrolidin-3-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		499
291	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-fluoropyrrolidin-3-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		499

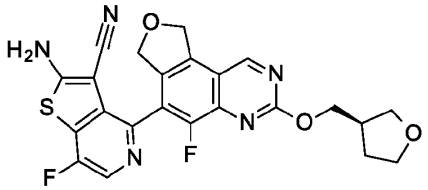
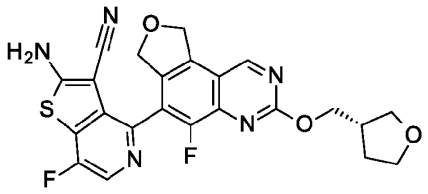
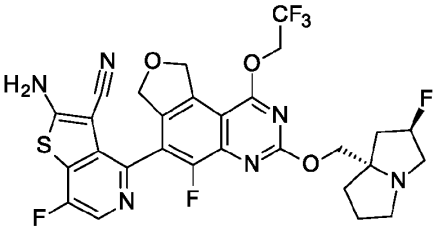
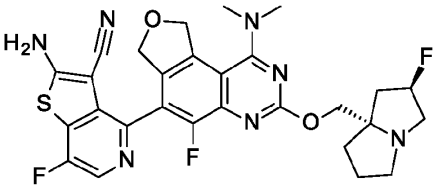
292	2-Amino-4-[3-[[(2S)-5,5-difluoro-1-methyl-2-piperidyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		545
293	2-Amino-4-[3-[[(2S)-4,4-difluoro-1-methyl-2-piperidyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		545
294	2-Amino-7-fluoro-4-[5-fluoro-3-[[(1R,2S,5S)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		507
295	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-1-methyl-4-(trifluoromethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		563

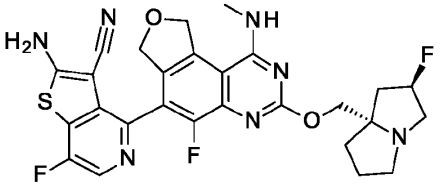
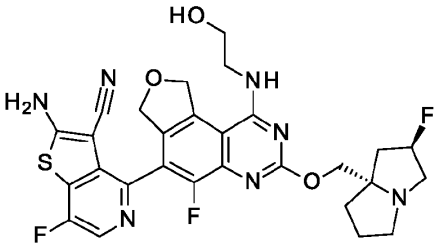
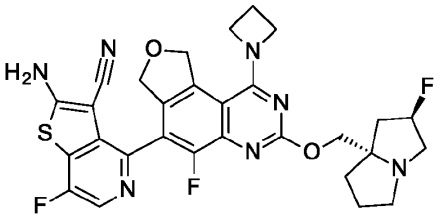
296	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-1-methyl-4-(trifluoromethyl)pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		563
297	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		551
298	2-Amino-4-[3-[[(8S)-6,6-difluoro-2,3,5,7-tetrahydro-1H-pyrrolizin-8-yl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		557
299	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-hydroxycyclobutyl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		482

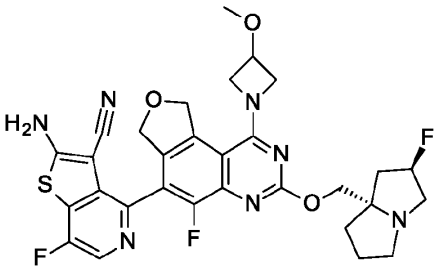
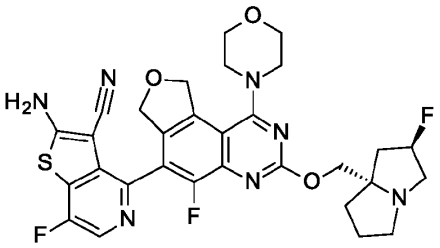
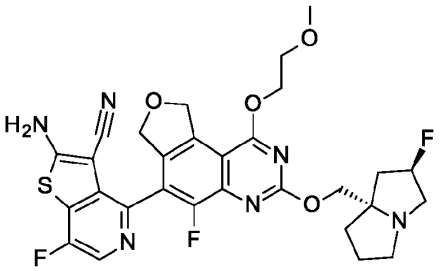
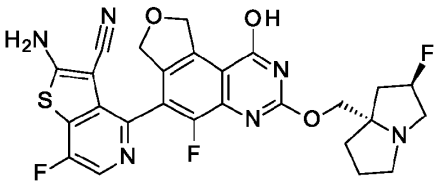
300	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-hydroxycyclobutyl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		482
301	2-Amino-7-fluoro-4-[5-fluoro-3-[[(3S)-4-methylmorpholin-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		511
302	2-Amino-7-fluoro-4-[5-fluoro-3-[[(3R)-4-methylmorpholin-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		511
303	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		482

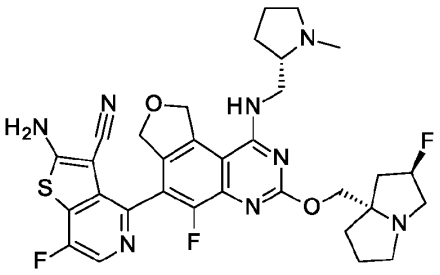
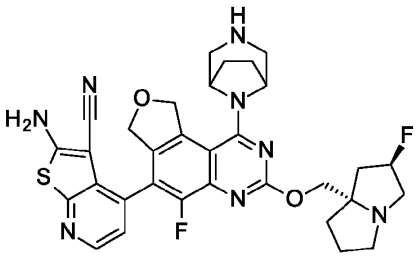
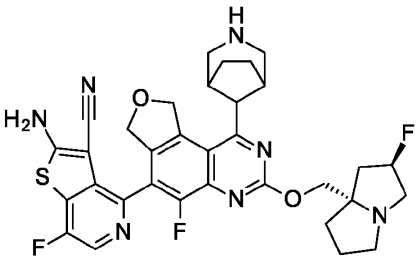
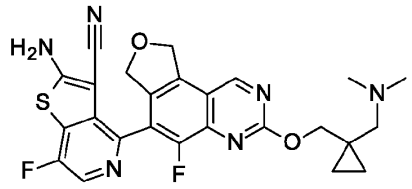
304	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		482
305	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		513
306	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		513
307	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		481

308	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		481
309	2-Amino-7-fluoro-4-[5-fluoro-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		511
310	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		511
311	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		511

312	2-Amino-7-fluoro-4-[5-fluoro-3-[[(3R)-tetrahydrofuran-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		482
313	2-Amino-7-fluoro-4-[5-fluoro-3-[[(3S)-tetrahydrofuran-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		482
314	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2,2,2-trifluoroethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		637
315	2-Amino-4-[1-(dimethylamino)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		582

316	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(methylamino)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		568
317	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2-hydroxyethylamino)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		598
318	2-Amino-4-[1-(azetidin-1-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		594

319	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methoxyazetidin-1-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		624
320	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-morpholino-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		624
321	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(2-methoxyethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		613
322	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-hydroxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		555

323	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[[(2S)-1-methylpyrrolidin-2-yl]methylamino]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		651
324	2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[2,3-b]pyridine-3-carbonitrile		631
325	2-Amino-4-[1-(3-azabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		648
375	2-Amino-4-[3-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		509

[1]single diastereomer

[2]single atropisomer (from precursor in Preparation 157)

[3]single atropisomer (from precursor in Preparation 266)

[4]single atropisomer (from precursor in Preparation 248)

[5]single atropisomer (from precursor in Preparation 296)

[6]single atropisomer (from precursor in Preparation 251)

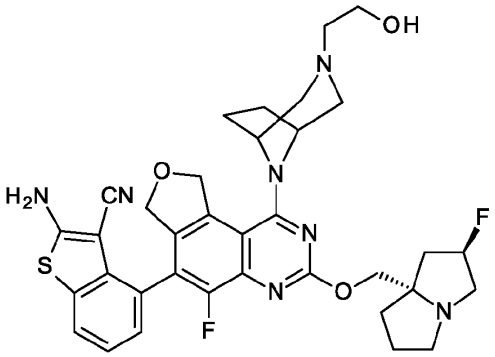
[7]single atropisomer (from precursor in Preparation 255)

[8]single atropisomer (from precursor in Preparation 298)

[a] measured in MS (ES)$^-$

Example 46

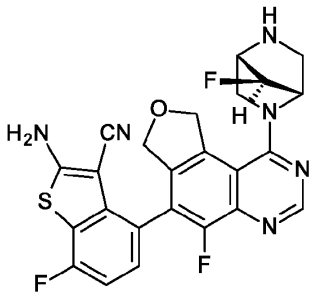
2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile



A solution of *tert*-butyl N-[4-[1-[3-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-3-cyano-benzothiophen-2-yl]carbamate (0.250 g, 0.281 mmol) in THF (2 mL) was treated with 1M TBAF in THF (0.7 mL, 0.7 mmol) and was stirred at RT for 1.5 h. A second portion of 1M TBAF in THF (0.7 mL, 0.7 mmol) was added and the mixture was stirred for ~ 18 h. The mixture was concentrated and dried *in vacuo*. The residue was dissolved in DCM (5 mL), treated with TFA (2 mL) and stirred at RT for ~ 18 h. The mixture was concentrated. DCM was added, and the mixture was concentrated again. The residue was dissolved in DCM/MeOH and loaded onto SCX, eluting with MeOH and DCM, then with 1:1 2N NH_3/MeOH:DCM. The ammoniated eluent was concentrated *in vacuo*, and residue was further purified by reversed phase flash chromatography on C18, eluting with 5-50% ACN in 10 mM aq. NH_4HCO_3 with 5% MeOH) to obtain the title compound (0.111 g, 59%) as an off-white solid. MS (ES) *m/z*=674 (M+1).

Example 47

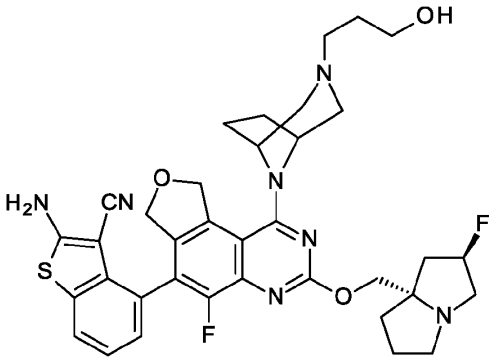
2-Amino-7-fluoro-4-[5-fluoro-1-[(1S,4S,7S)-7-fluoro-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile



Benzyl (1S,4S,7R)-5-[6-[2-(*tert*-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-5-fluoro-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-7-fluoro-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (280 mg, 0.384 mmol) was stirred in TFA (10.0 mL) at RT. The resulting mixture was then stirred for 5 h at 70 °C. The mixture was concentrated under reduced pressure and was diluted with DMF (3 mL). The mixture was then basified to pH 9 with NH_3H_2O. The mixture was purified on C18, eluting with a gradient of 46% to 65% ACN in 10 mM aq. NH_4HCO_3 to afford the title compound (39.5 mg, 20.2%) as a white solid. MS (ES) *m/z*=495 (M+1).

Example 48

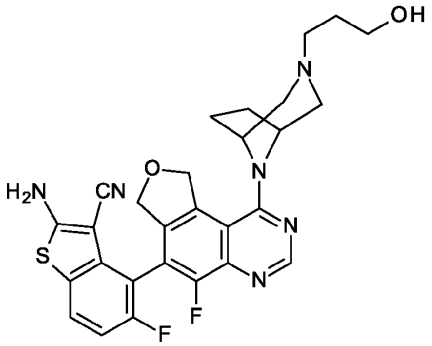
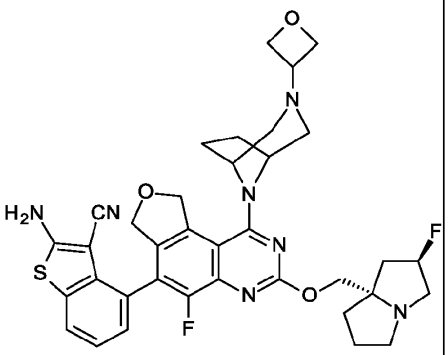
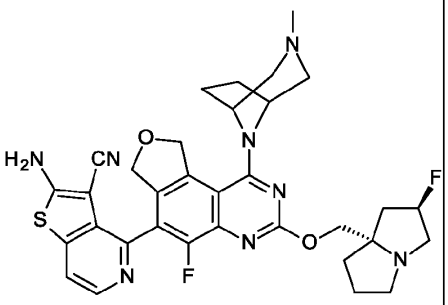
2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile

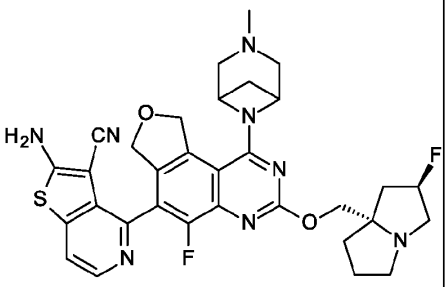
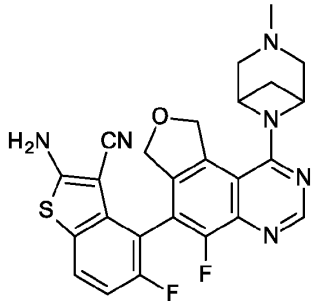
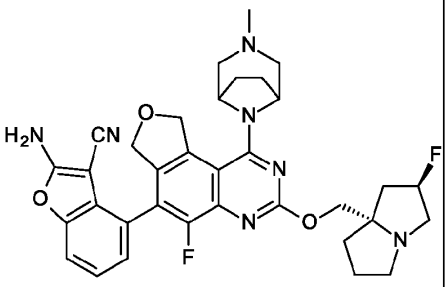


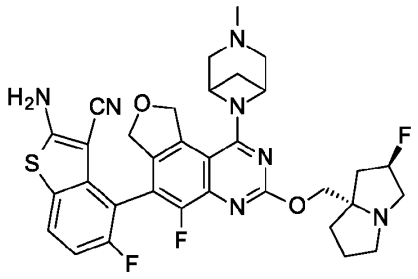
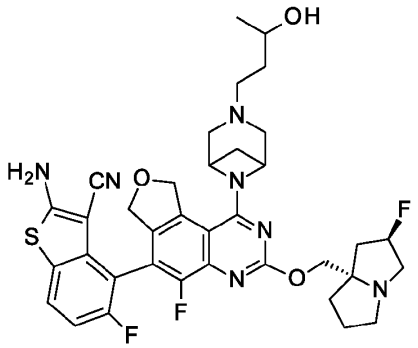
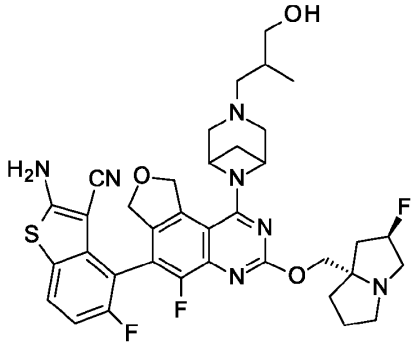
A solution of 2-amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile (0.800 g, 1.27 mmol) in DCM (13 mL) and MeOH (2.5 mL) was treated with 3-[(*tert*-butyldimethylsilyl)oxy]-1-propanal (0.756 g, 3.81 mmol) and $NaBH(OAc)_3$ (0.850 g, 3.81 mmol). After stirring at RT for 1 h, the reaction mixture was poured directly onto SCX, eluting first with MeOH and DCM, then with 1:1 2N NH_3/MeOH:DCM. The ammoniated fractions were concentrated. The residue was dissolved in DCM/MeOH and passed over SCX a second time. The residue from concentration of the ammoniated fraction was purified on silica (eluting with 0% to 5% 7N NH_3/MeOH in DCM) followed by reversed phase flash chromatography on C18 (eluting with 5% to 51% ACN in 10 mM aq. NH_4HCO_3 with 5% MeOH) to obtain the title compound (0.541 g, 62%) as a light-beige solid. MS (ES) *m/z*=688 (M+1).

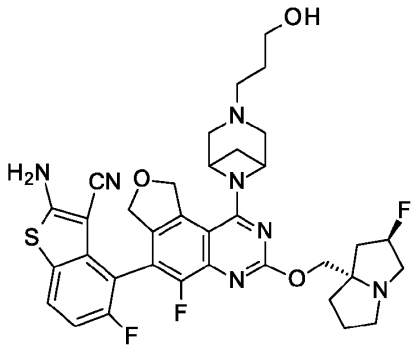
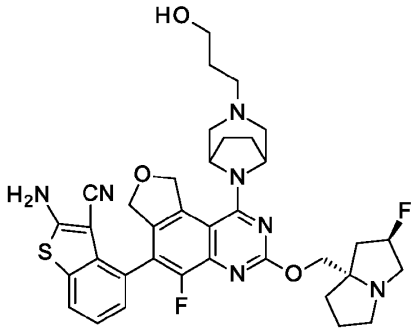
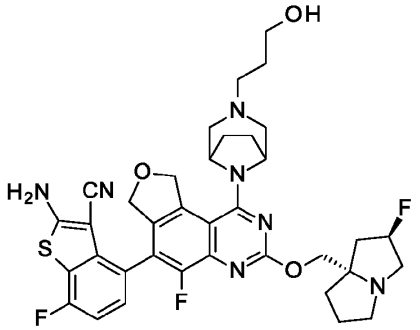
The Example compounds in Table 15 were prepared in a similar manner as described for Example 48. Various methods were used to purify the compounds, which would be apparent to one skilled in the art. Chiral purification methods (if applicable) for the Examples of Table 15 are located in Table 18.

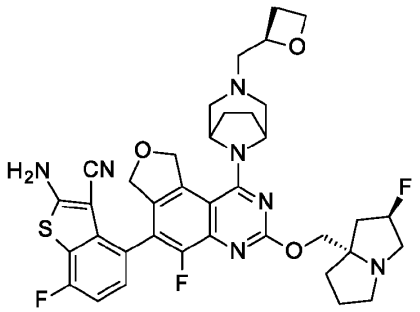
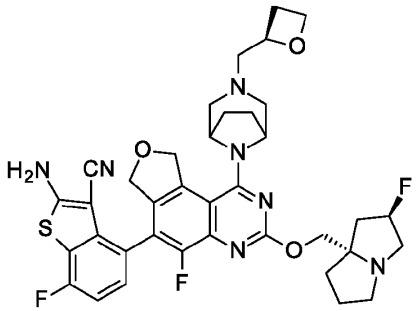
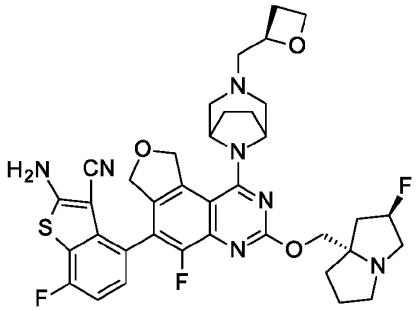
Table 15:

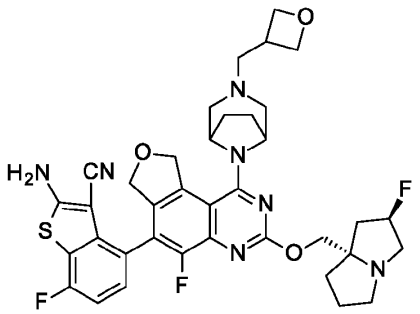
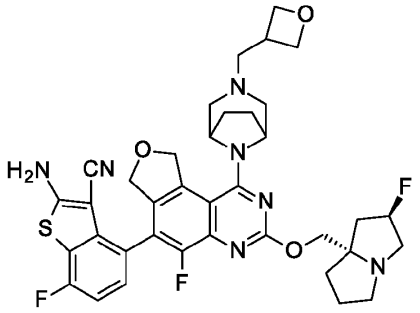
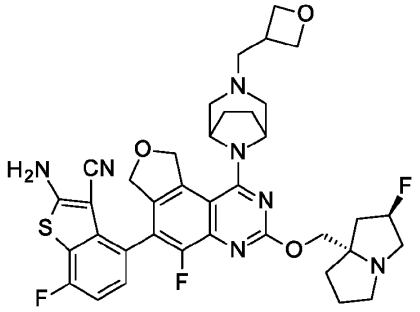
Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)
49[1]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		549
50	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		686
51[2]	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-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		645

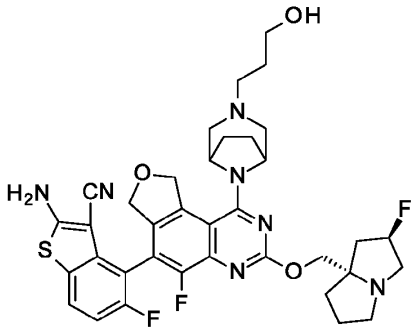
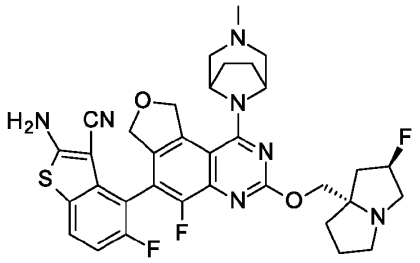
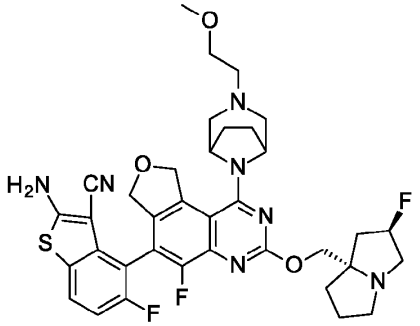
52	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		631
53	2-Amino-5-fluoro-4-[5-fluoro-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		491
54	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		628

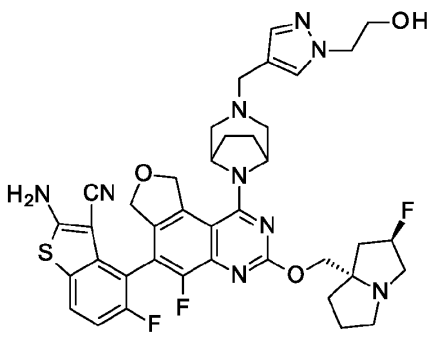
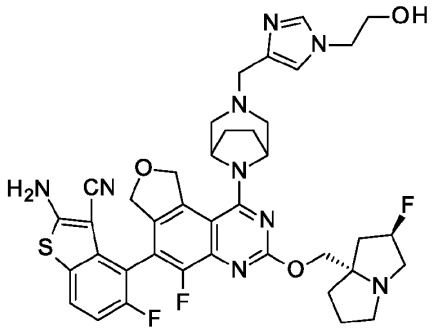
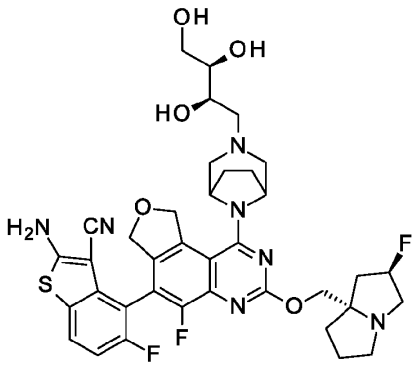
95[3]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		648
96[3]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxybutyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		706
97[3]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxy-2-methyl-propyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		706

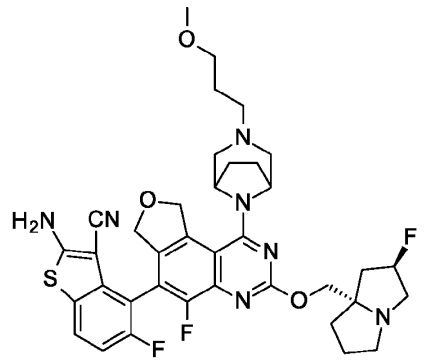
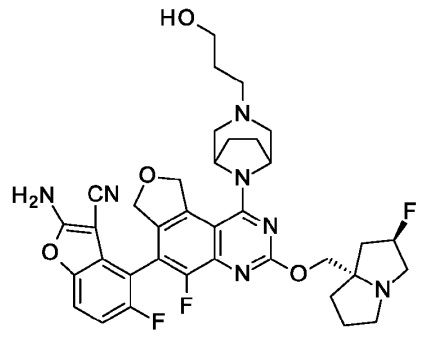
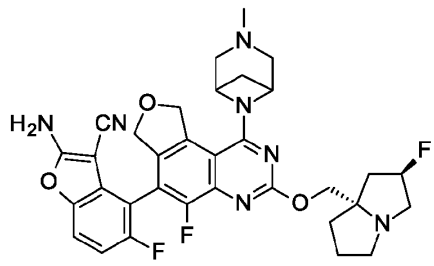
98[3]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		692
99	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		688
100	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		706

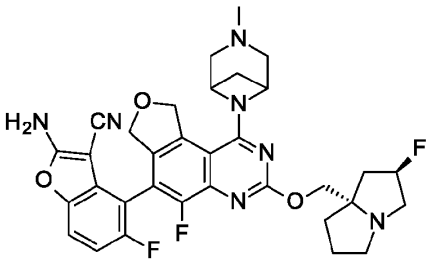
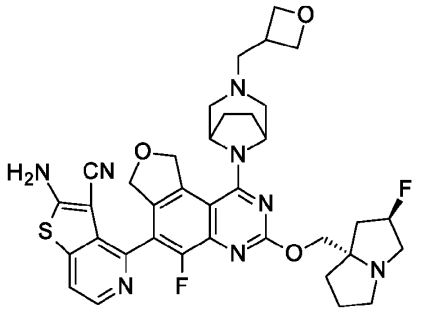
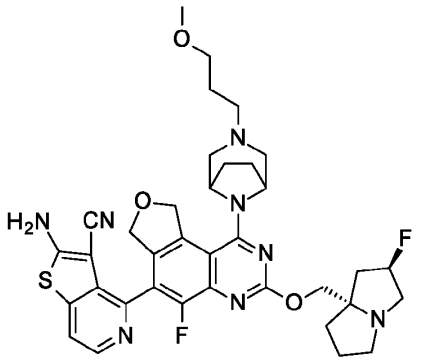
101	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[(2R)-oxetan-2-yl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		718
102	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[(2R)-oxetan-2-yl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		718
103	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[(2R)-oxetan-2-yl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		718

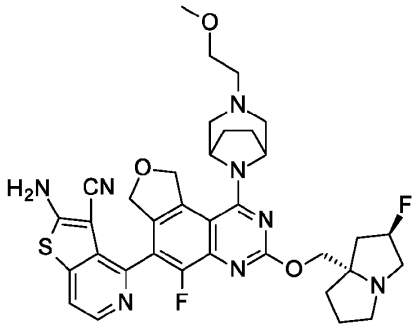
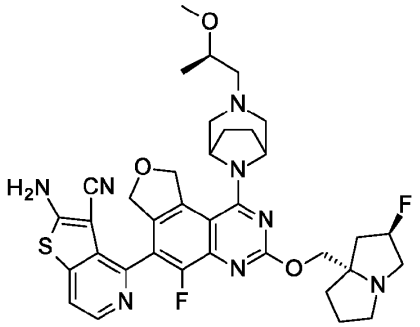
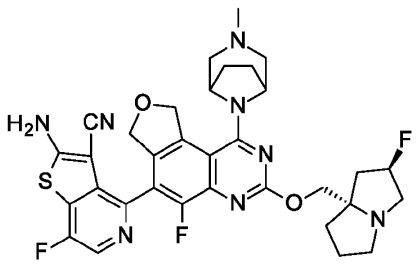
104	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		718
105	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		718
106	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		718

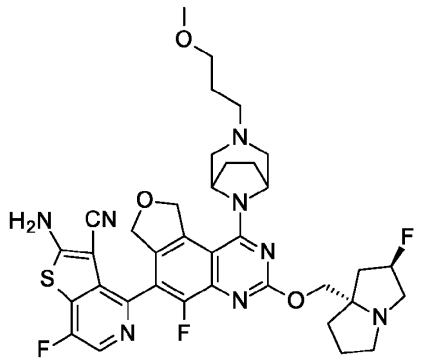
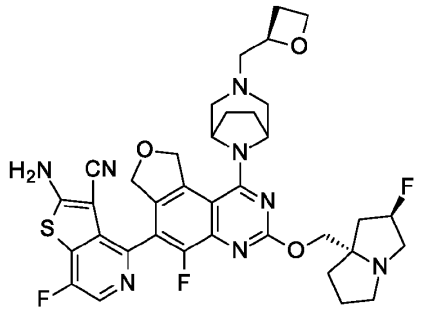
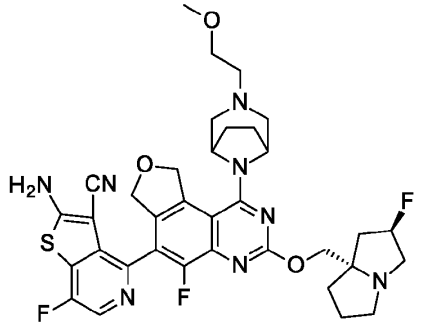
107	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		718
108[4]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		662
109[4]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		706

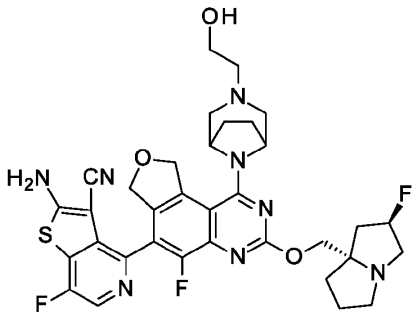
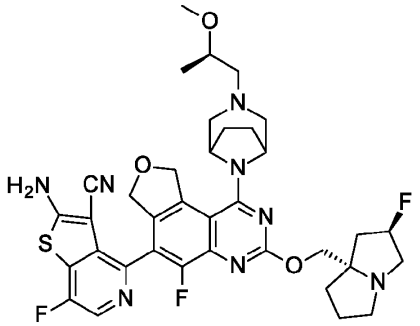
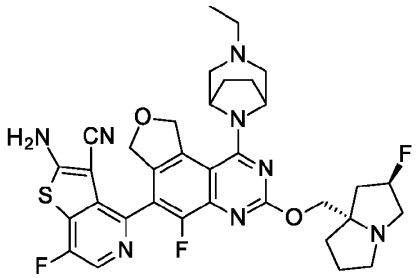
110	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[1-(2-hydroxyethyl)pyrazol-4-yl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		772
111	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[1-(2-hydroxyethyl)imidazol-4-yl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		772
112	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R,3R)-2,3,4-trihydroxybutyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		752

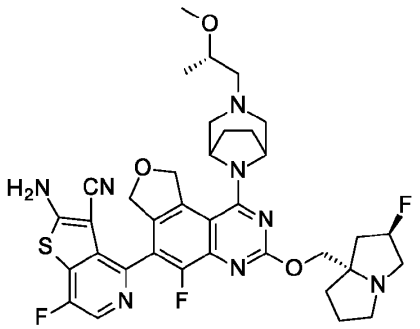
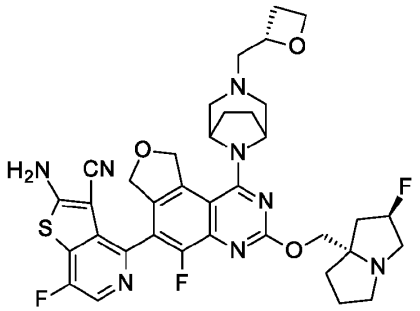
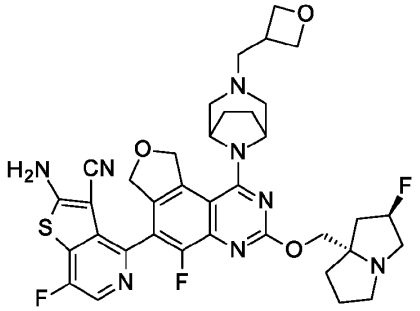
113[4]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		720
114[5]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		690
115	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		632

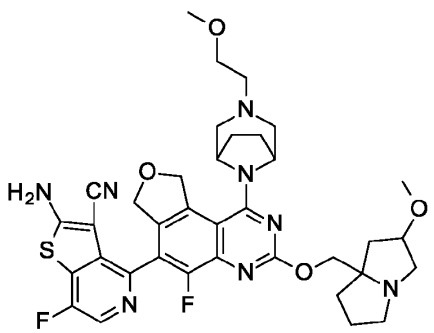
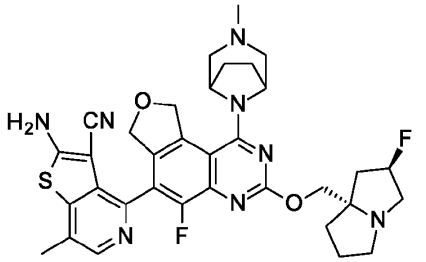
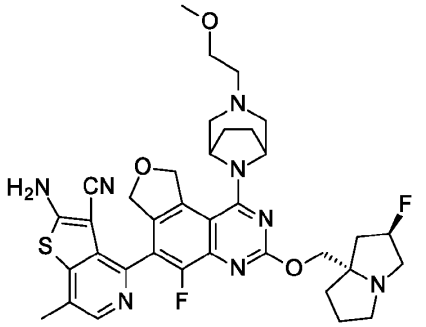
116	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile, Isomer 1		632
117	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		701
118	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-methoxypropyl)-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		703

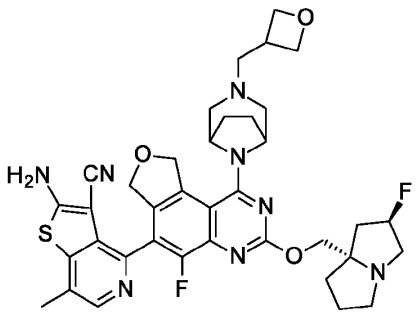
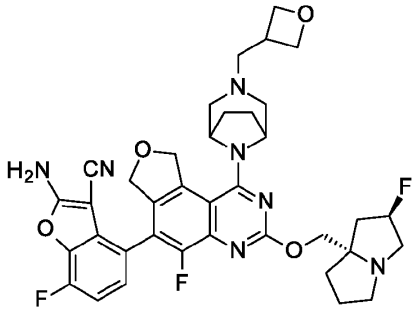
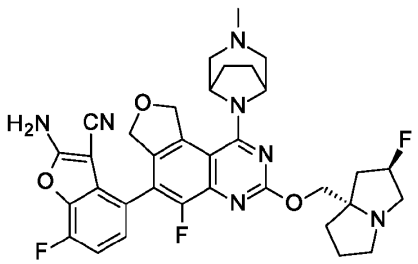
119	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		689
120	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-methoxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		703
121	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-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		663

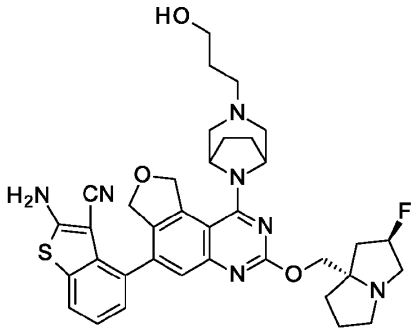
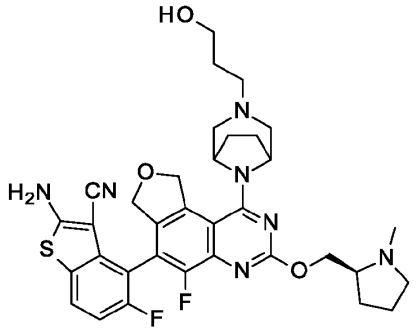
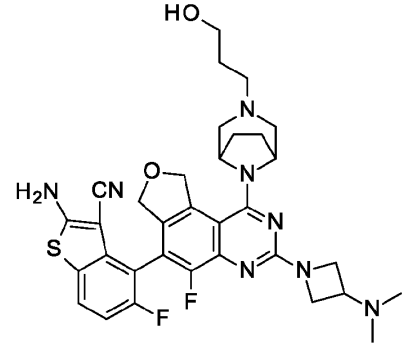
122	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		721
123	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[(2R)-oxetan-2-yl]methyl]-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
124	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]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		707

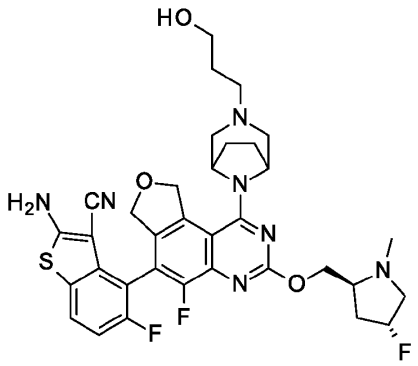
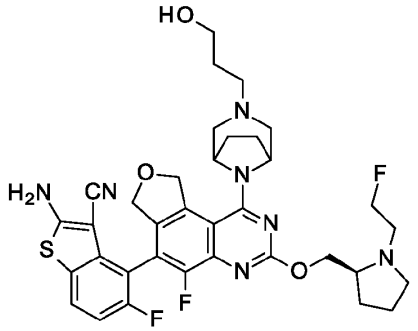
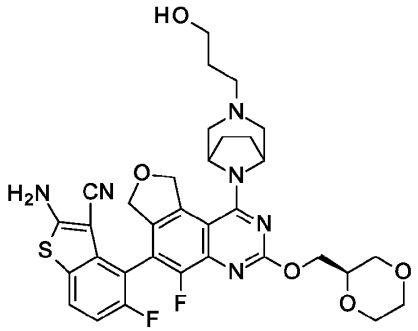
125	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		693
126	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-methoxypropyl]-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
127	2-Amino-4-[1-(3-ethyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		677

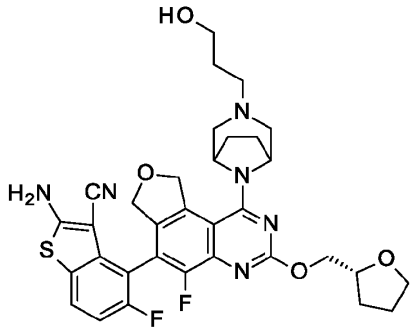
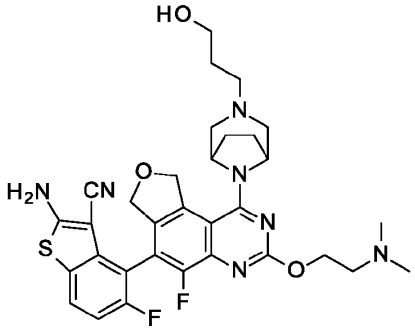
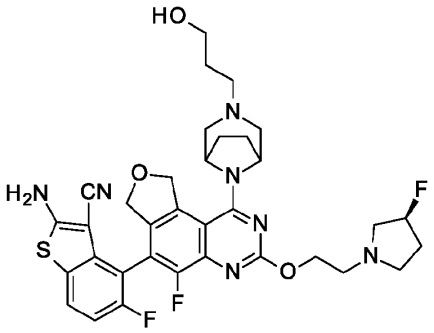
128	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2S)-2-methoxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		721
129	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[(2S)-oxetan-2-yl]methyl]-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
130	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-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

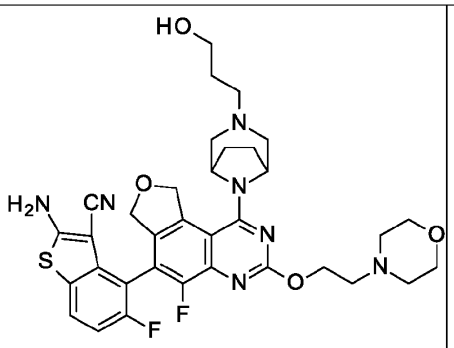
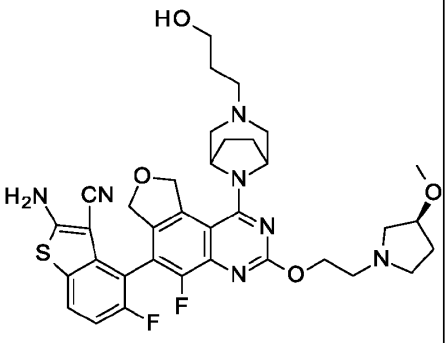
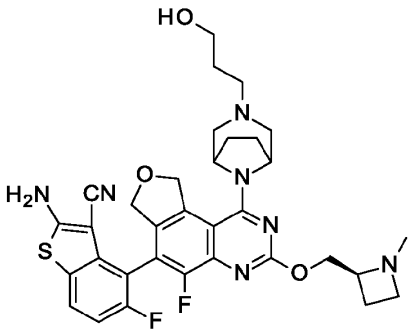
131	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		719
132	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-methyl-thieno[3,2-c]pyridine-3-carbonitrile		659
133	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-methyl-thieno[3,2-c]pyridine-3-carbonitrile		703

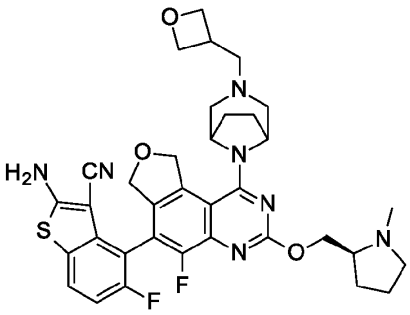
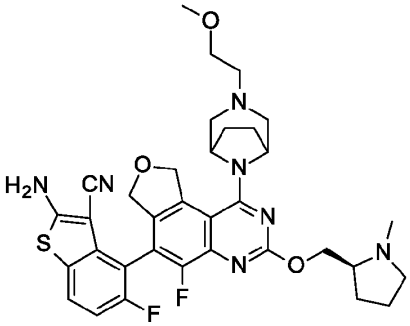
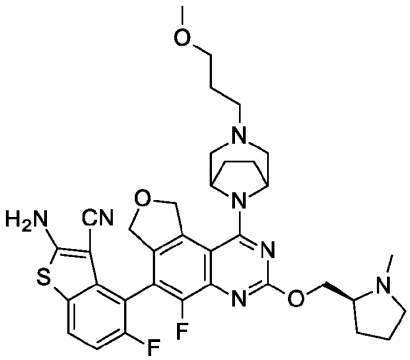
134	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-methyl-thieno[3,2-c]pyridine-3-carbonitrile		715
135	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		702
136	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		646

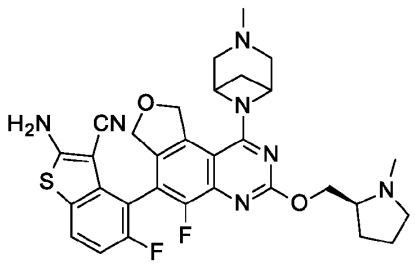
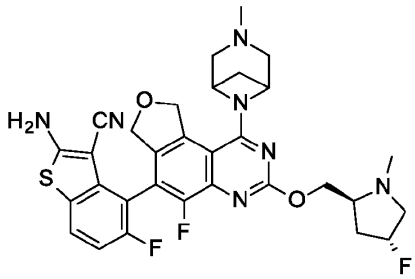
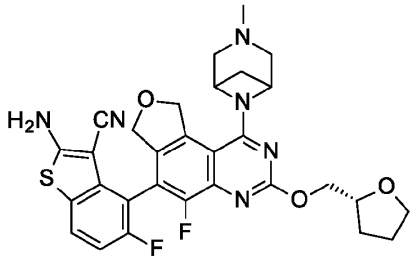
137	2-Amino-4-[3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		670
138[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		662
139[4]	2-Amino-4-[3-[3-(dimethylamino)azetidin-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]-5-fluoro-benzothiophene-3-carbonitrile		647

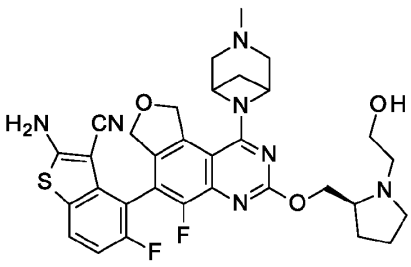
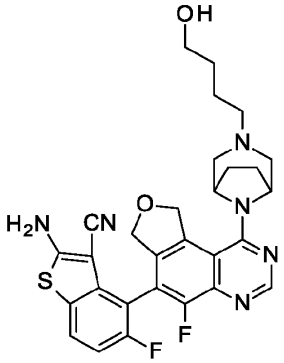
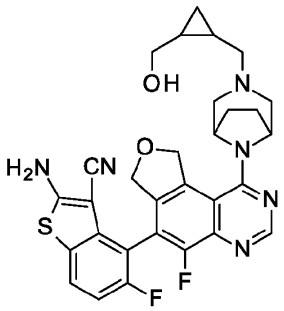
140[4]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		680
141[4]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S)-1-(2-fluoroethyl)pyrrolidin-2-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		694
142[4]	2-Amino-4-[3-[[(2R)-1,4-dioxan-2-yl]methoxy]-5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		665

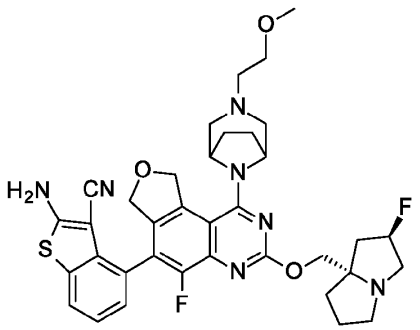
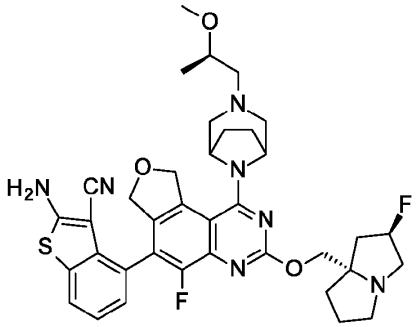
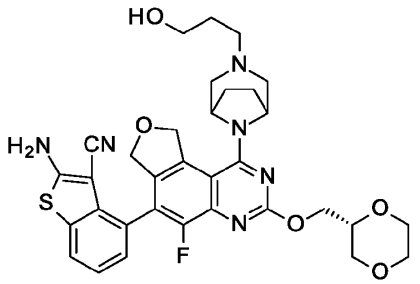
143[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		649
144[4]	2-Amino-4-[3-[2-(dimethylamino)ethoxy]-5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		636
145[4]	2-Amino-5-fluoro-4-[5-fluoro-3-[2-[(3S)-3-fluoropyrrolidin-1-yl]ethoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		680

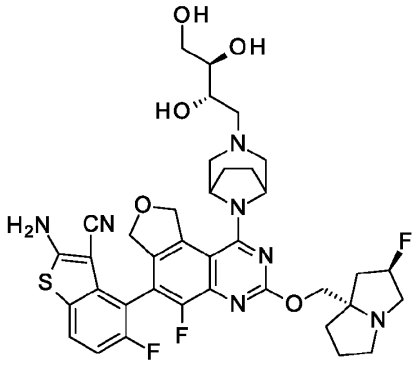
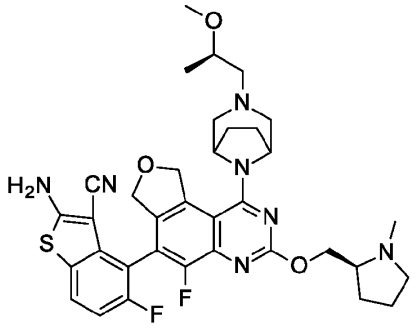
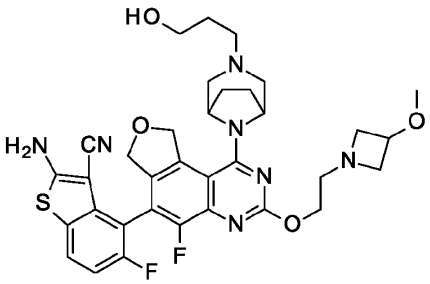
146[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		678
147[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[2-[(3S)-3-methoxypyrrolidin-1-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		692
148[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		648

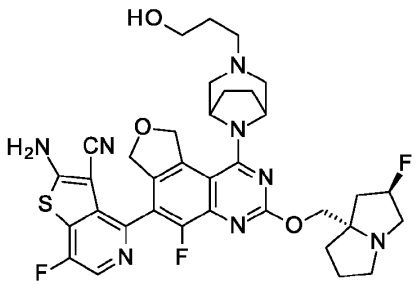
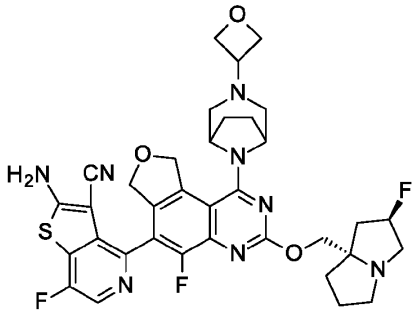
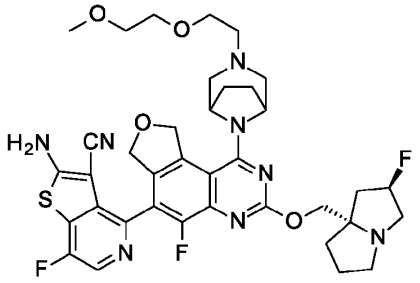
149[4]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		674
150[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		662
151[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		676

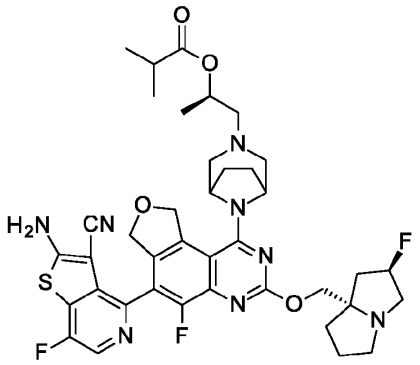
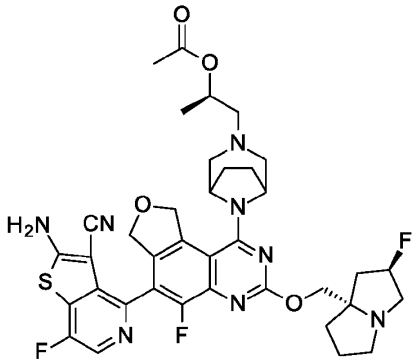
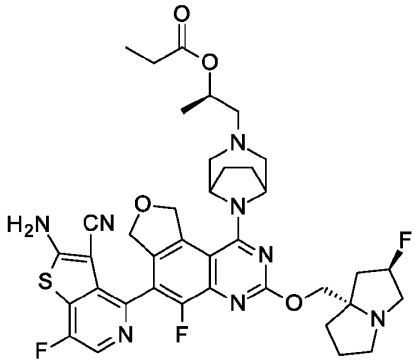
152[6]	2-Amino-5-fluoro-4-[5-fluoro-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		604
153[6]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		622
154[6]	2-Amino-5-fluoro-4-[5-fluoro-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-3-[[(2R)-tetrahydrofuran-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		591

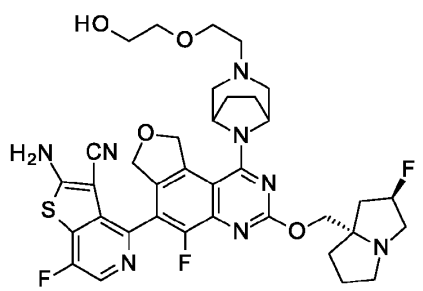
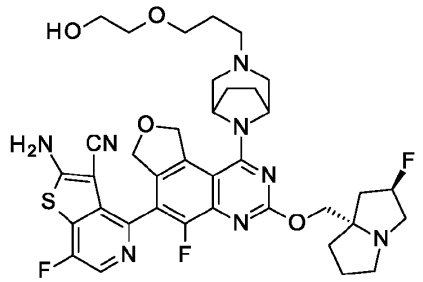
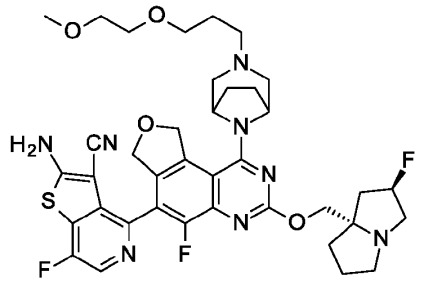
155[6]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		634
156[7]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(4-hydroxybutyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		563
157[7]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-[[2-(hydroxymethyl)cyclopropyl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		575

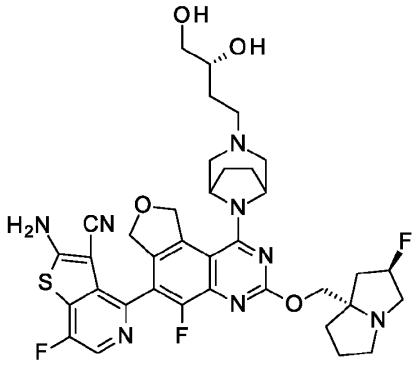
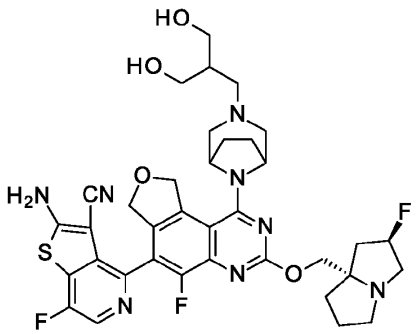
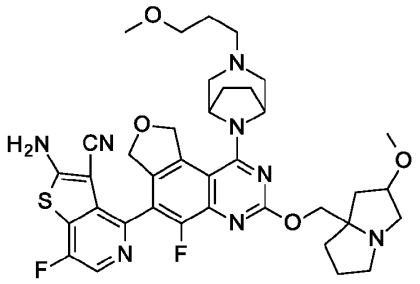
212	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		688
213	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-methoxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		702
214	2-Amino-4-[3-[[(2R)-1,4-dioxan-2-yl]methoxy]-5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		647

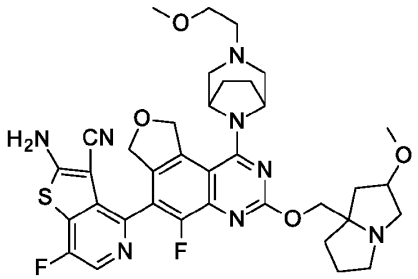
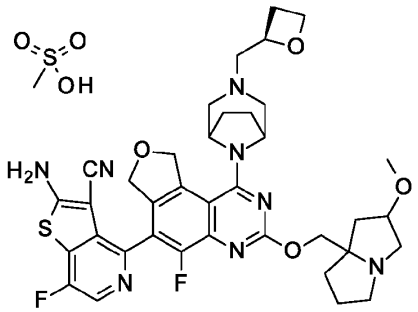
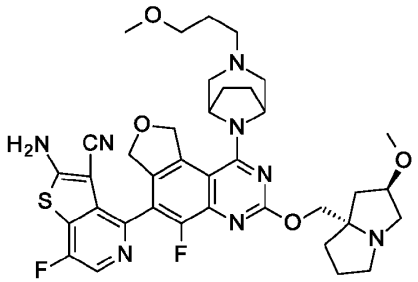
215	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2S,3R)-2,3,4-trihydroxybutyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		752
216[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-[(2R)-2-methoxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		676
217[4]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[2-(3-methoxyazetidin-1-yl)ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		678

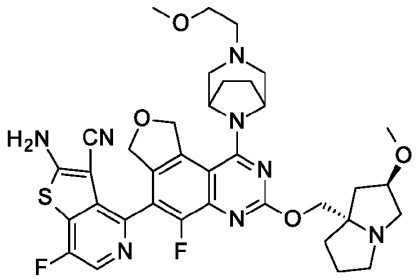
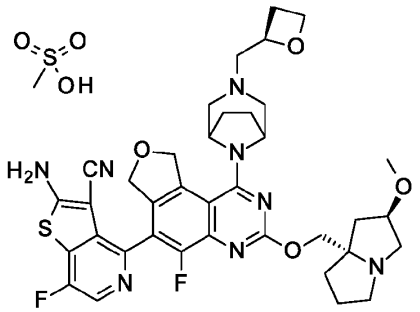
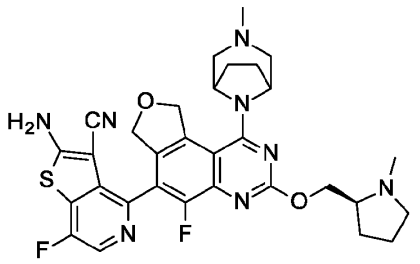
218	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		707
219	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		705
220	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[2-(2-methoxyethoxy)ethyl]-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		751

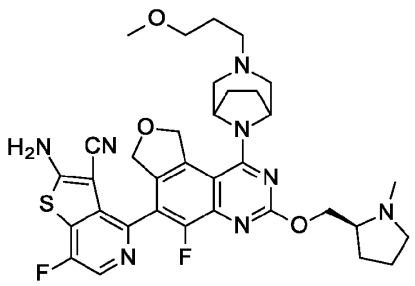
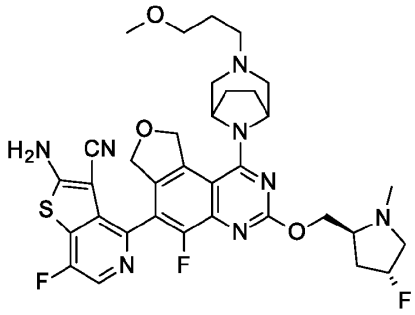
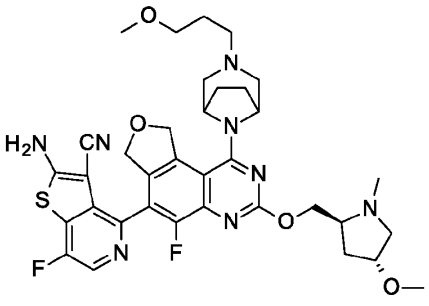
221	[(1R)-2-[8-[6-(2-Amino-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-1-methyl-ethyl] 2-methylpropanoate		777
222	[(1R)-2-[8-[6-(2-Amino-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-1-methyl-ethyl] acetate		749
223	[(1R)-2-[8-[6-(2-Amino-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-1-methyl-ethyl] propanoate		763

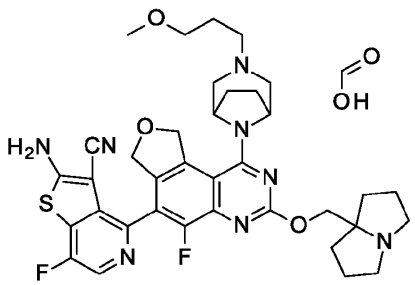
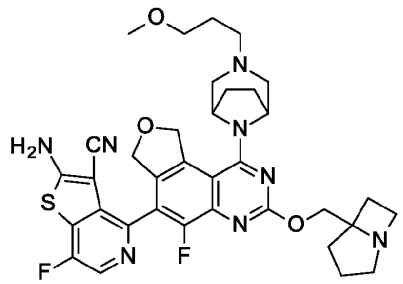
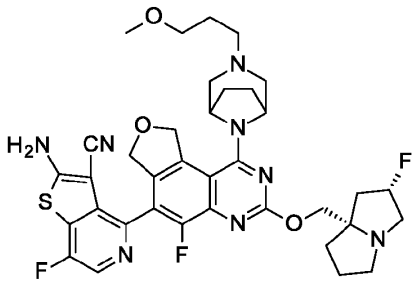
224	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[2-(2-hydroxyethoxy)ethyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		737
225	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[3-(2-hydroxyethoxy)propyl]-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		751
226	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[3-(2-methoxyethoxy)propyl]-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		765

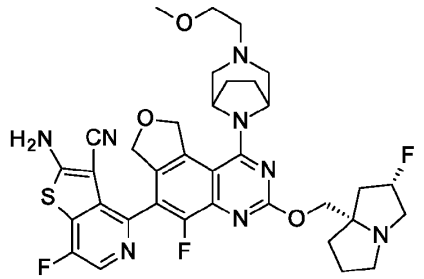
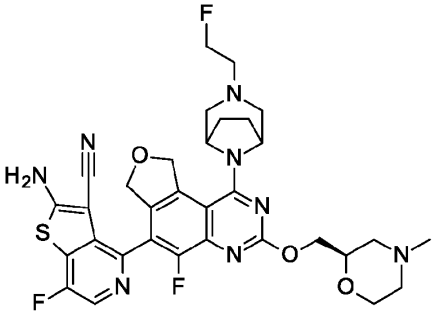
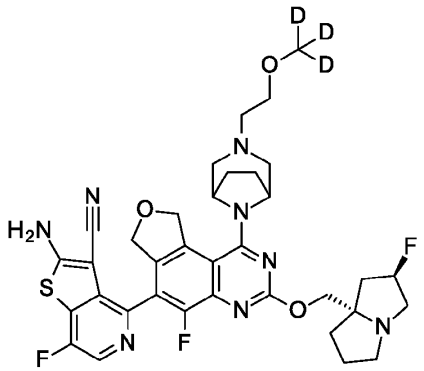
227	2-Amino-4-[1-[3-[(3R)-3,4-dihydroxybutyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		737
228	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[3-hydroxy-2-(hydroxymethyl)propyl]-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		737
229	2-Amino-7-fluoro-4-[5-fluoro-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methoxy]-1-[3-(3-methoxypropyl)-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		733

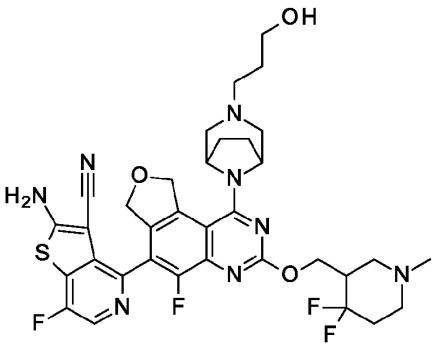
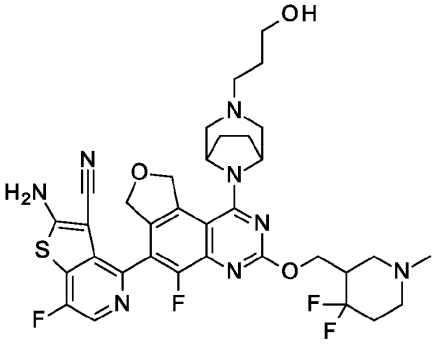
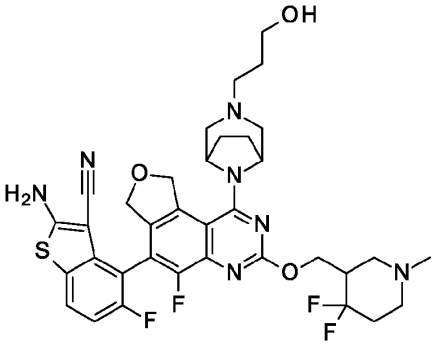
230	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		719
231	2-Amino-7-fluoro-4-[5-fluoro-3-[(2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl)methoxy]-1-[3-[[(2R)-oxetan-2-yl]methyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile methanesulfonic acid		731
232	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-methoxypropyl)-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		733

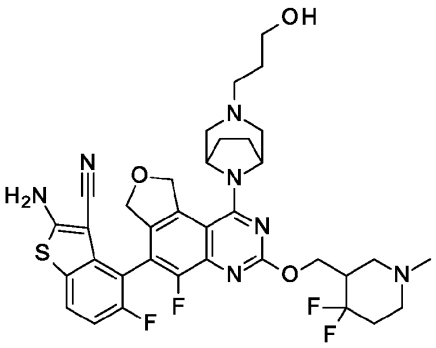
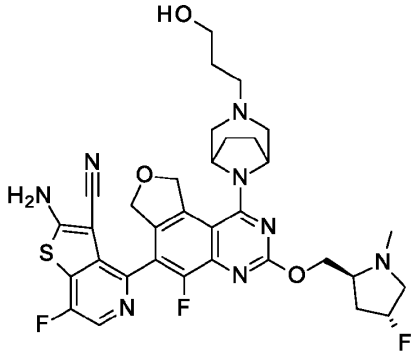
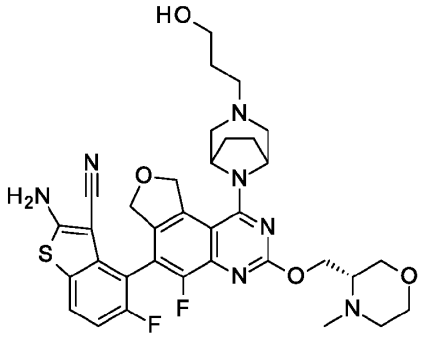
233	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2R,8S)-2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		719
234	2-amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-methoxy-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[[(2R)-oxetan-2-yl]methyl]-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 methanesulfonic acid		731
235	2-Amino-7-fluoro-4-[5-fluoro-1-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		619

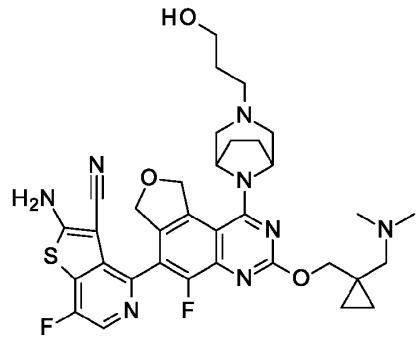
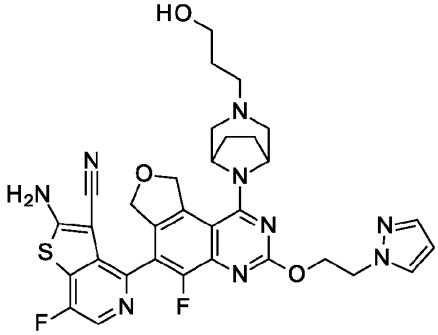
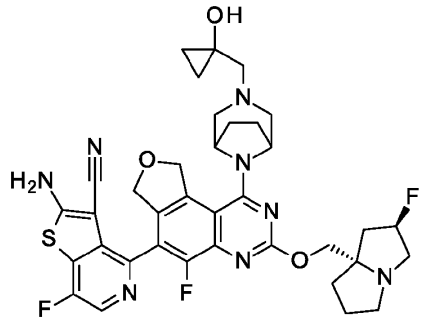
236	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		677
237	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		695
238	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-(3-methoxypropyl)-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

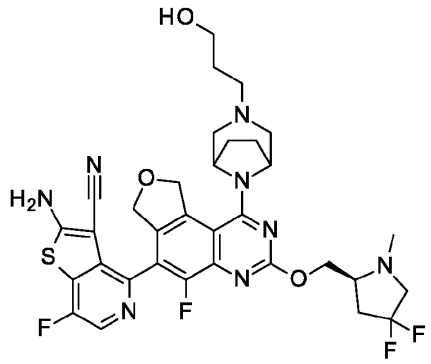
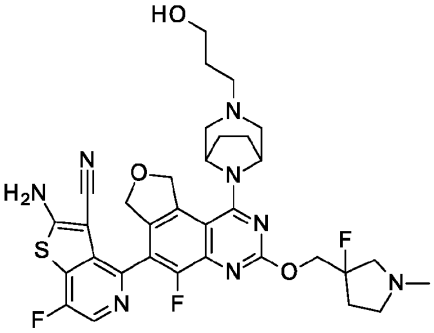
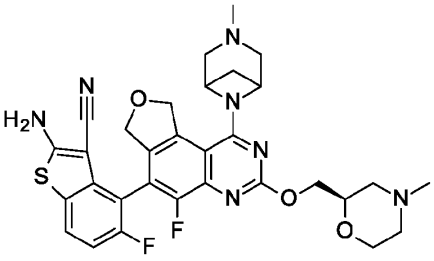
239	2-Amino-7-fluoro-4-[5-fluoro-3-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile formic acid		703
240	2-Amino-4-[3-(1-azabicyclo[3.2.0]heptan-5-ylmethoxy)-5-fluoro-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		689
241	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2SR,8SR)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-methoxypropyl)-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

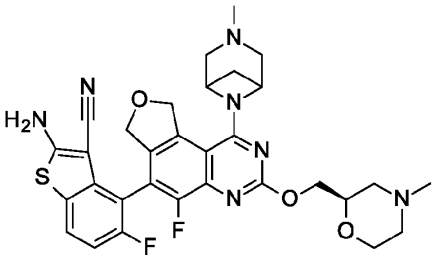
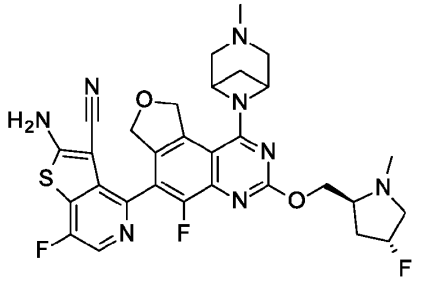
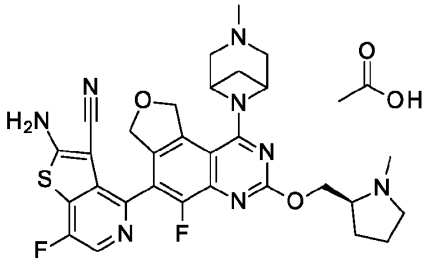
242	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2SR,8SR)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-methoxyethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		707
326	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		667
327	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[2-(trideuteriomethoxy)ethyl]-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		710

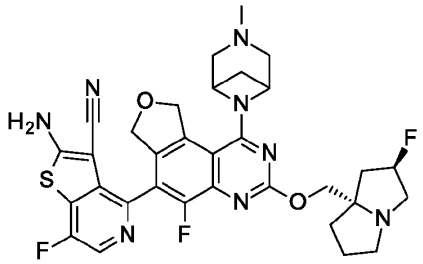
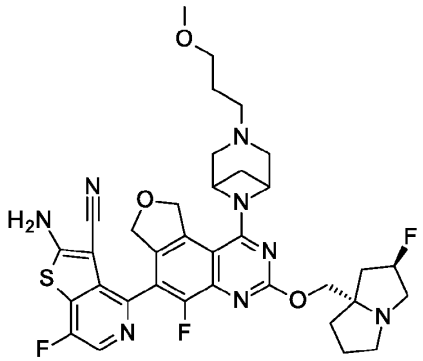
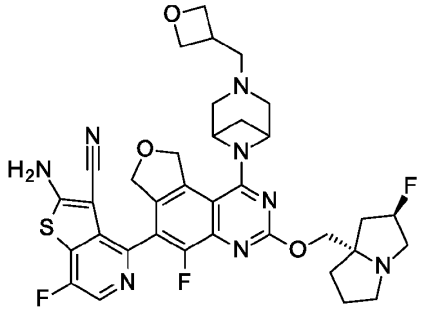
328	2-Amino-4-[3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		713
329	2-Amino-4-[3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		713
330[4]	2-Amino-4-[3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile, Isomer 1		712

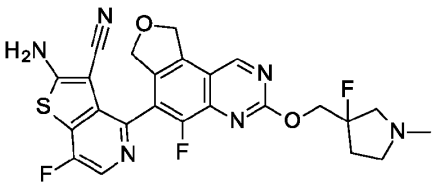
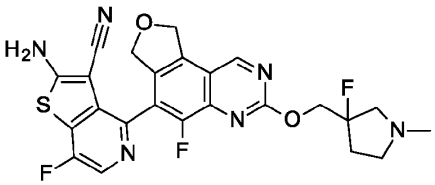
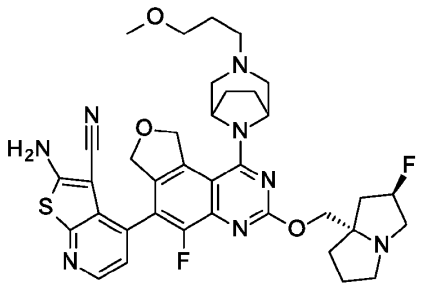
331[4]	2-Amino-4-[3-[(4,4-difluoro-1-methyl-3-piperidyl)methoxy]-5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile, Isomer 2		712
332	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		681
333	2-Amino-5-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(3S)-4-methylmorpholin-3-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		678

334	2-Amino-4-[3-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-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-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		677
335	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(3-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-(2-pyrazol-1-ylethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		660
336	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(1-hydroxycyclopropyl)methyl]-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

337	2-Amino-4-[3-[[(2S)-4,4-difluoro-1-methyl-pyrrolidin-2-yl]methoxy]-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-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		699
338	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-fluoro-1-methyl-pyrrolidin-3-yl)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		681
339	2-Amino-5-fluoro-4-[5-fluoro-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		620

340	2-Amino-5-fluoro-4-[5-fluoro-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		620
341	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-(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		623
342	2-Amino-7-fluoro-4-[5-fluoro-1-(3-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile; acetic acid		605

343	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-(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		649
344	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-methoxypropyl)-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		707
345	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(oxetan-3-ylmethyl)-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		705

346	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-fluoro-1-methyl-pyrrolidin-3-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile, Isomer 1		513
347	2-Amino-7-fluoro-4-[5-fluoro-3-[(3-fluoro-1-methyl-pyrrolidin-3-yl)methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile, Isomer 2		513
348	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-methoxypropyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[2,3-b]pyridine-3-carbonitrile		703

[1]single atropisomer (from precursor in Example 1)

[2]Prepared using 37 wt% aq. formaldehyde, no MeOH co-solvent.

[3]single atropisomer (from precursor in Preparation 266)

[4]single atropisomer (from precursor in Preparation 248)

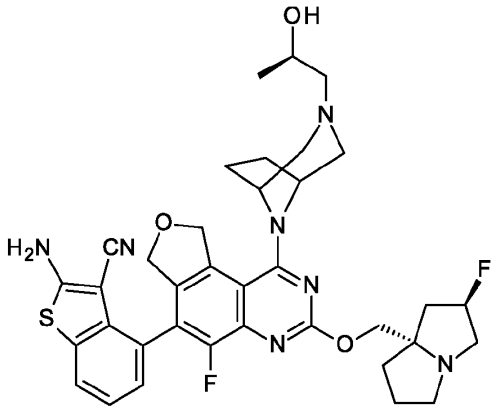
[5]single atropisomer (from precursor in Preparation 296)

[6]single atropisomer (from precursor in Preparation 251)

[7]single atropisomer (from precursor in Preparation 255)

Example 55

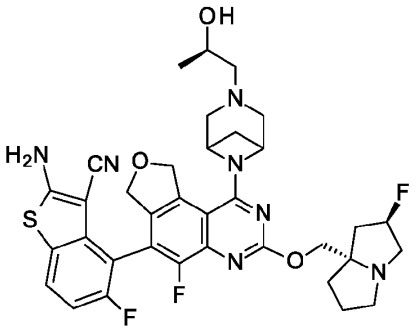
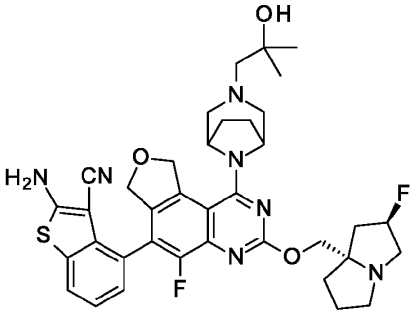
2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile

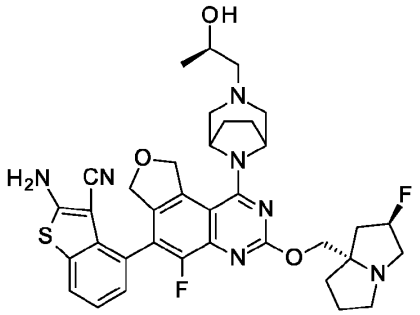
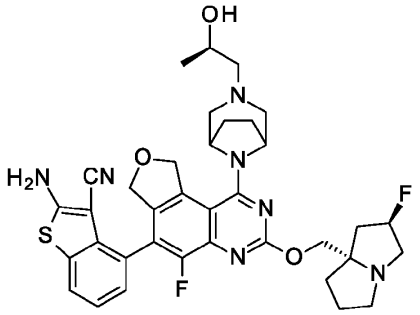
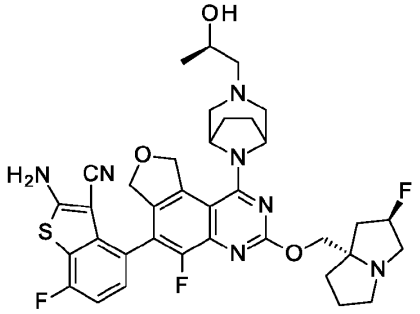


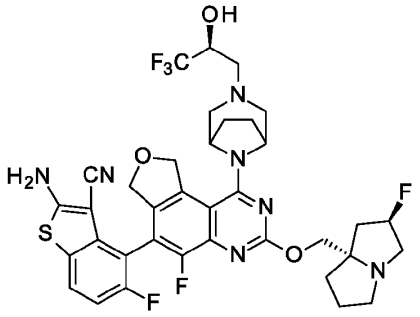
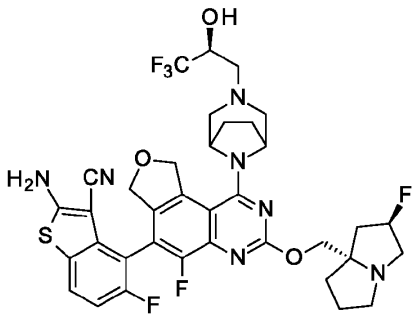
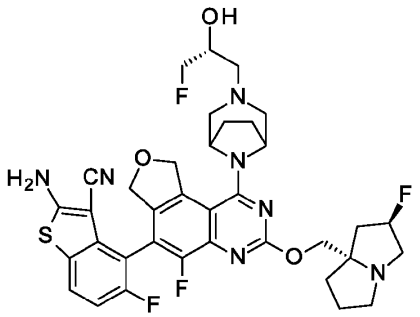
A solution of 2-amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile (0.120 g, 0.191 mmol) in MeOH (4 mL) was treated with (R)-(+)-propylene oxide (0.056 g, 0.945 mmol). The mixture was heated in a sealed tube at 70 °C for 2 h, then was concentrated. The residue was purified by reversed phase flash chromatography on C18 (eluting with 5% to 64% ACN in 10 mM aq. NH_4HCO_3 with 5% MeOH) to obtain the title compound (0.089 g, 62%) as a light-beige solid. MS (ES) *m/z*=688 (M+1).

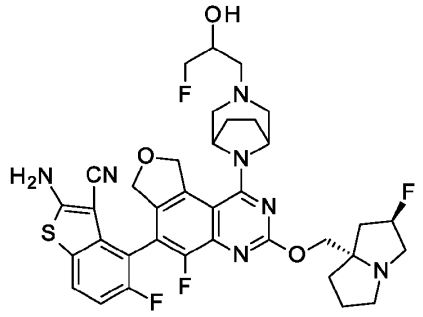
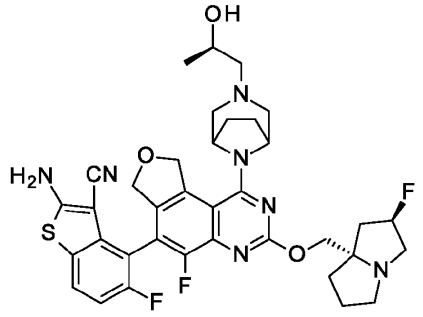
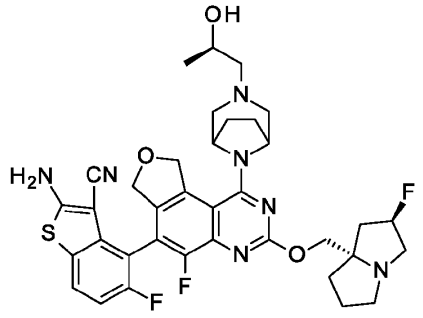
The Example compounds in Table 16 were prepared in a similar manner as described for Example 48 or Example 55. Various methods were used to purify the compounds, which would be apparent to one skilled in the art. Chiral purification methods (if applicable) for the Examples of Table 16 are located in Table 18.

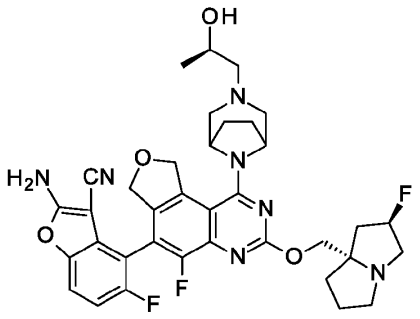
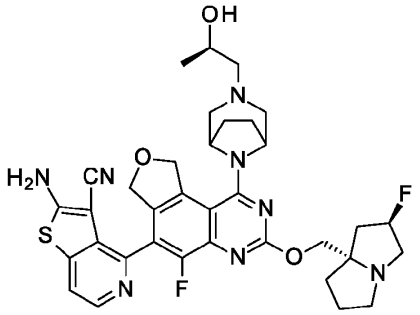
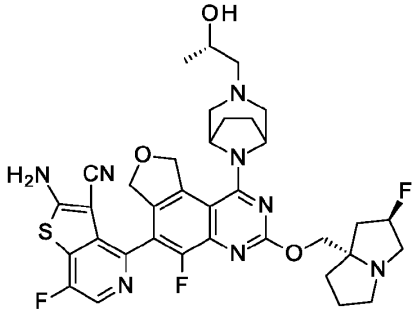
Table 16:

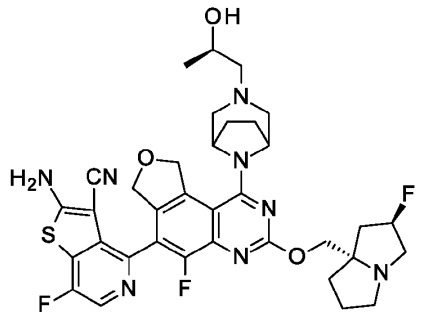
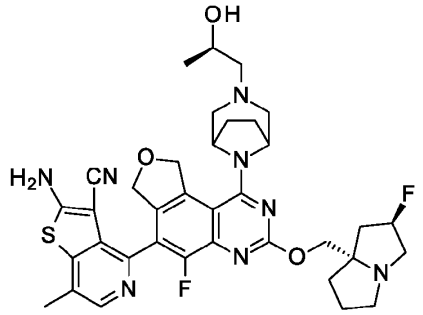
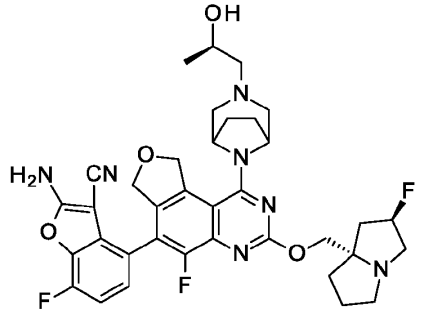
Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)
158	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		692
159	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-hydroxy-2-methyl-propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		702

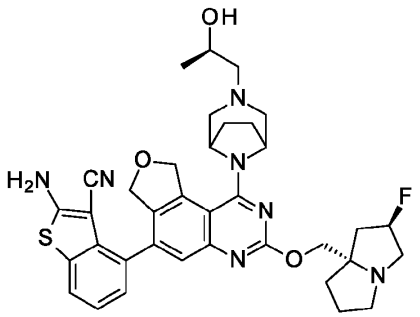
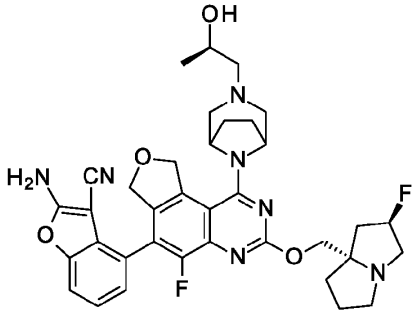
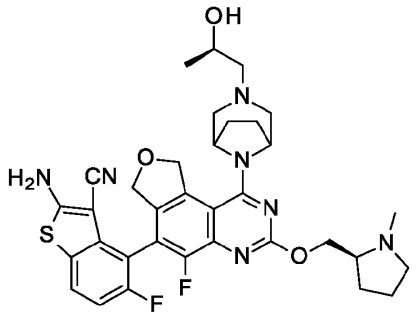
160	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		688
161	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		688
162	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		705

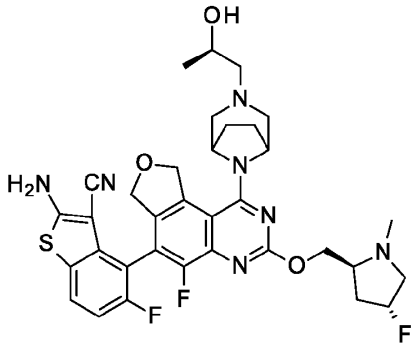
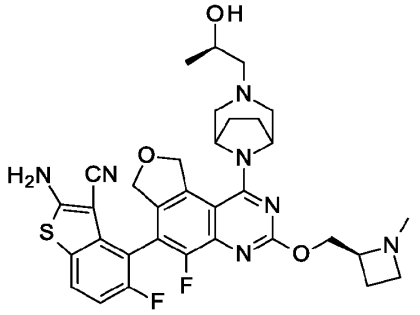
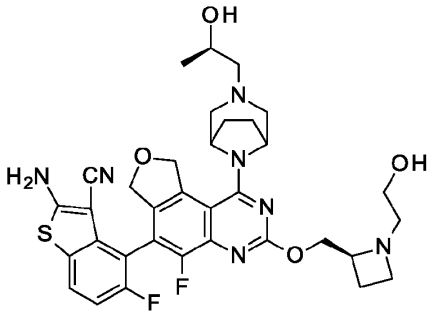
163	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2S)-3,3,3-trifluoro-2-hydroxy-propyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		760
164	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2S)-3,3,3-trifluoro-2-hydroxy-propyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		760
165	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-3-fluoro-2-hydroxy-propyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		724

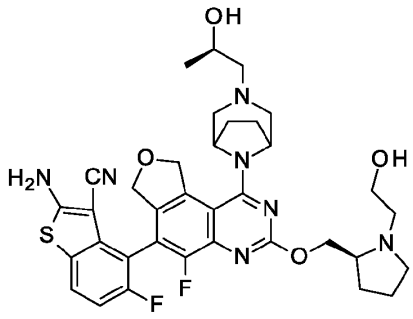
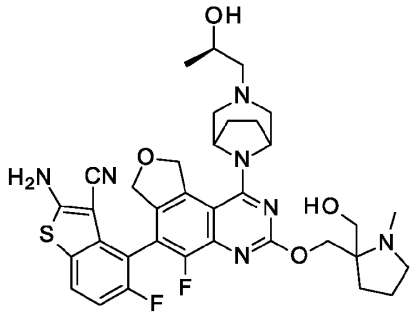
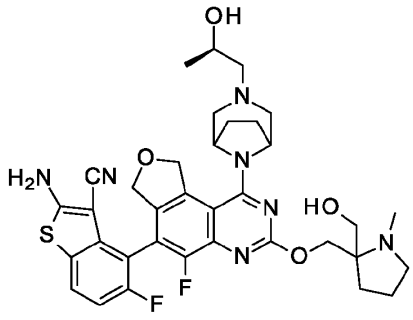
166	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-fluoro-2-hydroxy-propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		724
167	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		706
168	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		706

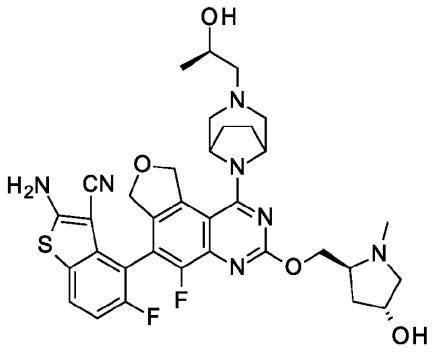
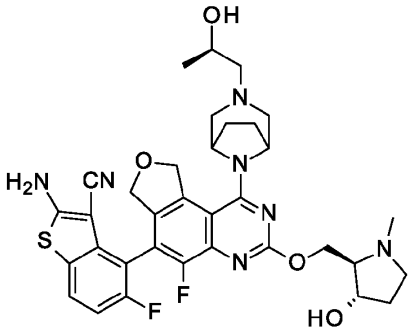
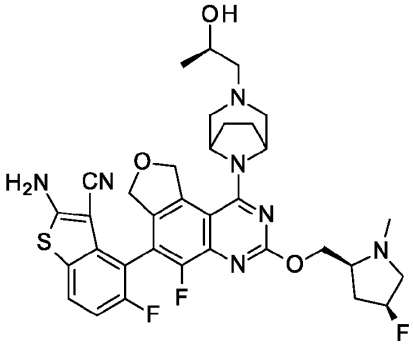
169[1]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		690
170	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		689
171	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2S)-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

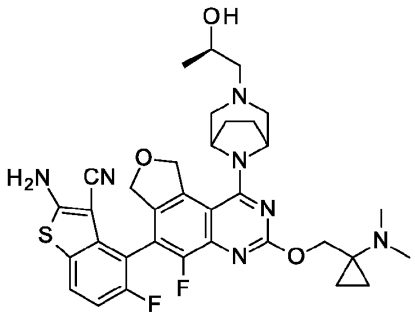
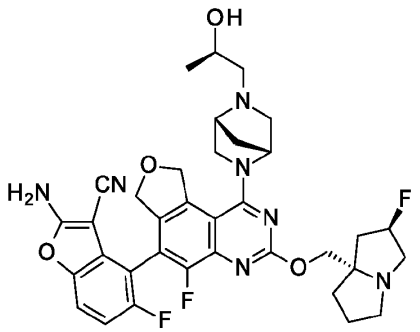
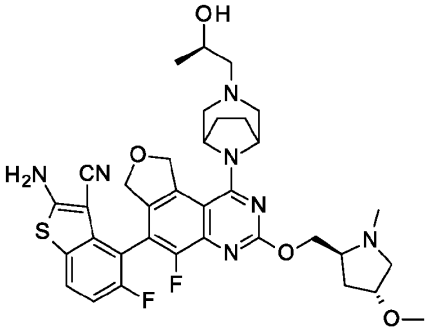
172	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		707
173	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-methyl-thieno[3,2-c]pyridine-3-carbonitrile		703
174	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		690

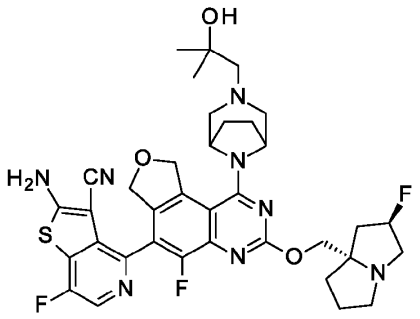
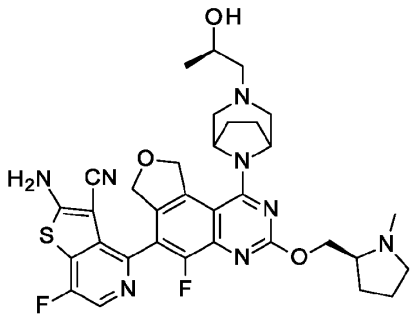
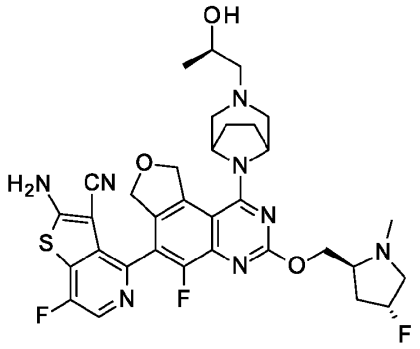
175	2-Amino-4-[3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		670
176	2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		672
177[2]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		662

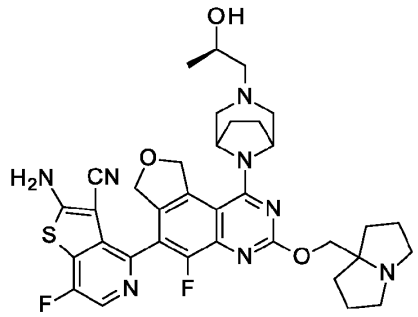
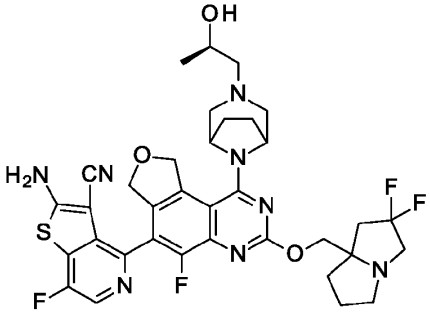
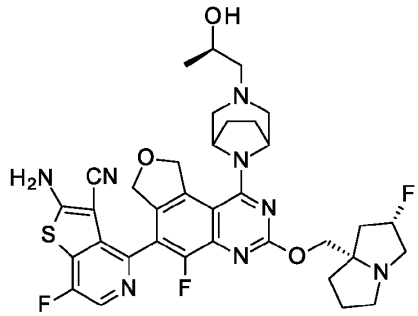
178[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		680
179[2]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylazetidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		648
180[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)azetidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		678

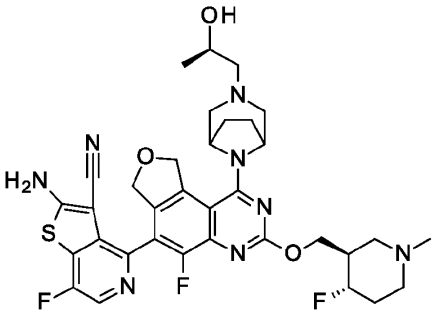
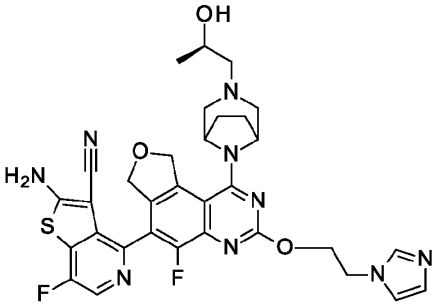
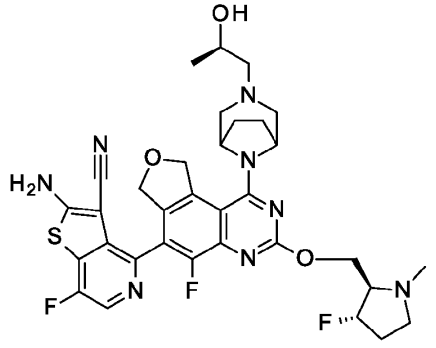
181[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		692
182[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		692
183[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[2-(hydroxymethyl)-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 2		692

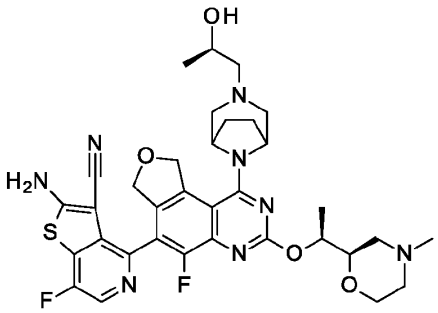
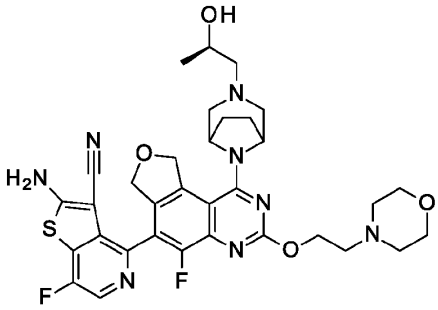
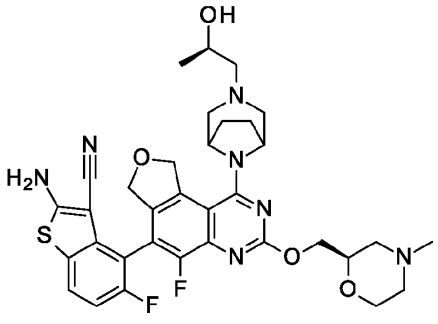
184[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		678
185[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,3S)-3-hydroxy-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		678
186[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		680

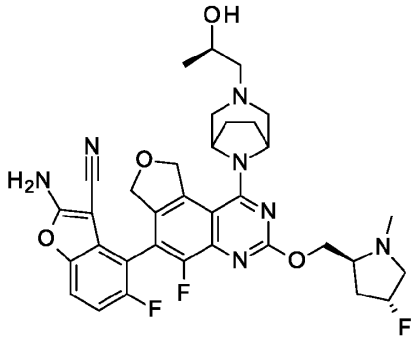
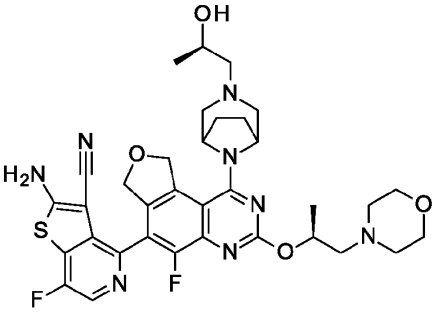
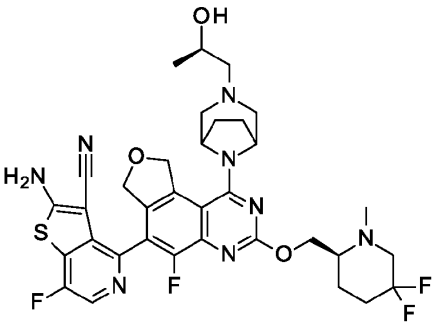
187[2]	2-Amino-4-[3-[[1-(dimethylamino)cyclopropyl]methoxy]-5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile		662
188[3]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[(1R,4R)-5-[(2R)-2-hydroxypropyl]-2,5-diazabicyclo[2.2.1]heptan-2-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		676
243[2]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S,4R)-4-methoxy-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		692

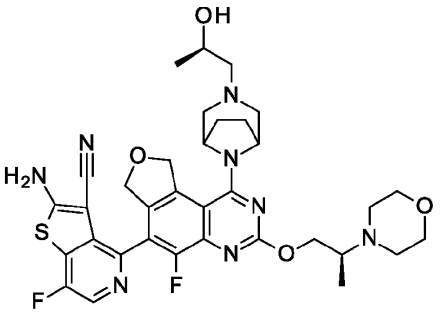
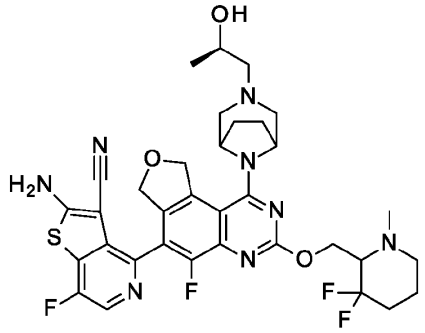
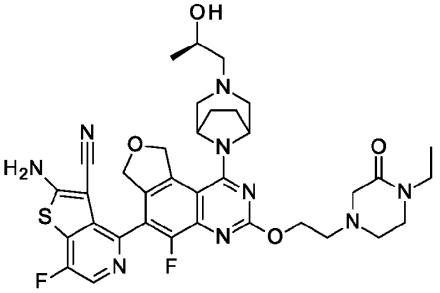
244	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(2-hydroxy-2-methyl-propyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		721
245	2-Amino-7-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		663
246	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-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		681

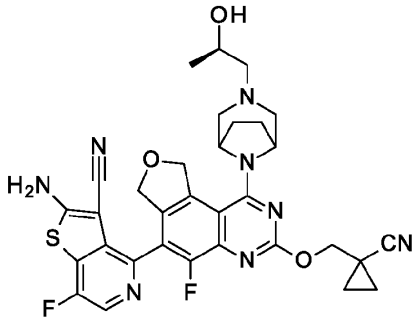
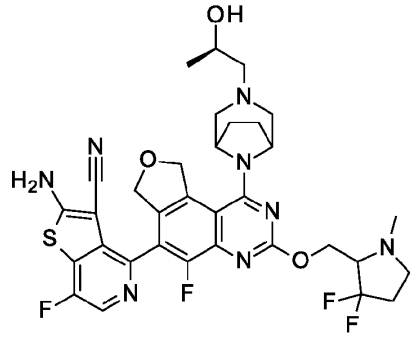
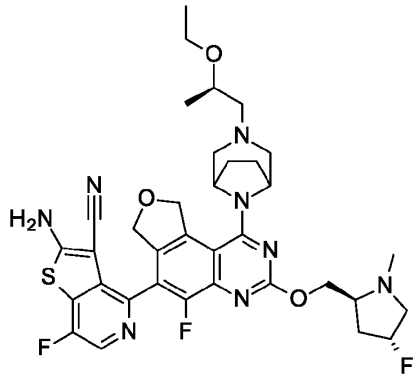
247	2-Amino-7-fluoro-4-[5-fluoro-3-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		689
248	2-Amino-4-[3-[(6,6-difluoro-2,3,5,7-tetrahydro-1H-pyrrolizin-8-yl)methoxy]-5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		725
249	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2SR,8SR)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-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

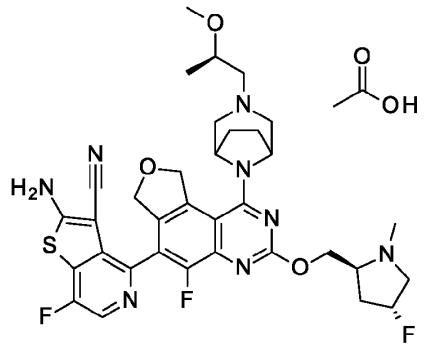
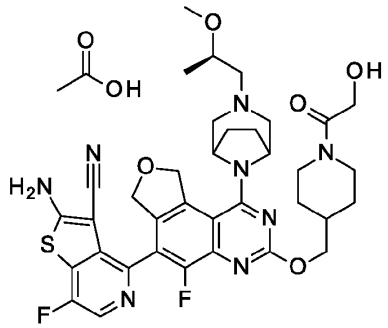
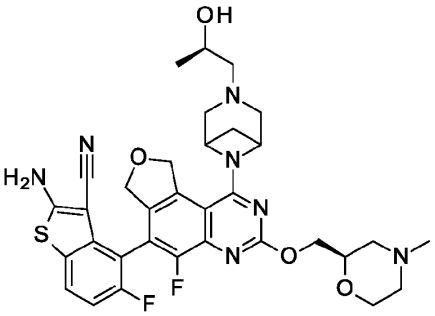
349	2-Amino-7-fluoro-4-[5-fluoro-3-[[(3RS,4SR)-4-fluoro-1-methyl-3-piperidyl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		695
350	2-Amino-7-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-(2-imidazol-1-ylethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		660
351	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,3S)-3-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-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		681

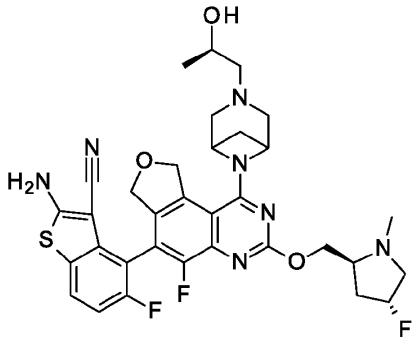
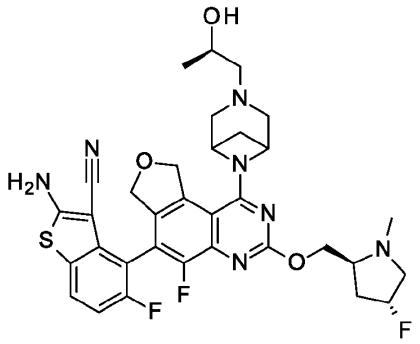
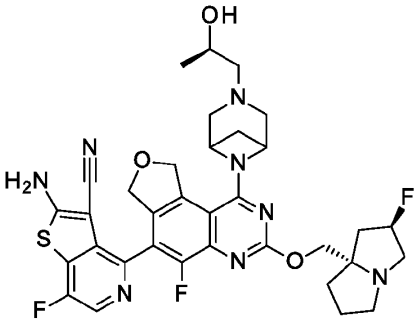
352	2-Amino-7-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[(1SR)-1-[(2RS)-4-methylmorpholin-2-yl]ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		693
353	2-Amino-7-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-(2-morpholinoethoxy)-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		679
354[2]	2-Amino-5-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		678

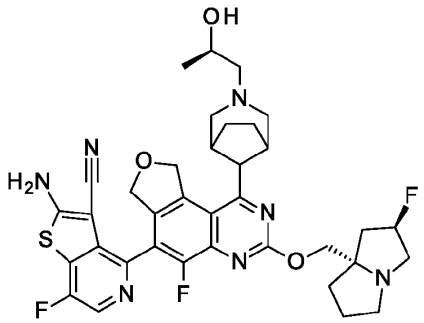
355	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzofuran-3-carbonitrile		664
356	2-Amino-7-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[(1S)-1-methyl-2-morpholino-ethoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		693
357	2-Amino-4-[3-[[(2S)-5,5-difluoro-1-methyl-2-piperidyl]methoxy]-5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		713

358	2-Amino-7-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[(2S)-2-morpholinopropoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		693
359	2-Amino-4-[3-[(3,3-difluoro-1-methyl-2-piperidyl)methoxy]-5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		713
360	2-Amino-4-[3-[2-(4-ethyl-3-oxo-piperazin-1-yl)ethoxy]-5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		720

361	2-Amino-4-[3-[(1-cyanocyclopropyl)methoxy]-5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		645
362	2-Amino-4-[3-[(3,3-difluoro-1-methyl-pyrrolidin-2-yl)methoxy]-5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		699
363	2-Amino-4-[1-[3-[(2R)-2-ethoxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		709

364	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-methoxypropyl]-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; acetic acid		695
365	2-Amino-7-fluoro-4-[5-fluoro-3-[[1-(2-hydroxyacetyl)-4-piperidyl]methoxy]-1-[3-[(2R)-2-methoxypropyl]-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; acetic acid		735
366	2-Amino-5-fluoro-4-[5-fluoro-1-[3-[(2R)-2-hydroxypropyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]-3-[[(2R)-4-methylmorpholin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		664

367	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		666
368	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3,6-diazabicyclo[3.1.1]heptan-6-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile, Isomer 1		666
369	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-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		693

370	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2R)-2-hydroxypropyl]-3-azabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		706

[1]single atropisomer (from precursor in Preparation 296)

[2]single atropisomer (from precursor in Preparation 248)

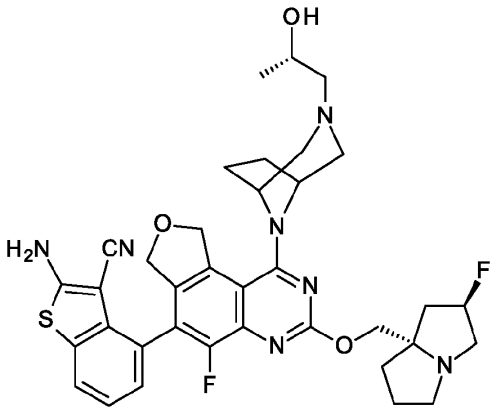
[3]single atropisomer (from precursor in Preparation 298)

Examples 56 and 57

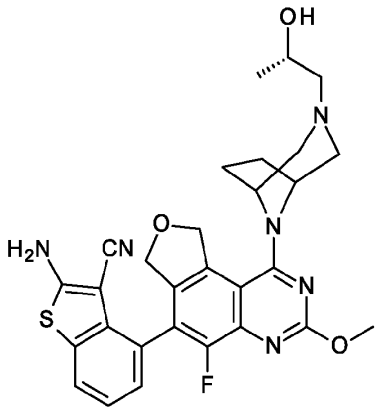
2-Amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2S)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile

and

2-Amino-4-[5-fluoro-1-[3-[(2S)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-methoxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile



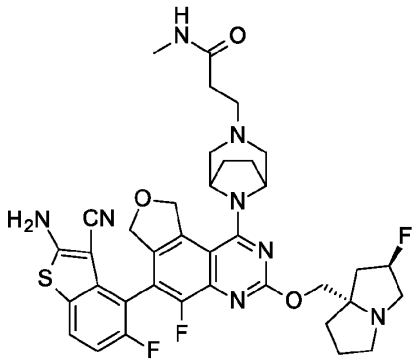
and



2-Amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile was used in a manner analogous to the method described in Example 55 using (S)-(-)-propylene oxide and heating the reaction at 70 °C for ~ 18 h. Upon purification of the residue by reversed phase flash purification on C18, eluting with 5% to 50% ACN in 10 mM aq. NH_4HCO_3 with 5% MeOH, two products were isolated to give 2-amino-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[(2S)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile (0.033 g, 37%) as a peach-colored solid, MS (ES) *m/z*=688 (M+1), and 2-amino-4-[5-fluoro-1-[3-[(2S)-2-hydroxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-methoxy-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile (0.020 g, 26%) as an off-white solid. MS (ES) *m/z*=561 (M+1).

Example 189

3-[8-[6-(2-amino-3-cyano-5-fluoro-benzothiophen-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-N-methyl-propanamide

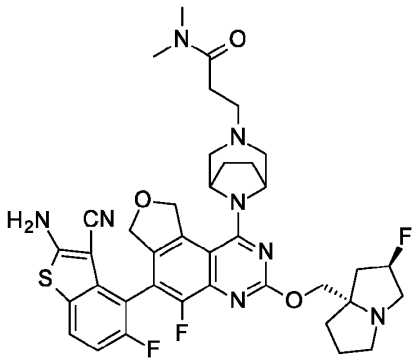


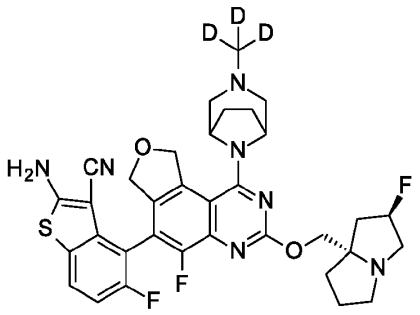
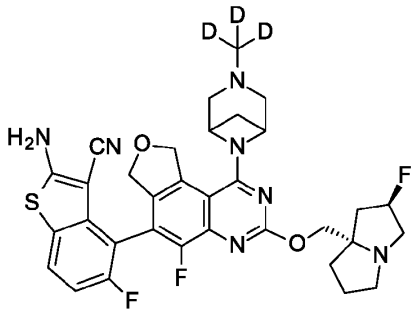
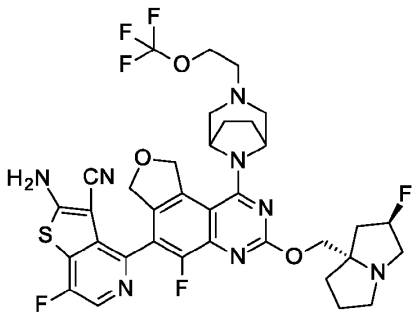
A mixture of 2-amino-4-[1-(3,8-diazabicyclo[3.2.1]octan-8-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5-fluoro-benzothiophene-3-carbonitrile (single atropisomer, from precursor in Preparation 248, 0.060 g, 0.093 mmol), 3-chloro-N-methylpropanamide (0.056 g, 0.465

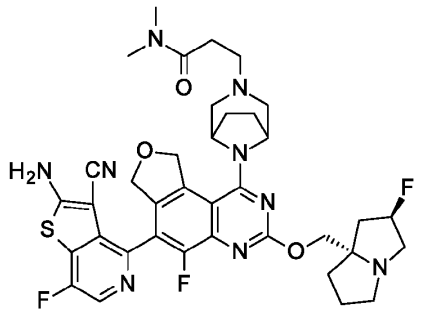
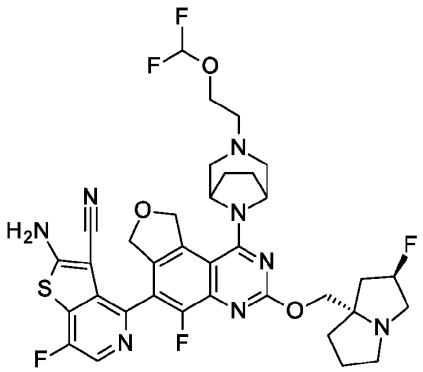
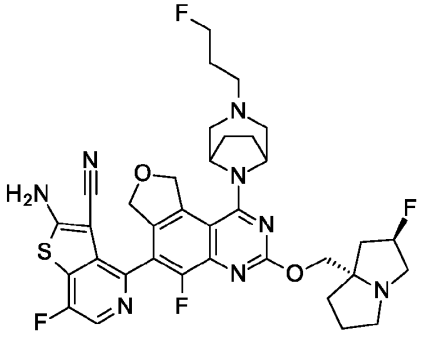
mmol), potassium iodide (0.0077 g, 0.046 mmol), and triethylamine (0.019 g, 0.186 mmol) in acetonitrile (3 mL) was heated at 80 °C for ~ 12 h. The mixture was concentrated, diluted with DMF (2 mL), and purified by reversed phase flash purification on C18, eluting with 35% to 51% ACN in 10 mM aq. NH_4HCO_3 with 0.1% NH_4OH, to give the title compound (0.021 g, 30%) as a white solid. MS (ES) *m/z*=733 (M+1).

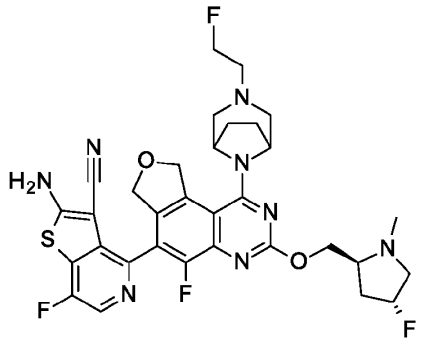
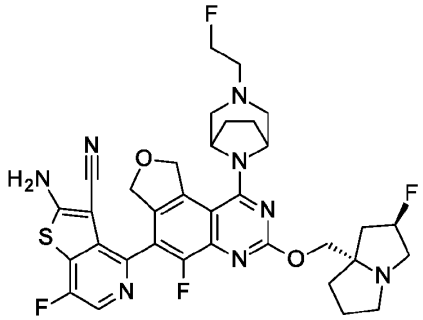
The Example compounds in Table 17 were prepared in a similar manner as described for Example 189. Various methods were used to purify the compounds, which would be apparent to one skilled in the art. Chiral purification methods (if applicable) for the Examples of Table 17 are located in Table 18.

Table 17:

Example	Chemical Name	Structure	MS (ES) *m/z* (M+1)
190[1]	3-[8-[6-(2-Amino-3-cyano-5-fluoro-benzothiophen-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-N,N-dimethyl-propanamide		747

191[1]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(trideuteriomethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		665
192[2]	2-Amino-5-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(trideuteriomethyl)-3,6-diazabicyclo[3.1.1]heptan-6-yl]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]benzothiophene-3-carbonitrile		692
193	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-[2-(trifluoromethoxy)ethyl]-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		761

250	3-[8-[6-(2-Amino-3-cyano-7-fluoro-thieno[3,2-c]pyridin-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]-N,N-dimethyl-propanamide		748
371	2-Amino-4-[1-[3-[2-(difluoromethoxy)ethyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-7-fluoro-thieno[3,2-c]pyridine-3-carbonitrile		743
372	2-Amino-7-fluoro-4-[5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-1-[3-(3-fluoropropyl)-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		709

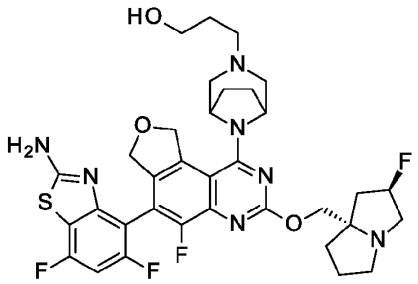
373	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		669
374	2-Amino-7-fluoro-4-[5-fluoro-1-[3-(2-fluoroethyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]thieno[3,2-c]pyridine-3-carbonitrile		695

[1]single atropisomer (from precursor in Preparation 248)

[2]single atropisomer (from precursor in Preparation 266)

Example 194

3-[8-[6-(2-Amino-5,7-difluoro-1,3-benzothiazol-4-yl)-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-1-yl]-3,8-diazabicyclo[3.2.1]octan-3-yl]propan-1-ol



tert-Butyl N-[4-[1-[3-[3-[*tert*-butyl(dimethyl)silyl]oxypropyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]-5-fluoro-3-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7,9-dihydrofuro[3,4-f]quinazolin-6-yl]-5,7-difluoro-1,3-benzothiazol-2-yl]carbamate was used in an analogous manner to the method of Example 1 to obtain the title compound (0.028 g, 16%). MS (ES) *m/z*=700 (M+1).

Chiral purification methods for the Example compounds in Tables 14-17 are in Table 18.

Table 18: Purification Methods.

Example	Method	Stationary Phase	Mobile Phase
3	SFC	Chiralpak® IC[a]	40% MeOH (w/ 0.5% DMEA): CO_2
4	SFC	Chiralpak® AD-H[a]	35% IPA (w/ 0.5% DMEA): CO_2
5	SFC	Chiralpak® AD-H[a]	35% EtOH (w/ 0.5% DMEA): CO_2
9	SFC	Chiralpak® AS-H[a]	30% EtOH (w/ 0.5% DMEA): CO_2
15	SFC	Chiralpak® IC[a]	40% MeOH (w/ 0.5% DMEA): CO_2
21	SFC	Chiralpak® IC[a]	40% EtOH (w/ 0.5% DMEA): CO_2

22	Chiral HPLC	CHIRAL ART Cellulose SB™, c	A: Hexanes (10mM NH_3-MeOH); B: EtOH; Isocratic 30% B
29	SFC	Lux® Cellulose[d]	40% EtOH (w/ 0.5% DMEA): CO_2
30	Chiral HPLC	Chiralpak® IE[a]	A: Hexanes (10mM NH_3-MeOH); B: EtOH; Isocratic 20% B
31	Chiral HPLC	Chiralpak® IE[a]	A: Hexanes (10mM NH_3-MeOH); B: EtOH; Isocratic 30% B
34	Chiral HPLC	Chiralpak® IE[a]	A: Hex (10mM NH_3-MeOH); B: EtOH; Isocratic 20% B
35	Chiral HPLC	Chiralpak® IE[a]	A: Hex(10mM NH_3-MeOH); B: EtOH; Isocratic 20% B
36	Chiral HPLC	Chiralpak® IE[a]	A: Hex (10mM NH_3-MeOH); B: EtOH; Isocratic 70% B
38	Chiral HPLC	Chiralpak® IE[a]	A: Hex (10mM NH_3-MeOH); B: EtOH; Isocratic 20% B
39	Chiral HPLC	Chiralpak® IE[a]	A: Hex (10mM NH_3-MeOH); B: DCM: EtOH=9:1; Isocratic 20% B
40	1) Chiral HPLC 2) Chiral HPLC	1) Chiralpak® IE[a] 2) CHIRAL ART Amylose-C NEO™, c	1) A: Hex (10mM NH_3-MeOH); B: EtOH; Isocratic 30% B 2) Hex (10mM NH_3-MeOH); B: EtOH; Isocratic 15% B

41	1) Chiral HPLC 2) Chiral HPLC	1) Chiralpak® IE[a] 2) Chiralpak® IE[a]	1) A: Hex (10mM NH_3-MeOH); B: EtOH: MeOH=1:3; Isocratic 20% B 2) A: MTBE (10mM NH_3-MeOH); B: EtOH:IPA=1:1; Isocratic 20% B
43	SFC	Chiralpak® IG[a]	50% EtOH (0.5% 2M NH_3-MeOH): CO_2
44	SFC	Chiralcel® OJ-H	25% EtOH (0.5% DMEA): CO_2
53	SFC	Chiralpak® AS-H[a]	25% MeOH (w/0.5% DMEA): CO_2
99	SFC	Chiralpak® AD-H[a]	30% IPA (w/ 0.5% DMEA): CO_2
102	SFC	Chiralpak® AD-H[a]	30% IPA (w/ 0.5% DMEA): CO_2
103	SFC	Chiralpak® AD-H[a]	30% IPA (w/ 0.5% DMEA): CO_2
105	SFC	Chiralpak® AD-H[a]	40% IPA (w/ 0.5% DMEA): CO_2
106	SFC	Chiralpak® AD-H[a]	40% IPA (w/ 0.5% DMEA): CO_2
107	SFC	Chiralpak® AS-H[a]	30% EtOH (w/ 0.5% DMEA): CO_2
116	SFC	Chiralpak® IC[a]	40% IPA (w/ 0.5% DMEA): CO_2
158	SFC	Chiralpak® IC[a]	50% EtOH (w/ 0.5% DMEA): CO_2
160	SFC	Chiralpak® AD-H[a]	35% IPA (w/ 0.5% DMEA): CO_2
161	SFC	Chiralpak® AD-H[a]	35% IPA (w/ 0.5% DMEA): CO_2
166	SFC	Chiralpak® AS-H[a]	25% MeOH (w/0.5% DMEA): CO_2
168	SFC	Chiralpak® AD-H[a]	30% IPA (w/ 0.5% DMEA): CO_2

182	Chiral HPLC	Chiralpak® IE[a]	A: 1:1 Hex:MTBE (0w/ 0.1% DMEA); B: EtOH; Isocratic 15% B
183	Chiral HPLC	Chiralpak® IE[a]	A: 1:1 Hex:MTBE (0w/ 0.1% DMEA); B: EtOH; Isocratic 15% B
207	SFC	Chiralpak® AD-H[a]	35% IPA (w/ 0.5% DMEA): CO_2
208	SFC	Chiralpak® AD-H[a]	35% IPA (w/ 0.5% DMEA): CO_2
209	SFC	Lux® Cellulose[d]	50% MeOH (w/0.5% DMEA): CO_2
210	SFC	Lux® Cellulose[d]	50% MeOH (w/0.5% DMEA): CO_2
214	SFC	Chiralpak® AS-H[a]	25% MeOH (w/0.5% DMEA): CO_2
328	SFC	Chiralpak® AD-H[a]	30% EtOH (w/ 0.5% DMEA): CO_2
329	SFC	Chiralpak® AD-H[a]	30% EtOH (w/ 0.5% DMEA): CO_2
330	SFC	Chiralpak® IH[a]	40% MeOH (w/0.5% DMEA): CO_2
331	SFC	Chiralpak® IH[a]	40% MeOH (w/0.5% DMEA): CO_2
340	SFC	Chiralpak® AS-H[a]	30% MeOH (w/0.5% DMEA): CO_2
366	SFC	Chiralpak® IC-H[a]	35% MeOH (w/0.5% DMEA): CO_2
368	SFC	Chiralpak® IC-H[a]	35% EtOH (w/ 0.5% DMEA): CO_2

[a] Chiralpak® Columns available from Daicel Chiral Technologies; West Chester, PA.

[b] XBridge Columns available from Waters Corp.; Milford, MA.

[c] Chiral ART Columns available from YMC America, Inc.; Devens, MA.

[d] Lux® Columns available from Phenomenex, Inc.; Torrance, CA.

Biological Assays

The following assays demonstrate that the exemplified compounds are potent inhibitors of Kras G12D and inhibit growth of certain tumors *in vitro* and/or *in vivo*.

Example 376

PANC-1 Cellular Active RAS GTPase ELISA (KRas G12D Mutation)

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.

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.

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.

In the above assay, compounds of Examples 1-5, 7-12, 14-18, 20-26, 28-59, 62, 64, 67, 68, 93-192, 194, 206-209, 211-239, 241-250, 279, 323, 327, 328, 331, 332, 334, 336, 340-345, 348, 351, 354-356, 358, 363, 364, 367-372, and 374 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 Formulae I-VIII (including Ia-VIIa) 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.

Example 377

MKN-45 Cellular Active RAS GTPase ELISA (KRas Wild-type)

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.

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.

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.

Compounds of Examples 1, 3, 5, 7, 9-11, 13-18, 20, 22-28, 45, 46, 48, 49, 51-58, 62, 64, 68, 95, 96, 98-100, 103, 106-108, 110, 113, 114, 116-127, 130-146, 148-151, 153, 156-158, 161, 162, 170-187, 189-192, 194, 212-214, 216-218, 220, 224-229, 231, 232, 234-239, 241-243, 247-249, 327, 328, 330-332, 334-338, 340, 341, 343, 344, 348, 349, 351, 354-356, 358, 363, 364, 366, 367, and 372-374 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.

Example 378

Cellular Phospho-ERK AlphaLISA® Assay for KRAS Inhibition

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 19). 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 19). MEF cells were used to confirm KRAS selectivity of the test compounds.

Table 19: 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

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).

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 (**Error! Reference source not found.**). The final c ompound 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.

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:

$$\%\ Activity = 100x\ (1 - \frac{(treated\ value - positive\ control)}{(negative\ control - positive\ control)}) \qquad eq.\ 1$$

% Activity values are fit to a four-parameter non-linear logistic equation using Genedata Screener® 17.0.3. to -determine IC_{50} values:

$$y = Bottom + \frac{Top - Bottom}{1 + \left(\frac{10^{Log(IC_{50})}}{10^{x}}\right)^{h}} \quad eq.\ 2$$

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.

In the above assays, compounds of Examples indicated herein 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 2, 24, 29, 32, 35, 37, 40, 42-45, 48, 55, 56, 59, 68, 93, 95-97, 101, 103, 106-109, 113, 114, 116, 129, 152, 159, 161, 162, 164-166, 168, 169, 172, 190-192, 206, 208, 211-213, 218, 219, 243, 244, 280-289, 292-318, 320, 321, 343, 346, 347, 370, and 375), KRAS G12D (Examples 2, 14, 24, 29, 35, 37, 42-45, 48, 55, 56, 59, 68, 93, 95-97, 101, 103, 106-109, 113, 114, 116, 129, 152, 159, 161, 162, 164-166, 168, 169, 175, 188, 190-193, 212, 213, 218-220, 229, 231, 233, 243, 244, 280-289, 292-313, 316, 318, 343, 346, 347, 370, and 375), KRAS G12V (Examples 29, 30, 32, 35, 37-40, 42-45, 59, 93, 97, 108, 109, 165, 166, 168, 209, 211, 219, 280-289, 292-318, 320, 321, 346, 347, 370, and 375), or KRAS WT (Examples 2, 29, 30, 32, 35, 37-40, 42-45, 48, 56, 59, 62, 93, 95-97, 101, 103, 107-109, 113, 114, 116, 129, 159, 161, 162, 164-166, 168, 169, 190-192, 209, 211, 218, 219, 244, 280-289, 292-314, 316-318, 320, 321346, 347, 370, and 375), with a relative IC50 of <500 nM. Compounds of Examples 2, 14, 24, 45, 48, 49, 55, 56, 59, 68, 95-97, 101, 103, 106-109, 113, 114, 116, 121-124, 126, 129, 130, 142, 152, 159, 161, 162, 164-166, 168, 169, 172, 175, 188, 190-193, 211-213, 218-220, 229, 231, 233, 243, 244, 280-289, 293, 295-302, 305-311, 314-322, 343, 346, 347, 370 and 375 were tested in the Mouse Embryonic Fibroblasts cell line assays above (MEF-NRAS, MEF-HRAS) and all exhibited a relative IC50 of >2 μM.

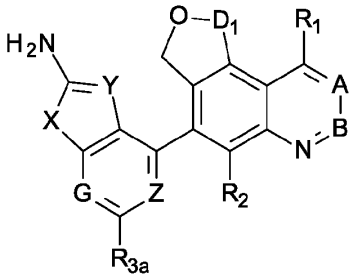
This data shows that compounds of Formulae I-VIII (including Ia-VIIa) as described herein are potent inhibitors of KRAS human cancer cells expressing KRAS demonstrating the ability to inhibit KRAS G12C, G12D or G12V mutants with a significant selective inhibition preference for KRAS mutants over HRAS or NRAS.

Table 10: 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-;

B is -C(R_4)- or -N-;

D_1 is -CH_2-, -CH_2CH_2-, or -CH(CH_2CN)-;

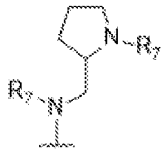
X is -O- or -S-;

Y is -C(CN)- or -N-;

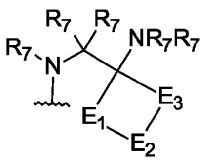
Z is -C(R_{3c})- or -N-;

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

R_1 is H, hydroxyl, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, azetidine, N-linked piperazine, piperidine, morpholine, or a group of the formula selected from



or



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wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, azetidine, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl,

trideuteromethyl, methoxy, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, difluoromethoxy, -O-trideuteromethyl, cyclopropyl, oxetane, pyrazole, imidazole, amino, $-CONR_7R_7$, $-O-(CH_2)_p-OC_{1-3}$ alkyl, $-O-(CH_2)_p-OH$, or -O-CO-C_{1-3} alkyl, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a hydroxyl or a C_{1-3} alkyl substituted with one or more hydroxyl;

E_1 is $-(CR_7R_7-)_n$, E_2 is $-CR_7R_7-$, $-NR_7-$ or -O- and E_3 is $-(CR_7R_7-)_m$, wherein m + n is 1, 2, 3 or 4;

p is 1, 2, or 3;

R_2 is H, halogen, or methyl;

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

R_4 is H, methyl, $-CH_2-OH$, $-O-R_5-R_6$, $-O-R_6$, or azetidine optionally substituted with NR_7R_7, wherein R_5 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2-CH_2-$, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl, 2-oxo-1,3-dihydrobenzimidazole, imidazole or pyrazole, wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more oxo, halogen, hydroxyl, methoxy, difluoromethoxy, NR_7R_7, C_{1-4} alkyl, C_{1-4} alkenyl, -CN, or $-CO-CH_2OH$, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen, hydroxyl, methoxy, or NR_7R_7, wherein the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, or the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally bridged with a C_{1-3} alkyl and wherein if R_4 is H then R_1 is not H; and

each R_7 is independently H, or C_{1-3} alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein G is -N-, or a pharmaceutically acceptable salt thereof.

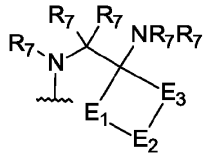
3. The compound according to claim 1, wherein G is -N-, and Z is -C(R_{3c})-, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, wherein G is -C(R_{3b})-, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1, wherein G is -C(R_{3b})-, and Z is -N-, or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 4 or 5, wherein R_{3b} is F, or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein G is -C(R_{3b})-; R_{3a}, R_{3b}, and R_{3c} are each independently H, or halogen; R_1 is H, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, N-linked piperazine, piperidine, or a group of the formula



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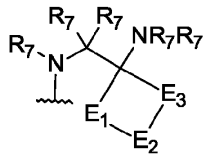
wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, cyclopropyl, oxetane, pyrazole, imidazole, amino, -$CONR_7R_7$, -O-$(CH_2)_p$-OC_{1-3} alkyl, -O-$(CH_2)_p$-OH, or -O-CO-C_{1-3} alkyl, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a C_{1-3} alkyl substituted with one or more hydroxyl; and

R_4 is H, methyl, -CH_2-OH, -O-R_5-R_6, -O-R_6, or azetidine optionally substituted with NR_7R_7, wherein R_5 is -CH_2-, -$CH(CH_3)$-, or -CH_2-CH_2-, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl or 2-oxo-1,3-dihydrobenzimidazole, wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more halogen, hydroxyl, methoxy, NR_7R_7, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, or the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally bridged with a C_{1-3} alkyl and wherein if R_4 is H then R_1 is not H; or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1, wherein G is -$C(R_{3b})$-; R_{3a}, R_{3b}, and R_{3c} are each independently H, or halogen; and R_1 is H, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, N-linked piperazine, piperidine, or a group of the formula



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wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, cyclopropyl, oxetane, pyrazole, imidazole, amino, or -$CONR_7R_7$, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a C_{1-3} alkyl substituted with one or more hydroxyl; and R_4 is H, methyl, -CH_2-OH, -O-R_5-R_6, -O-R_6, or azetidine optionally substituted with NR_7R_7, wherein R_5 is -CH_2-, -$CH(CH_3)$-, or -CH_2-CH_2-, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{3-6} cycloalkyl, C_{4-6} heterocycloalkyl or 2-oxo-1,3-dihydrobenzimidazole, wherein the C_{1-3} alkyl, C_{3-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more

halogen, hydroxyl, methoxy, NR_7R_7, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, or the C_{3-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally bridged with a C_{1-3} alkyl and wherein if R_4 is H then R_1 is not H; or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1, wherein G is $-C(R_{3b})-$; R_{3a}, R_{3b}, and R_{3c} are each independently H, or halogen; R_1 is H, C_{1-4} alkyl, C_{2-4} heteroalkyl, or N-linked piperazine, wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, cyclopropyl, oxetane, or amino, and wherein the N-linked piperazine is optionally bridged by the C_{1-3} alkyl; and

R_4 is H, methyl, $-CH_2-OH$, $-O-R_5-R_6$, or $-O-R_6$, wherein R_5 is $-CH_2-$, $-CH_2(CH_3)-$, or $-CH_2-CH_2-$, wherein R_6 is H, C_{1-3} alkyl, C_{2-3} heteroalkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl, wherein the C_{1-3} alkyl, C_{4-6} cycloalkyl, or C_{4-6} heterocycloalkyl are optionally substituted with one or more halogen, hydroxyl, methoxy, C_{1-4} alkyl, or C_{1-4} alkenyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen or hydroxyl, wherein the C_{4-6} cycloalkyl or C_{4-6} heterocycloalkyl are optionally fused with the C_{1-4} alkyl to form a bicyclic ring, and wherein if R_4 is H then R_1 is not H; or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1-9, wherein X is -S-, or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of claims 1-10, wherein Y is -C(CN)-, or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1-9, wherein X is -O- and Y is -C(CN)-, or a pharmaceutically acceptable salt thereof.

13. The compound according to any one of claims 1-4, 6-12, wherein Z is -C(R_{3c})-, or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 13, wherein R_{3a} and R_{3c} are each independently H or F, or a pharmaceutically acceptable salt thereof.

15. The compound according to any one of claims 1-14, wherein R_{3a} is H, or a pharmaceutically acceptable salt thereof.

16. The compound according to any one of claims 1-12, wherein Z is -N-, or a pharmaceutically acceptable salt thereof.

17. The compound according to any one of claims 1-16, wherein A is -N-, or a pharmaceutically acceptable salt thereof.

18. The compound according to any one of claims 1-16, wherein A is -C(H)-, or a pharmaceutically acceptable salt thereof.

19. The compound according to any one of claims 1-18, wherein B is -C(R_4)-, or a pharmaceutically acceptable salt thereof.

20. The compound according to any one of claims 1-18, wherein B is -C(H)-, or a pharmaceutically acceptable salt thereof.

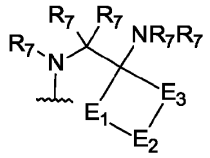
21. The compound according to any one of claims 1-20, wherein D_1 is -CH_2-, or a pharmaceutically acceptable salt thereof.

22. The compound according to any one of claims 1-21, wherein R_1 is N-linked piperazine, or a pharmaceutically acceptable salt thereof.

23. The compound according to any one of claims 1-8, 10-21, wherein R_1 is N-linked piperazine optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, cyclopropyl, oxetane, pyrazole, imidazole, amino, or -$CONR_7R_7$, and optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl,

imidazole, or pyrazole are each optionally substituted with a C_{1-3} alkyl substituted with one or more hydroxyl, or a pharmaceutically acceptable salt thereof.

24. The compound according to any one of claims 1-8, 10-21, wherein R_1 is H, methoxy, C_{1-4} alkyl, C_{2-4} heteroalkyl, N-linked piperazine, piperidine, or a group of the formula



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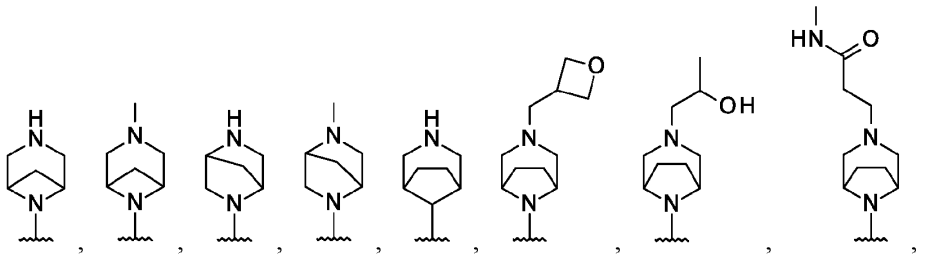
wherein the C_{1-4} alkyl, C_{2-4} heteroalkyl, piperidine, or N-linked piperazine are optionally substituted with one or more of amino, hydroxyl, methyl, trideuteromethyl, oxetane, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, cyclopropyl, oxetane, pyrazole, imidazole, amino, or $-CONR_7R_7$, wherein the piperidine or the N-linked piperazine are optionally bridged by a C_{1-3} alkyl and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a C_{1-3} alkyl substituted with one or more hydroxyl; or a pharmaceutically acceptable salt thereof.

25. The compound according to any one of claims 1-6, 10-21, wherein R_1 is H, methoxy, $-CH_2-CH_2-NH_2$, or a group of the formula



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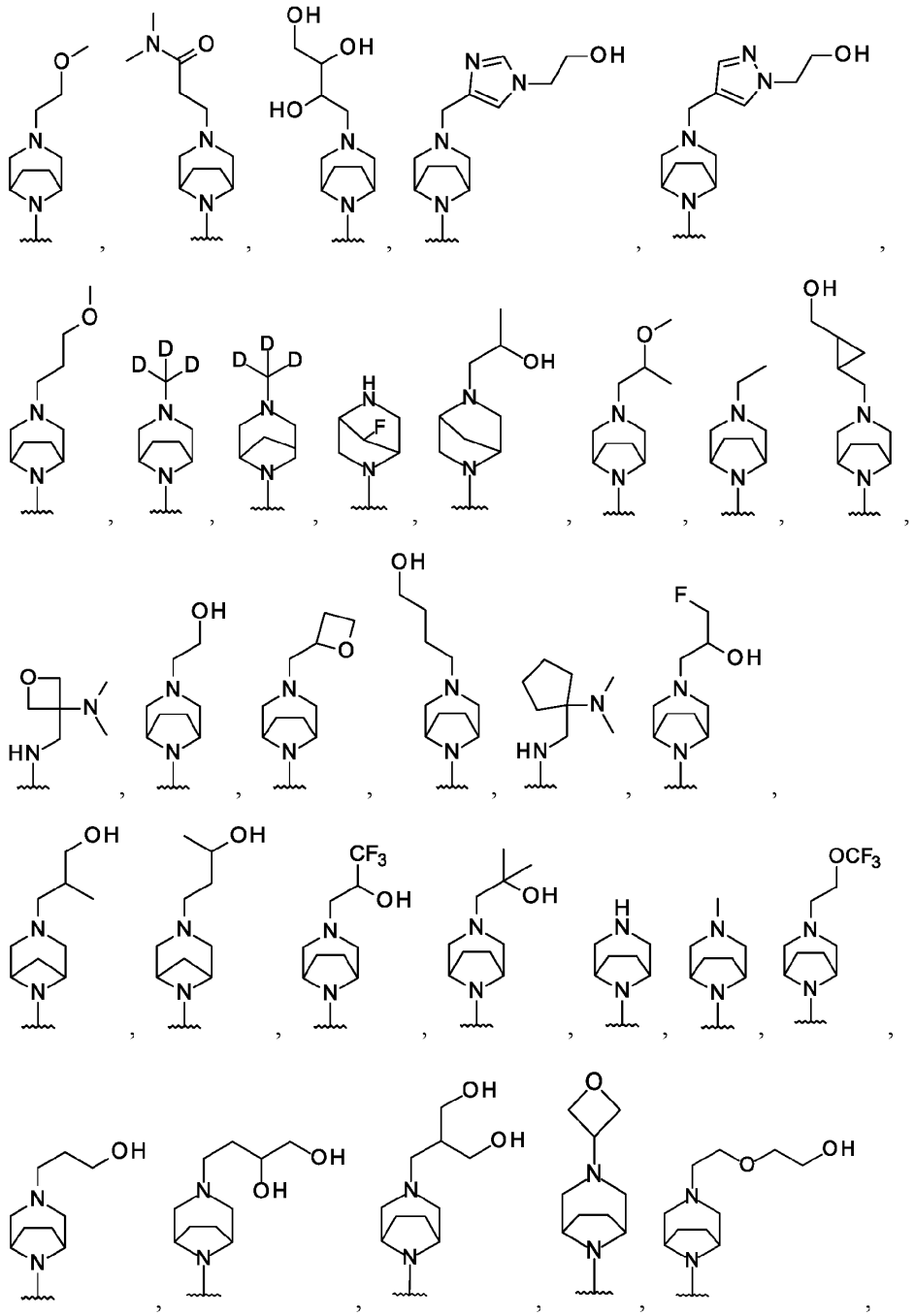

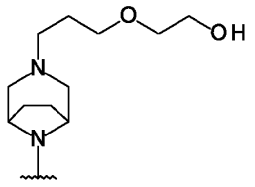
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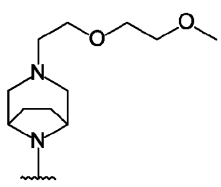
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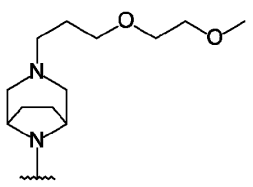
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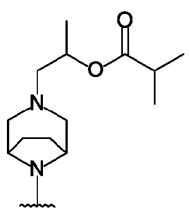
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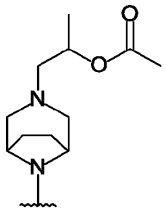
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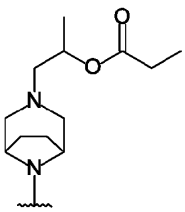
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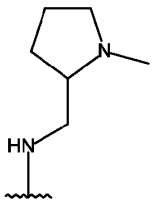
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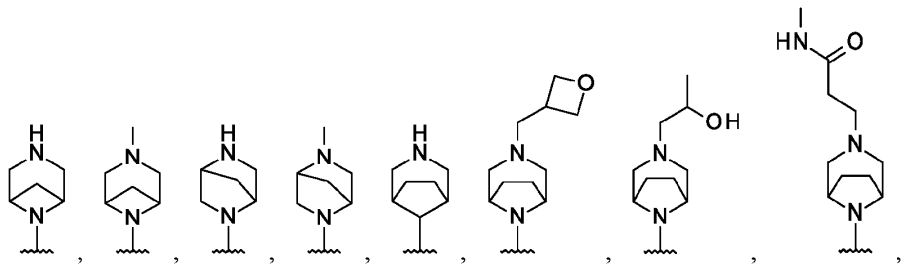
or a pharmaceutically acceptable salt thereof.

26. The compound according to any one of claims 1-8, 10-21, wherein R_1 is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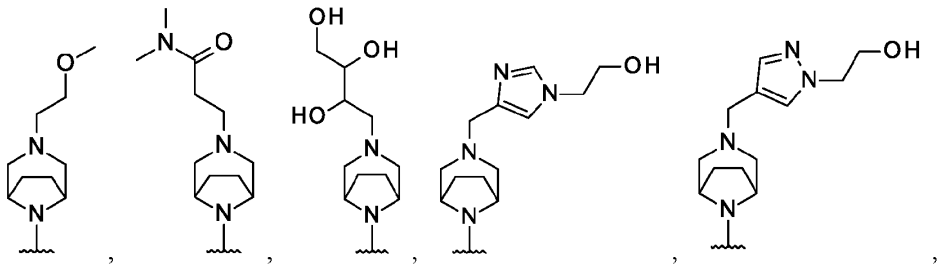
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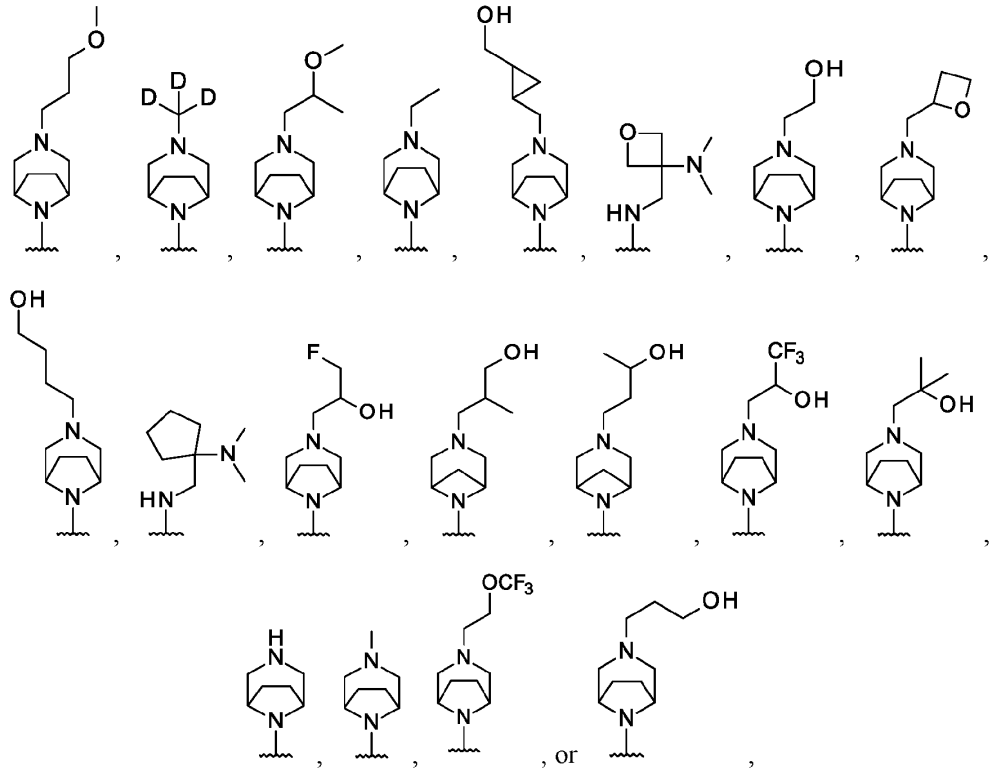
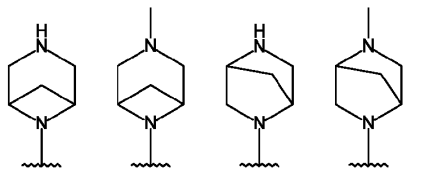
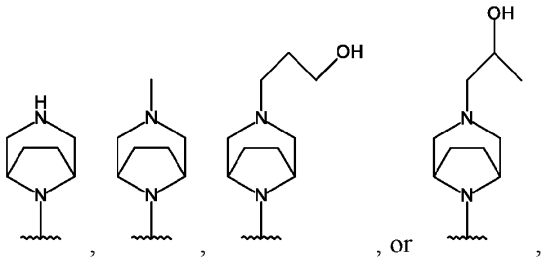


or a pharmaceutically acceptable salt thereof.

27. The compound according to any one of claims 1-21, wherein R_1 is





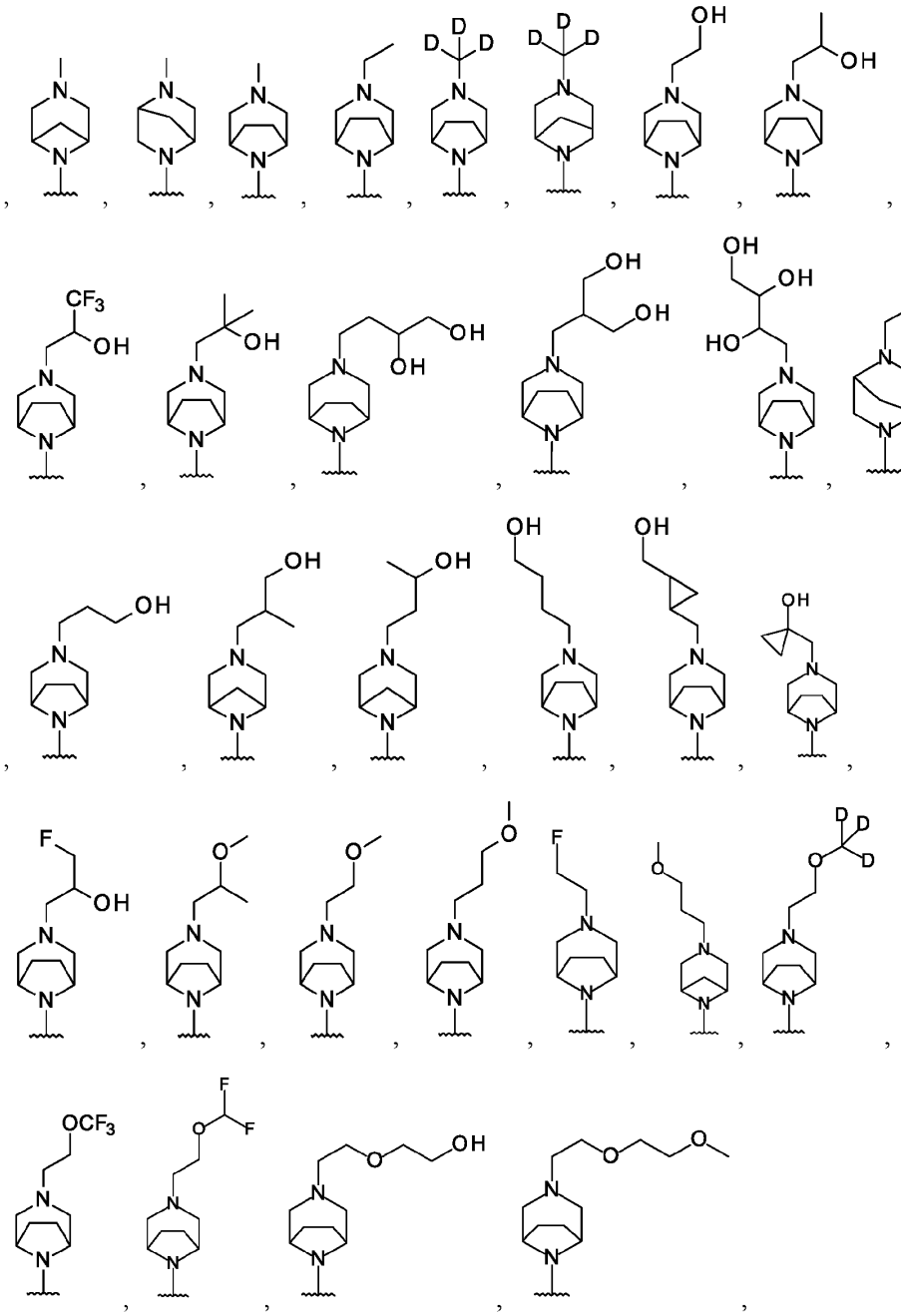
, , , or ,

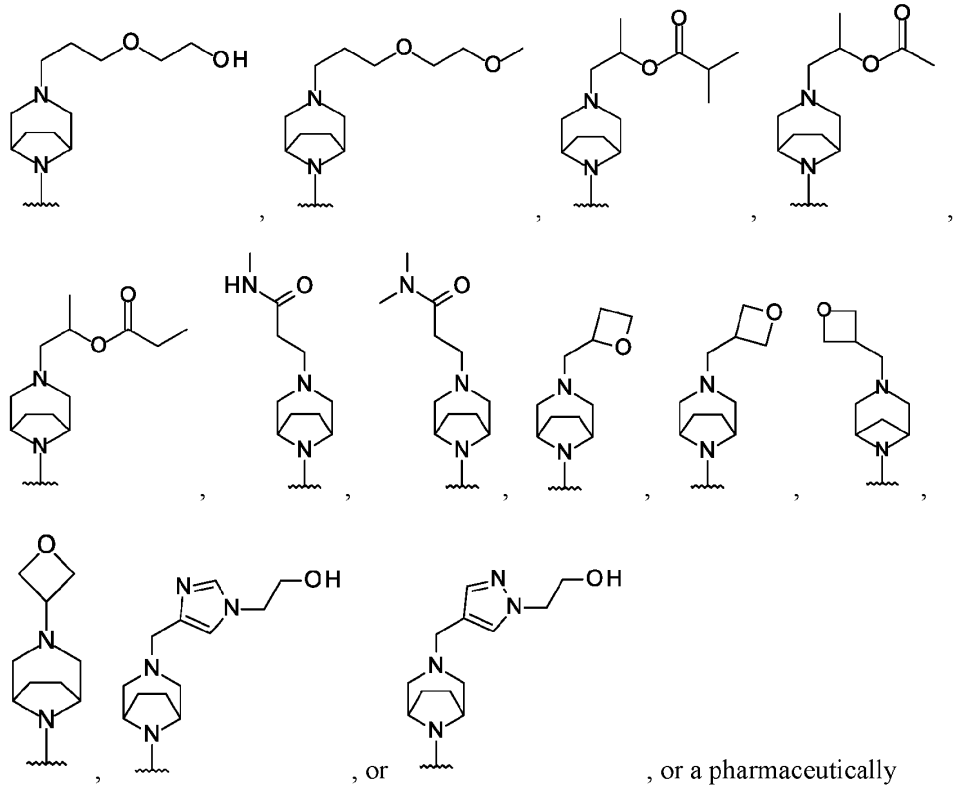
or a pharmaceutically acceptable salt thereof.

28. The compound according to any one of claims 1-21, wherein R_1 is H, or a pharmaceutically acceptable salt thereof.

29. The compound according to any one of claims 1-6, 10-21, wherein R_1 is N-linked piperazine substituted with one or more of methyl, trideuteromethyl, or C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by one or more halogen, hydroxyl, methyl, hydroxymethyl, methoxy, trifluoromethoxy, difluoromethoxy, -O-trideuteromethyl, cyclopropyl, oxetane, pyrazole, imidazole, $-CONR_7R_7$, $-O-(CH_2)_p-OC_{1-3}$ alkyl, $-O-(CH_2)_p-OH$, or $-O-CO-C_{1-3}$ alkyl, and wherein the cyclopropyl, imidazole, or pyrazole are each optionally substituted with a hydroxyl or a C_{1-3} alkyl substituted with one or more hydroxyl, and wherein the N-linked piperazine is bridged by a C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

30. The compound according to any one of claims 1-6, 10-21, wherein R_1 is selected from



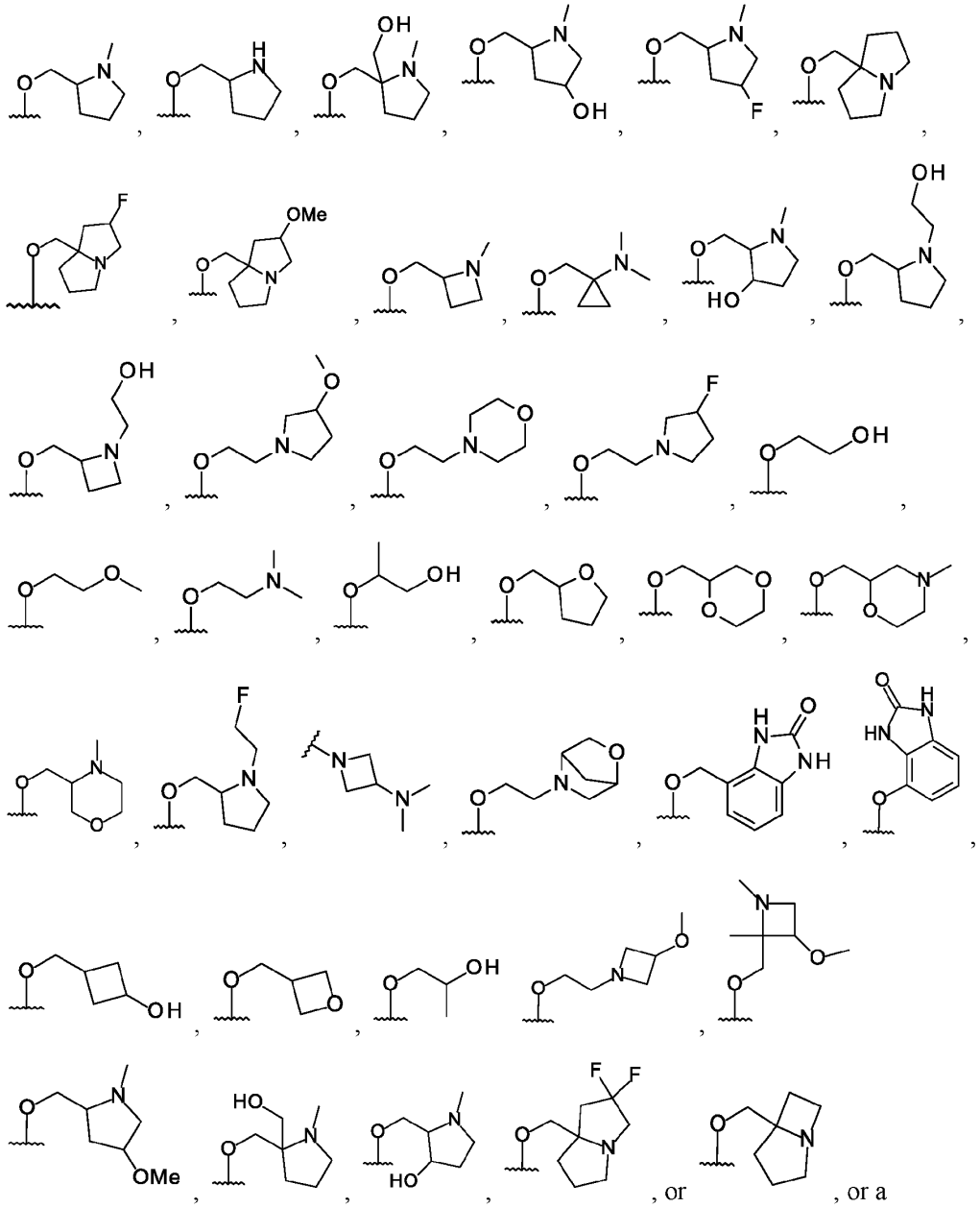


acceptable salt thereof.

31. The compound according to any one of claims 1-19, or 21-30, wherein R_4 is $-O-CH_2-R_6$ or a pharmaceutically acceptable salt thereof.

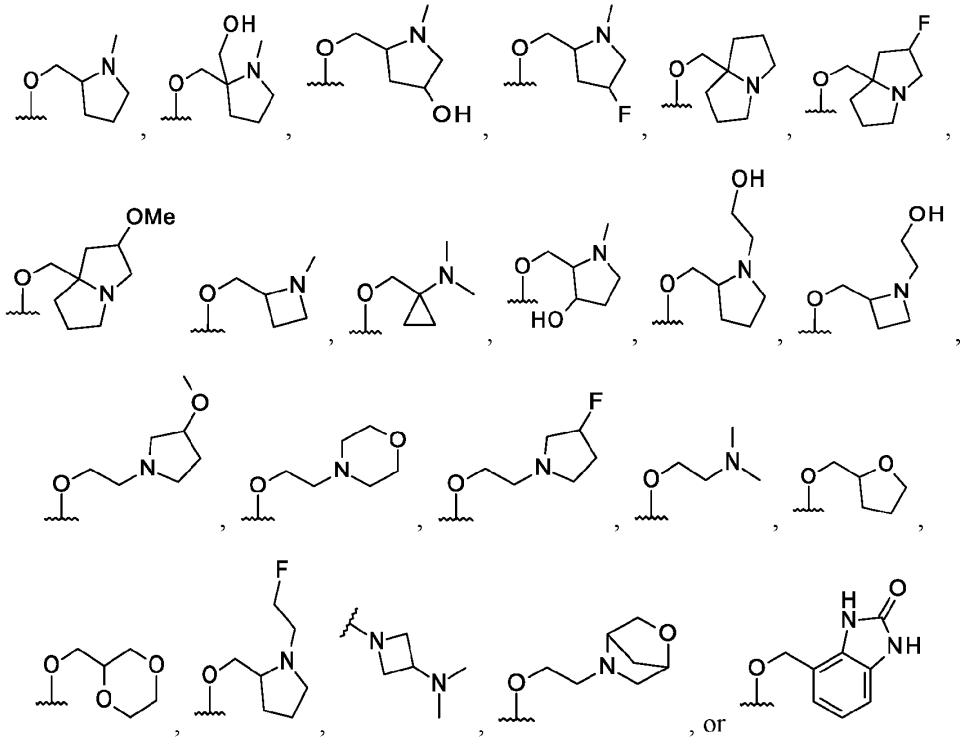
32. The compound according to claim 31, wherein R_6 is azetidine, pyrrolidine, piperidine, oxetane, tetrahydrofuran, morpholine, cyclobutane, or 1,4-dioxane, or a pharmaceutically acceptable salt thereof.

33. The compound according to any one of claims 1-6, 10-19, or 21-30 wherein R_4 is methyl, methoxy, $-CH_2-OH$, or a group of the formula



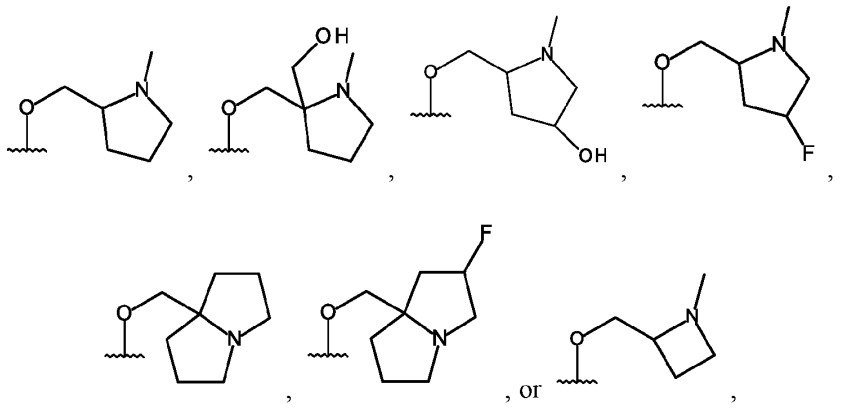
pharmaceutically acceptable salt thereof.

34. The compound according to any one of claims 1-8, 10-19, or 21-31, wherein R_4 is



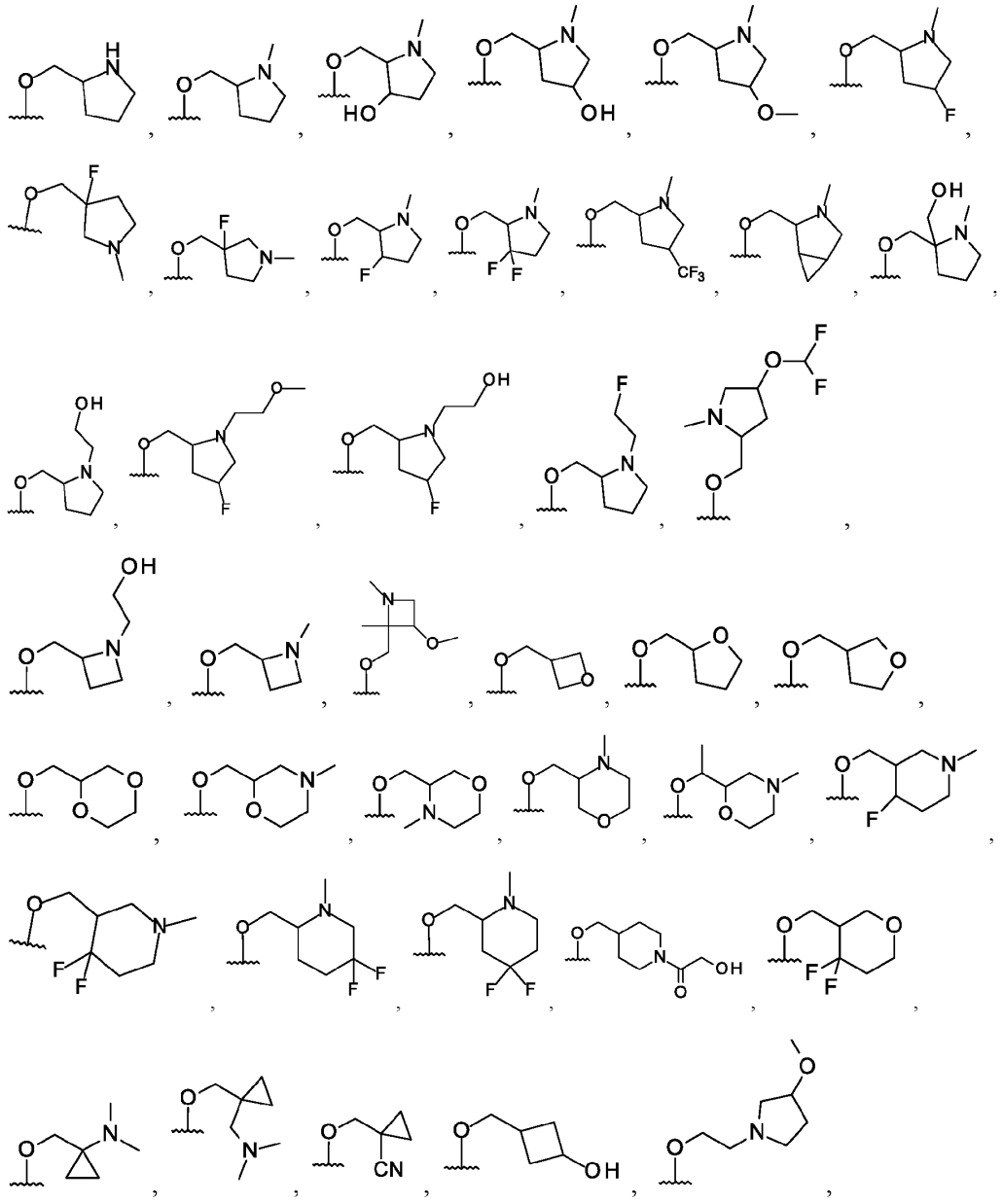
or a pharmaceutically acceptable salt thereof.

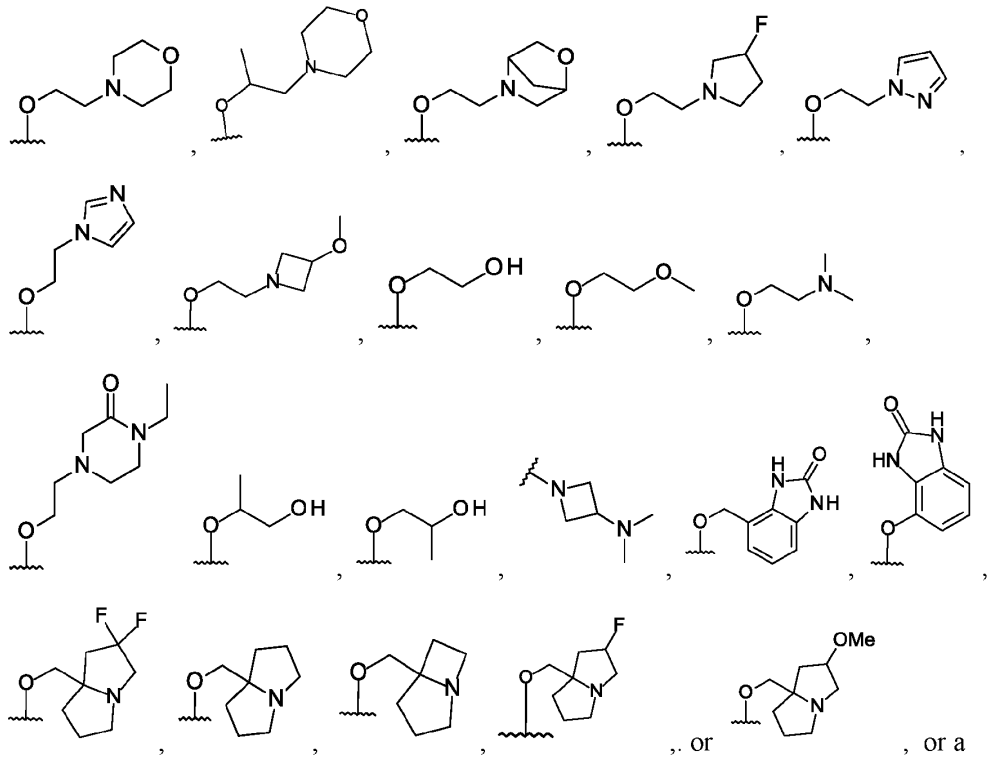
35. The compound according to any one of claims 1-19, or 21-31, wherein R_4 is



or a pharmaceutically acceptable salt thereof.

36. The compound according to any one of claims 1-6, 10-19 or 21-31, wherein R_4 is selected from





pharmaceutically acceptable salt thereof.

37. The compound according to any one of claims 1-36, wherein R_2 is F or Cl or a pharmaceutically acceptable salt thereof.

38. The compound according to any one of claims 1-37, wherein R_2 is F, or a pharmaceutically acceptable salt thereof.

39. The compound according to any one of claims 1-37, wherein R_2 is Cl, or a pharmaceutically acceptable salt thereof.

40. The compound according to claim 1, wherein X is S, Y is -C(CN)-, Z is -C(R_{3c})-, R_2 is F or Cl, R_{3a} is H, R_{3b} is H, R_{3c} is F, and D_1 is -CH_2-, or a pharmaceutically acceptable salt thereof.

41. A pharmaceutical composition comprising a compound according to any one of claims 1-40, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

42. A method of treating a patient for cancer, comprising administering to a patient in need thereof, an effective amount of a pharmaceutical composition according to claim 41, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

43. A method of treating a patient for cancer, comprising administering to a patient in need thereof, an effective amount of a compound according to any one of claims 1-40, or a pharmaceutically acceptable salt thereof, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

44. The method according to claims 42 or 43 wherein the cancer is non-small cell lung cancer, and wherein one or more cells express KRas G12D mutant protein.

45. The method according to claims 42 or 43 wherein the cancer is colorectal cancer, and wherein one or more cells express KRas G12D mutant protein.

46. The method according to claims 42 or 43 wherein the cancer is pancreatic cancer, and wherein one or more cells express KRas G12D mutant protein.

47. The method according to claims 42 or 43 wherein the patient has 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.

48. The method according to claims 42 or 43 wherein the cancer is non-small cell lung cancer, and wherein one or more cells express KRas G12C, G12D, and/or G12V mutant proteins.

49. The method according to claims 42 or 43wherein the cancer is colorectal cancer, and wherein one or more cells express KRas G12C, G12D, and/or G12V mutant proteins.

50. The method according to claims 42 or 43 wherein the cancer is pancreatic cancer, and wherein one or more cells express KRas G12C, G12D, and/or G12V mutant proteins.

51. The method according to claims 42 or 43 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.

52. 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 any one of claims 1-40, or a pharmaceutically acceptable salt thereof.

53. The method according to claim 52, wherein the cancer is selected from 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.

54. The method according to claim 53, wherein the cancer is KRas G12D mutant non-small cell lung cancer.

55. The method according to claim 53, wherein the cancer is KRas G12D mutant colorectal cancer.

56. The method according to claim 53, wherein the cancer is KRas G12D mutant pancreatic cancer.

57. A method of treating a patient with a cancer that has a KRas G12C, G12D, and/or G12V mutations comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1-40, or a pharmaceutically acceptable salt thereof.

58. The method according to claim 57, wherein the cancer is selected from 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 G12D mutant cholangiocarcinoma, and KRas G12C, G12D, and/or G12V mutant colorectal cancer.

59. The method according to claim 58, wherein the cancer is KRas G12C, G12D, and/or G12V mutant non-small cell lung cancer.

60. The method according to claim 58, wherein the cancer is KRas G12C, G12D, and/or G12V mutant colorectal cancer.

61. The method according to claim 58, wherein the cancer is KRas G12C, G12D, and/or G12V mutant pancreatic cancer.

62. The method according to any one of claims 42-61, wherein the patient is also administered an effective amount of 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.

63. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-40, for use in therapy.

64. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-40 for use in the treatment of cancer.

65. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 64 wherein the cancer has a KRas G12D mutation.

66. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 64 wherein the cancer has a KRas G12C, G12D, and/or G12V mutation.

67. The compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 64-66 wherein the cancer is selected from lung cancer, pancreatic

cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

68. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-40 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.